HIV

ACOI Board Review 2019

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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.; (36.9 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
- 38,000 newly diagnosed each year will present with advanced disease (16,000 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

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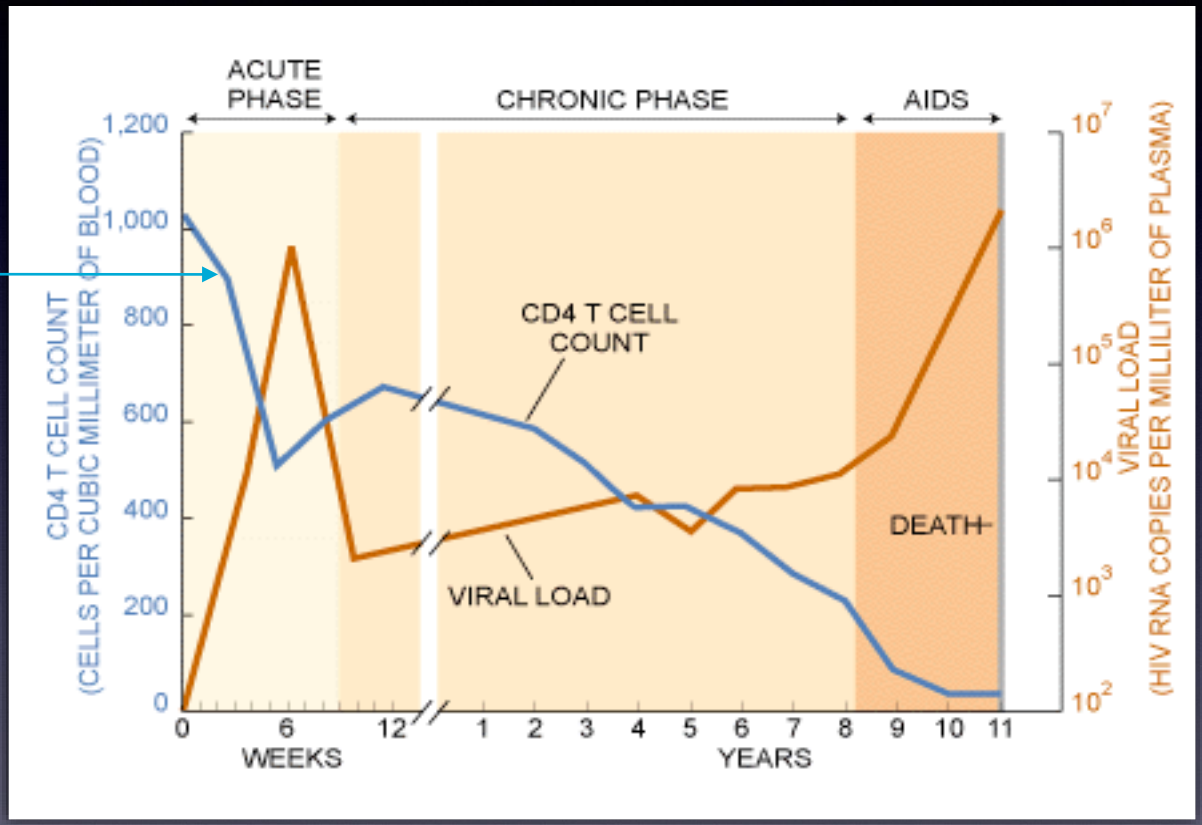
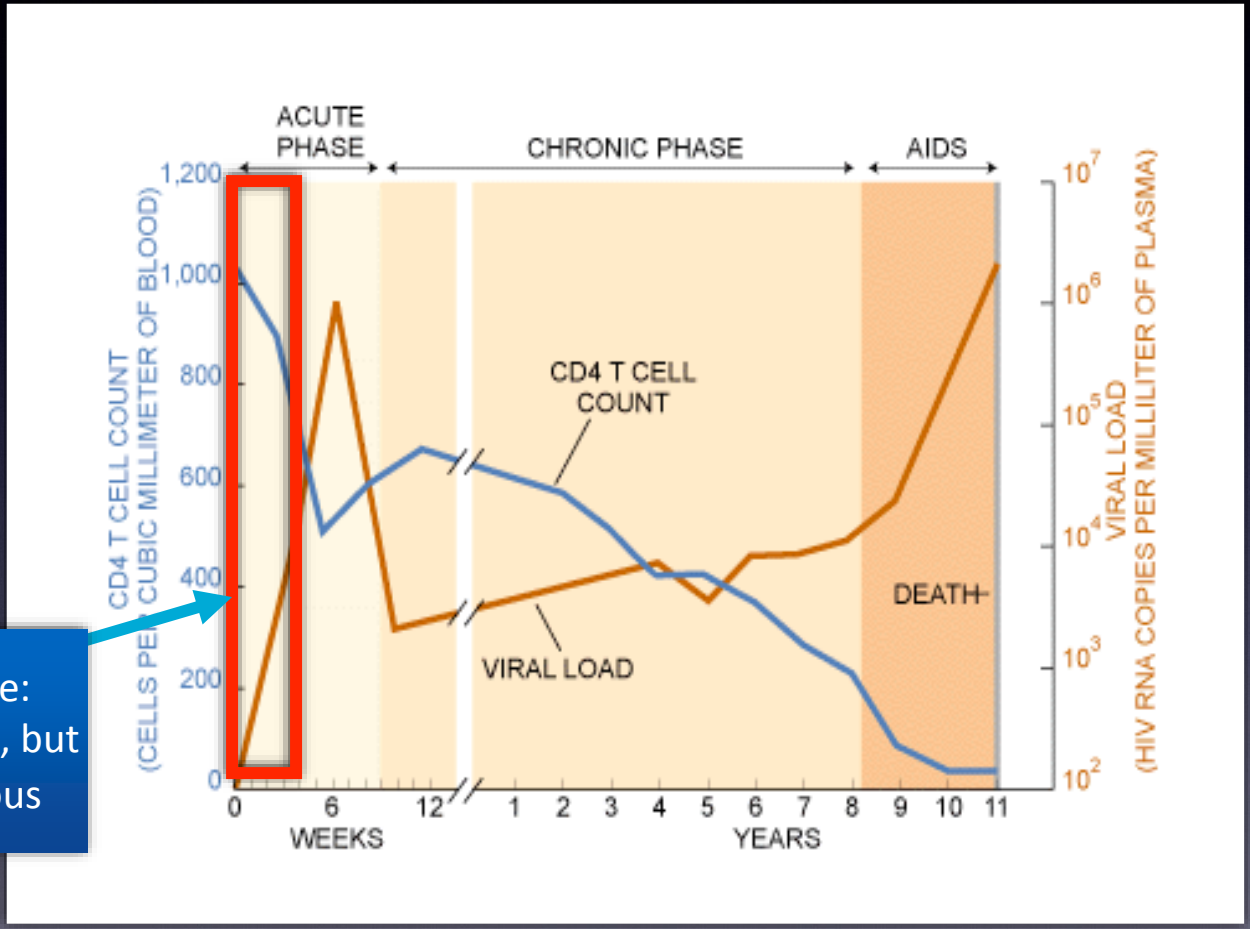


Courtesy: AETC

*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 individuals are 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 w/ “adequate” CD4 count

AIDS Defining Malignancies
(in the setting of HIV +)

- invasive cervical carcinoma
- Kaposi sarcoma
- systemic non-Hodgkin lymphoma
- primary CNS lymphoma

Kennedy-LeJeune E, Cataldo VD. N Engl J Med 2017;376:1268-1268.

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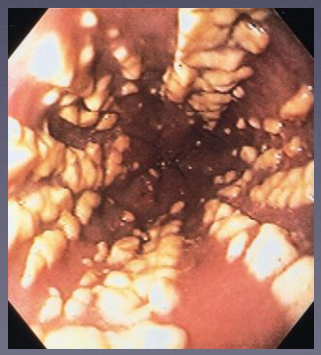
Non-AIDS Defining Malignancies Increased in HIV + Individuals

- lung
- liver
- kidney
- anus
- head & neck
- skin, including melanoma
- Hodgkin's lymphoma

O I's/neoplasms relative to CD4 counts

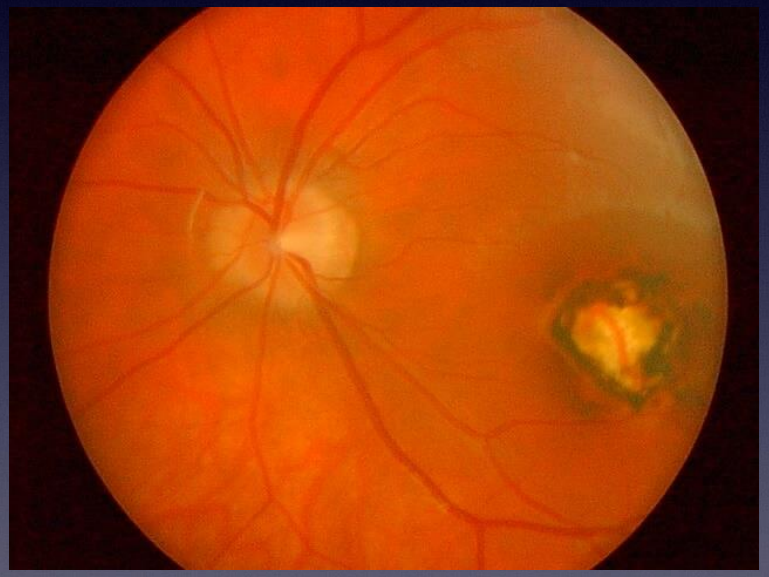
200 - 500 or above

- 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 - PJP
  - Disseminated TB
  - Esophageal candidiasis
  - Cryptococcal meningitis; PML
  - Cryptosporidium
  - Non-Hodgkin’s lymphoma
  - Disseminated histoplasmosis, coccidioidmycosis
  - wasting; dementia
- < 100
  - CNS toxo, lymphoma; disseminated CMV, MAC

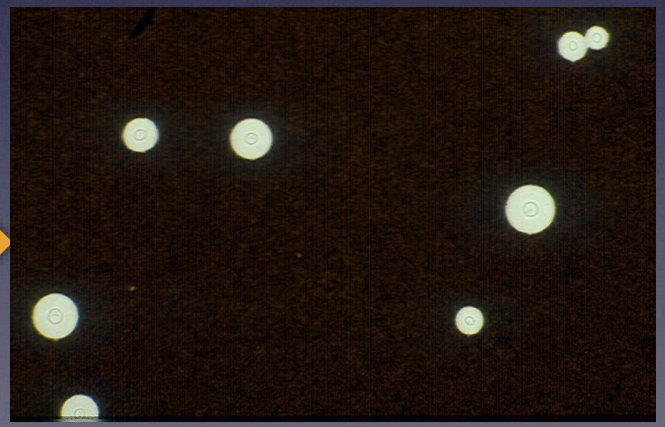
CMV



Toxo: intensely white focal lesions w/ vitreous inflammation

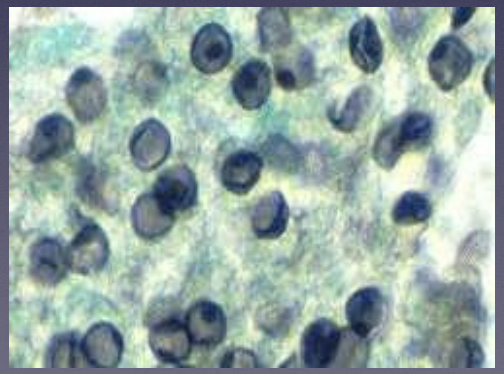
Cryptococcal Meningitis

- Subacute, progressive headache; w/ or w/o fever
- Few to no WBC's in CSF
- + india ink, cryptococcal Ag
- Tx: Amphotericin B +/- flucytosine, fluconazole
- T cell deficiencies



Still common: PCP (PJP)(P. jirovecii)

- 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); DFA, PCR on sputum®
- Tx: trimethoprim/sulfa; pentamidine if allergic
- Steroids if pO2 < 70 (may not apply to HIV neg pts)

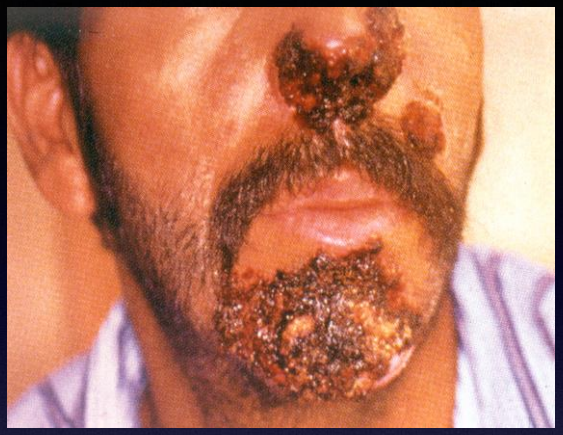


See JAMA: June 24, 2009

Warning:

- 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)



HSV

Kaposi’s sarcoma (HSV-8)

Bacillary Angiomatosis (Bartonella sp.)

CMV Esophagitis

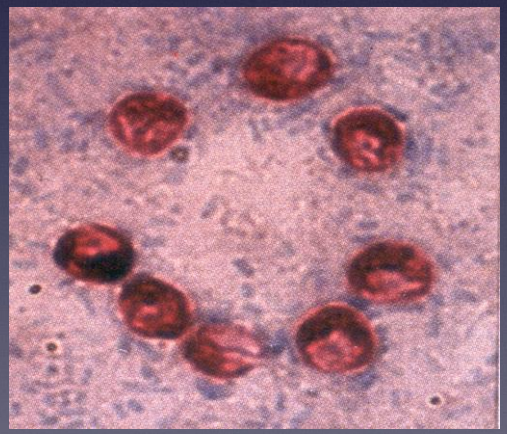
(D/D: CMV, HSV, Candida, apthous ulcer)

Hairy Leukoplakia
(EBV)

GI Presentations

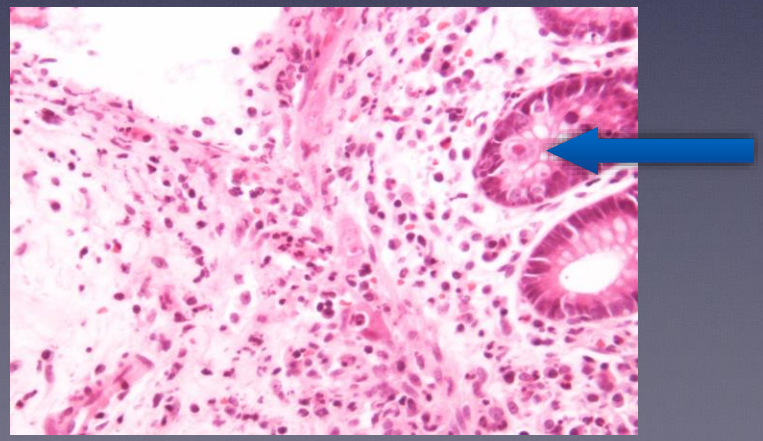
(Note: Tx will most always emphasize treating underlying HIV)

- 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

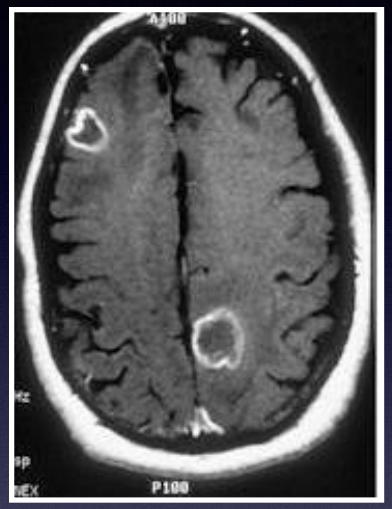


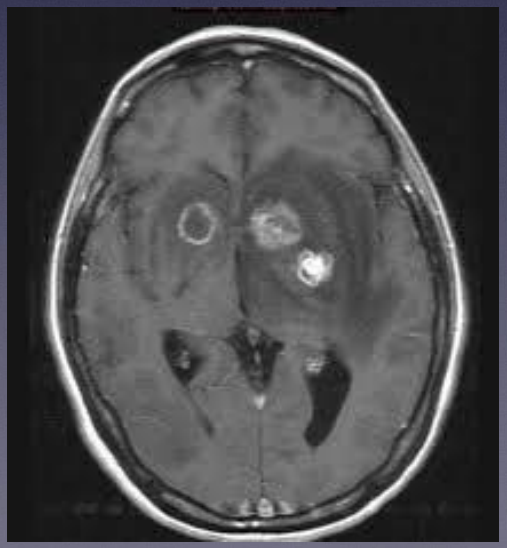
Tx: Ganciclovir

Focal CNS syndromes

Toxoplasmosis

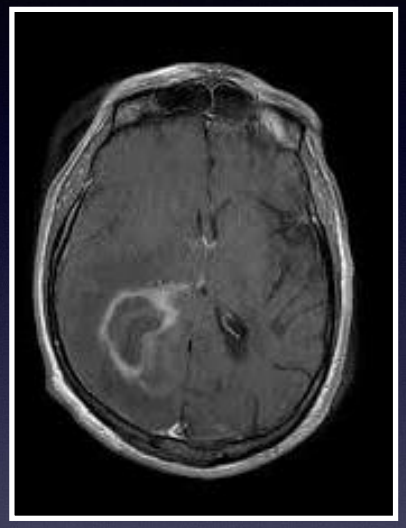
- Acute w/ multiple contrast + lesions w/ + serology (basal ganglia most often)
- Fever
- Mass effect





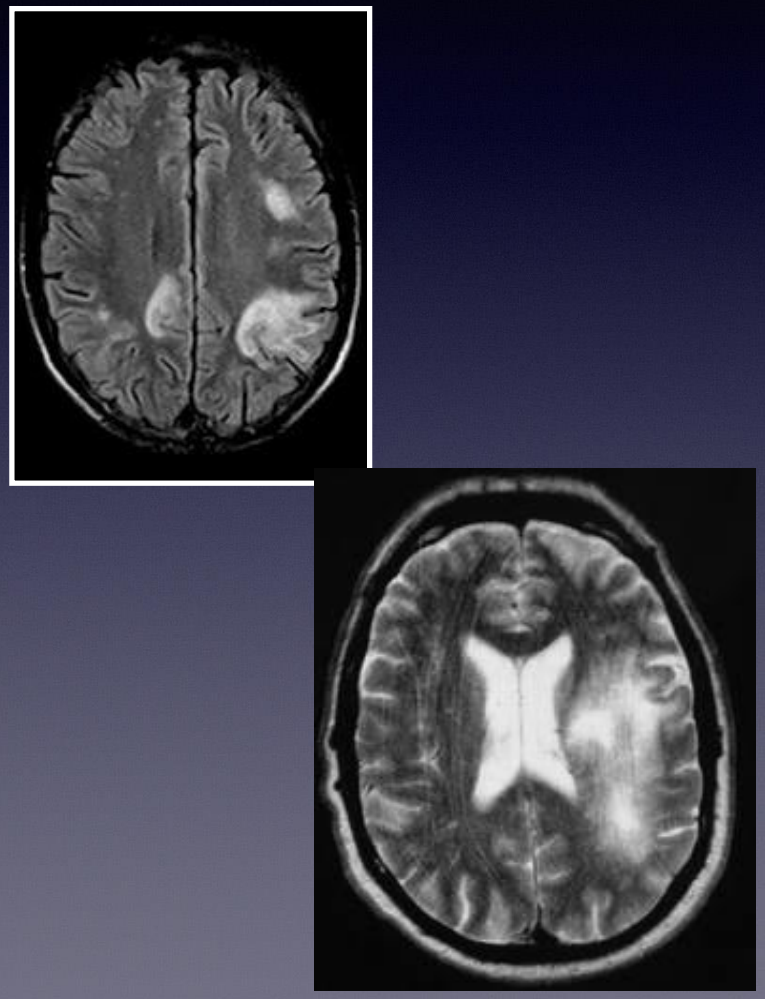
Focal CNS syndromes

- 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*

PCP	CD4 < 200	TMP-SMX
TB	Previous + PPD** or +PPD > 5mm	INH x 9 mos (and others)
Toxoplasmosis	+ serology w/ CD4 < 100	TMP-SMX
M. avium complex	CD4 < 50	azithromycin or clarithromycin

*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/ their 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?
(HHS Guidelines - Oct. 25, 2018)

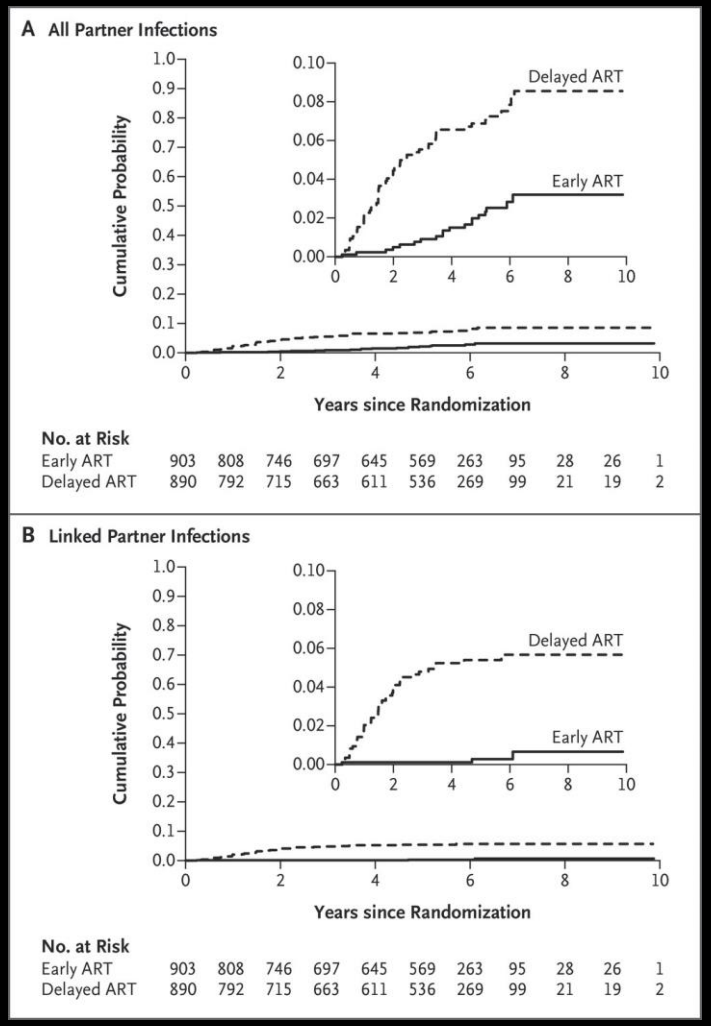
All - upon diagnosis,
including “Test and Treat” same day Rx

Benefits of Early Treatment

- Decrease in transmission (undetectable viremia eliminates 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”



Cohen MS et al. N Engl J Med 2016;375:830-839.

The NEW ENGLAND JOURNAL of MEDICINE

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

U = U

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

Treatment

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)

Initial RX of Treatment-Naïve Patients HHS Guidlines, Oct. 2018

- An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (also known as a booster; the two drugs used for this purpose are cobicistat and ritonavir).

- A pregnancy test should be performed for those of childbearing potential prior to the initiation of antiretroviral therapy (AIII).

The Panel on Antiretroviral Guidelines for Adults and Adolescents classifies the following regimens as Recommended Initial Regimens for most people with HIV (October, 2018):

- Bictegravir/tenofovir alafenamide/emtricitabine (AI) [Biktarvy®]
- Dolutegravir/abacavir/lamivudine—only for patients who are HLA-B*5701 negative (AI) [Triumeq®]
- Dolutegravir (DTG) [Tivicay®] plus tenofovir/emtricitabine (AI) [Truvada®]
- Raltegravir [Isentress®] plus tenofovir/emtricitabine (BI for tenofovir disoproxil fumerate [Truvada®], BII for tenofovir alafenamide [Descovy®])

- Preliminary data have raised concerns about an increased risk of neural tube defects in infants born to people who were receiving DTG at the time of conception.

New:

- Dolutegravir (Tivicay®), or in any combination (Triumeq®), contraindicated if at risk of becoming pregnant and in early pregnancy
  - increased neural tube defects if taken prior to pregnancy and **continuing at time of conception**
  - if initiated in early pregnancy, no increase in neural tube defects; however, currently not recommended
- Unknown if this is unique to dolutegravir, of if this is a drug class effect

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 disoproxil (Viread ®) (or Truvada ® as combination Rx)
- Jaundice (indirect hyperbilirubinemia) w/ atazanivir (Reyataz ®)
- Dolutegravir (Tivicay®) - neural tube defects if taken at time of conception

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-inflammatories and continue ART

Prevention:

- "Treatment as Prevention" - both of infection and complications of same
- Pre-exposure Prophylaxis ("PrEP"):
  - Once daily Truvada ®, (? Descovy ® in future)
  - 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!
    - 44.6increased incidence of syphillis!!!

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

- http://www.aidsinfo.nih.gov - Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Oct. 25,2018
- Cohen MS et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. N Engl J Med 2016;375:830-839.
- Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. The INSIGHT START Study Group. N Engl J Med 2015; 373:797-807
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- 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!