Clinician Core Seminar:
Clinical Management of HIV Disease

Disclosure of Interest

The presenters for this program have the following financial interest/relationship with manufacturers of commercial products.

Gender

Cisgender/cis: term for someone who exclusively identifies as their sex assigned at birth.

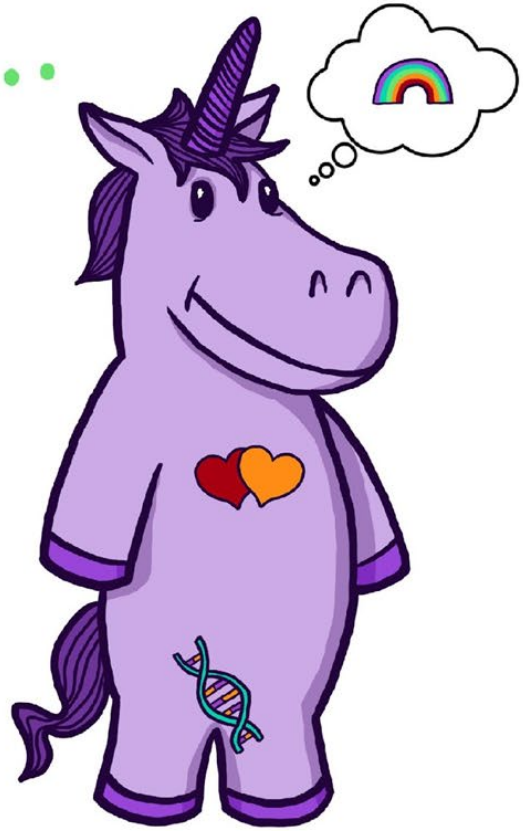
Transgender/Trans: encompassing term of many gender identities of those who do not identify or exclusively identify with their sex assigned at birth.

Gender non-binary, genderqueer, gender non conforming, gender fluid: term used by people who do not identify or express their gender within the gender binary

Cis/trans is not indicative of gender expression, sexual orientation, hormonal makeup, physical anatomy, or how one is perceived in daily life.

The Gender Unicorn

Graphic by:
TSER
Trans Student Educational Resources



Gender Identity
- Female / Woman / Girl
- Male / Man / Boy
- Other Gender(s)

Gender Expression
- Feminine
- Masculine
- Other

Sex Assigned at Birth
Female | Male | Other/Intersex

Physically Attracted to
- Women
- Men
- Other Gender(s)

Emotionally Attracted to
- Women
- Men
- Other Gender(s)

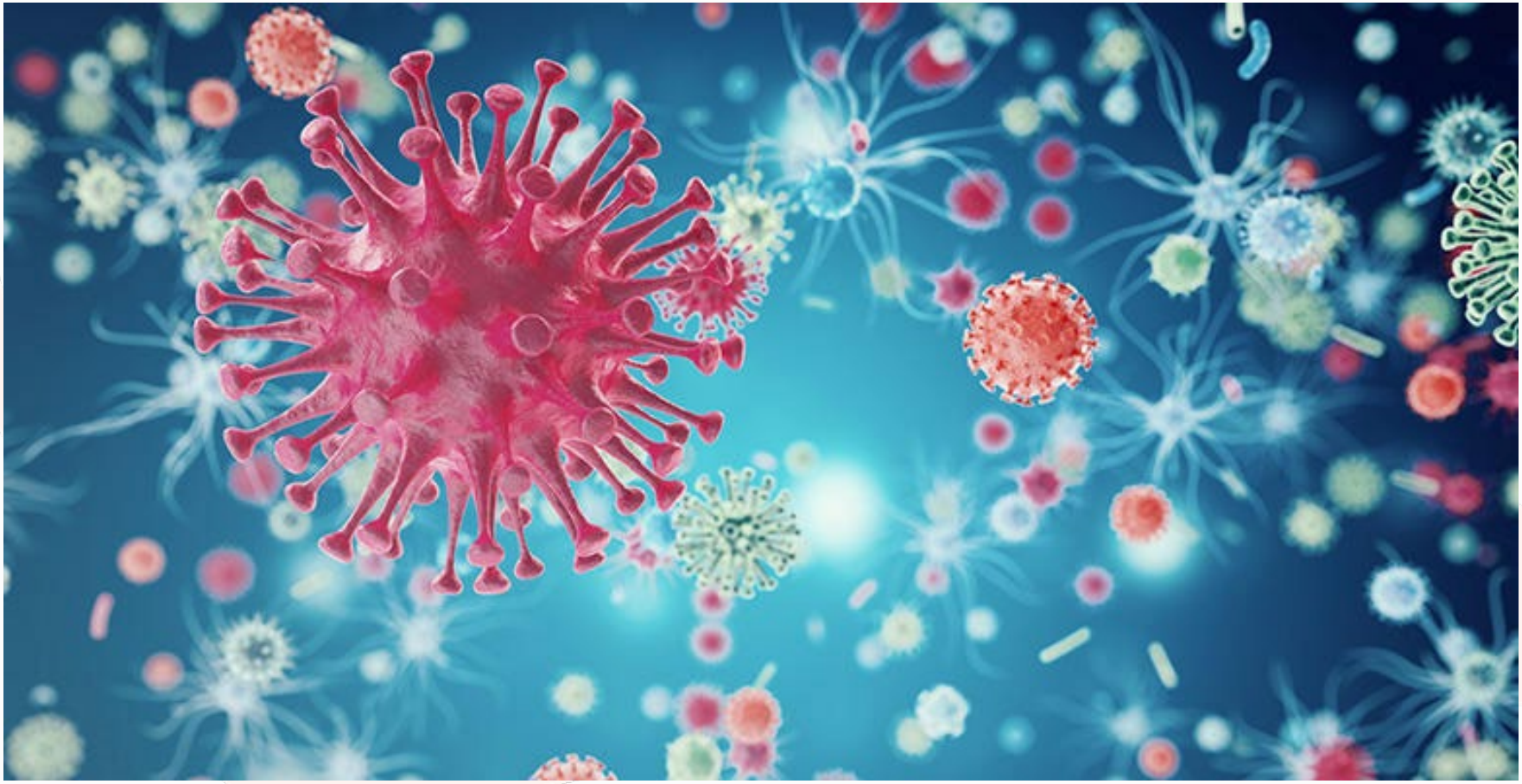
To learn more, go to:
www.transstudent.org/gender

Design by Landyn Pan and Anna Moore

Introductions

- Name
- Gender pronoun
- Workplace/Agency
- Your goals for this program

Human Immunodeficiency Virus (HIV) Epidemiology



Objectives

- Discuss worldwide, United States and local epidemiologic HIV trends
- Describe the HIV cascade and its importance to clinical practice
- Describe how routine testing can be integrated into all medical practices

HIV/AIDS: The New Paradigm

- Once a universally terminal illness, now a chronic, manageable disease
- Similar to other chronic, manageable diseases
  - Examples??
- Today, persons living with HIV (PLWH) are more likely to die from non-HIV related causes
  - World-wide: tuberculosis
  - U.S.: cardiac, non-HIV related cancers, COPD, liver-related
- There is an optimism and a strategic plan to strive to get to zero new infections in Illinois by the year 2030

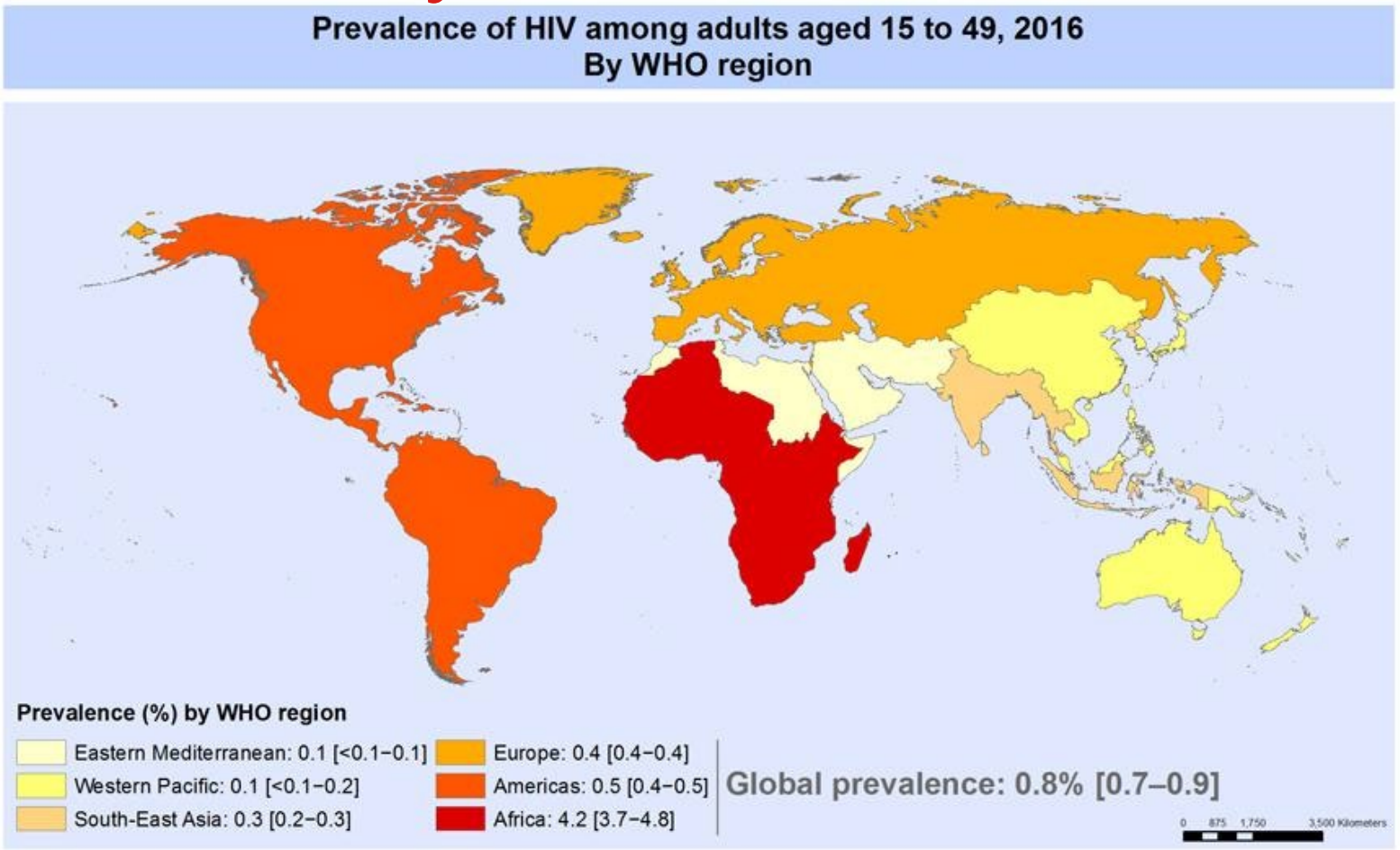
What part of the world leads in HIV disease burden?

A. United States and Europe

B. Asia

C. Africa

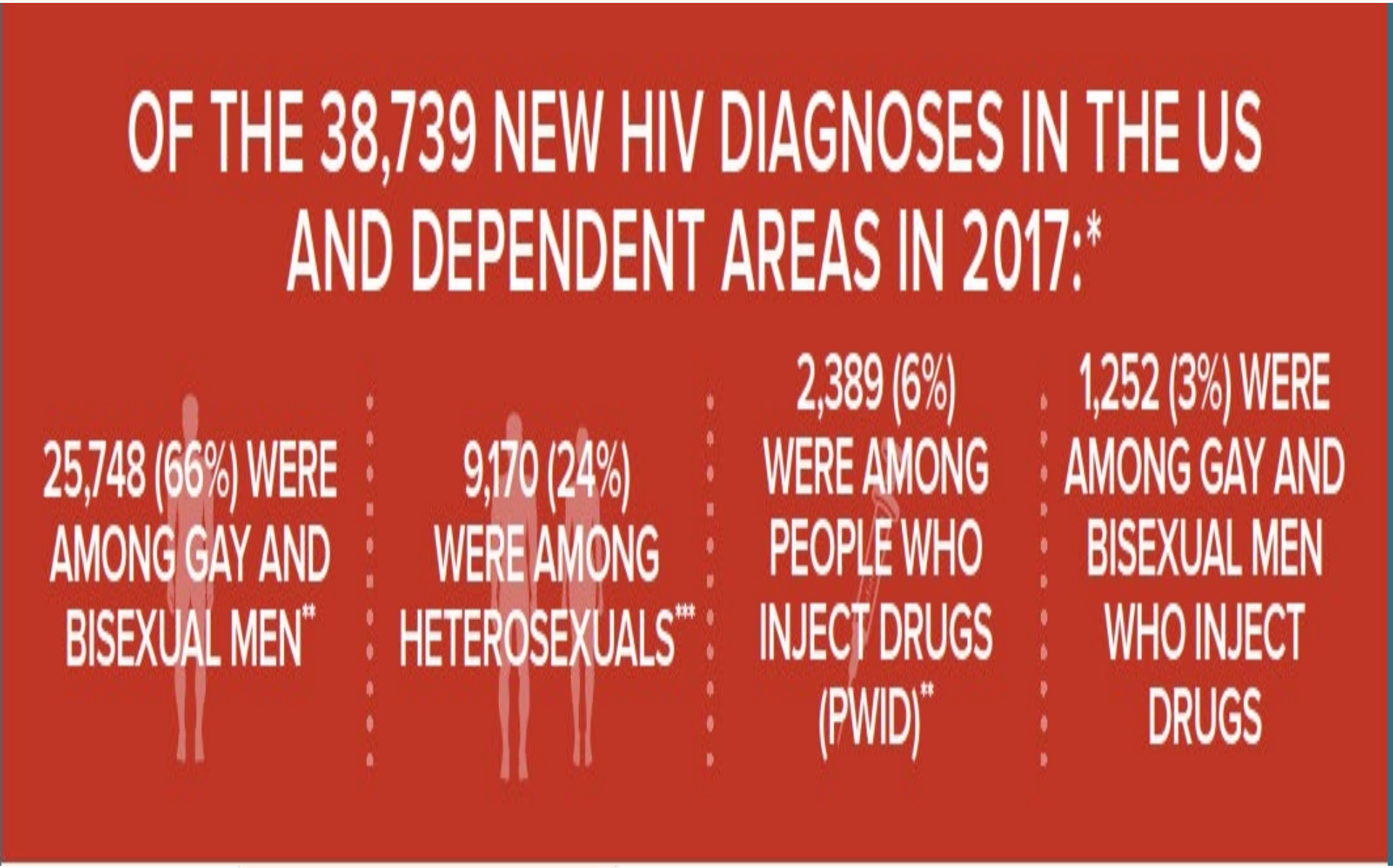
HIV Globally



Review of HIV Epidemiology

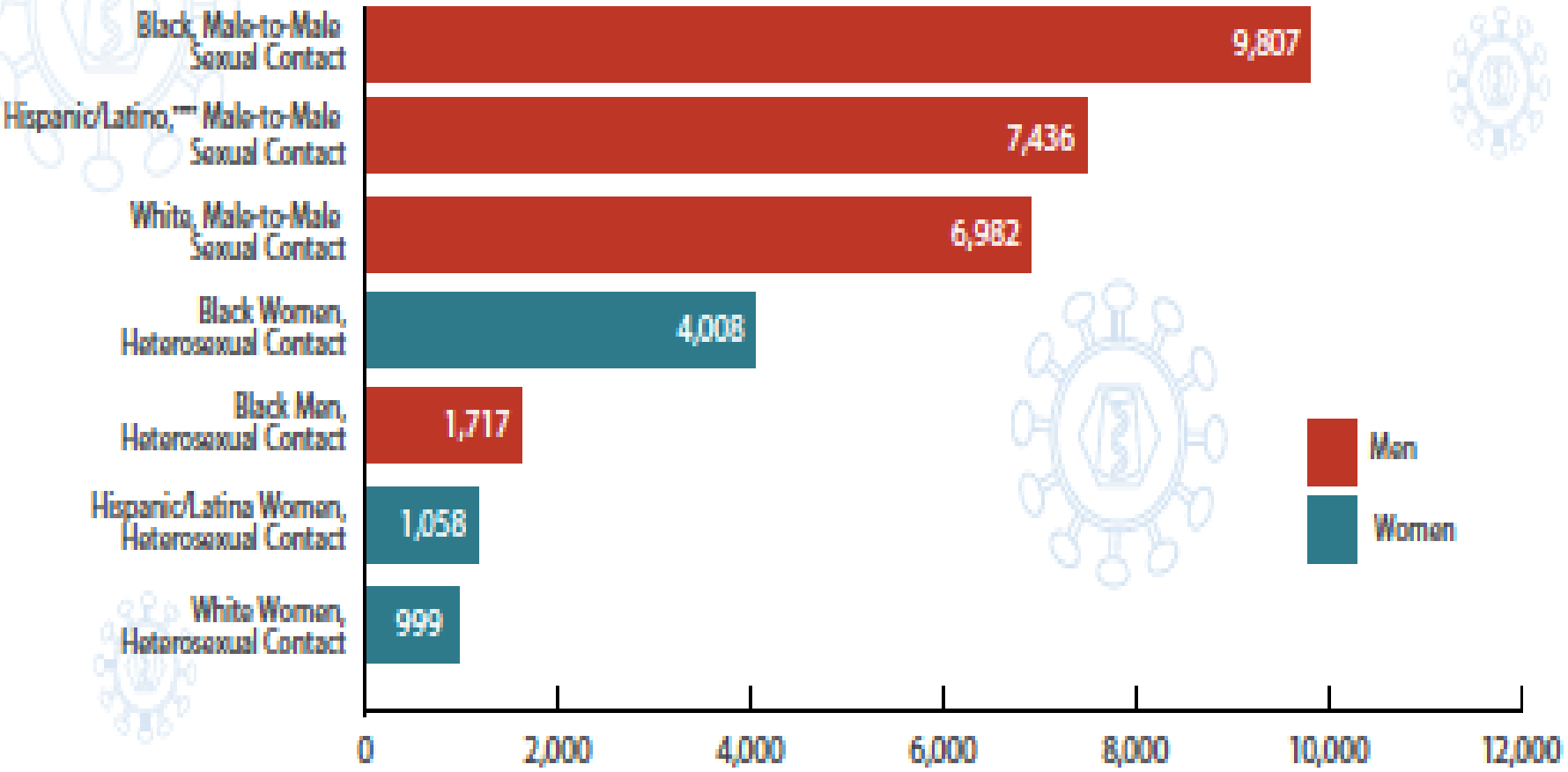
- Continental Africa still has the majority of HIV infections worldwide, followed by the Americas and Europe
- HIV no longer leading cause of death in Africa
  - #2, after lower respiratory infections
- In Eastern and Southern Africa, the number of people living with HIV on antiretroviral therapy has more than doubled since 2010, reaching almost 12.5 million people by June 2017.
- New HIV infections in Eastern and Southern Africa have declined by a third in just six years, while AIDS-related deaths in the region plummeted by 42% over the same period.

http://www.unaids.org/en/resources/presscentre/featurestories/2018/april/turning-point-for-africa



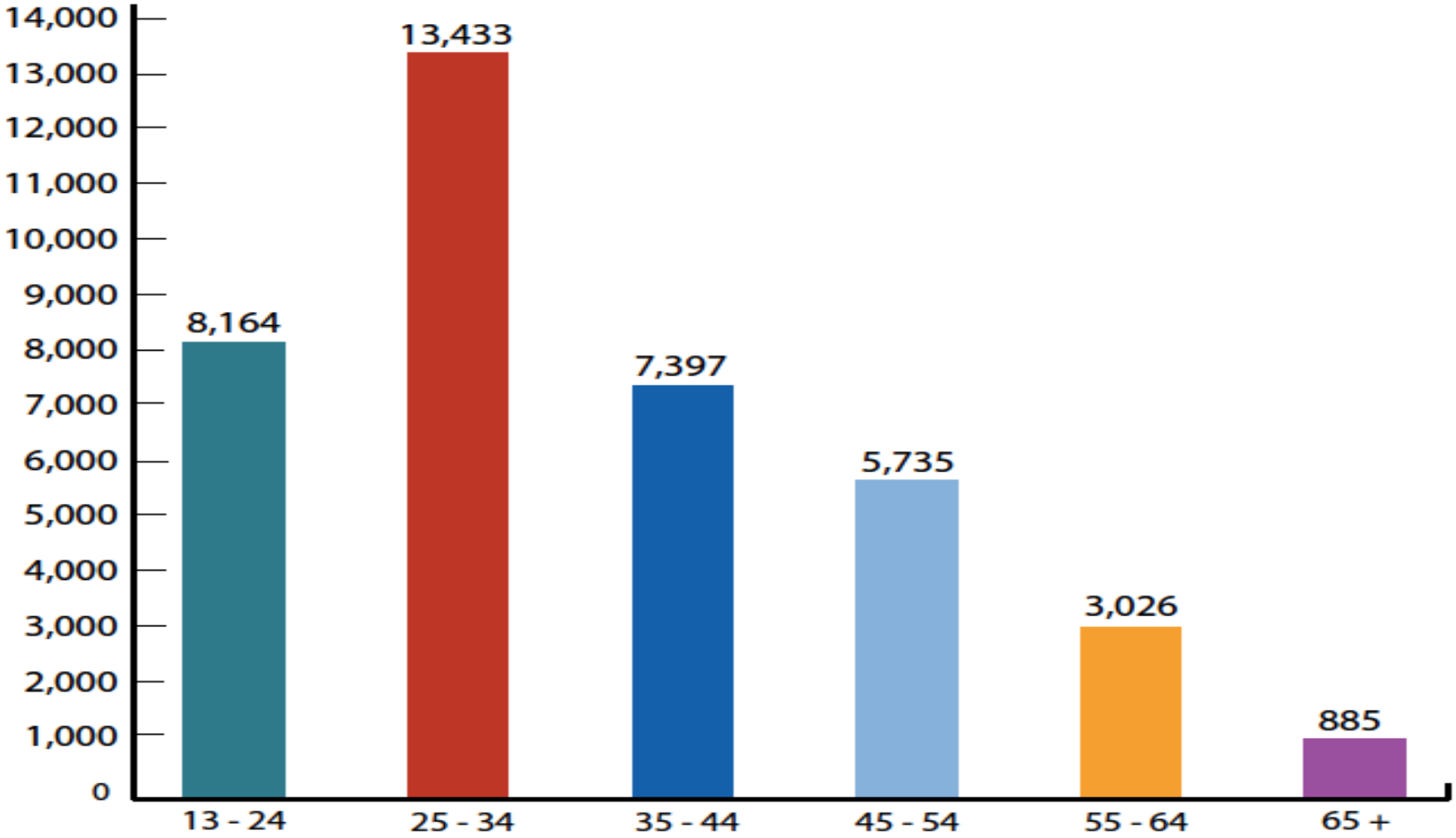
Source: https://www.cdc.gov/hiv/pdf/statistics/overview/cdc-hiv-us-ataglance.pdf

New HIV Diagnoses in the US and Dependent Areas for the Most-Affected Subpopulations, 2017



Source: https://www.cdc.gov/hiv/pdf/statistics/overview/cdc-hiv-us-ataglance.pdf

New HIV Diagnoses by Age in the US and Dependent Areas, 2017



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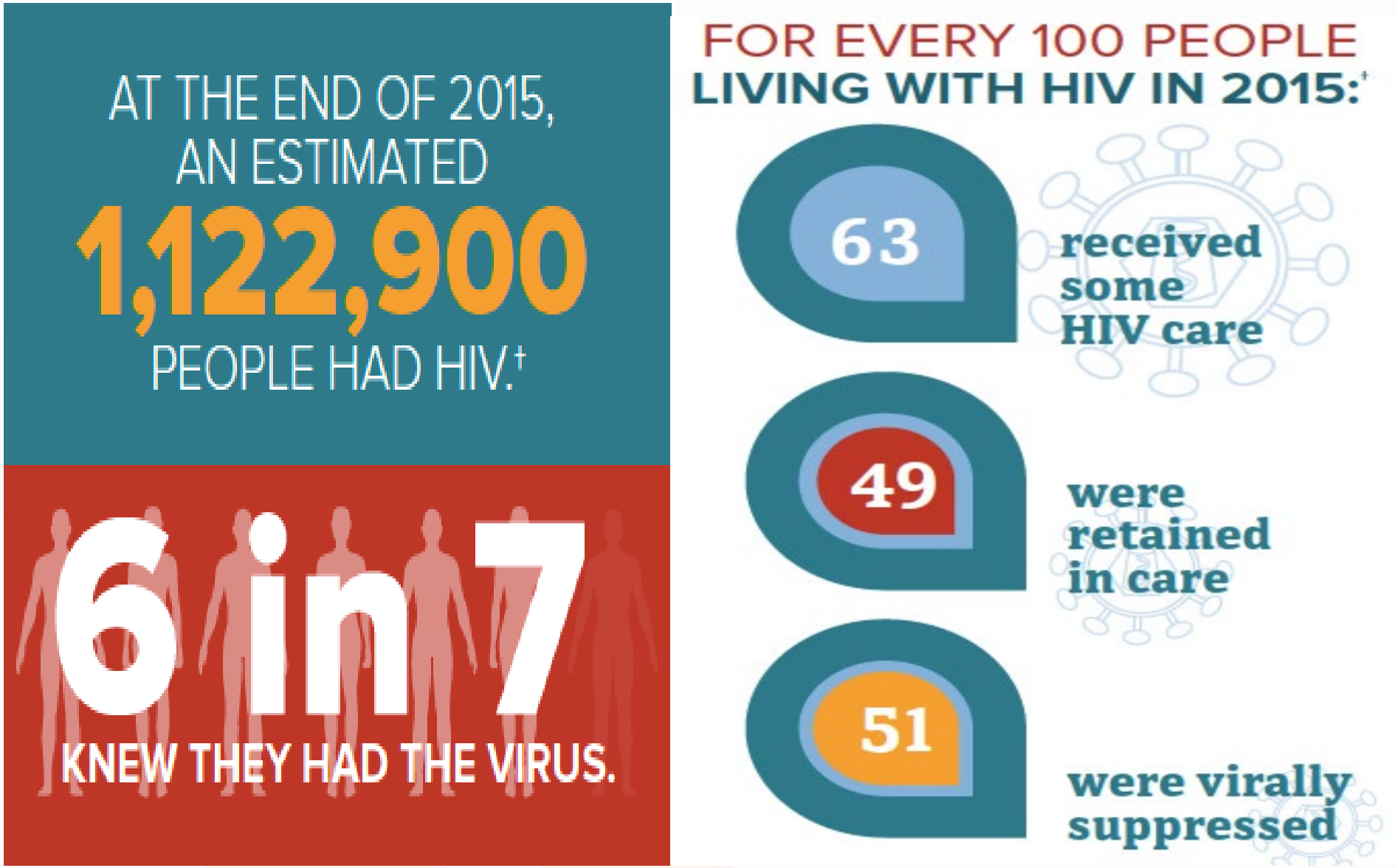

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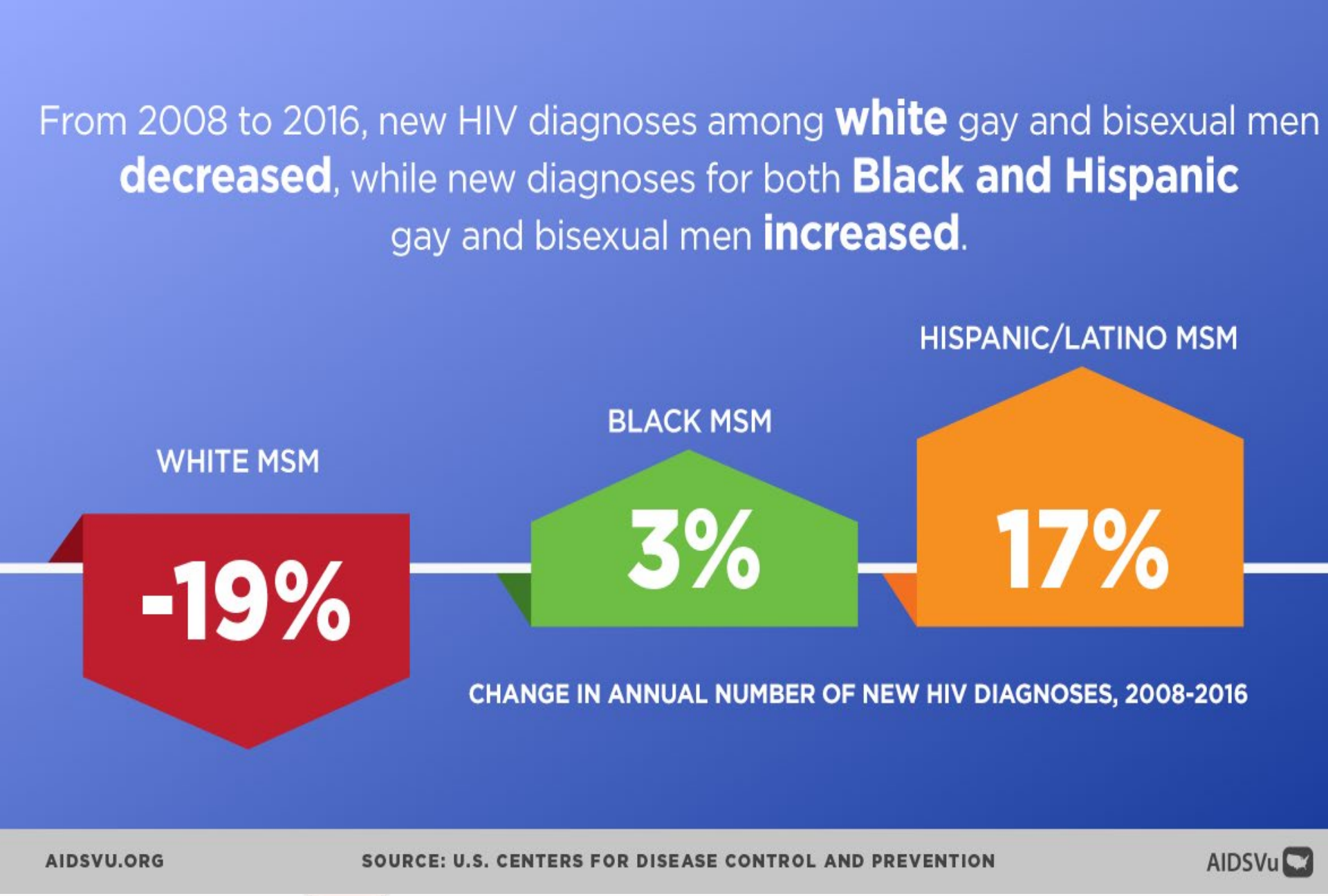
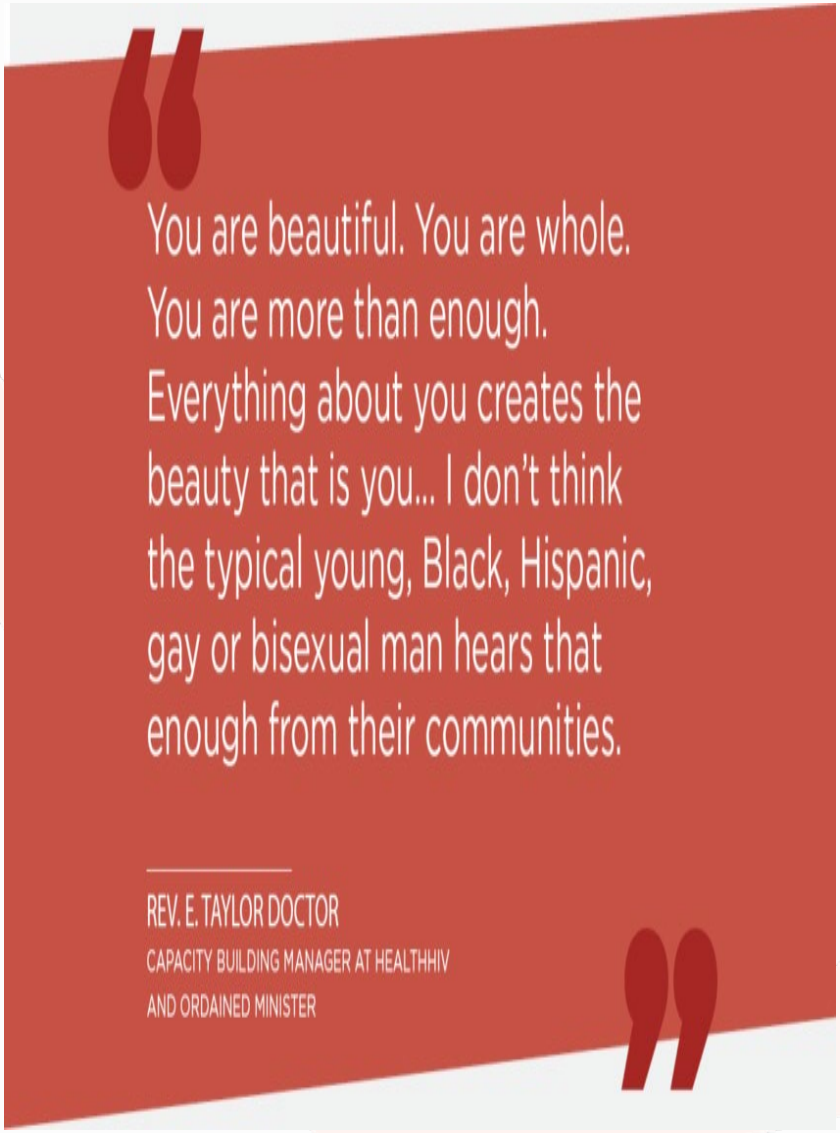
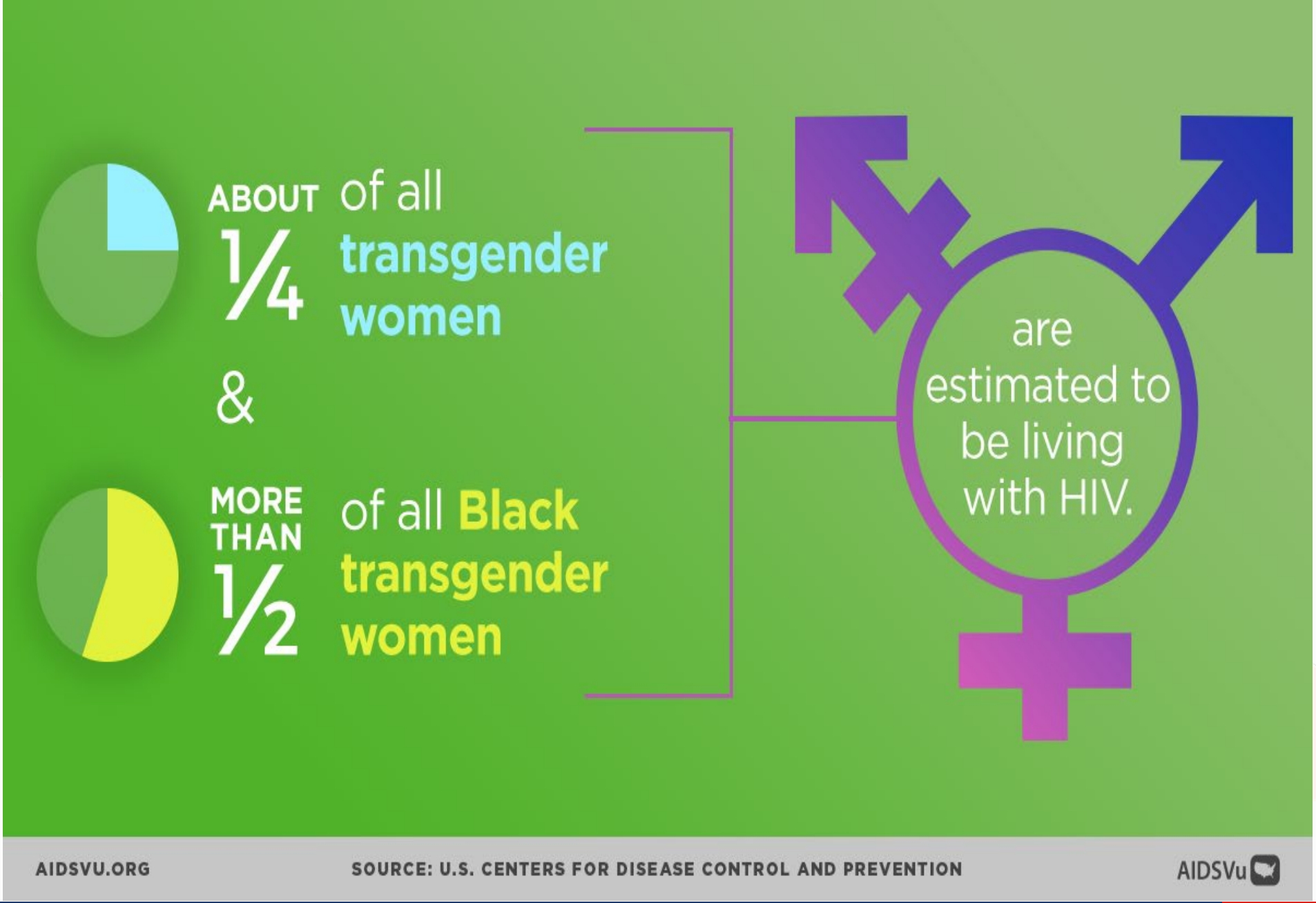
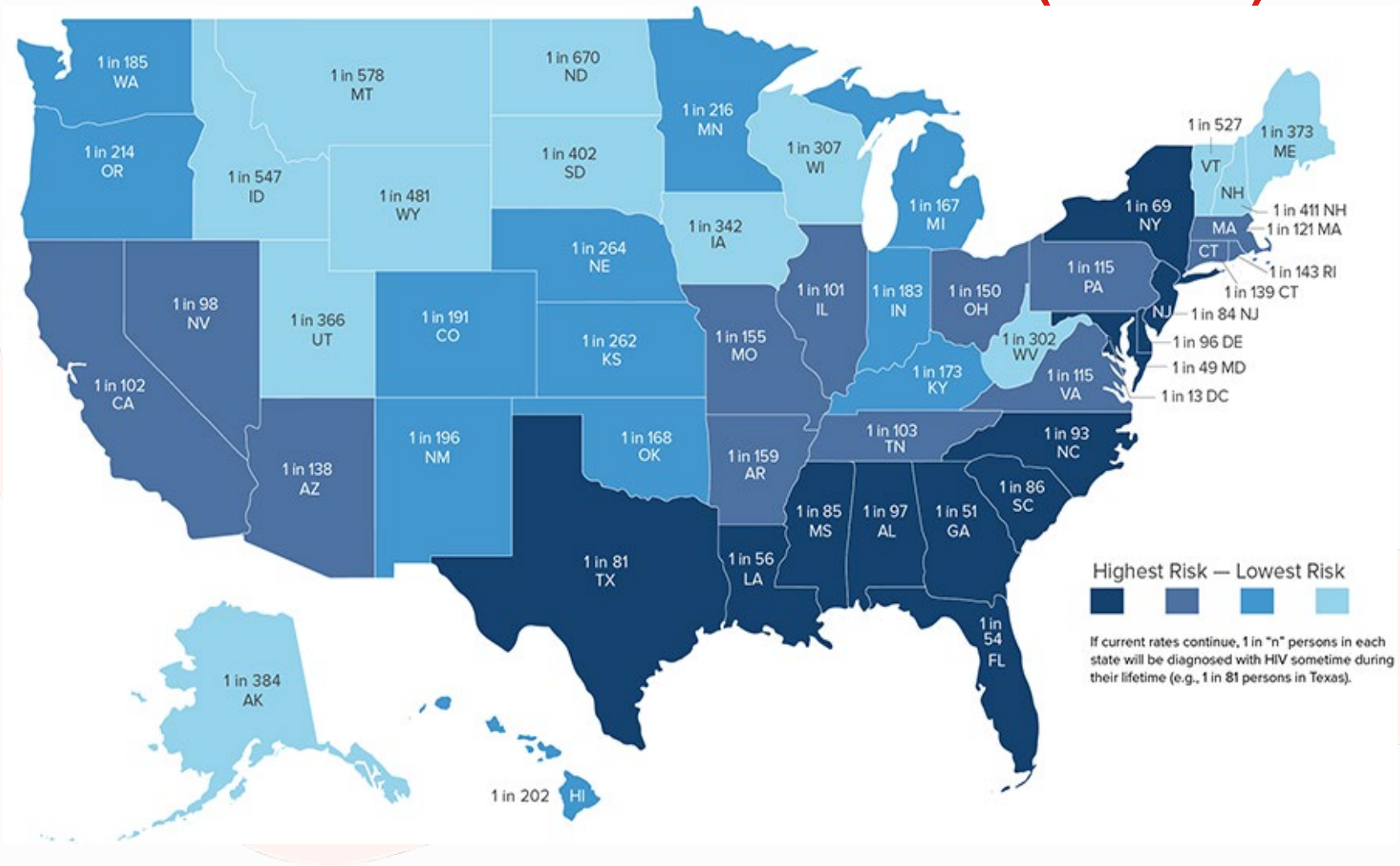

From 2008 to 2016, new HIV diagnoses among white gay and bisexual men decreased, while new diagnoses for both Black and Hispanic gay and bisexual men increased.
WHITE MSM
-19%
BLACK MSM
3%
HISPANIC/LATINO MSM
17%
CHANGE IN ANNUAL NUMBER OF NEW HIV DIAGNOSES, 2008-2016
AIDSVU.ORG
SOURCE: U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION
AIDSVu

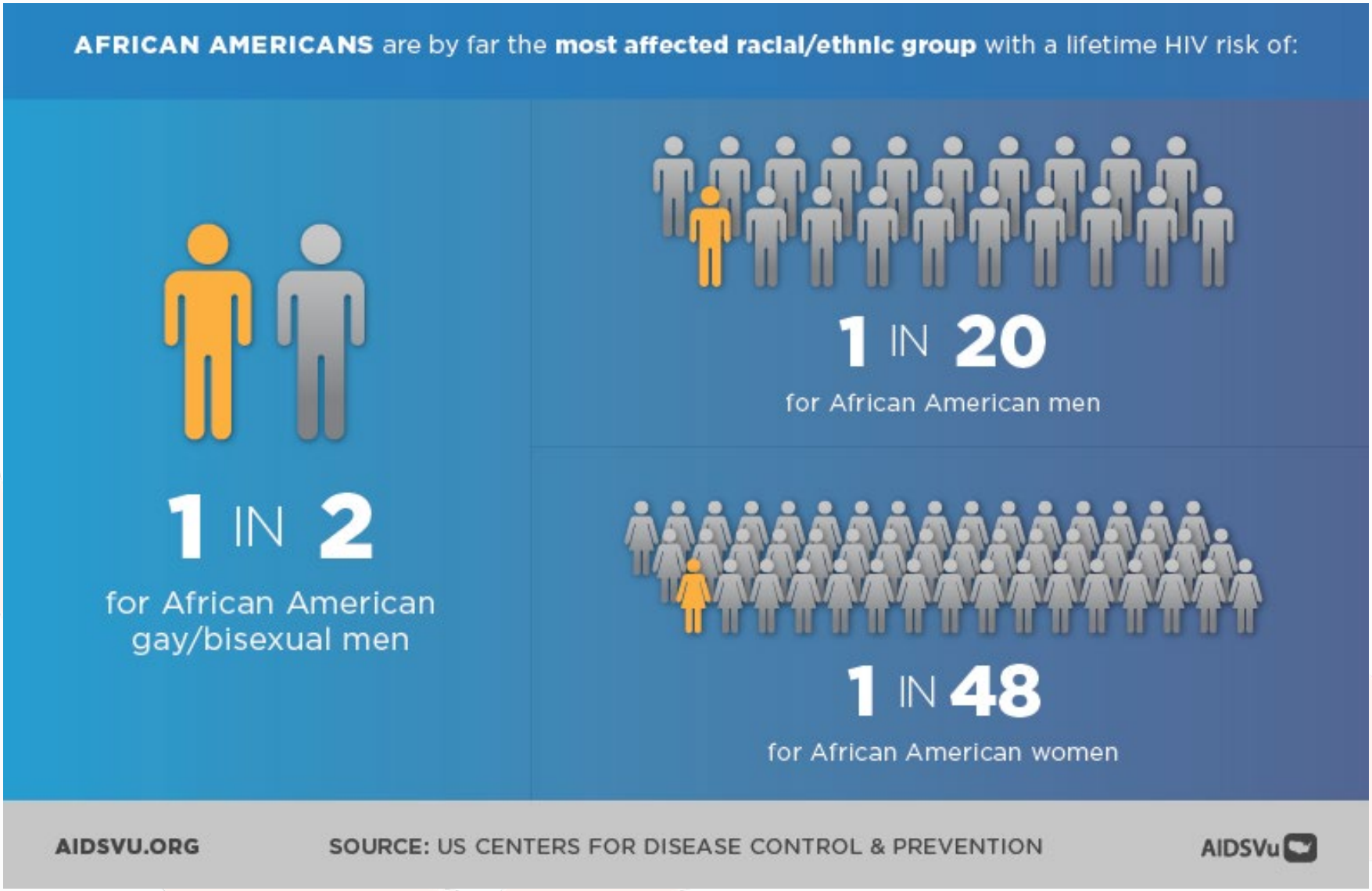


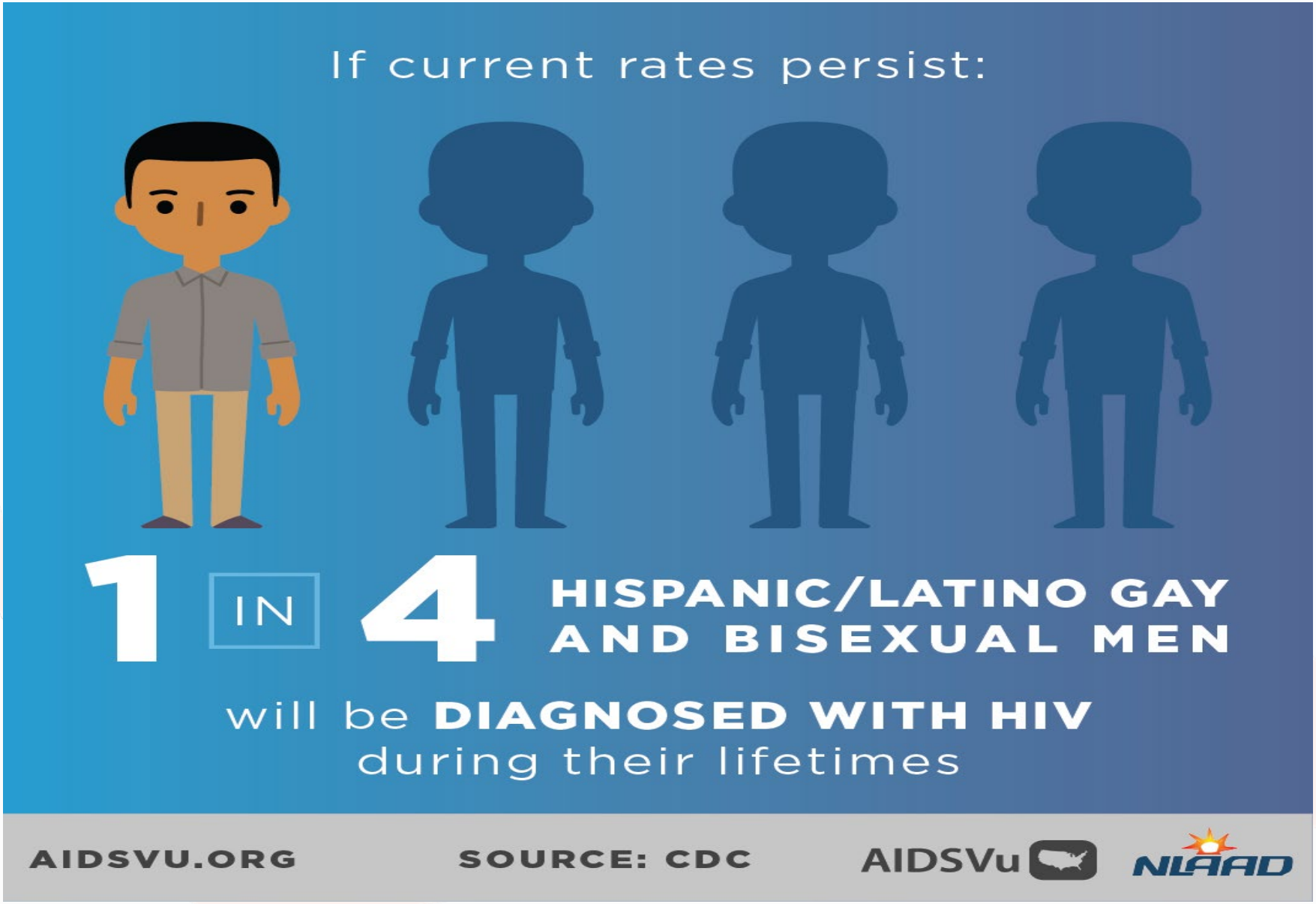
Source: https://aidsvu.org/etd/


ABOUT 1/4 of all transgender women
&
MORE THAN 1/2 of all Black transgender women
are estimated to be living with HIV.
AIDSVU.ORG
SOURCE: U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION
AIDSVu

Lifetime Risk of HIV in US (CDC)




AFRICAN AMERICANS are by far the most affected racial/ethnic group with a lifetime HIV risk of:
1 IN 2
for African American gay/bisexual men
1 IN 20
for African American men
1 IN 48
for African American women
AIDSVU.ORG
SOURCE: US CENTERS FOR DISEASE CONTROL & PREVENTION
AIDSVu


If current rates persist:
1 IN 4 HISPANIC/LATINO GAY AND BISEXUAL MEN
will be DIAGNOSED WITH HIV during their lifetimes
AIDSVU.ORG
SOURCE: CDC
AIDSVu
NLAAD

Chicago Statistics, 2016

New Diagnoses

Number of new HIV diagnoses in 2016

824

Number of new HIV diagnoses in 2012-2016, by Sex

84.1% male

15.9% female

Number of new HIV diagnoses in 2012-2016, by Race

53.7% Black | 21.8% Hispanic/Latinx | 18.9% White

Mortality

Number of deaths of people with diagnosed HIV in Chicago in 2016

258

Number of deaths of people with diagnosed HIV in Illinois in 2015

539

Source: https://aidsvu.org/state/illinois/chicago/

Prevalence

Number of people living with HIV in 2016

20,474

Number of people living with HIV in 2016, by Race

50.3% Black | 20.5% Hispanic/Latinx | 23.2% White

Number of people living with HIV in 2016, by Sex

81.5% male

18.5% female

Source: https://aidsvu.org/state/illinois/chicago/

HIV IN ILLINOIS

In 2015, an estimate

38,314

people were living with HIV in Illinois

New HIV transmissions in Illinois dropped by nearly

28%

over the decade from 2006-2015

Illinois has nearly

ELIMINATED

perinatal HIV transmission

1/3

of people living with HIV in the state are covered by the ACA and Medicaid

Gay, bisexual and other men who have sex with men made up

63%

of persons living with HIV in the state in 2015

Source: https://gtzillinois.hiv

What is the Treatment Cascade?

A. The steps that PLWH go through in the stages of care from diagnosis to viral suppression
B. A musical group of healthcare professionals
C. A way to define where patients receive duplicate treatments during care for the same illness

HIV Care Continuum

- HIV care continuum=HIV treatment cascade=HIV continuum of care
  - Model that outlines the sequential steps or stages of HIV medical care for PLWH
    - initial diagnosis to achieving the goal of viral suppression
    - shows the proportion of individuals living with HIV who are engaged at each stage
  - Diagnosed
  - Linked to care
  - Engaged and/or retained in care/prescribed ART
  - Virally suppressed (<200 copies per milliliter (c/mL))

https://www.cdc.gov/hiv/pdf/library/factsheets/cdc-hiv-care-continuum.pdf

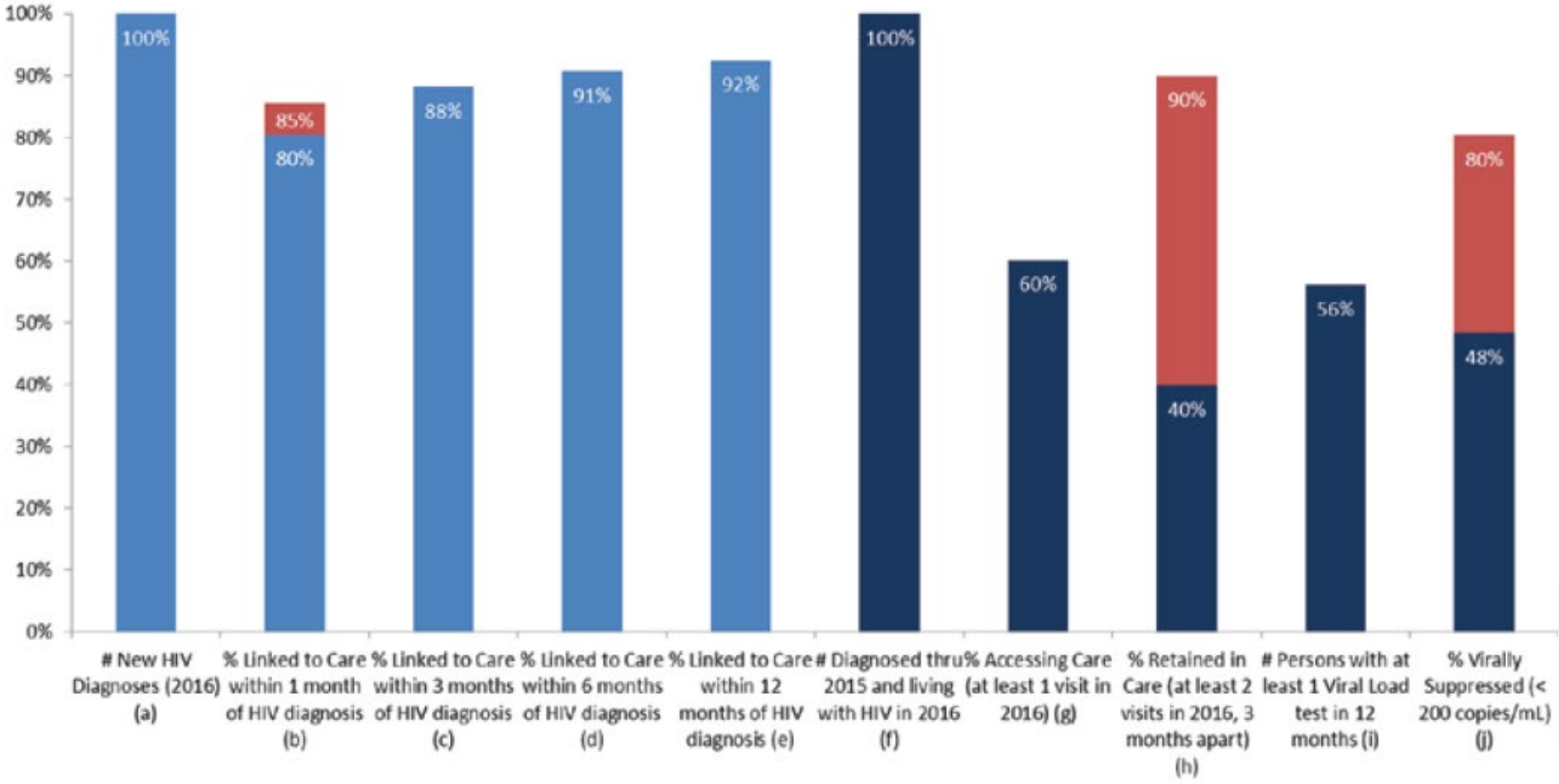
Stories Across the HIV Continuum

HIV Continuum of Care, Chicago, 2016

- 80% of those diagnosed w HIV were linked to HIV medical care within one month of diagnosis
- By 12 months post-diagnosis, 92% of the newly diagnosed had been linked to medical care
- 60% had accessed care (having at least 1 medical visit)
- 40% were retained in care (having at least 2 visits)
- 48% were considered to be virally suppressed (HIV viral load < 200 copies/mL)

https://www.chicago.gov/content/dam/city/depts/cdph/HIV_STI/HIV_STISurveillanceReport2016_12012017.pdf

Figure 1.1: HIV Continuum of Care Among Cases 13 Years and Older, Chicago, 2016 (as of 9/26/2017) with 2020 National HIV/AIDS Strategy Indicators #4-6(red)



https://www.chicago.gov/content/dam/city/depts/cdph/HIV_STI/HIV_STISurveillanceReport2016_12012017.pdf

National HIV Prevention Objectives for 2020

- Increasing the percentage of PLWH who are diagnosed to 90%
- Increasing the percentage of persons newly diagnosed PLWH who are linked to care within one month to 85%
- Increasing the percentage of PLWH who are retained in care and taking ART to 90%
- Increasing the percentage of PLWH with viral suppression to 90%, with an emphasis on youth and persons who inject drugs

https://www.hiv.gov/federal-response/national-hiv-aids-strategy/overview

National HIV/AIDS Strategy Goals

- Reduce new infections
- Increase access to care and improve health outcomes for people living with HIV
- Reduce HIV-related health disparities and health inequities
- Achieve a more coordinated national response to the HIV epidemic

https://www.hiv.gov/federal-response/national-hiv-aids-strategy/overview

National HIV/AIDS Strategy for the United States: Updated to 2020 has goals of (diagnosed-on ART-virally suppressed)

A. 90-90-90

B. 90-90-80

C. 90-80-90

D. 80-90-90

National HIV/AIDS Strategy for the United States: Updated to 2020 has goals of (diagnosed-on ART-virally suppressed)

A. 90-90-90

B. 90-90-85

C. 90-85-90

D. 85-90-90

UNAIDS goal for 2020

Have you, as a health care consumer, ever been offered an HIV test?

A. Yes

B. No

C. Uncertain

Have you ever had to advocate for yourself and request a provider to test you?

A. Yes
B. No
C. Uncertain

Routine HIV Screening

Since 10/2006, CDC has recommended routine HIV screening in all health care settings for all patients 13-64 years of age

Repeat screening is recommended annually for those at continued risk

- every 3 months for high risk individuals
- age recommendations expanded based on social history

- Illinois permits HIV testing based on a patient's verbal consent after being given mandatory pretest information (nature of test and ability to refuse); also allows opt-out testing (consent given with other treatment consent)
- USPSTF, AAFP, others have similar recommendations

In practice, why test?

- ~ 14% HIV cases are undiagnosed
- Routine testing reduces HIV-related stigma
- Awareness of sexual risk factors leads to reduced high-risk sexual behaviors and fewer new infections
- Early initiation of ART (antiretroviral therapy) is now the standard of care
- Getting patients enrolled in routine care early helps maintain optimal health
- Sustained ART achieves viral suppression and reduces further transmission (treatment as prevention--TasP)

Illinois law

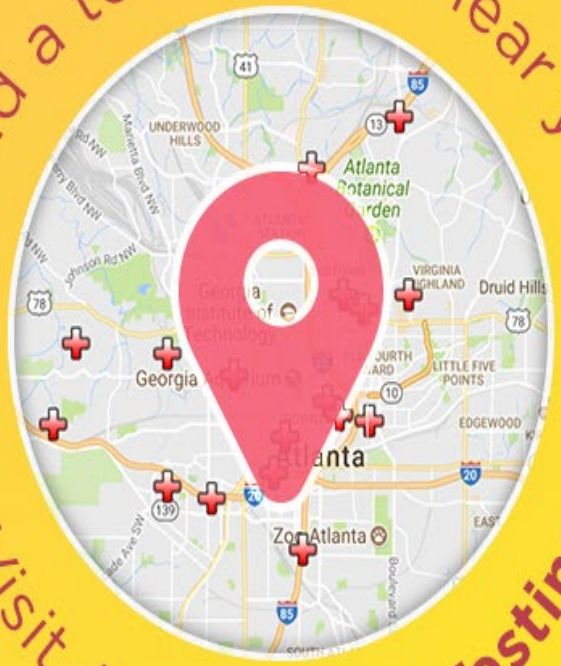
- Opt-out testing since 6/1/08
- Minors age 12 and older may consent for testing
  - If positive, provider may but NOT REQUIRED to inform parents
- Only sexual partner who provider may notify is legal spouse (NOT REQUIRED, high intimate partner violence risk)
- Test results must be delivered “by personal contact” whenever possible
- Persons who test positive must be referred for counseling and appropriate HIV care
- Although not required by law, high-quality screening and treatment programs will also counsel HIV negative patients about risk-reduction
- PLWH are not required to disclose status if using condoms

https://www.aidschicago.org/resources/legacy/pdf/2008/adv_HIV_testing_guide_clinicians.pdf

Only **50%**

of women
have ever been
tested for HIV.

Find a testing site near you



Visit **AIDSVu.org/Testing**

AIDSVU.ORG

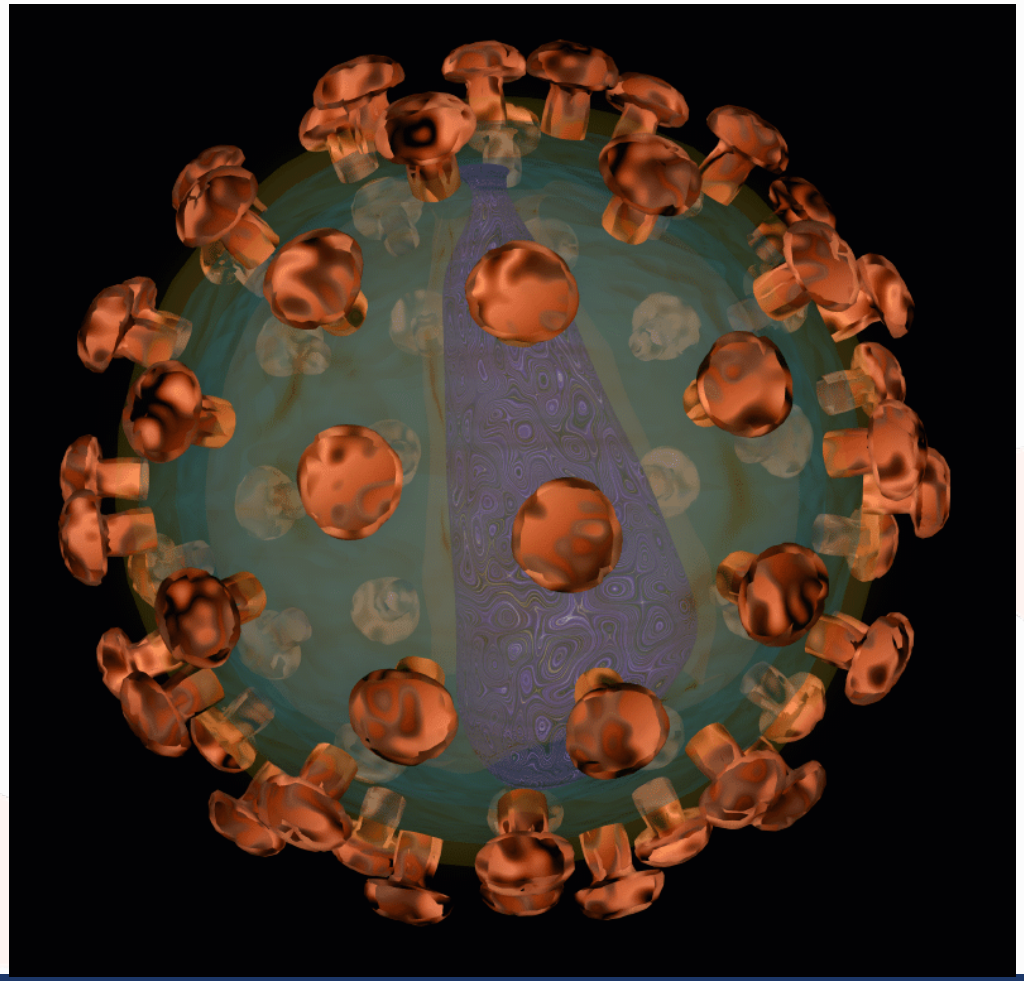
SOURCE: U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

AIDSVu

DISCUSS: Challenges of Implementing CDC HIV Testing Guidelines

- Why have we been so slow and ineffective in implementing CDC HIV testing guidelines in all practice settings?
- Brainstorming: What can we, as clinicians, do to promote the uptake of HIV testing?
- What impact would increased HIV testing potentially have "downstream"?

Clinical Spectrum of HIV Disease



Objectives

- Describe HIV pathogenesis
- Discuss the stages of HIV disease
- Describe the common manifestations of HIV disease

Stages of HIV Infection

Stages of HIV Infection

- Acute/Primary HIV infection
- Early asymptomatic HIV infection (Chronic)
- Late Symptomatic Disease (AIDS)

Definition of AIDS

- CD4 < 200, on two separate occasions

  AND/OR/BOTH
- AIDS defining illness
  - 26 different opportunistic infections and/or cancers

https://aidsinfo.nih.gov/education-materials/fact-sheets/19/46/the-stages-of-hiv-infection

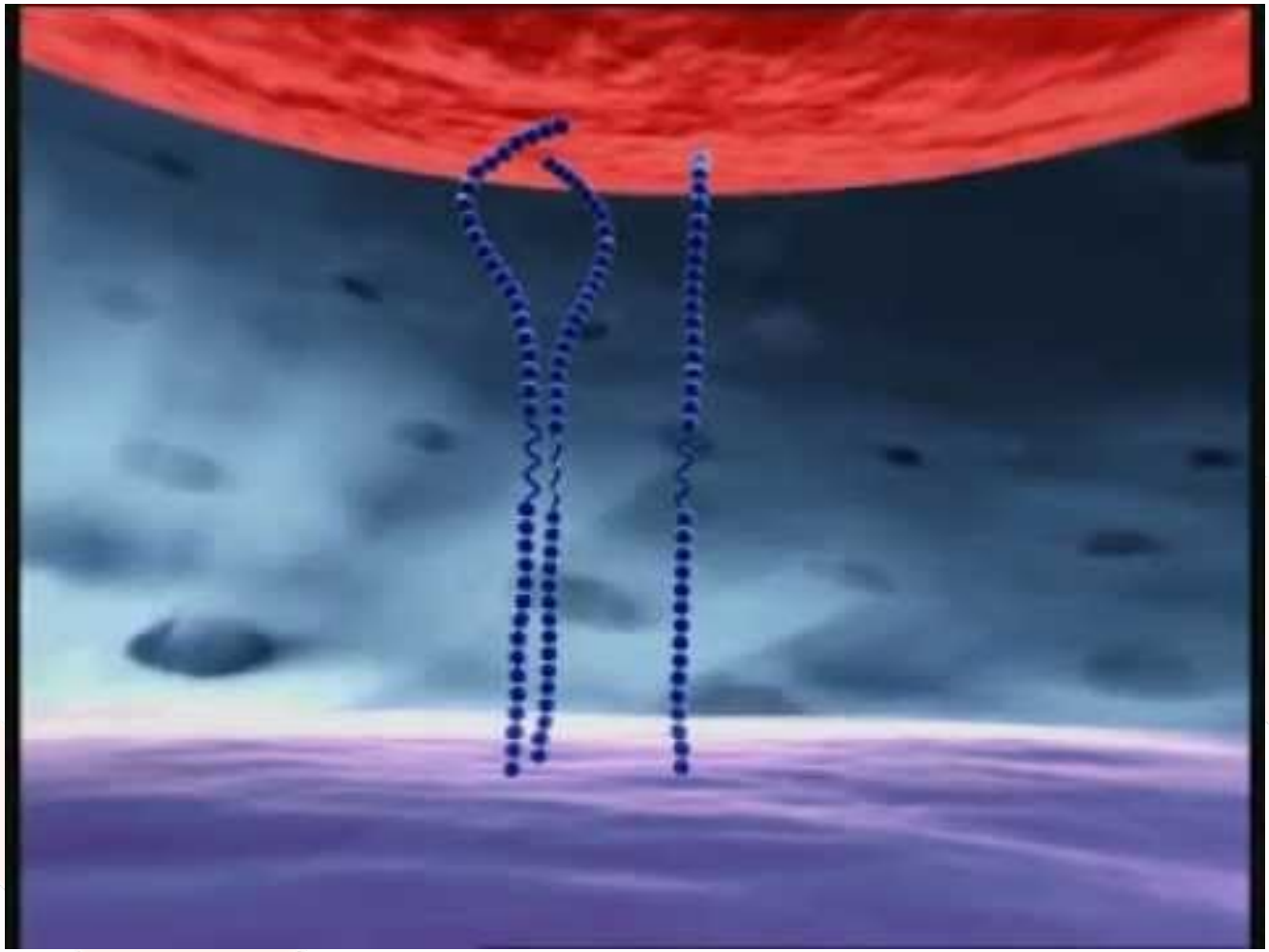
Fast facts

- HIV cannot multiply on its own
- HIV attaches to an immune system cell - the CD4 cell
  - it then fuses with the cell
  - it releases viral RNA into the cell
  - it uses the cell's machinery to make a DNA copy of the RNA
  - it integrates the DNA copy into the cell's DNA
  - it uses the DNA to make HIV proteins and new HIV RNA
  - these assemble into full HIV viruses as they are released
- Different HIV treatment medications stop these steps: attachment, fusion, copying the RNA into DNA, integration, protein assembly, and maturation

Destruction of CD4 Cells by HIV

- HIV uses CD4 cells' genetic material to create more HIV virions
  - HIV virions bud off the host cell, utilizing the CD4 cell membrane, destroying it
- When CD4 cells are destroyed, multiple functions of the immune system are lost
  - Eventually PLWH become vulnerable to opportunistic infections
- Antiretroviral therapies can interfere with the replication process, inhibit viral production and prevent further CD4 cell destruction

HIV Lifecycle



Relationship between CD4 Count and Viral Load

T-Cell Count+ distance to crash, HIV RNA= speed of train

Viral load = Speed

1000

10,000

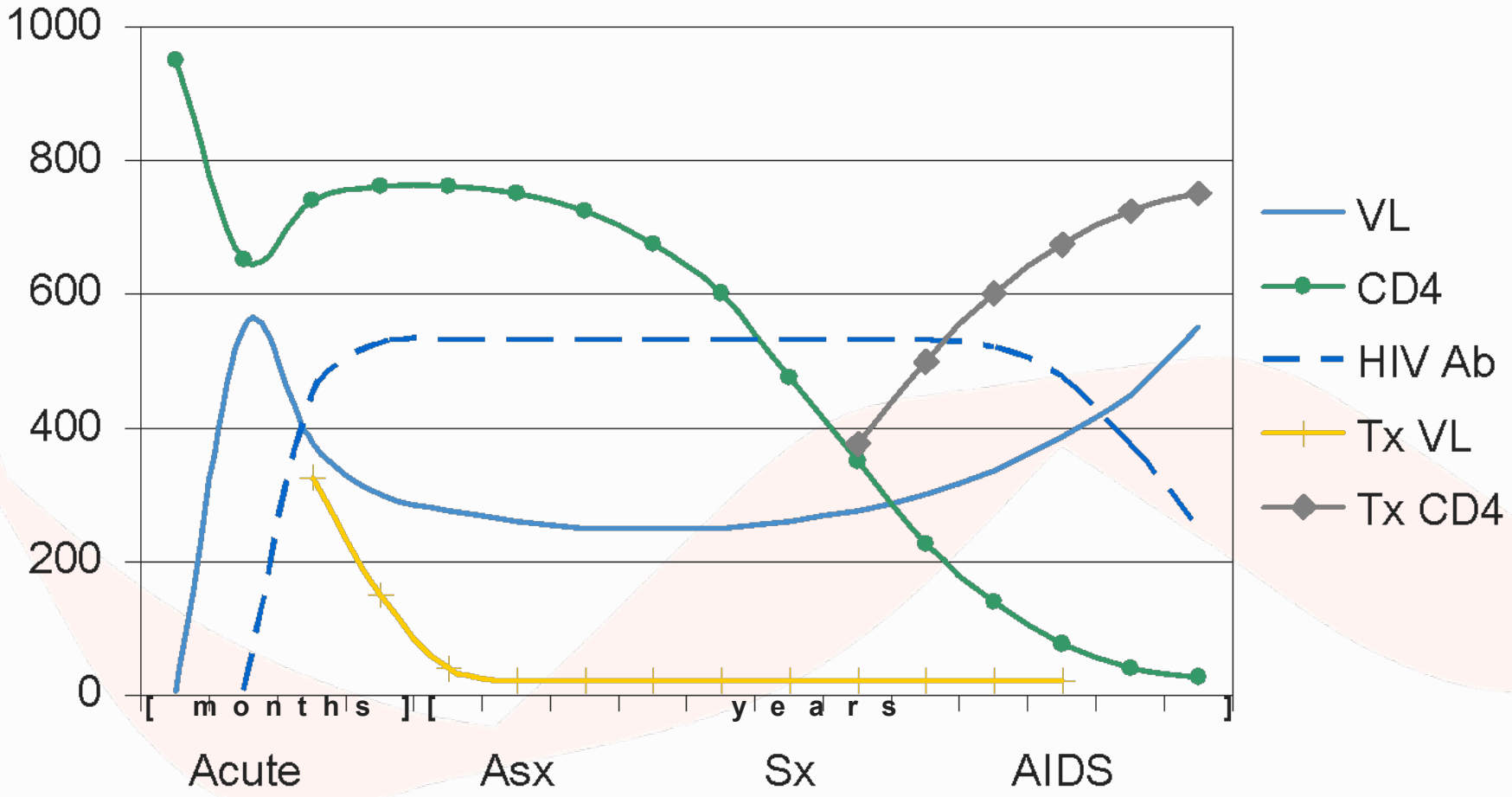
100,000

AIDS

1000 900 800 700 600 500 400 300 200

CD4+ Count = Distance

Course of HIV Disease



Case Study: Calvin

Calvin is a 22 yo cisgender man who presents to the ED with a 1-week history of headaches, fever, chills, rash, and fatigue.

He was camping with friends about a month ago and remembers having a tick bite.

Calvin

- He has sex with men and women.
- He uses condoms with partners most of the time, though not with his girlfriend of 2 years.
- His last HIV test was negative, 6 months ago.
- He uses tobacco and alcohol occasionally, but denies any injection drug use.
- Other than an allergy to sulfa drugs, Calvin reports no significant past medical history.

Case Study: Calvin

- Physical Exam Findings
  - T: 99.5 F P: 75 BP: 120/75 RR: 18
  - Rapid HIV test: nonreactive
  - General: awake, alert, oriented x 3, in no acute distress
  - O/P: erythematous w/o exudate, multiple shallow ulcers
  - Neck: bilateral cervical and submandibular lymphadenopathy
  - Lungs: clear to auscultation bilaterally
  - Abdomen: +BS, soft, non-tender, +splenomegaly
  - Skin: diffuse erythematous macular-papular rash on his chest and thighs
  - Neuro: no focal defects noted

Case Study: Calvin

What diagnostic tests would you order?

A. HIV Ab/Ag
B. HIV PCR
C. RPR
D. CMP
E. HBV / HCV
F. GC/CT x 3
G. CBC
H. RMSF Ab titer

What is likely to be Calvin's diagnosis or diagnoses?

A. Secondary Syphilis Infection

B. Acute HIV Infection

C. Acute HIV Infection and Secondary Syphilis

D. Acute Hepatitis C Infection

Case Study: Calvin

- Diagnostic Test Results

- HIV Ab/Ag (indeterminate)
- HIV RNA PCR (> 500K)
- RPR (1:128)

- CMP (↑ LFTs)
- HBV / HCV (neg)
- GC / CT (neg x 3)
- RMSF Ab titer (neg)

- CBC:

  WBC (1.9)

  Hgb (14.8)

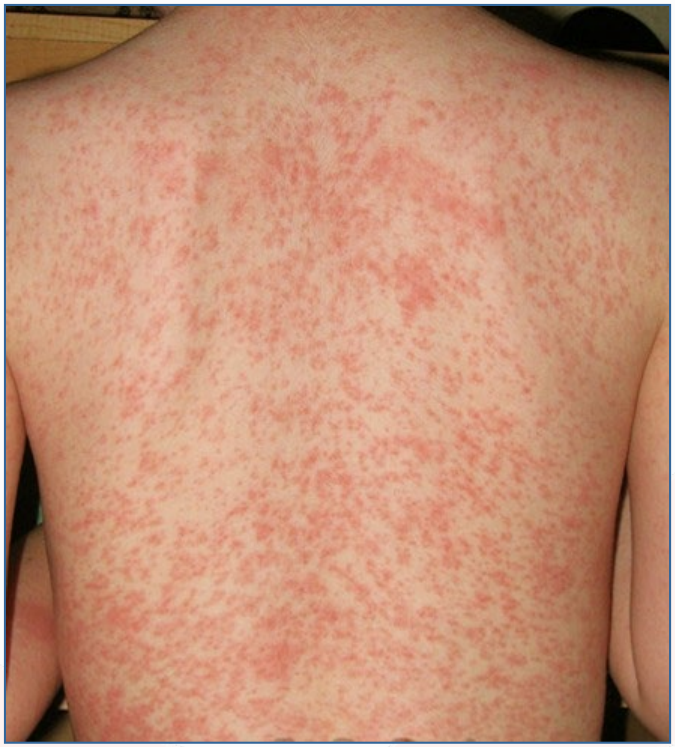
  Plt (98,000)

Acute / Early Primary HIV Infection

Many patients who have recently acquired HIV have signs and symptoms of an acute viral syndrome:

- Fever 96%
- Adenopathy 74%
- Pharyngitis 70%
- Rash 70%
- Fatigue 68%
- Myalgia/arthralgia 54%
- Thrombocytopenia 51%
- Leukopenia 38%
- Headache 32%
- Diarrhea 32%
- Oral or genital ulcers 28%
- Nausea/vomiting 27%
- Hepatosplenomegaly 14%
- Weight loss > 5 lbs 13%
- Neurologic symptoms 12%
- Oral thrush 12%

Rash of Primary HIV Infection



Characteristics

- diffuse, reddish, macular-papular, non-pruritic
- distribution: truncal, proximal limbs, not palms/soles
- often resolves prior to pt presentation

Case Study: Calvin

Calvin returns in 3 days to get his test results, and you inform him that his HIV test is positive (detectable HIV viral load).

You connect him with the case manager in your clinic, to sign up for insurance and the AIDS Drug Assistance Program (ADAP), among other things.

What additional things will you, as the provider, need to assess as you begin to provide and coordinate care for Calvin?

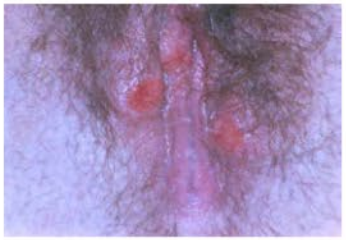
Additional Things to Look For

- Last syphilis screening result, if any
- If you can confirm nonreactive (or stable baseline titer) in last year, 1 injection Benzathine PCN, if not, 3 injections (unless secondary)
- Titers ≥1:32, need neurologic history and exam
  - Include assessment of visual/neuro complaints
- Monitor at 3, 6, 9 at 12 at 24 months
- Goal of Tx is a 4 fold decrease in titer by 6-12 months for early syphilis OR 12-24 months for late syphilis or of unknown duration syphilis
- In Calvin's case, 1:128 should decrease to 1:32 in next 1-2 years (typically in 1 year, PLWH can take up to 2 years)

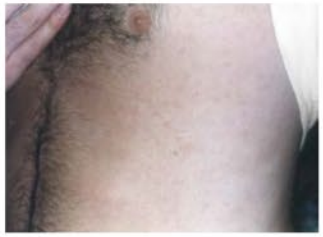
Early Syphilis

Primary → **Secondary** ⟷ **Late Syphilis**

Latent → **Tertiary**



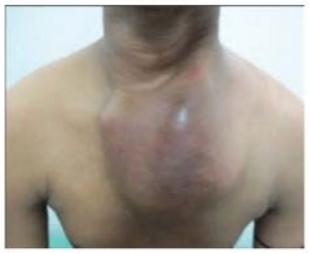
~ 3 weeks after infection



~ 6 weeks after infection

Early | Late

Weeks to years after infection



Years to Decades after infection

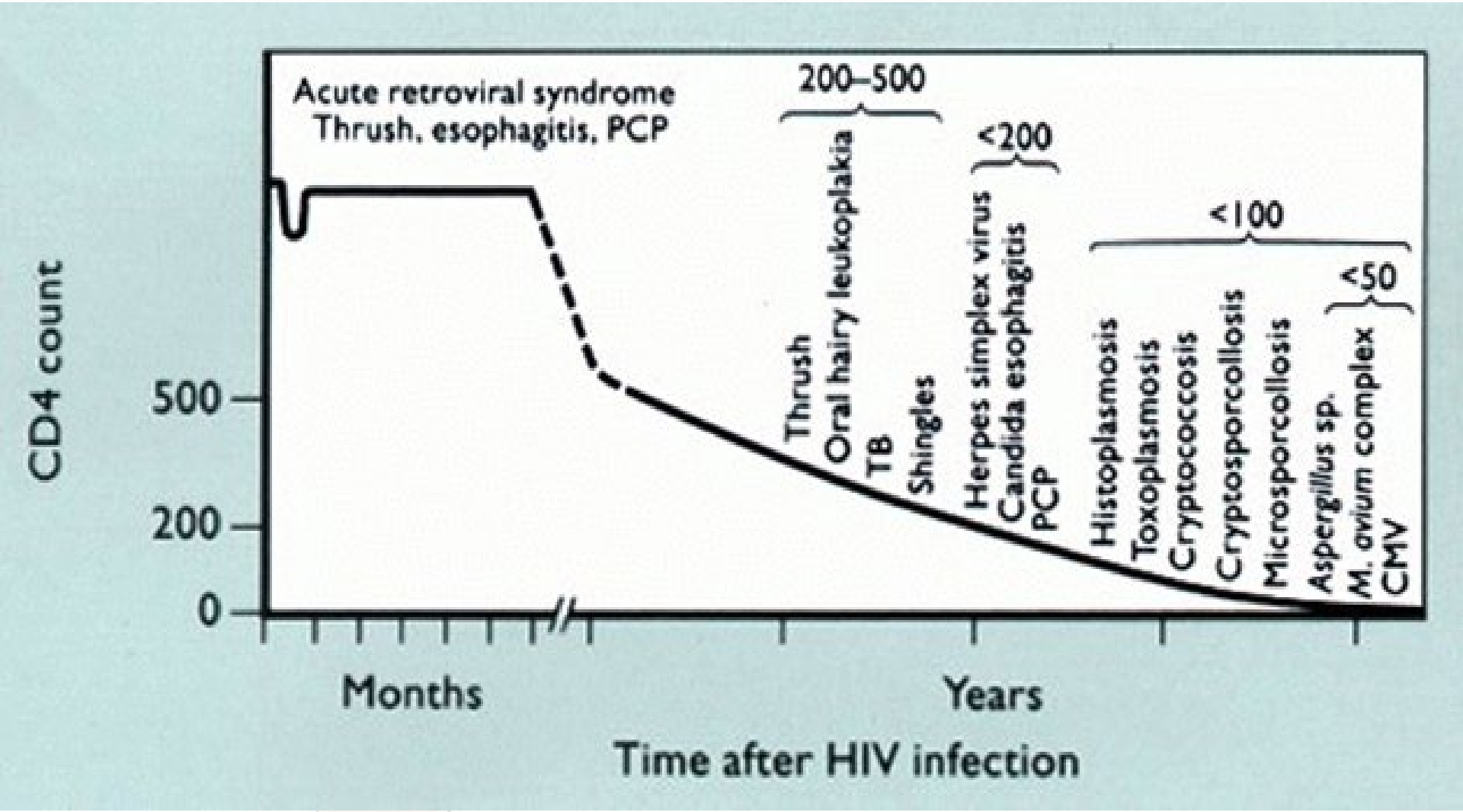
Can be transmitted congenitally, most likely during early stages

Neurologic complications can occur at any stage of syphilis

ODPHP | Office of Disease Prevention and Health Promotion

CDC

CD4 & Risk of Clinical Disease



years

Early Symptomatic HIV Disease

Common Symptoms

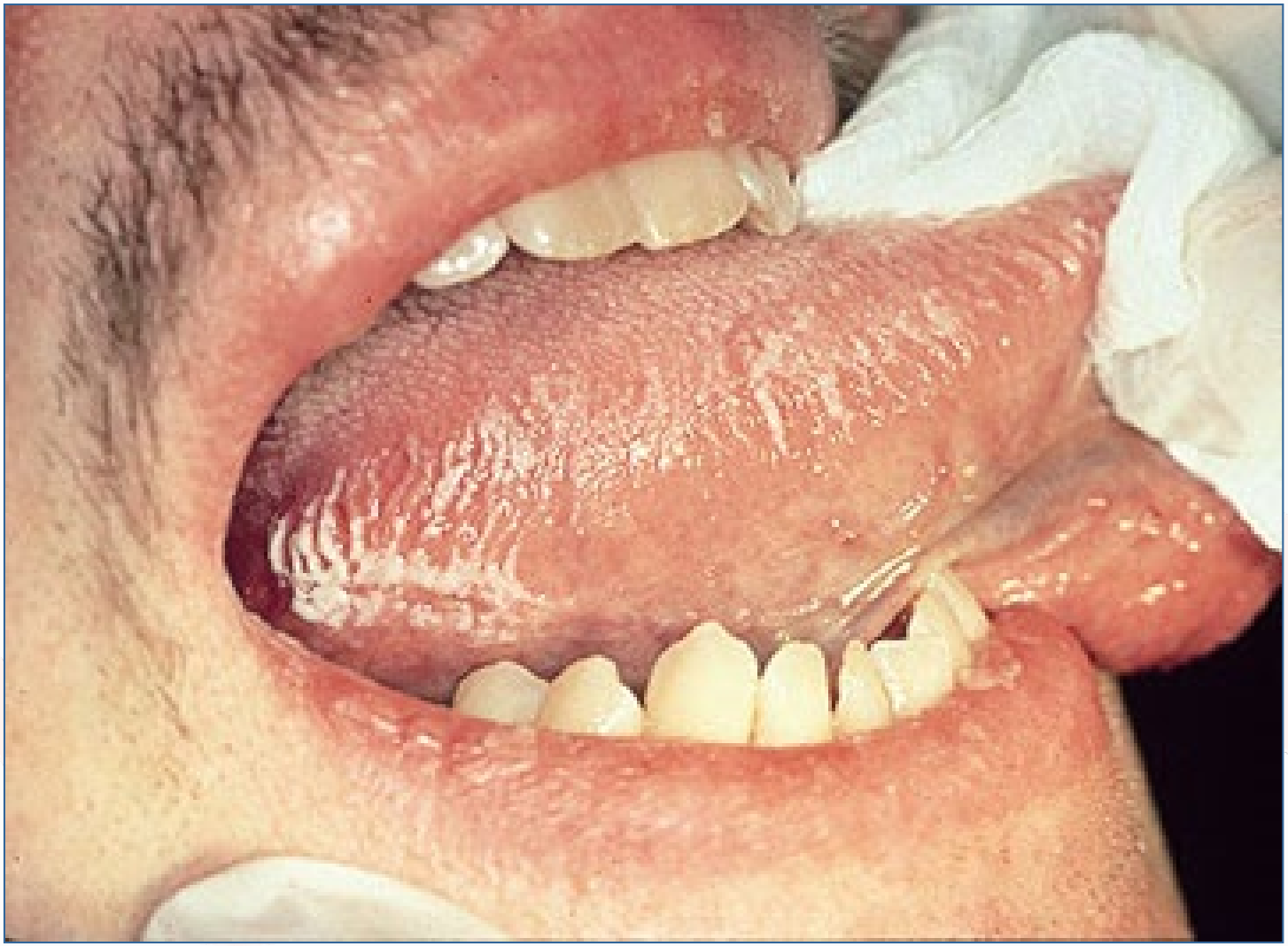
- persistent fatigue
- recurrent fevers
- chills/night sweats
- persistent diarrhea
- weight loss

Clinical Findings:

- generalized adenopathy
- thrush/recurrent vaginitis
- oral hairy leukoplakia
- herpes zoster/shingles
- dermatitis/seborrhea
- recurrent bacterial infections

HIV-Associated Infections

Oral Hairy Leukoplakia



Oral Hairy Leukoplakia (OHL)

Presentation

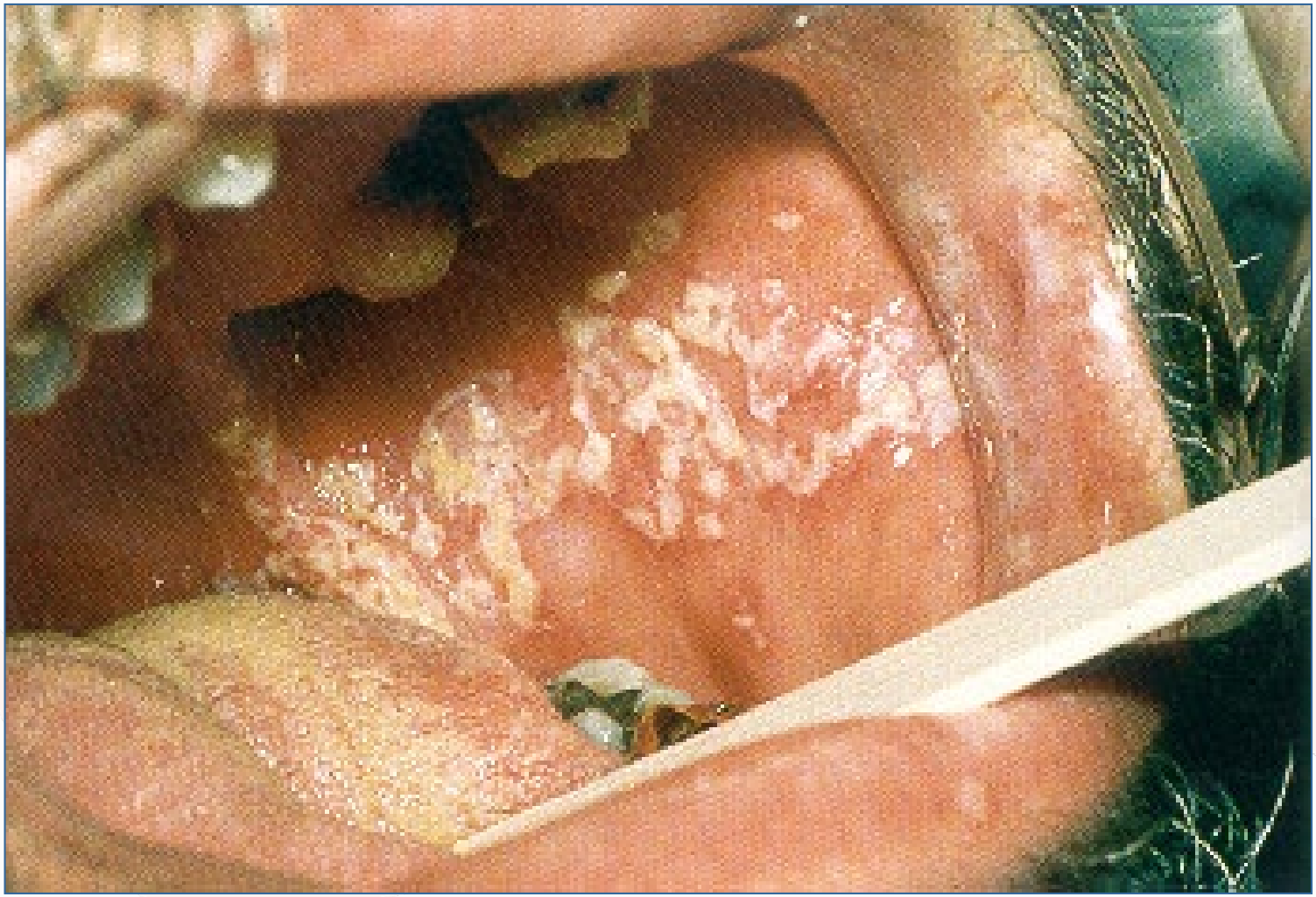
- benign, painless white striated plaques on the lateral border of the tongue with no erythema
- does not wipe off with gauze or tongue blade
- Related to Epstein Barr Virus (EBV)

Diagnosis:

- biopsy (EBV grows from cultures)
- pathognomonic for HIV infection

Treatment: none (initiate ART)

Oral Candidiasis / Thrush



Oral Candidiasis / Thrush

Presentation

- cheesy, creamy patches with erythema on the tongue, palate, and/or buccal mucosa
- does wipe off with gauze or tongue blade
- Causes difficulty eating or swallowing
- Bad taste in mouth (metallic) or food can taste bad
- Can be painful, sore throat, clearing of throat, cough

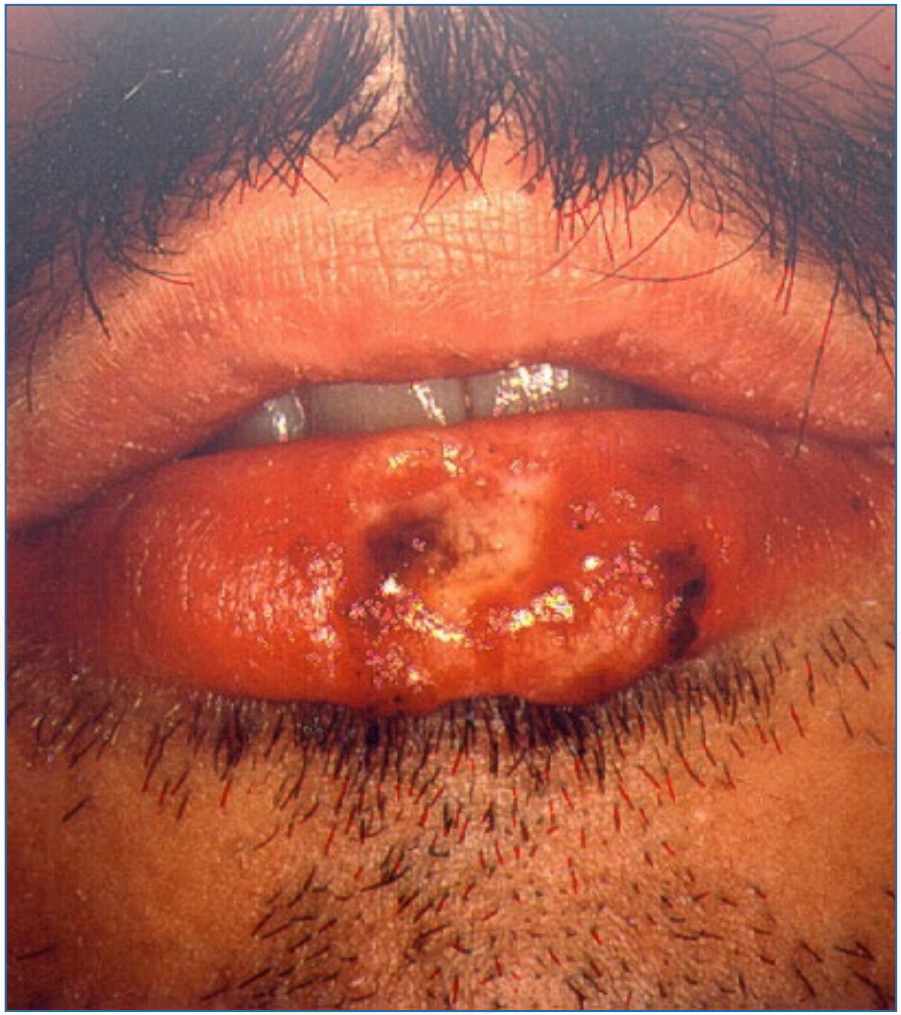
Diagnosis:

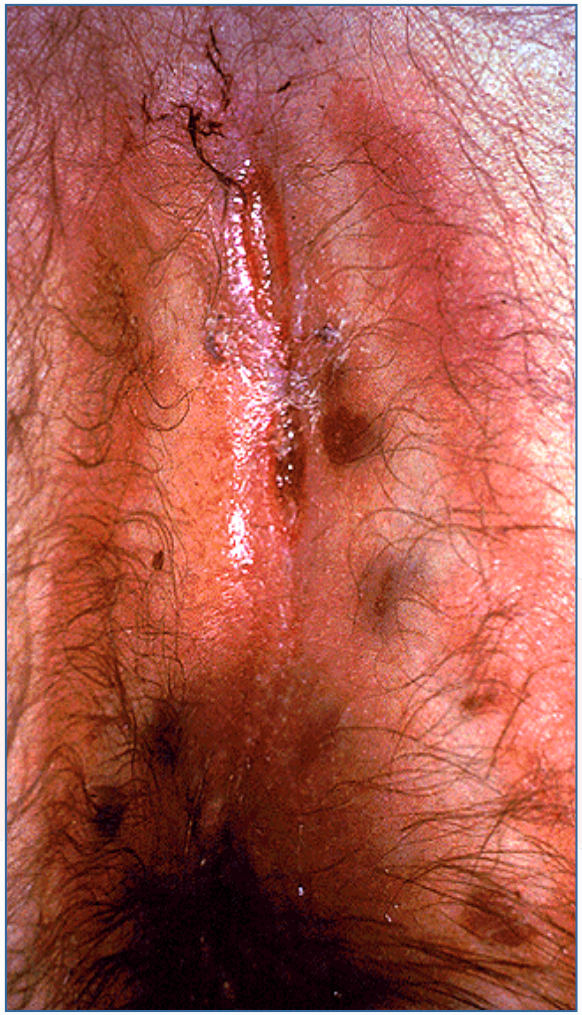
- KOH prep, wet mount (hyphae and budding yeast)

Treatment:

- topical antifungal agents (nystatin, mycelex)
- systemic agents (fluconazole, etc.) preferred

Herpes Simplex





Herpes Simplex

Presentation

- recurrent, painful blisters/ulcers in the perioral, genital, and/or perirectal tissue
- may not see crusting with perirectal lesions

Diagnosis:

- empiric: history and clinical presentation
- definitive: culture or PCR (HSV-1 and/or HSV-2)
- serum testing not appropriate

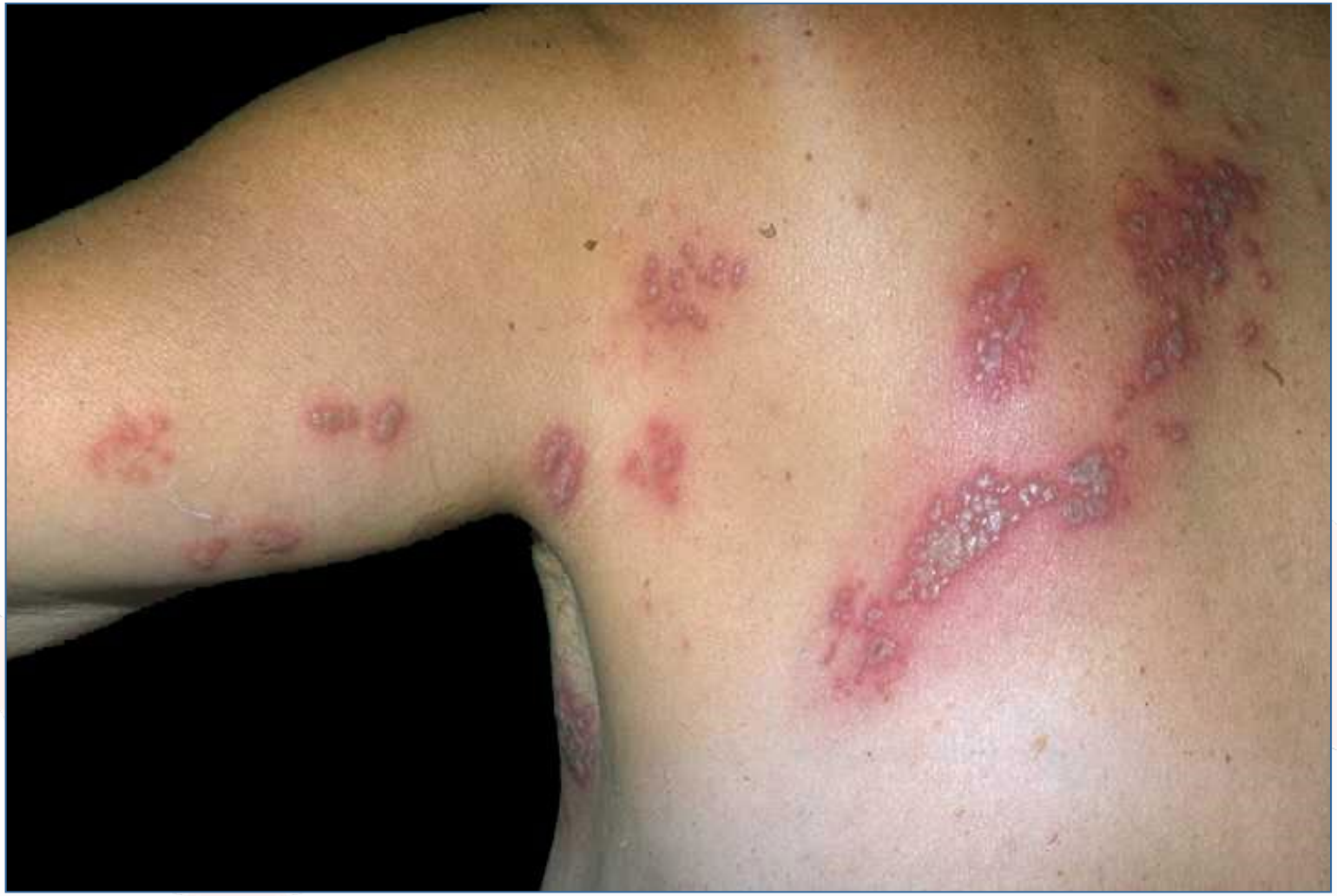
Treatment:

- anti-herpes agent (acyclovir, valacyclovir, etc)

Case Study: Yvonne

- Yvonne is a 26 yo woman who presented to an ED with shingles across her right chest and was referred to her PCP for follow up. She lives with her husband of 6 years and reports no prior shingles or any other current or past medical problems.
- What would you look for on physical exam (expected and red flags)?
- What further work up would you recommend?

Herpes Zoster / Shingles



Herpes Zoster / Shingles

Presentation

- dermatomal distribution of painful blisters/ulcers
- look for dissemination (multiple dermatomes, crossing the midline, visceral involvement, etc)

Diagnosis:

- empiric: history & clinical presentation
- definitive: culture (Varicella Zoster Virus)

Treatment:

- oral anti-herpes agent (acyclovir, valacyclovir, etc)
- likely requires pain management
- close follow-up for PLWH

Opioid Vs. Non-Opioid Pain Management in Shingles

- When to use opioids?
  - Consider for initial pain if no response to NSAIDs
  - Limited quantity and no refills
  - May need to add agents (gabapentin, etc.)
- Post-herpetic syndrome
  - Pain persisting 90 days or longer
  - Topical capsaicin or lidocaine
  - gabapentin and tricyclic antidepressants
  - NSAIDS

Late Symptomatic Disease / AIDS

- Pneumocystis pneumonia: *Pneumocystis jiroveci* pneumonia (PJP), formerly known as *Pneumocystis carinii* pneumonia (PCP)
- Tuberculosis
- MAC (*Mycobacterium avium* Complex)
- HIV Associated Neurologic Disease
- Toxoplasmosis, Cryptococcal meningitis, Histoplasmosis
- CMV retinitis

Case Study: Jason

Jason is a 43 year old male diagnosed with HIV 8 years ago.

- He was initially on antiretroviral therapy (ART), but has been off for the last year.
- His nadir CD4 was 150
- Last CD4 (one year ago, on while on ART) was 450
- He presents with 1 week of productive cough, low-grade fever, and sweats
  - some DOE climbing stairs
  - one episode of hemoptysis
- No known TB exposure

Case Study: Jason

- Exam:
  - T=100.3F RR=20 BP=105/70 P=94
  - HEENT: mild oral thrush
  - Neck: supple, few shotty nodes
  - Lungs: crackles left mid/lower lung field
  - Remainder of exam unremarkable
- What additional tests can be done in the clinic to evaluate this patient?

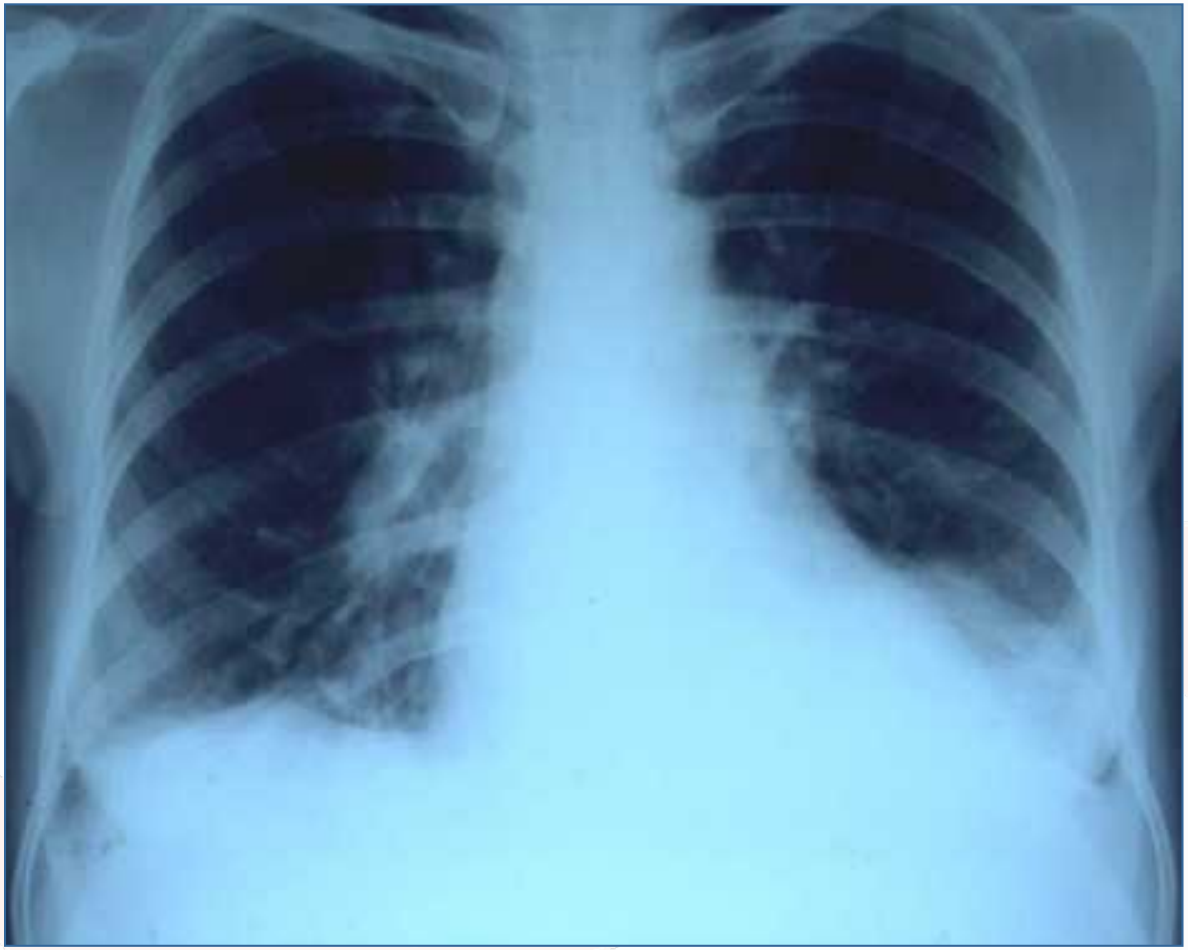
Case Study: Jason

- Labs:
  - O2 sat = 93% on RA at rest
  - WBC = 11.8
  - CXR shows patchy bilateral infiltrates, L>R
    - No cavitation or adenopathy noted
  - CD4 count is 75
  - Quantiferon Gold TB test positive

Case Study: Jason
What is your preliminary diagnosis?

A. PCP
B. TB
C. Bacterial: Strep pneumo, Atypical
D. Viral: influenza
E. Fungal: Blasto, histo, crypto (endemic fungi)

Tuberculosis



Tuberculosis

Presentation

- chronic fever, night sweats, anorexia, weight loss, productive cough, hemoptysis, dyspnea

Diagnosis:

- sputum AFB stain
- blood & sputum cultures
- CXR often atypical w/o apical infiltrates/cavities, likely to see lobar infiltrates & hilar adenopathy

Case Study: Jason who is off ART

Initiate daily treatment for TB first!

- Phase 1 (intensive): INH + RIF + PZA + EMB x 2 months
- Phase 2 (continuation): INH + RIF x 4 months

CD4<50, initiate ART within first two weeks of TB treatment

CD4>50, initiate ART by 8-12 weeks of TB treatment

ethambutol (EMB), pyrazinamide (PZA), rifampin (RIF), isoniazid (INH)

Tuberculosis in PLWH notes

- Active disease is treated for minimum 6 months
  - Recommended 9 months if person is not on ART
  - Consider extending if delayed response to therapy (ie culture positive after two months)
- Latent disease is treated with daily INH + B_6 for 9 months
- Patients with TB meningitis SHOULD NOT start ART before 8-10 weeks of TB treatment is completed, regardless of CD4 count. Why?

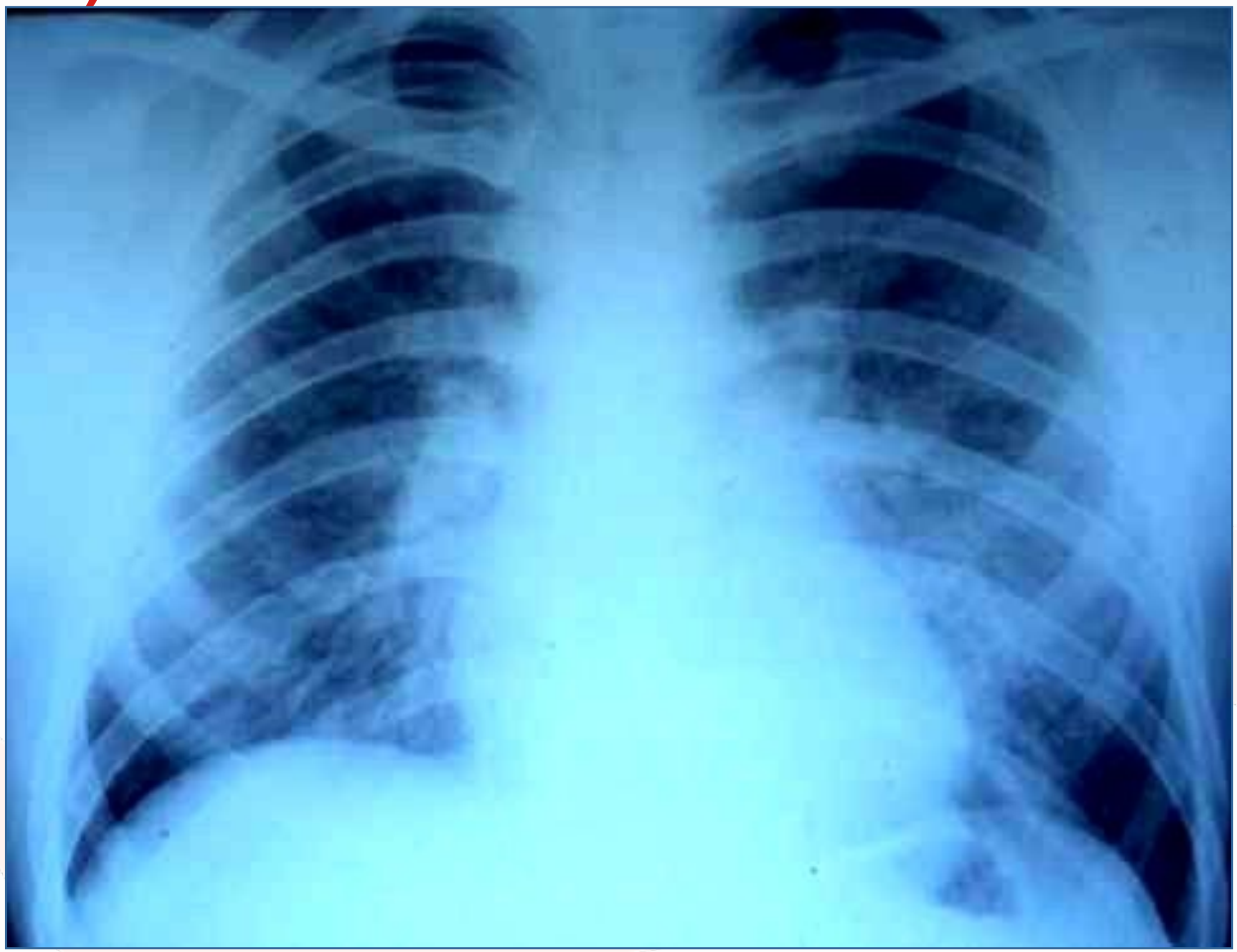
Case Study: Julio

- Julio is a 43 year old Hispanic male recently diagnosed with HIV with baseline CD4 = 152
- Started ART and TMP/SMX (Bactrim DS) prophylaxis 3 weeks ago
- Presents with
  - productive cough x 2 weeks
  - denies hemoptysis, fevers, sweats
  - some dyspnea with the cough
- No known exposure to TB but volunteers in local shelter

Case Study: Julio

- Physical exam:
  - Patient is in no acute distress
  - P: 88; R: 20; T: 99.2F; BP: 110/82
  - Lungs have bibasilar crackles on exam
  - Neck has shotty adenopathy
  - Remainder of exam unremarkable
- What is your differential diagnosis?
  - Influenza virus, PCP, pulmonary TB

Pneumocystis Pneumonia (PJP)



Pneumocystis Pneumonia (PJP)

Presentation

- Fever, dry cough, dyspnea, tachypnea, fatigue on exertion, low pO2

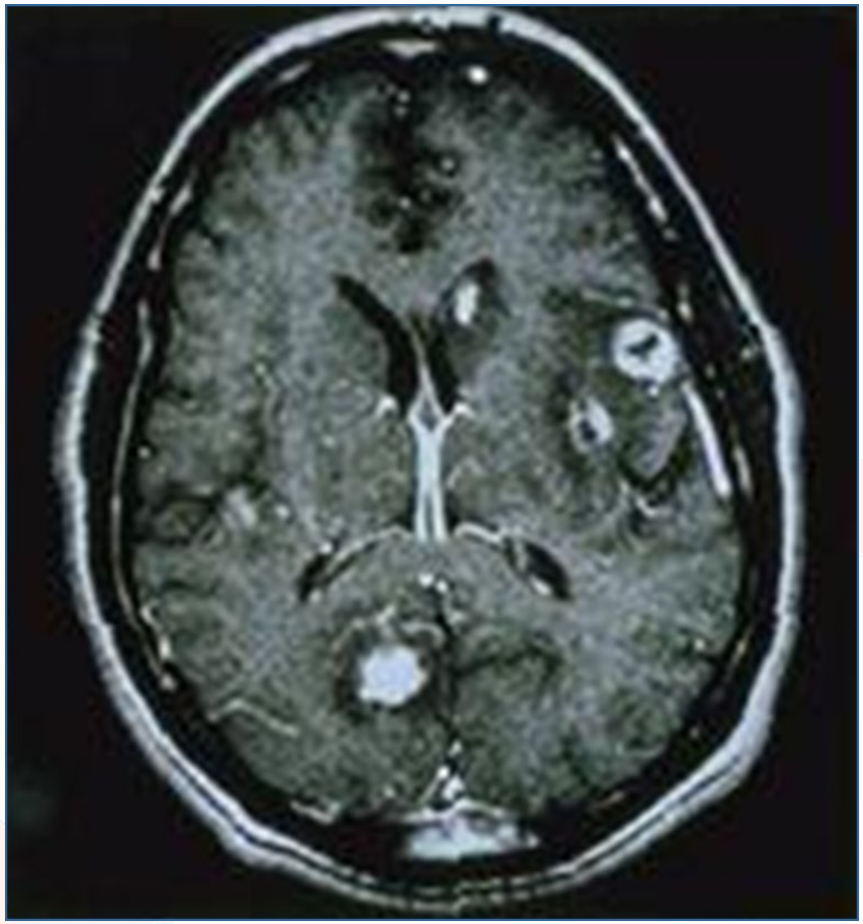
Diagnosis:

- Empiric: HIV+, CD4< 200, CXR or CT
- Clinical: desat on 6-Minute Walk Test
- Definitive: bronchoscopy or bronchoalveolar lavage

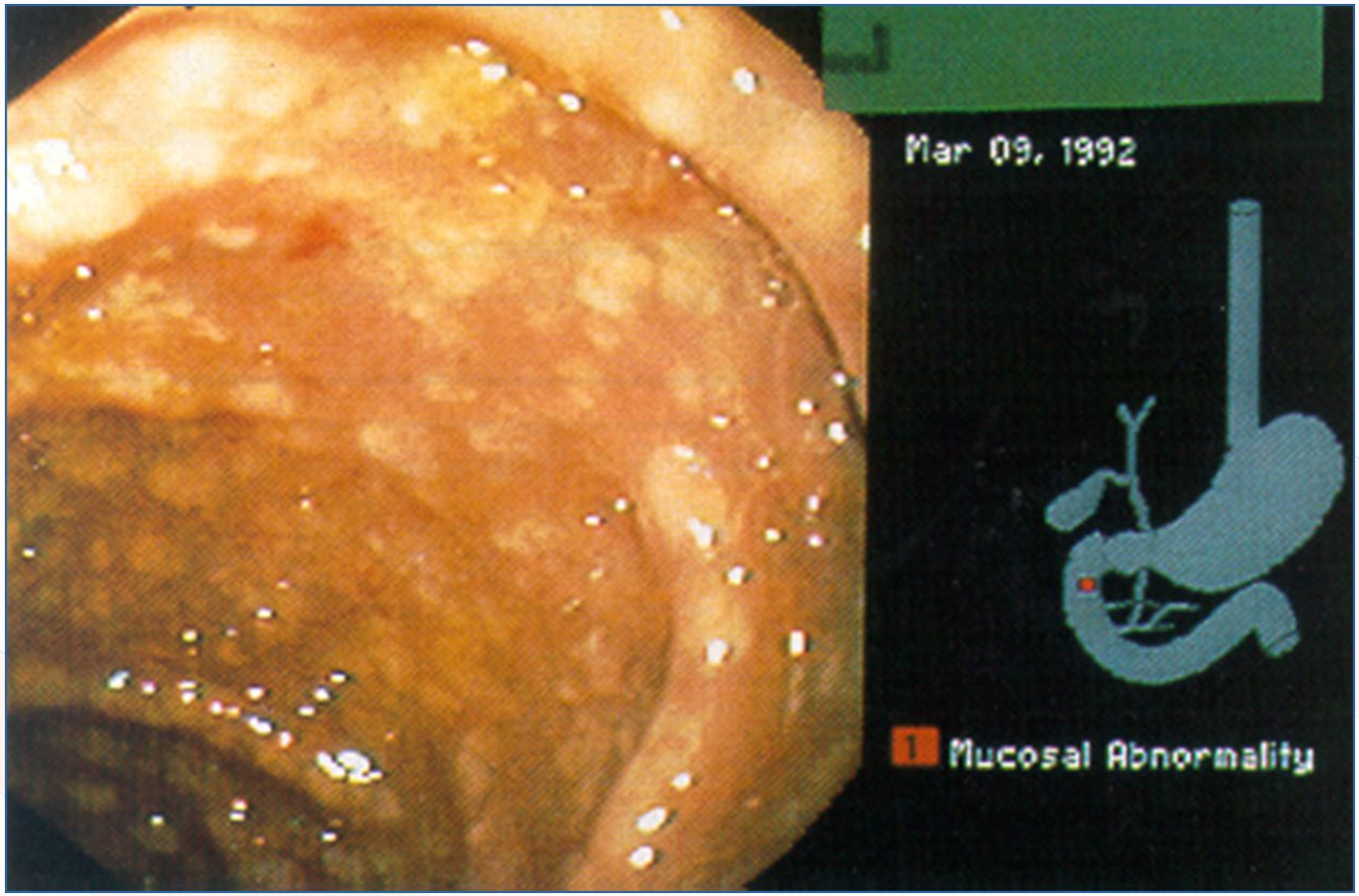
Treatment:

- IV or oral TMP-SMX (Bactrim) x 21 days
- Prednisone

Toxoplasmosis Encephalitis



Mycobacterium Avium Complex (MAC)



HIV Conditions Independent of CD4

Infections:

- Syphilis
- Tuberculosis
- Hepatitis C

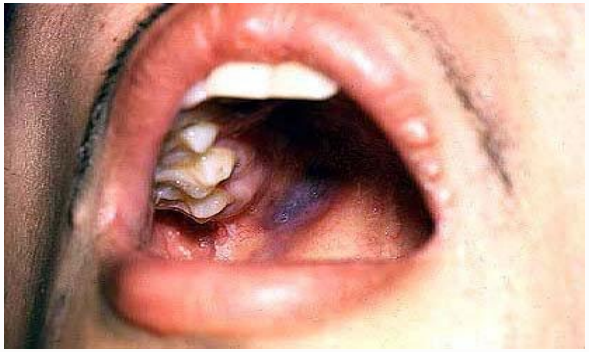
Nervous System:

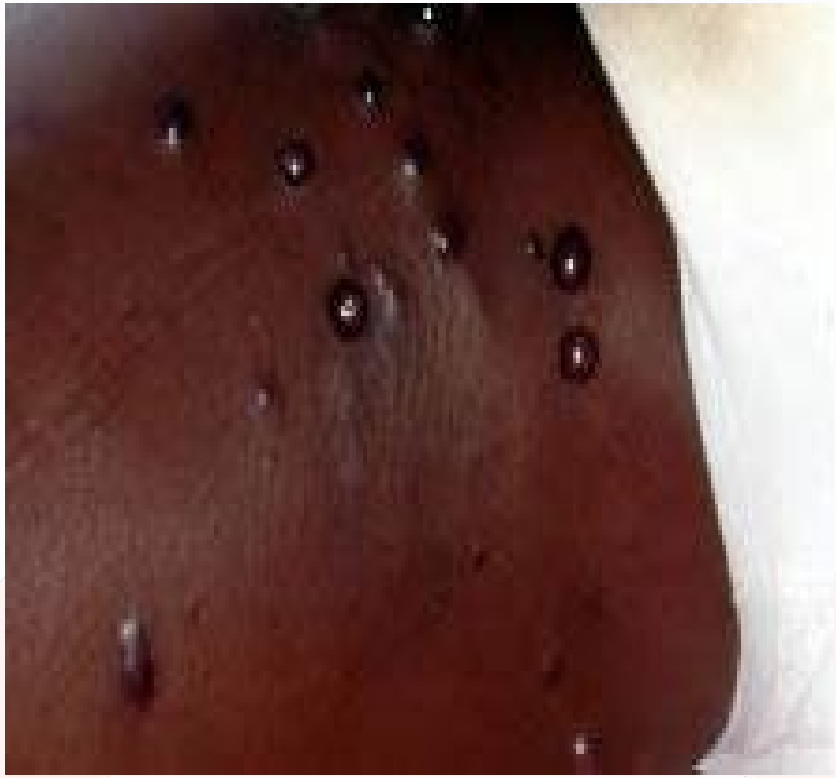
- HIV-associated neurologic disease
- Neuropathy

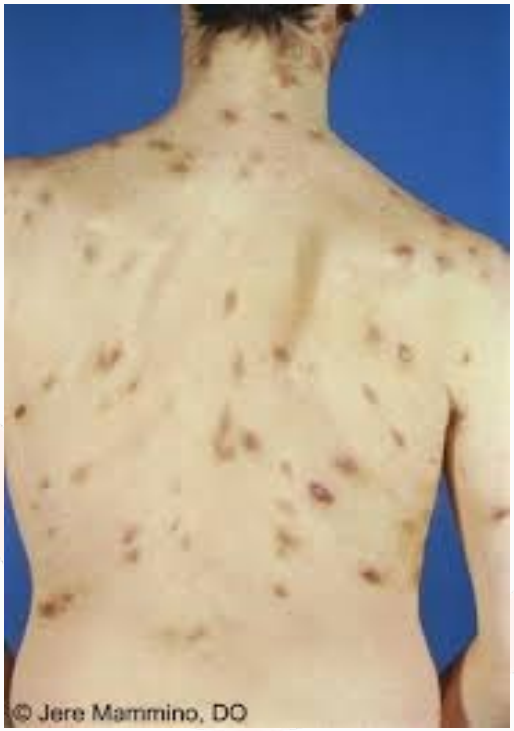
Malignancies:

- Kaposi Sarcoma (KS)
- Lymphoma
- HPV Dysplasias
  - Cervical dysplasia/carcinoma
  - Squamous cell dysplasia/carcinoma of anus

KS







HIV-Associated Neurologic Disease

Stage 1: Mild

- Fatigue, appetite and sleep disturbances
- Decreased concentration, attention, short-term memory
- Apathy, decreased interest, social withdrawal, flat affect

Stage 2: Moderate

- Decreased cognitive and/or gross motor functioning
- Long-term memory deficits, slowed mentation/speech
- Emotional lability

HIV-Associated Neurologic Disease

Definitions--3 categories:

- Asymptomatic neurocognitive impairment (ANI) is determined by neurocognitive testing and is not apparent clinically
- Mild neurocognitive disorder (MND) is a diagnosis of exclusion; it may be made clinically if neurocognitive testing is not available, and it involves mild functional impairment
- HIV-associated dementia (HAD) involves moderate to severe functional impairment.
  - Both MND and HAD are AIDS-defining conditions

HIV-Associated Neurologic Disease

Risk Factors

- Older age
- Female gender
- More advanced HIV disease, high viral load
- Comorbid conditions (especially anemia and infection with cytomegalovirus, Human Herpes virus 6, and JC virus)
- History of injection drug use (especially with cocaine)
- History of delirium

HIV-Associated Neurologic Disease

Incidence

- 30-50% of PLWH

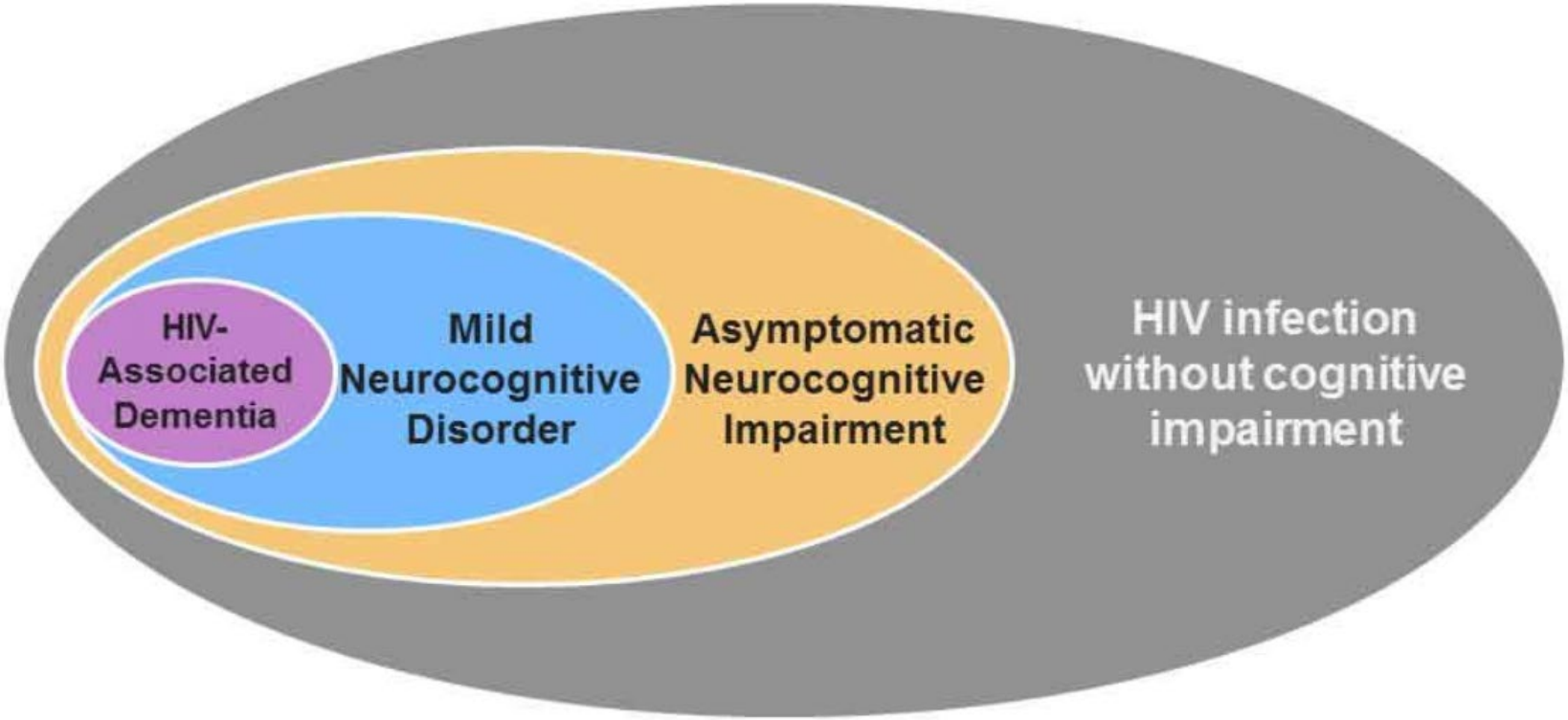
Diagnosis

- MoCA or MMSE (recall, spell word backwards)
- Full neuro exam to rule out all other etiologies

Treatment

- ART
- Nutrition, stress management, vitamin supplementation (especially B vitamins), medication adherence counseling, safe environment

Neuropsychological Impairment in the Era of Effective ART[4]



CHARTER Study (n=1,555 HIV-infected adults)
52% had NP impairment: HAD 2%, MND 12%, ANI 33%

Figure modified from Li, 2013[13]

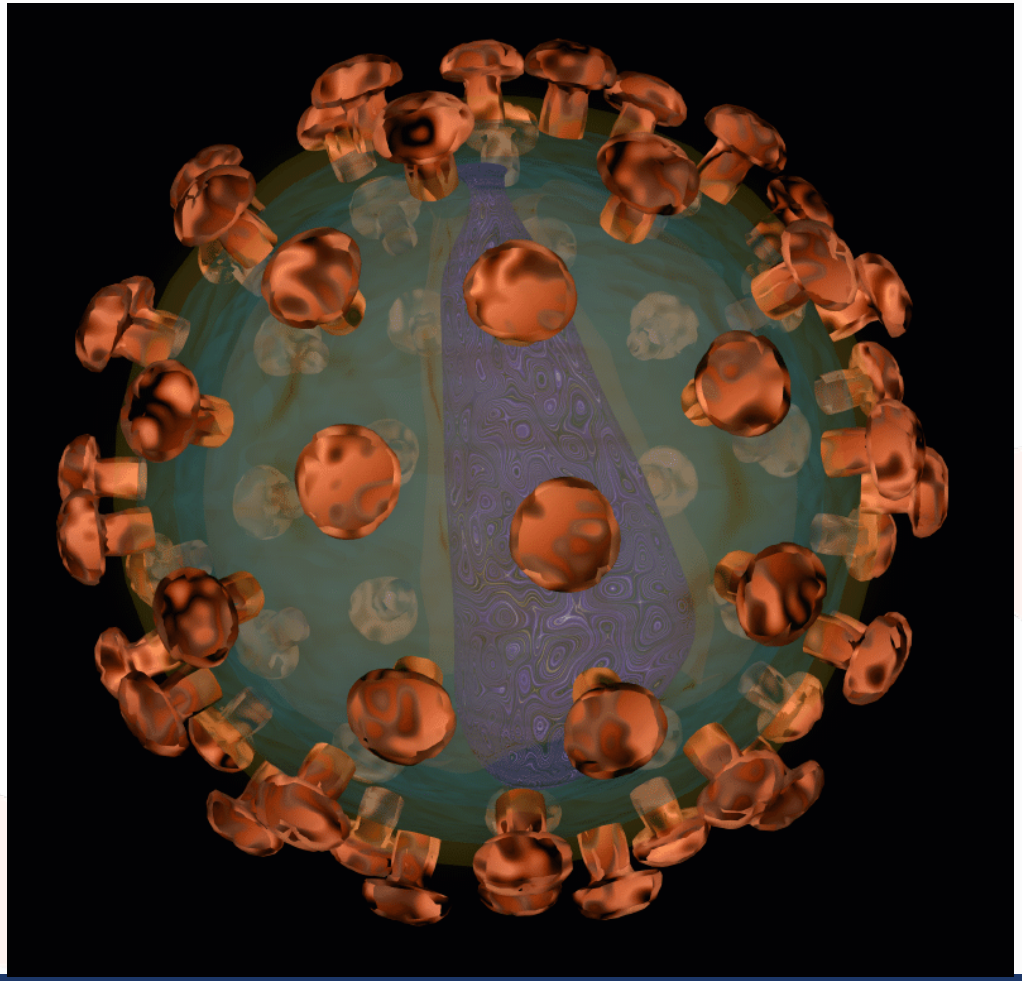
HIV/HCV Co-infection: An AETC National Curriculum

7

Other HIV-Associated Conditions

- Constitutional Disease / Wasting Syndrome
- Immune Reconstitution Inflammatory Syndrome (IRIS)
- Cervical and Anorectal Dysplasia/Neoplasia
- Non-Hodgkin's Lymphoma
- Solid tumors / Kaposi Sarcoma
- Cardiomyopathy
- Nephropathy
- Neuropathy

Diagnosis & Baseline Assessment

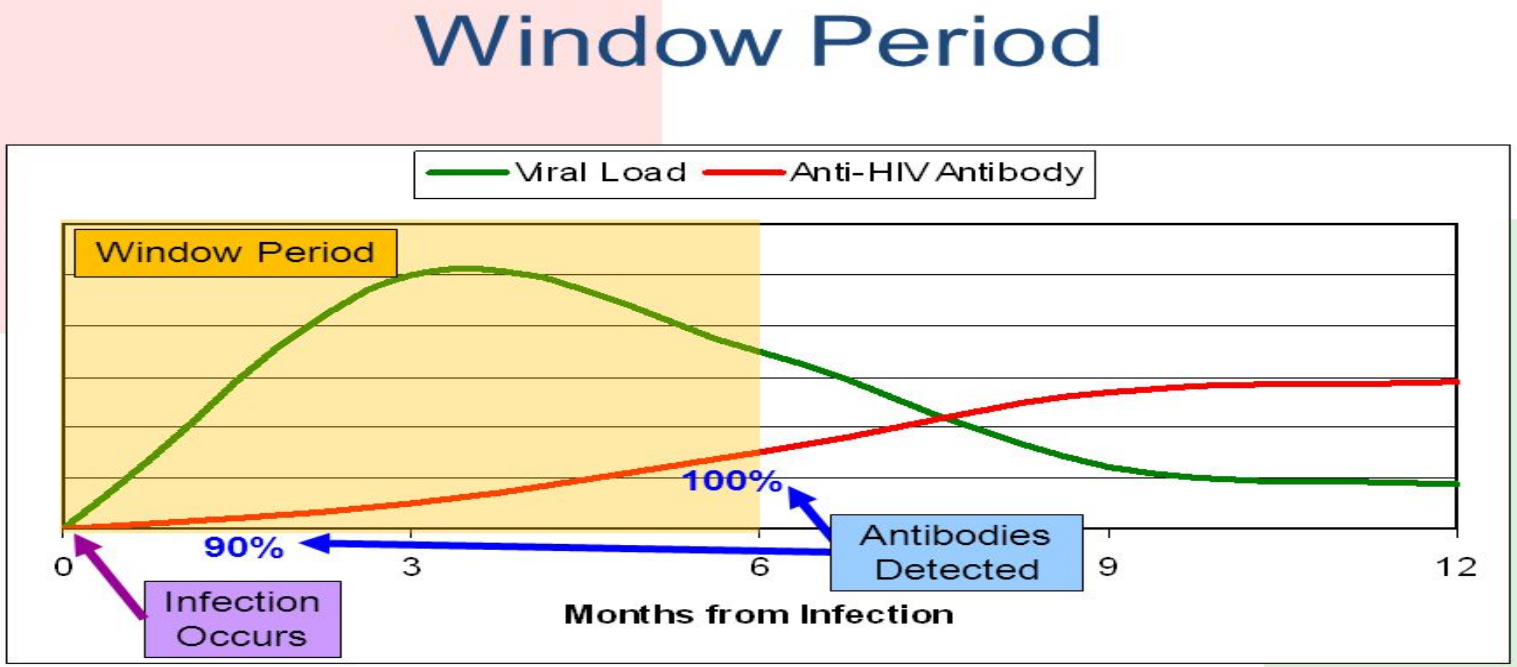


Objectives

- Review the diagnostic tests for HIV infection
- Discuss baseline assessments/lab tests for the newly diagnosed HIV patient

HIV Diagnosis Challenge

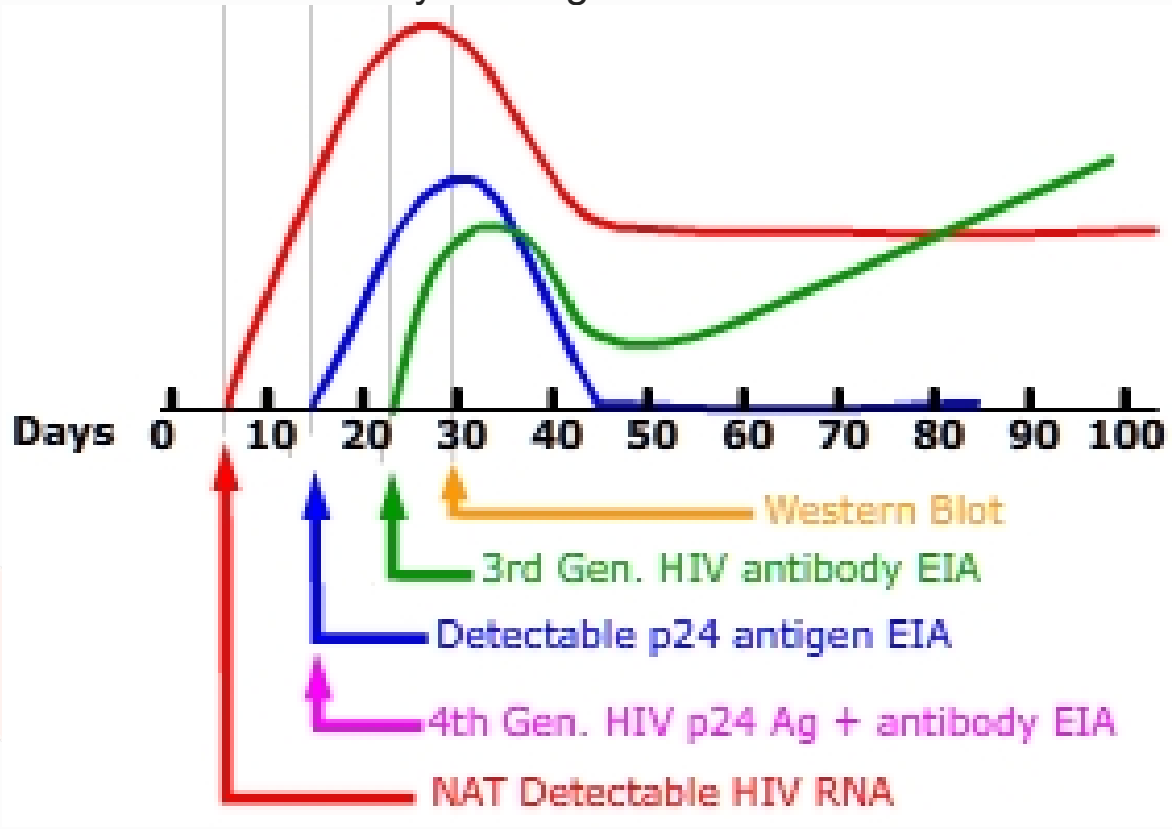
- The challenge with HIV diagnosis is the time it takes the body to develop antibodies



(90% diagnosed by 3 months, 100% diagnosed by 6 months)

Generations of HIV Tests

- In response to this delay, multiple “generations” of HIV testing have been developed
- Each generation has improved dramatically on the time from actual infection to being able to detect antibody or antigen

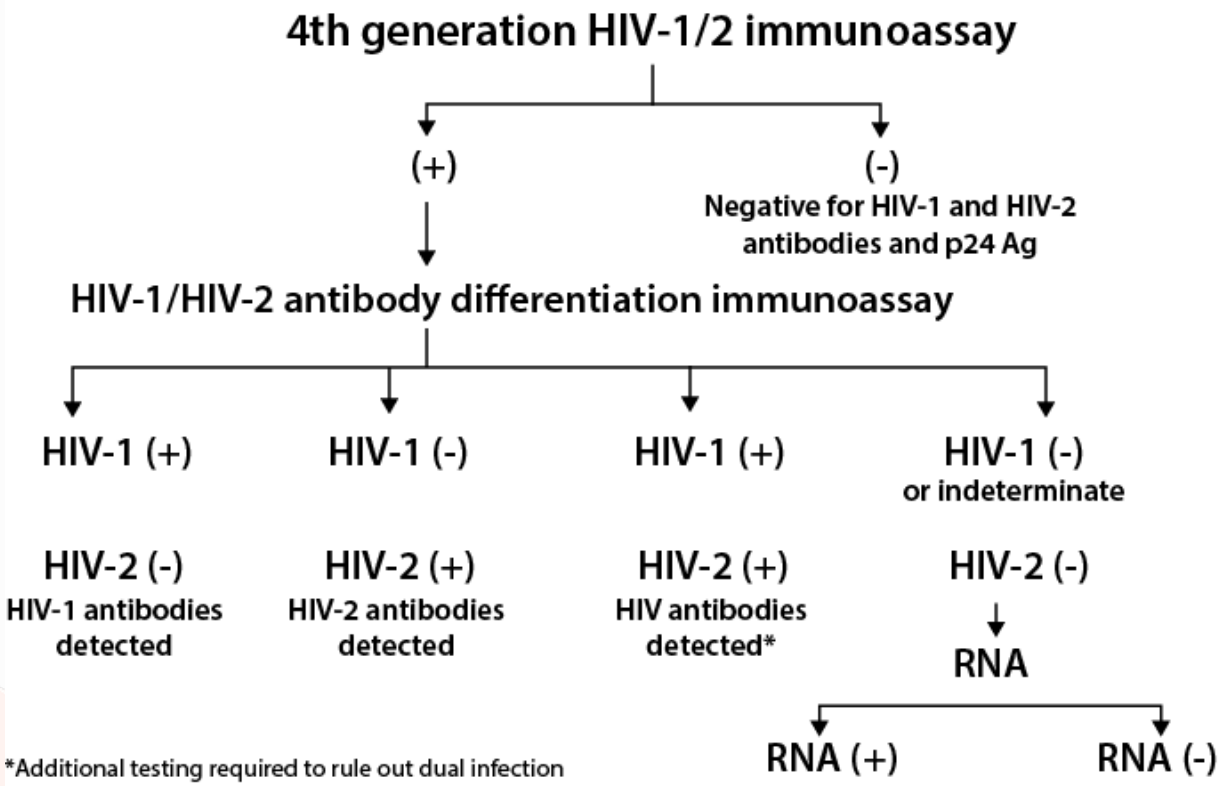


Diagnostic Tests for HIV Infection

	Assay Type	Indicated Uses
4th generation dual assay	Determine® HIV-1 / HIV-2 Ab / Ag	screening for both acute and chronic HIV infection

- detects p24 antigen within 10-14 days of infection
- detects antibodies to HIV-1 or HIV-2 within 4 wks
- positive Ag must be confirmed with NAT
- positive Ab must be confirmed with Multi-spot

4th Generation Testing



https://aidsetc.org/guide/expedited-hiv-testing

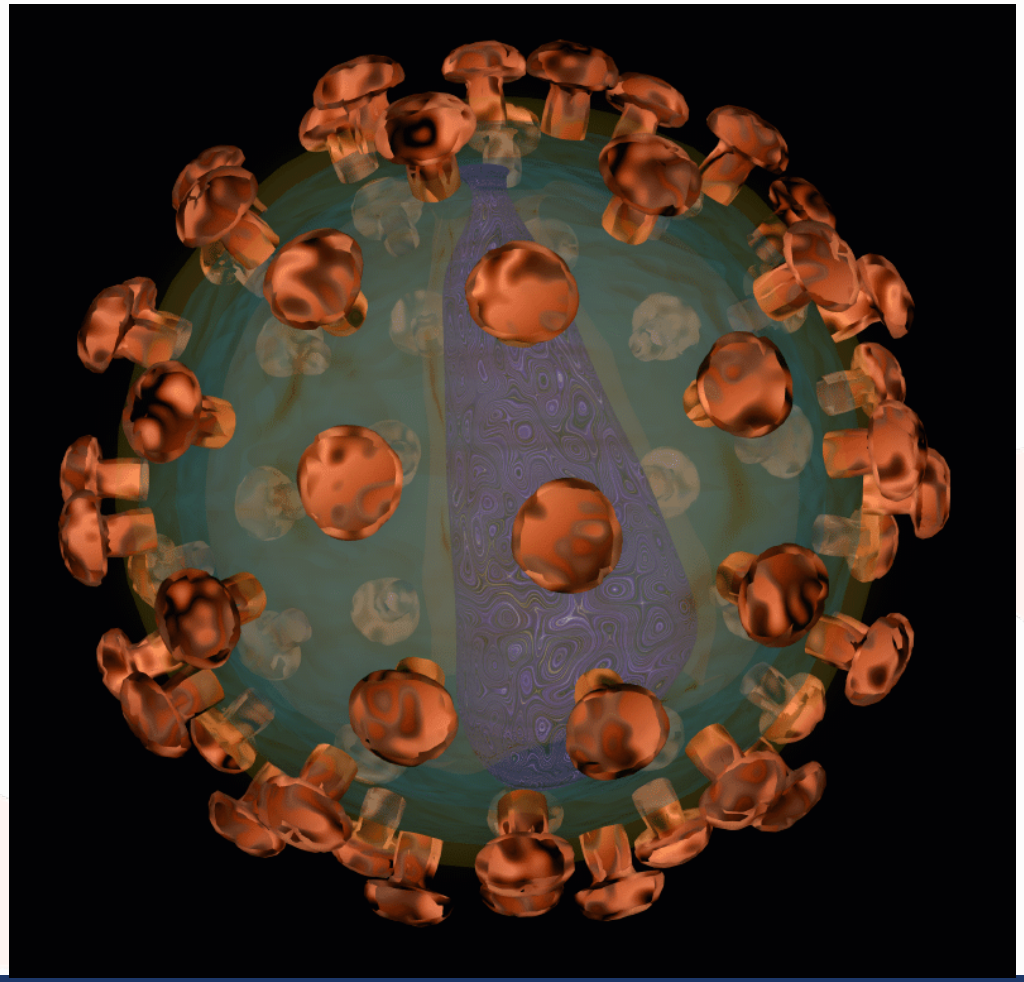
5th Generation Testing

- "5th Generation" (BioPlex 2200 HIV Ag-Ab assay) design
- Simultaneously detects and reports a screen and three individual HIV results:
  - HIV Ag-Ab Screen with
    - HIV-1 p24 Ag
    - HIV-1 Ab (Groups M & O)
    - HIV-2 Ab
      - Includes HIV-1 and HIV-2 Ab Differentiation & Enhanced sensitivity for p24 antigen detection
      - Very similar to generation 4, big difference is the addition of the HIV-1 Ab (groups M & O)

Diagnostic Tests for HIV Infection

	Assay Type	Indicated Uses
Viral	PCR – RNA	measure viral load or dx acute HIV highly sensitive; low VL may indicate false positive if testing for acute HIV
	PCR – DNA	dx HIV-exposed infants test w/in 48 hrs of birth, if neg retest at 14-21 days, 1-2 mo, and 4-6 mo

Primary Care Management of HIV



Objectives

- Explain the clinical management persons living with HIV (PLWH)

Case Study: Rodney

- Rodney is a 29 yo who recently tested positive for HIV, and was referred for clinical care. Prior to testing he experienced 1 month of recurrent fevers, fatigue, a 15 lb weight loss, and now has a diffuse rash.
- PE: normal except for weight loss, rash, and bilateral cervical lymphadenopathy.
- What baseline laboratory tests would you order?

Case Study: Rodney
Which baseline lab testing is NOT typically ordered at the time of diagnosis?

A. CBC w differential and CMP

B. CD4 Absolute # and CD4 percentage

C. HIV RNA PCR

D. HSV 1 & 2 Cultures

E. Quantiferon or other TB test

F. HIV Genotype

G. HBV/HCV testing

H. RPR, GC/CT

Baseline Laboratory Assessment

- ↘CBC (diff & platelets)
- ↘T-lymphocyte subsets (CD4 count / CD4 %)
- ↘HIV-RNA PCR (viral load assay)
- ↘Chem panel / GFR (LFTs, glucose, kidney function)
- ↘Fasting lipids (NNRTIs & PIs can cause ↑ lipids)
- ↘Resistance test (genotype to check for mutations)
- ↘HLA B-5701 [hypersensitivity to abacavir], optional
- ↘Calculate renal clearance (may impact choice of ART)

Baseline Laboratory Assessment

- Hepatitis studies:
  - Hepatitis BsAg, HepBcoreAb, HepBsAb
  - HepatitsC Ab with reflex PCR (if CD4 < 200 and hx needle use or elevated LFTs, then HCV RNA)
  - Hepatitis A Ab if MSM
- Urinalysis (check for proteinuria)
- Quantiferon or PPD (check for latent TB)
- RPR
- Chlamydia and Gonorrhea
- Toxoplasma IgG titer if low CD4 (+ means risk of toxoplasmosis)
- Pap test (refer for colposcopy if abnormal)
- Anal Pap test (if hx of anal sex)
- Chest X-ray (optional)
- Stool cultures (optional)

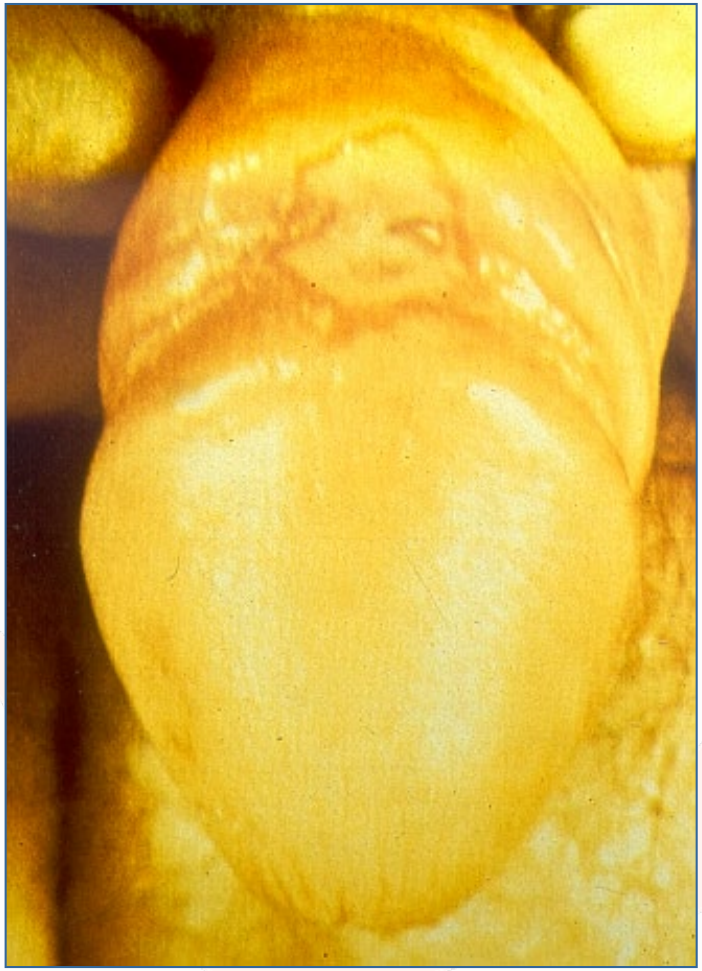
Case Study: Rodney

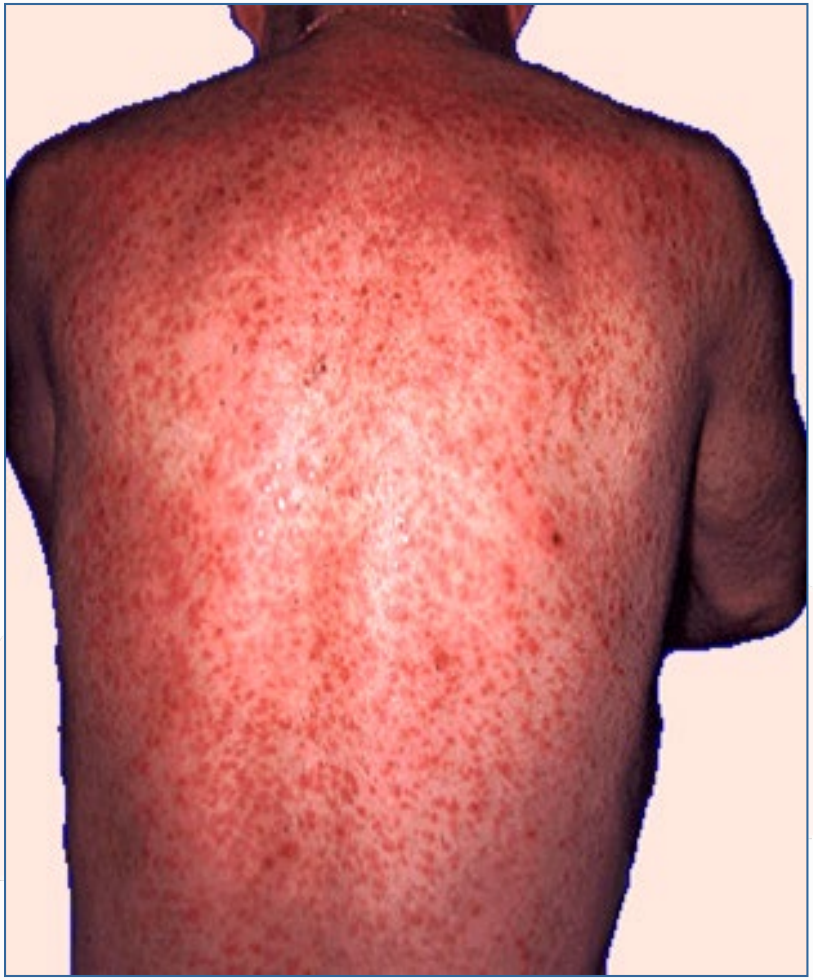
- Rodney is a 29 yo who recently tested postive for HIV, and was referred for clinical care.

- Labs:

  CD4 = 520 (30%) VL = 160,000 c/ml
  Toxo IgG: + HAV / HBV / HCV: neg
  RPR: + 1:64 Stool cultures: neg
  Quantiferon: positive; Anal Pap: not done
  Genotype: no resistance mutations found
  CBC, CMP, GFR, lipids, UA, & CXR normal

Primary and Secondary Syphilis





Primary and Secondary Syphilis

Presentation
- chancre; rash (palms/soles)

Diagnosis:
- RPR
- LP if neuro symptoms (per guidelines), assess for vision changes
- some experts recommend LP if titer >1:32 or CD4 <350

Treatment:
- benzathine penicillin G: 2.4 mil units IM
- If rash, can treat as secondary, regardless of screening hx
- monitor titer: 4-fold ↓ in 6-12 months

ART and Opportunistic Infection Treatment Guidelines

- ART should start as soon as possible after diagnosis, in some cases even the day of, if possible and feasible.
- Opportunistic infection prophylaxis will be initiated if CD4 counts are under 200, additional if below 100 and 50
- Newer recommendations offer flexibility of PJP prophylaxis for patients with undetectable viral loads whose CD4 count is between 150-200 for 3 months
- It is important to assess for drug allergies (Sulfa drugs) for patients who are prescribed SMP/TMX (Bactrim), and do a G6PD for those who are prescribed dapsone

https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/354/primary-prophylaxis

Case Study: Rodney

- Rodney is a 29 yo who recently tested HIV+ and was referred for clinical care. Prior to testing he experienced 1 month of fevers, fatigue, a 15 lb weight loss, and now has a diffuse rash.
- His last HIV test was negative about one year ago.
- He denies exposure to TB.

Case Study: Rodney

You diagnose Rodney with secondary syphilis (consider LP as indicated) and latent TB. His CD4=350.

He receives 2.4 MU penicillin IM as treatment for his syphilis.

He starts INH + B_6 x 9 months as prophylaxis for his latent TB.

What vaccines do you recommend for Rodney?

Vaccinations

- Prevnar prior to Pneumovax
- Pneumovax > 2 months after Prevnar, then in 5 yrs & age 65
- Influenza injection only
- Hepatitis A for all patients w/out documented immunity
- Hepatitis B for all patients w/out documented immunity
- HPV for males & non-preg females age 9 – 45
- Tdap as indicated and/or Td booster
- Polio inactivated vaccine only
- MMR for unvaccinated born after 1957 & non-preg; contraindicated if CD4 <200
- Varicella for non-immune born after 1980 & non-preg; contraindicated if CD4 <200
- Zoster consider in patients >age 60 with CD4 >200
- MCV meningococcal conjugate vaccine (Menactra® or Menveo®
- Shingrex (preferred) If CD4>200 and age 50=>, or Zostrix if age =>60

Figure 2. Recommended immunization schedule for adults aged 19 years or older by medical condition and other indications, United States, 2018

This figure should be reviewed with the accompanying footnotes. This figure and the footnotes describe indications for which vaccines, if not previously administered, should be administered unless noted otherwise.

Vaccine	Pregnancy[1-6]	Immuno-compromised (excluding HIV infection)[3-7,11]	HIV infection CD4+ count (cells/μL)[3-7,9-10] <200	HIV infection CD4+ count (cells/μL)[3-7,9-10] ≥200	Asplenia, complement deficiencies[7,10,11]	End-stage renal disease, on hemodialysis[7,9]	Heart or lung disease, alcoholism[7]	Chronic liver disease[7-9]	Diabetes[7,9]	Health care personnel[3,4,9]	Men who have sex with men[6,8,9]
Influenza[1]	1 dose annually										
Tdap[2] or Td[2]	1 dose Tdap each pregnancy	1 dose Tdap, then Td booster every 10 yrs									
MMR[3]	contraindicated			1 or 2 doses depending on indication							
VAR[4]	contraindicated			2 doses							
RZV[5] (preferred)					2 doses RZV at age ≥50 yrs (preferred)						
or					or						
ZVL[5]	contraindicated			1 dose ZVL at age ≥60 yrs							
HPV–Female[6]		3 doses through age 26 yrs			2 or 3 doses through age 26 yrs						
HPV–Male[6]		3 doses through age 26 yrs			2 or 3 doses through age 21 yrs						2 or 3 doses through age 26 yrs
PCV13[7]		1 dose									
PPSV23[7]		1, 2, or 3 doses depending on indication									
HepA[8]	2 or 3 doses depending on vaccine										
HepB[9]	3 doses										
MenACWY[10]	1 or 2 doses depending on indication , then booster every 5 yrs if risk remains										
MenB[10]	2 or 3 doses depending on vaccine										
Hib[11]	3 doses HSCT recipients only			1 dose							

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended for adults with other indications

Contraindicated

No recommendation

Case Study: Rodney

- Rodney is a 29 yo who recently tested positve for HIV, and was referred for clinical care. You have diagnosed his with secondary syphilis and latent TB, and treated him appropriately.
- Vaccines: Prevnar; Pneumovax (≥ 2 months); influenza; HAV/HBV; and TdaP; Menactra series (2 doses), consider HPV (recently extended to persons up to the age of 45 years old)
- How often do you want to monitor his condition?

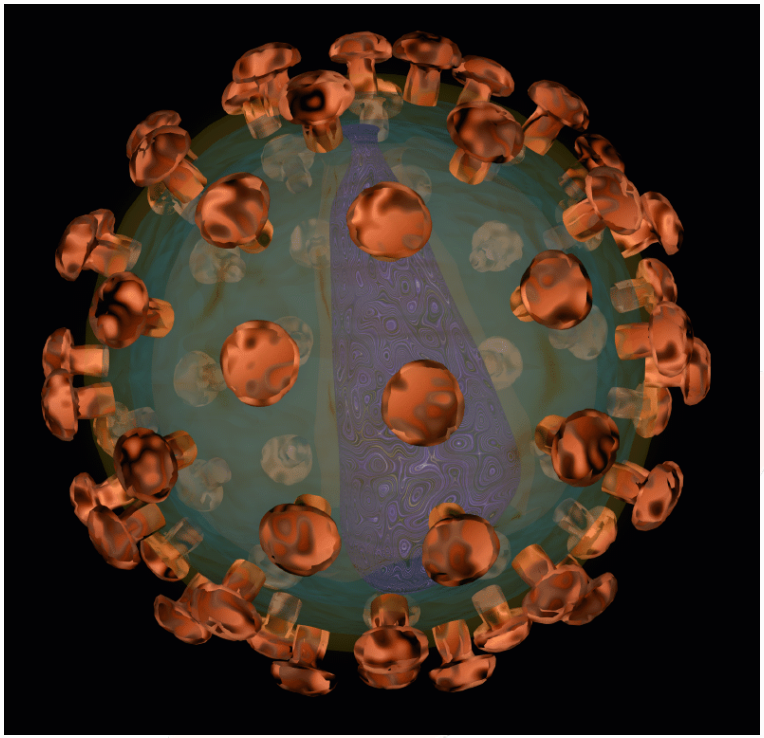
Routine Laboratory Tests

Viral load	q3-4 mo after achieving undetectable VL, then every 6 months to a year if suppressed consistently, and in care
CD4 count	q3 mo until undetectable VL and > 200, then q3-6 mo until undetectable VL x 2yrs. May be extended to every 6-12 months with suppressed viral load, good adherence and consistent care. ADAP requires q 6 months labs to recertify
CMP/lipids	q6 mo x 1yr on ART, then yearly if stable
Pap	cervix: upon initiation of care, repeated at 6 months and annually thereafter if results are normal. Women with atypical squamous cells , glandular cells, low or high-grade intraepithelial lesions or squamous carcinoma should undergo colposcopy and directed biopsy, with further treatment as indicated
PPD or Quantiferon	q6 mo, then yearly if neg x 2, or Quantiferon
UA	baseline urinalysis and calculated creatinine clearance or estimated glomerular filtration rate. UA & calculated creatinine clearance assay should be done prior to initiation of nephrotoxic drugs
RPR	Yearly if any sex and every 3 months for high risk
Hepatitis C Ab with reflex RNA	Yearly for MSM
GC/chlamydia testing (include extra-genital sites)	Yearly if any sex and every 3 months for high risk

Health Maintenance

- Regular medical, dental and vision visits
  - Non-HIV chronic conditions may require more frequent health care visits
- Routine mental health assessment / referrals
- Medication Adherence
- Smoking cessation, limit alcohol, and other drug use
- Proper diet / nutritional counseling
- Adequate exercise and rest
- Safer sex / STI prevention practices
  - Regular testing (q3-6 months) with high-risk behaviors
- Family Planning
- Disclosure of Status/Recommend PrEP for partners

Antiretroviral Therapy



Objectives

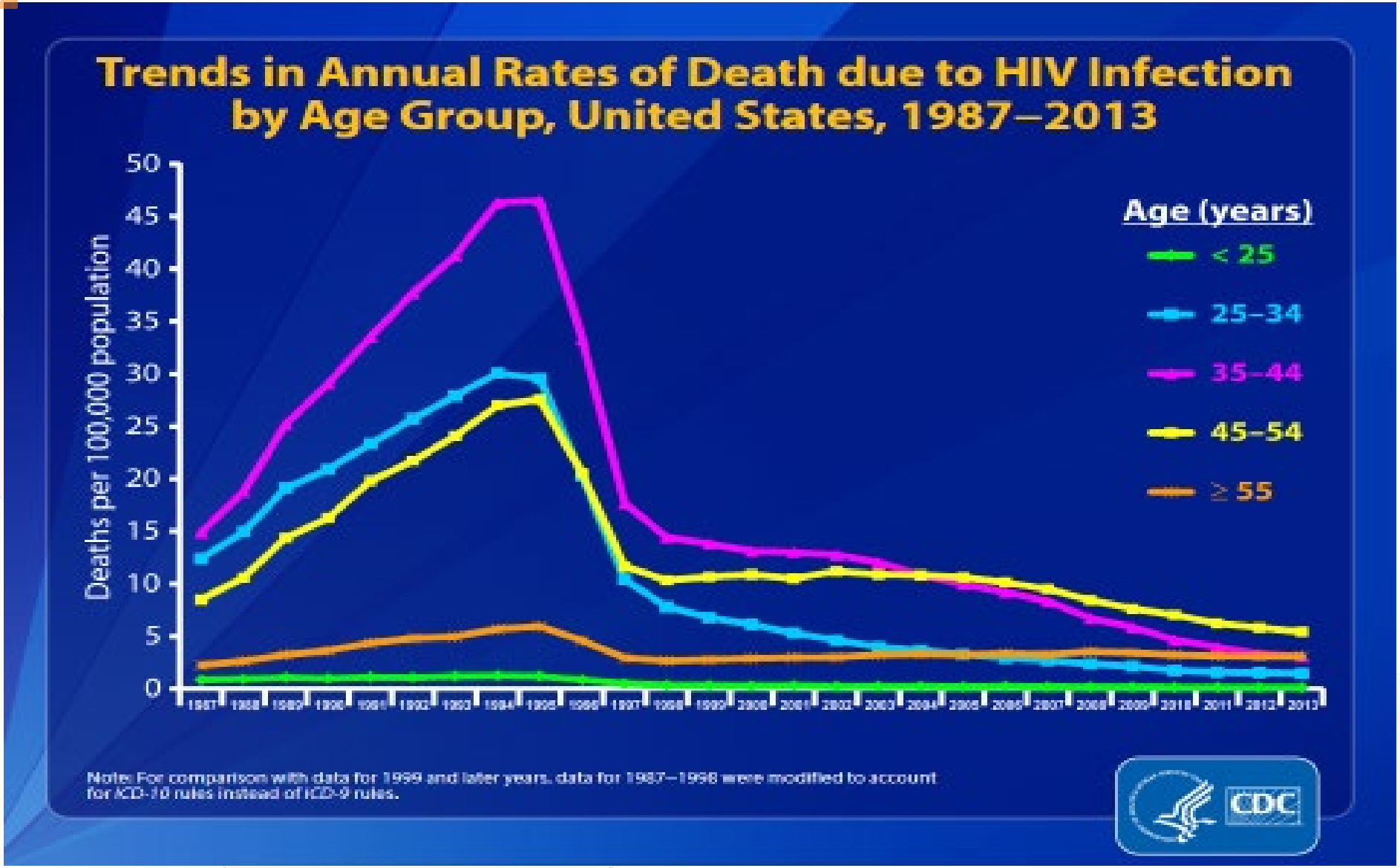
- Describe the goals & indications for antiretroviral therapy (ART)
- Discuss the classes of antiretroviral therapy (ART)
- Illustrate the prescription and management of antiretroviral therapy (ART) regimens
- Review side effect and resistance management

Goals of Therapy

- Maintenance of Viral Suppression
- Restore/Preserve Immunologic Function
- Reduce Morbidity and Mortality
- Improve Quality of Life

Surrogate Markers:

- Reduced Viral Load (viral suppression, undetectable viral load)
- Increased CD4 count, Monitor CD4 Percentage

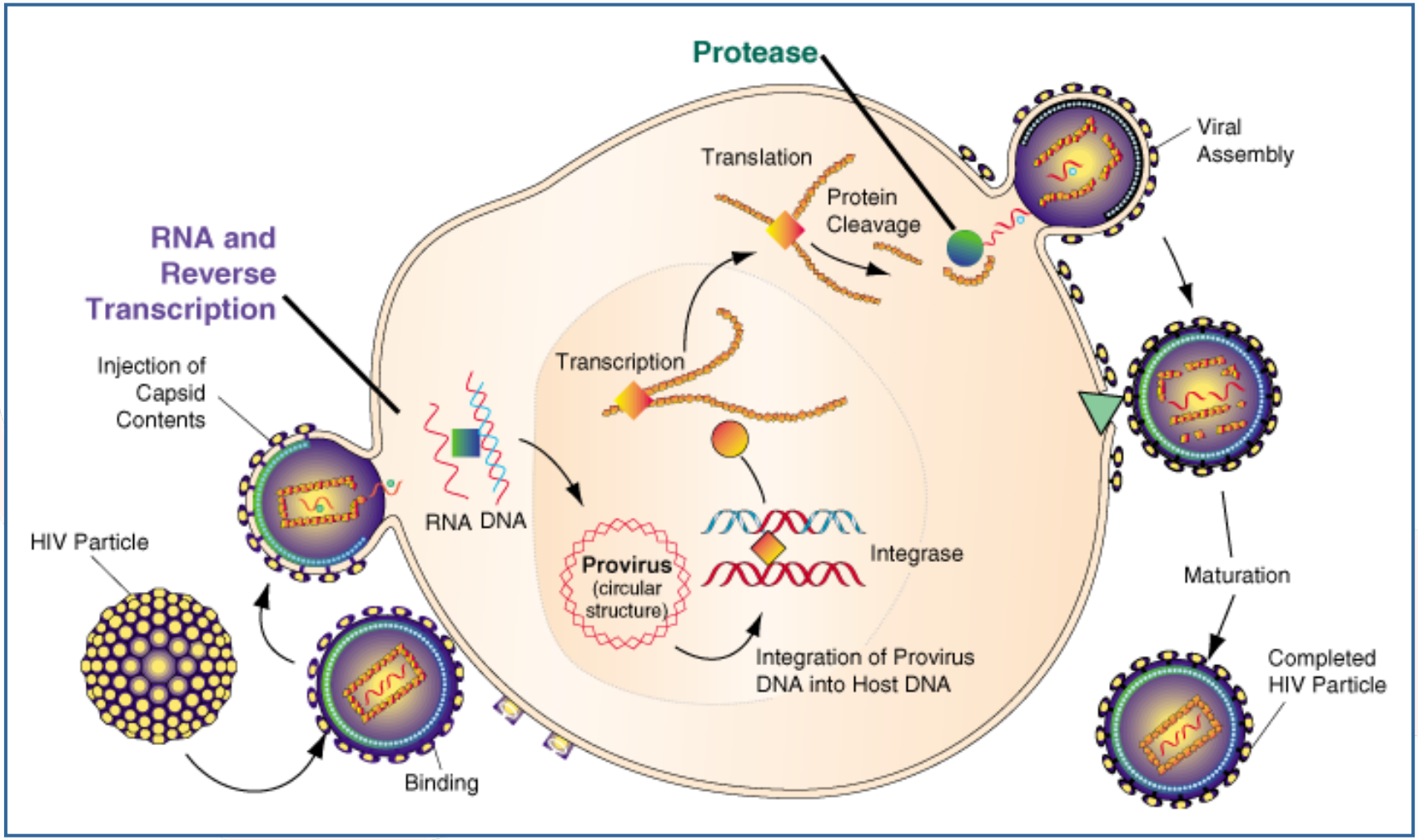

Trends in Annual Rates of Death due to HIV Infection by Age Group, United States, 1987–2013
Deaths per 100,000 population
50
45
40
35
30
25
20
15
10
5
0
Age (years)
< 25
25–34
35–44
45–54
≥ 55
Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.
CDC

Indications for Initiating ART

- Antiretroviral therapy (ART) is recommended for all persons living w HIV, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection (AI).
- ART is also recommended for all persons living with HIV individuals to prevent HIV transmission (AI).
- When initiating ART, it is important to educate patients regarding the benefits and considerations of ART, and to address strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as possible.

https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/10/initiation-of-antiretroviral-therapy

Lifecycle of HIV



Current ART Medications

NRTI

§ Abacavir (ABC)
§ Didanosine (ddI)
§ Emtricitabine (FTC)
§ Lamivudine (3TC)
§ Stavudine (d4T)
§ Tenofovir DF (TDF)
§ Tenofovir alafenamide (TAF)*
§ Zidovudine (AZT)

NNRTI

§ Delavirdine (DLV)
§ Efavirenz (EFV)
§ Etravirine (ETR)
§ Nevirapine (NVP)
§ Rilpivirine (RPV)
Doravirine (DOR)

PI

§ Atazanavir (ATV)
§ Darunavir (DRV)
§ Fosamprenavir (FPV)
§ Indinavir (IDV)
§ Lopinavir (LPV)
§ Nelfinavir (NFV)
§ Saquinavir (SQV)
§ Tipranavir (TPV)

Integrase Inhibitor

§ Dolutegravir (DTG)
§ Elvitegravir (EVG)
§ Raltegravir (RAL)
§ Bictegravir (BIC)

Entry Inhibitor

§ Enfuvirtide (ENF, T-20)
§Maraviroc (MVC)
§Trogarzo (Ibalizumab)

Pharmacokinetic (PK) Booster

§ Ritonavir (RTV)
§ Cobicistat (COBI)

*** TAF available only in coformulations: TAF/FTC, RPV/TAF/FTC, EVG/COBI/TAF/FTC**

Antiretroviral Agents

Entry Inhibitors

- Ibalizumab = *Trogarzo*
- recombinant humanized monoclonal antibody, blocks HIV-1 from infecting CD4+ T cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for the entry of HIV-1 virus particles into host cells; IV infusion
- Maraviroc =*Selzentry*
- after binding to a CD4 receptor HIV must bind to one of two co-receptors: CCR5 (R5) or CXCR4 (X4)
- binds to R5 co-receptors (but not X4 co-receptors) on CD4 cells blocking fusion of the virus to the cell
- requires a tropism assay to determine the patient's virus is R5 tropic and not R5/X4 dual/mixed tropic
- Enfuvirtide = *Fuzeon*
- binds to HIV blocking attachment to CD4 receptors; injectable

Antiretroviral Agents

Nucleoside Analog Reverse Transcriptase Inhibitors (NRTIs) "Nukes"

(structurally altered substitutes for DNA building blocks)

Abbreviation	Generic	Brand
AZT/ZDV	Zidovudine	Retrovir
TDF	Tenofovir Disoproxil Fumarate (TDF)	Viread
TAF	Tenofovir alafenamide (TAF)	Only available in co-formulations, Descovy, Genvoya and Odefsey
3TC	Lamivudine	Epivir
FTC	Emtricitabine	Emtriva
ABC	Abacavir	Ziagen

Antiretroviral Agents

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

"Non-nukes" (chemically bind to RT to prevent assembly of viral DNA)

Abbreviation	Generic	Brand
NVP	Nevirapine	Viramune
EFV	Efavirenz	Sustiva
RPV	Rilpivirine	Edurant
ETV	Etravirine	Intelence*
DOR	Doravirine	Pifeltro*

* approved for patients with demonstrated resistance to other NNRTIs

Antiretroviral Agents

Integrase Inhibitors

(block the integration of proviral DNA into the host genome)

Abbreviation	Generic	Brand
RAL	Raltegravir	Isentress & Isentress HD
EVG	Elvitegravir	Vitekta
DTG	Dolutegravir	Tivicay
BIC	Bictegravir	Only co-formulated

Antiretroviral Agents

Fixed Dose Combination (FDC) NRTIs

Abbreviation	Generic/*Brand*	FDC Brand
TDF/FTC	Tenofovir/Emtrictabine ***Viread/Emtriva***	**Truvada**
TAF/FTC	Tenofovir Alafenamide/Emtricitabine ***Tenofovir Alafenamide/Emtriva***	**Descovy**
ZDV/3TC	Zidovudine/Lamivudine *Retrovir/Epivir*	**Combivir**
ABC/3TC	Abacavir/Lamivudine ***Ziagen/Epivir***	***Epzicom***
ZDV/3TC/ABC	Zidovudine/Lamivudine/Abacavir ***Retrovir/3TC/ABC***	**Trizivir**

Antiretroviral Agents

Single Table Regimens (STRs)

Abbreviation	Generic/*Brand*	FDC Brand
TDF/FTC/EFV	Tenofovir/Emtricitabine/Efavirenz ***Truvada + Sustiva***	**Atripla**
TDF/FTC/EPV	Tenofovir/Emtricitabine/Rilpiverine ***Truvada/Edurant***	**Complera**
TDF/FTC/EVG/COBI	Tenofovir/Emtricitabine/Elvitegravir/COBI ***Truvada/Vitekta/Tybost***	**Stribild**
TAF/FTC/EVG/COBI	Tenofovir Alafenamide/Emtricitabine/ Elvitegravir/ COBI ***Descovy/Vitekta/Tybost***	**Genvoya**
TAF/FTC/RPV	Tenofovir Alafenamide/Emtricitabine/ Rilpiverine ***Descovy/Edurant***	**Odefsey**
ABC/3TC/DTG	Abacavir/Lamivudine/Dolutegravir ***Epzicom/Tivicay***	***Triumeq***
BIC/FTC/TAF	Bictegravir/Emtricitabine/Tenofovir Alafenamide ***Bictegravir/Descovy***	***Biktarvy***
DTG/RPV	Dolutegravir/Rilpiverine ***Tivicay/Edurant***	***Juluca***
DRV/COBI/TAF/EVG	Darunavir/COBI/Tenofovir Alafenamide/ Emtricitabine ***Prezista/Tyboost/Descovy***	***Symtuza***

5

Antiretroviral Agents

Protease Inhibitors (PIs)

(block cleavage of viral proteins & assembly of new virions)

Abbreviation	Generic/*Brand*	FDC Brand
DRV	*Darunavir*	Prezista
AZV	*Atazanavir*	Reyataz
LPV	*Lopinavir/r*	Kaletra
RTV	*Ritonavir*	Norvir

Newer FDCs of PIs:
Atazanavir (Reyataz) + Cobicistat = Evotaz
Darunavir (Prezista) + Cobicistat = Prezcobix

Appropriate Antiretroviral Regimens: How to Decide?

- Appropriate ART prescriptions should be client centered: What does this mean to you?
- Dependent on patient profile, a regimen may match the DHHS guidelines exactly
- If a patient is highly treatment-experienced or has a high degree of resistance, regimens may consist of uncommon combinations of drugs
- Assess patient's potential for successful adherence: patient's preference of taking with food or without food, time of day, QD vs BID dosing, number of pills, pill size

Medication Adherence

- Assessment of patient's potential for and barriers to consistent med adherence is extremely important
- Providing ongoing monitoring of med adherence is integral and essential; practice with multivitamins!
- Providing support and technical assistance can promote optimal adherence, promote patient empowerment
- Assessing patient's knowledge, attitudes and beliefs about ART can provide useful insight into motivation
- Providing appropriate medication teaching, what to anticipate with side effects, missed doses, empower to manage medication refills and pharmacy skills are helpful

Appropriate Antiretroviral Regimen

- All regimens need to contain at least 3 drugs from at least 2 different classes of ARVs
- A regimen may have combinations that look like this:
  - 1 INSTI + 2 NRTIs
  - 1 PK-boosted PI + 2 NRTIs
  - 1 NNRTI + 2 NRTIs

Basic ART Recipes

For treatment-experienced patients:

At least 2 fully active medications (preferably 3) from different drug classes

- Integrase Inhibitor
- Active NRTIs
- Active NNRTI (ie, *Intelence*)
- Active PI
- Entry Inhibitor

- Intelence is indicated for BID dosing (twice daily dosing); Isentress has typically been BID dosing, recently received indication for one daily, high-dose (HD) dosing

Initial Regimens: Recommended

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, discuss childbearing intentions, consider avoiding dolutegravir-based regimens.

- BIC/TAF/FTC **(AI)**
- DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
- DTG plus tenofovir/FTC (**AI** for both TAF/FTC and TDF/FTC)
- RAL plus tenofovir/FTC (**BI** for TDF/FTC, **BII** for TAF/FTC)

3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion

Recommended Initial Regimens in Certain Clinical Situations

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- EVG/c/tenofovirb/FTC (**BI** for both TAF/FTC and TDF/FTC)
- RALc plus ABC/3TCa **(CII)—if HLA-B*5701 negative and HIV RNA <100,000 copies/mL**

Boosted PI plus 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV)

- (DRV/c or DRV/r) plus tenofovirb/FTCa **(AI)**
- (ATV/c or ATV/r) plus tenofovirb/FTCa **(BI)**
- (DRV/c or DRV/r) plus ABC/3TCa **—if HLA-B*5701 negative (BII)**

3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion

Evolution of the STR (Single-Tablet Regimen)

Name	Year	Classes	Drugs
Atripla	2006	NNRTI + 2 NRTIs	Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)
Complera	2011	NNRTI + 2 NRTIs	Rilpivirine/ Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)
Stribild	2012	INSTI + COBI + 2 NRTIs	Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)
Triumeq	2014	INSTI + 2 NRTIs	Dolutegravir/Abacavir/Lamivudine
Genvoya	2015	INSTI + COBI + 2 NRTIs	Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenimide (TAF)
Odefsey	2017	NNRTI + 2 NRTIs	Rilpivirine/ Emtricitabine/Tenofovir Alafenimide (TAF)
Juluca	2017	INSTI + NNRTI	Dolutegravir/ Rilpivirine
Biktarvy	2018	INSTI + 2 NRTIs	Bictegravir/ Emtricitabine/Tenofovir Alafenimide (TAF)
Symtuza	2018	PI + COBI + 2 NRTIs	Darunavir/Cobicistat/ Emtricitabine/Tenofovir Alafenimide (TAF)
Delstrigo	2018	NNRTI + 2 NRTIs	Doravirine/Lamivudine/ Tenofovir Disoproxil Fumarate (TDF)
Symfi & Symfi Lo	2018	NNRTI + 2 NRTIs	Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate (TDF)

Combination Antiretrovirals

Atripla
(EFV/TDF/FTC)

Biktarvy
(BIC/TAF/FTC)

Combivir†
(ZDV/3TC)

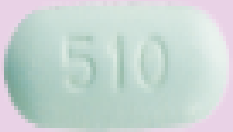
Complera
(RPV/TDF/FTC)

Delstrigo
(DOR/TDF/3TC)

Descovy
(TAF/FTC)

Epzicom†
(ABC/3TC)

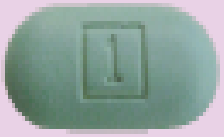
Genvoya
(EVG/COBI/TAF/FTC)



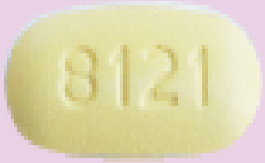
Juluca
(DTG/RPV)

Odefsey
(RPV/TAF/FTC)

Stribild
(EVG/COBI/TDF/FTC)



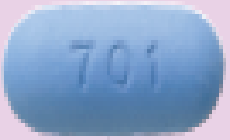
Symtuza
(DRV/COBI/TAF/FTC)



Triumeq
(DTG/ABC/3TC)

Trizivir†
(ABC/3TC/ZDV)

Truvada
(TDF/FTC)



Managing Adverse Effects

With all new ART, nausea and diarrhea are possible

Integrase Inhibitors: class effect = mostly well tolerated

Dolutegravir has been associated with headaches and insomnia, artifact renal impairment

NRTIs: class effect = lactic acidosis*, fat wasting

- Zidovudine = bone marrow suppression
- Tenofovir DF = bone thinning, renal issues*
- Abacavir = hypersensitivity reaction*, do an HLA B5701 before starting; concern for increased risk for cardiovascular events in some cohorts

*Indicates Black Box warning

Managing Adverse Effects

NNRTIs: class effect = CNS, hypertriglyceridemia

- Efavirenz = CNS effects: vivid dreams, insomnia, depression
- Rilpivirine = CNS effects (HA, insomnia, depression)
- Nevirapine = liver toxicity*; avoid in men with CD4 >400 and women with CD4 > 250
- Etravirine, Doravirine = Generally well tolerated

PIs: class effect = metabolic complications: elevated transaminases, hyperglycemia / diabetes, hyperlipidemias, lipodystrophy, osteopenia

- Atazanavir = Unconjugated hyperbilirubinemia

*Indicates Black Box warning

Drug-Drug Interactions

- Most common drug-drug interactions involve PPIs, corticosteroids, and boosting agents (ritonavir, cobicistat)
- Also important to monitor statin interactions with ARVs
- Certain medications require certain lab values to be interpreted differently (Cobicistat, kidney function, lipids)
- There is a wonderful database to check drug-drug interactions when considering HIV med choices (Liverpool)
- HCV drugs require special consideration, although most HCV therapies are short-term
- HBV requires special consideration because some HIV ARVs have dual activity with HBV medications (emtricitabine, tenofovir); if restarting must, monitor HBV viral loads, response, monitor for HBV flare

Monitoring Response to Initiation of Treatment

- Remote follow-up @ 1-2 weeks for side effects and adherence
- Repeat VL @ 4-8 weeks after starting therapy; then q8 weeks until undetectable (w/in 2-3 months if on INSTI based regimen)
- CD4 count @ 3 months then q3-6 months once undetectable

- Indications for changing therapy
  - ↘ Inadequate viral suppression
  - ↘ Sustained viral rebound after full suppression
  - ↘ Declining CD4 count or clinical deterioration

Case Study: Mark

- Mark is a 49 y.o. male, living with HIV since 2010. His medication adherence has been inconsistent. He reports missing doses a couple of times a week due to forgetfulness and going to bed before he takes his medication at night. He thinks that his adherence has improved since he started setting reminders on phone.
- He has not been ill, and has not been diagnosed with any OIs but on his current regimen of Atripla (Efavirenz, Emtricitabine, Tenofovir DF), and his viral load is 16,520 and his CD4 count is 91.
- What testing do you recommend?

Drug Resistance Testing Guidelines

Recommended Uses:

- At entry into care, at the time of ART initiation
- Managing suboptimal reduction in viral load or subsequent virologic failure of ART regimen
- With pregnant women living with HIV prior to start of ART or for those already on ART with detectable viral load
- Test results are most reliable if HIV-RNA > 1000 copies
- Draw assay while patient is on current regimen or immediately after discontinuing therapy (within 4 wks)

Resistance Tests

Genotype

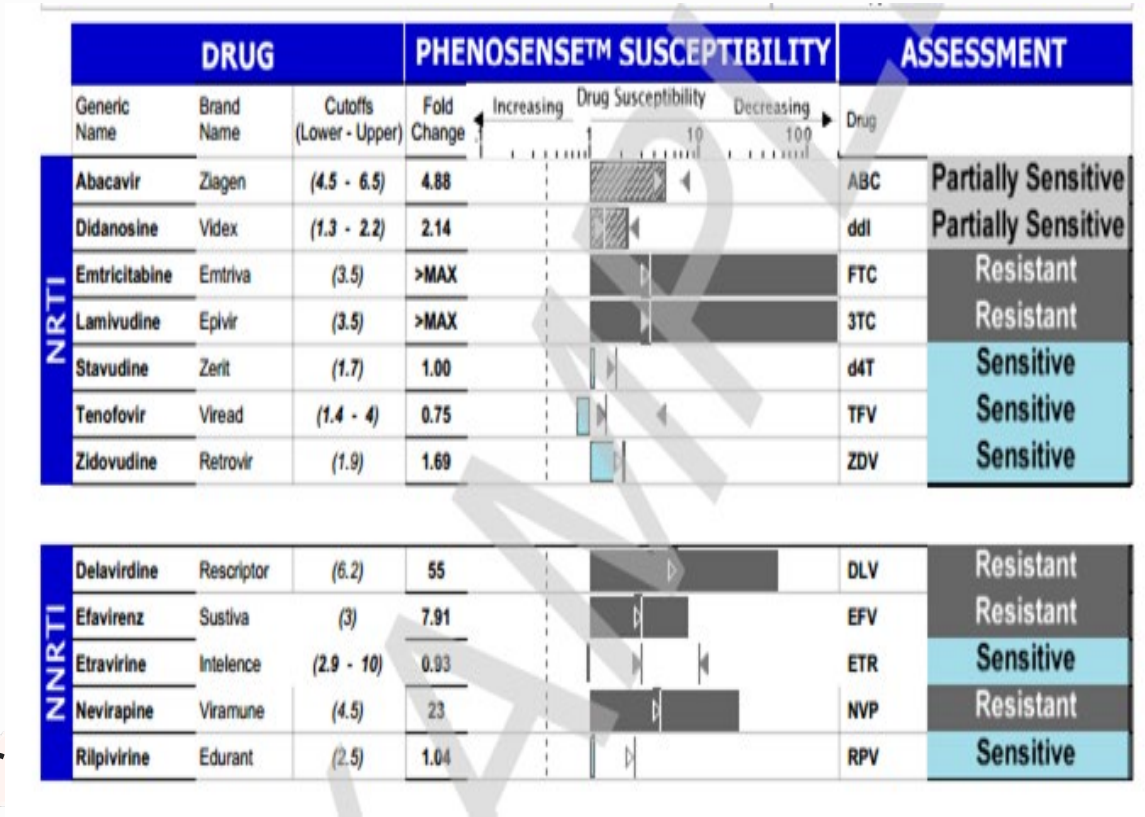
- indirect assay detects mutations in the genes coding for RT & PR
- lower cost, more rapid turnaround time
- may predict resistance before clinically apparent
- expert consultation recommended for patients with complex mutation patterns

	Drug		GenoSure PRIme®	Assessment*		Comments
	Generic Name	Brand Name	Drug Resistance Associated Mutations Detected	Drug		
NRTI	Abacavir	Ziagen	L74V, Y115F, M184V	ABC	Resistant	
NRTI	Didanosine	Videx	L74V, Y115F, M184V	ddI	Resistant	
NRTI	Emtricitabine	Emtriva	M184V	FTC	Resistant	
NRTI	Lamivudine	Epivir	M184V	3TC	Resistant	
NRTI	Stavudine	Zerit	None	d4T	Sensitive	1
NRTI	Tenofovir	Viread	Y115F	TFV	Sensitive	2
NRTI	Zidovudine	Retrovir	None	ZDV	Sensitive	2
NNRTI	Efavirenz	Sustiva	None	EFV	Sensitive	
NNRTI	Etravirine	Intelence	None	ETR	Sensitive	
NNRTI	Nevirapine	Viramune	None	NVP	Sensitive	
NNRTI	Rilpivirine	Edurant	None	RPV	Sensitive	

Resistance Tests

Phenotype

- direct assay measures ability of virus to grow in various drug concentrations
- expensive, longer turnaround time
- can assess consequences of mutational interactions
- relevance of small changes in susceptibility is unclear



	DRUG			PHENOSENSE™ SUSCEPTIBILITY		ASSESSMENT
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Drug	
NRTI	Abacavir	Ziagen	(4.5 - 6.5)	4.88	ABC	Partially Sensitive
NRTI	Didanosine	Videx	(1.3 - 2.2)	2.14	ddI	Partially Sensitive
NRTI	Emtricitabine	Emtriva	(3.5)	>MAX	FTC	Resistant
NRTI	Lamivudine	Epivir	(3.5)	>MAX	3TC	Resistant
NRTI	Stavudine	Zerit	(1.7)	1.00	d4T	Sensitive
NRTI	Tenofovir	Viread	(1.4 - 4)	0.75	TFV	Sensitive
NRTI	Zidovudine	Retrovir	(1.9)	1.69	ZDV	Sensitive
NNRTI	Delavirdine	Rescriptor	(6.2)	55	DLV	Resistant
NNRTI	Efavirenz	Sustiva	(3)	7.91	EFV	Resistant
NNRTI	Etravirine	Intelence	(2.9 - 10)	0.93	ETR	Sensitive
NNRTI	Nevirapine	Viramune	(4.5)	23	NVP	Resistant
NNRTI	Rilpivirine	Edurant	(2.5)	1.04	RPV	Sensitive

Barrier to Resistance for HIV Medications

- In general: NNRTI's have a lower barrier to resistance
  - One resistance mutation makes most of drug class ineffective
  - Not always the same mutation for every drug in the same class
- In general: protease inhibitors have a high barrier to resistance
  - Multiple resistance mutations must be present to make drug ineffective
  - Exception is Atazanavir- one mutation causes drug resistance
- Among the integrase inhibitors, dolutegravir has a high barrier to resistance, raltegravir and elvitegravir have a lower barrier
  - A rare integrase mutation, often confers resistance to all integrase inhibitors as well

Antiretroviral drugs	Resistance Predicted	Mutations Detected
NRTIs		
ZDV (zidovudine or Retrovir)	NO	
ABC (abacavir or Ziagen)	NO	
ddI (didanosine or Videx)	NO	
3TC (lamivudine or Epivir)	YES	M184I/V/M
FTC (emtricitabine or Emtriva)	YES	M184I/V/M
d4T (stavudine or Zerit)	NO	
TDF (tenofovir or Viread)	NO	
NNRTIs		
ETR (etravirine or Intelence)	NO	
EFV (efavirenz or Sustiva)	YES	K103N
NVP (nevirapine or Viramune)	YES	K103N
RPV (rilpivirine or Edurant)	NO	
PIs		
FPV (fos-amprenavir or Lexiva)	NO	
IDV (indinavir or Crixivan)	NO	
NFV (nelfinavir or Viracept)	NO	
SQV (saquinavir or Invirase)	NO	
LPV (lopinavir or Kaletra)	NO	
ATV (atazanavir or Reyataz)	NO	
TPV (tipranavir or Aptivus)	NO	
DRV (darunavir or Prezista)	NO	

Case Study Continued: Mark

- Mark's HIV RNA remained elevated and a genotype was done and showed M184V and K103N mutations.
- What medications are affected by the M184V, K103N mutations?
- What are the treatment options for Mark?

Take aways

- Older drugs have fallen out of favor due to more frequent dosing, toxicities and side effects
- Need to have at least 2-3 active drugs in at least 2 different classes
- Know when to say when, no shame in referral
- Stanford database extremely helpful

New IAS-USA Guidelines 2018

Recommended Laboratory Monitoring (Cont.)

- Once HIV RNA level is <50 c/mL, monitor **every 3 months until virus is suppressed for at least a year**. Then, monitoring can be reduced to **every 6 months** if the patient maintains adherence
- CD4 cell counts every 6 months until counts >250/μL for at least 1 year with concomitant viral suppression; **Then no longer monitor CD4 counts unless virologic suppression is lost**
- Age- and risk-appropriate screening for STIs at various anatomical sites, anal or cervical dysplasia, TB, general health, and medication toxicity is recommended
- Once a viral load is >50 c/mL, repeat test within 4 weeks and reassess for adherence and tolerability
- Measurement of viral load at 4 to 6 weeks after starting a new ART regimen is recommended

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Saag, Benson, Gandhi, et al. *JAMA*. 2018.

2018 IAS–USA Antiretroviral Guidelines: Key Updates

- Recommend initial regimens focus primarily on unboosted (InSTI) regimens
- Encourage rapid initiation of ART, including 'same day' initiation, if feasible
- Recommend against routine use of *Mycobacterium avium* complex prophylaxis for those with advanced disease on effective ART
- Recommend discontinuation of routine CD4+ counts once a patient has sustained undetectable HIV RNA for a year and has a CD4+ count >250 cells/uL
- Expand alternatives for preexposure prophylaxis for MSM who are uninfected with HIV but remain at risk for infection to include an episode-based "2-1-1" approach, where at risk individuals can take 2 ART pills prior to exposure followed by 1 pill once daily for 2 days after exposure (2-1-1)

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Saag, Benson, Gandhi, et al. *JAMA*, 2018.

Dolutegravir in Pregnancy: Background

- No fetal toxicity or teratogenicity in animal studies described in manufacturer's submission for regulatory approval[1]
- High placental transfer of DTG relative to other ARVs in an ex vivo study[2]
- "*Unexpected placental transfer of DTG with fetal accumulation and then slow neonatal clearance*"[3]
- ***18 May 2018: Report of Neural tube defects in 4/426 (0.9%) babies born to women taking DTG in Botswana…compared to 14/11,173 (0.1%) non-DTG[4]***

DOI: 10.1056/NEJMc1807653 ; 24 July 2018

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In response to the FDA alert, interim guidance has been issued by the HHS Antiretroviral Guidelines Panels regading dolutegravir (DTG).[2] The Office of AIDS Research Advisory Council will be reviewing for proposed guideline changes. The interim recommendations of the Panels are as follows[3]:

- Health care providers are encouraged to counsel women of childbearing age with HIV currently receiving DTG about this newly identified potential risk.
- Pregnant women with HIV who are currently taking DTG should not stop their ARV therapy and should speak with their health care provider for additional guidance.
- Women of childbearing age with HIV who desire to become pregnant should discuss alternative ARV regimen options with their health care provider.
- Women of childbearing age with HIV who are not planning to become pregnant may be on DTG-based regimens provided their pregnancy test before initiation of therapy is negative, and they consistently use a reliable contraceptive method.
- Health care providers are encouraged to report all pregnancy data to the Antiretroviral Pregnancy Registry (1-800-258-4263; http://www.apregistry.com).

https://hivcareconnect.com/wp-content/uploads/Dolutegravir-risk-HAB-5-23-18.pdf

What's new in the pipeline?

Coming soon

- Long acting injectables for HIV management: cabotegravir/rilpivirine
- Additional salvage medications: Fostemsavir (oral) and Cyto-Pro 140 (SQ injection weekly)
- Both agents are entry inhibitors
- Long acting injectable for PrEP
- TAF/FTC for PrEP
- HIV prevention vaccine ??

Earlier Case Study Follow Up: Calvin

- He is upset, and worried about his girlfriend Marie. They had sex last night without a condom.
- You tell Calvin that it would be great if he could tell Marie about his diagnosis, so that she can get tested and learn about her HIV prevention or treatment options.
- What are Marie's options?

PEP vs. PrEP

PEP	PrEP
Post-Exposure Prophylaxis	Pre-Exposure Prophylaxis
Prevention of HIV infection	Prevention of HIV infection
HIV medication given within 72 hours of exposure	Medication given prior to exposure to prevent HIV infection
Medication taken for a period of a month	Medication taken as long as needed
Antivirals prescribed based on exposure	Truvada (tenofovir DF/emtricitabine)

Treatment as Prevention (TasP)
U = U: Undetectable = Untransmittable

It is now generally widely accepted that PLWH who have an undetectable viral load for at least 6 months are not able to transmit the virus to others (PARTNERS 1 & 2 study).

- importance of retention in care of PLWH
- Importance of medication adherence to maintain viral suppression (in addition to reducing morbidity and mortality)

As a broad public health goal, increasing the prevalence of PLWH who are virally suppressed, and linking those who are still HIV negative to PrEP services, would promote a reduction in new HIV infections by reducing transmission and ability of HIV negative persons of acquiring HIV.

Results of Partners 2 Study Presented at AIDS 2018 Conference

TITLE

Risk of HIV transmission through condomless sex in MSM couples with suppressive ART: The PARTNER 2 Study extended results in gay men

Background: Although zero cases of HIV transmission in gay men have been reported in observational studies (PARTNER1 and Opposites Attract) of serodifferent couples where the positive person was on suppressive ART, the level of evidence for gay men remained less than for heterosexual couples. The aim of PARTNER 2 was to provide more precise estimates of transmission risk through condomless-sex in serodifferent gay male couples where the HIV-positive partner was on suppressive ART.

Conclusions: Despite almost 75,000 condomless-sex acts in gay serodifferent couples where the positive partner was on suppressive ART, we found zero cases of within couple HIV transmission. PARTNER 2 provides a similar level of confidence for gay men as for heterosexual couples in PARTNER 1.

Rodger A et al. *Risk of HIV transmission through condomless sex in gay couples with suppressive ART: the PARTNER2 study expanded results in gay men.* 22nd International AIDS Conference, Amsterdam, abstract WEAX0104LB, 2018.

Getting to Zero Campaign, Illinois

GOAL & VISION

We want to make sure that the HIV epidemic is no longer able to sustain itself by achieving both HIV prevention and access to care goals.
We want to see:

1. Zero new HIV transmissions

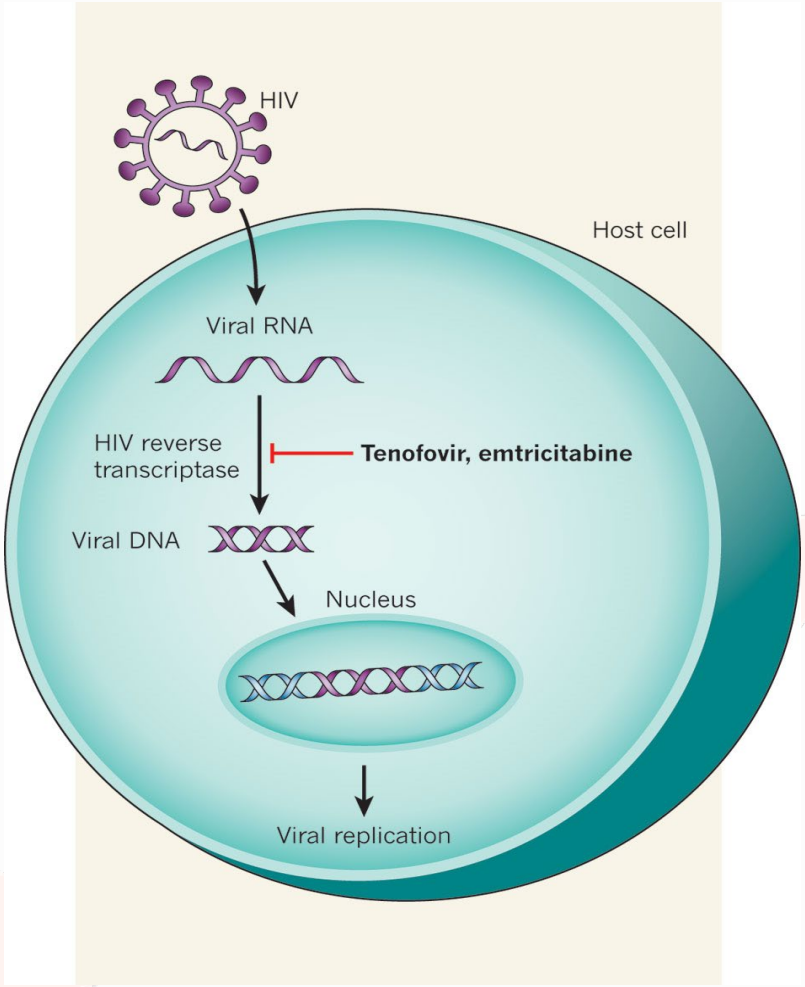
2. Zero people living with HIV who are not receiving treatment

Through increasing access and uptake of PrEP (pre-exposure prophylaxis), retaining more people living with HIV in care and the continued funding of ongoing supportive services, we can get to zero.

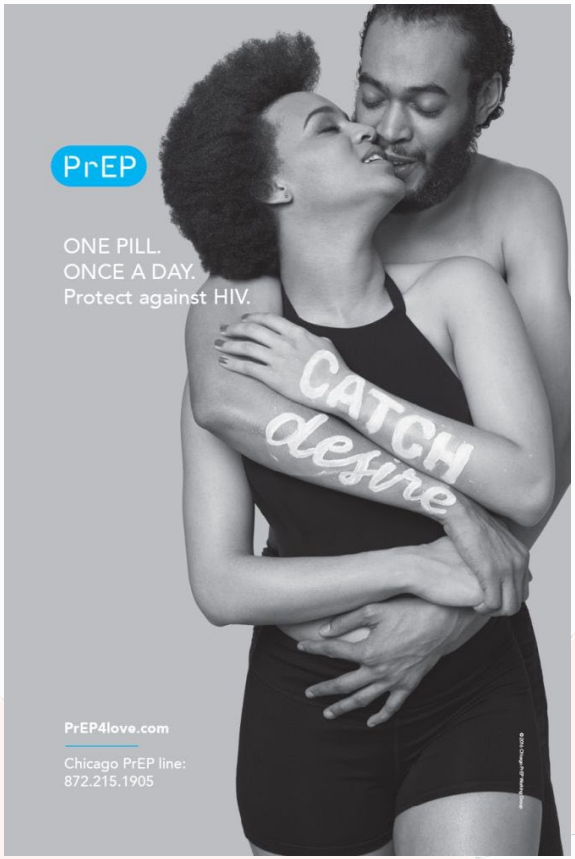
PrEP

- Truvada for prevention of HIV
  - Receptive Anal: protection after 7 days of daily use
  - Receptive vaginal and injection drug use: protection after 20 days of daily use
- Baseline monitoring of kidney function, HBV status
- Regular HIV testing (q90 days), must be HIV negative
- Regular STI screening (q90 days)
- PrEP has not been indicated for episodic use
- Evaluate the ongoing need for PrEP as appropriate
- Reinforce the necessity of condom use, harm reduction

How PrEP Works



Pre-Exposure Prophylaxis (PrEP)



US Public Health Service

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014

A CLINICAL PRACTICE GUIDELINE

UCSF Clinician Consultation Center

- **Call for a Phone Consultation**
- **(855) 448-7737** or **(855) HIV-PrEP**
- Monday – Friday, 11 a.m. – 6 p.m. EST

Post-Exposure Prophylaxis (PEP)

Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV— United States, 2016

from the
Centers for Disease Control and Prevention,
U.S. Department of Health and Human Services

Table 5. Preferred and alternative antiretroviral medication 28-day regimens for nPEP[a,b]

Age group	Preferred/ alternative	Medication
Adults and adolescents aged ≥ 13 years, including pregnant women, with normal renal function (creatinine clearance ≥ 60 mL/min)	Preferred	A 3-drug regimen consisting of tenofovir DF 300 mg *and* fixed dose combination emtricitabine 200 mg (Truvada[c]) once daily *with* raltegravir 400 mg twice daily *or* dolutegravir 50 mg once daily
	Alternative	A 3-drug regimen consisting of tenofovir DF 300 mg *and* fixed dose combination emtricitabine 200 mg (Truvada) once daily *with* darunavir 800 mg (as 2, 400-mg tablets) once daily *and* ritonavir[b] 100 mg once daily

Case Study: Calvin / Marie

- Marie is seen by your colleague, who answers Marie's questions about Calvin's diagnosis. Your colleague explains Marie's options for testing and prevention.
- Marie is offered a rapid HIV test and it is negative
- She has no signs of acute infection

She elects to start a month-long course of PEP, and also is treated for syphilis at this visit. She'll return in a month for repeat testing and will think about PrEP ongoing.

Case Study: Calvin / Marie

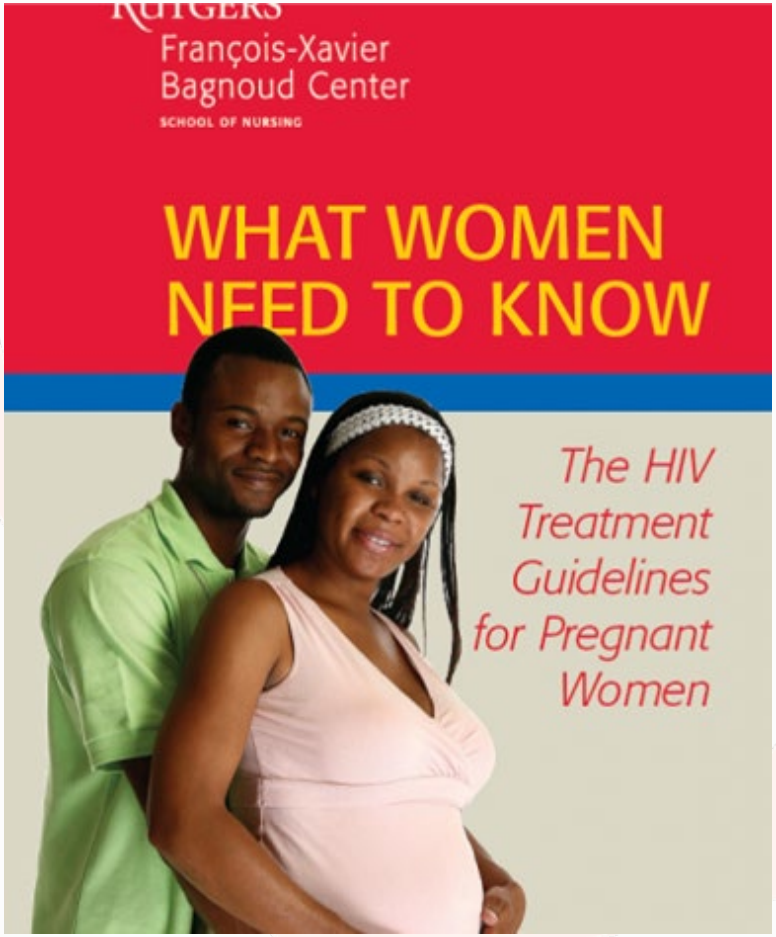
She wants to know- if she becomes positive, will she still be able to have a baby?

Currently, Marie is using an IUD for contraception. She was not planning to remove it until she finishes school. How does having an HIV positive sexual partner impact this choice?

Family Planning

- Almost anything is possible with regard to family planning goals for PLWH
- Male PLWH should be undetectable when trying to conceive, female partner may elect to be on PrEP
- Ideally, female partner should be undetectable at time of conception, chose a regimen that is safe for pregnancy in anticipation of conception (raltegravir-based)
- If a female is undetectable in early pregnancy, maintain regimen (except for Dolutegravir?), maintain viral suppression
- Consult high-risk pregnancy specialist, PACPI, registry

Case Study: Calvin / Marie



PACPI

Resources

PrEP Consultation Service for Clinicians M-F 11a-6p ET
855-448-7737 (1-855 HIV-PREP)
Warmline (National HIV telephone consult) M-F 8a-8p
800-933-3413
PEPline (National Clinicians post exposure prophylaxis hotline)
888-448-4911
Perinatal HIV hotline (National Perinatal HIV Consult/referral service)
888-448-8765
PACPI (Pediatric AIDS Chicago Prevention Initiative)
312-334-0972
Illinois HIV Care Connect
hivcareconnect.com

MIDWEST AIDS TRAINING + EDUCATION CENTER

QUESTIONS?