OPPORTUNISTIC INFECTIONS

Institute of Infectious Diseases, Pune India
DISCLOSURES

• Nothing to declare
Outline

• The problem

• Bacterial

• Fungal

• Protozoal

• Viral
Decline in OI prevalence in HAART era: USA
Declining OI’s in NA-ACCORD

ART: Impact on OI incidence in LMICs

Clin Infect Dis. 2016 15;62(12):1595-603
Why do OI’s still occur?

• Late HIV diagnosis, missed presentations (HIV Med. 2016 Aug 1 (epub), BMC Infect Dis. 2012;12:72-72)

• Sub-optimal adherence
  • ARV (Curr Opin HIV AIDS. 2015 Jul;10(4):219-25)
    • ART failure
    • Prophylaxis

• Delayed identification of ARV failure

• Immunologic disconnect (J Int AIDS Soc. 2014 Mar 3;17:18651)

• Functional immune reconstitution (Clin Infect Dis 2009;48:609–11)
Advanced disease at ART initiation

WHO guidelines for management of advanced HIV disease, 2017
Causes of hospital admissions in adult PLHIV

- AIDS related
- Bacterial
- Respiratory
- Psychiatric
- Renal
- Cardiovascular
- Liver
- Haematological
- Digestive
- Neurological
- Parasitic infections*
- Viral
- Endocrine/metabolic
- Drug toxicities
- Malignancies
- Malnutrition/wasting

Prevalence (%)
Causes of hospital admissions in adult PLHIV

<table>
<thead>
<tr>
<th>Category</th>
<th>Overall (95% CI)</th>
<th>AFRO (95% CI)</th>
<th>SEARO (95% CI)</th>
<th>WPRO (95% CI)</th>
<th>EMRO (95% CI)</th>
<th>EURO (95% CI)</th>
<th>AMRO N (95% CI)</th>
<th>AMRO S (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS related</td>
<td>46% (40–53)</td>
<td>63% (49–78)</td>
<td>66% (36–96)</td>
<td>79% (71–78)</td>
<td>68% (27–100)</td>
<td>31% (23–39)</td>
<td>28% (17–38)</td>
<td>40% (15–65)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>31% (20–42)</td>
<td>36% (22–50)</td>
<td>35% (20–49)</td>
<td>17% (0–33)</td>
<td>7% (5–9)</td>
<td>27% (23–32)</td>
<td>27% (20–35)</td>
<td>57% (21–92)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>9% (8–11)</td>
<td>&lt;1% (0–1)</td>
<td>&lt;1% (0–1)</td>
<td>1% (0–4)</td>
<td>NR</td>
<td>14% (5–22)</td>
<td>9% (6–12)</td>
<td>19% (11–28)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>9% (6–12)</td>
<td>1% (0–2)</td>
<td>8% (0–19)</td>
<td>NR</td>
<td>NR</td>
<td>13% (0–25)</td>
<td>6% (5–7)</td>
<td>9% (3–15)</td>
</tr>
<tr>
<td>Renal</td>
<td>9% (7–11)</td>
<td>7% (3–11)</td>
<td>NR</td>
<td>9% (0–27)</td>
<td>NR</td>
<td>11% (4–19)</td>
<td>5% (4–7)</td>
<td>6% (2–10)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>8% (6–10)</td>
<td>3% (2–4)</td>
<td>4% (1–7)</td>
<td>2% (0–6)</td>
<td>NR</td>
<td>12% (7–18)</td>
<td>7% (4–9)</td>
<td>9% (4–14)</td>
</tr>
<tr>
<td>Liver</td>
<td>7% (6–9)</td>
<td>2% (1–3)</td>
<td>3% (1–4)</td>
<td>&lt;1% (0–1)</td>
<td>10% (1–19)</td>
<td>10% (7–14)</td>
<td>1% (0–2)</td>
<td>17% (14–19)</td>
</tr>
<tr>
<td>Haematological</td>
<td>7% (5–9)</td>
<td>15% (5–24)</td>
<td>2% (0–5)</td>
<td>1% (1–2)</td>
<td>NR</td>
<td>6% (3–9)</td>
<td>16% (7–25)</td>
<td>5% (0–15)</td>
</tr>
<tr>
<td>Digestive</td>
<td>7% (5–9)</td>
<td>9% (3–14)</td>
<td>&lt;1% (0–1)</td>
<td>8% (0–20)</td>
<td>NR</td>
<td>5% (2–8)</td>
<td>5% (4–7)</td>
<td>13% (8–18)</td>
</tr>
<tr>
<td>Neurological</td>
<td>6% (5–7)</td>
<td>5% (4–6)</td>
<td>5% (0–12)</td>
<td>9% (2–16)</td>
<td>NR</td>
<td>8% (5–10)</td>
<td>1% (1–2)</td>
<td>15% (8–21)</td>
</tr>
<tr>
<td>Parasitic infections*</td>
<td>6% (4–7)</td>
<td>15% (9–21)</td>
<td>1% (0–4)</td>
<td>3% (0–9)</td>
<td>2% (0–5)</td>
<td>&lt;1% (0–1)</td>
<td>NR</td>
<td>3% (0–9)</td>
</tr>
<tr>
<td>Viral</td>
<td>5% (4–7)</td>
<td>3% (2–5)</td>
<td>5% (2–8)</td>
<td>2% (0–6)</td>
<td>NR</td>
<td>9% (0–24)</td>
<td>1% (1–1)</td>
<td>16% (4–19)</td>
</tr>
<tr>
<td>Endocrine/metabolic</td>
<td>4% (2–5)</td>
<td>3% (0–9)</td>
<td>4% (0–12)</td>
<td>2% (1–3)</td>
<td>NR</td>
<td>3% (1–6)</td>
<td>4% (4–5)</td>
<td>5% (5–6)</td>
</tr>
<tr>
<td>Drug toxicities</td>
<td>3% (2–4)</td>
<td>5% (2–7)</td>
<td>6% (1–10)</td>
<td>1% (0–3)</td>
<td>1% (0–2)</td>
<td>1% (0–2)</td>
<td>2% (1–2)</td>
<td>13% (12–14)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>3% (3–4)</td>
<td>4% (3–6)</td>
<td>&lt;1% (0–1)</td>
<td>5% (4–6)</td>
<td>4% (0–7)</td>
<td>4% (3–6)</td>
<td>3% (1–4)</td>
<td>2% (0–3)</td>
</tr>
<tr>
<td>Malnutrition/wasting</td>
<td>3% (2–4)</td>
<td>12% (7–18)</td>
<td>6% (0–18)</td>
<td>1% (0–1)</td>
<td>NR</td>
<td>1% (0–1)</td>
<td>&lt;1% (0–1)</td>
<td>6% (0–15)</td>
</tr>
</tbody>
</table>

Causes of in-hospital mortality

<table>
<thead>
<tr>
<th>Adults</th>
<th>Overall (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS related</td>
<td>57% (46–68)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>27% (20–34)</td>
</tr>
<tr>
<td>Toxoplasmic encephalitis</td>
<td>15% (10–20)</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>13% (9–16)</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>13% (7–19)</td>
</tr>
<tr>
<td>AIDS malignancies</td>
<td>6% (4–7)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>23% (17–30)</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>19% (12–25)</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>17% (8–26)</td>
</tr>
<tr>
<td>Neurological</td>
<td>8% (5–12)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>9% (2–16)</td>
</tr>
<tr>
<td>Liver</td>
<td>6% (4–8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Children</th>
<th>Overall (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS related</td>
<td>56% (30–81)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>30% (11–49)</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>29% (5–52)</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>36% (3–70)</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>9% (0–18)</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>31% (6–56)</td>
</tr>
<tr>
<td>Diarrhoea*</td>
<td>23% (3–43)</td>
</tr>
<tr>
<td>Malnutrition/wasting*</td>
<td>15% (7–22)</td>
</tr>
</tbody>
</table>
Outline

• The problem

• Bacterial

• Fungal

• Protozoal

• Viral

WHO global TB report 2016
Global TB incidence and deaths

WHO global TB report 2016
HIV/AIDS and TB deaths in 2015

WHO global TB report 2016
VL is independent risk factor for TB in SA
VL independent risk factor for TB in SA
Point of care CRP for TB screening for PLHIV initiating ART

Sensitivity

Specificity

A In reference to culture

\[ p = 0.0009 \text{ for difference in sensitivity}^* \]

\[ p = 0.65 \text{ for trend}^{†} \]

\[ p < 0.001 \text{ for trend}^* \]

\[ p < 0.001 \text{ for difference in specificity}^{†} \]

\[ p = 0.73 \text{ for trend}‡ \]

\[ p = 0.73 \text{ for trend}‡ \]

Lancet Infect Dis. 2017 Aug 25 (epub)
Sputum quality and diagnostic accuracy of Xpert

Unadjusted Yield Differences by Sputum Type

Unadjusted Sensitivity Differences by Sputum Type
Early morning urinary sample for TB-LAM
REMEMBER: EMPIRICAL ATT vs IPT with ART

![Graph showing failure probability of primary endpoint over weeks from study entry.](image)

Logrank p = 0.97
PredART: Prednisolone to prevent paradoxical TB IRIS

CROI 2017; abstr 81 LB
Syphilis incidence amongst HIV + MSM in Swiss HIV cohort study in ART era

Single dose BPG effective to treat early syphilis amongst PLHIV

Serological Response

- Standard BPG dose
- Enhanced BPG dose

Intention to Treat
Per-Protocol
Early ART reduces incidence of severe bacterial infections: START study

Lancet HIV. 2017;4(3):e105-e112
REALITY: Enhanced prophylaxis amongst African PLHIV with CD4<100 at ART initiation

HIV + Adults Children>5 yrs CD4<100 Initiating ART

Enhanced prophylaxis
TMP-SMX
Albendazole single dose
Azithromycin x 5 days
INH X 12 wks
Fluconazole x 12 weeks

Standard prophylaxis
TMP-SMX

Primary outcome
Death (any cause) up to 24 wks

Overall mortality at 48 weeks

- Standard prophylaxis: 12.2 (Week 24) vs 11.0 (Week 48)
- Enhanced prophylaxis: 8.9 (Week 24) vs 7.0 (Week 48)

**Week 24: Hazard ratio, 0.73 (95% CI, 0.55–0.98); P=0.03**

**Week 48: Hazard ratio, 0.76 (95% CI, 0.58–0.99); P=0.04**
Main causes of death at 48 weeks

Secondary or other outcomes at 48 wks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.76 (0.58–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>WHO 4 or death</td>
<td>0.73 (0.59–0.92)</td>
<td>0.006</td>
</tr>
<tr>
<td>WHO 3 or WHO 4 or death</td>
<td>0.77 (0.63–0.93)</td>
<td>0.008</td>
</tr>
<tr>
<td>New tuberculosis</td>
<td>0.67 (0.49–0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>New cryptococcal infection</td>
<td>0.38 (0.18–0.83)</td>
<td>0.01</td>
</tr>
<tr>
<td>New candida infection</td>
<td>0.42 (0.20–0.89)</td>
<td>0.02</td>
</tr>
<tr>
<td>Presumptive severe bacterial infection</td>
<td>1.26 (0.80–1.99)</td>
<td>0.32</td>
</tr>
<tr>
<td>IRIS</td>
<td>0.60 (0.44–0.81)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>0.84 (0.69–1.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>0.79 (0.64–0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Grade 4 adverse event</td>
<td>0.83 (0.68–1.03)</td>
<td>0.09</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse event</td>
<td>0.92 (0.79–1.08)</td>
<td>0.31</td>
</tr>
<tr>
<td>Grade 4 adverse event definitely, probably, or possibly related to prophylaxis</td>
<td>0.89 (0.63–1.26)</td>
<td>0.50</td>
</tr>
<tr>
<td>Grade 4 adverse event definitely or probably related to prophylaxis</td>
<td>1.63 (0.68–3.94)</td>
<td>0.27</td>
</tr>
<tr>
<td>Adverse event leading to prophylaxis drug modification</td>
<td>0.98 (0.47–2.07)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Enhanced Prophylaxis Better

Standard Prophylaxis Better

Good virologic and immunologic success
Outline

• The problem

• Bacterial

• Fungal

• Protozoal

• Viral
Annual incidence of cryptococcal infection: 2014

Lancet Infect Dis. 2017 Aug;17(8):873-88
Acridine orange vs India Ink for CM
Acridine orange vs India Ink for CM

![Venn Diagram showing the overlap and percentages of positive results for Acridine Orange, India Ink, and Culture.](image)

- Acridine Orange: 9.28%
- India Ink: 65.98%
- Culture: 10.83%

N = 194

ALL SAMPLES CRAG LFA POSITIVE

ACTA: Treatment of CM

Regimen 1:
Fluconazole 1200 mg/d +
5-FC 100 mg/kg/d
14 days

Regimen 2:
AmB 1 mg/kg/day +
Fluconazole 1200 mg/d
OR 5-FC 100 mg/kg/d
D1-7, FLU 1200 mg/d D7-14

Regimen 3:
AmB 1 mg/kg/day +
Fluconazole 1200 mg/d
OR 5-FC 100 mg/kg/d
14 days

FOLLOW UP TREATMENT
Fluconazole 800 mg/d until
ART (D28 +/- 3d), then 400 mg/d to 10 weeks, then 200 mg/d
ACTA: Mortality risk difference

IAS 2017; Abstr 5573
ACTA: Mortality risk difference

Hazard Ratio (95% CI)

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>Oral vs 2 weeks AmB</th>
<th>1 week AmB vs 2 weeks AmB</th>
<th>p-value (log-rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 week mortality</td>
<td>0.82 (0.54 to 1.25)</td>
<td>1.01 (0.68 to 1.51)</td>
<td>0.57</td>
</tr>
</tbody>
</table>
| 10 week mortality  | 0.83 (0.61 to 1.13) | 0.89 (0.66 to 1.21)       | 0.47                   

Log Rank p-value = 0.487

IAS 2017; Abstr 5573
10 week mortality: FLU: 45% (101/225)
5FC: 31% (71/228)

ACTA: FLU vs 5FC

Hazard Ratio (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>AmB+FLU vs AmB vs 5FC</th>
<th>p-value (log-rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 week mortality</td>
<td>1.62 (1.19 to 2.20)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Log Rank p-value = 0.0018
ACTA: Cumulative incidence of all cause mortality

IAS 2017; Abstr 5573
Cryptococcosis: role of steroids

Higher mortality in CrAG +ve in spite of preemptive fluconazole treatment
Talaromyces marneffei
AmpB vs itraconazole for talaromyces

A Cumulative Incidence of Death by Week 24

No. at Risk
Amphotericin B 217 194 189 187 187 185 165
Itraconazole 218 194 189 185 179 174 147

AmpB vs itraconazole for talaromyces

B Fungal Colony-Forming Units in Blood
Amphotericin B

Itraconazole

Quantitative Fungal Count (CFU/ml)

Day
Outline

• The problem

• Bacterial

• Fungal

• Protozoal

• Viral
Toxoplasma infection amongst PLHIV

Lancet HIV. 2017 Apr;4(4):e177-e188.
Higher prevalence of Toxo infection amongst PLHIV vs gen population

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shen (2016)</td>
<td>2.16 (0.73, 6.40)</td>
</tr>
<tr>
<td>Sanyaolu (2016)</td>
<td>1.56 (0.25, 9.67)</td>
</tr>
<tr>
<td>Bamba (2014)</td>
<td>4.44 (1.51, 13.09)</td>
</tr>
<tr>
<td>Walle (2013)</td>
<td>2.93 (1.42, 6.02)</td>
</tr>
<tr>
<td>Ogoina (2013)</td>
<td>1.51 (0.86, 2.66)</td>
</tr>
<tr>
<td>You (2012)</td>
<td>1.73 (1.02, 2.95)</td>
</tr>
<tr>
<td>Fernandes (2012)</td>
<td>1.07 (0.68, 1.68)</td>
</tr>
<tr>
<td>Daryani (2011)</td>
<td>1.10 (0.50, 2.43)</td>
</tr>
<tr>
<td>Sithoe (2010)</td>
<td>3.69 (1.56, 8.72)</td>
</tr>
<tr>
<td>Lago (2008)</td>
<td>1.26 (0.89, 1.79)</td>
</tr>
<tr>
<td>Simpore (2006)</td>
<td>1.58 (0.93, 2.67)</td>
</tr>
<tr>
<td>Nissapatorn (2002)</td>
<td>0.68 (0.38, 1.20)</td>
</tr>
<tr>
<td>Overall (I-squared = 52.0%, p = 0.018)</td>
<td>1.55 (1.18, 2.04)</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Acta Trop. 2017 Aug 4;176:162-167
Discontinuing TMP-SMX when CD4 100-200

<table>
<thead>
<tr>
<th>Current CD4</th>
<th>Event rate</th>
<th>Events</th>
<th>PYFU</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt;= 100</td>
<td>4.4</td>
<td>6</td>
<td>138</td>
<td>1.6</td>
<td>9.5</td>
</tr>
<tr>
<td>CD4 101-200</td>
<td>1.9</td>
<td>7</td>
<td>376</td>
<td>0.7</td>
<td>3.8</td>
</tr>
<tr>
<td>CD4 &gt; 200</td>
<td>0.5</td>
<td>16</td>
<td>3185</td>
<td>0.3</td>
<td>0.8</td>
</tr>
</tbody>
</table>

p = 0.1163

p = 0.0019
PI based regimens reduce malaria incidence

Kaplan-Meier failure estimates

log rank p-value = 0.052

Percentage with a malaria episode

Number at risk

Time since enrolment (years)

AIDS. 2017;31(4):577-582
Stopping TMP-SMX increases malaria amongst PLHIV in Kenya

Stopping TMP-SMX increases malaria amongst PLHIV in Kenya

Outline

• The problem
• Bacterial
• Fungal
• Protozoal
• Viral
Recurrence of PML despite immune recovery
Recurrence of PML despite immune recovery
Increasing HPV DNA prevalence with severity of cervical disease amongst WLHIV: Geographic distribution

Clin Infect Dis. 2017;64(9):1228-1235.
HPV type prevalence: Africa vs NA/Europe

Clin Infect Dis. 2017;64(9):1228-1235.
CMV serostatus and normalization of CD4:CD8 ratio on ART

All patients

Amongst CD4>500/mm3
HSV-2 shedding increases in 6 mo’s following ART initiation

Summary

• OI’s: Going, Going, but not gone

• Widespread testing for HIV, linkage to care and ART initiation key to reduce burden of OI’s

• Preventive strategies e.g. enhanced prophylaxis, vaccination, screening for cancers need to be implemented

• Clinicians must remain knowledgeable about optimal management and prevention of OI’s to provide high quality care
Late presenters in Netherlands

BMJ Open. 2016;6(1):e009688
Late presenters in Asia

![Graph showing the proportion of early and late presenters per year in Asia from 2003 to 2012.](image)

<table>
<thead>
<tr>
<th>Year</th>
<th>Early Presenters</th>
<th>Late Presenters</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>376</td>
<td>376</td>
</tr>
<tr>
<td>2004</td>
<td>333</td>
<td>333</td>
</tr>
<tr>
<td>2005</td>
<td>479</td>
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<td>2006</td>
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<td>2007</td>
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<td>2008</td>
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<td>2010</td>
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<td>599</td>
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<tr>
<td>2011</td>
<td>235</td>
<td>235</td>
</tr>
<tr>
<td>2012</td>
<td>39</td>
<td>39</td>
</tr>
</tbody>
</table>

Predicting AKI on AmpB: Urinary NGAL

Open Forum Infect Dis. 2017 Jun 20;4(3):ofx127
AKI on AmB: 12 mo mortality by Urinary protein quartiles

Open Forum Infect Dis. 2017 Jun 20;4(3):ofx127
AKI on AmpB: AKI by quartiles of Urinary protein

Open Forum Infect Dis. 2017 Jun 20;4(3):ofx127
Approach to toxoplasmosis treatment

Trop Parasitol. 2016 Jul-Dec 6(2):129-135