ACTHIV 2016: A State-of-the-Science Conference for Frontline Health Professionals
Not just HIV: OIs and Viral Hepatitis

Wari Allison MBBS PhD
Healthcare Australia (HCA)
Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Identify and manage common OIs in the HIV infected patient
• Describe how HIV affects the care of the patient with chronic HBV
• Describe how HIV affects the care of the patient with chronic HCV
Faculty and Planning Committee Disclosures

Please consult your program book.

Off-Label Disclosure:

There will be no off-label/investigational uses discussed in this presentation.
Presentation outline

• Susceptibility to OIs
• Prophylaxis against OIs
• Clinical presentation and management of specific OIs
  – *Pneumocystis jiroveci* (PCP)
  – *Mycobacterium tuberculosis* infection
  – Candida
  – Enteric opportunistic infections
  – IRIS (Immune reconstitution inflammatory syndrome)
  – HBV
  – HCV
Susceptibility to OIs

• Newly diagnosed with HIV infection
• Poorly adherent to ARVs (antiretrovirals) and OI prophylaxis/or not successfully accessing care
• Current CD4 count and viral load (VL)
  • CD4 > 200 less susceptible
  • VL < 50 less susceptible
• Not appropriately prescribed medication for primary prophylaxis
Question

A 25 year old woman in New York city is newly diagnosed with HIV infection with a CD4 count of 20 cells and a VL of 280,000. In addition to azithromycin which of the following would you Rx as primary prophylaxis for OIs?

a. Trimethoprim sulfamethoxazole
b. Fluconazole
c. Acyclovir
d. Voriconazole
e. Valganciclovir
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/spn3wnot
Primary OI prophylaxis indications

- *Pneumocystis* pneumonia
- *Toxoplasma gondii* encephalitis
- Disseminated *Mycobacterium avium complex* (MAC) disease
- CD4 <200, or < 14%, oral candidiasis, prior AIDS defining illness
- CD4 < 100 and Toxo IgG positive
- CD4 <50

www.aidsinfo.nih.gov
Primary prophylaxis regimens

- **PCP**
  - TMP-SMX daily.
  - Alternative:
    - TMP-SMX 3x a week, dapsone, atovaquone + pyrimethamine/leucovorin

- **Toxo**
  - TMP-SMX weekly, dapsone, atovaquone + pyrimethamine /leucovorin

- **MAC**
  - Azithromycin wkly or 2x wkly, clarithromycin
  - Alternative: Rifabutin (must r/o active TB)

**TMP-SMX = Trimethoprim sulfamethoxazole**

[www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov)
When to discontinue primary OI prophylaxis

- PCP or Toxo: CD4 > 200 for 3 months
- PCP: CD4 100-200 and VL < 50
- MAC: CD4 > 100 for 3 months
Important side effects of OI prophylactic drugs

• **TMP-SMX:**
  - reversible hyperkalemia,
  - acute renal injury (monitor renal function),
  - methemoglobinemia with G6PD deficiency:
    • Hb can not bind O2, ABG will show an adequate pO2 but sats will be low
    • Tx: ceasing drug usually sufficient, may require methylene blue

• **Dapsone**
  - methemoglobinemia, hemolytic anemia with G6PD deficiency

• **Atovaquone**
  - poorly tolerated due to rash and GI intolerance in approx 20%, needs fat for absorption
A 30 y/o HIV infected female with a CD4 count of 20 presents with 3 wks of cough and feeling unwell. CXR shows bilateral interstitial infiltrates & a L sided pneumomonthorax. The patient lives in Philly, works in an office and never travelled overseas or left the North East. The most likely cause is:

A. Aspergillosis
B. PCP
C. TB
D. Cryptococcosis
E. CMV
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/ssp6j04t0
Respiratory OI clinical presentation

- Onset
- Fever
- Sputum
- CXR

- < 3 days bacterial, > 3 days PCP/TB
- Usually febrile
- Purulent – bacterial, scant – PCP, TB, viral
- Classic patterns are suggestive but not definitive
PCP

- Early CXR may be normal, early CT never is
- Host of CXR patterns including normal
- Most common: diffuse symmetric interstitial infiltrates “butterfly pattern”

www.aidsinfo.nih.gov
PCP Treatment

• First line treatment:
  – TMP-SMX 5mg/kg (TMP) q8h PO or IV for 21 days

• 2nd line
  – number of options but if truly sulfur allergic, best is parenteral pentamidine (x-reactivity of TMP-SMX with dapsone is up to 50%)

• Be aware:
  – pentamidine and QT interval prolongation on ECG

• Adjunct corticosteroid indications:
  – PaO2 ≤70mmHg or A-a gradient > 35 mmHg
Active TB - clinical

- Usually pulmonary but *extra pulmonary more common in HIV* particularly with low CD4 counts
- Cough, fever, night sweats, wt loss, hemoptysis, SOB, chest pain
- Classic CXR: upper lobe infiltrates may be cavitary – *CXR more likely to be atypical in HIV*
- Note TB *may also be subclinical in HIV* at low CD4 counts
Active TB diagnostics

- Sputum AFB smear 50% sensitive – lower in HIV
- Nucleic acid amplification tests are sensitive and specific for AFB smear positive but less sensitive if smear negative or non respiratory specimen
- GeneXpert MTB/RIF – detects MTB and rifampin resistance directly in clinical specimens in approx 2 hours

Active TB treatment

• Check drug susceptibilities, treat with at least 2 drugs to which isolate is susceptible
• Start with, rifampin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB) for 8 weeks then INH and RIF
• Duration depends on site – most pulmonary and extra-pulmonary is 6 months, bone and CNS much longer
• RIF can be given with EFV but if on PIs, NRTIs, methadone replace with rifabutin
• DTG and RAL dose increases with RIF or use rifabutin, EVG/COBI/TDF/FTC not recommended with RIF or rifabutin

Question

A 28 year old male with HIV with a CD4 count of 80 on ART is diagnosed with active pulmonary TB. When should TB treatment be started?

A. 2 weeks after TB diagnosis
B. 4 weeks after TB diagnosis
C. Immediately
D. 6 weeks after TB diagnosis
E. 8 weeks after TB diagnosis
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/putdwvi
When to start ART with TB

• If already on ART at the time of TB diagnosis, continue ART and start TB Rx.

• If not on ART when to start depends on CD4 count:
  – CD4 < 50, start ART within 2 weeks of TB Rx.
  – CD4 > 50, start ART within 8-12 weeks of TB treatment.

• Some DOT regimens allow an increased interval greater than daily:
  - but if CD4 < 100 has to be daily for first 60 days and
  - with HIV can not be less frequent than 3x a week.

2015 DHHS Guidelines
Candida

- Mucosal is characteristic:
  - oral, esophageal, rectal, vaginal
- Invasive candida is NOT AIDS related
- Fluconazole ppx is not recommended
Candida treatment

• Oral:
  – clotrimazole troches
  – Alternative: oral fluconazole if no response to topical nystatin

• Esophagitis:
  – oral fluconazole
  – Alternative: oral voriconazole

• Vaginitis: topical
  – clotrimazole cream or vaginal tablet
  – oral fluconazole 150mg x1 dose

• Be aware of the possibility of azole resistance:
  – *albicans* is most common but others e.g *C. glabrata* and *C. krusei* may be resistant to azoles
  – would not routinely test susceptibility unless candidemia
Enteric OIs

- The most common diarrheal diseases in patients with HIV in the US are:
  - Clostridium difficile (54%)
  - Campylobacter (14%)
  - Shigella (14%)
  - Salmonella (7%)

- Salmonella and Shigella – should probably treat everyone to reduce bacteremia and transmission

- Salmonella:
  - Cipro for $\geq 14$ days, no definitive data on optimal treatment duration

- Shigella:
  - Cipro, treat for 1-6 weeks depending on response

Sanchez CID 2007
www.aidsinfo.nih.gov
Enteric OIs

• C. diff:
  – no major differences in clinical manifestations and diagnosis (PCR is gold standard)
  – preference is to routinely use oral vancomycin.

• Cryptosporidia:
  – protozoa, can cause chronic diarrhea in HIV infection
  - Diagnose with stool sample or bowel biopsy
  - Tx: symptomatic
    - diet and antimotility agents
    - nitazoxanide approved for children but effectiveness questionable
  - ART
HIV and HBV

• The natural course of HBV disease is altered by HIV infection by impairment of innate and adaptive humoral and cellular immunity, compared to HBV mono-infected patients
  – less chance to clear acute HBV infection
  – faster progression to cirrhosis and
  – higher risk of liver-related death

• The effects of HBV on the progression of HIV infection are controversial:
  – the data is conflicting but in general there is little evidence for HBV accelerating HIV disease progression however
  – HIV-HBV co-infected patients have a higher mortality rate

Phung et al World J Gastroenterol 2014 20(46): 17360
HIV and HCV

• In an Asian cohort of HIV-infected patients (Treat Asia Observational Database) HCV co-infection, but not HBV co-infection, was associated with lower CD4 cell recovery after ART and increased mortality.

• In another retrospective cohort study (Cambodia) both HBV and HCV co-infection were associated with worse ART outcomes (mortality, severe liver toxicity and increased CD4 counts)

• Four AIDS Clinical Trials Group HIV treatment studies' data were combined to compare initial ART responses between HCV/HIV-coinfected and HIV-mono-infected patients (virologic failure, CD4 cell measures, occurrence of AIDS/death) >> attenuated response to ART in co-infection

HBV and HCV screening

- Screen all patients for HBV and HCV at HIV diagnosis
- Screen all persons born between 1945-1965 at least once for HCV regardless of risk
- If HCV Ab positive confirm chronic infection with an RNA PCR viral load
- Annual testing for HCV is recommended in persons who inject drugs and HIV positive men who have unprotected sex with multiple men

CDC 2013
www.hcvguidelines.org
HBV vaccination

- Vaccinate all who are HBs Ab negative – ACIP guidelines

- Follow up titers one month post completion of series if < 10ug/ml re-immunize

- Check titers annually if at risk
Indications for HBV Tx in HIV+ patients

- sAg and eAg positive AND liver disease (ALT > 2X ULN or necroinflammation on liver bx)

- sAg and eAg positive AND HBV DNA > 2000 IU/mL AND evidence of liver inflammation (ALT > ULN or evidence of liver fibrosis)

WHO guidelines for prevention, care and treatment of persons with chronic hepatitis B infection, 2015
AASLD guidelines for treatment of chronic hepatitis B, 2015
HBV treatment in patients with HIV

- Use HBV active ART if ART is indicated
- ART using HBV active agents e.g. TDF/FTC + 3rd agent is indicated in all co-infected patients when HBV therapy is required
- If TDF is not tolerated used entecavir with 3TC or FTC
- If no ART is needed or patient wants treatment for HBV but not HIV consider telbivudine or PEG-IFN

WHO guidelines for prevention, care and treatment of persons with chronic hepatitis B infection, 2015
AASLD guidelines for treatment of chronic hepatitis B, 2015
HCV treatment in patients with HIV

- Very effective direct acting antivirals
- Mainly genotype 1 in the USA with some genotype 2
- The drugs are just as effective in patients with HIV as those without and treatment recommendations are the same (everyone except “those with limited life expectancy that cannot be remediated by transplantation or other directed therapy”)
- Need to be aware of drug interactions when patients on ARV are prescribed HCV treatment. HCV treatment options are rapidly evolving and will be discussed in the HCV session

www.hcvguidelines.org
HCV resources

• AASDL/IDSA guidelines:
  www.hcvguidelines.org

• Hepatitis C online (University of Washington, University of Alabama at Birmingham, IAS-USA CDC funded)
  http://www.hepatitis.uw.edu/

• Hepatitis C drug interactions
  http://www.hep-druginteractions.org/
Immune reconstitution inflammatory syndrome (IRIS)

• Diagnosis of exclusion
• Within days or months of ART initiation worsening or known infection or neoplasm or unmasking of occult OI or neoplasm
• Risk: low CD4 at initiation of ART and prior OI
• ALMOST ANYTHING is possible but common are PCP, TB, MAC
• Management: treat the underlying active infection, continue ART unless inflammatory response is life threatening, anti-inflammatories: NSAIDs and corticosteroids

Muller et al. Lancet Infect Dis 2010
Life threatening IRIS to watch for:

• Asymptomatic HBV positive patient started on ART without HBV activity (this would be rare in the US) – transaminase rise due to HBV reactivation

• Acute PCP started on ART early: look for initial improvement and then exacerbation

• Asymptomatic pt started on ART with new onset of visual disturbance (blurring) – think latent CMV and CMV retinitis

Muller et al. Lancet Infect Dis 2010
Conclusions

- Other OIs I have not had time to talk about today specifically MAC, Toxoplasmosis and cryptococcal meningitis
- Screen, commence primary prophylaxis and vaccinate appropriately in patients newly diagnosed with HIV
- HCV treatment is just as effective in patients with HIV as in those without: screen pts for HCV
- Be aware of IRIS and life threatening manifestations of it weeks or months after starting ART