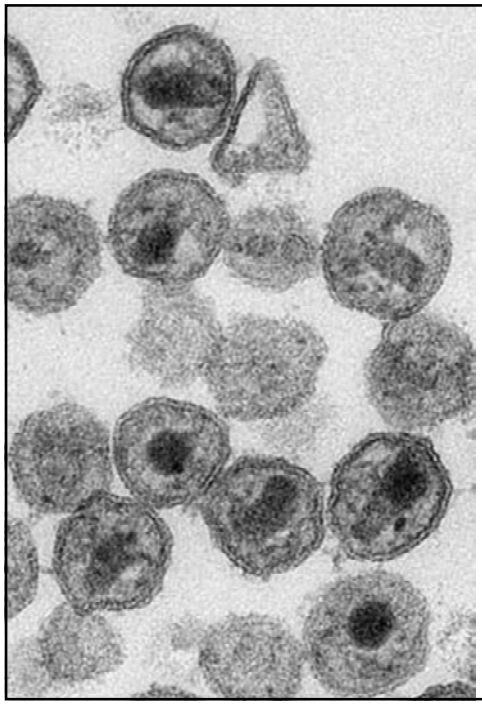
HIV for Hospitalists

Paul E. Sax, M.D.
Clinical Director, Division of Infectious Diseases
Brigham and Women's Hospital
Professor of Medicine, Harvard Medical School
psax@bwh.harvard.edu
@PaulSaxMD

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL



HIV for Hospitalists: Overview

- A refresher on HIV testing
- Key concepts for most people with HIV admitted to the hospital
- What you need to know about antiretroviral therapy (ART)
- Case-based, whenever possible

Electron micrograph of HIV
Science, 1984

Case

- 65-year-old woman admitted with confusion – got lost while driving home, police brought her to the hospital
- Family reports she's had subacute memory decline over past year
- PE normal except for neuro exam – moderate memory impairment
- HIV test done as part of a broad screen for early-onset neurocognitive disorder
- No reported HIV risk factors; born and raised in Boston area
- MRI: mild generalized atrophy

*Question

?

- HIV testing sent, with these results:
  - HIV 1/2 antigen/antibody assay – REACTIVE
  - HIV differentiation assay – NEGATIVE
  - Final interpretation – INDETERMINATE

What is the most likely outcome of her HIV work up?

A. HIV associated neurocognitive disease (HAND), or "AIDS dementia"
B. Acute (primary) HIV infection in the "window" period
C. Encephalopathy due to HIV-2
D. False-positive HIV 1/2 antigen/antibody test

*Question

- HIV testing sent, with these results:
  - HIV 1/2 antigen/antibody assay – REACTIVE
  - HIV differentiation assay – NEGATIVE
  - Final interpretation – INDETERMINATE

What is the most likely outcome of her HIV work up?

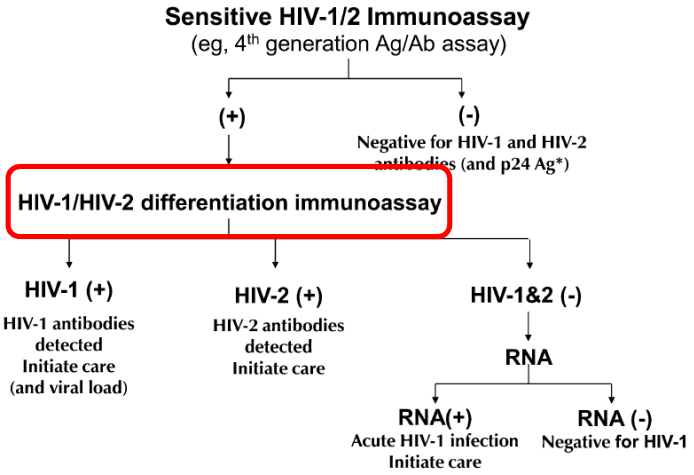
A. HIV associated neurocognitive disease (HAND), or "AIDS dementia"
B. Acute (primary) HIV infection in the "window" period
C. Encephalopathy due to HIV-2
D. False-positive HIV 1/2 antigen/antibody test

CDC Recommendations: Current HIV diagnostic testing algorithm

- Sequence of tests recommended
  - Initial screening tests to detect HIV p24 antigen *and* HIV antibody (4th Generation HIV screen)
  - If positive, confirmatory HIV-1/HIV-2 antibody differentiation test
  - Use of antibody-only testing with a confirmatory Western blot no longer recommended
- Change to antigen/antibody screen shortens window period of screening test by 3-4 weeks

CDC and Prevention and Association of Public Health Laboratories. Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. Available at http://stacks.cdc.gov/view/cdc/23447. Published June 27, 2014. Accessed February 17,2015.

Algorithm for HIV Testing

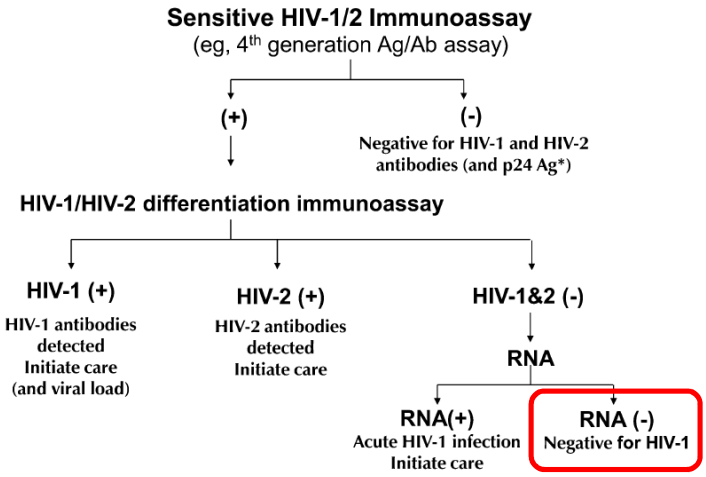


www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf; June 27, 2014.

Case Outcome

- HIV RNA (viral load): < 20 copies/mL
- Interpretation: False-positive HIV screening test

Interpretation: False-Positive Screening Test



www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf; June 27, 2014.

HIV testing: Why so many indeterminate results?

- Specificity of 4th Generation screening test: 99.4%
  - As many as 4/1000 test results may be false-positive (HIV RNA negative)
  - Prevalence of "acute" HIV in most populations tested is 2/10,000 or lower
  - In low-risk cases, a false-positive screen is more common than acute HIV
- False-positive rate of *both* screening test plus differentiation assay tests is 1/200,000 or lower

If you test a low-risk patient and result is indeterminate, check a viral load – the reactive screen is most likely a false positive.

Branson B (CDC); HIV Specialist 2014.

Case

- A 45-year-old man is seen urgently with fever, sore throat, rash, and diarrhea for 7-10 days
- He reports sexual activity with several men within the previous month, does not always use condoms; was on PrEP but discontinued 2 years ago
- PE: T 101.5; cervical adenopathy; rash; mild neck stiffness
- WBC 2.9 (8% atypical lymphs)
- Heterophile positive
- HIV testing sent

*Question

?

- HIV testing sent, with these results:
  - HIV 1/2 antigen/antibody assay – REACTIVE
  - HIV differentiation assay – NEGATIVE
  - Final interpretation – INDETERMINATE *[same as previous case]*
- What is the most likely explanation?

A. False-positive HIV screen due to mononucleosis
B. False-negative HIV 1/2 differentiation assay due to window period
C. Laboratory error
D. Lyme disease, as this is New England

*Question

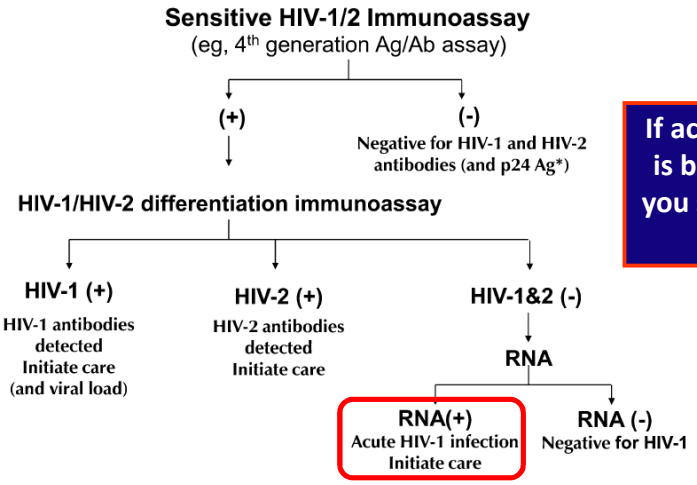
- HIV testing sent, with these results:
  - HIV 1/2 antigen/antibody assay – REACTIVE
  - HIV differentiation assay – NEGATIVE
  - Final interpretation – INDETERMINATE *[same as previous case]*
- What is the most likely explanation?

A. False-positive HIV screen due to mononucleosis
B. False-negative HIV 1/2 differentiation assay due to window period
C. Laboratory error
D. Lyme disease, as this is New England

Case Outcome

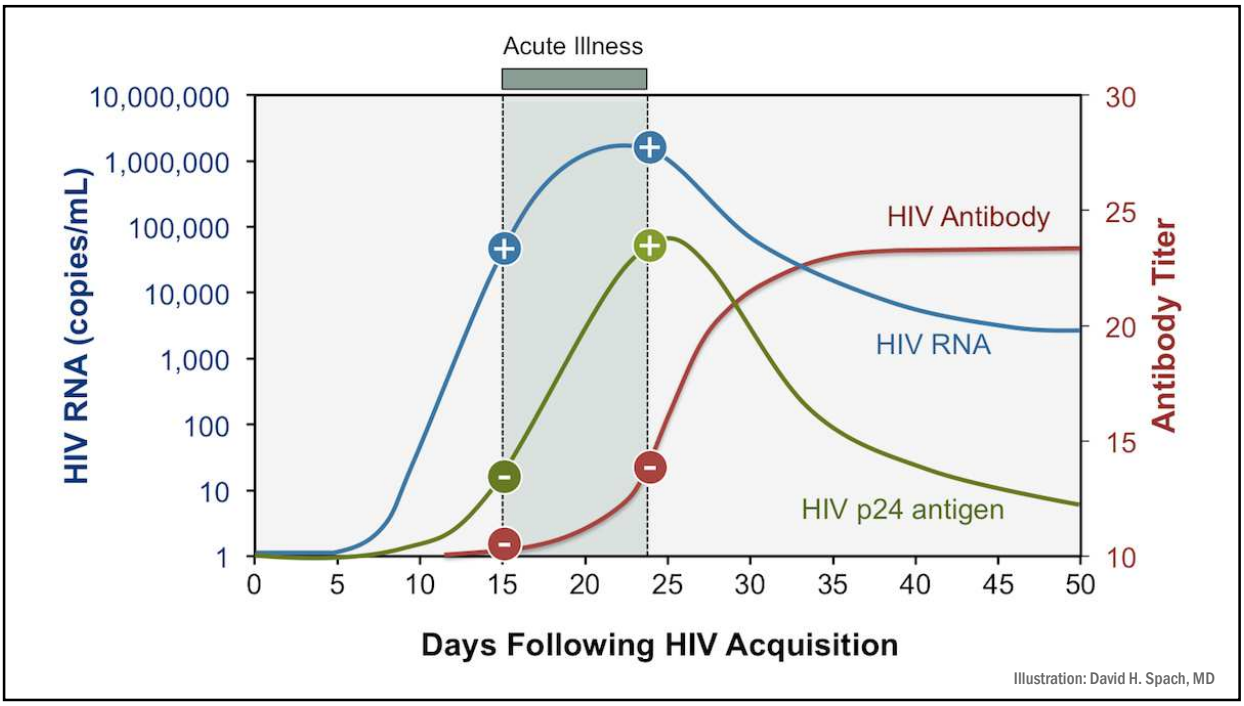
- HIV RNA > 10,000,000 copies/mL
- CD4 cell count 280 (14%)
- Diagnosis: Acute HIV with multi-system disease
- Started on HIV therapy the day the HIV RNA returned
- Discharged on hospital day 4

Interpretation: Acute HIV infection



If acute HIV infection is being considered, you should also order a viral load.

www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf; June 27, 2014.



Current HIV testing algorithm – Good, but not perfect

- Weaknesses:
  - Many reactive screens in low-risk patients are false-positives
  - The confirmatory test – the antibody-based HIV differentiation assay – may miss acute HIV infection
- The solution: HIV RNA (viral load) *should* be the confirmatory test
- Barriers
  - Most quantitative viral load tests validated for plasma, not serum
  - Limited number of HIV RNA tests FDA-approved for diagnosis
  - Molecular testing is much more expensive than antibody tests

Branson BB. Infect Dis Clin North Am. 2019 Sep;33(3):611-628.

Acute HIV: Most common clinical features

Features (%)	Overall ($n = 378$)
Fever	75
Fatigue	68
Myalgia	49
Skin rash	48
Headache	45
Pharyngitis	40
Cervical adenopathy	39
Arthralgia	30
Night sweats	28
Diarrhea	27

Adapted from Daar ES, et al. Current Opinion in HIV and AIDS 2008.

Acute HIV – Many clinical manifestations, wide range of severity

- Series of 290 people with acute HIV
- "Mononucleosis" illness in 70%
- Diverse other symptoms encountered, with multiple organ systems involved – GI tract particularly common
- Only 38% had diagnosis made at initial encounter
- 17% sick enough to warrant hospitalization
- **Consider acute HIV in any at-risk person with unexplained febrile illness**

Braun Dl, et al. Clin Infect Dis 2015.

Suspected Diagnosis	Frequency (%)
Acute retroviral syndrome	112 (38)
Viral infection other than HIV (eg, mononucleosis infectiosa)	49 (17)
Routine HIV test	35 (12)
Bacterial infection (eg, Streptococcal pharyngitis)	16 (6)
Gastroenteritis	11 (4)
Sexually transmitted infection (eg, syphilis)	10 (3)
Other[a]	55 (19)

"Other": Endocarditis, diverticulitis, appendicitis, meningitis, malignant lymphoma, Lyme disease, others.

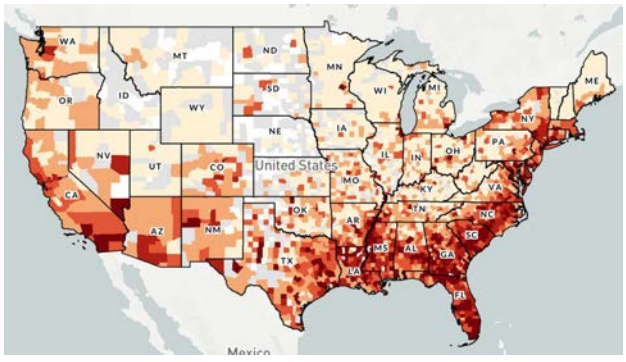
Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

- One-time testing for low-risk patients
- **Annual or more frequent testing for high-risk patients:**
  - MSM (at least yearly for all sexually active MSM)
  - People who inject drugs
  - Persons who exchange sex for money or drugs
  - Sex partners of HIV-infected, bisexual, IDU persons
  - Persons who have sex with partners whose HIV status is unknown
  - Pregnant women
  - Patients seeking evaluation or treatment for STD or who had contact with a partner with a STD should be routinely screened for HIV (regardless of known or suspected risk behavior for HIV infection)

Moyer VA. *Ann Intern Med*. 2013;159(1):51-60; Branson BM, et al. *MMWR Recomm Rep*. 2006;55(RR-14):1-17; CDC. *MMWR Morb Mortal Wkly Rep*. 2011;60(21):694-699; Workowski KA, et al. *MMWR Recomm Rep*. 2015;64(3):1-137; CDC and Prevention and Association of Public Health Laboratories. Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. www.stacks.cdc.gov/view/cdc/23447.

Epidemiology of HIV/AIDS in the United States

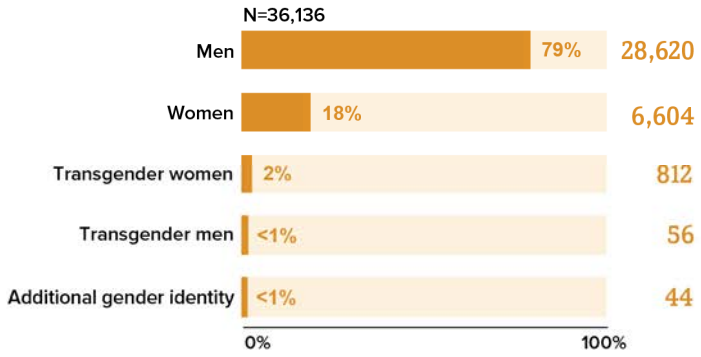
- Number of people with HIV: 1.1 million
- Geographic "hot spots" – urban areas, southeastern USA
- Number of new diagnoses: ~36,000 per year
  - ↓12% over last decade
  - Decline during COVID-19
- 1 in 7 people who have HIV are unaware
  - Marked improvement since 2006



Centers for Disease Control and Prevention (CDC), 2023. https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-34/index.htm; aidsvu.org

Differences in New HIV Diagnoses by Gender*

Men continue to be heavily affected by HIV, accounting for 79% of new HIV diagnoses in 2021.

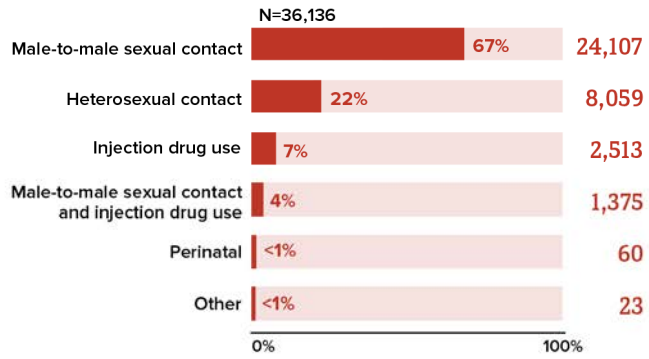


* Among people aged 13 and older.

Source: CDC. Diagnoses of HIV Infection in the United States and Dependent Areas, 2021. *HIV Surveillance Report* 2023;34.

Differences in New HIV Diagnoses by Transmission Category*†

Gay, bisexual, and other men who reported male-to-male sexual contact are the population most affected by HIV.



* Among people aged 13 and older.
† Transmission category is classified based on a hierarchy of risk factors most likely responsible for HIV transmission. Classification is determined based on the person's assigned sex at birth. Data have been statistically adjusted to account for missing transmission category.

Source: CDC. Diagnoses of HIV Infection in the United States and Dependent Areas, 2021. *HIV Surveillance Report* 2023;34.

Tips on handling HIV stigma and privacy issues in the hospital

- Never disclose HIV status to family or friends without explicit permission
  - "Is it okay if I discuss all your medical conditions in front of everyone, or would you rather talk in private"?
- Observe if the patient mentions HIV during the history
- Good substitute terms
  - Viral infection or condition, not HIV or AIDS
  - Treatment, not antiretroviral therapy
- Avoid "How did you get it?" questions – if necessary, "What led you to get tested?"
- The challenge of non-private hospital rooms

N Engl J Med 2018; 378:2157-2159

Case

- A 64-year-old man with an extensive smoking history is admitted with fevers, chills, cough
- Symptoms started approximately 1 week ago with URI, past 2 days much worse
- Diagnosed HIV+ 20 years ago; reports he is now on antiretroviral therapy (ART) with a single pill he takes once daily – can't remember the name
- Exam: T 101.5; rhonchi bilaterally with extensive wheezing
- CXR: Multifocal airspace disease, R >> L consistent with pneumonia

*Question

?

- If you could know only ONE THING about his HIV treatment history in managing him today, which would it be?

A. His HIV risk factor
B. The most recent CD4 cell count, and when it was done
C. The individual components of his single-pill ART regimen
D. Whether he refills his prescription for ART regularly

*Question

- If you could know only ONE THING about his HIV treatment history in managing him today, which would it be?

A. His HIV risk factor
B. The most recent CD4 cell count, and when it was done
C. The individual components of his single-pill ART regimen
D. Whether he refills his prescription for ART regularly

Case Continues

- Pharmacy confirms he regularly refills ART, and tells you he is receiving "SYMTUZA" – a single pill of:
  - Darunavir
  - Cobicistat
  - Tenofovir alafenamide
  - Emtricitabine
- Treated for CAP with ceftriaxone and azithromycin
- Also treated for a COPD exacerbation with inhalers, prednisone
- Outpatient records – viral load undetectable on last several measurements; CD4 normal when last checked 3 years ago

*Question

?

- You order the SYMTUZA, and the hospital pharmacy tells you that they don't have it
- He has no one at home who can bring it in for him
- What do you do now?

A. Hold ART during the hospitalization
B. Order the individual components separately, even if not all are available
C. Order the individual components separately, but only if all are available

*Question

- You order the SYMTUZA, and the hospital pharmacy tells you that they don't have it
- He has no one at home who can bring it in for him
- What do you do now?

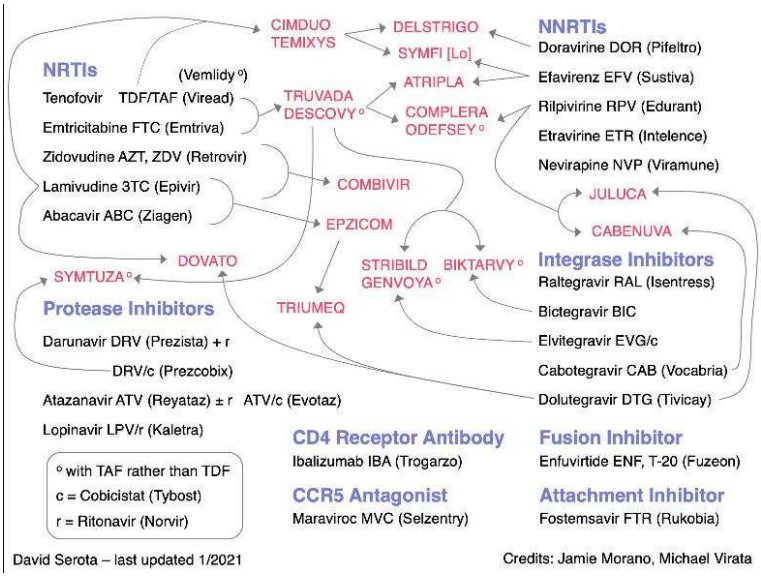
A. Hold ART during the hospitalization

B. Order the individual components separately, even if not all are available

C. Order the individual components separately, but only if all are ava

Do not allow ordering or administration of partial regimens.

Do you know your HIV meds?



Basics of ART

The *best* regimens consist of:

- A nucleoside reverse transcriptase inhibitor pair:
  - Usually tenofovir AF or DF/emtricitabine (TAF/FTC, Descovy or TDF/FTC, Truvada)
  - Tenofovir AF has less renal, bone toxicity than DF; associated with greater weight gain
- An integrase strand transfer inhibitor (INSTI) – bictegravir (BIC) or dolutegravir (DTG, Tivicay)
  - Bictegravir only comes in a combination pill with tenofovir AF/emtricitabine (Biktarvy) – the most commonly used treatment in the USA today
  - Some are treated with only two drugs – DTG/3TC (Dovato), CAB/RPV (Cabenuva)
- Caveat: Patients with long HIV treatment histories are on different regimens from these

Pet Peeve Alert!

- "HAART" (highly active antiretroviral therapy) is a horribly outdated term, and needs to be permanently retired
- "ART" is preferred
- Working on this one clinician at a time …

*Question

?

- How can you determine if an antiretroviral regimen is effective in a hospitalized patient?

A. HIV viral load
B. CD4 cell count
C. Both

*Question

- How can you determine if an antiretroviral regimen is effective in a hospitalized patient?

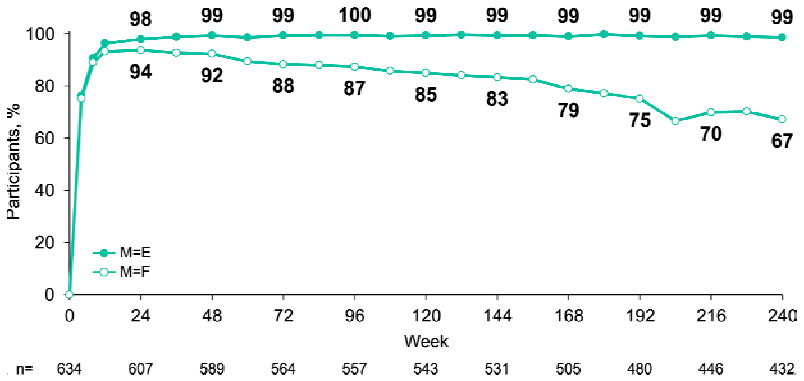
A. HIV viral load
B. CD4 cell count
C. Both

Currant ART works if you take it

5-year results of BIC/FTC/TAF-treated participants in two prospective clinical trials

No treatment failure with resistance

Drug-related adverse events leading to treatment discontinuation in < 1%

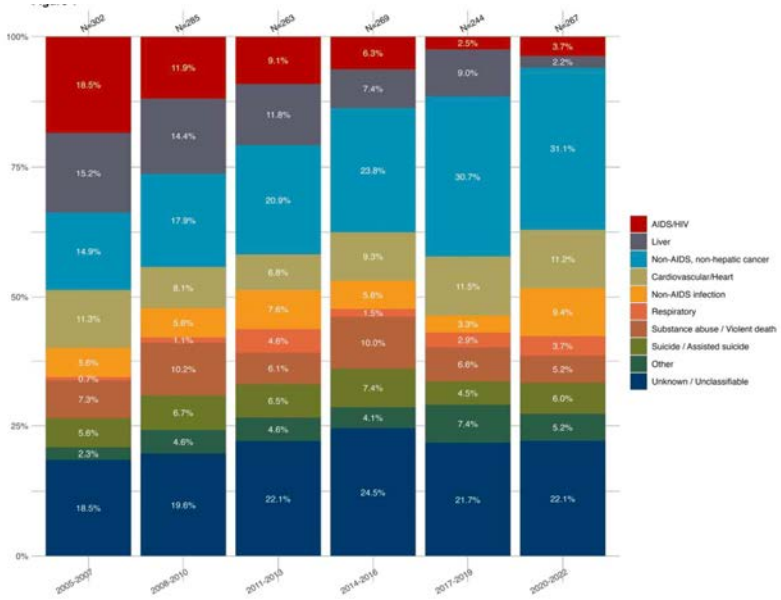


Sax PE, et al. eClinical Medicine 2023. 11:59:101991.

Causes of death for PWH in care, 2005-2022

Non-AIDS cancers have become the leading cause of death, followed by CVD

AIDS and liver complications have dropped dramatically



Weber MSR, et al. Clin Infect Dis 2024.

*Question

?

- HIV viral load and CD4 are both ordered
- The viral load returns at < 30 copies/mL (undetectable)
- The CD4 cell count is 180 (24% CD4)
- Should the patient be started on prophylaxis for *Pneumocystis jiroveci* pneumonia (PJP)?

A. Yes
B. No

*Question

- HIV viral load and CD4 are both ordered
- The viral load returns at < 20 copies/mL (undetectable)
- The CD4 cell count is 180 (24% CD4)
- Should the patient be started on prophylaxis for *Pneumocystis jiroveci* pneumonia (PJP)?

A. Yes
B. No

Approach to OI prophylaxis

- *Much* less important than ART – never urgent
- Start PJP prophylaxis if CD4 <200
  - No need to start if CD4 is close to 200 and patient is about start ART, or if its transiently < 200 due to acute illness
  - TMP/SMX 1 DS daily is preferred; dapsone, atovaquone alternatives
  - Can STOP if HIV VL undetectable >3 months and CD4 >100
- Prophylaxis for *M. avium* complex (MAC) no longer recommended

Image courtesy Mary Montgomery, MD

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV, https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/321/pneumocystis-pneumonia,

Case continues

- The patient significantly improves on antibiotics, steroids, and inhalers
- He experiences severe insomnia due to prednisone, treated with lorazepam
- Ready for discharge on hospital day 3
- Discharge medications:
  - fluticasone/salmeterol
  - cefpodoxime
  - lorazepam

*Question

?

- What potentially serious drug interaction with his HIV treatment was overlooked in his discharge plan?

A. Azithromycin
B. Fluticasone
C. Lorazepam
D. Salmeterol

*Question

- What potentially serious drug interaction with his HIV treatment was overlooked in his discharge plan?

A. Azithromycin
B. Fluticasone
C. Lorazepam
D. Salmeterol

CLINICAL CASE SEMINAR

Iatrogenic Cushing's Syndrome with Osteoporosis and Secondary Adrenal Failure in Human Immunodeficiency Virus-Infected Patients Receiving Inhaled Corticosteroids and Ritonavir-Boosted Protease Inhibitors: Six Cases

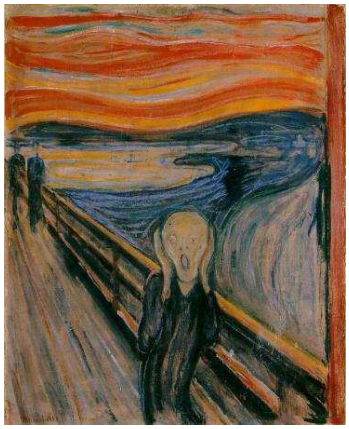
Katherine Samaras, Sarah Pett, Andrew Gowers, Marilyn McMurchie, and David A. Cooper

Department of Endocrinology (K.S.), St. Vincent's Hospital and St. Vincent's Clinic; Immunology and Infectious Diseases Unit (S.P., D.A.C.), St. Vincent's Hospital; National Centre for HIV Epidemiology and Clinical Research (S.P., D.A.C.), University of New South Wales; and Holdsworth House General Practice (A.G.), Darlinghurst, New South Wales 2010, Australia; and 407 Doctors General Practice (M.M.), Surry Hills, New South Wales 2010, Australia

Samaras K, et al. J Clin Endocrinol Metab 2005:90;4394-8.

Drug interactions in HIV

- Statins
- Inhaled, injected, or topical corticosteroids
- Erectile dysfunction drugs
- Benzodiazepines
- Rifampin/rifamycin
- Anticonvulsants
- Methadone
- Oral contraceptives
- Proton-pump inhibitors



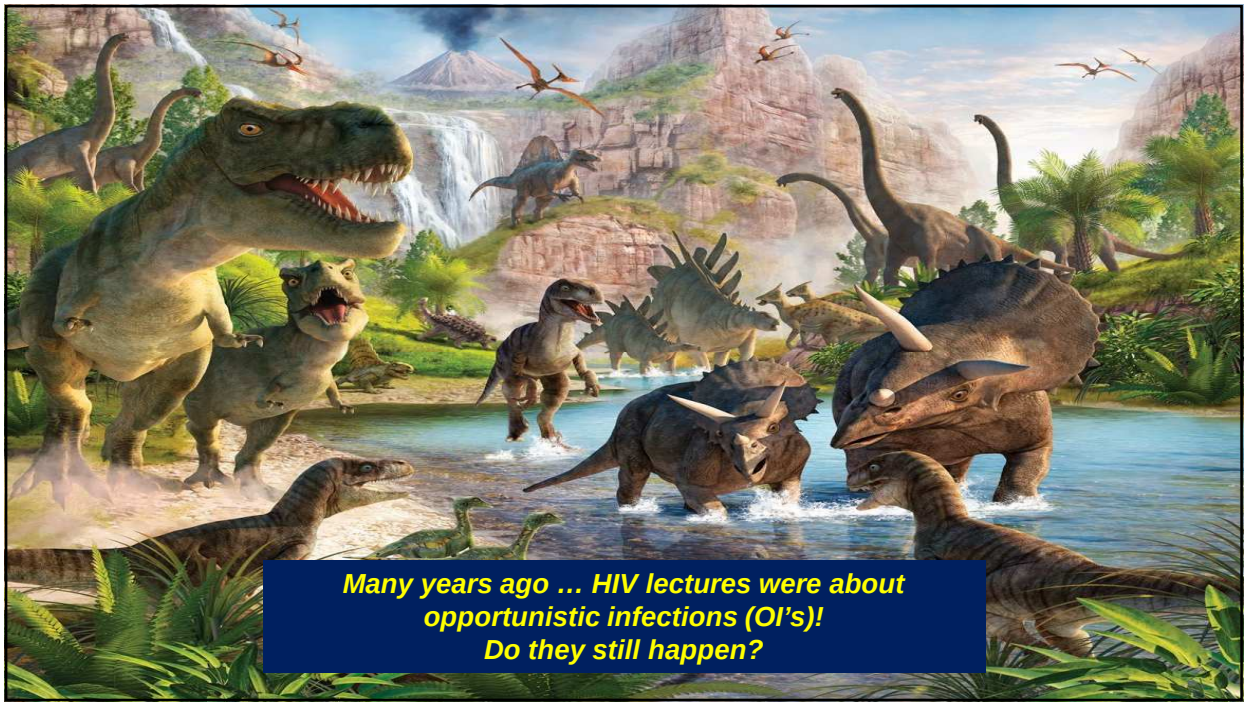
Ritonavir and cobicistat powerfully inhibit cytochrome p450 cyp3A4 – interact with MANY drugs

Some drug interactions of note in HIV

Scenario	Recommendation
Statins and ritonavir or cobicistat	Exposure increased 2X or more; start with low-dose atorvastatin, avoid simvastatin or lovastatin
Corticosteroids and ritonavir or cobicistat	Metabolism markedly slowed – avoid prolonged courses, watch for iatrogenic hypercortisolism
Cationic supplements (Fe, Mg, Ca) and integrase inhibitors	Stagger dosing; do not administer concurrently
Acid-reducing agents and rilpivirine, atazanavir	Avoid PPIs; stagger dosing with H2 blockers and antacids
Certain seizure medications (phenytoin, carbamazepine, phenobarbitol) and multiple ART agents	Use levetiracetam
Rifampin and multiple ART agents	ART options very limited (dolutegravir and efavirenz plus NRTIs); only use if strongly indicated

The University of Liverpool HIV Drug Interactions Site – Worth Its Weight in Gold!

www.hiv-druginteractions.org



Yes! But who gets OIs today?

- Those not on antiretroviral therapy because:
  - They *don't know* they have HIV, or
  - They *can't* take ART (severe side effects, or can't afford it/lose coverage) or
  - They *won't* take ART (addiction, or psychiatric illness, or visiting the longest river in Africa)
- Also – those on ART for < 1 year who started therapy with low CD4 counts – usually as part of the immune reconstitution inflammatory syndrome (IRIS)

Case

- 42 y.o. woman with weight loss
- Reports three month hx of gradual weight loss, anorexia, and fatigue. Outpatient w/u for pancytopenia unrevealing, including BM Bx. No longer able to work.
- Exam: T=99.8. O2 saturation 91%. Weight down 15 lbs from baseline. Thrush.
- LAB: WBC 2.2; chemistries normal except LDH 340. HIV antibody screen positive.
- CXR/CT: as shown

42 y.o. woman with fever, weight loss, positive HIV screen.

*Question

?

- What should you do now?

A. Begin empiric trimethoprim/sulfamethoxazole (T/S)
B. Begin empiric T/S and prednisone
C. Await the results of an induced sputum for PCP prior to starting treatment

*Question

- What should you do now?

A. Begin empiric trimethoprim/sulfamethoxazole (T/S)
B. Begin empiric T/S and prednisone
C. Await the results of an induced sputum for PCP prior to starting treatment

Tests for patients NOT on ART

High value – Order in all patients

- **CD4 cell count**
- **HIV RNA ("viral load" assay)**

Order if Specifically Indicated

- HIV resistance genotype
- Hepatitis serologies
- Toxoplasmosis IgG
- Cryptococcal antigen
- Beta glucan
- Syphilis screen
- IGRA or TST (TB testing)
- G6PD

hivinfo.nih.gov/guidelines.

*Question

- When do you get an ID consult on a case like this?

A. On admission or the next day
B. When ready to consider antiretroviral therapy
C. Only if treatment has complications
D. Never

*Question

?

- When do you get an ID consult on a case like this?

A. On admission or the next day

B. When ready to consider antiretroviral therapy

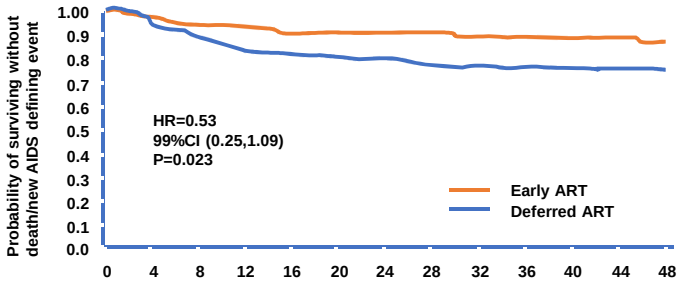
C. Only if treatment has complications

D. Never

Case outcome

- Started on empiric TMP/SMX and prednisone
- Diagnosis of *Pneumocystis* pneumonia (PCP) confirmed
  - Beta-glucan > 500 (normal < 80)
  - Induced sputum: PCR positive for *P jiroveci*
- Started on bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) on hospital day 3, with discharge on day 5
- **Outpatient follow-up arranged for 1 week after discharge**

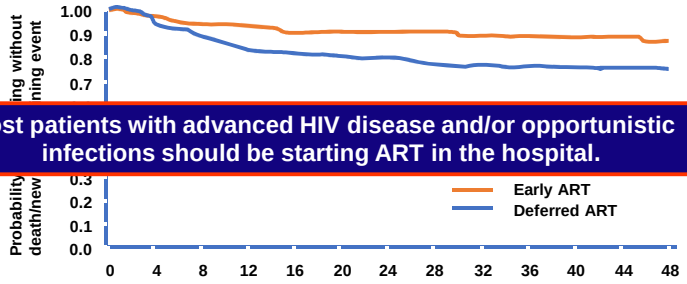
A5164: Early ART associated with reduced risk of AIDS/Death in patients with acute OIs



- No difference in rate of virologic suppression
- No difference in IRIS (10 immediate, 13 deferred) or need for ART changes
- Results strongly support starting antiretroviral therapy within 2 weeks of presentation

PLoS One. 2009;4(5):e5575. Epub 2009 May 18

A5164: Early ART associated with reduced risk of AIDS/Death in patients with acute OIs



Most patients with advanced HIV disease and/or opportunistic infections should be starting ART in the hospital.

- No difference in rate of virologic suppression
- No difference in IRIS (10 immediate, 13 deferred) or need for ART changes
- Results strongly support starting antiretroviral therapy within 2 weeks of presentation

PLoS One. 2009;4(5):e5575. Epub 2009 May 18

Immune Reconstitution Inflammatory Syndromes (IRIS)

- Observed most commonly with mycobacterial infections; reported with virtually all OIs
- Characterized by fever and worsening of the of the underlying infection
  - May "unmask" disease at previously uninvolved site, or make subclinical infection overt
- Onset in first 4-8 weeks after starting therapy in severely immunocompromised hosts
  - Many exceptions to this rule – disease onset earlier and much later
- Adjunctive corticosteroids effective for moderate-severe IRIS
- **Not a reason to delay ART except with *one* opportunistic infection – cryptococcal meningitis**

Meintjes et al., NEJM 2018

Reasons to get ID involved during hospitalization

- Confusing HIV test results
- New HIV diagnosis
- Suspected acute HIV or HIV-related opportunistic infection
- Advanced HIV disease (CD4 < 200)
- Detectable viral load but supposedly on ART
- Concern for ART-related toxicity or drug interactions
- When considering changing ART, or patient is on a non-standard or outdated regimens
- After a patient or healthcare provider has a possible exposure to HIV

Call us!

HIV for Hospitalist: Take home points

- HIV testing is accurate – but know its limitations
- Always consider acute HIV for febrile syndromes in at-risk populations
- HIV patients admitted on ART
  - Order HIV viral load – should be suppressed
  - Continue full ART regimen
  - Watch for drug interactions
  - Expect the same medical diagnoses as non-HIV patients – but cancer in particular
- HIV patients admitted *not* on ART
  - Order HIV viral load and CD4
  - Plan to start ART during hospitalization (exception: cryptococcal meningitis)
  - For suspected opportunistic infections, involve ID early
  - Discharge with close follow-up

Updated Online Resources

- HIV Treatment Guidelines: hivinfo.nih.gov/guidelines
  - Antiretroviral therapy
  - Opportunistic infections
  - Treatment of HIV in pregnancy
  - Pre- and Post-exposure prophylaxis
- HIV Drug Interactions: www.hiv-druginteractions.org
- USA HIV epidemiology: aidsvu.org

Thank you!