Important Concepts

- Epidemiology—(monograph)
- How to diagnose HIV
- Importance of CD4/viral load testing
- Starting antiretroviral therapy (ART)
- Common manifestations of AIDS
- Prophylaxis of opportunistic infections
- HIV prevention

Since the start of the epidemic...

- 77.3 million infected
- 35.4 million dead of AIDS-related illnesses

In 2017, 940,000 died of AIDS-related illnesses
- Down from 1.4 million in 2010, the peak

http://www.unaids.org/en/resources/factsheet
Adults and Adolescents Living with Diagnosed HIV Infection Ever Classified as Stage 3 (AIDS), by Sex, 1993–2014—United States and 6 Dependent Areas

- Prevalence is increasing in US and globally


- MSM category comprises majority of infections ~67%
- Increases in HIV in minority MSM (Hispanic/Latino, young AA)

**Case**

- A 26 year old man is seen in the ED with fever to 102°F, a rash, sore throat and enlarged cervical lymph nodes. He previously had been healthy, has not traveled and takes no medications. His labs are unremarkable except for a WBC=2.5K [nl 3.5-10K].
- Diagnosis?
A 26 year old man is seen in the ED with fever to 102°F, maculopapular erythematous rash, sore throat and enlarged cervical lymph nodes. He previously had been healthy and takes no medications. His labs are unremarkable except for a WBC=2.5K (nl 3.5-10K). Diagnosis?

1. Acute EBV infection
2. Acute CMV infection
3. Acute HIV infection
4. Secondary syphilis
5. Measles
6. Dengue fever
Primary (Acute) HIV Infection
- Onset 1-4 weeks after exposure
- 50-90% have at least some symptoms
- Nonspecific symptoms with many mimics
  - Fever 90%
  - Fatigue 90%
  - Pharyngitis 75%
  - Weight loss 75%
  - Myalgias 60%
  - Lymphadenopathy 50%
  - Thrombocytopenia, leukopenia 40-45%
  - Maculopapular rash 35%
  - Oral ulcers, headache, diarrhea, nausea, aseptic meningitis


Acute/Primary HIV Infection
- Characterized by high viral load and below normal CD4 count (Normal = 500-1200 cells/mm3)
- HIGH RISK OF TRANSMISSION
- VERY IMPORTANT to think of HIV and diagnose to impact the patient’s course AND try to reduce secondary transmission


Case
- The patient had unprotected sex with a male partner 2 weeks ago. You suspect HIV. Of the following options, what would be the best test to order to make the diagnosis?
  1. HIV antibody (ELISA, Western blot)
  2. CD4 count
  3. HIV RNA PCR
**4th generation** HIV tests
- Can detect not only HIV antibodies in the blood but also circulating virus (p24 antigen)
- Can detect very early infection prior to antibody development
- HIV ELISA and Western blot test are no longer recommended for detection of HIV infection
- Western blot testing too often led to false negative or indeterminate results early in infection


**HIV RNA Testing**
- HIV RNA PCR is another way to detect acute HIV infection prior to seroconversion due to high circulating viral loads
- If acute HIV is detected → earlier ART → decrease infections
- RNA PCR is also used to follow response to ART; should become “undetectable”, generally below 20-50 copies/mL if a patient is on effective ART

HIV Testing

- In 2006, CDC recommended HIV testing all persons aged 13-64
- Part of routine health care (opt-out rather than opt-in)
- Test persons at high risk annually (e.g., IVDU, HIV-infected partner, multiple partners, exchanging sex for drugs)
- Test all with STI, tuberculosis, illness compatible with HIV
- Test all pregnant women

You’ve diagnosed HIV, now what?

Baseline Evaluation of HIV

- History
  - Screen for other STIs, immunization status, travel history, sexual history
  - Psychosocial factors
    - Depression, support, substance abuse, access to food/housing/transportation
    - ROS directed at possible opportunistic complications
Baseline Evaluation of HIV

- Exam
  - Looking for evidence of more advanced HIV/opportunistic complications, STIs

Baseline Lab Evaluation of HIV

- HIV RNA PCR ("viral load" [VL]) and CD4 count
- HIV resistance testing (genotype)—any mutations to HIV medications?
- Chemistries, CBC, lipids, UA
- STI screening:
  - Gonorrhea/chlamydia screening, syphilis antibody screen
- TB screening:
  - PPD or QuantiFeron
- Hepatitis screening:
  - Hepatitis A, B, C antibodies
- Cervical Pap smear
- Toxoplasma IgG
- Labs for medication side effects (e.g., HLA B5701 for abacavir)

Question

- A 50 year old man is newly diagnosed with HIV. He feels well. His CD4 count is 700 cells/mm3, HIV RNA 12,000 copies/mL. He does not think he needs medication as he has no symptoms. You advise:
  1. Start antiretroviral therapy (ART)
  2. Start ART when the CD4 is < 500 cells/mm3
  3. Start ART when the viral load is >100,000 copies/mL
  4. Wait until symptoms related to HIV occur
When to Start ART

- Pendulum has swung back/forth about best time to start
- Numerous large cohort studies have shown survival benefit of starting earlier, esp with new less toxic/more convenient ART→how early??
- Effect of ART on prevention—public health benefit
- ART decreases transmission to sex partners


When to Start ART

- 2 randomized, controlled early vs deferred ART (START, TEMPRANO)
- Early ART: 50% fewer serious illnesses and deaths compared with waiting until CD4 350-500 or AIDS
- Benefits even if CD4 >500 or low VL
- Current DHHS guideline revised 1/2016: treat all persons with HIV regardless of CD4/VL
- Urgency greatest for low CD4


ART for HIV

- A medical success of the late 20th century

Goals:
- Improve survival
- Improve quality of life
- Improve immune function
- Even if CD4 is high
- Decrease HIV transmission

ART Over the Years


AIDS cases
HIV-1 isolated
AZT intro
Triple drug therapy
Single tablet regimens
Integrate inhibitors
Long acting injectables

Modified from Eron, IAS-USA San Francisco, CA 2016

One Pill, Once Daily

>45 HIV medications;
US Ave Wholesale Price
~$13,500 - 42,000/yr
11 complete single tablet regimens


Question

- Life expectancy of 20 year old diagnosed with HIV today and treated with ART? [Normal would be 66 yrs so a person without HIV would live to age 86]
  1. 25 years
  2. 35 years
  3. 45 years
  4. More than 50 years
Life expectancy with HIV
Diagnosis at age 20 Yrs

Age-Adjusted Mortality Rates

HIV and ART

- ART does not fully restore health; still a gap in lifespan for those with HIV vs no HIV
- Persons with HIV remain at increased risk of non-HIV complications—CV disease, non-AIDS cancers, osteoporosis, renal disease, neurocognitive decline
- HIV and its treatment may be risks for accelerated aging/organ damage
- Due to chronic inflammation triggered by HIV
- Side effects of ART (diabetes, lipid/renal/CV disorders)


HIV Care Continuum

Lowest in 13-34 yr age groups

Monitoring HIV

- CD4 and VL at baseline and every 3-6 months
- Can check CD4 less often once suppressed/stable
- Check VL 2-8 weeks after starting/changing ART
- Regular chemistries, CBC to monitor side effects
- Yearly screening for TB/STIs (latter more often if high risk)


Question

- Your patient’s CD4 is 400 and his viral load is 700,000 copies/ml. You start him on ART and his viral load becomes <20 copies/ml after 3 months. Your patient asks you how to prevent transmission to his partners. You tell him:
  1. Abstinence is recommended
  2. Short of abstinence, condoms are the only way to prevent transmission
  3. Effective ART will prevent transmission to his partners even in the absence of condoms
U=U

- When ART results in viral suppression ("undetectable"), it prevents sexual HIV transmission
- 3 large studies of sexual HIV transmission in thousands of serodiscordant couples and thousands of condomless sex acts
- No case of sexual transmission of HIV from a virally suppressed HIV-positive person to their HIV-negative partner
- *Not enough data yet on PWID

Complications of HIV

- Primary
- >500
- 200-500
- <200
- Thrush
- Herpes zoster
- Pneumonia (bacterial)
- Non-CNS lymphoma
- Toxoplasma
- Herpes zoster
- Tuberculosis
- Pneumonia (bacterial)
- Non-CNS lymphoma
- Neuropathy
- Bell's palsy
- Low platelets
- Pharyngitis
- Rash
- CD4

Month: 1 2 3 4 5 6 7 8 9 10 11 12

Years: 0 200 400 600 800 1000 1200
Case

A 26 yr old woman with HIV presents to the ED. She has a history of depression and has been on and off ART. She has had cough for 2 weeks and 1 week of fever. A CD4 count when last checked was 190. On exam, her O2 saturation on room air is 92%, she appears wasted and has oral thrush. A CXR looks normal.

Case

The cause of the cough and fever is treated with:
1. Ceftriaxone
2. Trimethoprim-sulfamethoxazole
3. Fluconazole
4. Isoniazid, rifampin, pyrazinamide, ethambutol

Common Lung Diseases in HIV

- Bacterial pneumonia (S. pneumonia)
- PJP (CD4 < 200, wasting, thrush)
- Tuberculosis
- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis (SW US)
- Cryptococcus
- Respiratory viruses (Influenza)
- Tumors: lymphoma, Kaposi’s sarcoma

Diagnosis:
- Sputum
- Bronchoscopy
- Antigen testing
Pneumonia radiography

Pneumocystis Pneumonia
- Often insidious symptoms present x weeks
- Exam often normal, desaturation with walking
- Elevated LDH (nonspecific)
- Chest x-rays may be normal in 10-39% of patients with PJP
  - Bilateral reticulonodular interstitial infiltrates, perihilar
  - CT more sensitive
- Risk factors: CD4 < 200 cells/mm³ or oropharyngeal candidiasis or AIDS-defining illness


Pneumocystis jiroveci
- Diagnosis on sputum or BAL: PJP DFA or PCR, or cytology
- Treatment: Trimethoprim-sulfamethoxazole (TMP-SMX)
  - Prednisone if significant hypoxia
- Prevention: TMP-SMX until CD4 remains > 200 cells/mm³ for > 3 mos
  - Alternative dapsone (if G6PD normal), atovaquone, or inhaled pentamidine

Case

- 30 year old man with advanced HIV has been having headaches for >2 weeks and is brought to the ED after having a seizure. On exam, he is afebrile and confused. His CD4 count was 85 several months ago. You obtain a brain MRI.

Case

- Your next step is to:
  1. Ask for a brain biopsy
  2. Start antibiotics for meningitis—ceftriaxone, vancomycin, ampicillin
  3. Request an Oncology consultation
  4. Start sulfadiazine and pyrimethamine

Complications of HIV
Ring-Enhancing Brain Lesions

- CNS Lymphoma
- Toxoplasmosis
- Bacterial abscess (IVDU)
- Chagoma

Less common
- Tuberculoma
- Cryptococcoma
- Histoplasmosis
- Metastatic cancer

Toxoplasmosis

Primary infection occurs after eating undercooked meat with tissue cysts or ingesting cysts that have been shed in cat feces
- Protozoal disease, reactivation
- Obtain toxoplasma IgG in baseline evaluation: [11% IgG+ US; 50-80% Europe, Latin America, Africa]
- Toxoplasmosis unusual if IgG negative
- Occurs CD4 counts < 100 cells/mm3, esp < 50
- Typical manifestation is encephalitis with multiple brain lesions, often “ring-enhancing”, basal ganglia

Toxoplasmosis

- Symptoms may be nonspecific [lethargy, altered mentation] or HA, focal neuro deficits can occur
- If toxo IgG positive, empiric treatment and assessment of response
- If safe, LP with T. gondii PCR (50% sensitivity)
- If toxo IgG negative or lack of response to empiric therapy, brain biopsy is indicated
Toxoplasmosis

- **Treatment**
  - Sulfadiazine + pyrimethamine
  - Clindamycin + pyrimethamine
  - TMP-SMX
- **Prevention:** TMP-SMX daily until CD4 > 200 cells/mm³ for > 3 mos
- Avoid raw/undercooked meat, shellfish
- Avoid changing litter box, keep cats indoors, no raw meat

CNS Lymphoma in HIV

- Nearly always due to EBV reactivation
- CD4 < 100
- MRI: Often single lesion with contrast enhancement and edema/mass effect
- Lethargy, headache, focal neurologic signs, altered mentation
- Treatment with chemotherapy and radiation, ART

Cryptococcus

- Fungus, in environment
- CD4 usually < 100
- Fever, HA, altered mentation, pneumonia, skin lesions
- Lumbar puncture with opening pressure → death related to ICP
- Cryptococcal antigen and fungal culture
- Treatment: Amphotericin B + 5-flucytosine then fluconazole; maintain normal CSF pressure
Other Brain Lesions in HIV

CMV Retinitis
- Reactivation of latent infection
- Retinal disease most common in HIV
- Usually CD4 < 50 cells/mm³
- Floaters often an initial symptom
- "Scrambled eggs and ketchup"
- Treatment with ganciclovir

Immune Reconstitution Inflammatory Syndrome (IRIS)
- Occurs after ART initiation, increase in CD4
- Systemic inflammatory syndrome with signs and symptoms identical to the infection
- Not related to uncontrolled infection, but to the improved immune response from ART
- Paradoxical worsening of infection (TB, PJP, MAC, Cryptococcus, KS)
- Short term corticosteroids may be helpful

Phillips, Clin Infect Dis 2005 41:1483
A 35 year old woman is seeing you in December for recently diagnosed HIV infection. Her CD4 count is 290 cells/mm³, HIV RNA is 62,000 copies/mL. Hepatitis testing is negative. Which vaccinations would you prescribe?

1. Human papillomavirus (HPV) vaccination
2. Hepatitis B vaccination
3. Hepatitis C vaccination
4. Intranasal influenza vaccination

### Prophylaxis in HIV

<table>
<thead>
<tr>
<th>Infection</th>
<th>Indication</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystsis jiroveci</td>
<td>CD4 &lt; 200 OR Oral Candida OR AIDS-defining illness</td>
<td>TMP-SMX 1 SS or DS daily OR 1 DS three times weekly</td>
</tr>
<tr>
<td>Toxoplasma</td>
<td>CD4 &lt; 100 &amp; Toxo IgG +</td>
<td>TMP-SMX 1 DS daily</td>
</tr>
<tr>
<td>Mycobacterium TB</td>
<td>PPD or QuantiFERON</td>
<td>INH 300mg daily x 9 months + pyridoxine</td>
</tr>
<tr>
<td>MAC*</td>
<td>CD4 &lt; 50 AND not viremically suppressed</td>
<td>Azithromycin 1200mg weekly OR 600mg twice weekly OR Clarithromycin</td>
</tr>
<tr>
<td>Vaccinations</td>
<td>HIV</td>
<td>Pneumococcal, meningococcal, hepatitis, influenza, HPV, Tdap, RD, MMR, VZV, DTaP, CD4 &lt; 250 and transmission</td>
</tr>
</tbody>
</table>


### Preventing transmission

- **Education on reducing high-risk behavior**
- **Access to care (mental health, substance use), testing**
- **ART**—can significantly decrease transmission to uninfected partner—adherence important
- **PrEP**—underutilized
  - Tenofovir-emtricitabine (Truvada®) approved for use in high-risk HIV-negative persons to prevent transmission
- **Circumcision**
  - Decreases HIV acquisition in heterosexual men
HIV Cure

H.I.V. Is Reported Cured in a Second Patient, a Milestone in the Global AIDS Epidemic

NYT, March 5, 2019

The “London patient”:
Cure vs. long-term remission?

- BMF for lymphoma
- Off ART 18 mos with no sign of virus

Berlin Patient Cure

- Chemo: TBI
- Graft
- Donor stem cells

- CCR5 WT
- HIV+ AML ART 60
- CCR5−

No plasma RNA/DNA no culturable virus off ART >10 yrs

Questions??

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