Update on Opportunistic Infections: What’s New

Constance A. Benson, MD

Learning Objectives

After attending this presentation, participants will be able to:

- Describe the recent epidemiology of opportunistic infections in persons treated with antiretroviral drugs.
- Understand recent data supporting changes to guidelines for treatment and prevention of key opportunistic infections in the post-antiretroviral therapy era.
- Evaluate when to start antiretroviral therapy during treatment for an acute opportunistic infection.

OI Epidemiology Update

HIV-CAUSAL Collaboration AIDS 2014; 28:2461
**OI Guidelines Update**

- Key references:
  - Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America
  - AASLD/IDSA/IAS-USA Recommendations for Testing, Managing and Treating Hepatitis C
    [http://www.HCVguidelines.org](http://www.HCVguidelines.org)

**Recent Updates to the Guidelines for Prophylaxis of Select OIs**

**Do we need Pneumocystis prophylaxis?**

- 2,180 pts in Uganda randomized 1:1 to stop or continue co-trimoxazole (CTX) prophylaxis
  - Median age 41 yrs; median CD4+ T-cell count 518 cells/μL; median 48 months on ART
  - Primary endpoint CTX preventable events excluding malaria
  - 50 events in the CTX arm; 74 in the placebo arm
  - aHR 1.35 (90% CI 1.00, 1.81); difference 0.9/100 person-years
  - Despite high CD4 counts and viral suppression on ART, significant clinical benefit of continued CTX prophylaxis

  Munderi P, et al. CROI 2015; Abstr. 94
TB Prevention: ART Reduces TB Risk

CIPRA HT001: Starting ART at CD4 200-350 vs. < 200 reduced TB incidence by 50%; HPTN 052: Starting ART at CD4 ≥ 350 reduced TB risk by 47%

Severe P et al. NEJM 2010

ANRS Temprano Trial: ART + IPT for ART Initiation
• ART initiation strategy RCT 2 x 2 factorial superiority design in 9 health centers in Cote d’Ivoire (N=2,056)
  – Arms 1 and 2 = WHO-ART +/- 6 mos IPT
    • Based on WHO guidelines at the time
  – Arms 3 and 4 = Immediate ART +/- 6 mos IPT
  – ART regimen EFV/TDF/FTC (LPV/r or ZDV substituted for women who were previously treated with NNRTI for PMTCT, or pregnant women)
  – Median CD4 465 cells/mL; 41% > 500; 58% in Arms 1 & 2 vs. 100% in Arms 3 & 4 started ART; median time on ART 14.8 mos and F/U 29.9 mos

Danel C, et al. CROI 2015; Abstr. 115LB

ANRS Temprano Trial: ART + IPT for ART Initiation

Severe HIV morbidity (N=2056)

- No significant interaction between Early ART and IPT
- 44% reduction in risk with Early ART
- 35% reduction in risk with IPT

aHR: adjusted Hazard Ratio (adjusted for the other strategy and for center)
ANRS Temprano Trial: ART + IPT for ART Initiation

Severe HIV morbidity, Baseline CD4 ≥ 500/mm³ (n=849)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>WHO ART</th>
<th>ART/IPT</th>
<th>aHR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.1</td>
<td>5.3</td>
<td>0.56</td>
<td>0.03</td>
</tr>
<tr>
<td>24</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
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</tr>
</tbody>
</table>

- No significant interaction between Early ART and IPT
- 44% reduction in risk with Early ART
- 39% reduction in risk with IPT

**ANRS Temprano Trial Clinical Events**

<table>
<thead>
<tr>
<th>Episodes</th>
<th>Overall</th>
<th>WHO ART</th>
<th>WHO ART/IPT</th>
<th>Early ART</th>
<th>Early ART/IPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause deaths</td>
<td>204</td>
<td>75</td>
<td>60</td>
<td>41</td>
<td>28</td>
</tr>
<tr>
<td>TB</td>
<td>85</td>
<td>41</td>
<td>16</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Bacterial</td>
<td>56</td>
<td>14</td>
<td>28</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>4</td>
<td>14</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>13</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Urogenital</td>
<td>11</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Cancer Non-AIDS</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cancer AIDS</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cancer Other</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

**Prevention of TB in HIV Co-Infection**

- Preferred regimen:
  - INH 300 mg PO QD or 900 mg PO twice/week x 9 mos + pyridoxine 25 mg PO QD
  - INH 900 mg + rifapentine 900 mg orally once per wk x 3 months

- Alternative regimens:
  - 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; Sterling T, et al. CROI 2014; Abstr. 817
Pre-Emptive Therapy for Cryptococcal Disease?

The controversy over CRAG screening...
• Biorepository case-control study using stored sera from the MACS and WIHS (McKenney J, et al. Clin Infect Dis 2015; 60:959)
  – HIV, CD4 < 100 cells/µL on or off ART w/wo prior h/o cryptococcal disease (N=1,872 samples tested for CRAG)
  – 2.9% CRAG+ (95% CI 0.2, 3.8); only 10 had prior h/o cryptococcal disease
  • 2.5% prevalence of asymptomatic CRAG+ with no prior h/o cryptococcosis
  • 4.3% prevalence for those with CD4 < 50 cells/µL
  – In pts with no prior CM, mean survival positive CRAG cohort 2.8 yrs vs. 3.8 yrs for negative CRAG cohort (mean difference 1.0 year, p= 0.03)

Proposed Changes to OI Guidelines
• “Routine testing of newly diagnosed asymptomatic HIV-infected persons for serum CRAG is recommended by some experts for pts with CD4+ ≤ 100 cells/µL, particularly those ≤ 50 cells/µL”
  – A positive test should prompt CSF evaluation for meningitis
• Patients with isolated CRAG without meningitis can be treated similarly to pts with focal pulmonary cryptococcosis
  – Treatment with fluconazole 400 mg/d for 12 months combined with effective ART (BIII)
Updates: Diagnosis and Treatment of OIs

GeneXpert for TB Screening in Low TB Prevalence Settings

2 Xperts missed no AFB+/TB+ patients, identified all TB pts requiring respiratory isolation; 1 or 2 Xperts each more sensitive/specific than 3 AFB smears for identifying Cx+ pts; (Luetkemeyer A, et al. CROI 2015, Abstr. 834)

<table>
<thead>
<tr>
<th></th>
<th>AFB +</th>
<th>1 Expert +</th>
<th>P value</th>
<th>2 Xperts ≥1 positive</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 AFB Smears</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=91)</td>
<td>62/91 (68.1%)</td>
<td>75/88 (85.2%)</td>
<td>0.001</td>
<td>82/90 (90.1%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AFB(+) (n=62)</td>
<td>59/61 (96.7%)</td>
<td>62/62 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB(-) (n=29)</td>
<td>16/27 (59.3%)</td>
<td>20/28 (71.4%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3 AFB Smears</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=53)</td>
<td>32/53 (60.4%)</td>
<td>41/50 (82.0%)</td>
<td>0.006</td>
<td>46/52 (88.5%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AFB(+) (n=32)</td>
<td>30/31 (96.8%)</td>
<td>32/32 (100%)</td>
<td></td>
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</tr>
<tr>
<td>AFB(-) (n=21)</td>
<td>11/19 (57.9%)</td>
<td>14/20 (70.0%)</td>
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</tbody>
</table>

How Reliable is Detection of Drug Resistance by Xpert MTB/RIF?

• Identifies RIF resistance mutations in a 81 bp region of rpoB (codons 426-452); explains ~80-85% of RIF resistance

• National survey of drug resistance in Swaziland (TB prevalence 945 cases per 100,000 persons)
  −38/125 MDRTB isolates had the rpoB I491F mutation – not detected by the Xpert MTB/RIF
  Sanchez-Padilla E, et al. NEJM 2015; 372:1181
Xpert MTB/RIF Ultra: Sensitivity Equal to Culture?

- Xpert MTB/RIF pooled sensitivity only 67% for smear (-)/culture (+) TB
- Modifications to Xpert MTB/RIF → Ultra MTB/RIF
  - 2 different multi-copy TB targets IS6110/IS1081
  - Fully nested amplification; more rapid thermal cycling; improved fluidics
  - Larger DNA reaction chamber/cartridge
  - Increased RIF mutation target detection; detection of mixtures
- Blind test of 32 frozen MTB samples
  - Smear (-)/culture (+) 94% sensitivity vs. 84.4% and 69.3% for single MGIT or LJ
  
  Aland D, et al. CROI 2015, Abstr. 91

High Dose RIF, SQ109, Moxi for Treating TB: PanACEA MAMS-TB

Study Design: Randomisation
All drugs at standard doses unless otherwise stated

<table>
<thead>
<tr>
<th>Control</th>
<th>Q</th>
<th>20RQ</th>
<th>20RM</th>
<th>35R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin 10mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide 20mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid 3mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol 20mg/kg</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Streptomycin 30mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kanamycin 30mg/kg</td>
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<td></td>
<td></td>
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<tr>
<td>Ethambutol 30mg/kg</td>
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<tr>
<td>Isoniazid 30mg/kg</td>
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<tr>
<td>Rifampicin 30mg/kg</td>
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</tbody>
</table>

Boeree MJ, et al. CROI 2015; Abstr. 95LB

High Dose RIF, SQ109, Moxi for Treating TB:
PanACEA MAMS-TB

Time to stable culture conversion on MGIT liquid media

- 35R
- 20RM
- Control
- Q
- 20RQ

Boeree MJ, et al. CROI 2015; Abstr. 95LB
**Moxifloxacin, Pretonamid (Pa-824) and PZA for Treatment of DS and MDR-TB**

- 207 pts with DS-TB randomized to:
  - MPa100Z (N=60)
  - MPa200Z (N=62)
  - HRZE (N=59)
- N=26 pts with MDR-TB
  - Assigned to MPa200Z (DRMPa200Z)

- Primary endpoint = mean rate of MTB CFU/ml reduction/d
  - Bactericidal activity of MPa200Z significantly > HRZE
  - N/V, hyperuricemia most common AEs; no QTc > 500 msec


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**Updates: When to Start ART During Acute OIs**

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

- Delay
  - Cryptococcal meningitis: until completion of induction and consolidation Rx if CD4 > 50-100 or increased ICP
  - 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 2014; http://aidsinfo.nih.gov
**Cryptococcal Optimal ART Timing (COAT) Trial**

HIV-infected, ART-naïve persons with Cryptococcal Meningitis
Study entry at 7-11 days of anti-fungal therapy

**Early ART Group**
Start ART at <48h after study entry
n=250

**Standard ART Group**
Start ART at ≥24 weeks after study entry
n=250

Randomization stratified by site and by altered mental status
Boulware D, et al. NEJM 2014

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**Overall Survival**

Cumulative probability of survival

- 1. Early ART
- 2. Deferred ART

Number at risk
1: 88 54 51 47 47 45 44
2: 89 71 65 60 60 58 57

Overall
88 (100.0%) 89 (100.0%)

P=0.03

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**Pts with IRIS Events By Treatment Group (Adjudicated)**

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Early ART</th>
<th>Deferred ART</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least one event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite/Probable CM-IRIS</td>
<td>5 (5.7%)</td>
<td>5 (5.6%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Possible CM-IRIS</td>
<td>9 (10.2%)</td>
<td>2 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>No CM-IRIS</td>
<td>74 (81.8%)</td>
<td>62 (69.6%)</td>
<td></td>
</tr>
<tr>
<td>Died before ART</td>
<td>2 (2.3%)</td>
<td>20 (22.4%)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>88 (100.0%)</td>
<td>89 (100.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Definite/Probable/Possible CM-IRIS

14 (16.2%) 7 (10.1%) 0.347

Odds Ratio: 1.7 (95% CI: 0.65–4.54) for IRIS with early ART
Boulware D, et al. NEJM 2014
**Early ART in CM in High-Income Settings**

- 235 ART-naïve pts from 28 NA & European cohorts diagnosed with CM between 1998-2009
- Database analysis to mimic RCT comparing ART within 14d vs. deferred to 14-56d after diagnosis of CM

7/62 (11%) deaths early ART vs. 11/88 (12%) deaths with deferred ART; aHR 1.30 (0.66-2.55) for deferred vs. early ART cohorts

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**Proposed Update to CM Treatment Recommendations**

- Delay initiation of ART at least until antifungal induction therapy (first 2 wks) and possibly until total induction/consolidation (10 wks) has been completed.
  - Delay in ART may be particularly important in those with increased intracranial pressure or low CSF white blood cell counts.
- Timing of ART administration should be considered between 2 – 10 wks after start of antifungal therapy
  - Precise start dates based on individual conditions and local experience (BIII).
  - If effective ART is to begin prior to 10 weeks, aggressively address complications of IRIS such as elevated ICP.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Earlier: 2-4 wks after TB treatment started</th>
<th>Later: 8-12 wks after TB treatment started</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMILLA</td>
<td>34%, p=0.004</td>
<td>25%, p=0.025</td>
</tr>
<tr>
<td>STREIDE</td>
<td>42%, p=0.02</td>
<td>30%, p=0.06</td>
</tr>
<tr>
<td>SAPPH</td>
<td>68%, p=0.06</td>
<td>55%, p=0.04</td>
</tr>
</tbody>
</table>
Greater Reduction in Mortality at Lower CD4

% decrease in death/AIDS with earlier ART

P = 0.004
P = 0.45
P = 0.73


Early vs. Delayed ART in Pts with Newly Diagnosed Pulmonary TB

CD4 220-349
RR 0.80, 95% CI 0.46-1.39; p=0.6

CD4 > 350
RR 1.01, 95% CI 0.63-1.62; p=0.4

N=1,675 pts; median CD4 367 (range 289-456)
Primary endpoint: Death/TB failure or recurrence

TB IRIS Greater in Earlier vs. Later Arms

p=0.009
p=0.02

Havlir NEJM 2011, Abdool Karim NEJM 2011
Discordant Early Immune Markers Distinguish TB IRIS & Risk of Death

- 159 pts with HIV, TB, CD4+ < 125 cells/mL tested for inflammatory biomarkers at baseline and 4 wks post-ART initiation (Ravimohan S, et al. CROI 2015, Abstr. 810)
  - 116 controls, 33 TB IRIS, 11 deaths

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>TB IRIS OR (95% CI)*</th>
<th>Death OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>1.9 (1.2-2.9)**</td>
<td>1.6 (0.9-2.9)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>1.5 (1.0-2.3)**</td>
<td>1.1 (0.6-1.9)</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>1.4 (1.0-2.0)**</td>
<td>1.7 (0.9-3.3)</td>
</tr>
<tr>
<td>IL-17α</td>
<td>1.4 (1.0-2.1)**</td>
<td>1.5 (0.8-2.6)</td>
</tr>
<tr>
<td>IL-8</td>
<td>1.4 (1.0-2.0)**</td>
<td>1.5 (1.0-3.0)</td>
</tr>
<tr>
<td>GCSF</td>
<td>1.5 (1.0-2.1)**</td>
<td>2.4 (1.2-4.7)**</td>
</tr>
<tr>
<td>IL-3</td>
<td>1.1 (0.8-1.6)</td>
<td>2.4 (1.2-5.0)**</td>
</tr>
<tr>
<td>IL-10p40</td>
<td>3.2 (0.99-1.8)</td>
<td>1.7 (0.6-5.0)**</td>
</tr>
<tr>
<td>IL-15</td>
<td>1.3 (0.92-1.9)</td>
<td>2.2 (1.2-4.0)**</td>
</tr>
<tr>
<td>IL-1RA</td>
<td>3.1 (0.76-1.8)</td>
<td>1.1 (0.6-2.1)**</td>
</tr>
<tr>
<td>CD4 count</td>
<td>1.2 (0.85-1.6)</td>
<td>0.55 (0.16-1.79)**</td>
</tr>
<tr>
<td>PPD response</td>
<td>1.7 (0.76-1.9)</td>
<td>0.75 (0.37-1.5)</td>
</tr>
</tbody>
</table>

Other Recent Updates

- Hepatitis C treatment
  - AASLD/IDSA/IAS-USA Recommendations for Testing, Managing and Treating Hepatitis C (http://www.HCVguidelines.org)
- CMV retinitis
  - Ganciclovir implant no longer being manufactured; induction therapy with IV GCV or intravitreal GCV + oral valganciclovir 900 mg BID
- Mucocutaneous candidiasis
  - Posaconazole – new oral suspension formulation
- Bacterial enteric infections
  - Shigella spp. with reduced sensitivity to azithromycin in MSM; no longer recommended for treatment

Questions?