HIV
Opportunistic Infections with a focus on Bacterial Infections

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Conflicts

- NONE

First HIV Report in MMWR

1981 June 5;30:250—2

Pneumocystis Pneumonia — Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation CMV titer in October 1980 was 256; in May 1981 it was 32.* The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed *P. carinii* pneumonia in April 1981 after a 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.

Patient 3: A 30-year-old man was well until January 1981 when he developed esophageal and oral candidiasis that responded to Amphotericin B treatment. He was hospitalized in February 1981 for *P. carinii* pneumonia that responded to oral TMP/SMX. His esophageal candidiasis recurred after the pneumonia was diagnosed, and he was again given Amphotericin B. The CMV complement-fixation titer in March 1981 was 8. Material from an esophageal biopsy was positive for CMV.

Patient 4: A 29-year-old man developed *P. carinii* pneumonia in February 1981. He had had Hodgkins disease 3 years earlier, but had been successfully treated with radiation therapy alone. He did not improve after being given intravenous TMP/SMX and corticosteroids and died in March. Postmortem examination showed no evidence of Hodgkins disease, but *P. carinii* and CMV were found in lung tissue.

Patient 5: A previously healthy 36-year-old man with a clinically diagnosed CMV infection in September 1980 was seen in April 1981 because of a 4-month history of fever, dyspnea, and cough. On admission he was found to have *P. carinii* pneumonia, oral candidiasis, and CMV retinitis. A complement-fixation CMV titer in April 1981 was 128. The patient has been treated with 2 short courses of TMP/SMX that have been limited because of a sulfa-induced neutropenia. He is being treated for candidiasis with topical nystatin.

The diagnosis of *Pneumocystis* pneumonia was confirmed for all 5 patients ante-

Centers for Disease Control (CDC). Pneumocystis pneumonia--Los Angeles. [Case Reports. Journal Article] MMWR - Morbidity & Mortality Weekly Report. 30(21):250-2, 1981 Jun 5.

History of HIV

- First cases on PCP and Kaposi Sarcoma in homosexual men were identified in California and New York in 1980.
- First reported series of 5 PCP cases in Los Angeles was published in MMWR in June ’81
- By August ’81, MMWR reported 70 more cases of PCP & KS in mostly homosexual or bisexual men, 40% had died

Pathogenesis of HIV

- Within 24hrs, mucosal dendritic cells exposed to infected secretions are shown to be infected in monkeys exposed to SIV
- Infected DC cells can carry HIV virus to lymph nodes were CD4+ T-cells can be readily infected
- Macrophages are also CD4+ and CCR5+, and can be infected by HIV
- HIV infection in macrophages is non-cytopathic and they may produce virions for long periods of time
- Activated CD4+ T-cells are the main target for HIV

Pathogenesis of HIV

- **Lymphoid organs** may have greater levels of infection than peripheral blood
- Follicular DC cells may serve as filters in the lymph nodes to reduce circulating viremia
- As the asymptomatic infection progresses, follicular DC cells are lost and lymph node architecture is progressively disrupted
- **In late HIV, the lymph nodes may appear as "burn out"** with low lymphocyte counts and absence of germinal centers

Pathogenesis of HIV: Immunodeficiency

- Decreased CD4+ T-cells counts
  - Decreased production
  - Lysis of infected & uninfected T-cells
- Functional defects in HIV-1 infected cells
- Eventual decline in cellular immunity leads to opportunistic infections in patients with HIV

Pathogenesis of HIV: Natural History

- Initial phase of infection is known as **Primary HIV Infection**
- Primary HIV Infection may be asymptomatic or can be similar to infectious mononucleosis
- 50-70% of patients may have constitutional symptoms (fever, muscle pains, rash, lymphadenopathy)
- Levels of infectious virus are very high (>10^6) in plasma during primary HIV infections
- Symptoms last 1-2 weeks

Opportunistic Infections and Cancers

- Opportunistic infections (OIs) are defined as infections that are more frequent or more severe because of immunosuppression.

- About 20% of HIV infected persons present initially with an Opportunistic Infection (OI) or Cancer as there indicator of HIV/AIDS disease.

- Remember: Opportunistic infections occur in Transplant, Cancer, Autoimmune Diseases and patients on IS therapy

BEST THERAPY FOR OPPORTUNISTIC INFECTIONS?

Benefits of Combination ART

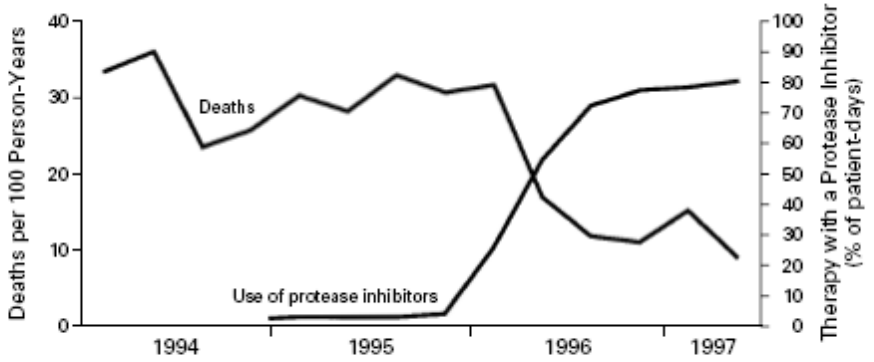


Figure 1. Mortality and Frequency of Use of Combination Antiretroviral Therapy Including a Protease Inhibitor among HIV-Infected Patients with Fewer Than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

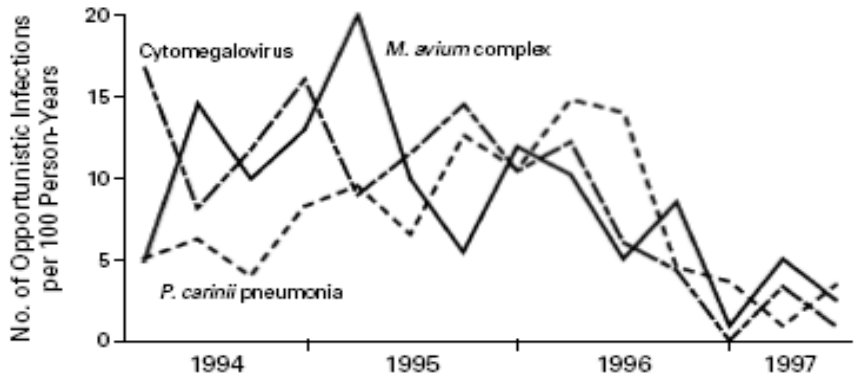
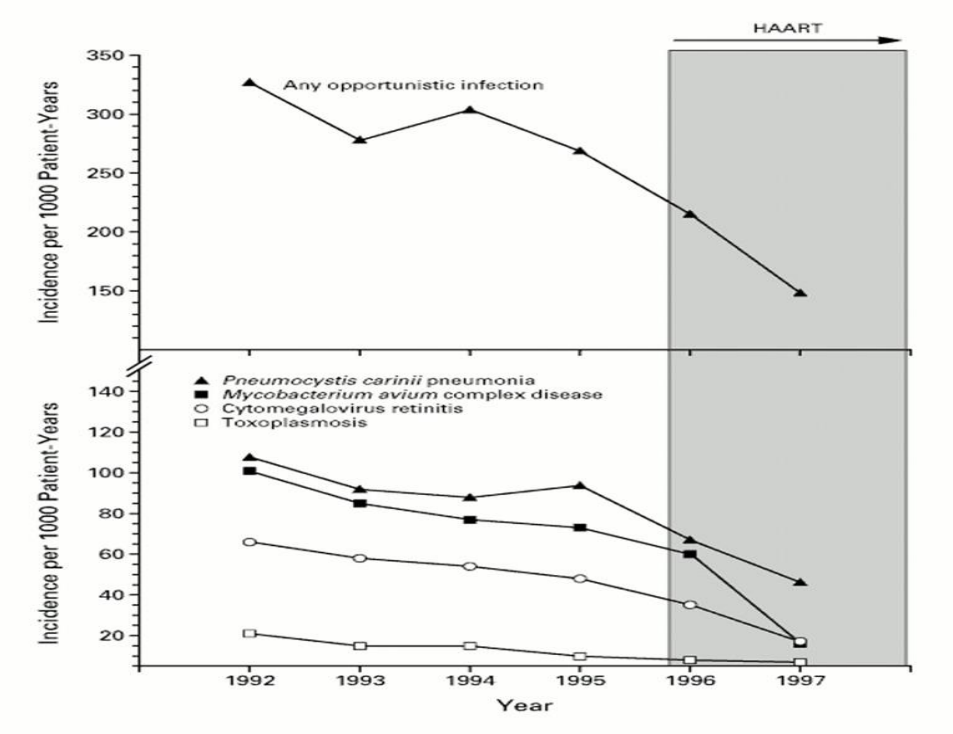


Figure 2. Rates of Cytomegalovirus Infection, *Pneumocystis carinii* Pneumonia, and *Mycobacterium avium* Complex Disease among HIV-Infected Patients with Fewer Than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

Palella FJ Jr. Delaney KM. Moorman AC. Loveless MO. Fuhrer J. Satten GA. Aschman DJ. Holmberg SD. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. [Journal Article] New England Journal of Medicine. 338(13):853-60, 1998 Mar 26.

ART is the Best Policy

Incidence of Selected Opportunistic Infections in Patients with HIV Infection, 1992 through 1997, Based on Data from the Adult/Adolescent Spectrum of HIV Disease Cohort Study



Kovacs J, Masur H. N Engl J Med 2000;342:1416-1429

Summary incident risk by region for antiretroviral therapy (ART)–naive (A) and ART-exposed (B) patients.

Table 2. Estimated Summary Incident Risk for Opportunistic Infections and Other Infections, by Antiretroviral Status

Opportunistic Infection	Summary of Incident Risk, % (95% CI) (No. of Studies)		Unadjusted Odds Ratio (95% CI)[a]
	ART Naive	ART Exposed	
Cryptococcus neoformans meningitis	0.55 (.10–1.36) (3)	0.25 (.04–.66) (4)	0.42 (.11–1.83)
Pneumocystis pneumonia	3.48 (1.23–6.82) (7)	2.49 (.34–6.54) (7)	0.71 (.50–1.01)
Oral and esophageal candidiasis	8.29 (3.75–14.39) (8)	3.20 (1.71–5.15) (8)	0.37 (.29–.46)
CMV retinitis	0.82 (.15–2.04) (2)	0.85 (.01–3.69) (2)	0.99 (.24–4.71)
Varicella zoster virus	4.69 (2.44–7.62) (3)	8.40 (4.78–12.91) (5)	1.88 (1.23–2.87)
Herpes simplex	1.59 (.43–3.48) (5)	1.33 (.23–3.32) (5)	0.86 (.53–1.41)
Kaposi sarcoma	NA	0.06 (.01–.14) (2)	NA
Cerebral toxoplasmosis	3.06 (.85–6.59) (3)	0.72 (.15–1.71) (5)	0.23 (.13–.43)
Cryptosporidium diarrhea	2.92 (.00–10.97) (3)	0.31 (.01–1.06) (7)	0.10 (.05–.22)
Mycobacterium tuberculosis (unspecified types)	12.36 (7.95–17.59) (15)	8.84 (5.21–13.31) (18)	0.69 (.63–.75)
Pulmonary tuberculosis	9.78 (5.37–15.34) (10)	3.99 (2.66–5.56) (9)	0.38 (.32–.46)
Extrapulmonary tuberculosis	7.26 (3.00–13.18) (4)	1.12 (.40–2.18) (6)	0.15 (.10–.21)
Bacterial pneumonia	25.01 (14.50–37.91) (9)	22.11 (11.58–34.89) (7)	0.85 (.78–.92)
Isolated bacteremia	NA	7.50 (.25–1.50) (1)	NA
Bacterial meningitis	0.95 (.48–1.56) (3)	0.80 (.36–1.42) (3)	0.85 (.33–2.12)
Bacterial sepsis	3.95 (1.46–7.58) (4)	2.39 (.00–9.19) (4)	0.59 (.47–.75)

Abbreviations: ART, antiretroviral therapy (combines both specified and unspecified); CI, confidence interval; CMV, cytomegalovirus; NA, numbers insufficient to perform analysis.

[a] Reference is naive population.

Marie-Renée B-Lajoie, et al. Clin Infect Dis. 2016 Jun 15;62(12):1586-1594.

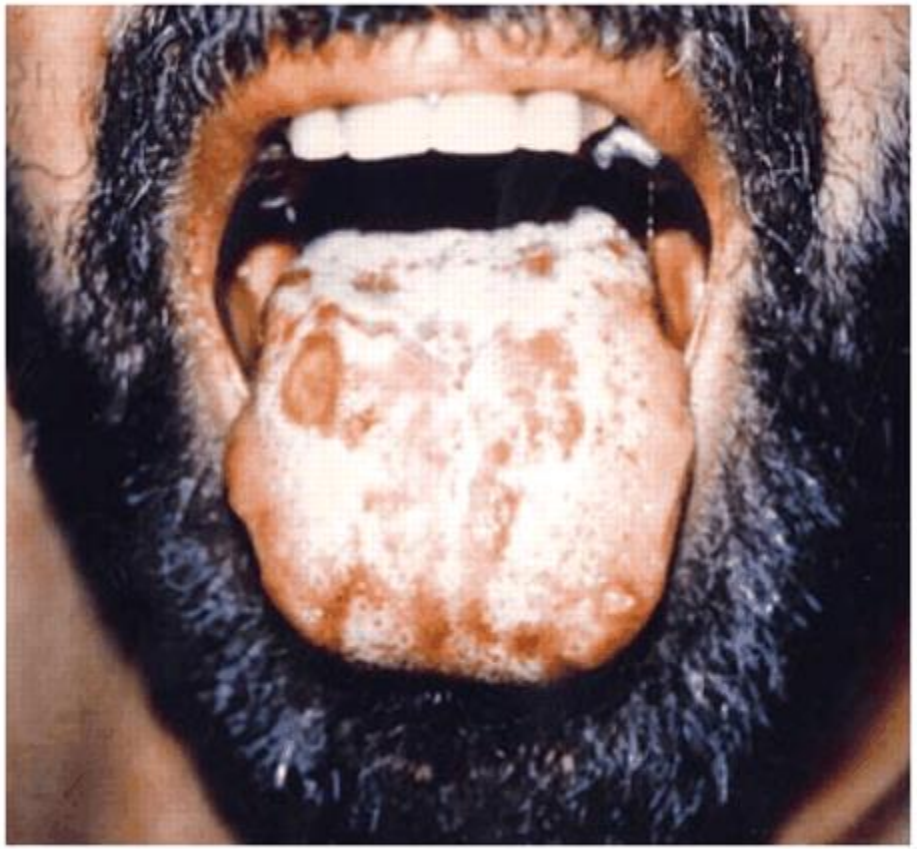
ACUTE HIV

Acute HIV Presentation

Common Findings

- Fever (38-40C)
- Lymphadenopathy (axillary, cervical, occipital)
- Sore throat (thrush, tonsillitis,
- Maculopapular Rash (after 48hrs from onset of fever)
- Myalgia/arthralgia
- Nausea/Diarrhea
- Weight loss
- Headaches
- HIV VL >100,000 copies/mL
- Acute drop in CD4 counts
- Atypical lymphocytes
- Positive heterophile antibody test

Acute HIV Patient

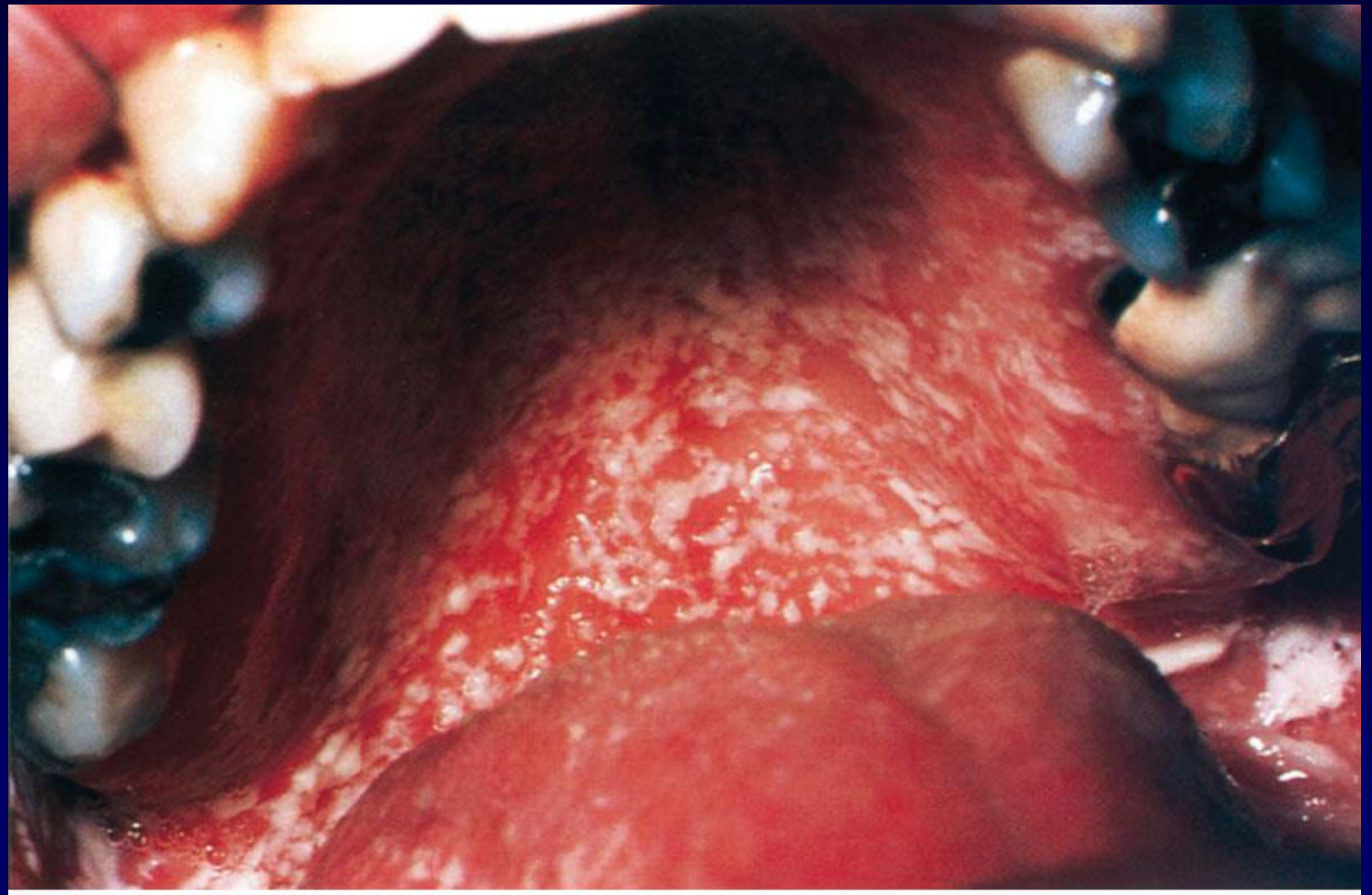


Oral Thrush

Kahn J and Walker B. N Engl J Med 1998;339:33-39

The NEW ENGLAND JOURNAL of MEDICINE

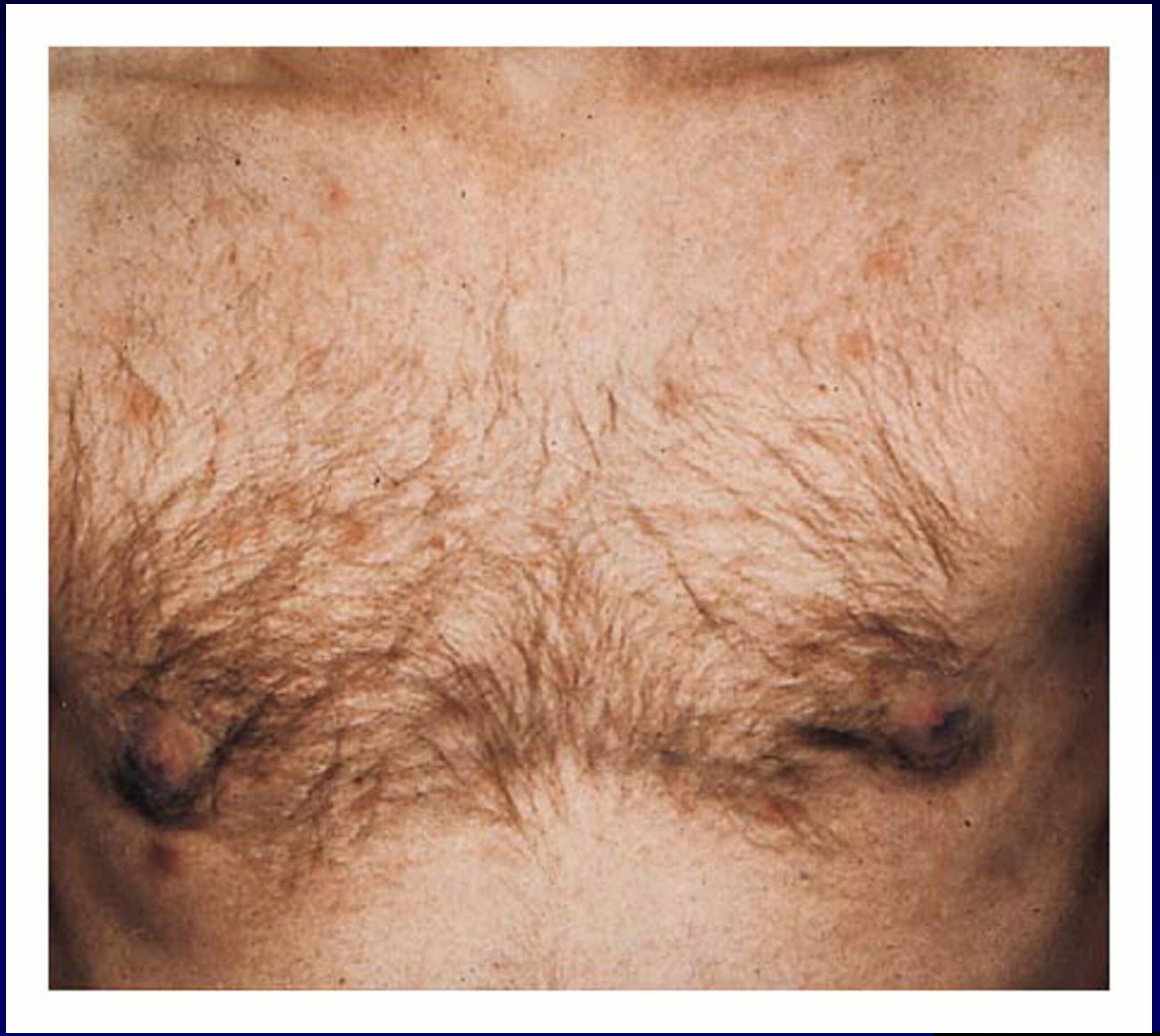
Oral Candidiasis



Acute HIV- Opportunistic Infections

- Oral and Esophageal Candidiasis
- CMV Infection (Hepatitis, Colitis, Proctitis)
- Pneumocystis jirovecii pneumonia
- Cyptosporidiosis

Cutaneous Manifestations of Acute HIV-1 Infection



HIV Macular Rash

Kahn J and Walker B. N Engl J Med 1998;339:33-39

The NEW ENGLAND JOURNAL of MEDICINE

CHRONIC HIV/AIDS

NEW in the DHHS Guidelines

- Stopping PCP prophylaxis in patients with CD4 counts between 100-200 cells/mm3 and plasma VL below the detection limits
- Primary prophylaxis for MAC in PLWH who initiate ART is no longer recommend, regardless of CD4 cell count
- Guidance of using rifabutin with
  - Rilpivirine, Doravirine
  - INSTI (elvitegravir/cobi, bictegravir)

Pathogenesis: Monitoring the Infection

- In 1986 and in 1993, the CDC provided a classification of the stages of HIV infections
- The revised CDC classification did not take into account patients viral loads or the advent of combination antiretroviral therapy

CD4 cell count	A	B	C
≥500	A1	B1	C1
200-500	A2	B2	C2
<200	A3	B3	C3

A: asymptomatic, generalized lymphadenopathy, or acute HIV infection
B: symptomatic, not A or C
C: AIDS indicator condition

WHO Criteria for HIV Infection

Clinical Stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)
- Performance scale 1: asymptomatic, normal activity

Clinical Stage 2

- Weight loss, <10% of body weight
- Minor mucocutaneous manifestations
- Herpes zoster, within the last 5 years
- Recurrent upper respiratory tract infections (e.g., bacterial sinusitis)
- And/or performance scale 2: symptomatic, normal activity

WHO Criteria for HIV Infection

Clinical stage 3

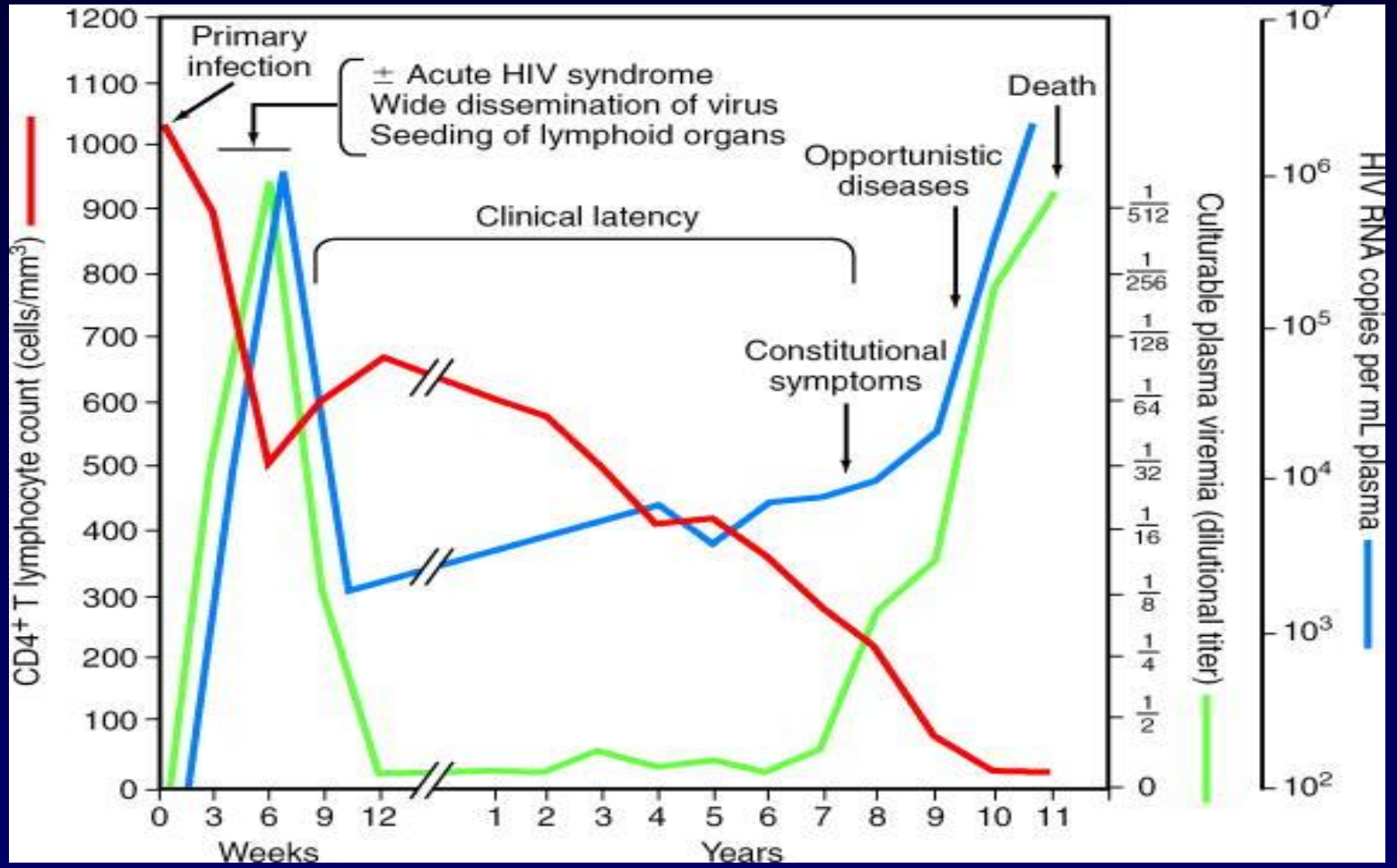
- Weight loss, >10% of body weight
- Unexplained chronic diarrhea, >1 month
- Unexplained prolonged fever (intermittent or constant), >1 month
- Oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis, within the past year
- Severe bacterial infections (e.g., pneumonia, pyomyositis)
- And/or performance scale 3: bedridden, >50% of the day during the last month

WHO Criteria for HIV Infection

Clinical stage 4

- HIV wasting syndrome, as defined by CDC
- Pneumocystis jirovecii/carinii pneumonia
- CNS Toxoplasmosis
- Cryptosporidiosis with diarrhea, >1 month
- Cryptococcosis-extrapulmonary
- Cytomegalovirus (CMV) disease of an organ other than liver, spleen, or lymph nodes
- Herpes simplex virus (HSV) infection, mucocutaneous >1 month, or visceral any duration
- Progressive multifocal leukoencephalopathy (PML)
- Any disseminated endemic mycosis (e.g., histoplasmosis, coccidioidomycosis)
- Candidiasis of the esophagus, trachea, bronchi, or lungs
- Atypical mycobacteriosis, disseminated
- Nontyphoid Salmonella septicemia
- Extrapulmonary tuberculosis
- Lymphoma
- Kaposi's sarcoma (KS)
- HIV encephalopathy, as defined by CDC
- And/or performance scale 4: bedridden, >50% of the day during the last month

Opportunistic Infections



Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunopathogenic mechanisms of HIV infection. Ann Intern Med. 1996;124:654–663

Opportunistic Infections

- As the CD4 cell count declines the patients become more susceptible to a variety of infections and cancers
  - Oral Candida infections
  - Streptococcal Pneumonia
  - Tuberculosis and Pneumocystis Pneumonias
  - Toxoplasmosis, Cryptosporidium and MAC
  - Kaposi Sarcoma, Lymphomas, Rectal and Anal Cancers
  - Etc.

Opportunistic Infections

- As the CD4 cells declines,
  - At CD4 counts >500 or all counts: Higher risk of community acquired pneumonia and Tuberculosis
  - At CD4 counts ≤ 250: (Arizona/California) monitor for Coccidiomycosis, fluconazole tx for new conversions
  - At CD4 counts <200: PCP pneumonia, oral & esophageal candidiasis, histoplasmosis (Bactrim DS)
  - At CD4 counts < 100: Toxoplasmosis, Cryptococcus risk increases
  - At CD4 counts <50 cells/ml: MAI, Severe HIV Diarrhea, CMV, Cryptosporidium infections and other opportunistic infections (Azithromycin)

Non-AIDS Defining Illnesses

- Non-AIDS defining illnesses
  - In one study- 29 cases per 1000 py, 318 diagnosis
  - Risk reduced by ART, CD4 increases
- Most common
  - Psychiatric –depression 70%
  - Liver disease
  - Cancers- lung 20%, NHL 14%, Head & Neck 12%, liver 9%, Anal 9%
  - Kidney disease
  - CV disease

Masia M et al. *Risk, predictors, and mortality associated with non-AIDS events in newly diagnosed HIV-infected patients: role of antiretroviral therapy.* AIDS 26, online edition. DOI: 10.1097/QAD.0b013e32835a1156, 2012.

Bacterial Enteric Infections

- Rates of GNB enteric infections are at least 10 fold higher in PLWH than the general population
- Higher risk with CD4 <200
- Pathogens:
  - Salmonella enterica
  - Shigella
  - Campylobacter
  - Diarrheagenic E coli

Bacterial Enteric Infections

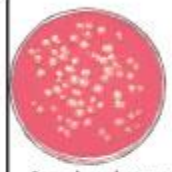
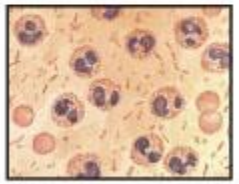
- C difficile is common in PLWH
  - CD4 counts <50 cells/mm3 may be an independent risk factor
- Fecal-oral sexual exposure has a potential for direct & indirect exposure to Shigella and Campylobacter
- Clinical syndrome for GN enteric bacterial infections can be from self-limited to bacteremia & sepsis.

Bacterial Enteric Infections

- Antibiotic prophylaxis is not recommended
- Probiotics have not been adequately study for safety or effectiveness in PLWH
- PLWH with CD4 >500, with non-bloody diarrhea, no fever may only require IV fluids, no antibiotics
- PLWH with CD4 200-500, severe diarrhea, may benefit from short antibiotic course
- PLWH with CD4 <200, severe diarrhea (>6x day)
  - Empiric Ciprofloxacin (1st line), Ceftriaxone or Cefotaxime IV

Bacterial Enteric Infections- CAVEATS

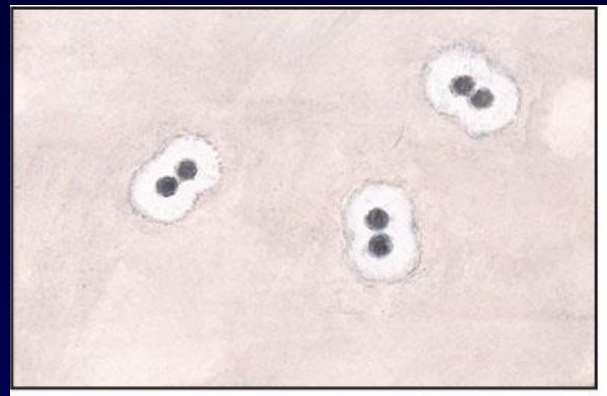
- Fluoroquinolone resistant Campylobacter jejuni is prevalent in Southeast Asia
- MDR Enterobacteriaceae acquisition is more frequent with travel and should be considered with poor response with empiric therapy
- Limited data on FMT for CDI in HIV but reports suggest it may be safe and effective, no clear data on ART impact of CDI recurrence.*

Etiologic organisms	*E. coli* (enterotoxigenic)	*Shigella*	*Salmonella*	*C. jejuni*	*V. parahemolyticus*	*Rotavirus Norovirus*	*E. histolytica*	*G. lamblia*
Approximate relative incidence of common infectious agents in travelers' diarrhea	50%	15%	5%	10%	2%	14%	2%	2%
Typical clinical features	Diarrhea, nausea, vomiting, malaise, fever	Diarrhea, tenesmus, cramps, fever	Diarrhea, cramps, nausea, vomiting, fever	Diarrhea, cramps, anorexia, fever, malaise	Diarrhea, cramps, vomiting, headache	Diarrhea, cramps, vomiting, fever, myalgia	Diarrhea, alternating with constipation, nausea, gas, cramps, fatigue	Foul diarrhea, cramps, foul gas, distention, rumbling, fatigue, weight loss
Incubation period	4-24 hours	1-3 days	6-48 hours	1-7 days	12-24 hours	18-48 hours	1-3 weeks	12-14 days
Duration of illness	3-4 days	2-7+ days	3-4 days	1-7+ days	1-3 days	1-7 days	3-14+ days	7+ days
Blood in stool	–	+	±	+	±	–	±	–
Proctoscopy: ulcers, friable and hemorrhagic mucosa	–	+	±	+	±	–	±	–
Diagnostic method	Clinical features and exclusion of other agents	 Stool culture: EMB agar		 Stool culture: selective blood agar	 Stool culture: TCBS agar	Rotavirus antigen detection assays of stool by ELISA Norovirus clinical features and exclusion of other agents	 Stain Stool examination for parasites  Stained slide Concentration	
 Fecal leukocytes (seen with invasive bowel pathogens)	–	+	+	+	±	–	Stool ELISA antigen test +	+

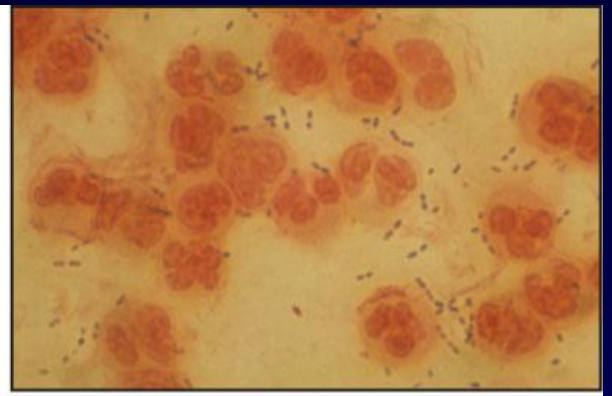
Bacterial Respiratory Disease

- Incidence of bacterial pneumonia has declined with ART from 22.7 to 9.1 per 100 person-years
- *Streptococcus* pneumonia and *Haemophilus* species are the most frequent causes of CAP in PLWH
- Risk factors:
  - CD4 <200
  - No or intermittent ART
  - Smoking
  - IVDU
  - Chronic viral Hepatitis

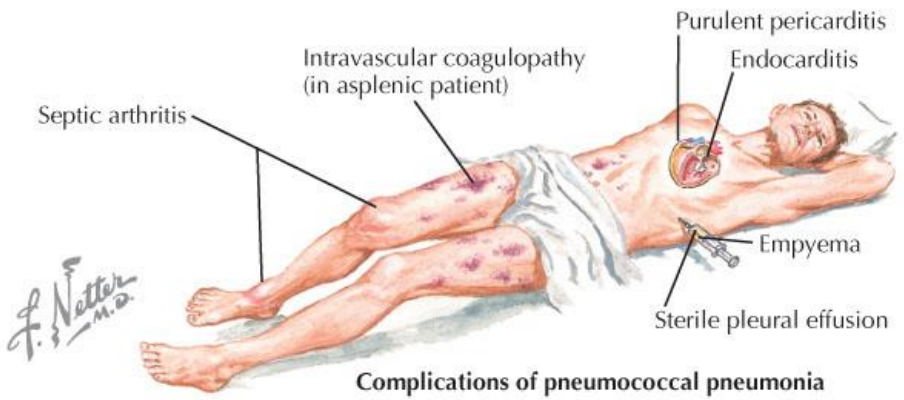
S pneumoniae pneumonia



Quellung reaction. Swelling of bacterial capsule when exposed to antibody



Purulent sputum with pneumococci (Gram stain)



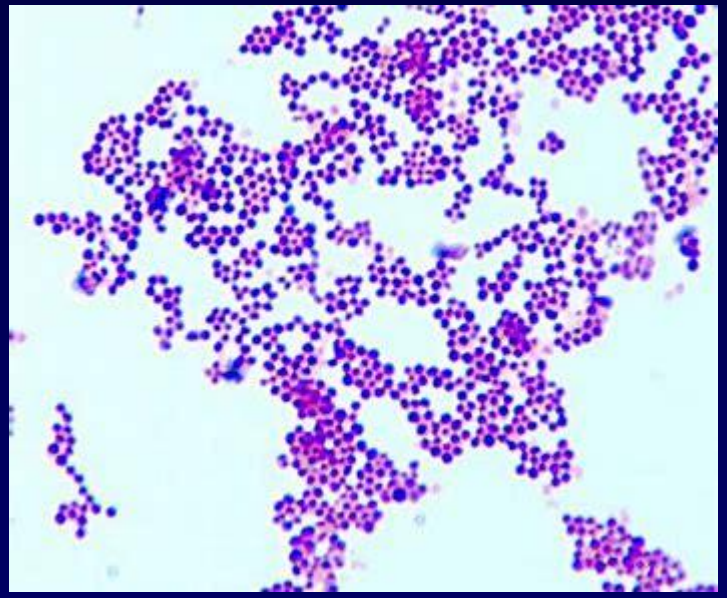
Complications of pneumococcal pneumonia

Bacterial Respiratory Disease

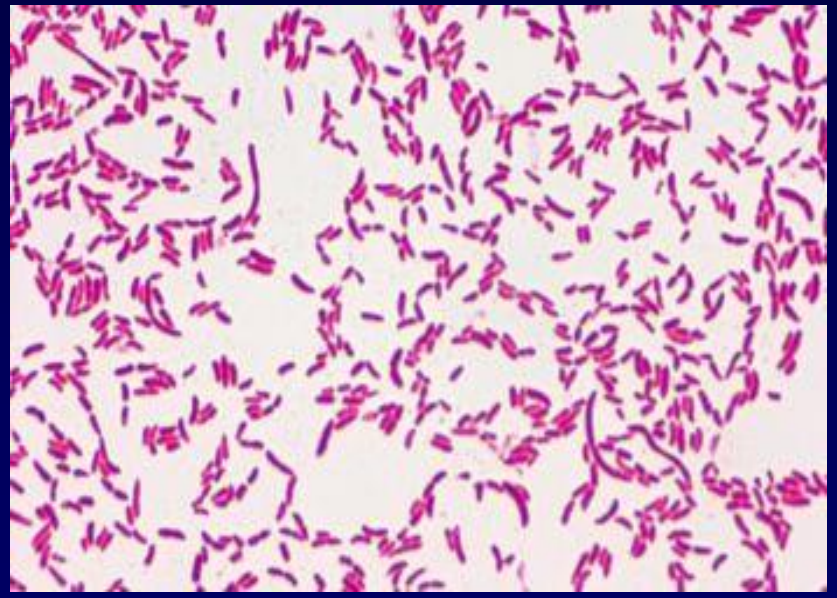
- ***Pseudomonas aeruginosa*** **and** ***Staphylococcus aureus*** **as community-acquired pathogens is higher in HIV-infected individuals than in those not HIV infected.**
- **MRSA carriage is common in PLWH and in lower CD4 counts**
- **MRSA pneumonia is associated with preceding Influenza illness**
- **Rates and mortality from pneumonia are increased in PLWH (especially with lower CD4 counts) as compared to non-HIV infected population**

HCAPs

S aureus



Pseudomonas



Bacterial Respiratory Disease Prevention

- Indications for Pneumococcal Vaccination: All HIV-infected persons regardless of CD4 count
- For Individuals Who Have Not Received Any Pneumococcal Vaccination:
- Preferred Vaccination:
  - One dose of PCV13 (AI), followed by:
  - For patients with CD4+ count ≥200 cells/μL: PPV23 should be given at least 8 weeks after receiving PCV13 (AII); or
  - For patients with CD4 count <200 cells/μL: PPV23 can be offered at least 8 weeks after receiving PCV13 (CIII) or can await increase of CD4 count to >200 cells/μL on ART (BIII)

Bacterial Respiratory Disease Prevention

- Re-vaccination of PPV
  - A dose of PPV23 is recommended for individuals 19–64 years old if ≥5 years have elapsed since the first dose of PPV **(BIII)**
  - Another dose should be given for individuals 65 years or older, if at least 5 years have elapsed since previous PPV23 dose **(BIII)**
- *Vaccine Dosing:*
- PCV13 - 0.5 mL IM; PPV23 - 0.5 mL IM

Influenza Vaccination

- **Preventing Influenza and Bacterial Pneumonia as a Complication of Influenza**
- *Indication for Influenza Vaccination:* All HIV-infected persons during influenza season **(AIII)**
- *Vaccination:*
  - Inactivated influenza vaccine per recommendation of the season **(AIII)**
- **Note:** Live attenuated influenza vaccine is **contraindicated** in HIV-infected persons **(AIII)**

Bartonellosis

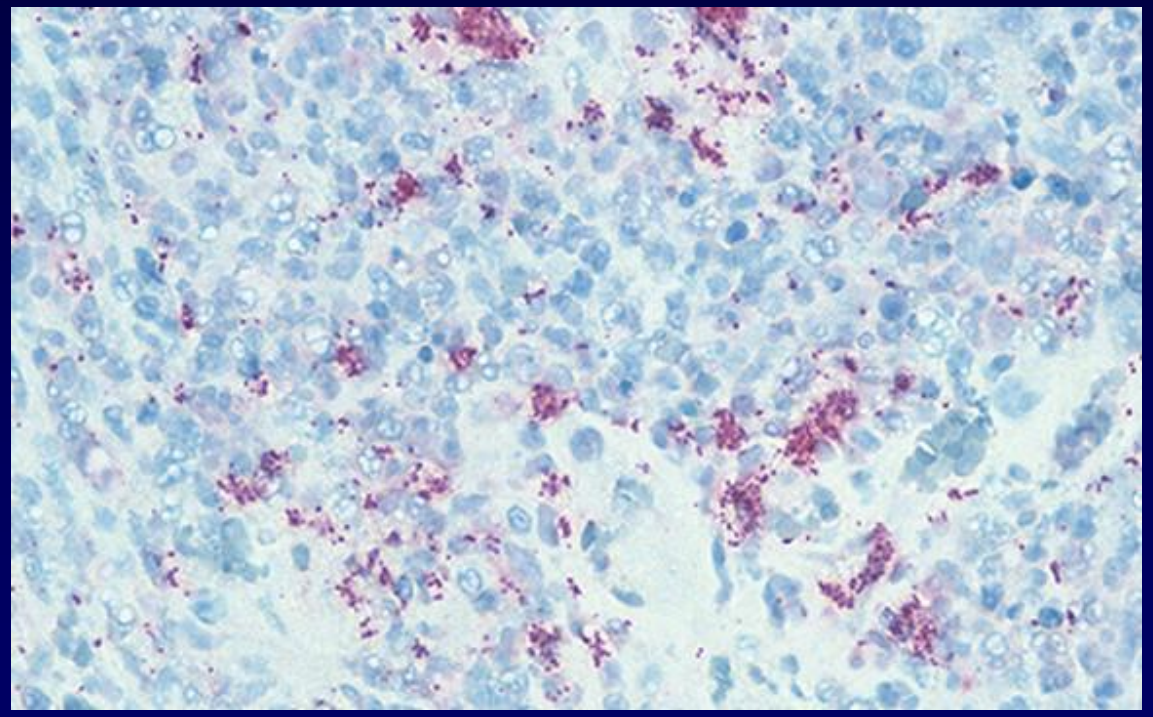
- 8 species of Bartonella are associated with human disease
  - *B. quintana and B. henselae* identified in HIV patients
- Bacillary angiomatosis (BA) most often occurs late in AIDS when CD4 < 50 cells/mm3
  - Usually chronic illness, months to years
  - Intermittent bacteremia
- BA from B. henselae is linked to cat exposure
  - In some areas of the US, 50% of house cats are infected
- BA from B. Quintana is linked to body louse infestation, cat fleas

Bartonellosis

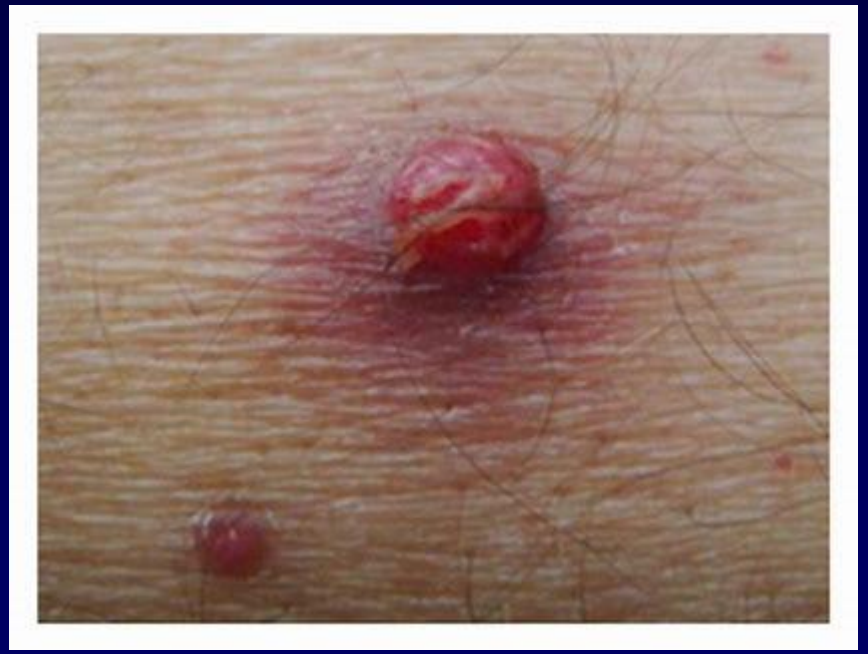
- Cutaneous lesions can mimick KS, pyogenic granuloma or other skin lesions
  - Subcutenaous nodules may be present
- *B. quintana* is associated with osteomyelitis
- *B . henselae* is the only cause for bacillary peliosis hepatis
- Hematogenous spread of the infection occurs
- Fever, weight loss, night sweats.
- Consider it if CD4 <100 cells/mm3
- BA a common cause for culture negative IE (Bq >>Bh)

Bartonellosis

B henselae



Skin lesions with Bartonella



Bartonellosis

- **Diagnosis**
  - Serology: CDC (best) and local labs. Issues with sensitivity and specificity
  - Histopathology: lesions with vascular proliferation, positive modified silver stain (Warthin-Starry stain)
  - Culture, including blood. 25% of culture positive patients never develop antibodies
  - PCR not widely available
- **Treatment : Doxycycline first line**
  - CNS – Doxycyline +/- rifampin
  - IE- Doxycycline + 2 weeks of gentamicin or rifampin

Preferred Therapy

For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis:

- Doxycycline 100 mg PO or IV q12h **(AII)**, *or*
- Erythromycin 500 mg PO or IV q6h **(AII)**

For Infections Involving the CNS:

- Doxycycline 100 mg PO or IV q12h +/- rifampin 300 mg PO or IV q12h **(AIII)**

For Confirmed Bartonella Endocarditis:

- (Doxycycline 100 mg IV q12h + gentamicin 1 mg/kg IV q8h) x 2 weeks, then continue with doxycycline 100 mg IV or PO q12h **(BII)**, *or*
- For patients with renal insufficiency: (doxycycline 100 mg IV q12h + rifampin 300 mg IV or PO q12h) x 2 weeks, then continue with doxycycline 100 mg IV or PO q12h **(BII)**

For Other Severe Infections

- Doxycycline 100 mg PO or IV q12h + rifampin 300 mg PO or IV q12h **(BIII)**, *or*
- Erythromycin 500 mg PO or IV q6h + rifampin 300 mg PO or IV q12h **(BIII)**

Alternative Therapy for Bartonella Infections (Not for Endocarditis or CNS Infections):

- Azithromycin 500 mg PO daily **(BIII)**, *or*
- Clarithromycin 500 mg PO BID **(BIII)**

Duration of Therapy:

- At least 3 months

Indication for Long-Term Suppressive Therapy

If a relapse occurs after a ≥3 month course of primary treatment:

- A macrolide or doxycycline as long as the CD4 count remains <200 cells/mm^3 **(AIII)**

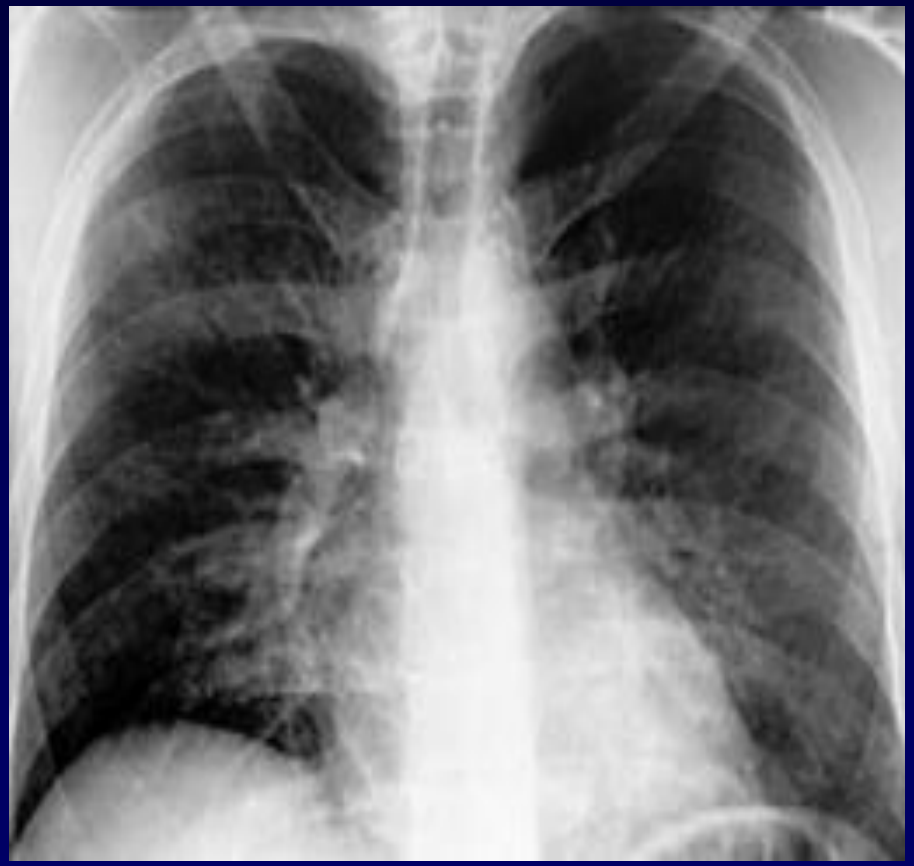
*Indications for Discontinuing Long-Term Suppressive Therapy **(CIII)**:*

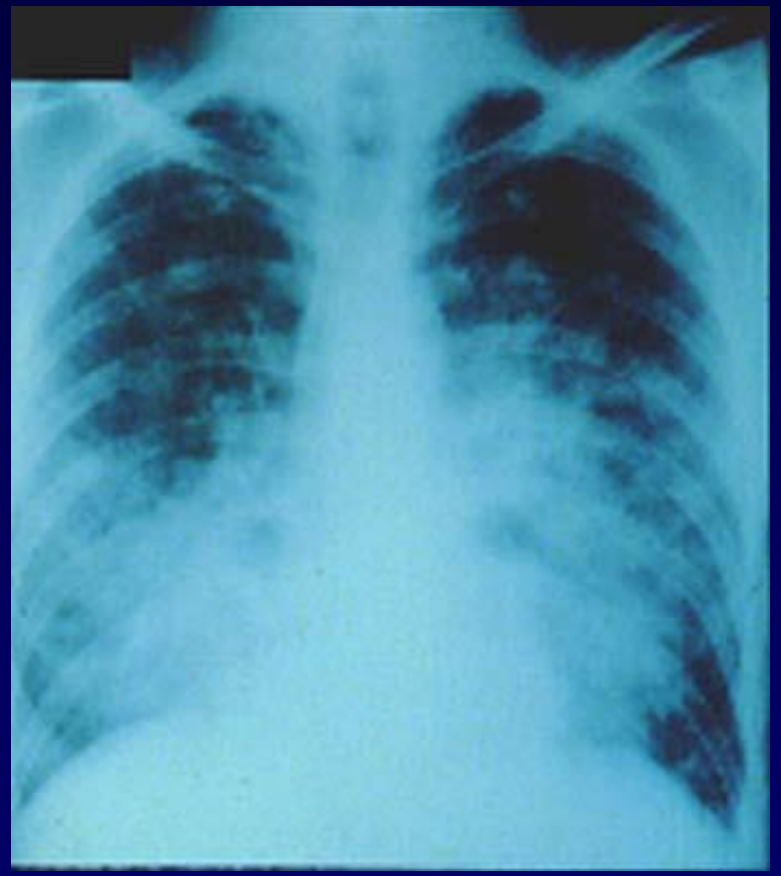
- Received at least 3 to 4 months of treatment; and
- CD4 count >200 cells/mm^3 for at least 6 months
- Some specialists would only discontinue therapy if *Bartonella* titers have also decreased by four-fold

Other Considerations

- Rifampin is a potent hepatic enzyme inducer and may lead to significant interaction with many drugs; including ARV agents (see Table 5 for dosing recommendations)

Pneumonia?





PJP

Pneumocystis

- Pneumocystis pneumonia (PCP or PJP) is caused by P. *jirovecii*, an ubiquitous fungus.
- Two third of children by the age of 4 have antibodies
- Without prophylaxis, PCP occurs in up to 80% of AIDS patients with an up to 40% mortality rate

- Risk for PCP
  - CD4 counts <200 or <14%
  - Prior episode of PCP
  - Oral thrush
  - Recurrent Pneumonias
  - Unintentional weight loss
  - Higher HIV viral loads

Pneumocystis

- Presentation
  - Chronic non-prod cough
  - Dyspnea
  - Chest pains
  - Tachycardia
  - Rales-dry
  - Oral thrush
  - Hypoxemia
  - LDH >500
- Diagnosis
  - Chest Xray can be NORMAL or diffuse infiltrates
  - Up to 18% patients have PCP with another condition like TB or CAP
  - Respiratory sample staining
    - Induced sputum <50%- 90%
    - BAL 90-99%
    - Transbronchial Bx 95-100%
    - Open lung Bx 95-100%

Pneumocystis

- Polymerase chain reaction (PCR)
  - HIGHLY sensitive
  - Does not distinguish between colonization and infection
- qPCR with quantitation of organisms loads may be helpful
- 1,3 β-D glucan is also a component of PJP cell wall maybe elevated but PCP is unlikely with levels <80 pg/mL and has low specificity

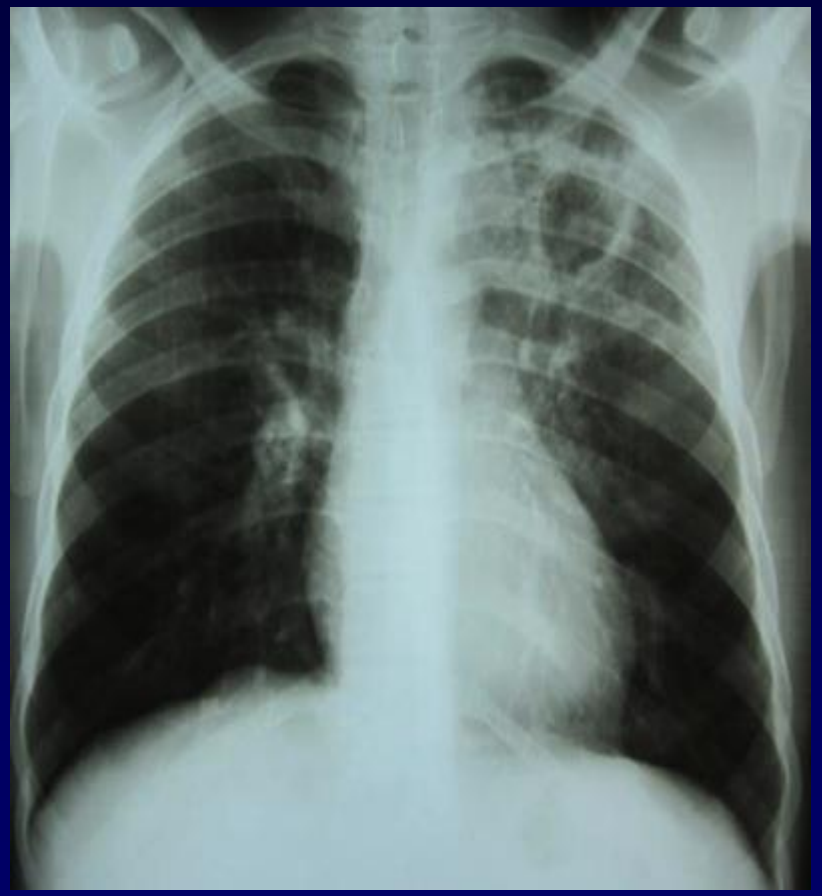
- Prophylaxis: CD4<200-
  - Bactrim SS or DS QD, provides protection against Toxoplasmosis
  - Dapsone, Dapsone+pyrimethamine+leucovorin
  - Aerosolized pentamidine
  - Atovaquone

PCP Treatment

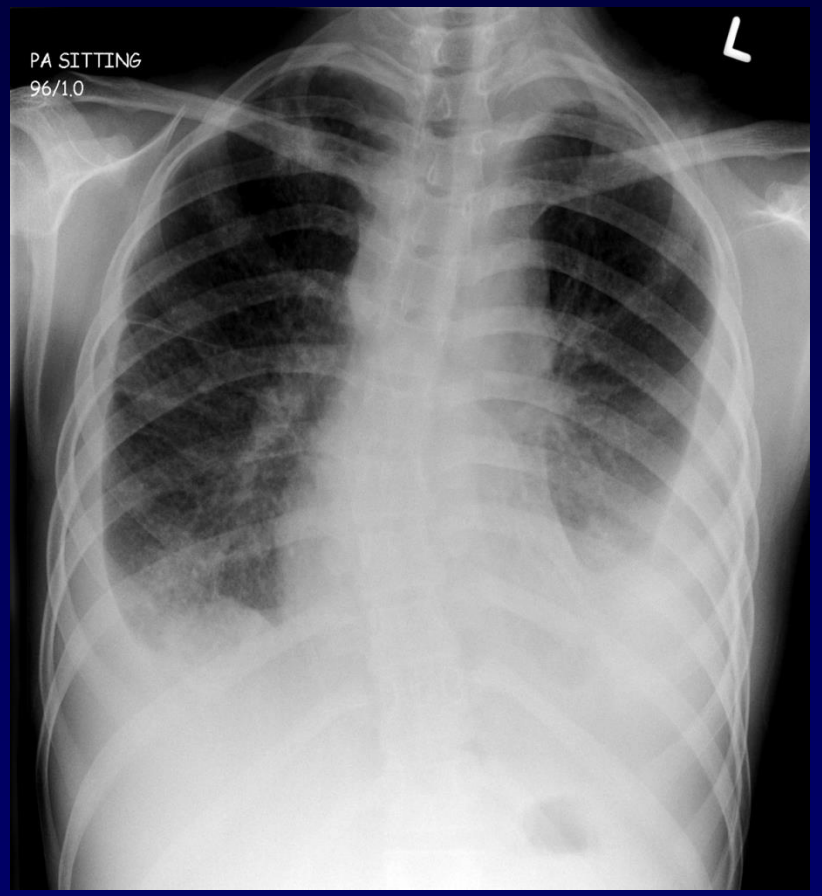
- Bactrim is the treatment of choice
  - IV therapy for severe disease
  - PO for mild to moderate
- Hypoxemia with
  - pO2 at room air <70mmHg or
  - O2 gradient ≥ 35mmHg
  - ADD STEROIDS BEFORE TX or within 72hrs
- ALT: Oral Primaquine +Clindamycin, atovaquone
- Treatment with Bactrim and steroids is for 21 days
- Common AE
  - Rash
  - Fever
  - Leukopenia, thrombocytopenia
  - Azotemia, hyperkalemia
  - Hepatitis
  - IRIS rare

Pulmonary Infections

- Tuberculosis



- Primary Tuberculosis



Latent Tuberculosis

- Traditionally LTBI has been defined as a positive PPD (TST) >5 mm of induration at 48-72hrs.
- Now, a positive TB quantiferon assay is used for evaluation, has higher specificity, less interaction with BCG vaccine.
- However, both assays are affected by decreased sensitivity as CD4 counts decline, reproducibility of positive test results is limited, as 33% of IGRA positive tests in low ranges were followed by negative assays.

Treatment of LTBI

HIV negative LTBI

- INH and RIF daily for 3 months (3HR)
- Rifampin daily for 4 mo (4R)
- INH and rifapentine weekly for 3 mo (3HP)
- INH daily for 6-9 months (6H, 9H)

HIV positive LTBI

- INH plus pyridoxine for 9 months
- Shorter 3HP regimen
- Determine first drug-drug side effects

Tuberculosis

- **Risk factors for progression from LTBI to active TB**
  - **Abnormal Chest Radiograph**
  - **Contact with active TB case**
  - **Positive PPD or TB quantiferon for LTBI**
  - **Origin or travel to high TB incidence rate country**
  - **Uncontrolled HIV and Low CD4 T cell counts (<200 cells/mm3)**
- **The risk for HIV person with a positive PPD to progress from LTBI to TB- 3-16% per year.**
- **Prevalence of LTBI in general population is 4.7%**

Guidelines for the prevention and treatment of OI in Adults and adolescents with HIV

Latent Tuberculosis

- **LTBI Regimens for PLWH**
  - **Isoniazid 300mg po QD or Twice weekly for 9 months (Preferred- AII)**
  - **Isoniazid 900mg po plus Rifapentine 900 mg po once weekly for 12 weeks**
  - **Rifampin (or rifabutin) 600mg po QD for 4 months**
  - **Remember Vitamin B6 (pyridoxine) 25-50mg po QD prophylaxis**
- **Monitor response and toxicity**
  - **AST, ALT, total bilirubin**
  - **Increase risk of toxicity with ETOH, other drugs, liver disease, chronic viral hepatitis,**

Guidelines for the prevention and treatment of OI in Adults and adolescents with HIV

LTBI as per CDC

- **CDC continues to recommend 3HP for treatment of LTBI in adults and now recommends use of 3HP**
  - **1) in persons with LTBI aged 2–17 years;**
  - **2) in persons with LTBI who have HIV infection, including acquired immunodeficiency syndrome (AIDS), and are taking antiretroviral medications with acceptable drug-drug interactions with rifapentine; and**
  - **3) by DOT or self-administered therapy (SAT) in persons aged ≥2 years.**

Borisov AS, Bamrah Morris S, Njie GJ, et al. Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent *Mycobacterium tuberculosis* Infection. MMWR Morb Mortal Wkly Rep 2018;67:723–726. DOI: http://dx.doi.org/10.15585/mmwr.mm6725a5external icon.

Latent TB Infection Treatment Regimens

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH)* and Rifapentine (RPT)[j]	3 months	Adults and Children aged 12 years and older: INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg 900 mg maximum Children aged 2–11 years: INH*: 25 mg/kg; 900 mg maximum RPT[j]: as above	Once weekly[c]	12
Rifampin (RIF)[k]	4 months	Adult: 10 mg/kgChildren: 15–20 mg/kg[l] Maximum dose: 600 mg	Daily	120
Isoniazid (INH)	9 months	Adult: 5 mg/kg Children: 10–20 mg/kg[d] Maximum dose: 300 mg	Daily	270
		Adult:15 mg/kgChildren: 20–40 mg/kg[d] Maximum dose: 900 mg	Twice weekly[c]	76
	6 months	Adult: 5 mg/kgChildren: Not recommended Maximum dose: 300 mg	Daily	180
		Adult: 15 mg/kgChildren: Not recommended Maximum dose: 900 mg	Twice weekly[c]	52

https://www.cdc.gov/tb/topic/treatment/ltbi.htm

Active Tuberculosis

- Active disease (Isolation- Airborne)
  - Isoniazid + Rifampin + Ethambutol + Pyrazinamide
  - For drug susceptible- Induction 2 months, Continuation 4 months
  - For MDR TB- other agents may include Levofloxacin, Moxifloxacin, aminoglycosides, capreomycin,
  - Adjunctive steroid therapy, dexamethasone 0.3-0.4mg/kg/day for 2-4 weeks should be considered for CNS or Pericardial TB
- ART should be started (if not on)
  - Within 2 weeks if CD4 count <50 cells/mm3
  - Within 8 weeks for CD4 counts >50 cells/mm3

THANK YOU

…to be continued

HIV OI Guideline LTBI and TB Treatments

Treating LTBI (to prevent TB disease)

- Preferred Therapy (Duration of Therapy = 9 Months):
  - INH 300 mg PO daily + pyridoxine 25-50 mg PO daily (AII) or INH 900 mg PO twice weekly (by DOT) + pyridoxine 25-50 mg PO daily (BII)
- Alternative Therapies:
  - RIF 600 mg PO daily x 4 months (BIII) or

RFB (dose adjusted based on concomitant ART) x 4 months (BIII) or

- RPT (weight-based, 900 mg max) PO weekly + INH 15 mg/kg weekly (900 mg max) + pyridoxine 50 mg weekly x 12 weeks – in patients receiving an EFV- or RAL-based ART regimen (BIII)