HIV

ACOI Board Review 2020

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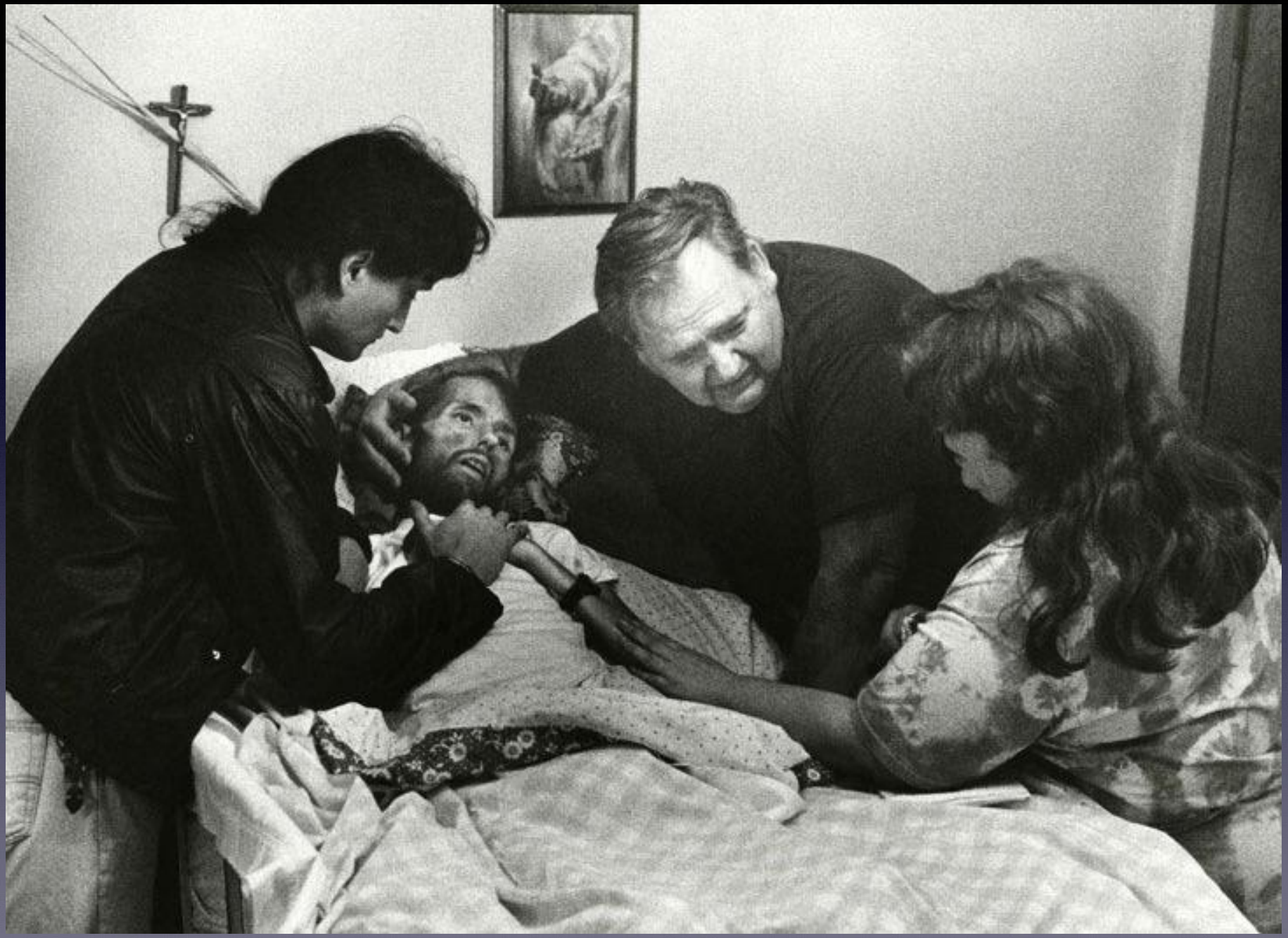
David Kirby's mother, Kay, holds a photograph of her son -- taken by Ohio photographer Art Smith -- before AIDS took its toll.
Therese Frare



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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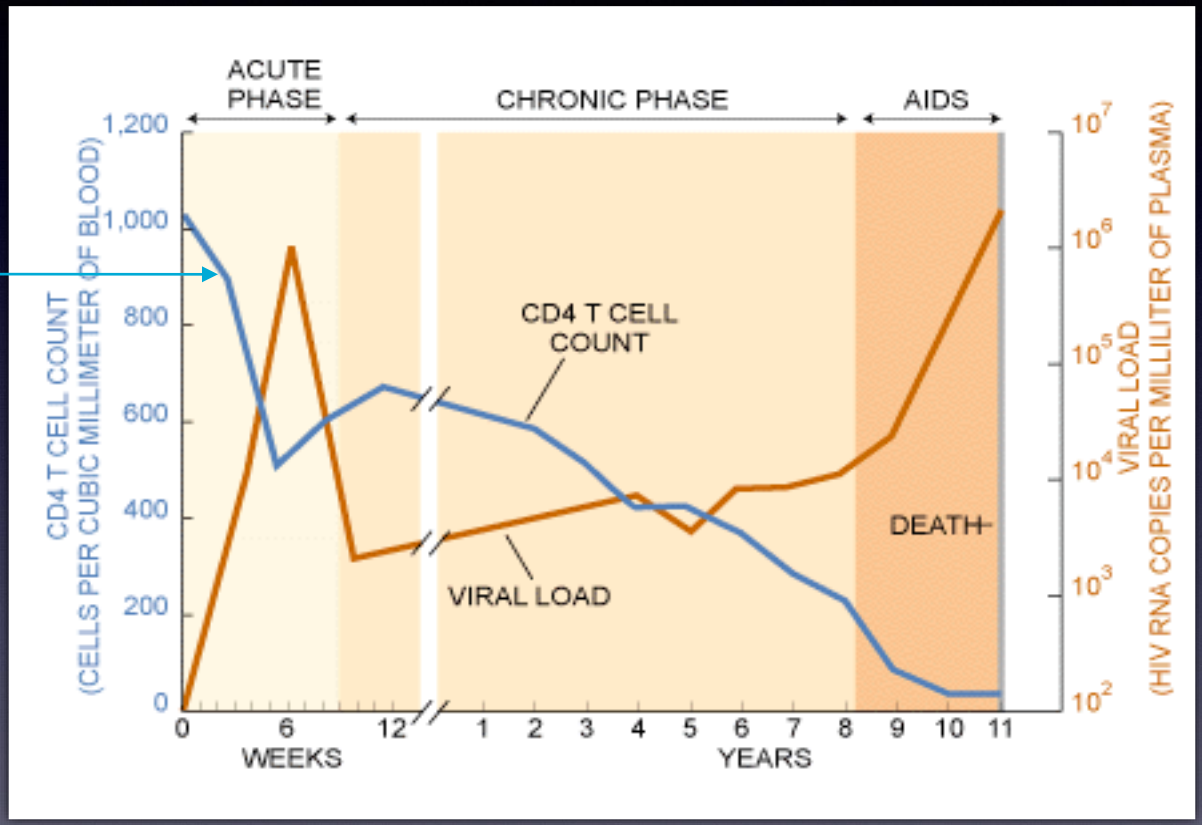
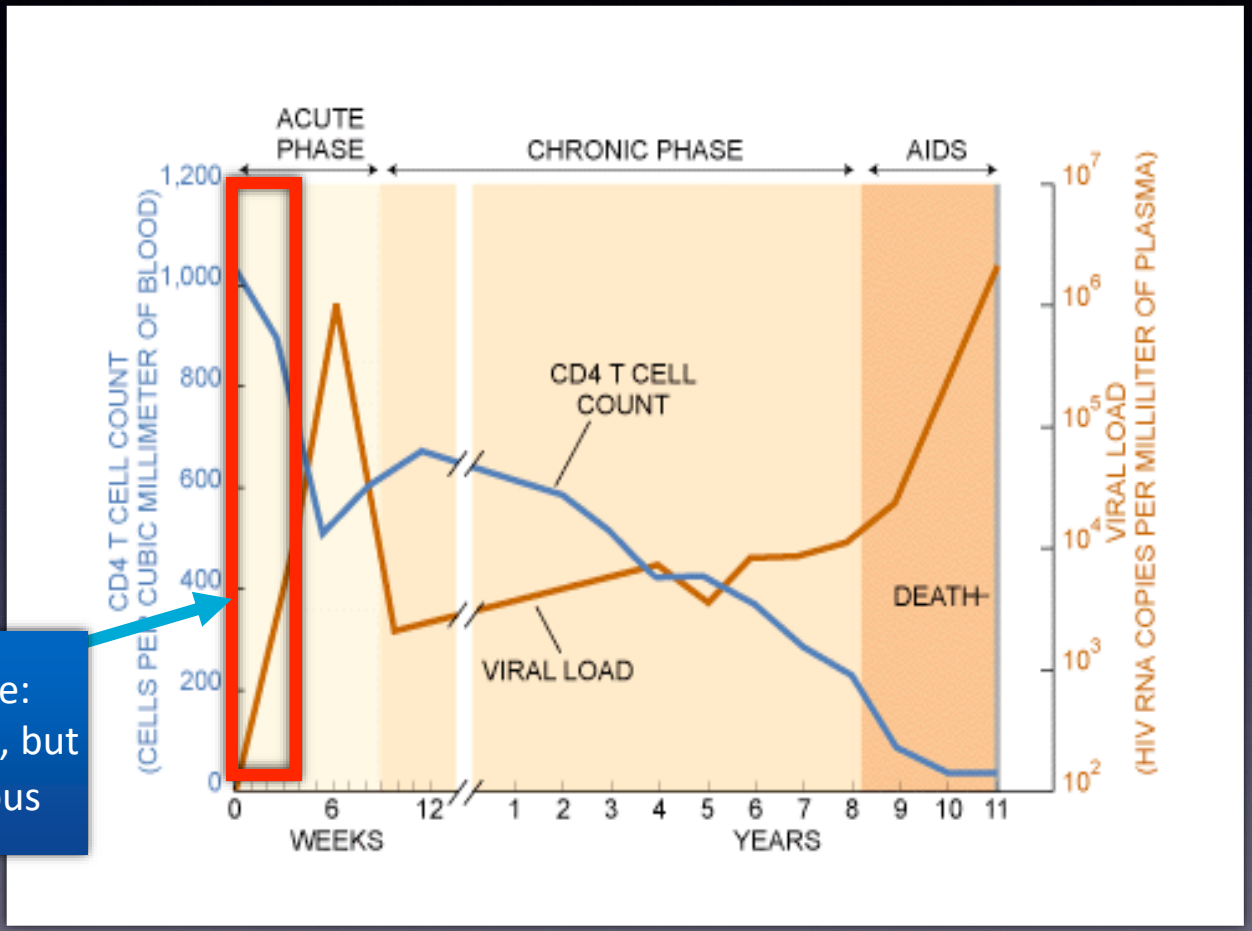


Courtesy: AETC

*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:

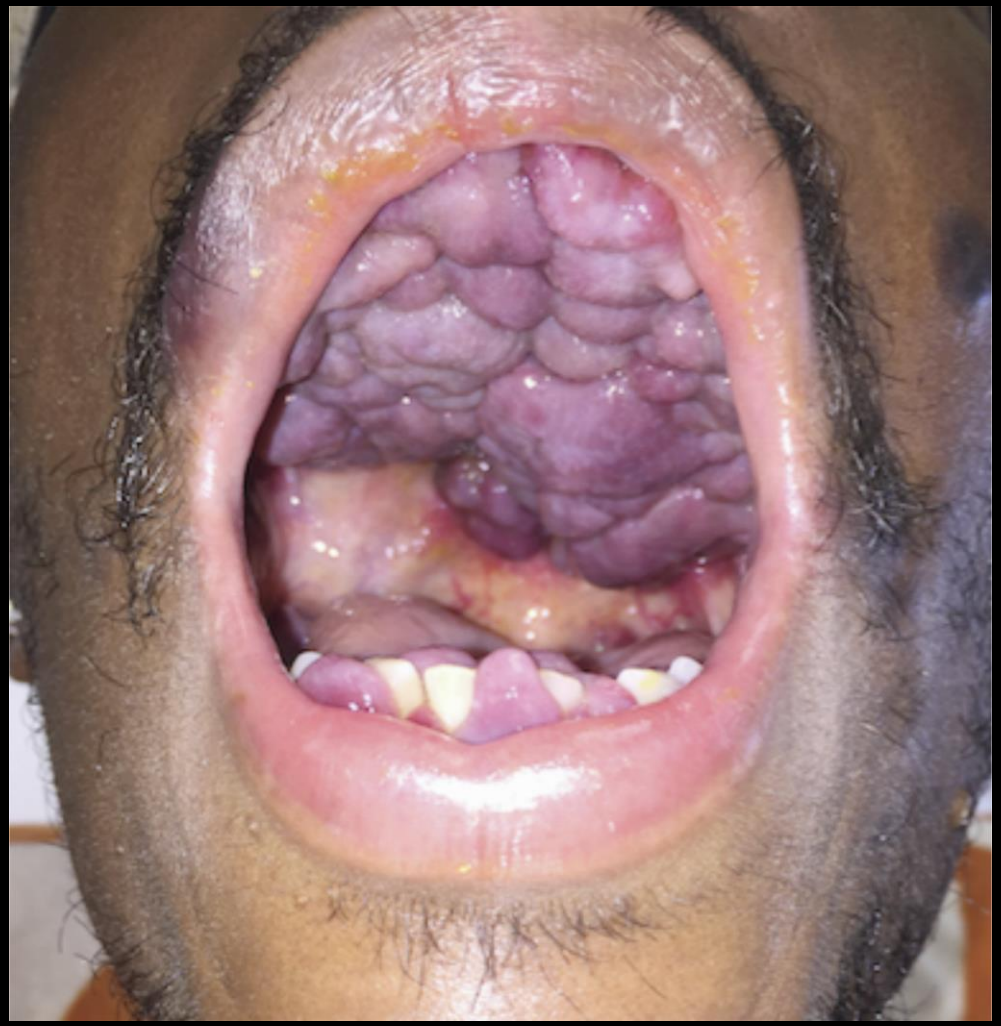
- Unusual presentation of a common illness
  - Pneumococcal pneumonia w/ bacteremia in a young person
  - Salmonella, shigella, campylobacter bacteremia
  - Severe or recurrent thrush, vaginal candidiasis
- Presentation of an unusual illness
  - Uncommon dx, e.g. cryptococcal meningitis
  - More advanced/severe 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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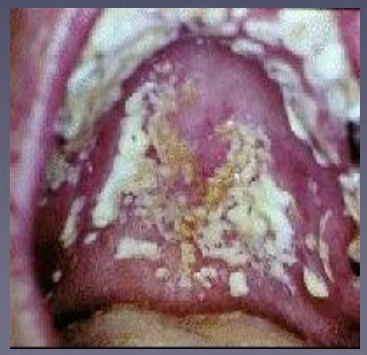
Non-AIDS Defining Malignancies Increased in HIV + Individuals

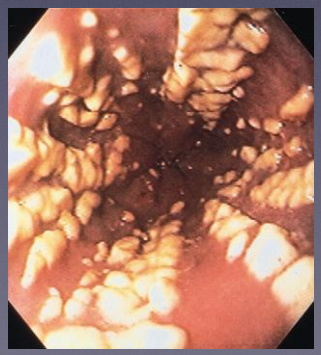
- lung
- liver
- kidney
- anus
- head & neck
- skin, including melanoma
- Hodgkin’s lymphoma

O I's/neoplasms relative to CD4 counts

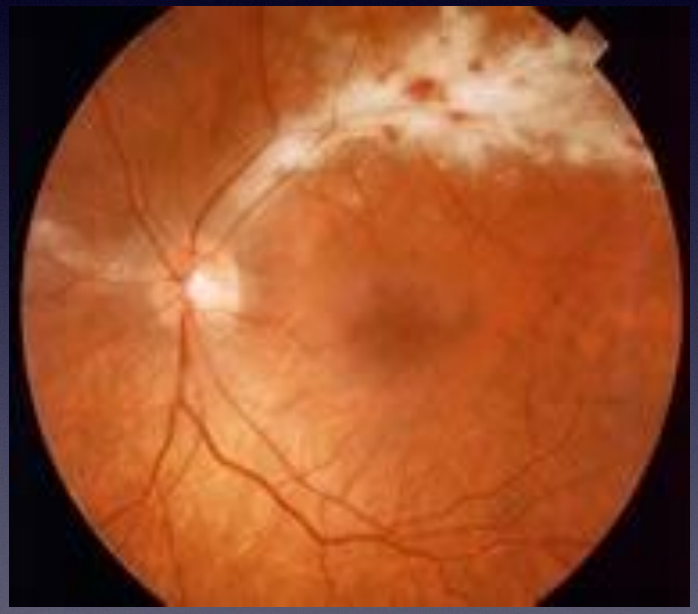
200 - 500 or above

- pulmonary TB
- bacterial pneumonia (pneumococcus most common)
- H. zoster
- cervical CA, Kaposi's sarcoma, Hodgkin's lymphoma
- oral/vaginal candidiasis; anemia; ITP; nephropathy (FSGS)

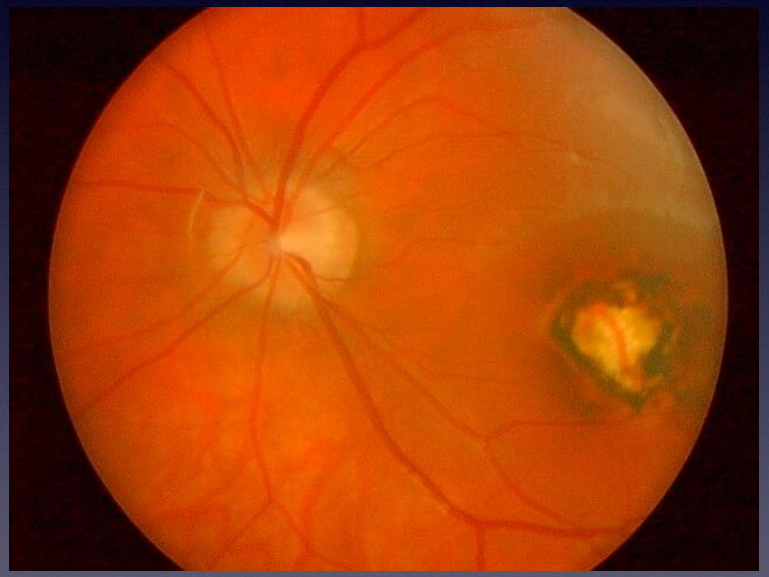




- < 200 - PJP
  - Disseminated TB
  - Esophageal candidiasis
  - Cryptococcal meningitis; PML
  - Cryptosporidium
  - Non-Hodgkin's lymphoma
  - Disseminated histoplasmosis, coccidioidmycosis
  - wasting; dementia
- < 100
  - CNS toxoplasmosis, lymphoma; disseminated CMV, MAC



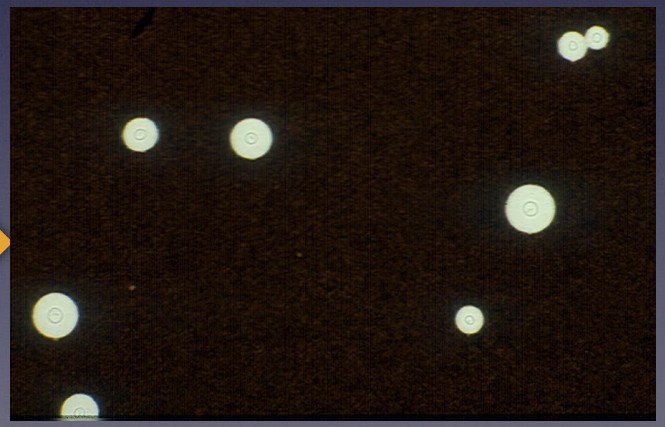
CMV



Toxo: intensely white focal lesions w/ vitreous inflammation

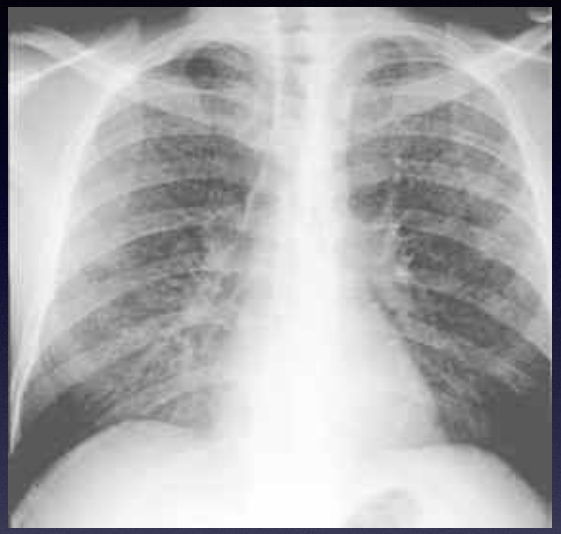
Cryptococcal Meningitis

- 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

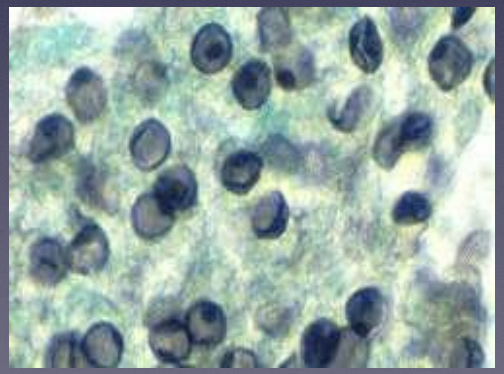


Still common: PCP (PJP)(P. jirovecii)

- 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®



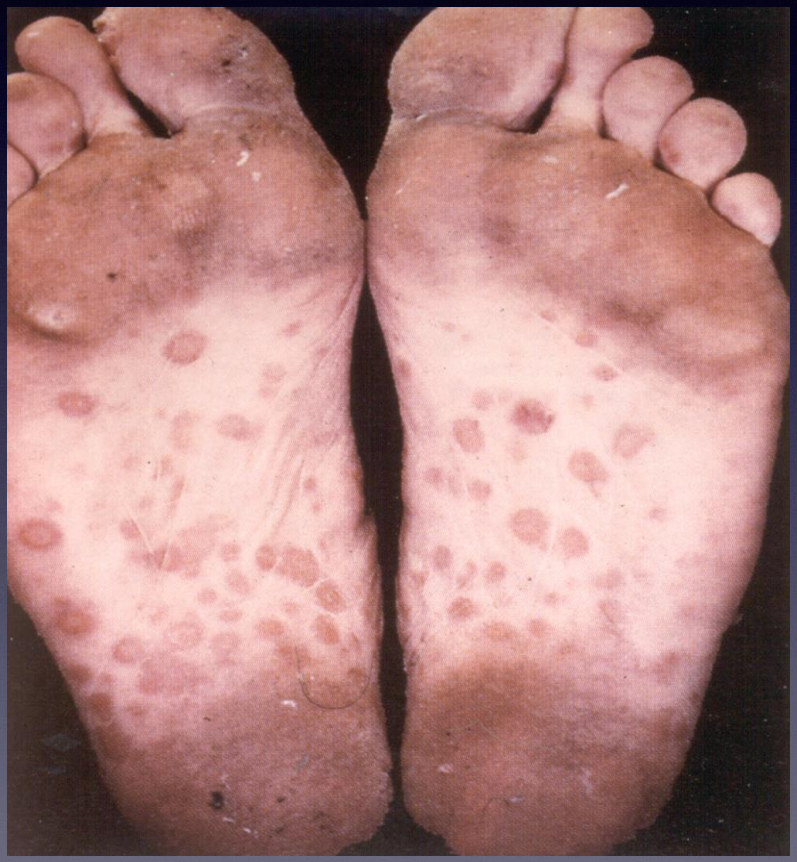
- Tx: trimethoprim/sulfa; pentamidine if allergic
- Steroids if pO2 < 70 (may not apply to HIV neg pts)

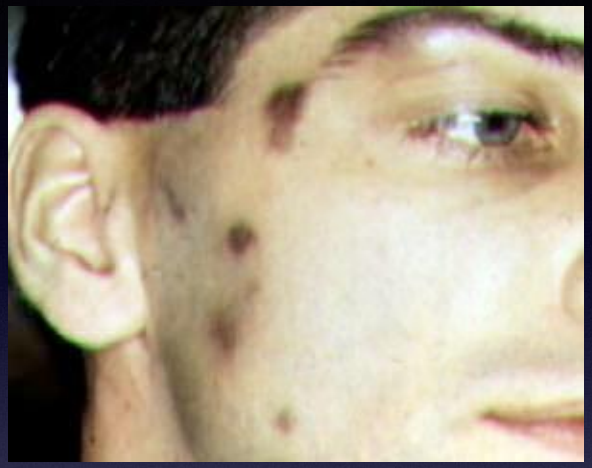
See JAMA: June 24, 2009

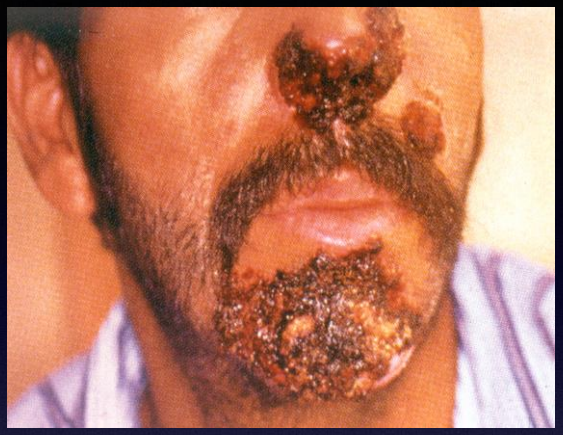
Warning:

- 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

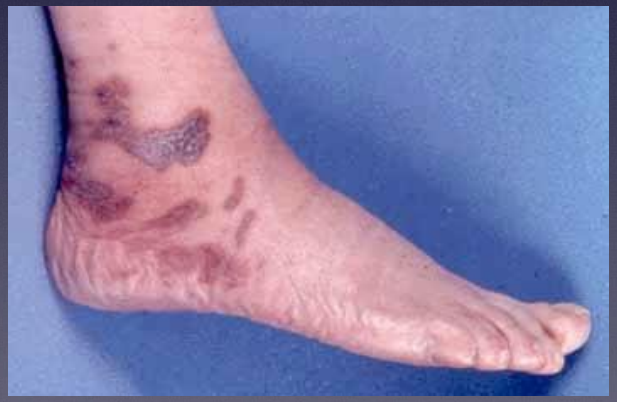
Other Clues:
(if one STD, r/o others)



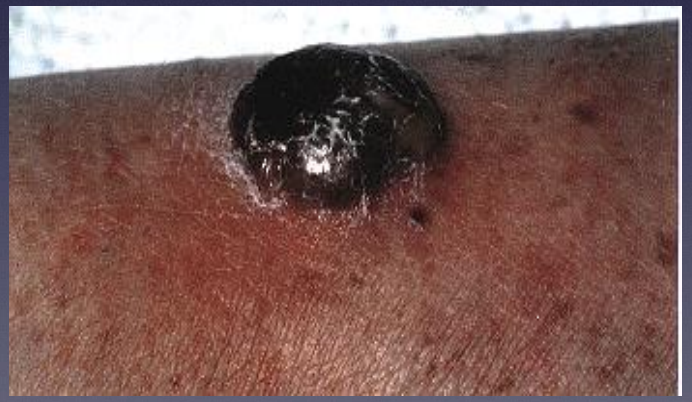




HSV



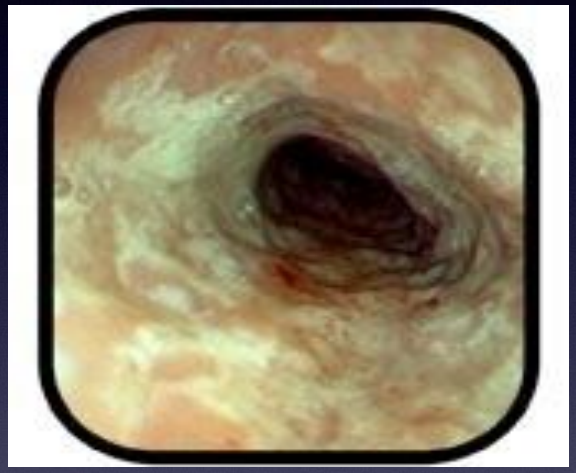
Kaposi’s sarcoma (HSV-8)



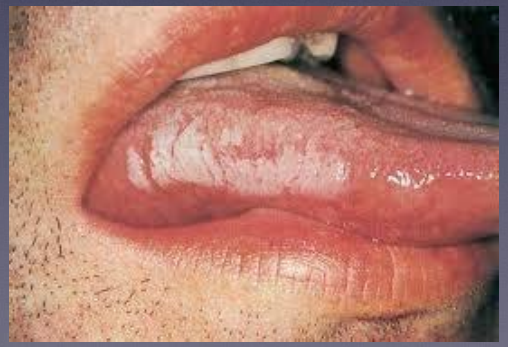
Bacillary Angiomatosis (Bartonella sp.)

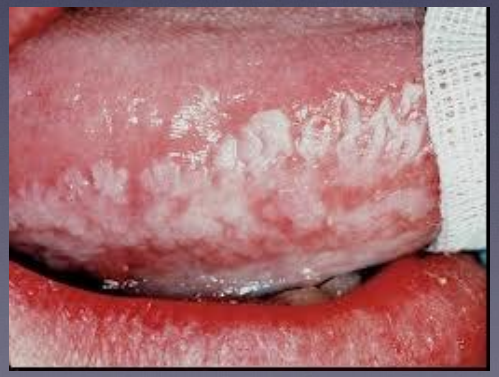
CMV Esophagitis

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



Hairy Leukoplakia
(EBV)

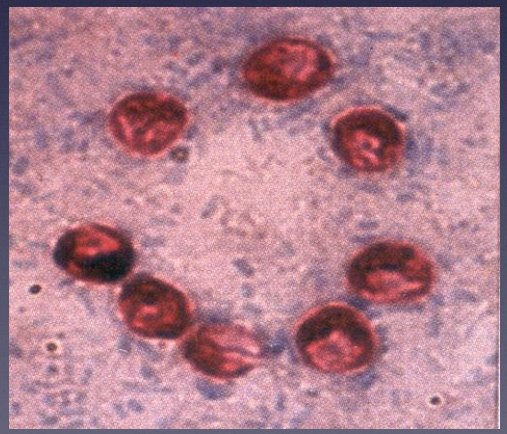




GI Presentations

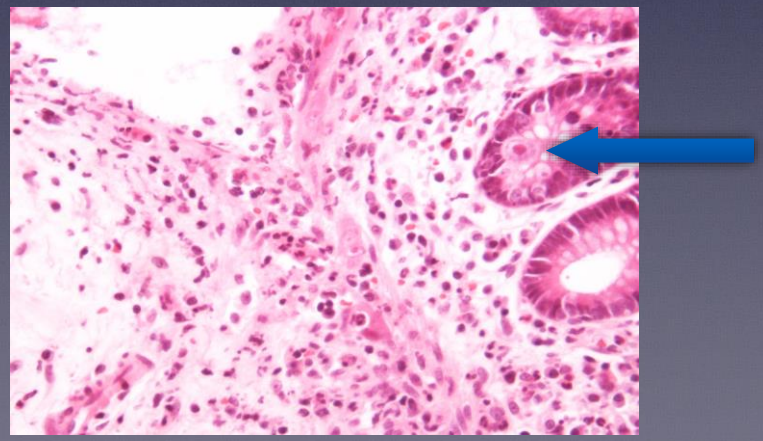
(Note: Tx will most always emphasize treating underlying HIV)

- 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

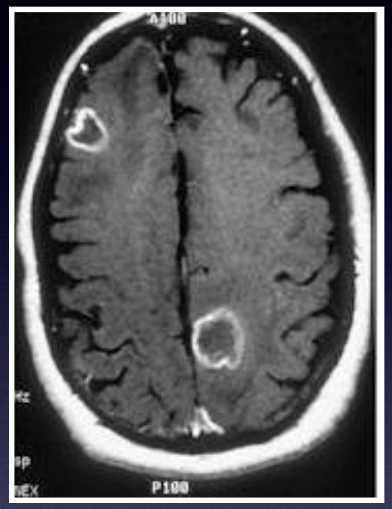


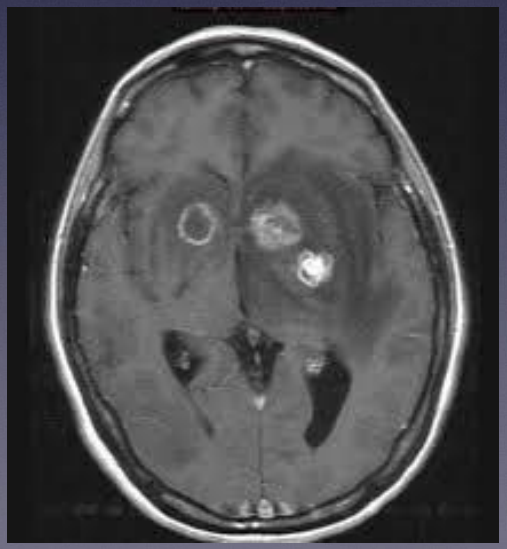
Tx: Ganciclovir

Focal CNS syndromes

Toxoplasmosis

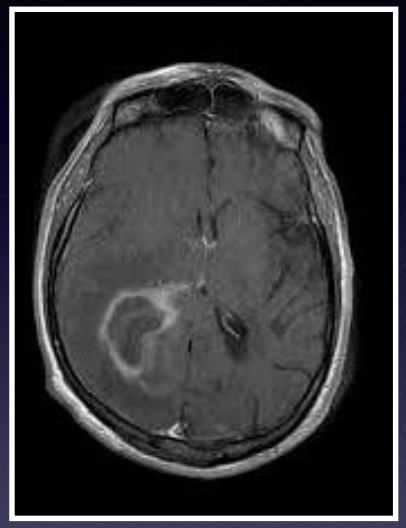
- Acute w/ multiple contrast + lesions w/ + serology (basal ganglia most often)
- Fever
- Mass effect

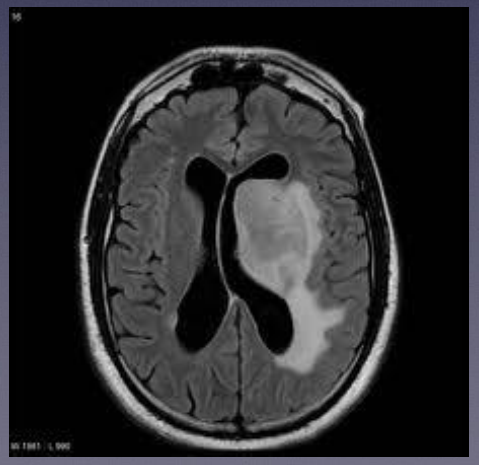




Focal CNS syndromes

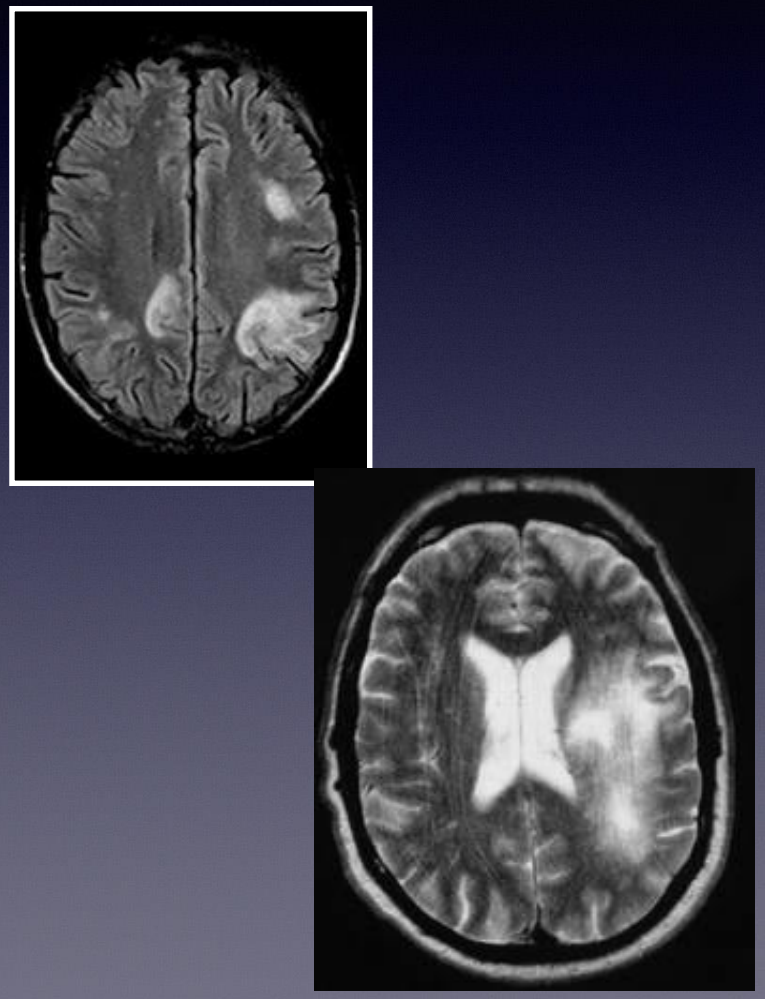
- Lymphoma (Usually diffuse, large B-cell)
  - Subacute presentation
  - Usually single contrast + lesion
  - Mass effect
  - Usually no fever
  - + PCR for EBV (?)





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 - Dec. 2019)

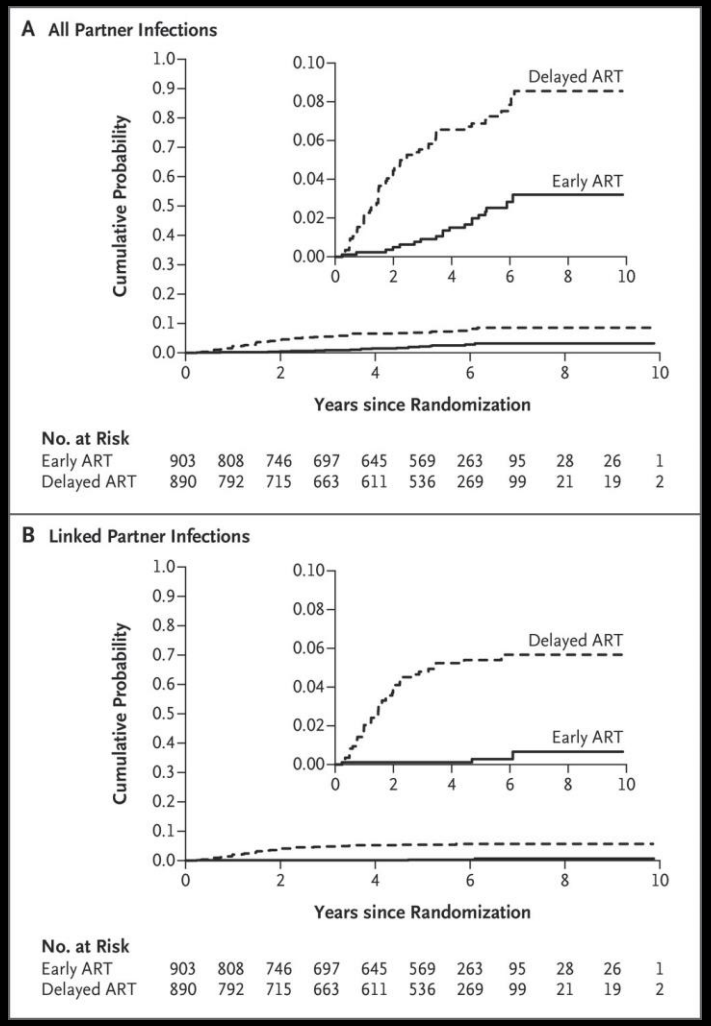
All - upon diagnosis,
including “Test and Treat” same day Rx

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.

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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

(abbreviated) Recommended Initial Antiretroviral Regimens for most people with HIV (December, 2019 Guidelines):

- Bictegravir/tenofovir alafenamide/emtricitabine (AI) [Biktarvy®]
- Dolutegravir(DTG)/abacavir/lamivudine—only for patients who are HLA-B*5701 negative and w/o chronic HBV coinfection (AI) [Triumeq®]
- Dolutegravir [Tivicay®] plus emtricitabine or lamivudine plus tenofovir alafinamide or tenofovir disoproxil fumerate(AI)
- Dolutegravir plus lamivudine[Dovato®]) except for individuals w/ VL > 500,000, confection with HBV (A1)

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

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 ® but not yet in Guidelines)
  - Controversial, expensive, but effective if taken as rx'd ("PrEP on demand"?)
  - (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 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

Good Luck!