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 against specific OIs
  - Highly active antiretroviral therapy (HAART)
- Prevention of OIs remains one of the highest priorities for HIV-infected persons

**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
• *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

**Prevention of Hepatitis A Disease in HIV Infected Persons**

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

  **Hepatitis A vaccine 2 doses**

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**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 48 hours)

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**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, nefrafavir, ampranavir and ritonavir (avoid with hard-gel saquinavir or delavirdine, data lacking with soft-gel)

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

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
  - cidcovir 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Median Time to Progression</th>
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<tbody>
<tr>
<td>IO GCV implant</td>
<td>196-226</td>
</tr>
<tr>
<td>IV GCV</td>
<td>47-104</td>
</tr>
<tr>
<td>IV FCN</td>
<td>49-70**</td>
</tr>
<tr>
<td>IV CDF</td>
<td>53-93</td>
</tr>
<tr>
<td>PO GCV</td>
<td>64-120</td>
</tr>
<tr>
<td>IV GCV and FCN</td>
<td>29-56**</td>
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<td>131</td>
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*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 mutations
  - 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

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<th>Discont.</th>
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<tbody>
<tr>
<td>Nadir CD4</td>
<td>109 ± 58</td>
<td>103 ± 58</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;/2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>162/9</td>
<td>155/6</td>
</tr>
<tr>
<td>Mo. of HAART response</td>
<td>8.6</td>
<td>7.4</td>
</tr>
<tr>
<td>CD4 at entry</td>
<td>375 ± 125</td>
<td>362 ± 120</td>
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<tr>
<td>Mo. on proph. at entry</td>
<td>36 ± 20</td>
<td>35 ± 21</td>
</tr>
<tr>
<td>Mean ± SD follow up</td>
<td>6.4 ± 3.9</td>
<td>6.9 ± 4</td>
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<tr>
<td>PCP/deaths</td>
<td>0/1</td>
<td>0/0</td>
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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