HIV Infection – Managing Opportunistic Infections

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Background

- Definition of opportunistic infections
- Importance of CD4 count
- Highlight selected opportunistic infections
- Effect of antiretroviral therapy and prophylaxis

Guidelines from the CDC, NIH and HIVMA on OI prevention and treatment were recently published in by the CDC. *MMWR 2009 ; 58: 1 – 198.*

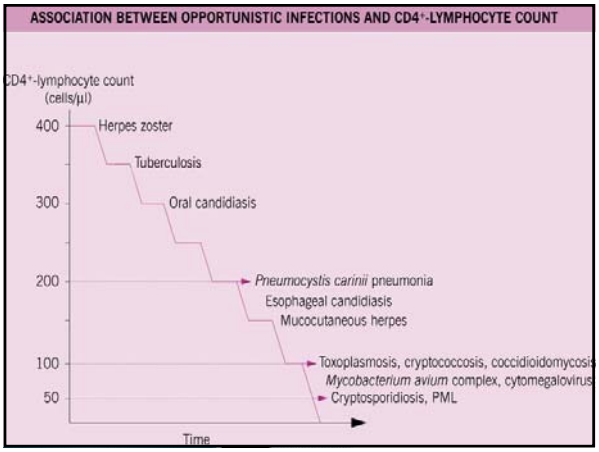
Definition

- Opportunistic infections are those cause disease with increased frequency and/or of increased severity among HIV-infected persons, presumably because of immunosuppression.

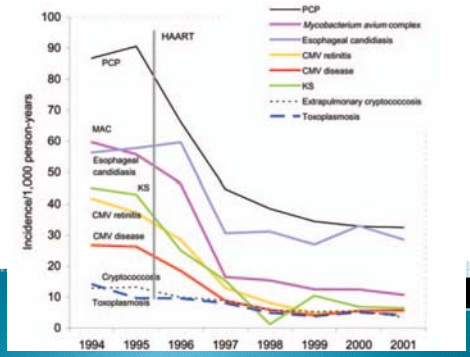
Kaplan JE, et al. Clin Infect Dis 1995

Definition of AIDS– 1993

- Opportunistic infections and tumors
- CD4<200 cells/μL
- Pulmonary TB
- Recurrent pneumonia
- Invasive cervical cancer

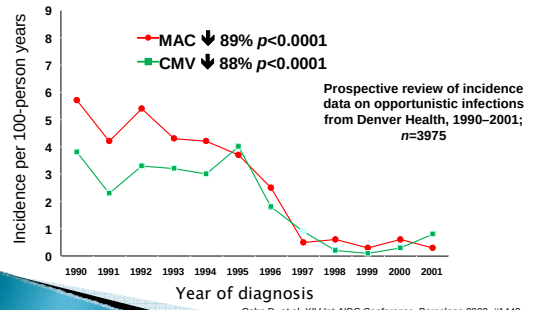


Opportunistic Infections in the US



Ref: CDC

Benefits of ARV therapy: decrease Incidence of OI's



Cohn D, *et al. XIV Int AIDS Conference*, Barcelona 2002, #1443

Table 1. Characteristics of Cases of Pneumocystis Pneumonia (PCP) at Grady Memorial Hospital, Atlanta, 1991–2001.*

Characteristic	Overall	Introduction of HAART		P Value
		Before (1991–1995)	After (1996–2001)	
	no./total no. (%)	number		
No. of cases	488†	234	254	—
PCP as initial manifestation of HIV infection	186/488 (38)	92	94	0.90
ICU care required	145/488 (32)	72	73	0.90
Patient died when PCP was initial manifestation of HIV infection	90/186 (48)‡	48	42	0.90
PCP prophylaxis prescribed	151/488 (30)	72	79	0.96
HAART prescribed	71/254 (27)	—	71§	—

* HAART denotes highly active antiretroviral therapy, HIV human immunodeficiency virus, and ICU intensive care unit.
† The median CD4+ T-cell count at diagnosis was 18 cells per cubic millimeter, with no differences before and after HAART came into use.
‡ Overall mortality was 41 percent (202 of 488 patients died).
§ After HAART came into use, only 44 percent of patients (71 of 160) known to be infected with HIV and eligible for HAART according to the Department of Health and Human Services guidelines were prescribed HAART before an episode of PCP.

Pneumocystis carinii pneumonia

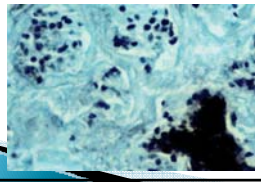
- "Outbreak" of PCP led to the recognition of AIDS (MMWR 1981; 31:305-7)
- Became the most common presenting clinical manifestation of AIDS in North America and Europe.
- In many regions PCP has become less common as a result of prophylaxis and use of HAART.

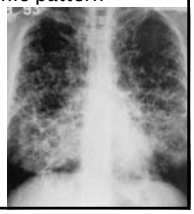
Pneumocystis carinii: Taxonomy

- *Pneumocystis* can be found in a wide variety of animals but each species is infected by a distinct form.
  - *P. carinii* – rodents
  - *P. jirovecii* – humans
- Environmental reservoir unknown and human-to-human transmission (airborne) is likely form of acquisition.
- 2/3 of healthy children have antibodies by age 2 – 4 years.
- Thought to be a protozoon that occurs in three forms: cysts, tachyzoite and sporozoite.
- However, classified as a fungus by mRNA sequence, enzymes and cell wall.

PCP: Clinical Manifestations

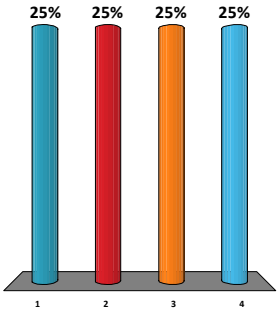
- Almost always presents as pulmonary dysfunction:
  - Early: minimal cough and exertional dyspnea.
  - May have normal chest radiograph.
  - Classic: fever, dry cough, shortness of breath, diffuse interstitial infiltrates on chest radiograph.
  - Almost every conceivable radiographic pattern has been reported with PCP.





A 25 y/o male with prior HIV Dx who is not in care is admitted to the hospital with diffuse pulmonary infiltrates, non-productive cough and oral thrush. You suspect PCP. For the diagnosis of PCP you would order?

1. Sputum C&S
2. A gallium scan
3. Bronchoscopy with transbronchial Bx
4. Induced sputum stained with DFA

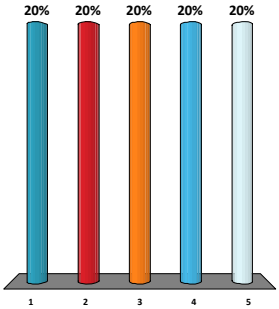


Diagnosis of PCP

Technique	Sensitivity	Comments
Expectorated sputum	10 - 30%	Not useful
Induced sputum	<50 - > 90%	Sensitivity and speciticity depends on technique
Nonbronchoscopic lavage	10 - 50%	Good if bronchoscopy not available
Bronchial washing/brushing	30 - 70%	
BAL	95 - 99%	Procedure of choice
Biopsy	95 – 99%	Rarely necessary

PCP is diagnosed. The patient has a history of Bactrim allergy and a O2 Sat on RA of 65%. You would recommend?

1. TMP/SMZ 1 DS PO BID
2. Atovoquone 750 mg PO BID
3. Prednisone 40 mg PO
4. All of the above
5. Only 2 and 3

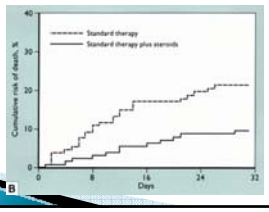


PCP treatment

- First choice:
  - TMP/SMX: 2 DS tabs PO q 8° or IV (25 mg/Kg SMX) **(AI)**
- Second choice:
  - TMP (320 mg PO q 8°) + Dapsone (100 mg PO qd) **(BI)**
  - Pentamidine 300 mg IV qd **(AI)**
  - Atovoquone 750 mg PO BID **(BI)**
  - Clindamycin (300 – 450 mg IV/PO q 6°) + Primaquine (15 – 30 mg PO qd) **(BI)**

PCP treatment: role of steroids

- Recommended in moderate-to-severe disease
  - Prednisone should be part of therapy for patients whose initial room air PaO_2 is < 70 mmHg or A-a gradient > 35 mmHg on RA.
- Dosing:
  - Prednisone (PO/IV) 40 mg q 12° x 5 days then 40 mg qd x 5 days then 20 mg qd x 11 days.



NEJM 1990

Primary prophylaxis of PCP

- Indications for primary prophylaxis:
  - CD4<200 **(AI)** or previous PCP
  - Oropharyngeal candidiasis **(AII)**
  - CD4 % < 14 or an AIDS defining illness but who have a CD4 > 200 but < 250 **(BII)**
- Best regimen
  - TMP-SMX 1DS or SD qd **(AI)** (desensitize, if necessary). Also reduces risk of toxoplasmosis and bacterial infections*****
- Alternative regimens
  - TMP-SMX 1 DS 3x per week **(BI)***
  - Dapsone, 100 mg qd **(BI)**
  - Aerosol pentamidine, 300 mg q month **(BI)**
  - Atovoquone 1,500 mg PO daily **(BI)***
  - Dapsone + pyrimethamine + leucovorin **(BI)***
  - Atovoquone plus pyrimethamine/leucovorin **(CIII)***

also offers cross protection against toxoplasmosis

Secondary prophylaxis for PCP

- Patients with a history of PCP should be administered chemoprophylaxis for life **(AI)** unless immune reconstitution occurs as a consequence of HAART.

PCP – discontinuing prophylaxis

- Primary Prophylaxis
  - CD4 > 200 cells/μL for >3 months on effective ART **(AI)**

  When to restart:
  - CD4 falls to <200 cells/μL **(AIII)**
- Secondary Prophylaxis

  CD4 >200 cells/μL for >3 months on effective ART **(BII)**

  When to restart:
  - CD4 falls to <200 cells/μL **(AIII)**

PCP: Summary

- Etiology: – Parasite or fungus?
- Epidemiology: – Reactivation of latent infection
  – In past, occurred in 60–85% of patients
- Clinical: – Fever, cough, shortness of breath
- Diagnosis: – CXR, induced sputum, BAL
- Treatment: – TMP/SMX is the drug of choice.
  – Prednisone improves survival in moderate to severe disease
- Prevention: – TMP/SMX, Dapsone

Disseminated *Mycobacterium avium* Complex (MAC)

- Epidemiology: Ubiquitous organism found in soil, water; 7 –12% of adults previously infected with MAC
- Incidence: 20–40% of patients with AIDS; directly related to CD4<100
- Clinical: Fever, weight loss, sweats
- Diagnostic tests: AFB blood cultures, bone marrow culture/biopsy

MAC: treatment

- Recommendations:
  - Claritromycin (o Azitro **AIII**) + Ethambutol **(AI)**
  - Amikacin IV o Rifabutin orally can be added, especially in very ill patients **(CI)**
- Patients should receive life-long therapy **(AII)** unless immune reconstitution occurs as a consequence of HAART

M avium Complex: Primary Prophylaxis

Indication:
- CD4 <50 cells/µL **(AI)**

When to consider discontinuation:
- CD4 >100 cells/µL for >=3 months on effective ART **(AI)**

When to restart:
- CD4 falls to <50 cells/µL **(AIII)**

Regimens for DMAC Prophylaxis

	Rifabutin	Azithromycin	Clarithromycin
Efficacy	50-55%	60-65%	60-65%
Interactions	Multiple	?	Few
Resistance	Not seen	0-11%	30-40%
Annual Cost	$1,478	$1,253	$1,087

M avium Complex: Primary Prophylaxis

Preferred Regimen:
- Azithromycin 1,200 mg PO per week *or*
- Clarithromycin 500 mg PO BID **(AI)**

Alternative Regimens:
- Rifabutin* 300 mg PO QD **(BI)** *or*
- Azithromycin 1,200 mg PO per wk+ rifabutin* 300 mg PO QD **(CI)**

* Adjust dosage for concurrent PI or NNRTI

M avium Complex: Secondary Prophylaxis

Indication:
- Upon completion of MAC treatment **(AII)**

When to consider discontinuation:
- CD4 >100 cells/µL for >=6 months on effective ART + 12 months treatment + asymptomatic **(BII)**

When to restart:
- CD4 falls to <100 cells/µL **(AIII)**

M avium Complex: Secondary Prophylaxis

Preferred Regimen:
- Clarithromycin 500 mg PO BID + ethambutol 15 mg/kg PO QD +/- rifabutin*† 300 mg PO QD

Alternative Regimen:
- Azithromycin 500 mg PO QD + ethambutol 15 mg/kg PO QD +/- rifabutin* 300 mg PO QD

* Adjust dosage for concurrent PI or NNRTI
† Rifabutin reduces levels of clarithromycin by 50%

Tuberculosis

- Etiology: *Mycobaceterium tuberculosis*
- Epidemiology: It is the most common opportunistic infection worldwide among patients with AIDS and also the main cause of death
- Incidence: 5% per year among patients with HIV infection who have a + PPD+ (40-60% cumulative incidence)
- Clinical course: Fever, weight loss, cough, night sweats
- Diagnosis: The x-ray image may be "atypical" and can even be normal, PPD (frequently -), sputum AFB, blood cultures, biopsy

TB in the United States

- Case rates continue to decline with 4.4 per 100,000 (13,299 cases) reported in 2007
  - About 13% are HIV+ and 30% HIV-unknown
- 4% prevalence of LTBI
  - 12.9 per 1,000 person-years will develop active TB
  - 35 – 162 per 1,000 person years if HIV co-infected

Tuberculosis and HIV/AIDS

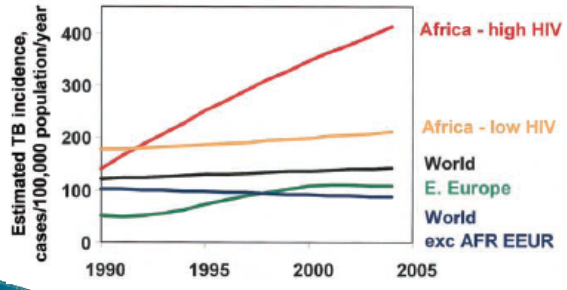
- TB remains the most common AIDS-associated infection in many developing countries (40-60% cumulative incidence)
- Debate on the long-term efficacy of isoniazid prophylaxis and role of life-long prophylaxis in developing countries is unresolved[1]
- In Brazil, antiretroviral therapy improved mortality in HIV-positive patients with TB[2]
- Treatment and prophylaxis may be complicated by drug interactions

[1] Lugada E, *et al*. XIII IAC, Durban, 2000. Abstract 276; [2] Teixeria E, *et al.* XIII IAC, Durban, 2000. Abstract 2295

TB – Clinical manifestations

- Influenced by the degree of immunodeficiency
  - CD4 > 350 -> similar to HIV-uninfected
  - Extrapulmonary disease more common in HIV, especially if CD4 < 200 cells/uL
- TB can involve multiple organs
- Radiographic manifestations may be atypical and CXR may even be normal yet pt AFB+
- In patients with severe immunodeficiency TB can present with rapid progression and sepsis-like syndrome.
- TB can be unmasked by ART

Impact of HIV on Global TB Incidence



Nunn P, Reid A, De Cock KM. Tuberculosis and HIV infection: the global setting. *J Infect Dis* 2007;196;S5-14

TB – diagnosis of LTBI

- All HIV-infected patients should be tested for LTBI **(AII)**
- If CD4 < 200 and LTBI test(s) negative the patient should be retested when CD4 > 200 after ART **(AIII)**
- Either a TST (PPD) or an IGRA are recommended for diagnosing LTBI
  - PPD + if induration ≥5 mm at 48 – 72 hrs
  - IGRA better if pt received BCG
- If + for LTBI then pt should have a CXR and clinical evaluation to r/o TB **(AI)**

Case Presentation

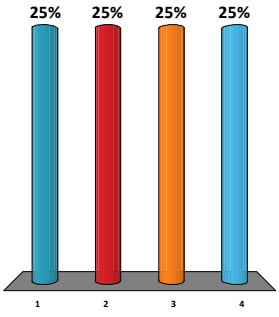
- A 32 year old AA woman comes to a clinic with one month of fever, cough, night sweats and a 15 kg weight loss
- She was prescribed Azithromycin x 5 days at a local ED but has had no improvement
- Physical Exam – thrush, seborrhea, crackles in the left mid-lung
- Labs – WBC 3400, Hct 32%, AST 19
- Chest X-Ray – left lower lobe infiltrate, no cavity, hilar adenopathy
- Sputum smears – 2+ AFB

Case Presentation – cont

- Referred for treatment to Health Department
- Symptoms improve, thrush resolves on nystatin
- Culture positive for *M Tb.* – pansensitive
- HIV test is +
  - CD4 = 220 cells/uL
  - HIV Viral load = 350,000 copies/ml

How long should this patient's TB be treated since she is HIV+?

1. 6 months
2. 9 months
3. 12 months
4. 18 months followed by INH suppressive therapy for life



Tuberculosis: treatment of disease

- Treatment of drug-susceptible TB similar to HIV uninfected adults
- Recommended:
  - INH + Rif (or rifabutin) + Ethambutol *+ PZA for 2 months followed by INH + RIF for 4 months **(AI)**
  - Respiratory isolation
  - DOT's

  The fever should resolve in 10-14 days

  Monthly follow up with sputum AFB's/culture

  In extrapulmonary TB 6 – 9 months of treatment recommended **(AIII)**
- There may be a paradoxical response after HAART is initiated
  - May require steroids

*can be D/C'ed before 2 months if pansusceptible TB

Preventing exposure to TB

- HIV + persons should be advised that certain activities and occupations might increase the likelihood of exposure to TB **(BIII)**:
  - Employment in healthcare facilities
  - Correctional institutions
  - Nursing homes
  - Shelters for the homeless

Tuberculosis: treatment of LTBI

- HIV-infected persons who have a + PPD (or IGRA) should receive treatment for LTBI regardless of age:
  - INH daily **(AII)** or twice weekly **(BII)** for 9 months
  - If the person cannot receive INH or has been exposed to an INH-resistant strain then Rifampin or rifabutin alone for 4 months is recommended **(BIII)**
  - Unclear what to do with patients exposed to MDR or XDR-TB

Candidiasis

- Etiology: *C. albicans* and other *Candida spp*.
- Epidemiology: Mucosal infection in 60-80%
  Esophageal disease in 15-30%
- Clinical: Mucosal disease: oral cavity, vagina, etc,
  Esophagitis: dysphagia and odinophagia
- Diagnosis: Clinical or histology (tissue exam)
  EGD

Candida: treatment

- Recommended:
  - Floconazole PO/IV **(AI)**
  - Itraconazole PO/IV (**AI** but less well tolerated than fluconazole; posoconazole is better tolerated
  - Clotrimazole, nystatin susp PO **(BII)**
- Other:
  - Ketoconazol **(DIII)**
  - Caspofungin or voriconazole IV **(BI)**

Prophylaxis of Fungal Infections

Results of ACTG 981: Fluconazole vs. Clotrimazole CD4<100, 3 year follow-up

	Fluconazole	Clotrimazole
Invasive fungal infection	**4.2%**	**10.9%**
Cryptococcosis	**1.9%**	**7.1%**
Esophageal candidiasis	**1.5%**	**6.3%**
Superficial fungal infection	**15.0%**	**47.0%**
Death	**45.0%**	**42.0%**

Primary prophylaxis not recommended for fungal infections)

Cryptococcal Meningitis

- Etiology: *Cryptococcus neoformans*
- Epidemiology: Fungus distributed worldwide, found in soil
- Incidence: 6-10% of patients with AIDS
  May be declining with use of azoles
- Clinical: Fever, headache, nausea, dizziness
  Disseminated disease often occurs
- Diagnosis: Lumbar puncture, cultures, antigen

Cryptococcal disease: treatment

- Recommended:
  - Amphotericin B IV + flucytosine (25 mg/Kg q 6hrs) **(AI)**
  - Lipid formulations of Ampho OK but dose unclear
- Other treatment approaches:
  - Ampho B + Fluconazole **(BII)**
  - Fluconazole + flucytosine **(CII)**
- It is important to manage the associated intracranial hypertension

Cryptococcal disease: preventing recurrence

- Patients who have completed at least 2 weeks of induction therapy should be given lifelong suppressive treatment **(AI)** unless immune reconstitution occurs as a consequence of HAART
- Fluconazole is superior to itraconazole for preventing relapse **(AI)**

Cryptococcal Disease: Primary prophylaxis

- Routine testing of asymptomatic persons for serum cryptococcal antigen is not recommended because of low probability that the results will affect clinical decisions **(DIII)**
- Rationale:
  - Prospective controlled trials indicate that fluconazole and itraconazole can reduce the frequency of cryptococcal disease however the majority of HIV specialists do not recommend routine use of prophylaxis
- Controversies:
  - Lack of survival benefit
  - Relative cost to prevent a case ($100,000)
  - Interaction with other drugs
  - Development of resistance

Cryptoccocosis: discontinuing prophylaxis

- Discontinuing chronic maintenance therapy in patients who have achieved an increase in their CD4 count > 200 cells/μL is a reasonable consideration **(BII)**
- Restarting maintenance therapy:
  - Should be reintroduced if CD4 < 200 cells/μL **(AIII)**

Cytomegalovirus Disease

- Etiology: Cytomegalovirus (CMV)
- Epidemiology: Infection in 60-100%
  Disease in 15-30% of AIDS cases
  Late stage- CD4 <50
- Clinical: Retinitis: visual loss, field cuts
  Colitis: diarrhea, fever
  Other: biliary disease, encephalitis, pneumonia
- Diagnosis: Clinical or histology (tissue exam)
  Culture of virus may or may not be helpful

CMV: treatment

- Retinitis – best regimens **(AI):**
  - Valganciclovir PO
  - Gancyclovir IV
  - Foscarnet IV
  - Cidofovir IV
  - Intraocular gancyclovir implants + valganciclovir PO
- Colitis or esophagitis:
  - Ganciclovir or foscarnet IV **(BII)**

CMV disease: preventing recurrence

- After initial therapy secondary prophylaxis is recommend for life **(AI)** unless an immune reconstitution occurs after HAART.
- Regimens:
  - Parenteral or oral valganciclovir
  - Parenteral foscarnet
  - Combined parenteral gancyclovir + foscarnet
  - Parentral cidofovir
  - Gancyclovir via intraocular implants (in patients with only CMV retinitis).

Primary Prophylaxis of CMV Disease

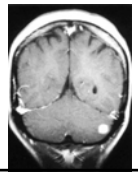
- Best prevented with ART to maintain CD4 > 100 cells/uL
- If patient:
  - CD4 <50
  - CMV seropositive
  - Not starting ART
- Could recommend....but:
  - oral valganciclovir (DI)
- Primary method of preventing severe disease is recognition and early management of retinitis **(CIII)**

Toxoplasma Encephalitis

- Etiology: *Toxoplasma gondii*
- Epidemiology: 20–40% of HIV-infected adults are seropositive (~15% in gen pop)
- Occurrence: In past, 20–33% of seropositive HIV+ developed CNS toxoplasmosis when CD4 < 50 cells/uL
- Clinical: Fever, headache, focal neurologic deficits, seizures
- Diagnosis: Presumptive by CT or MRI
  Serology (rare if seronegative)
  Brain biopsy

Toxoplasmosis – clinical

- Focal encephalitis with headache, confusion or motor deficit and fever
- Characteristic CT or MRI with multiple contrast-enhancing lesions with edema
- Serology (IgG) + in virtually all
- Most patients diagnosed empirically and after response to therapy



Toxoplasmosis: treatment

- Sulfadiazine + Pirimethamine + leucovorin **(AI)**
- Clindamycin + Pirimethamine + leucovorin **(AI)**

Toxoplasmosis: preventing exposure

- HIV+ persons should be tested for antibodies to Toxoplasma (IgG) to detect latent infection **(BIII)**
- IgG – persons should be advised not to eat raw or undercooked meat, they should wash fruits and vegetables well before eating them raw and they should be advised about the risks associated with cats **(BIII)**

Primary Prophylaxis of Toxoplasmosis

- Indications
  - CD4 < 100 **(AII)**
  - Preexisting toxoplasma antibody
- Best regimen
  - TMP-SMX1 DS PO BID **(AII)**
- Alternative regimens
  - TMP-SMX 1 DS 3 x per week **(BIII)**
  - Dapsone + pyrimethamine + levoquin **(BI)**
  - Atovaquone with/without pyrimethemine **(CIII)**

Toxoplasmosis: discontinuing prophylaxis

- Primary prophylaxis:
  - When the CD4 count is > 200 for > 3 months on HAART **(AI)**
- Restarting primary prophylaxis:
  - Should be reintroduced if CD4 < 100 – 200 cells/μL **(AIII)**

Secondary Prophylaxis of Toxoplasmosis

- Patients who have completed initial therapy should be prescribed life-long prophylaxis **(AI)**
- Best regimens:
  - Pyrimethamine + sufadiazine + leucovorin **(AI)**
  - Pyrimethamine + clindamycin **(BI)**

Toxoplasmosis: discontinuing prophylaxis

- Secondary prophylaxis:
  - When the CD4 count is > 200 for > 6 months on HAART **(BI)**
- Restarting primary prophylaxis:
  - Should be reintroduced if CD4 < 200 cells/µL **(AIII)**

Summary of OIs for Which Prevention Is Recommended

Primary Prophylaxis

- *Pneumocystis jiroveci* pneumonia (PCP)*
- Tuberculosis*
- Toxoplasmosis*
- *Mycobacterium avium* complex (MAC)*
- *S pneumoniae* infections†
- Hepatitis A and B†
- Influenza†

* Standard of care
† Generally recommended

OIs for Which Prevention Is Not Routinely Indicated

Primary Prophylaxis

- Bacteria (neutropenia)†
- Cryptococcosis†
- Histoplasmosis†
- Cytomegalovirus†

Secondary Prophylaxis

- Herpes simplex virus§
- Candida §

† Evidence for efficacy but not routinely indicated

§ Recommended only if subsequent episodes are frequent or severe

Vaccines: Routine Use

Agent	Indication
Hepatitis B	HBsAb negative, HBsAg negative
Hepatitis A	Risk* + HAV Ab (IgG) negative
S pneumoniae	CD4 >200 cells/µL (consider at any CD4 count)
Influenza	Annually, October-December

*Risk = IDU, MSM, hemophilia, chronic HBV or HCV

Other Adult Vaccines: Use in HIV-infected patients

Agent	Indication
HPV	Women up to age 26
Tetanus	Td/TdAP for all adults
Measles,Mumps, Rubella	Do not give for "severe immunosuppression"

Conclusions

- The great majority of OI's in HIV/AIDS can be prevented
- The "best prophylaxis" is the use of HAART
- In many patients OI's continue to be the initial presentation of HIV-infection and the reason for the initial diagnosis.