Recurring and Emerging Questions Related to Management of HIV-Related Opportunistic Infections

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Objectives

▪ To understand epidemiologic trends in DC that relate to the occurrence of opportunistic infections
▪ To describe the population in the US at risk for HIV related opportunistic infections
▪ To identify the most common HIV related opportunistic infections in 2017-2018
▪ To recognize changes in the NIH CDC IDSA Guidelines for Management of HIV Related Opportunistic Infections
▪ To anticipate guideline changes likely to occur in the near future

Estimated Number of Newly Infected HIV Cases by Year, District of Columbia, 2012-2016

<table>
<thead>
<tr>
<th>Year</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>500-631</td>
<td>319-405</td>
<td>312</td>
<td>312</td>
<td>309-528</td>
</tr>
</tbody>
</table>

www.doh.dc.gov/hahsta

Proportion of Residents Diagnosed and Living with HIV by Race/Ethnicity, District of Columbia, 2016

What percent of patients with known HIV in DC are virally suppressed?
Question 1

What percent of patients with known HIV in DC are virally suppressed?

A) 93%
B) 83%
C) 73%
D) 63%
E) 53%

Care Dynamics among HIV Cases Living District of Columbia, 2016

<table>
<thead>
<tr>
<th>Living in DC</th>
<th>Ever linked to HIV care</th>
<th>Ever retained in care in 2016</th>
<th>Virally suppressed in 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>12,732</td>
<td>12,430</td>
<td>9,702</td>
<td>7,367</td>
</tr>
</tbody>
</table>

HIV Care Dynamic among Youth Living in the District of Columbia, 2016

<table>
<thead>
<tr>
<th>Living in DC</th>
<th>Ever linked to care</th>
<th>Retained in care in 2016</th>
<th>Ever virally suppressed</th>
<th>Virally suppressed in 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>462</td>
<td>438</td>
<td>357</td>
<td>265</td>
<td>219</td>
</tr>
</tbody>
</table>
Question 2

What percent of persons with newly diagnosed HIV in DC have a CD4 count <200 at time of diagnosis?

A) 11%
B) 21%
C) 31%
D) 41%
E) 51%
Surrogate Marker for Incidence of HIV-Related Opportunistic Infections

How often are guidelines accessed online?

Guideline Page Views

March 1, 2017 - February 28, 2018

Adult ARV
Adult OI
Perinatal
Ped ARV
Ped OI

Adult Opportunistic Infection Guidelines

Page Views

What's New
PCP
TB Drug Dosing
Toxo
MAC

April 26, 2018, Washington, DC
Seven Most Commonly Asked Questions
Regarding HIV-Related
Opportunistic Infections

#1: Use of PCR Diagnostics-How to Interpret Results
- Upper respiratory
- Lower respiratory
- Diarrhea
- CSF
- Blood

Question 3 (Non ARS)
- A 35 year old patient, recently diagnosed with HIV (nadir CD4 count 90 cells/μL) has been on dolutegravir/emtricitabine/tenofovir alafenamide for 3 weeks
- He presents with low grade fever and cough to your hospital based clinic in Feb 2018 in DC
- Nasal swab is sent for Biofire Panel
Question 3 (Non ARS)

- A 35 year old patient, recently diagnosed with HIV (nadir CD4 count 90 cells/μL) has been on dolutegravir/emtricitabine/tenofovir alafenamide for 3 weeks
- He presents with low grade fever and cough to your hospital based clinic in Feb 2018 in DC
- Nasal swab - Nasopharyngeal Swab is sent for Biofire Panel

Respiratory Viruses in Biofire 2 Respiratory Panel (Nasopharyngeal Swab)

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td></td>
</tr>
<tr>
<td>Coronavirus H1N1</td>
<td>Influenza A</td>
</tr>
<tr>
<td>Coronavirus H1N1-2009</td>
<td>Influenza A</td>
</tr>
<tr>
<td>Coronavirus 229E</td>
<td>Influenza A</td>
</tr>
<tr>
<td>Coronavirus OC43</td>
<td>Influenza A</td>
</tr>
<tr>
<td>Human Metapneumovirus</td>
<td>Influenza B</td>
</tr>
<tr>
<td>Human Rhinovirus/Enterovirus</td>
<td>Respiratory Syncytial Virus</td>
</tr>
<tr>
<td>Coronavirus HKU1</td>
<td></td>
</tr>
<tr>
<td>Coronavirus NL63</td>
<td></td>
</tr>
<tr>
<td>Coronavirus NL63-2009</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Parainfluenza 1</td>
<td></td>
</tr>
<tr>
<td>Parainfluenza 2</td>
<td></td>
</tr>
<tr>
<td>Parainfluenza 3</td>
<td></td>
</tr>
<tr>
<td>Parainfluenza 4</td>
<td></td>
</tr>
<tr>
<td>Respiratory Syncytial Virus</td>
<td></td>
</tr>
<tr>
<td>SARS-CoV</td>
<td></td>
</tr>
<tr>
<td>Human Rhinovirus/Enterovirus</td>
<td></td>
</tr>
</tbody>
</table>

40 minutes later the lab calls with the results. Which of the following result would be convincing evidence that the identified pathogen is the only cause of the respiratory syndrome?

- Any of the pathogens included
- None of the pathogens included
- Depends on past history and other test results
Question 3

- 60 minutes later the lab calls with the results
- Which of the following result would be convincing evidence that the identified pathogen is the only cause of the respiratory syndrome?
  A) Any of the pathogens included
  B) None of the pathogens included
  C) Depends on how past history and other test results

Question 4

- A 35 year old patient, recently diagnosed with HIV (nadir CD4 count 90 cells/uL) has been on dolutegravir/emtricitabine/tenofovir alafenamide for 3 weeks
- He presents with low grade fever and cough to your hospital based clinic in Feb 2018 in DC; he looks toxic, has diffuse bilateral infiltrates and O2 Sat 91% / room air
- The pulmonologist performs a BAL: since this is a lower respiratory tract sample, a different PCR panel is performed
- PCR results for BAL are available in 60 minutes.

Likely Coming in 2018: Biofire Lower Respiratory Panel

- Molds
- Yeast including Cryptococcus
- PCP
- Herpesviruses
  - CMV, VZV, HSV
- Legionella
**Question 4 (No Right Answer)**

Which of the following positive results would be convincing evidence that the indicated pathogen is the likely cause of the pulmonary dysfunction?

A) Pneumocystis  
B) CMV  
C) Cryptococcus  
D) Toxoplasmosis  
E) Coronavirus

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**Comments**

What published data are there about the clinical significance of nucleic acid in a respiratory sample?

- Are they accurate if negative to exclude a diagnosis?
- Are they useful if positive to ascertain the causative agent?
Similar Issues with PCR Panels for Stool, CSF, Blood

Prevention

#2: MAC Prophylaxis

How many of you currently prescribe MAC Prophylaxis for patients with newly diagnosed HIV, ready to start ART, and CD4 <100 cells?
Rate of MAC in Johns Hopkins Cohort Fell from 16% pre 1996 to 4% Post 1996….Not All Attributable to ART


Opportunistic Infections Among HIV Infected Persons Are Declining But…They Still Occur

NA-ACCORD, 2000–2010, United States and Canada, no. 63,541

Buchacz K et al. J Infect Dis 2016;214:862–72

Is Primary Mycobacterium avium Complex Prophylaxis Necessary in Patients with CD4<50 Cells/µL Who Are Virologically Suppressed on cART?

HIV Outpatient Study (HOPS)
- When patients with low nadir CD4 Count (<50) were started on effective ART
- 41 No MAC Prophylaxis
- 30 With MAC Prophylaxis
- 0 Cases of MAC occurred

Buchacz for HOPS (n=369)
AIDS Patient Care STD 2014; 28:292
Survival After AIDS-Defining Opportunistic Illness Among HIV-Infected Persons—San Francisco, 1981–2012 (n=20,858)

Guidelines Recommendations for Prevention of MAC, 2018
- IAS USA and NIH-CDC-IDSA
  - Primary Mycobacterium avium complex prophylaxis is not recommended if effective ART is initiated immediately and viral suppression achieved (evidence rating AIIa)

#3: Should You Be Screening Your HIV-Infected Patients (CD4<100) for Serum Crypt Ag?
- CROI 2018: THEMED DISCUSSION: OUTCOMES OF PREVENTION STRATEGIES FOR CRYPTOCOCCAL MENINGITIS

WHO Recommendation Since 2011
- Screening for cryptococcal antigen followed by preemptive antifungal therapy among cryptococcal antigen positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for persons with HIV who have a CD4 count <100 (strong recommendation, moderate certainty evidence) and may be considered at CD4<200 (conditional recommendation, moderate certainty evidence)
Guideline Recommendation for Screening for Crypt Ag

- In US cryptococcal antigen occurs in asymptomatic patients
  - CD4<100: 2.9%
  - CD4<50: 4.6%
- A positive test: mandatory LP
- If CSF is unremarkable
  - Fluconazole 400 mg qd x 12 months
- If CSF positive
  - Treat at crypto meningoencephalitis
Uncertainty About Screening

- Potential Advantages
  - Earlier crypt treatment leads to better outcome
  - Reduce IRIS by treating crypt for 2-8 weeks before ART

- Evidence
  - Very little in US that outcomes are better with monitoring

#4: For Cryptococcal Meningitis, Are There Any Recommended Regimens That Do NOT Include Liposomal Amphotericin?

- Amphotericin B is the only fungicidal drug
- Azoles are all fungistatic
  - Fluconazole 400-2000 mg PO or IV qd
  - Voriconazole
  - Posaconazole
  - Isavuconazole
  - Fluconazole plus Flucytosine

Higher High Dose Fluconazole for the Treatment of Cryptococcal Meningitis

Wadzanai Samaneka
Parirenyatwa Clinical Research Site
Harare, Zimbabwe
All Regimens Must Use Liposomal Amphotericin (in US)

- Regimen of choice for cryptococcal meningitis (and other serious or disseminated forms) continues to be
  - Liposomal Amphotericin B plus Flucytosine
    - Liposomal Amphotericin B plus Flucytosine has comparable mortality but slower CSF sterilization
  - Unlike TB meningitis, corticosteroids should NOT be routinely administered
  - Based on an Asian/African study (n=451) of Amphotericin B plus Fluconazole +/- dexamethasone which demonstrated higher rate of poor outcomes and AEs with dexamethasone
  - But...
    - For focal pulmonary disease or asymptomatic crypt antigenemia with effective ART, Fluconazole alone is probably adequate x 12 months

#5: Which Zoster Vaccine Should be Used for Persons with HIV Infection?

- Zoster Vaccine Live-ZVL (Zostavax)
  - Attenuated vaccine
  - Contraindicated if CD4 <200 cells
- Recombinant Adjuvant (Shingrix)
  - 2-dose, subunit vaccine containing recombinant glycoprotein E in combination with a novel adjuvant (AS01B)
  - 68% effective post HSCT recipients
  - Data on HIV
  - Two small studies have assessed safety and immunologic response, but not clinical efficacy
#6 Therapy For Toxo Encephalitis

- If Pyrimethamine is either unavailable from the supplier or too costly for the insurance plan
  - Is TMP-SMX an appropriate initial therapy for Toxoplasma encephalitis?
  - Is TMP-SMX superior to Atovaquone?

Efficacy and Safety of TMP-SMX for Therapy of HIV-Associated Toxoplasmosis

- Large Observational Trial
  - Dose: Variable x 4-6 weeks followed by one DS qd
  - Clinical Response: 77/83 (93%)
  - Failures: Bacterial (1), PCP (2) days 4-21 and Lost (1), Suicide (1)
  - Second episodes successfully re-treated with TMP SMX: 26/28
  - Treatment Limiting Toxicity: 6/83 (7%)
  - Skin (4), Pancreatitis (2)
- Conclusion
  - Results comparable to pyrimethamine-sulfamethoxazole
  - Beraud Am J Trop Med Hyg. 80(4), 2009

Toxoplasmosis: Conclusions

- Drugs of Choice for Toxoplasmosis Based on Extent and Quality of Evidence
  - Pyrimethamine plus sulfadiazine (+leucovorin)
  - Pyrimethamine plus clindamycin (+leucovorin)

- Alternative Regimen
  - TMP-SMX (BI)
  - Atovaquone +/- (sulf or pyr)-BII

- NOTE
  - TMP-SMX is the ONLY all IV regimen
Hepatitis A Outbreak in California

- The outbreak began in San Diego County in November 2016 and spread to Santa Cruz, Los Angeles, and Monterey counties
- Cases: 704
  - Hospitalizations: 461
  - Deaths: 21
- Epidemiologic Associations with Acquisition
  - Poor sanitation: homelessness and PWID
- Correlates with morbidity/mortality
  - HBV and HCV
  - Not HIV
What is the recommended therapy for asymptomatic cryptococcal antigenemia in an asymptomatic person with HIV (CD4 30 cells/UL) who has a negative LP and is starting ART?

A) Liposomal amphotericin B alone
B) Liposomal amphotericin B plus flucytosine
C) Fluconazole alone
D) Voriconazole alone
E) Fluconazole plus flucytosine

Answer

- Amphotericin B therapy produces more rapid sterilization of the CSF than therapy with any of the azoles. Amphotericin B plus flucytosine is more rapidly fungicidal than Amphotericin B alone. Thus, for cryptococcal meningitis the preferred therapy is Liposomal amphotericin B plus flucytosine (Amphotericin B plus fluconazole is probably almost comparable).
- For non CNS disease the is not life threatening, an azole alone is adequate. Thus, fluconazole alone therapy is recommended for asymptomatic crypt antigenemia if an LP reveals normal CSF.
Post Test

For the therapy of toxoplasma encephalitis in a patient with HIV infection (CD4<50 cells/UL, ready to start ART), the recommended therapy would be which of the following if pyrMETHAMINE (DARAPRIM) were unavailable?

A) Sulfadiazine plus clindamycin  
B) Sulfadiazine plus primaquine  
C) Sulfamethoxazole plus trimethoprim (Bactrim/Septra)  
D) Azithromycin plus clindamycin

- If pyrMETHAMINE is unavailable, either trimethoprim-sulfamethoxazole or atovaquone would be reasonable options. Atovaquone takes longer to get to steady state (3 days) and has erratic absorption if the drug is not taken with a fatty meal. Thus, TMP-SMX is likely to be the more reliable option. Most clinicians try to keep a 2 hour post dose sulfa level at 100-150ug/ml.
How Important Are HIV-Related Opportunistic Infections?

- Therapy clearly reduces the incidence of most HIV-related opportunistic infections
- Even with effective ART
  - Several OIs lack effective therapy other than ART
  - JC encephalitis, cryptosporidia/microsporidia
How Important Are HIV-Related Opportunistic Infections?

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- Even with effective ART
  - Several OIs lack effective therapy other than ART
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  - Several HIV-related opportunistic infections continue to occur at enhanced rates despite ART
    - Pneumococcus, Herpes zoster, Tuberculosis
- JC encephalitis, cryptosporidia/microsporidia
- Several HIV-related opportunistic infections continue to occur at enhanced rates despite ART
  - Pneumococcus, Herpes zoster, Tuberculosis
- Pneumococcus, Herpes zoster, Tuberculosis
- Many infections continue to occur with high frequency due to lifestyle: STDs, MRSA, Enteric infections, endocarditis, Hep A
- Distinguishing IRIS from active infection is complicated
How Important Are HIV-Related Opportunistic Infections in 2018?

Clinical Trials for HIV-Related OIs Are Sparse in Era of Changing Diagnostics and Therapeutics