Prevention and Treatment of Selected Opportunistic Infections: A Guidelines Update

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Disclosures

• All disclosures are attributed to my spouse
  – Scientific Advisory Board
    • Merck
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    • Merck
    • Gilead
    • Boehringer-Ingelheim
    • Vertex
    • Bristol Myers Squibb

• This presentation may contain discussion of off-label uses
Learning Objectives

• Apply recommended best practices for preventing major HIV-associated OIs, including best practices for when to initiate ART in HIV-infected persons at risk for OIs.

• Apply recommended best practices for treatment of major HIV-associated OIs, including best practices for when to initiate ART in HIV-infected persons being treated for active OIs.
Introduction (1)

• Complementary lectures at this conference
  – Presentation on epidemiology, risk factors, and clinical presentation of key OIs of concern in clinical practice (L. Besch)
  – Focused discussion of prevention and treatment strategies for select OIs (C. Benson)
Introduction (2)

• Prevention and treatment of:
  – *Pneumocystis jirovecii* pneumonia
  – *Toxoplasma gondii* encephalitis
  – Disseminated *Mycobacterium avium* complex
  – Cryptococcal meningitis
  – Cytomegalovirus infection
  – Esophageal candidiasis
  – Tuberculosis

• When to start antiretroviral therapy in persons with acute OIs
OI Guidelines Update

• Key references for recommendations:
  • Undergoing final revisions for 2012; references provided where updates depart from published guidelines
**Pneumocystis jiroveci** Pneumonia

**Treatment (Preferred)**

- **Severe:** TMP 15-20 mg/kg/d and SMX 75-100 mg/kg/d IV Q6 or Q8h
  - If Pa02 < 70 mmHg or A-a O2 gradient > 35 mmHg ➔ Prednisone 40 mg Q12h days 1-5, 40 mg QD days 6-10, 20 mg QD days 11-21
  - **Mild/Moderate:** TMP 15 mg/kg/d + SMX 75-100 mg/kg/d or 2 DS TMP-SMX tabs orally TID
  - **Duration:** 21 days

**Treatment (Alternative)**

- **Severe:** Pentamidine 3-4 mg/kg IV QD - or -
  - Primaquine 30 mg PO QD + clindamycin 600 mg Q6h or 900 mg Q8h IV or 300 mg Q6h or 450 mg Q8h PO
- **Mild/Moderate:** TMP 15 mg/kg/d + dapsone 100 mg/d in divided oral doses
  - Primaquine + clindamycin PO
  - Atovaquone 750 mg PO BID
Pneumocystis jiroveci Pneumonia

• Primary prophylaxis
  – Recommended for all HIV-infected persons with:
    • CD4+ T cells counts < 200 cells/µL (<14%)
    • Oropharyngeal candidiasis
    • H/O AIDS defining illness
    • CD4+ T cell count between 200 and 250 if not possible to closely monitor every 1-3 months

• Secondary prophylaxis
  – Prior episode of PCP (in the absence of a response to potent ART)


**Pneumocystis jiroveci Pneumonia: Prophylaxis**

- **Preferred:**
  - TMP-SMX one DS or one SS tab QD

- **Alternatives:**
  - TMP-SMX one DS tab 3x/week
  - Dapsone 100 mg daily or 50 mg BID or QD or 3x/week
  - Dapsone 50 mg QD + [pyrimethamine 50 mg + leucovorin 25 mg weekly]
  - Dapsone 200 mg + [pyrimethamine 75 mg + leucovorin 25 mg weekly]
  - Aerosolized pentamidine 300 mg per Respirgard II/month
  - Atovaquone 1500 mg QD
  - Atovaquone 1500 mg + [pyrimethamine 25 mg + leucovorin 10 mg QD]
Toxoplasma gondii Encephalitis

- Preferred therapy
  - Pyrimethamine 200 mg PO x 1, then:
    - 50 mg PO QD + sulfadiazine 1 gm PO q6h + leucovorin 10-25 mg PO QD if < 60 kg
    - 75 mg PO QD + sulfadiazine 1.5 gm PO q6h + leucovorin 10-25 mg PO QD if ≥ 60 kg
  - Duration: 6 wks or longer

- Alternative therapy
  - Pyrimethamine (leucovorin) + clindamycin 600 mg IV or PO q6h
  - TMP 5 mg/kg + SMX 25 mg/kg IV or PO BID
  - Atovaquone 1.5 gm PO BID + pyrimethamine (leucovorin)
  - Atovaquone + sulfadiazine 1-1.5 gm PO q6h
  - Atovaquone 1.5 gm PO BID
  - Pyrimethamine (leucovorin) + azithromycin 900-1200 mg PO QD
**Toxoplasma gondii** Encephalitis

- **Indications for primary prophylaxis**
  - Toxoplasma IgG positive and CD4+ count 100 cells/µL
  - Seronegative patients receiving PCP prophylaxis not active against toxo should have serology repeated if CD4+ count declines to < 100 cells/µL
  - Prophylaxis should be started if seroconversion occurs

- **Indications for secondary prophylaxis (chronic maintenance therapy)**
  - Prior toxoplasmic encephalitis diagnosis and lack of response to ART
Toxoplasma gondii Encephalitis

• Preferred primary prophylaxis
  – TMP-SMX one DS PO QD

• Preferred chronic maintenance therapy
  – Pyrimethamine 25-50 mg PO QD + sulfadiazine 2-4 gm PO (in 2-4 divided doses) + leucovorin 10-25 mg PO QD

• Alternative primary prophylaxis
  – TMP-SMX one SS tab PO QD
  – Same as for PJP except not aerosolized pentamidine

• Alternative chronic maintenance therapy
  – Pyrimethamine 25-50 mg + leucovorin 10-25 mg PO daily + clindamycin 600 mg PO q8h
  – Atovaquone 750 mg-1.5 gm PO BID
  – Atovaquone 750 mg-1.5 gm PO BID + [pyrimethamine 25 mg + leucovorin 10 mg QD]
  – Atovaquone + sulfadiazine 2-4 gm PO daily in 2-4 divided doses
Disseminated *Mycobacterium avium* complex

**Preferred therapy**
- At least 2 drugs to include clarithromycin 500 mg BID + ethambutol 15 mg/kg/d
- Addition of 3rd or 4th drug in pts with CD4+ count < 50 cells/µL; mycobacterial load > 2 log CFU/ml; or absence of effective ART
  - Rifabutin 300 mg/d
  - Amikacin 10-15 mg/kg/d IV
  - Levofloxacin 500 mg PO QD
  - Moxifloxacin 400 mg PO QD
- Duration: ≥ 12 months

**Alternative therapy**
- Azithromycin 500-600 mg PO QD + ethambutol 15 mg/kg/d
- Addition of 3rd or 4th drug according to same criteria
MAC Disease Prophylaxis

- **Indications:**
  - CD4+ cell count < 50 cells/μL

- **Preferred:**
  - Azithromycin 1200 mg PO once weekly
  - Clarithromycin 500 mg PO BID
  - Azithromycin 600 mg PO twice weekly

- **Alternative:**
  - Rifabutin 300 mg QD
    - Adjust doses when used with ARVs
Cryptococcal Meningitis

• Preferred induction therapy (for 2 weeks)
  – Liposomal amphotericin B 3-4 mg/kg IV QD + flucytosine 25 mg/kg PO QID
  – Amphotericin B deoxycholate 0.7 mg/kg IV QD + flucytosine 25 mg/kg PO QID

• Alternative induction therapy (for 2 weeks)
  – Amphotericin B lipid complex B 5 mg/kg IV QD + flucytosine 25 mg/kg PO QID
  – Liposomal amphotericin B 3-4 mg/kg IV QD + fluconazole 800 mg PO or IV QD
  – Amphotericin B deoxycholate 0.7 mg/kg IV QD + fluconazole 800 mg PO or IV QD
  – Fluconazole 400-800 mg PO or IV QD + flucytosine 25 mg/kg PO QID
  – Fluconazole 1200 mg PO or IV QD
Cryptococcal Meningitis

- Preferred consolidation therapy (for 8 weeks)
  - Fluconazole 400 mg PO or IV QD

- Preferred maintenance therapy
  - Fluconazole 200 mg PO QD

- Alternative consolidation therapy (for 8 weeks)
  - Itraconazole 200 mg PO BID

- Alternative maintenance therapy
  - Same as preferred
Esophageal Candidiasis

• Preferred therapy (for 14-21 days)
  – Fluconazole 100 mg (up to 400 mg) PO or IV QD
  – Itraconazole oral solution 200 mg PO QD

• Alternative therapy (for 14-21 days)
  – Voriconazole 200 mg PO or IV BID
  – Posaconazole 400 mg PO BID
  – Caspofungin 50 mg IV QD
  – Micafungin 150 mg IV QD
  – Anidulafungin 100 mg IV x 1 then 50 mg IV QD
  – Amphotericin B deoxycholate 0.6 mg/kg IV QD
CMV Retinitis Treatment Options

- Preferred induction therapy (14-21 days)
  - Immediate sight-threatening:
    - Ganciclovir implant + oral valganciclovir 900 mg BID
  - Peripheral lesions:
    - Oral valganciclovir 900 mg BID

- Alternative induction therapies (14-21 days)
  - IV GCV 5 mg/kg q12h
  - IV foscarnet 60 mg/kg/Q8h or 90 mg/kg q12h
  - IV cidofovir 5 mg/kg/week IV x 2 weeks (+ probenecid 2 gm PO 3h before and 1 gm PO 2h and 8h after dose + saline hydration)
CMV Retinitis Treatment Options

- Preferred chronic maintenance therapy
  - Ganciclovir implant + oral valganciclovir 900 mg PO QD

- Alternative maintenance therapies
  - IV GCV 5 mg/kg 5-7d/week
  - IV foscarnet 90-120 mg/kg QD
  - IV cidofovir 5 mg/kg/week IV every other week (+ probenecid 2 gm PO 3h before and 1 gm PO 2h and 8h after dose + saline hydration)
CMV Treatment Options

• GI tract disease or documented pneumonitis
  – Preferred: IV GCV 5 mg/kg for 21-42 days
  – Alternative: Oral valganciclovir 900 mg BID if no interference with oral absorption or IV foscarnet 90 mg/kg q12h or 60 mg/kg q8h
  – Chronic maintenance therapy not usually necessary

• CNS disease – combination IV GCV + IV foscarnet until disease stabilized
  – Maintenance with oral valganciclovir + IV foscarnet
CMV Treatment Options

• Strategies for treatment of progressive retinitis:
  – Re-induction/maintenance with alternative agent
  – Re-induction/maintenance with combination therapy
  – Ocular implant + systemic therapy with alternative agent
  – IV cidofovir
  – Intravitreal injection +/- systemic therapy
CMV Prophylaxis

• Primary prophylaxis not recommended
  – Pre-emptive therapy with oral valganciclovir may be appropriate for high risk patients

• Secondary prophylaxis/chronic maintenance therapy
  – Continued for life unless a sustained CD4+ cell count response occurs after initiation of ART
## Criteria for Discontinuing & Restarting Primary OI Prophylaxis

<table>
<thead>
<tr>
<th>Opportunistic Infection</th>
<th>When to Stop</th>
<th>When to Restart</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis pneumonia</em></td>
<td>CD4 &gt; 200 cells/μL for &gt; 3 months in response to ART</td>
<td>CD4 &lt; 200 cells/μL</td>
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<tr>
<td><em>Toxoplasma gondii</em> encephalitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated MAC disease</td>
<td>CD4 &gt; 100 cells/μL for &gt; 6 months in response to ART</td>
<td>CD4 &lt; 50 cells/μL</td>
</tr>
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</table>
## Criteria for Discontinuing & Restarting Secondary OI Prophylaxis

<table>
<thead>
<tr>
<th>Opportunistic Infection</th>
<th>When to Stop</th>
<th>When to Restart</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis</em> pneumonia <em>Toxoplasma gondii</em> encephalitis</td>
<td>CD4 &gt; 200 cells/µL for ≥ 3-6 months on ART</td>
<td>CD4 &lt; 200 cells/µL or if PCP recurred at CD4+ &gt; 200 cells/µL</td>
</tr>
<tr>
<td>Disseminated MAC disease</td>
<td>Asymptomatic after completing 12 mos of Rx and &gt; 100 cells/µL for ≥ 6 mos on ART</td>
<td>CD4 &lt; 100 cells/µL</td>
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<tr>
<td>Cryptococcal meningitis</td>
<td>CD4 &gt; 100 cells/µL for ≥ 3-6 months on ART</td>
<td>CD4 &lt; 100 cells/µL</td>
</tr>
<tr>
<td>CMV retinitis</td>
<td>CD4+ &gt; 100 cells/µL for &gt; 3-6 mos on ART; ophthalmologist monitoring every 3 mos</td>
<td>CD4 &lt; 100 cells/µL</td>
</tr>
</tbody>
</table>
Prevention of Tuberculosis in HIV

• Latent TB Infection (LTBI) detection
  – Any positive test for LTBI (TST or IGRA) in a person with no clinical, laboratory or XR evidence of active TB
  – Mantoux tuberculin skin test (TST) – 5TU/0.1 mL of tuberculin-purified protein derivative (PPD) by intradermal injection → 5 mm induration after 48-72h
  – Interferon gamma release assays (IGRAs) – release of IFN-γ by T lymphocytes in response to MTB-specific proteins (ELISA)
  – TST and IGRA are not used to diagnose active TB

CDC; MMWR 2010; 59 (No. RR-5):1-25
## Recommendations: IGRA vs TST

<table>
<thead>
<tr>
<th>Situation</th>
<th>IGRA Preferred</th>
<th>TST Preferred</th>
<th>Either TST or IGRA</th>
<th>Both TST and IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low rate of return for interpretation</td>
<td>++</td>
<td></td>
<td></td>
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<tr>
<td>Received BCG</td>
<td>++</td>
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<tr>
<td>Children &lt; 5 yrs</td>
<td></td>
<td>++</td>
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<tr>
<td>Recent contacts of active TB suspects</td>
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<td>++</td>
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<tr>
<td>Periodic screening for occupational exposure</td>
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<tr>
<td>Initial neg. but high risk; ? active TB</td>
<td></td>
<td></td>
<td></td>
<td>++</td>
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<tr>
<td>Initial pos. but additional confirmation needed; low risk</td>
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<tr>
<td>Indeterminate or borderline test</td>
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</tbody>
</table>

CDC; MMWR 2010; 59 (No. RR-5):1-25
Treatment of LTBI

• Preferred regimen:
  – INH 300 mg PO QD or 900 mg PO twice/week x 9 mos + pyridoxine 25 mg PO QD

• Alternative regimens:
  – INH 900 mg + rifapentine 900 mg PO once/wk x 3 mos*
  – Rifampin 300 mg daily for 4 mos (also for INH-R strain exposure)
  – Rifabutin 300 mg daily for 4 mos (or dose adjusted based on ART regimen)

• Exposure to MDR TB
  – PZA + EMB or fluoroquinolone
  – 4-5 drug regimen as for treatment until susceptibility results available from source contact (XDR TB)

*Sterling TR, et al. NEJM 2011; 365:2155-66
Options for Initial TB Treatment

- Initial intensive treatment phase
  - INH, RIF, PZA, EMB daily (56 doses within 8 weeks)
- Continuation phase
  - INH, RIF daily x 4 months (126 doses)
- Twice or thrice per week dosing schedules for DOT are not recommended for HIV-infected patients
- Extend duration....
  - 9 months for severe cavitary or extrapulmonary disease if culture (+) at 2 months
  - 9-12 months for CNS, bone, joint disease
Management of MDR-TB and XDR-TB

• Primary
  – Drug susceptibility testing (DST) for second line agents
  – INH/RIF/PZA/EMB + fluoroquinolone + 2 additional drugs empirically until DST results are known

• Acquired
  – DST for second line agents
  – Start with at least 4 new drugs not previously used
  – Modify based on DST results to provide at least 4 active drugs

• Treat for 18-24 months

• Options for XDR-TB treatment quite limited
  – Individualize with DST for second line drugs
When to Start Antiretroviral Therapy in Acute Opportunistic Infections
When to Start ART for OIs Excluding TB

- RCT of “early” ART (within 14 days of OI treatment) vs “later” (after completion of OI treatment) (N=282)
  - Stratified by OI and CD4 count at entry
  - Primary endpoint: AIDS progression or death at 48 weeks
  - OI distribution
    - PCP 63%
    - Crypto meningitis 12%
    - Serious bacterial infection 12%

OR of AIDS/death 0.51; 95% CI 0.27-0.94 favoring early ART

When to Start ART During Acute OIs Excluding TB

- **Within 1\textsuperscript{st} two weeks of OI treatment**
  - *Pneumocystis* pneumonia
  - *Toxoplasma gondii* encephalitis
  - *Mycobacterium avium* complex disease
  - CMV disease
  - Esophageal candidiasis
  - Tuberculosis (CD4 < 50 cells/\(\mu\)L)
  - Cryptococcal meningitis (CD4 < 50 cells/\(\mu\)L)
  - Bacterial infections, PML, others

- **Delay**
  - Cryptococcal meningitis (until completion of acute therapy if CD4 > 50-100)
  - HCV (until completion of therapy if CD4 > 500)
  - TB (until 8-12 weeks for CD4 > 250)

DHHS Guidelines for the Use of ARVs in HIV-Infected Adults and Adolescents 2012; http://aidsinfo.nih.gov
What ART to Start for TB?

- EFV preferred ART during TB treatment
- Rifampin reduces levels EFV: AUC 78% of normal
- However, EFV-based ART equivalent with or without TB treatment in South African cohort
- EFV 800 mg associated -> increased CNS side effects
- EFV+Rifabutin: increase rifabutin to 450 QD

- EFV 600 mg + Rifampin is preferred HIV/TB regimen

Boule JAMA 2008, Brennan-Benson AIDS 2005
Summary

• Prevention and treatment of:
  – *Pneumocystic jirovecii* pneumonia
  – *Toxoplasma gondii* encephalitis
  – Disseminated *Mycobacterium avium* complex
  – Cryptococcal meningitis
  – Cytomegalovirus infection
  – Esophageal candidiasis
  – Tuberculosis

• When to start antiretroviral therapy in persons with acute OIs
Effect of ART Timing on TB Death (CAMELIA) or Death/AIDS (STRIDE, SAPIT)

- Earlier: 2-4 weeks after TB treatment started
- Later: 8-12 weeks after TB treatment started

CAMELIA
- Earlier: 34% ↓ p=0.004
- Later: 19% ↓ p=0.45

STRIDE
- Earlier: 19% ↓ p=0.45
- Later: 11% ↓ p=0.73

SAPIT

All Studies Showed Significant Reduction in Death/AIDS Among Those with TB and CD4 < 50

- Earlier: 2-4 wks after TB treatment started
- Later: 8-12 wks after TB treatment started

Greater Reduction in Mortality at Lower CD4

% decrease in death/AIDS with earlier ART

CAMELIA: P = 0.004
STRIDE: P = 0.45
SAPIT: P = 0.73

Median baseline CD4 cell count

TB IRIS Greater in Earlier vs. Later Arms

Havlir NEJM 2011, Abdool Karim NEJM 2011
Earlier vs. Later ART

- No difference between earlier vs. later:
  - HIV RNA and CD4 cell count responses
  - Drug toxicity

- No improvement in time to AFB smear or culture negativity (PART study)\(^1\)

\(^1\)Chamie CID 2010
HIV Treatment is TB prevention

• CIPRA HT001: Starting ART between 200-350 vs. < 200 reduced TB by 50%

• HPTN 052: Early ART in HIV+ patient with CD4 ≥ 350 led to a 47% reduction in risk of TB

\(^1\)Severe NEJM 2010, \(^2\)Grinstein B, et al. 6th IAS MOAX0105, 2011