06, 16, & 31

Management of AIDS-Related Opportunistic Infections I, II, & III
SYLLABUS SUPPLEMENT

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Some Other Information and Cases You Might Want to Know…Covered Elsewhere But Reviewed Here in HIV OI Context

FOR AT-HOME REVIEW
A 55-year-old man with HIV (CD4=180 cells/µL, VL 30,000 copies/µl) presented with a 1-month history of multiple painless, ulceronecrotic skin lesions without any constitutional symptoms. The patient’s palms and soles were unaffected.

Which of the following is most likely to be useful to identify the STD causing these lesions:

a) Routine bacterial culture
b) Serology
c) PCR
d) Gram stain
What is Lues Maligna?

- Severe ulcer nodular form of secondary syphilis
- Probably associated with immune suppression especially HIV

Screening for STDs in HIV Infected Patients

- Preventive Screening is important
  - At least annually for sexually active patients
- Recommended by CDC
  - RPR /VDRL
  - GC and Chlamydia
    - First catch urine or urethral/cervical swab for NAAT
  - All women
    - Wet mount for trichomonas
  - If Rectal Sex
    - Rectal culture for GC and Chlamydia
  - If Passive Oral Sex
    - Throat Culture for GC
- Notes
  - NAAT: use only for urine, cervix, urethra, not for rectum, throat
  - Chlamydia of throat uncommon, so screening not necessary

www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm
HPV Disease

- Most common STD for general population
  - 50-80% population infected at some time
- HPV is associated with cancers in general population
  - Types 16,18 with cervical cancer (both vaccines)
  - Types 6,11 genital warts (non oncogenic) (bivalent vaccine)
  - HPV 16 associated with most other cancers
    - Penis, vagina, vulva, anal, oropharynx
- Low CD4 count is risk factor for cervical CA
- HPV screening is controversial for cervix and rectum
- HPV vaccine is not well studied in HIV+ kids/adolescents
  - No safety contraindication in HIV+
  - Administer to adolescents prior to sexual exposure
Clinical Manifestations of HPV

Benign
- Verrucous or accumulate wart
- Flat or interepithelial condyloma
- Giant Condyloma

Premalignant
- Cervical intraepithelial neoplasia (CIN)
- Vaginal, vulvar, anal, penile (VAIN, VIN, AIN, PIN)

Malignant
- Invasive squamous and adenocarcinoma of cervix
- Invasive squamous cell anus, penis, vagina, vulva

HPV Related Oral Cancers
Type 16/Oral Sex/Number of Partners
No clear HIV association

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HIV Associated Bacillary Angiomatosis

• Causative Organism
  – B. henselae >> B. quintana

• Clinical Presentations
  – Cutaneous lesions
  – Peliosis hepatis (B. henselae almost exclusively)
  – Other focal: bone (more likely B. quintana)

• Therapy
  – Azithro or Erythro x at least 3 months
  – Doxycycline but NOT Quinolone

Cutaneous and Subcutaneous Lesions of Bacillary Angiomatosis

Koehler JE: http://hivinsite.ucsf.edu/InSite?page=kb-05-01-03
Peliosis Hepatis in HIV Patient

Definition
Blood filled cavities

Causes
Drugs (steroids)
Tumors
Infections

Bacillary Angiomatosis
Question

For which of the following is a dark field examination likely to be diagnostic for syphilis?

A.  B.  C.  D.

Condyloma

HPV
Condyloma Acuminatum
Warts

HPV Secondary
Syphilis
Condyloma Lata

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Answer

Correct: C

The pictures here are admittedly difficult to distinguish, but the teaching point is that the lesions in C are flat, and more typical of condyloma lata which is caused by secondary syphilis, which can be diagnosed by darkfield of a lesion smear. These typically occur in warm, moist areas and are teeming with treponemes.

Lesion A is condyloma acuminata (cauliflower like lesions) although HPV lesions can be verrucous or pedunculated.

Lesion B is a simple HPV related wart which is not premalignant. HPV lesions are spread by direct contact from skin or mucous membranes.

The tongue lesion in D could be syphilis, HSV or carcinoma but dark field would not be useful because the mouth has non syphilitic, non pathogenic treponemes as part of the normal flora. Thus the presence of treponemes would be meaningless for establishing a diagnosis.

HIV Associated Syphilis

- **Manifestations**
  - No major differences from HIV negative
  - Primary chancres more likely atypical/absent-
  - Neurosyphilis may be more frequent

- **Diagnosis**
  - No major differences other than neurosyphilis (CSF WBC cut off—maybe 20 cells vs 10 cells)

- **Therapy**
  - Same therapeutics but perhaps more failures
Secondary Syphilis
Mucous Patches (Oral, Genitals, Larynx) Condyloma
lata (Intertriginous) (Many Organisms)

Skin and Hair Lesions

Distinguish from Condyloma acuminata due to HPV

Tertiary Syphilis
Late Syphilis - Ulcerating Gumma
CNS Gumma with Spirochete Demonstrated
Cardiovascular Syphilis - narrowing of coronary ostia in aortus
Diagnosis of Neurosyphilis

- LP Indicated
  - Auditory, ophthalmic, neurologic manifestations
  - Treatment failure for primary/secondary/latent
  - Other manifestations of tertiary disease
- If no signs/symptoms of neurosyphilis
  - LP not clearly necessary
- Laboratory diagnosis of neurosyphilis
  - Controversial

Neurosyphilis Diagnosis

- Be suspicious if:
  - Serum VDRL/RPR ≥1:32
  - CD4 < 350
  - Treatment failure
- CSF Diagnosis of Neurosyphilis is controversial
  - WBC > 10 (>20 cells is more specific but less sensitive)
  - PCR positive (available at CDC and...)
  - VDRL/RPR Positive
    - Remember: in CSF VDRL is SPECIFIC BUT NOT SENSITIVE
    - PCR
- Note:
  - Elevated protein alone is sensitive but not specific

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Look for Cases of Neurosyphilis And Treat Them As Neurosyphilis

• Cranial nerve palsies (especially unilateral)
  – Optic atrophy (II)
  – Ocular Palsies (III, IV, VI)
  – Deafness (VIII)
• Anterior Uveitis
• Mass lesions: gummas
• Acute meningitis often with uveitis
  – Most common with secondary
• Syphilitis vasculitis presenting as stroke
• Dementia
• Tabes dorsalis

HBV

• If HBV PCR is positive in HIV infected patient
  – Treat for both regardless of CD4 count, HIV viral load, HBV viral load, liver biopsy result
HIV-HBV Co-infection
from Gulick Lecture

• Some ART has activity against HBV
  – lamivudine (3TC), emtricitabine (FTC),
    tenofovir (TDF)
• Some HBV drugs have activity
  against HIV
  – entecavir
• If treatment started, treat both
  optimally
  – 2 active agents for HBV
  – 3 active agents for HIV
  – e.g. TDF/FTC + 3rd drug

HBV Treatment

• All HBV drugs without full ART will lead to
  HIV resistance---except adeovir
• Treatment should be indefinite, i.e. don’t
  stop
  – IRIS occurs when HBV Rx stopped, esp low
    CD4 count
  – If LFT flare: try not to stop HBV Rx
    • Look for other causes of LFT flare
      • other drugs,
      • HBV resistance
      • Hbe seroconversion
      • Alcohol
      • other viruses

DHHS Guidelines 3/27/12 and Gulick
**Principles of HBV Therapy**

- **Non-Response**
  - Failure of HBV DNA to fall 1 log at wk 12
- **Complete Response**
  - Undetectable DNA at 24-48 weeks

**HIV-HCV Co-Infection (From Gulick Lecture)**

- Optimal time to treat HCV with concurrent HIV infection is unknown.
- Ribavirin
  - ddI (and d4T) → life-threatening mitochondrial toxicity, hepatomegaly/steatosis, pancreatitis, lactic acidosis
  - ZDV → high rates of anemia
- Boceprevir → OK with RAL; not recommended with ATV/r, DRV/r, LPV/r, or efavirenz (EFV)
- Telaprevir → OK with RAL, ATV/r, or increased-dose EFV; not recommended with DRV/r, FPV/r, LPV/r

DHHS Guidelines 3/27/12 and Gulick
Mycobacteria

• Fred Gordin will include HIV related mycobacterial diseases in his talk
• These slides overlap his material, but are here if you wish to review in the context of HIV OIs

Mycobacterial Infections in HIV Infected Patients

• Tuberculosis Many presentations
• Avium complex Dissemination
• Genovense Dissemination
• Scrofulaceum Adenitis, Dissemination
• Xenopi infiltrates Lung nodules or
• Hemophilum Cutaneous abscesses
• Bovis Adenitis, Dissemination
• BCG (Bovis) Dissemination
• Chelonei Joint Skin, Soft Tissue, Bone,
• Malmoense rings Cavitary lung, CNS
Question

A 45 year old male with HIV (CD4<10 cells/cc3, VL> 100k) has been taking TMP-SMX and Efavirenz-Tenofovir-3TC only intermittently.

For the past 3 weeks he has had a low grade fever, mild weight loss, and a lesion which is shown on the next slide.

Aspiration of the lesion showed many AFB rods, non branching, but after 6 weeks nothing grew.

The lesion is to be aspirated again.

See next slide
Question

What advice do you give the lab and hospital epi:

a. This should grow at 37C
b. This should grow on conventional TB culture media
c. This most likely was acquired by acupuncture or some other manipulation.
d. This is treatable with trimethoprim-sulfamethoxazole
e. This can be cultured only at 32C with iron enriched medium

Mycobacterium Tuberculosis Complex

An organism identified as TB might be one of the following species

- M. tuberculosis
- M. africanum
  - no difference clinically from TB
- M. Bovis
  - acquisition by ingestion, PZA resistant, less likely to be pulmonary
- M. bovis BCG
  - dissemination after vaccine or bladder injection (used as bladder cancer rx)
- Mycobacterium microti-rodent strain rare in humans
- Mycobacterium canetti
- Mycobacterium pinnipedii
- Mycobacterium mungi.
Mycobacterium Africanum

- Not likely to be on the boards
- Part of M.tuberculosis complex
- Clinically there is no reason to distinguish this from M.tb in terms of clinical presentation, therapy, transmission etc

Prophylaxis for Tuberculosis in HIV Infected Patients

- PPD Negative
  - Prophylax only if recently exposed OR fibrotic lesions on CXR and no history of treatment
  - Repeat PPD annually if at risk
  - Repeat PPD if previously neg and if CD4 rises to >200

- PPD Positive (>5mm)
  - Do not factor BCG in: pos PPD = TB, not BCG!
  - INH with pyridoxine x 9 months (qd or biw) or
  - Rifampin or Rifabutin x 3-4 months
  - INH plus rifapentine weekly x 12 (not proven for HIV)
  - Beware drug interactions
Clinical Presentations of Tuberculosis in Patients with HIV

- High CD4
  - Similar to HIV negative patients but more extrapulmonary
  - Cavitation common and thus more organisms
- Low CD4
  - less cavitation
  - More lower lobe, cavities, nodes, effusion
  - more extrapulmonary
  - fewer organisms
- Syndromes to watch for:
  - Sepsis
  - Pericardial
  - Normal xray
  - Meningitis
  - Lymphadenitis
  - Lung biopsy with no granuloma
  - Positive AFB blood culture

Association between timing of HAART and the risk of an IRIS event

Vernon et al. ICAAC 2004
TB and HIV

- TB risk is always increased in HIV infected patients compared to HIV negative at all CD4 counts
  - ART and rise in CD4 reduces risk of TB but....
  - ART does not restore risk to that of HIV negative
- Frequency of TB Activation After Infection
  - HIV negative: 5-10% lifetime
  - HIV positive: 10% per year
- CD4 Count
  - Influences likelihood of activation
  - Influences clinical manifestations
- After ART Initiated, TB can occur for several reasons
  - Uncover incubating cases, new infection, IRIS

When to Start HIV Therapy After Initiation of TB Therapy is Too Controversial for Boards
Treatment of TB in HIV-Infected Patients with CD4 < 100 cells

• Induction Phase: First two months
  – Daily therapy with 4 drugs (drop Eth if pan sensitive)

• Continuation Phase: Months 2-6 or 2-9
  – Daily or thrice weekly

Do Not use once or twice weekly regimens if CD4<100
Do not use rifapentine

HIV-TB Co-infection

• Treat active TB the same with or without HIV.
• All HIV+ pts with TB should start TB meds immediately.
• In HIV+ patients with TB, timing of ART depends on CD4 count
  – For CD4 <50, start ART within 2 weeks of TB rx
  – For CD4 >50 with severe disease, start ART within 2-4 weeks of TB rx
  – For CD4 >50 without severe clinical disease, start ART within 8-12 weeks of TB rx
• For MDR or XDR TB, start ART within 2-4 weeks of TB rx.

Gulick and DHHS Guidelines 3/27/12
HIV-TB Co-infection (2)

- Include a rifamycin in the regimen.
  - rifampin
    - significantly ↓ ALL PIs – cannot use together
    - ↓ RAL concentrations (need to ↑ RAL to 800 mg bid)
    - ↓ NNRTI concentrations: EFV 600 (or ↑ to 800) mg daily
  - rifabutin: preferred; more manageable drug interactions with protease inhibitors

- For IRIS, continue both ART and TB meds while managing the syndrome.
- DOT of TB rx strongly recommended.

Extension of TB Therapy > 6 Months

- Some experts prefer 9 months routinely
- Most experts recommend at least 9 months if
  - Cavitary disease and/or
    - Slow sputum conversion (> 2 months)
- Extend to 6-9 months
  - Extrapulmonary
- Extend to 9-12 months
  - Bone and Joint
  - CNS (meningitis or tuberculoma)
- Only use Corticosteroids (6-8 wks and taper)
  - Pericarditis
  - Meningitis
  - Severe IRIS
Mycobacterium avium Intracellulare Complex

• Epidemiology
  – Ubiquitous in dirt, animals etc
• Avium: 95% isolates
• Transmission
  – Respiratory and GI
  – Person-to-person NOT likely
  – Environmental isolates correlate poorly with human isolate

Mycobacterium Avium Intracellulare

• Risk factors
  – CD4 < 50, GI / respir colonization, High VL

• Incidence pre HAART: 20-40% (North America)
  – Now declining with HAART and prob non-HAART

• Clinical manifestations
  – Fever, wasting, nodes, liver, spleen
  – Rare as cause of lung disease
  – Lab: ↑Alk Phos, ↓Hg, ↓Albumen
  – Immune Reconstitution: No positive blood culture
    • Focal adenitis
    • Mesenteric adenitis
    • Pneumonitis
    • Pericarditis
    • Osteomyelitis
    • Skin lesion
    • CNS mass
**Mycobacterium Avium-Intracellulare: Diagnosis**

- **Source of Isolates**
  - Blood
    - Bactec (7-14 days), solid (21 days)
  - Sputum/Stool/Urine
    - High relative hazard (long interval)
    - Low predictive value
- **Lab Identification**
  - Specific DNA Probes for specimens/cultures

**MAC: Susceptibility Testing**

- **Susceptibility Testing**
  - Recommended for primary isolates
  - Bactec radiometric testing: Clari and Azithro
    - Background resistance in untreated patients: 17%
    - Other drug testing not validated for MAC
Treatment for MAC

- Preferred
  - Clarithro (or Azithro) + Ethambutol
  - Rifabutin optional, esp if severe
  - Beware drug interactions with clari or rifabutin
- Possibly Useful
  - Amikacin, Ciproflox, Moxiflox, Mefloquine, Linezolid,
  - Steroids useful anecdotally for severely symptomatic
- ARV
  - Can start after 2 weeks of anti mac therapy
- Response:
  - Fever should decline within 2-4 weeks
  - Blood cultures should be negative in 2-4w
  - Repeat blood cultures only if symptoms
- Stop maintenance:
  - CD4 > 100 x 6M, asx and therapy >12 m

Salvage Therapy for MAC

- Not for the boards
- Too complicated: no consensus
# Primary Prophylaxis for MAC in Patients with HIV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Azithromycin or Clarithromycin (Rifabutin also effective)</th>
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<tbody>
<tr>
<td>Start 1°</td>
<td>CD4 &lt;50</td>
</tr>
<tr>
<td>Stop 1°</td>
<td>CD4 &gt;100 x 3 M and asx</td>
</tr>
<tr>
<td>Restart 1°</td>
<td>CD4 &lt;50-100</td>
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