The Hospitalized HIV+ Patient

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Santa Rosa Family Medicine Residency

Objectives

- List 3 ways of risk-stratifying known or suspected HIV+ inpatients
- Perform differential diagnosis and workup of suspected Opportunistic Infections
- List 3 common reasons for ART medication errors in hospitalized HIV+ patients

Known or Suspected HIV+ Inpatient

Assess Risk
- End organ damage to Immune System?
- Clinical exam: Thrush, LAD, Wasting
- Absolute Lymphocyte Count <1000?
- CD4: <200, <14%
- HIV Viral Load: Detectable?
- HIV Urgency/Emergency: Pregnant? Needlestick?

Stable HIV

- Continue ART (formulary)
- Adherence
- Drug Interactions
- Renal Insufficiency
- NPO
- IRIS (recently stable)

Unstable HIV (new diagnosis or out of care)

Baseline labs

- Pulm
- Gastroint
- Neuro
- Oncology
- other

Assess for end-organ damage to Immune System

- Absolute Lymphocyte Count: <1000?
- Nadir or current CD4: <200? <14%

Typical Course of HIV Infection

Exposure Type | Source with Known HIV Infection
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HIV-infected Class 1* | Recommend basic 3-drug PEP
HIV-infected Class 2* | Recommend expanded 3-drug PEP

Less Severe
- Solid needle
- Superficial injury

More Severe
- Large-bore, hollow needle
- Deep puncture
- Visible blood on device
- Needle in patient's artery or vein

www.nccc.ucsf.edu/about_nccc/pepline/
The Stable HIV Inpatient

- Continue ART (formulary)
- Adherence
- Drug Interactions
- Renal Insufficiency
- NPO
- IRIS (recently stable)

Formulary/Adherence

Lipid-Lowering Agents and PiIs: Drug-Drug Interactions

- Use cautiously
- Low interaction potential
- Contraindicated

Gastric Acid Modulators and Atazanavir

<table>
<thead>
<tr>
<th>Treatment Naive</th>
<th>Treatment Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Atazanavir Dosing Recommendation</td>
</tr>
<tr>
<td>Antacids</td>
<td>2 hrs before or 1 hour after antacids</td>
</tr>
<tr>
<td>H2 Receptor Antagonists (H2RA)**</td>
<td>300 mg ATv/100 mg RTV: simultaneously or 10 hrs after H2RA</td>
</tr>
<tr>
<td>Proton Pump Inhibitors (PPI)**</td>
<td>400 mg ATv/100 mg RTV: &gt;2 hrs before or &gt;10 hrs after H2RA</td>
</tr>
</tbody>
</table>

**H2RA < dose comparable to 20 mg fexofenadine bid for H2RA: 20 mg bid or (cimetidine 150 mg bid)

Acid Modulators and Rilpivirine

- **Antacids:** Rilpivirine should be administered 2 hours after or at least 4 hours before antacids
- **H2 Receptor Antagonists:** Rilpivirine should be administered 12 hours after or at least 4 hours before H2RAs
- **Proton Pump Inhibitors:** Contraindicated
Contraindications with common ICU medications

<table>
<thead>
<tr>
<th>Contraindicated with NNRTIs (both with Efavirenz)</th>
<th>Contraindicated with PIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam/Triazolam</td>
<td>Proton-Pump Inhibitors (Atazanavir)</td>
</tr>
<tr>
<td>H2-blockers (if bid with Atazanavir)</td>
<td>Amiodarone (Indinavir, Ritonavir or Tipranavir)</td>
</tr>
<tr>
<td>Propafenone (Lopinavir/Ritonavir, Ritonavir, Tipranavir)</td>
<td>Quinidine (Ritonavir or Tipranavir)</td>
</tr>
</tbody>
</table>

All NRTIs (except Abacavir) need renal dosing

<table>
<thead>
<tr>
<th>Formulation</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid</td>
<td>Zidovudine, Lamivudine, Abacavir, Nevirapine, Emtricitabine, Fosamprenavir</td>
</tr>
<tr>
<td>- OK for NG/feeding tubes</td>
<td>Ritonavir, Lopinavir/Ritonavir</td>
</tr>
<tr>
<td>- Impractical or powder</td>
<td>Nelfinavir (very impractical), Stavudine, (moderately impractical), Didanosine (somewhat cumbersome), Delavirdine (100mg), Efavirenz, Nelfinavir</td>
</tr>
<tr>
<td>OK to open capsules or crush/dissolve tablets (immediately)</td>
<td>Atazanavir, Delavirdine (100mg), Darunavir, Efavirenz, Emtricitabine, Nelfinavir, Tenofovir</td>
</tr>
<tr>
<td>Not OK to crush/dissolve tablets</td>
<td>ALL COFORMULATIONS</td>
</tr>
<tr>
<td>Injectable formulations available</td>
<td>Enfuvirtide (SQ), Zidovudine (IV)</td>
</tr>
</tbody>
</table>

Table 2: Potentially Life-Threatening and Serious Adverse Effects of Antiretroviral Agents.

<table>
<thead>
<tr>
<th>Life-Threatening or Adverse Effect</th>
<th>Principal Antiretroviral Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic hypersensitivity reaction</td>
<td>Abacavir</td>
</tr>
<tr>
<td>Stevens–Johnson syndrome or toxic epidermal necrosis</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>All antiretroviral agents, especially nevirapine</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Didanosine and stavudine</td>
</tr>
<tr>
<td>Lactic acidosis syndrome, hepatotoxicity, and hepatic steatosis</td>
<td>NRTIs, especially stavudine, didanosine, and zidovudine</td>
</tr>
<tr>
<td>Nephrototoxicity and acute renal failure</td>
<td>Indinavir and tenofovir</td>
</tr>
</tbody>
</table>
Improved survival in ICU for HIV patients


Common ART medication errors

<table>
<thead>
<tr>
<th>Error class</th>
<th>Rx as ordered</th>
<th>Specific error</th>
<th>Day 1 Errors (N=145)</th>
<th>Day 2 Errors (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete regimen</td>
<td>Darunavir 600bid/ Ritonavir100bid</td>
<td>Missing additional Tenofovir/FTC</td>
<td>64 (58%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Incorrect dosage</td>
<td>Darunavir 600bid/ Ritonavir100bid/ Abacavir 600qg/ Lamivudine 50 qd</td>
<td>Lamivudine dosage 150mg qd based on CrCl=40</td>
<td>42 (38%)</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Incorrect schedule</td>
<td>Lopinavir 200mg/Ritonavir 50mg two tabs qd and TDF/FTC qd</td>
<td>Kaletra tablets are dosed bid</td>
<td>25 (23%)</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Non-recommended drug-drug</td>
<td>Atazanavir 300mg/Ritonavir 100mg and TDF/FTC qd with Inhaled Fluticasone daily</td>
<td>Fluticasone and Ritonavir can cause Cushing’s</td>
<td>14 (13%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Antiretroviral medication errors remain high but are quickly corrected among hospitalized HIV-infected adults.


Conclusion: ART medication errors are typically corrected within 48 hours

(if you have two ID specialist Pharm D's reviewing all medication orders for:

- ART medication errors and
- ART drug interaction errors)

Immune Reconstitution Inflammation Syndrome (IRIS)

- Unmasking IRIS
  - Clinical presentation of preexisting, subclinical OI after HAART initiation
  - Viable pathogens
  - Usually ≤ 3 months of HAART
  - Example: Non-tuberculous mycobacteria (MAC), TB
- Paradoxical IRIS
  - Exacerbation and/or return of sx of currently or recently treated OI
  - Non-viable antigens of pathogens
  - Usually ≤ 3 months of HAART
  - Months to years for immune recovery (CMV) uveitis
  - Examples: TB, Cryptococcal disease, Kaposi’s sarcoma (KS)
**Opportunistic Infections (OIs) in HIV/AIDS**

May 2011

Jeffrey Reed, MD, AETC
Joanna J. Gluck, RN, AART
AIDS Training Center

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**Natural history of untreated HIV infection and relationship of specific opportunistic infections to CD4 count.**

Lymphoma
Kaposi's sarcoma
Tuberculosis
Pneumocystis
Thrush
Candida oesophagitis
Herpes simplex virus oesophagitis
Idiopathic oesophageal ulcer
Microsporidiosis
Cryptosporidiosis
Mycobacterium avium complex
Cytomegalovirus disease

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**When to Suspect PCP**

- CD4 count < 200 (or CD4% < 14) + symptoms
- Thrush or oral hairy leukoplaia
- Hypoxemia with normal CXR
- CXR –
  - Diffuse bilateral symmetrical interstitial infiltrates
  - Pneumothorax with AIDS (think PCP)
  - Cavitation, adenopathy and effusions not common
- Non-specific:
  - Increased LDH > 500, O2 desat with exercise

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**Diagnosis of PCP - 2**

**Sensitivity of stained respiratory secretions**

<table>
<thead>
<tr>
<th>Source</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induced sputum</td>
<td>&lt; 50% - 90%</td>
</tr>
<tr>
<td>BAL**</td>
<td>90% - 99%</td>
</tr>
<tr>
<td>Trans-bronchial Bx</td>
<td>95% - 100%</td>
</tr>
<tr>
<td>Open lung bx</td>
<td>95% - 100%</td>
</tr>
</tbody>
</table>

Early BAL allows focused therapy [1-2 drugs instead of 7], ID of co-infection(s), & earlier release from isolation.

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**Pneumocystis jiroveci Pneumonia**

- **Treatment (Preferred)**
  - Severe: TMP 15-20 mg/kg/d and SMX 75-100 mg/kg/d IV Cef or Q8h
  - If PaO2 < 70 mmHg or A-a gradient > 35 mmHg → Prednisone 40 mg Q24h
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 DZTPM-SMX tabs orally TID
  - Duration: 21 days

- **Treatment (Alternative)**
  - Severe: Pentamidine 3-4 mg/kg IV QD - or –
  - Primamune 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
  - Primamune + clindamycn PO
  - Atovaquone 750 mg PO BID
CNS Disease in AIDS

Differential diagnosis:
- Toxoplasmic encephalitis
- TB
- PML (fever absent)
- Primary CNS lymphoma
- Cryptococcal meningitis

Symptoms:
- Headache and fever, focal encephalitis, confusion, motor weakness
- PML - insidious focal neurologic defects (no fever)

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
  - Azithromycin 1.5 gm PO BID + pyrimethamine (leucovorin)
  - Azithromycin + sulfadiazine 1.5-1.5 gm PO q6h
  - Azithromycin 1.5 gm PO BID
  - Pyrimethamine (leucovorin) + azithromycin 900-1200 mg PO QD

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 + flucytosine 800 mg PO or IV QD
  - Amphotericin B deoxycholate 0.7 mg/kg IV QD + flucytosine 800 mg PO or IV QD
  - Flucytosine 400-600 mg PO or IV QD + flucytosine 25 mg/kg PO QID
  - Flucytosine 1200 mg PO or IV QD

Diarrhea: Differential Diagnosis

- Viral
  - Cytomegaloviral colitis
  - HIV enteropathy
  - KS of the bowel

- Parasitic
  - Cryptosporidium
  - Isospora belli
  - Cyclospora
  - Microsporidial species
  - Giardia lamblia
  - Entamoeba

- Bacterial
  - Salmonella
  - Shigella
  - Nitrosi
  - Campylobacter
  - Mycobacterial
  - Clostridium difficile

- Fungal
  - Candidal overgrowth of the large bowel
Disseminated Mycobacterium avium complex

- **Preferred therapy**
  - At least 2 drugs to include clarithromycin 500 mg QID + 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
  - Aminoglycoside 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

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
  - Amphotericin B deoxycholate 0.6 mg/kg IV QD

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)**
  - 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%

When to Start ART During Acute OIs Excluding TB

- **Within 1st two weeks of OI treatment**
  - Pneumocystis pneumonia
  - Toxoplasmic 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 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

Questions?