Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus

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Opportunistic Infections (OIs) in Persons Infected with HIV

- Incidence of OIs has significantly decreased
  - Chemoprophylaxis agaisnt specific OIs
  - Highly active antiretroviral therapy (HAART)
- Prevention of OIs remains one of the highest priorities for HIV-infected persons
- USPHS/IDSA 1995, 1997 and 1999 Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus MMWR 1999;48(RR-10):1-66

Pneumocystis carinii: Treatment of Mild to Moderate Acute Infection

- trimethoprim (TMP)/sulfamethoxazole (SMZ)
- TMP + dapsone
- atovaquone
- pentamidine
- clindamycin + primaquine

trimetrexate + leucovorin + dapsone

Pneumocystis carinii: Treatment of Moderate to Severe Acute Infection

- trimethoprim (TMP)/sulfamethoxazole (SMZ)
- pentamidine
- clindamycin + primaquine

- trimetrexate + leucovorin + dapsone
- PO2 < 70mmHg or (A-a)O2 35mmHg
    - prednisone PO 40 mg bid x 5d; 40 mg qd x 5d, 20 mg qd to completion of Rx (21d)

Primary and Secondary Prevention of Pneumocystosis in HIV Infected Persons

- all patients: CD4<200, or oropharyngeal candidiasis,
    - **TMP/SMZ** 1 DS or SS PO qd
    - **TMP/SMZ** 1 DS PO tiw
    - **dapsone** 100 mg PO qd
    - **dapsone + pyrimethamine + folinic acid** PO
    - **aerosolized pentamidine** 300mg/m
    - **Atovaquone** 1500 mg PO qd
    - **pyrimethamine + sulfadiazine** for toxoplasmosis is adequate for PCP

MMWR 1999;48 (RR-10):1-66

Is it Safe to Discontinue Primary Prophylaxis Against *Pneumocystis carinii*?

Current Indications to Discontinue Primary Prophylaxis Against PCP

- sustained increase in CD4+ T-lymphocyte counts from < 200 to > 200 cells/uL for at least 3-6 months
- sustained reduction in viral load for at least 3-6 months (< 5,000-10,000 HIV RNA copies/ml)
- primary prophylaxis should probably be restarted if above conditions are reversed

Causes of Pulmonary Disease in AIDS Patients

- *Pneumocystis carinii*
- *M. tuberculosis*
- *Mycobacterium avium-complex* (MAC)
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*
- Kaposis's sarcoma
- Lymphoma
- Bacterial pneumonia
  - *S. pneumoniae*
  - *H. influenzae*
- Lymphoid Interstitial Pneumonitis (children)
- *Rhodococcus equi*
- Aspergillus and other fungi
- Nocardia
- Cytomegalovirus?

Treatment of Acute or Primary Toxoplasmosis in AIDS Patients

- Recommended
  - Pyrimethamine + sulfadiadize + folinic acid
  - Pyrimethamine + clindamycin + folinic acid
- Alternatives
  - Pyrimethamine + atovaquone or dapsone or azithromycin or clarithromycin
  - trimethoprim (TMP)/sulfamethoxazole (SMZ)
- Do not use monotherapy

Maintenance Treatment for Toxoplasmosis in AIDS Patients

- Same regimens as for acute treatment but at half-doses
- Clindamycin containing regimens have a higher relapse rate
- Consider
  - Pyrimethamine/sulfadoxine (Fansidar)

Prevention of Toxoplasmosis Infection in HIV Infected Persons

- primary
  - all patients: *T. gondii* +IgG antibody and CD4 < 100
    - TMP/SMZ 1 DS or SS PO qd
    - TMP/SMZ 1 DS PO tiw
    - dapsone + pyrimethamine + folinic acid PO
    - Atovaquone 1500 qd PO ± pyrimethamine + folinic acid PO

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Prevention of Tuberculosis in HIV Infected Persons

- all patients: PPD 5 mm or prior positive PPD without treatment or contact with case of active tuberculosis
  - **INH** 300 mg + pyridoxine 50 mg PO qd x 9 m
  - **INH** 900 mg + pyridoxine 100 mg PO biw x 9 m
  - **RFP** 600 mg + **pyrazinamide** 20mg/kg PO qd x 2 m
  - Alternatives
    - **rifabutin** + **pyrazinamide** x 2 m

- **RFP or rifabutin** X 4 m

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Prevention of MAC Disease in HIV Infected Persons

- all patients: CD4 < 50
  - azithromycin 1200 PO qw
  - clarithromycin 500 mg PO bid
  - rifabutin 300 mg PO qd
  - rifabutin + azithromycin

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Prevention of *S. pneumoniae* Disease in HIV Infected Persons

- all patients
  - pneumococcal vaccine 0.5 ml IM x 1
  - might reimmunize if initial immunization was given when CD4 < 200 and if CD4 increases to > 200 on HAART

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Prevention of Influenza Disease in HIV Infected Persons

- all patients (anually before influenza season)
  - whole or split virus, 0.5 ml IM qy

- rimantadine 100 mg PO bid or amantadine 100 mg PO bid

MMWR 1999;48 (RR-10):1-66

Prevention of Hepatitis A Disease in HIV Infected Persons

- all susceptible (anti-HAV-negative) patients with chronic hepatitis C

Hepatitis A vaccine 2 doses

MMWR 1999;48 (RR-10):1-66

Prevention of Hepatitis B Disease in HIV Infected Persons

- all susceptible patients (anti-HBc negative)
- Hepatitis B vaccine 3 doses
  - Recombivax HB, 10 um IM x 3
  - Energix B, 20 um IM x 3

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Prevention of VZV Disease in HIV Infected Persons

- all patients with significant exposure to chickenpox or shingles with no history of either condition or, if available, negative antibody to VZV
  - VZV immune globulin (VZIG), 5 vials (1.25 ml each) IM 96 hours after exposure (ideally 48hours)

MMWR 1999;48 (RR-10):1-66

Prevention of Recurrent OIs in HIV Infected Persons

- prophylaxis for life after first episode
  - toxoplasmic encephalitis
  - deep fungal infection (?)
  - PCP (?)
  - disseminated MAC (?)
  - CMV disease (probably not)

Should chemoprophylaxis be discontinued when a patient's CD4 count rises above a given threshold in response to antiretroviral therapy?

Impact of HIV Protease Inhibitors on the Treatment of HIV-Infected Tuberculosis Patients with Rifampin

- rifamycins accelerate the metabolism of protease inhibitors (potent inducer of the hepatic cytochrome P450 enzyme system)
  - subtherapeutic levels of the protease inhibitors.
- protease inhibitors retard the metabolism of rifamycins
  - increased serum levels of rifamycins and the likelihood of increased drug toxicity

MMWR 1996;45:921-925

Impact of HIV Protease Inhibitors on the Treatment of HIV-Infected Tuberculosis Patients with Rifampin

- rifampin should not be administered with protease inhibitors (PI) or nonnucleoside reverse transcriptase inhibitors (NNRTI)

- rifabutin at lower doses is an acceptable alternative in combination with indinavir, nefilnavir, amprenavir and ritonavir (avoid with hard-gel saquinavir or delavirdine, data lacking with soft-gel)

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Initial anti-TB Therapy for Drug-Susceptible TB

- 3-drug regimen is recommended only in areas drug resistance rates are < 4%
- in all other areas, a 4-drug regimen is recommended (pending results of drug-susceptibility tests)
    - isoniazid
    - rifampin
    - pyrazinamide
    - either ethambutol or streptomycin

MMWR. 1993;42(RR-7):1-8

Initial anti-TB Therapy for Suspected or Proven Drug-Resistant TB

- patients with TB should be evaluated for possible drug resistance
- managed in consultation with clinicians who are experienced at treating such cases
- resistance to either INH or RFP can usually be overcome by the substitution of other first-line drugs
- if resistance to both INH and RFP is suspected, the initial drug regimen should include INH, RFP, PZA, and 3 drugs to which local MDR TB strains are susceptible

MMWR. 1993;42(RR-7):1-8

Preventive Therapy for *M. tuberculosis* infection in HIV-infected Individuals

- tuberculin skin testing is recommended for all HIV-infected persons (PPD+ 5 mm)
- preventive therapy with INH decreases the risk of active TB in HIV-infected persons latently infected with *M. tuberculosis*
- in a controlled trial in Haiti, incidence over a 3-year period was more than 5-fold lower among PPD+ HIV-infected patients receiving INH for 12 months than among PPD+ HIV-infected patients receiving placebo

Pape, JW. Lancet. 1993;342:268-272

CMV Retinitis in Patients with AIDS

- affects one third of patients with AIDS (USA)
- until recently, daily IV ganciclovir or foscarnet were the only available options
- in the last 3 years 11 randomized clinical trials of 4 new treatment options have been reported
- the new HAART for HIV may change the incidence and natural history of CMV retinitis in patients with AIDS

Jacobson, MA. NEJM 1997337:105-114

Initial Therapy for CMV Retinitis in Patients with AIDS

- systemic agents
  - ganciclovir IV or PO
  - foscarnet IV
  - cidofovir IV
- local agents

- intraocular ganciclovir implant

Discontinuation of Secondary Prophylaxis (chronic maintenance therapy) for CMV disease

- several studies have found that maintenance therapy can be discontinued in patients with CMV retinitis whose CD4 counts have increased to > 100 - 150 cells and whose HIV plasma RNA levels have been suppressed in response to HAART
- so far, disease free: > 30-90 wks vs. pre-HAART: 6-8 wks
- consider discontinuation in patients with sustained CD4 increase (> 100 - 150) and viral suppression (HIV viral load < 5000) for at least 3-6 months

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Efficacy of Drugs Used in the Treatment of CMV Retinitis in Patients with AIDS

	Median Time to Progression
IO GCV implant	196-226
IV GCV	47-104
	49-70**
IV FCN	53-93
IV CDF	64-120
PO GCV	29-56**
IV GCV and FCN	131

***from the start of induction therapy**

****from the start of maintenance therapy**

Toxicity of Drugs Used in the Treatment of CMV Retinitis in Patients with AIDS

- IV ganciclovir
  - neutropenia, thrombocytopenia, central-venous-catheter infection
- PO ganciclovir
  - neutropenia, pancreatitis
- IO ganciclovir implant
  - retinal detachment, intravitreal bleeding, endophthalmitis

Toxicity of Drugs Used in the Treatment of CMV Retinitis in Patients with AIDS

- foscarnet
  - nephrotoxicity, hypocalcemia, genital ulcers, fluid overload, central-venous-catheter infection
- cidofovir
  - nephrotoxicity, neutropenia, low intraocular pressure, uveitis, neuropathy

Ganciclovir

- a nucleoside analogue
- inhibits viral DNA polymerase
- requires intracellular triphosphorylation
- first phosphate is added by a kinase unique to CMV (CMV UL97 gene product)
- the other two phosphates are added by cellular kinases
- CMV resistant isolates
  - UL97 mutaions
  - DNA polymerase mutations

Foscarnet

- a pyrophosphate analogue
- inhibits viral DNA polymerase
- does not require intracellular triphosphorylation
- CMV resistant isolates
  - DNA polymerase mutations

Cidofovir

- a nucleotide analogue
- inhibits viral DNA polymerase
- requires intracellular diphosphorylation
- two phosphates are added by cellular kinases only
- CMV resistant isolates
  - DNA polymerase mutations
  - clinical isolates with high-level resistance to GCV resulting form a mutation of DNA polymerase may also be resistant to cidofovir

Incidence and Risk Factors for Developing CMV Retinitis in HIV-infected Patients Receiving Protease Inhibitor Therapy

- prospective, multicenter (Spain)
- 172 HIV-CMV infected patients, CD4+ <100 at the time of PI initiation
- cumulative incidence of CMV retinitis was 5% at 1 yr. and 6% at 2yrs.
- a positive CMV PCR at initiation of PI was associated with development of CMV disease ($p<0.00001$)

Arrizabalaga et al. 6th CROI, Chicago Jan 31-Feb 4, 1999

Incidence and Risk Factors for Developing CMV Retinitis in HIV-infected Patients Receiving Protease Inhibitor Therapy

- mean CMV load was higher in those who developed CMV retinitis (3700 vs 384 copies/ml, $p<0.002$)
- only 2% of patients persisted CMV positive after 3 months of PI Rx
- CMV viremia was not associated with a worse response to HAART

Arrizabalaga et al. 6th CROI, Chicago Jan 31-Feb 4, 1999

Three-fold Higher Mortality Among Severely Ill Patients with AIDS-associated PCP When Corticosteroids Given by CDC Guidelines

- chart review from 7 states, 66 hospitals (US)
- 735 patients were eligible for adjunctive corticosteroids according to CDC guidelines
- (A-a O_2 > 35 mmHg or PO_2 < 70 mmHg)
- 606 received corticosteroids within 72 hours
- among patients with confirmed PCP who were severely ill (A-a O_2 > 50 mmHg) and received corticosteroids per CDC guidelines, mortality rate was higher (18% vs 6%, $p = 0.02$)

McIlrait et al. 6th CROI, Chicago Jan 31-Feb 4, 1999

Discontinuation of PCP Prophylaxis in HIV-infected Patients with Immunological Recovery from HAART

- open, randomized, multicentric trial (Spain)
- previous PCP or CD4+ < 200

- response to HAART: CD4+ > 200 and VL < 5,000 for more than 3 months
- 95% of patients were on TMP-SMZ

Lopez et al. 6th CROI, Chicago Jan 31-Feb 4, 1999

Discontinuation of PCP Prophylaxis in HIV-infected Patients with Immunological Recovery from HAART

	Discont.	Cont.
Nadir CD4	109 ± 58	103 ± 58
$1^{ry}/2^{ry}$	162/9	155/6
Mo. of HAART response	8.6	7.4
CD4 at entry	375 ± 125	362 ± 120
Mo. on proph. at entry	36 ± 20	35 ± 21
Mean ± SD follow up	6.4 ± 3.9	6.9 ± 4
PCP/deaths	0/1	0/0

Lopez et al. 6th CROI, Chicago Jan 31-Feb 4, 1999

Therapy of AIDS-associated Cryptococcal Meningitis

- Ampho B (0.7 - 1.0 mg/kg/d) ± 5FC (25 mg/kg q 6h) x 2 weeks or until clinically stable
- Fluconazole 400 mg qd x 10 wks
- Fluconazole 200 mg qd indefinitely