HIV

ACOI Board Review 2018
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(No Disclosures)
David Kirby's mother, Kay, holds a photograph of her son -- taken by Ohio photographer Art Smith -- before AIDS took its toll.

Therese Frare
Bill Kirby tries to comfort his dying son, David, 1990.
Therese Frare
• 1.1 million HIV + in U.S.; (36.7 million worldwide)
  • 1 in 7 unaware of their HIV +; many others in denial
    • responsible for up to 30% of transmission!
  • < 1/3 completely virally suppressed
• 37,600 newly infected each year in U.S.; over 1/2 MSM
• 37,000 newly diagnosed each year will present with advanced disease (13,000 will die)
Over half of HIV+ pts in U.S. are 50 y.o. or older; (by 2030, estimated ~73% will be over 50 y.o.) -> accelerated and/or increased incidence of:

- CV Dx
- Diabetes
- Osteoporosis
- COPD
- Slower immune recovery
- Malignancies
- Other dx usually associated w/ aging, including cognitive disorders (or is it the meds?)
- Drug interactions
HIV

• estimated to have entered the human population ~ 1920

• AIDS first described in U.S. in 1981; antibody testing first available 1985

• effective treatment first available in 1996; downside - tremendous pill burden, brutal side effects
*irrevocable depletion of CD4 cells in GI tract and other lymphoid tissue
  - without tx, approx. 10 yrs to develop AIDS
  - initial presentation may be anywhere along this spectrum
The Acute Retroviral Syndrome

- Non-specific febrile illness often misdiagnosed as "mono" or "aseptic meningitis", occurring 1 - 6 weeks following infection
  - chills, myalgias, adenopathy, maculopapular rash
  - pharyngitis, N/V, diarrhea
  - headache (LP-> mild pleocytosis) “aseptic meningitis”
  - elevated LFT’s
- Though HIV ab may be negative or indeterminate, these folks can be highly contagious (if suspected, obtain HIV “Viral Load”)
- Spontaneous resolution over next few weeks
Window phase: tests neg for HIV, but highly contagious

Courtesy: AETC
Diagnosis

• Screening: EIA antibody (or other rapid tests)
  • Testing now recommended as part of routine medical care (yearly if “high risk”). **CDC recs: yearly from ages 13 - 64**
  • Newer assays that include p24 antigen (4th generation”) may be positive as early as 10 - 14 days after infection

• Confirmation: Western Blot
  • Time to positive: 4 - 5 weeks
  • Any two: p24, gp41, gp120/160 -> positive
  • one of above bands +, or other + bands -> “indeterminate”
    • if indeterminate, obtain quantitative assay for HIV by PCR - “viral load”
Clues to possible (untreated, advanced) HIV:

- Unusual presentation of a common illness
- Pneumococcal pneumonia w/ bacteremia in a young person
- Salmonella, shigella, campylobacter bacteremia
- Severe or recurrent thrush, vaginal candidiasis
- Presentation of an unusual illness
- Uncommon dx, e.g. cryptococcal meningitis
- More advanced/severe dx than expected
- Unusual age for illness
- TB, especially w/ unusual presentation
- Other STDs
Correlation of CD4 count to presentation of Opportunistic Infections/Malignancies

- Infections common in the non-HIV infected population tend to occur at higher CD4 counts. As CD4 counts fall, these same infections may develop, but often with more extensive or disseminated disease. (TB, HSV-1 or 2, H. zoster, candidiasis)

- Infections rarely, if ever, seen in the non-immunosuppressed host tend to occur at the lowest CD4 counts e.g. disseminated CMV (100), MAC (50)

- Certain malignancies more common, even with “adequate” CD4 count
AIDS Defining Malignancies

- invasive cervical carcinoma
- Kaposi sarcoma
- systemic non-Hodgkin lymphoma
- primary CNS lymphoma
Non-AIDS Defining Malignancies Increased in HIV + Individuals

- lung
- liver
- kidney
- anus
- head & neck
- skin, including melanoma
- Hodgkin’s lymphoma
O I’s/neoplasms relative to CD4 counts

- **200 - 500 or above**
  - pulmonary TB
  - **bacterial pneumonia** *(pneumococcus most common)*
  - H. zoster
  - cervical CA, Kaposi’s sarcoma, Hodgkin’s lymphoma
  - oral/vaginal candidiasis; anemia; ITP; nephropathy *(FSGS)*
• < 200
  • PCP
  • Disseminated TB
  • Esophageal candidiasis
  • Cryptococcal meningitis; PML
  • Cryptosporidium
  • Non-Hodgkin’s lymphoma
  • Disseminated histoplasmosis, coccidioidomycosis
  • wasting; dementia
• < 100
  • CNS toxo, lymphoma; disseminated CMV, MAC (elevated alk. phos)
CMV

Toxo: intensely white focal lesions w/ vitreous inflammation
Cryptococcal Meningitis

- Subacute, progressive headache; w/ or w/o fever
- Few to no WBC’s in CSF
- + india ink, cryptococcal Ag
- Tx: Amphotericin B +/- flucytosine by fluconazole
- T cell deficiencies
Subacute to acute pneumonia — still a common presentation in patients who are unaware of their HIV status or are otherwise untreated

Diagnosis includes serum for: (1 -> 3) - beta - D - Glucan (Fungitell ®; Note: also used for invasive candidiasis and aspergillosis)®

Tx: trimethoprim/sulfa; pentamidine if allergic

Steroids if pO2 < 70 (may not apply to HIV neg pts)

See JAMA: June 24, 2009
Multiple questions regarding trimethoprim/sulfa, including:

- Side effects:
  - Maculopapular rash
  - Stevens-Johnson syndrome
  - TEN
  - Bone marrow suppression, other blood dyscrasias
  - Hyperkalemia
  - Volume overload w/ IV

- Treatment of side effects
- G6PD deficiency
Other Clues:
(if one STD, r/o others)
Kaposi’s sarcoma (HSV-8)  Bacillary Angiomatosis (Bartonella sp.)
Hairy Leukoplakia (EBV)

CMV Esophagitis
(D/D: CMV, HSV, Candida, apthous ulcer)
GI Presentations
(Note: Tx will most always emphasize treating underlying HIV)

- Often chronic diarrheal syndrome
  - Cryptosporidiosis - no fever; + AFB
    - AFB +
      - Cryptosporidium (3-6 microns)
        - also dx by direct immunofluorescense
        - Rx: ART; ? paromomycin, nitazoxanide
      - Cyclospora (7.5-10 microns)
        - Rx: TMP-SMX
      - Isospora (new: Cystoisospora)
        - Rx: TMP-SMX
    - Mycobacterium Avium-Complex “M.A.C.”
      - Rx: Clarithro/Ethambutol/Rifabutin
• Other chronic diarrheal syndromes
  • Microsporidia (Enterocytozoon spp.) - no fever; bx w/ special stains
    Rx: Tx HIV, albendazole
  • CMV - bloody diarrhea w/ fever; bx
    Rx: ganciclovir
  • MAC - fever, wasting, diffuse abdominal pain; culture, +AFB
    Rx: azithro or clarithro + ethambutol +/- rifabutin

Tx: Ganciclovir
Focal CNS syndromes

- **Toxoplasmosis**
  - Acute w/ multiple contrast + lesions w/ + serology (basal ganglia most often)
- Fever
- Mass effect
Focal CNS syndromes

- Lymphoma (Usually diffuse, large B-cell)
  - Subacute presentation
  - Usually single contrast + lesion
  - Mass effect
  - Usually no fever
  - + PCR for EBV (?)
Other Focal CNS syndromes

- **PML**
- Multiple, contrast negative lesions of white matter
- No mass effect
- No fever
- + PCR for JC virus
# OI Prophylaxis*

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<thead>
<tr>
<th></th>
<th>CD4 &lt; 200</th>
<th>TMP-SMX</th>
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<tbody>
<tr>
<td><strong>PCP</strong></td>
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<tr>
<td><strong>TB</strong></td>
<td>Previous + PPD**</td>
<td>INH x 9 mos (and others)</td>
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<td></td>
<td>or +PPD &gt; 5mm</td>
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<tr>
<td><strong>Toxoplasmosis</strong></td>
<td>+ serology w/ CD4 &lt; 100</td>
<td>TMP-SMX</td>
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<tr>
<td><strong>M. avium complex</strong></td>
<td>CD4 &lt; 50</td>
<td>azithromycin or clarithromycin</td>
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*can usually be d/c’d upon return of CD4 count to above threshold parameters after ~3 months

**QFG assays similar to PPDs, but also w/ it’s own difficulties in interpretation
Clinical Course

- **Viral load:**
  - Correlates with degree of contagiousness, rate of immune deterioration (as reflected in CD4 ct)
  - "Cumulative viremia" w/ its resultant persistent inflammation and stimulation of the immune system may be responsible for many of the long term complications of HIV, e.g.,
    - Increased risk of CV and other diseases usually associated w/ aging
    - Increased risk of malignancy (including non-AIDS defining malignancies)
Clinical Course

- **CD4 lymphocyte count** (not the entire story):
  - Reflects immune status (as affected by VL)
  - Correlates w/ development of opportunistic infections (OI’s)
  - Correlates to some extent w/ risk of malignancies, particularly if very low CD4 count prior to treatment
    - 27% of HIV-related deaths due to HIV-related malignancies
    - Risk of NHL > 76 times that of non-HIV infected individual
  - Restoration may approach normalcy, but probably never completely
Who/When to Treat?

Offer to all upon diagnosis, including same day Rx
Benefits of Early Treatment

• Decrease in transmission (undetectable viremia minimizes risk of transmission)

• Decrease in illnesses associated w/ impaired immune system e.g. various infections, cancers

• Decrease in illnesses associated w/ chronic inflammation/accelerated aging e.g. heart disease, cancer
“Treatment as Prevention (of transmission)”

“No linked infections were observed when HIV-1 infection was stably suppressed by ART in the index participant”
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group - N Engl J Med 2015; 373:797-807

- 4685 HIV + patients
  - median VL of 12,759 copies/ml
  - median CD4 count of 651

- After 3 years, those started immediately on ART experienced less than half of serious AIDS-related events (including reduced cancer risk by 64%) than those whose therapy was deferred to later
HIV and Pregnancy

- Overall risk of transmission if infected mother not identified (and not on tx): 25-33%
- IF infected mother identified (and appropriately treated): 1-3% or less
- Test at initial visit and at near term. Treat if positive
At least **three drugs** from at least **two different classes** of anti-retrovirals

- **Usually** two **NRTIs** (nucleoside reverse transcriptase inhibitor)

  **plus** either a

  - **NNRTI**

  or a

  - **PI/r** (ritonavir “boosted” protease inhibitor)

  or a

  - **InSTI** (integrase inhibitor)
Integrase inhibitor based:

• Dolutegravir (Tivicay®) + abacavir/lamivudine = Triumeq® - ONLY for pts who are HLA-B*5701 negative or….

• Dolutegravir + [Emtricitabine/tenofovir (Truvada®)] or….

• Elvitegravir/cobicistat + [Emtricitabine/tenofovir (Truvada®) / Descovy®] = Stribild® / Genvoya® or….

• Raltegravir (Isentress®) + [Emtricitabine/tenofovir (Truvada®)]

Note: Other sources have more extensive lists of acceptable options; certain two drug Rx’s may be acceptable for long term suppression
Coinfection w/ Hepatitis B/C

• With hepatitis B:
  Include combination of emtricitabine or lamivudine + tenofovir whenever possible, as these have dual activity for treating both infections
  • Discontinuation may lead to serious liver damage from reactivation of Hepatitis B

• With hepatitis C:
  most treat hepatitis C before initiating rx for HIV unless CD4 < 200
Possible ?’s:

• Hypersensitivity rxn to abacavir (Ziagen ®) if + for HLA-B*5701 (more common in caucasians). DO NOT RX; if prior reaction, DO NOT RE-CHALLENGE!!!

• Renal insufficiency, bone resorption w/ tenofovir (Viread ®) (or Truvada ® as combination Rx)

• Jaundice (indirect hyperbilirubinemia) w/ atazanivir (Reyataz ®)
Immune Reconstitution Inflammatory Syndrome ("IRIS")

- An exaggerated inflammatory response to a previously relatively quiescent condition as a result of restoration of immune competence following initiation of HAART
  - Focal MAC
  - CMV vitreitis
  - TB
  - Cryptococcal meningitis
  - Hepatitis C
  - PML, HSV
- Rx: add anti-inflammatory and continue ART
Prevention:

- “Treatment as Prevention” - both of infection and complications of same

- Pre-exposure Prophylaxis (“PrEP”):
  - Once daily Truvada ®
  - Controversial, expensive, but effective if taken as rx’d
  - (Select) long term discordant sexual partners. Probably not necessary if partner undetectable VL
  - Commercial sex workers
  - but......among MSM using PrEP:
    - 25.3 increased incidence of N. gonorrhea!
    - 11.2 increased incidence of chlamydia!
    - 44.6 increased incidence of syphilis!!
Prevention:

- **Post-exposure Prophylaxis (“PEP”)**
  - Occupational: Effective
  - Non-occupational (“nPEP”): at least partially effective
  - ~72 hr window for Rx
- **Condoms; Circumcision**
Potential ?’s

Acute Retroviral Syndrome

IRIS

Adverse Rxns to TMX/Sulfa

Presentations of HIV

- Correlation of CD4 count w/ opportunistic infection

- Histology of renal disease in HIV+ individuals: FSGS

Prophylaxis/Rx of OI’s, e.g.:

- Steroids in the treatment of PJP

- Immune deficiency associated w/ Cryptococcal infections

- TB prophylaxis / PPD skin test
References


• Grant et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. NEJM 2010; 363 (epub).

• Kitahata et al. Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival. NEJM 2009;360: 1815-1826


• Zoufaly et al. Cumulative HIV Viremia during Highly Active Antiretroviral Therapy is a Strong Predictor of AIDS-Related Lymphoma. JID 2009;200: 79-87
Good Luck!