HIV BASICS

April 11, 2018

Anna K. Person
Associate Professor of Medicine
Program Director Infectious Disease Fellowship
Vanderbilt Comprehensive Care Clinic

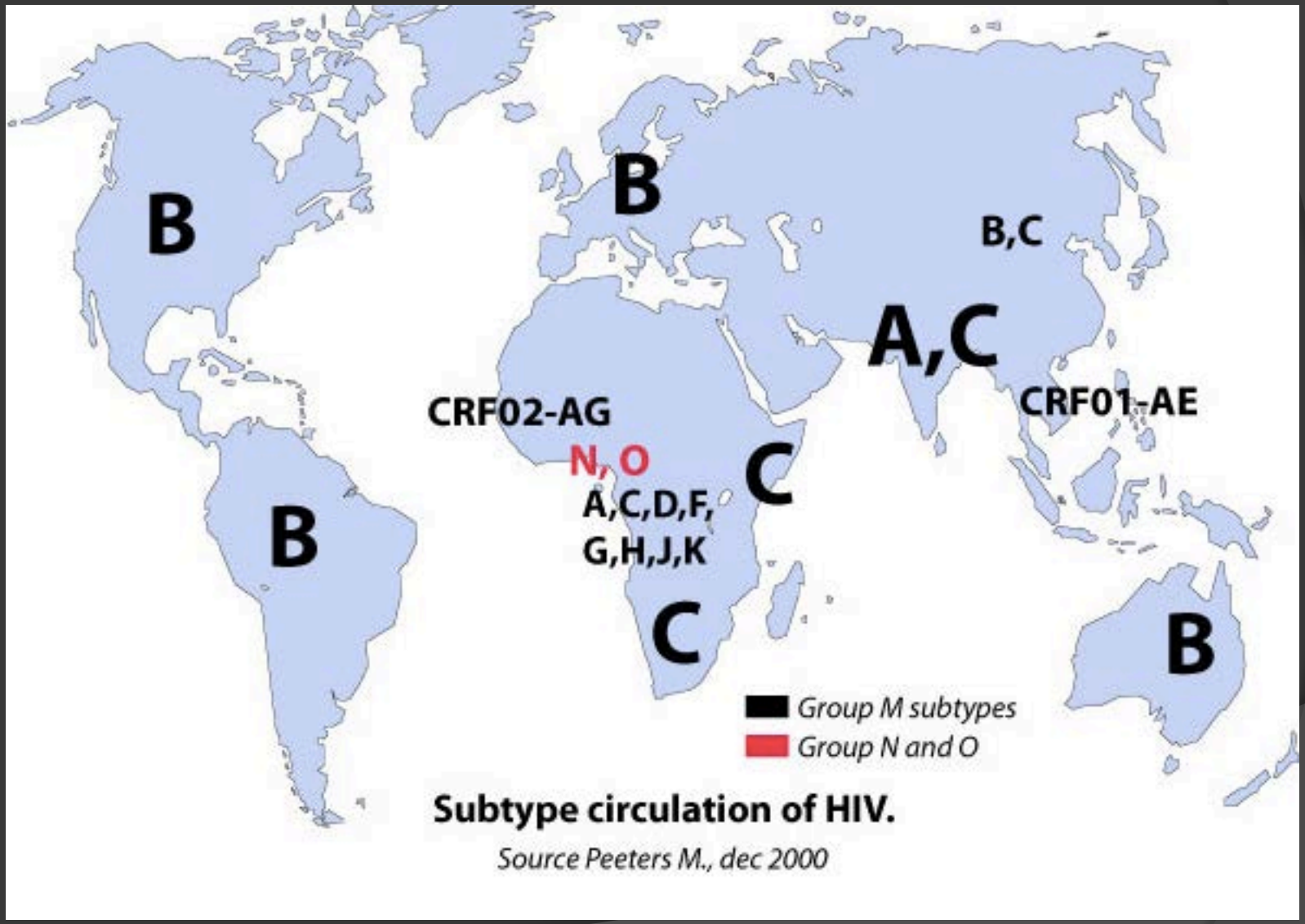
Outline

- HIV – a global view
- HIV- a local view
- Advances/failures
- HIV pathogenesis
- HIV testing

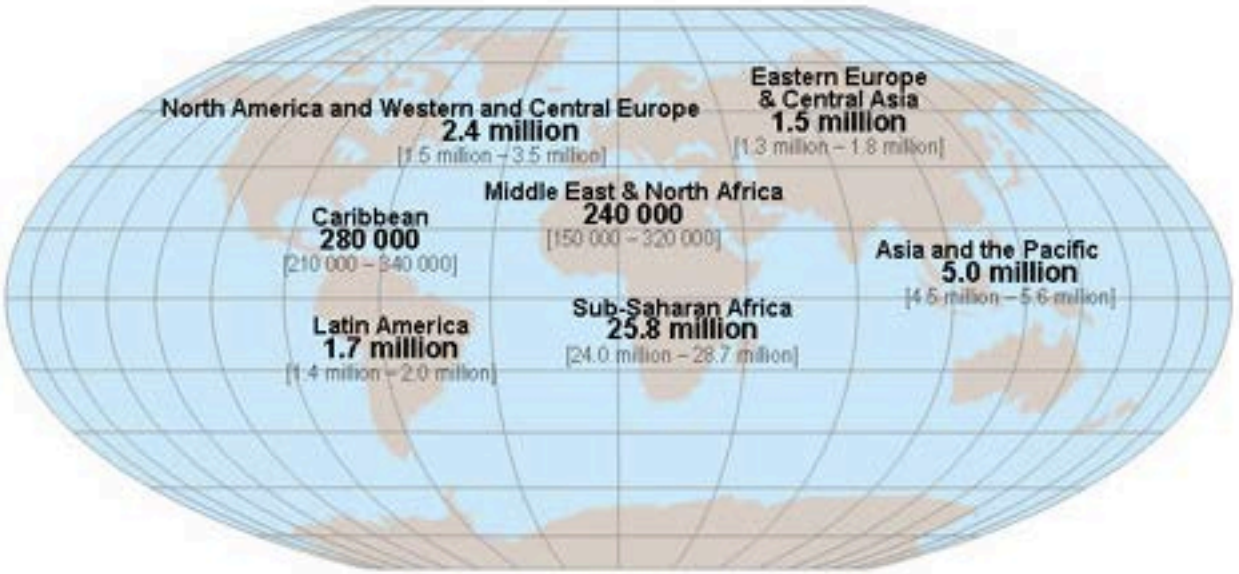
Origin of HIV

- Evolved from SIV
  - Monkeys from Bioko
  - Chimps from Cameroon
- Hunting bushmeat?
- HIV-1 viral groupings:
  - M is “main”- majority
  - O outlier (1%, W. Africa)
  - N (non-M/non-O) only in Cameroon
  - P related to SIV, only 2 patients

Group M- divided into 9 clades. C accounts for 50%.



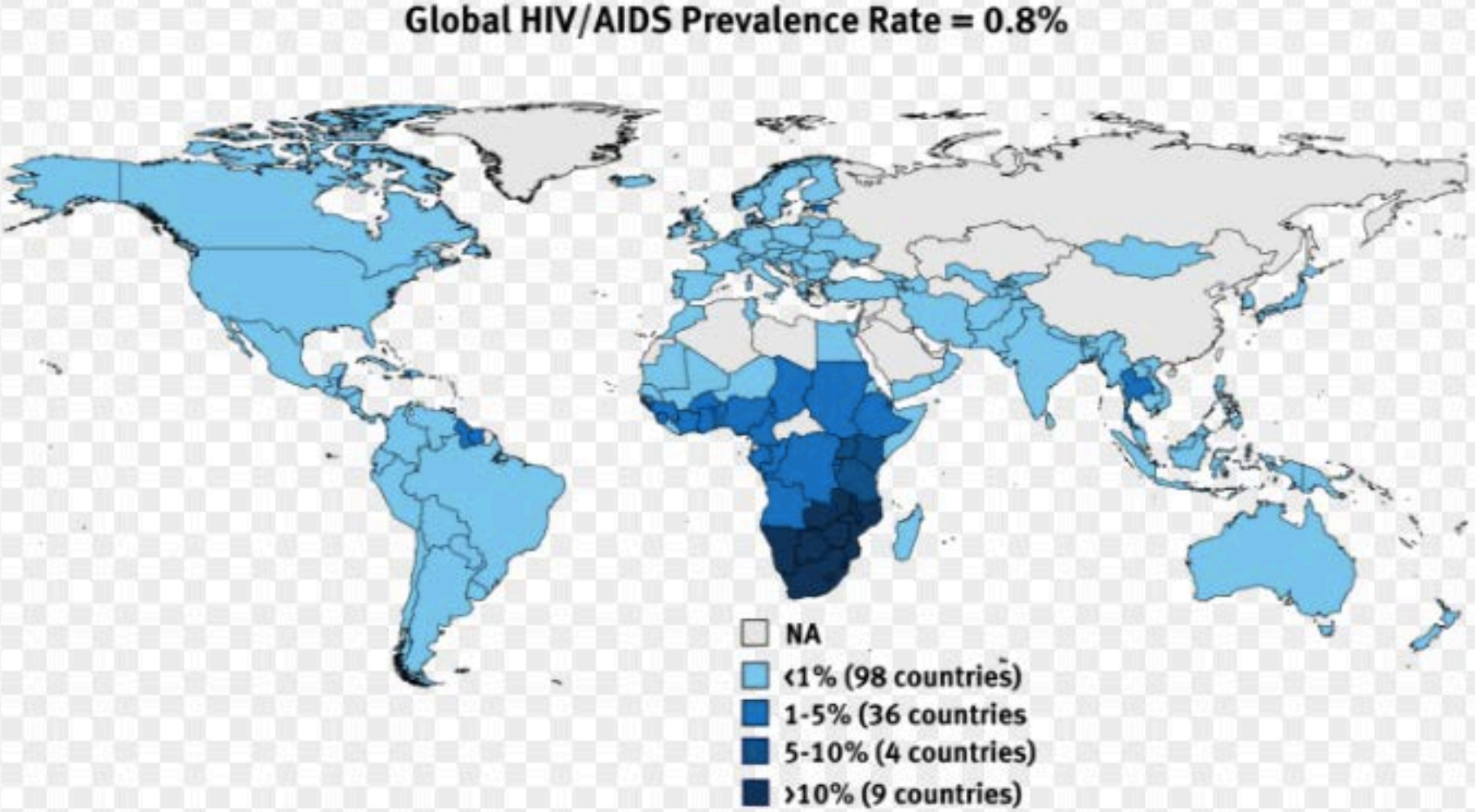
Adults and children estimated to be living with HIV | 2014



Total: 36.9 million [34.3 million – 41.4 million]

UNAIDS

Adult HIV Prevalence Rate, 2012



NOTES: Data are estimates. Prevalence rates include adults ages 15-49. The estimate for Sudan represents data for South Sudan. An estimate was not provided for Sudan.
SOURCE: Kaiser Family Foundation, www.GlobalHealthFacts.org, based on UNAIDS, Report on the Global AIDS Epidemic; 2013.

THE HENRY J. KAISER FAMILY FOUNDATION

HIV-2

- 1-2 million of the 35 million globally with HIV have HIV-2.
- Originally transmitted from West African Sooty mangabeys to humans
- Mainly West Africa (Senegal, Gambia, Ivory Coast, Guinea-Bissau).
- Reported in US and Canada, S. America, Europe, Middle East, Asia.
- Only 166 cases in US from 1987 to 2009

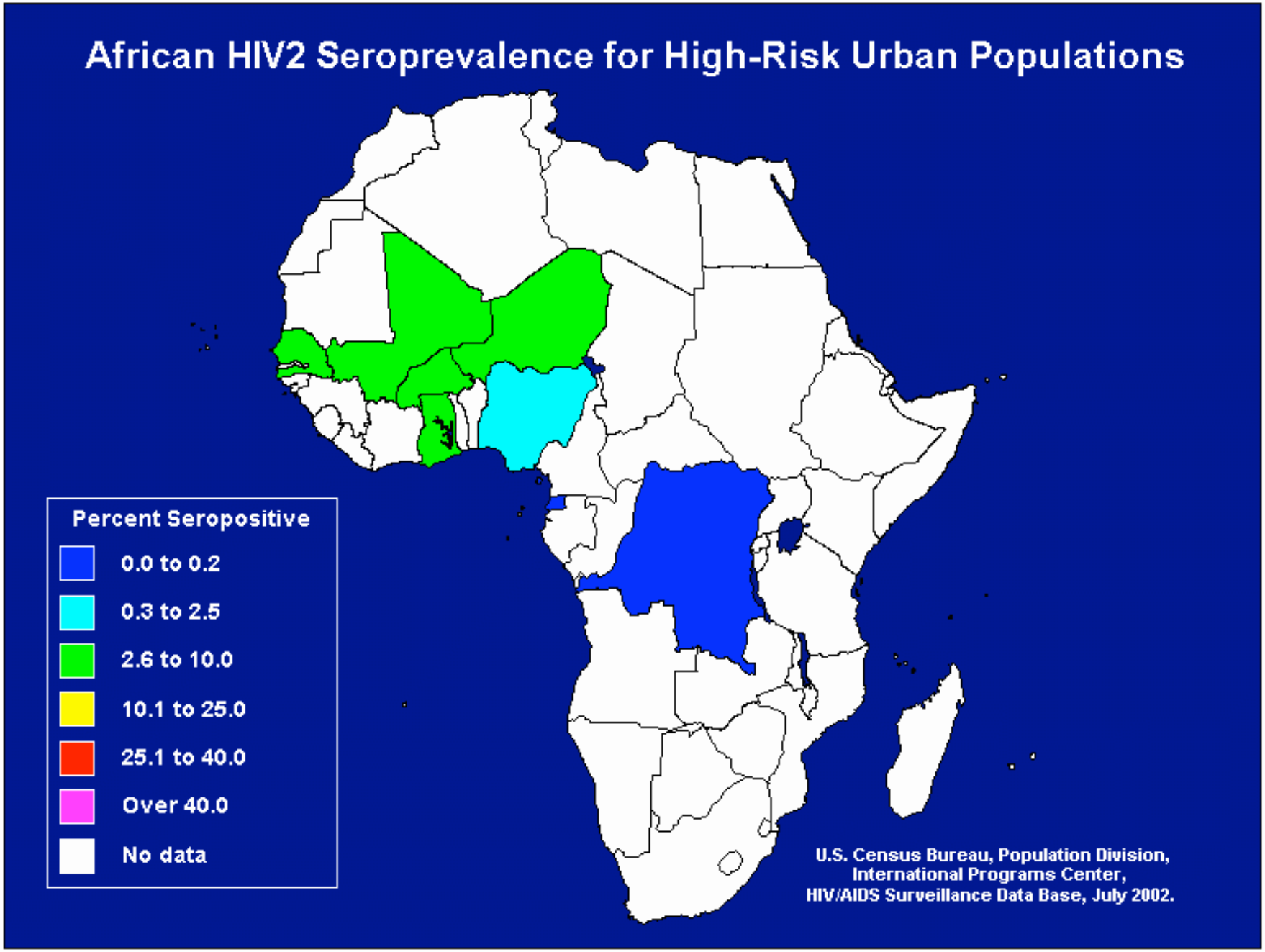
UNAIDS Global Report 2013
www.cdc.gov/hiv/resources/factsheets/hiv2.htm

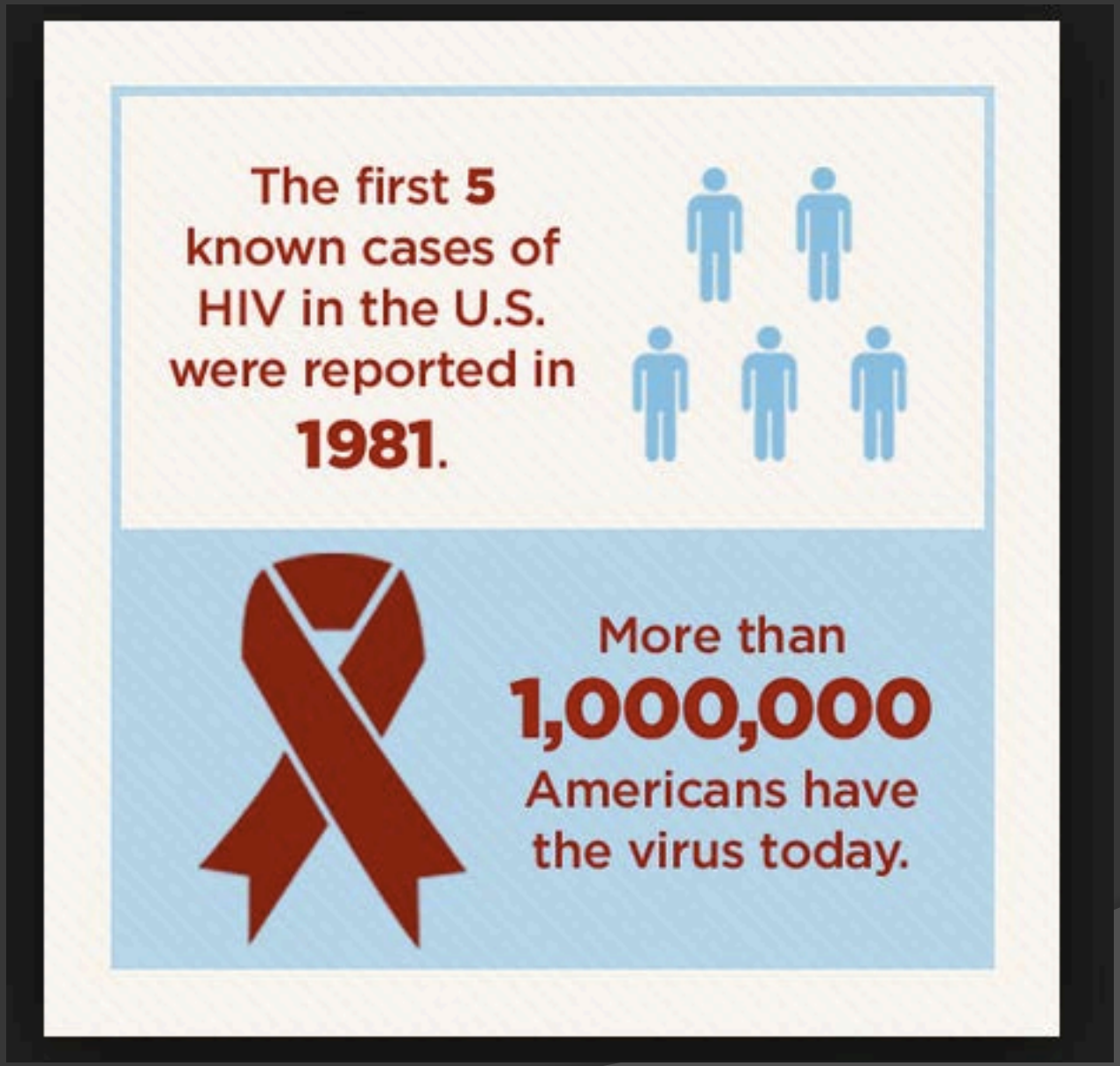
HIV-2

- HIV-2 less efficient transmission vs HIV-1 (lower vertical transmission rates)
- Less pathogenic with slower CD4 cell declines and lower viremia
- Same transmission risk factors
- CD4 count predicts survival, HIV-2 RNA VL testing in US is limited (send out)
- Resistant to NNRTIs and possibly fusion inhibitors

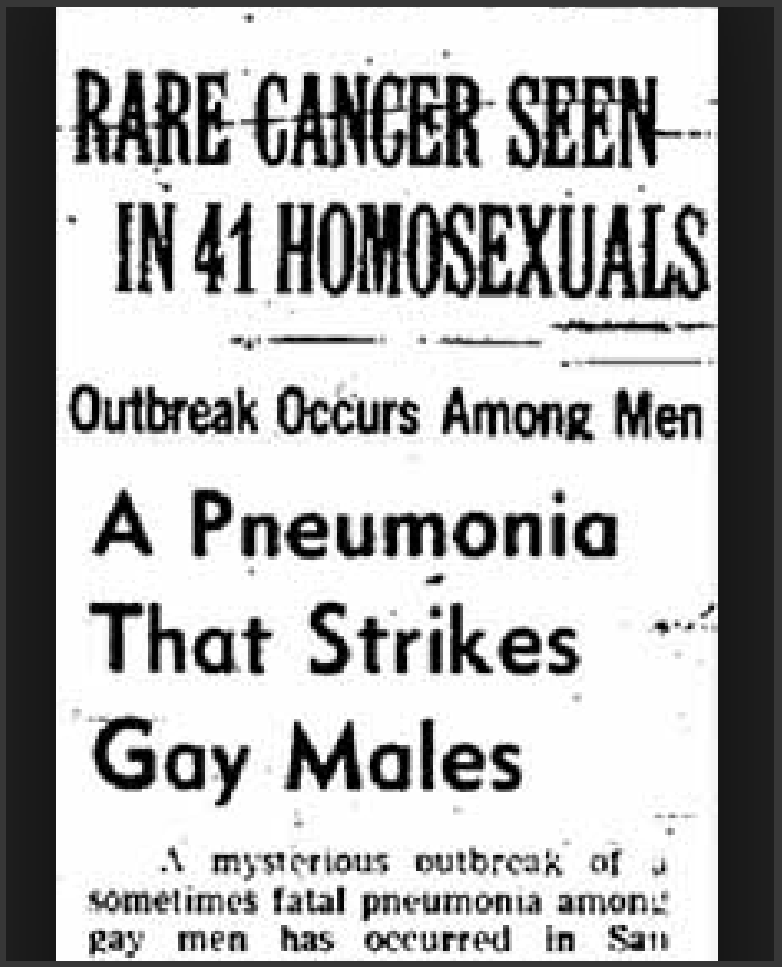
Adjorlolo-Johnson et al. JAMA 1994

African HIV2 Seroprevalence for High-Risk Urban Populations




The first 5 known cases of HIV in the U.S. were reported in 1981.
More than 1,000,000 Americans have the virus today.

History- US

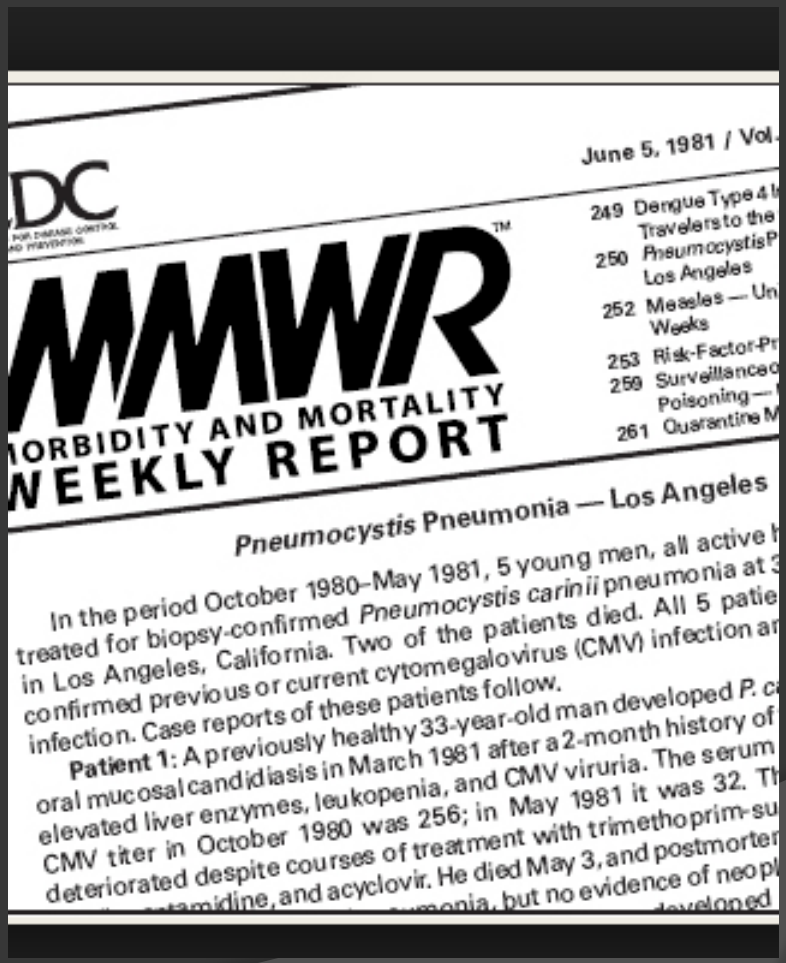


RARE CANCER SEEN IN 41 HOMOSEXUALS

Outbreak Occurs Among Men

A Pneumonia That Strikes Gay Males

A mysterious outbreak of a sometimes fatal pneumonia among gay men has occurred in San



DC

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

June 5, 1981 / Vol.

249 Dengue Type 4 I... Travelers to the...
250 Pneumocystis P... Los Angeles
252 Measles — Un... Weeks
253 Risk-Factor-Pr...
259 Surveillance... Poisoning —...
261 Quarantine M...

Pneumocystis Pneumonia — Los Angeles

In the period October 1980–May 1981, 5 young men, all active h... treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3... in Los Angeles, California. Two of the patients died. All 5 patie... confirmed previous or current cytomegalovirus (CMV) infection ar... infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. c*... oral mucosal candidiasis in March 1981 after a 2-month history of ... elevated liver enzymes, leukopenia, and CMV viruria. The serum ... CMV titer in October 1980 was 256; in May 1981 it was 32. Th... deteriorated despite courses of treatment with trimethoprim-su... ...tamidine, and acyclovir. He died May 3, and postmorter... ...monia, but no evidence of neop... ...eveloped

History- US

- 1980's: AIDS described, PCP kills 90% of pts., clinicians develop skills in diagnosing, treating and preventing complications.
- 1990's: First effective treatments, patients respond, death rates drop.
- 2000's: New toxicities arise, resistance is critical, adherence issues emerge, limitations of therapy become apparent.
- 2018: Paradigm shift in treating HIV→ earlier is better (again). New focus on discordant couples. Cure back on agenda. PrEP focus.

HIV Drugs 2018

- NRTI
  - Zidovudine
  - Didanosine
  - Stavuidine
  - Lamivudine
  - Abacavir
  - Tenofovir
  - Emtricitabine
  - Tenofovir alafenamide
- NNRTI
  - Nevaripine
  - Efavirenz
  - Etravirine
  - Rilpivirine
- PI
  - Saquinavir
  - Indinavir
  - Ritonavir
  - Fosamprenavir
  - Nelfinavir
  - Lopinavir/r
  - Atazanavir
  - Darunavir
  - Timpranivir
- Integrase Inhibitor
  - Raltegravir
  - Elvitegravir
  - Dolutegravir
- Fusion Inhibitor
  - T-20/Enfuviritide
- CCR5 Inhibitor
  - Maraviroc

OPOD plus™

OPOD

- Atripla (EFV/TDF/FTC)
- Complera (RPV/TDF/FTC)
- Odefsy (RPV/TAF/FTC)
- Stribild (EVG/c/TDF/FTC)
- Triumeq (DTG/ABC/3TC)
- Genvoya (EVG/c/TAF/FTC)
- Biktarvy (DTG/TAF/FTC)

New Kids on the Block

- Prezcobix (DRV/c)
- Evotaz (ATV/c)
- Vemlidy (TAF)
- Descovy (FTC/TAF)

Advances: Life Expectancy

- HIV infected adults Kaiser Permanente 1996-2011 with HIV-uninfected members matched 10:1 on age, gender, medical center, and year.

- 25,768 HIV-infected and 257,600 HIV-uninfected individuals

CROI Feb 2016, absract #54
Narrowing the Gap in Life Expectancy for HIV+ Compared With HIV- Individuals
Julia L. Marcus et al.

Advances: Life Expectancy

- In 1996-2006, life expectancies at age 20 among HIV-infected and HIV-uninfected individuals were 36.0 and 62.3 years, respectively
  - Corresponding with a gap of 26.3 years
- In 2007-2011, life expectancy at age 20 for HIV-infected individuals increased to 48.5 years, narrowing the gap to 13.8 years
- The lowest life expectancies at age 20 for HIV patients in 2007-2011 were among African Americans (45.2 years) and those with a history of injection drug use (42.6 years).

CROI Feb 2016, absract #54
Narrowing the Gap in Life Expectancy for HIV+ Compared With HIV- Individuals
Julia L. Marcus et al.

Advances: Life Expectancy

- In 2007-2011, HIV patients who initiated ART with ≥500 cells/μL had a life expectancy at age 20 of 53.8 years
  - Corresponding with a gap of 8.5 years.
- The gap narrowed further to 6-7 years in subgroups without a history of hepatitis B or C infection, drug/alcohol abuse, or smoking.

CROI Feb 2016, absract #54
Narrowing the Gap in Life Expectancy for HIV+ Compared With HIV- Individuals
Julia L. Marcus et al.

HPTN 052 and PARTNER Study

- Risk of transmission HPTN 052
  - 96% reduction in HIV transmission when positive partners started on ART early (heterosexual)
- PARTNER Study
  - European study, 900 couples (MSM) not using condoms
  - ZERO transmissions when pos member had UD VL
- U=U

Coehn et all NEJM Sept 1, 2016
Rodgers et al, JAMA 2016

HIV Incidence

- New HIV infections drop 18% from 2008-2014.
- Incidence dropped:
- 56% among IVDUs
- 36% among heterosexuals
- 18% among young gay and bisexual males ages 13 to 24
- 18%among white gay and bisexual males

https://www.cdc.gov/nchhstp/newsroom/2017/croi-hiv-incidence-press-release.html

BUT....

- Gay and bisexual men were the only group that did not experience an overall decline in annual HIV infections from 2008 to 2014.
- This is because reduced infections among whites and the youngest gay and bisexual men were offset by increases in other groups.

https://www.cdc.gov/nchhstp/newsroom/2017/croi-hiv-incidence-press-release.html

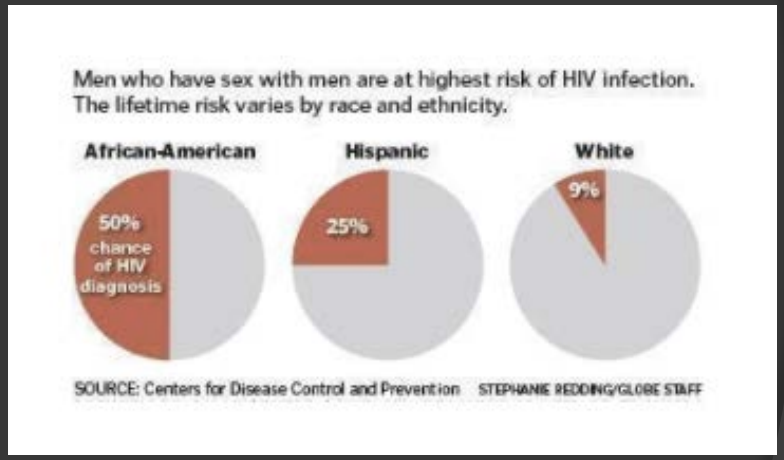
Increased incidence in:

- 35% among 25- to 34-year-old gay and bisexual males
- 20% among Latino gay and bisexual males
- THE SOUTH- home to 37% of the U.S. population but accounted for 50% of estimated infections in 2014.

https://www.cdc.gov/nchhstp/newsroom/2017/croi-hiv-incidence-press-release.html

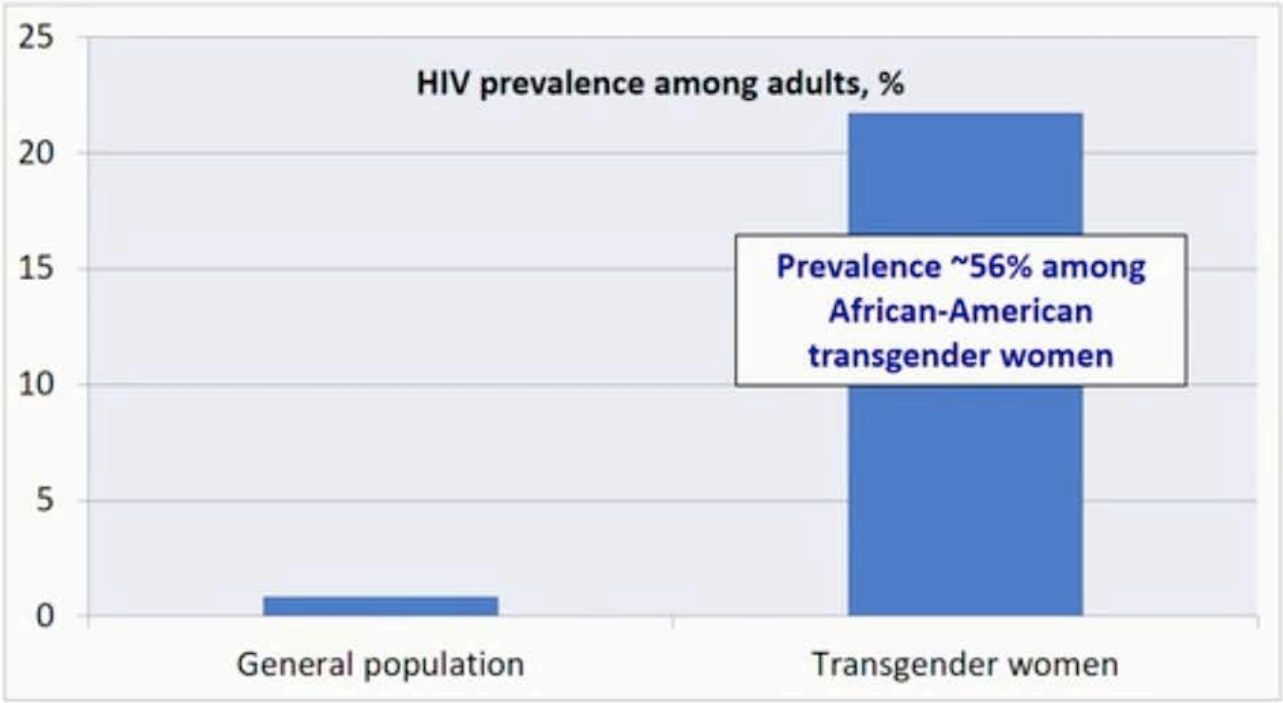
Epidemic within an epidemic...

- If current HIV diagnoses rates persist, 1 in 2 black MSM and 1 in 4 Latino MSM in the US will be diagnosed with HIV during their lifetime.



https://www.cdc.gov/nchhstp/newsroom/2016/croi-press-release-risk.html

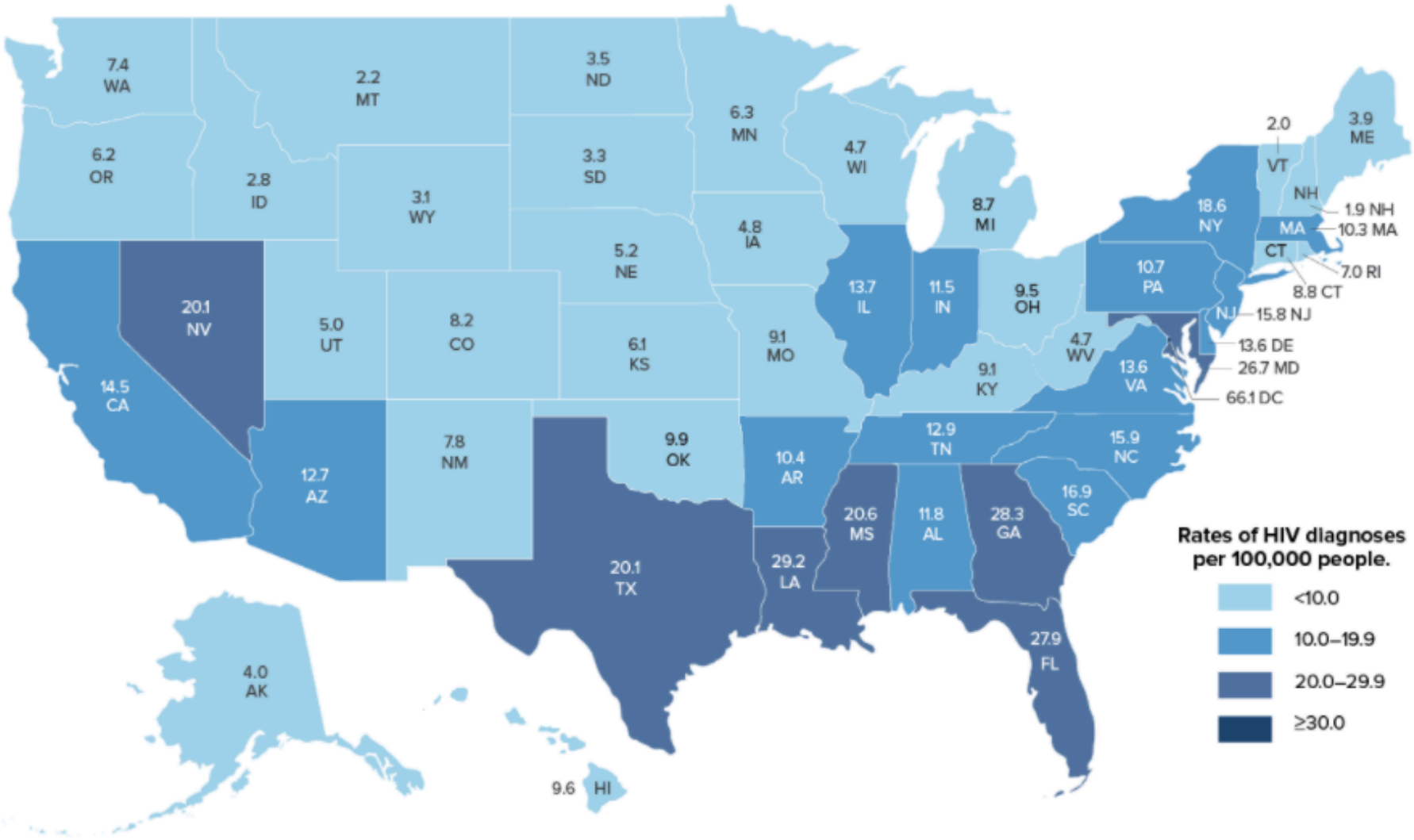
HIV disproportionately burdens transgender women.



1. Baral SD, Poteat T, Stromdahl S, Wirtz AL, Guadamuz TE, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13(3):214.
2. Herbst JH, Jacobs ED, Finlayson TJ, et al. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. AIDS Behav. 2008;12(1):1.

The rates (per 100,000 people) of HIV diagnoses in 2015 were 16.8 in the South, 11.6 in the Northeast, 9.8 in the West, and 7.6 in the Midwest.[c]

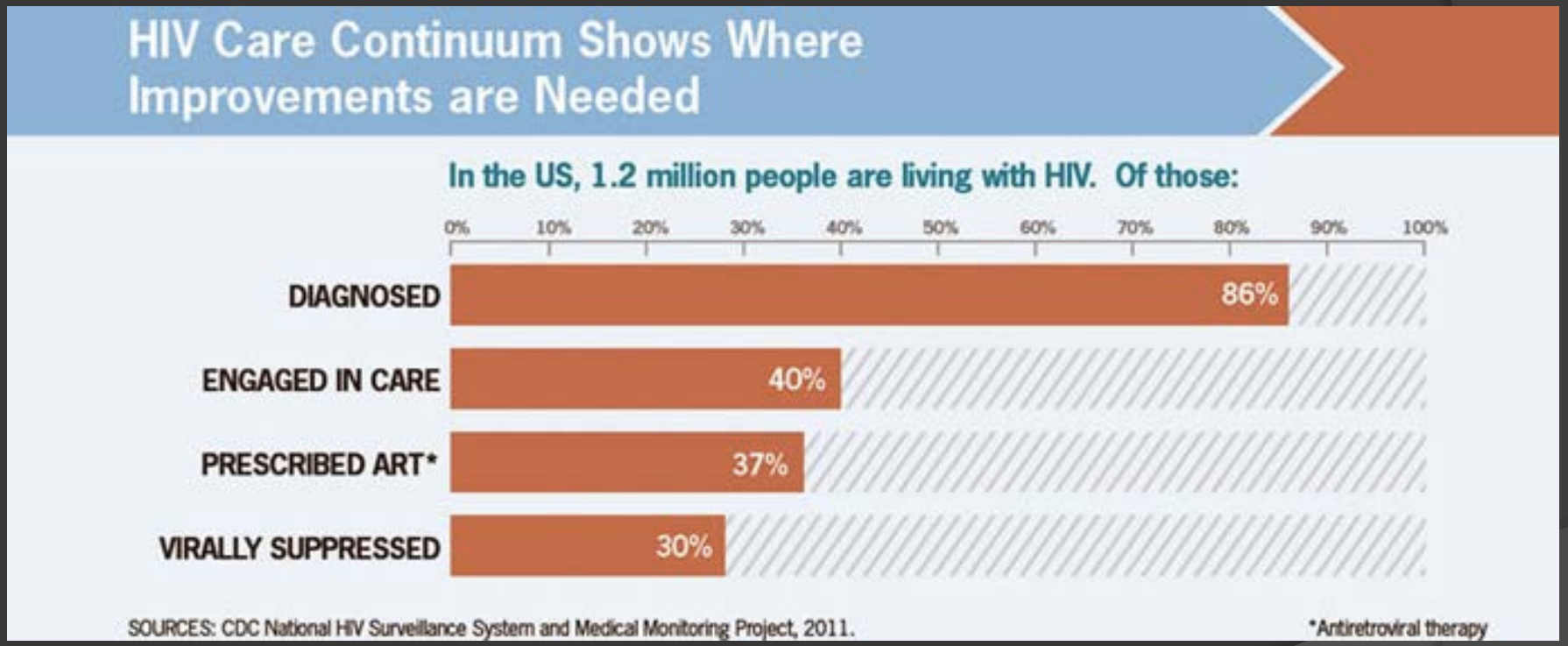
Rates of HIV Diagnoses Among Adults and Adolescents in the US in 2015, by State



Source: CDC. Diagnoses of HIV infection in the United States and dependent areas, 2015. *HIV Surveillance Report* 2016;27.


HIV CARE CONTINUUM:
THE SERIES OF STEPS A PERSON WITH HIV TAKES FROM INITIAL DIAGNOSIS THROUGH THEIR SUCCESSFUL TREATMENT WITH HIV MEDICATION
DIAGNOSED WITH HIV
LINKED TO CARE
ENGAGED OR RETAINED IN CARE
PRESCRIBED ANTIRETROVIRAL THERAPY
ACHIEVED VIRAL SUPPRESSION

Failures:
The Continuum of Care



Middle TN and VCCC

- Number of HIV/AIDS cases in Middle TN has increased in 20% in last 5 years
- We serve over 3,000 patients at the VCCC
- 50% of the patients we serve fall below poverty line
- 95% fall below 300% of the poverty level
- 47% of patients in Middle TN were not in care
- At CCC 90% retained in care, 76% suppressed

Middle TN and the VCC

- From 2009 to 2011 the % of males aged 15-24 w/ HIV increased 20% in the state and 27% in the greater Nashville area
- 24% of our patients did not have enough food to eat 3 or more days in a row
- 20% were homeless in the last year
- 14% were in jail/prison in last year
- 43% needed help in dealing w/ sadness or stress
- 19% needed help in dealing w/ etoh or drug use

Ryan White Care Act

- First authorized in 1990, the Ryan White HIV/AIDS Program is currently funded at $2.3 billion.
- Reaches 52% of all PLWHA in the US.
- 100% free medications, MD visits, lab work for those enrolled.
- Generally <300% poverty level.

2016 Federal Poverty Levels

Size of Household	Household Annual Income					
	138%	150%	200%	250%	300%	400%
1	$16,105	$17,505	$23,340	$29,175	$35,010	$46,680
2	$21,708	$23,595	$31,460	$39,325	$47,190	$62,920
3	$27,311	$29,685	$39,580	$49,475	$59,370	$79,160
4	$32,913	$35,775	$47,700	$59,625	$71,550	$95,400
5	$38,516	$41,865	$55,820	$69,775	$83,730	$111,640

If your total annual household income is within these levels you may qualify for premium subsidy (discounted health insurance premium)

Crisis in Funding

- In our clinic, we have a 10-15% increase in need for RW funding per year
- Each year we have a 5-10% cut in RW funding from last years level.
- No TN expansion of Medicaid.
- What happens now?
- Waiting lists can hit each state.


I HAVE AIDS
Please hug me
I can't make you sick

Screening for HIV

Screening for HIV Infection

- In all health-care settings, screening for HIV infection should be performed routinely for all patients aged 13-64 years.
- All patients seeking treatment for STDs should be screened routinely for HIV.

Repeat Screening

- Health-care providers should subsequently test all persons likely to be at high risk for HIV at least annually.

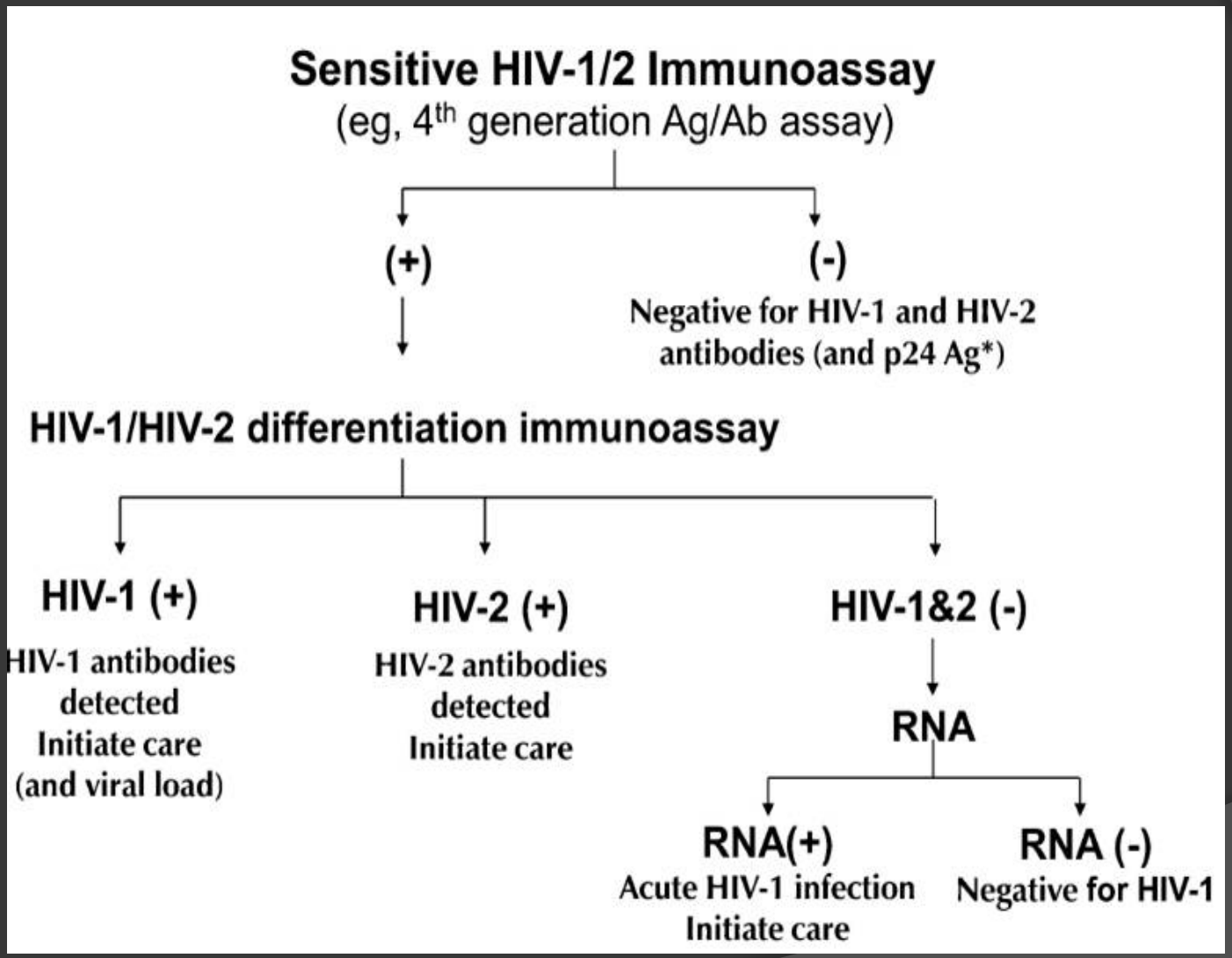
MMWR Sept 2006
Revised Recommendations
For HIV Testing

New HIV Testing Guidelines

- 1 in 6 Americans living w/ HIV don't know they are infected
- Half of all new HIV infections are transmitted by people in the acute or early stage of infection.
- People with acute infection are more likely to transmit the virus.
- CDC's new testing algorithm allows diagnosis of HIV as much as 3-4 weeks earlier than the previously recommended sequence of tests using the Western blot.
- As a result, the HIV-1 Western blot is no longer part of the recommended algorithm.

http://www.cdc.gov/hiv/testing/lab/guidelines/index.html

New HIV Testing Guidelines



http://www.cdc.gov/hiv/testing/lab/guidelines/index.html

HIV Testing- A History

Time to test positivity

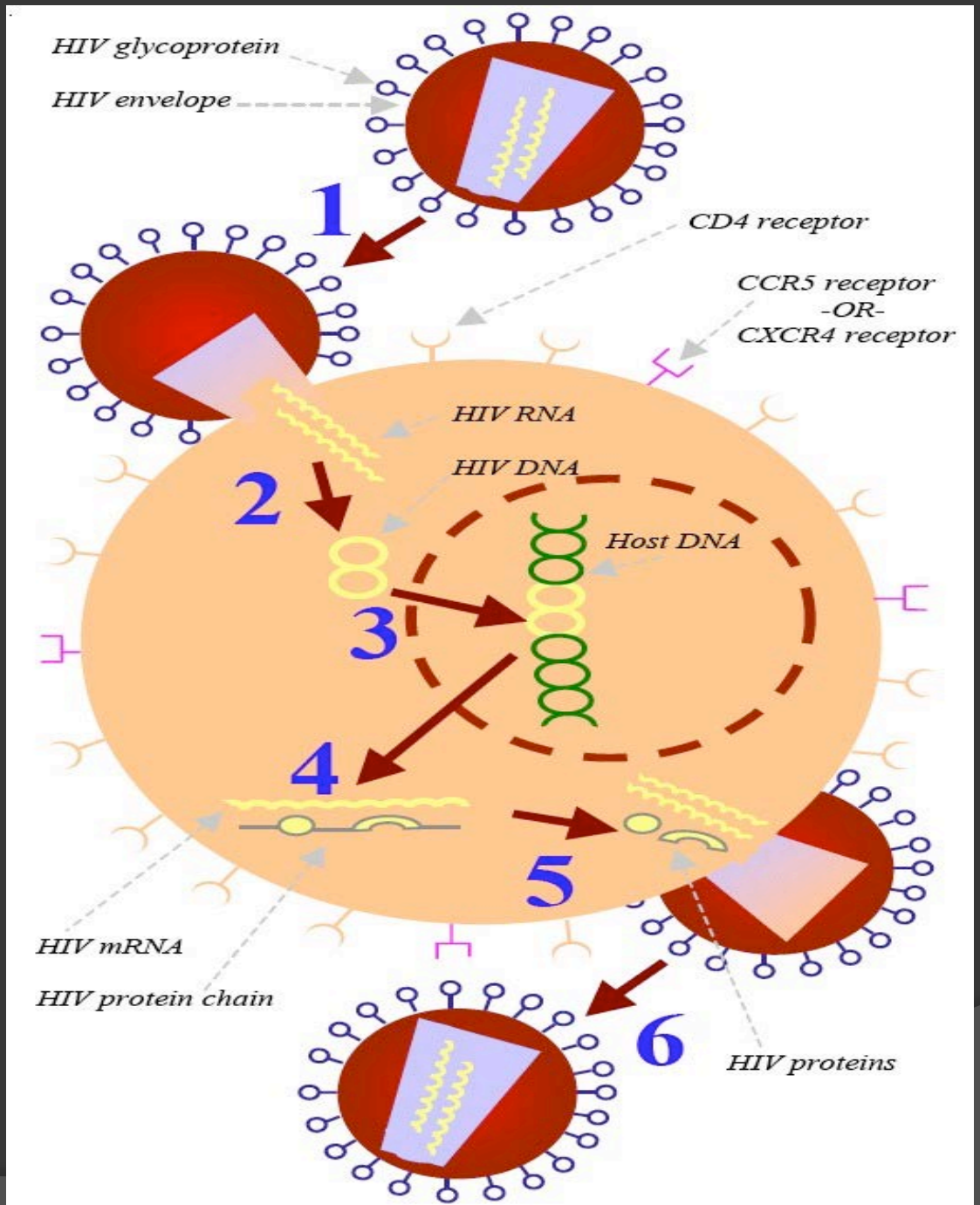
Test	Target of detection	Approximate time to positivity (days)
Enzyme-linked immunoassay		
First generation	IgG antibody	35 to 45
Second generation	IgG antibody	25 to 35
Third generation	IgM and IgG antibody	20 to 30
Fourth generation	IgM and IgG antibody and p24 antigen	15 to 20
Western blot		
	IgM and IgG antibody	35 to 50 (indeterminate)
		45 to 60 (positive)
HIV viral load test		
Sensitivity cut-off 50 copies/mL	RNA	10 to 15
Ultrasensitive cut-off 1 to 5 copies/mL	RNA	5

This table demonstrates the approximate time to positivity following infection for various diagnostic tests for HIV.

References:

1. *Branson BM, Stekler JD. Detection of acute HIV infection: We can't close the window. J Infect Dis 2012; 205:521.*
2. *Owen SM. Testing for acute HIV infection: implications for treatment as prevention. Curr Opin HIV AIDS 2012; 7:125.*
3. *Cohen MS, Gay CL, Busch MP, et al. The detection of acute HIV infection. J Infect Dis 2010; 202:S270.*

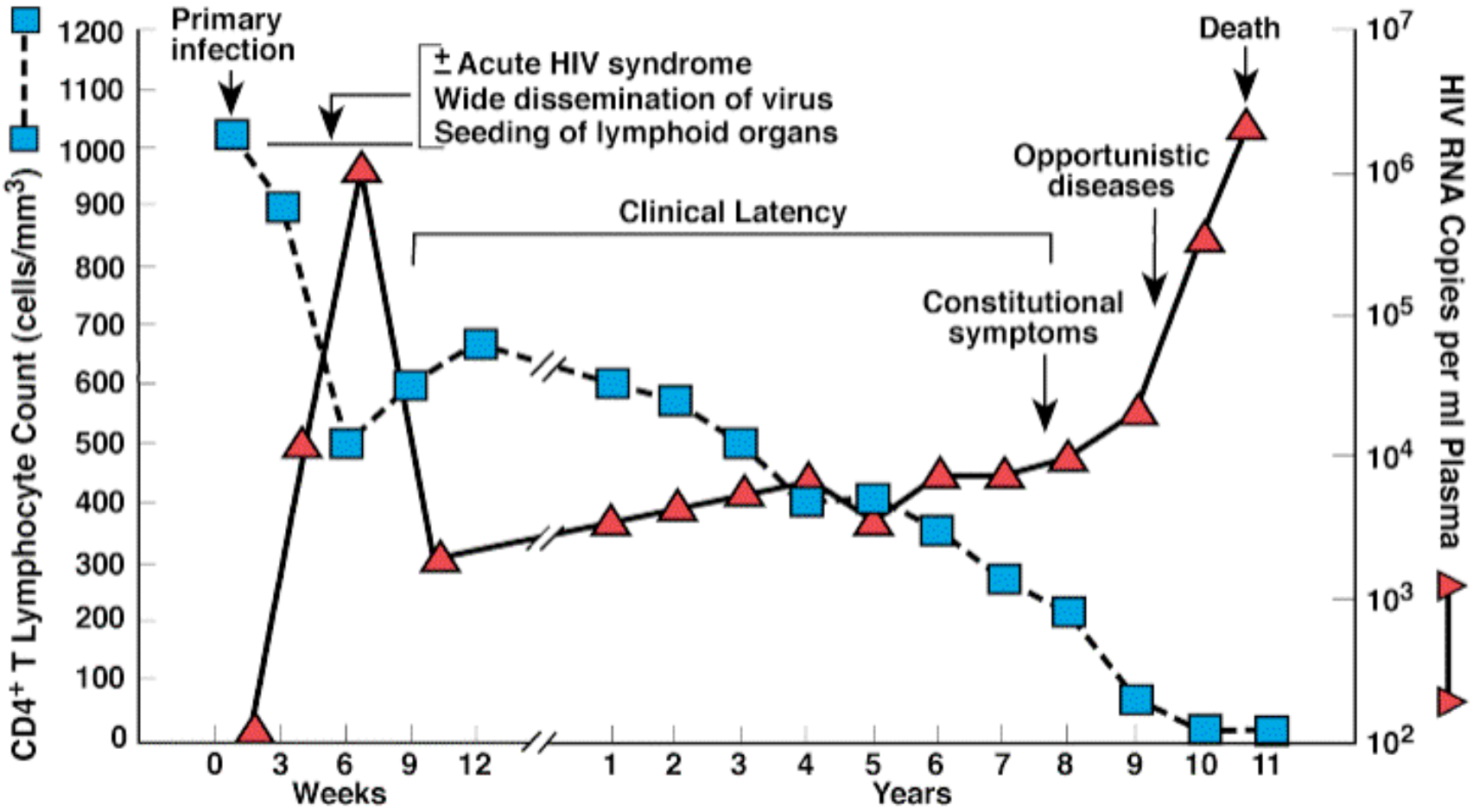
AIDS Defining Events/ Opportunistic Infections


HIV glycoprotein
HIV envelope
1
CD4 receptor
CCR5 receptor
-OR-
CXCR4 receptor
HIV RNA
HIV DNA
2
Host DNA
3
4
5
HIV mRNA
HIV protein chain
6
HIV proteins

Refresher

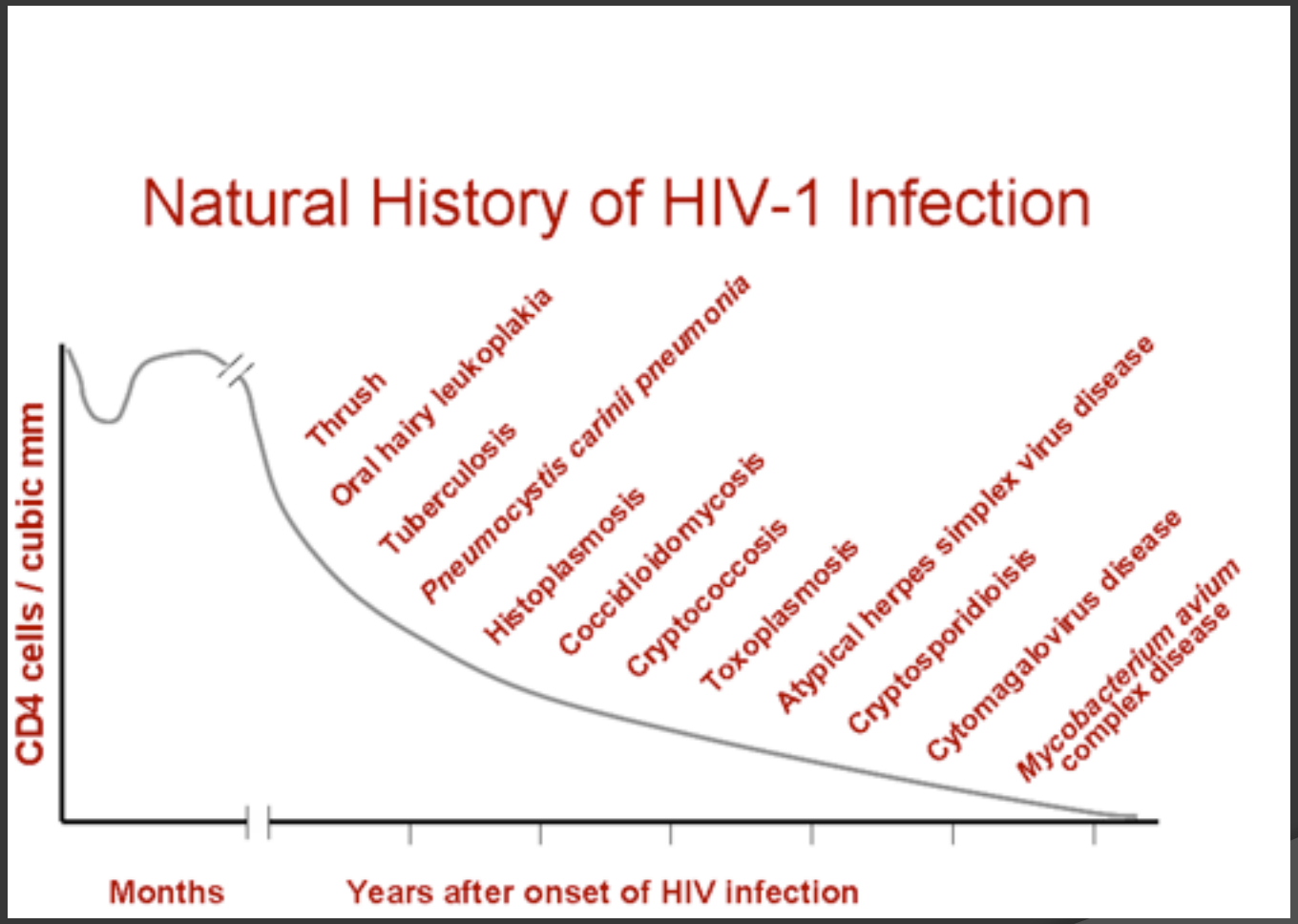
- CD4 count
  - Normal 800-1200 cells/mm^3
  - How far the train has gone
- Viral load
  - Goal “undetectable”
  - <40 copies/mL, < 20 copies/ mL
  - How fast the train is going

Typical Course of HIV Infection



Modified From: Fauci, A.S., et al, *Ann. Intern. Med.*, 124:654, 1996

Why We Treat HIV



1. Candidiasis of bronchi, trachea, or lungs
2. Candidiasis esophageal
3. Coccidioidomycosis, disseminated or extrapulmonary
4. Cryptococcosis, extrapulmonary
5. Cryptosporidiosis, chronic intestinal for longer than 1 month
6. Cytomegalovirus disease (other than liver, spleen or lymph nodes)
7. Cytomegalovirus retinitis (with loss of vision)
8. Encephalopathy (HIV-related)
9. Herpes simplex: chronic ulcer(s) (for more than 1 month); or bronchitis, pneumonitis, or esophagitis
10. Histoplasmosis, disseminated or extrapulmonary
11. Isosporiasis, chronic intestinal (for more than 1 month)
12. Kaposi's sarcoma
13. Lymphoma, Burkitt's
14. Lymphoma, immunoblastic (or equivalent term)
15. Lymphoma, primary, of brain
16. Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
17. Mycobacterium, other species, disseminated or extrapulmonary
18. Mycobacterium tuberculosis, any site (extrapulmonary)
19. Pneumocystis jirovecii pneumonia (formerly Pneumocystis carinii)
20. Progressive multifocal leukoencephalopathy
21. Salmonella septicemia (recurrent)
22. Toxoplasmosis of the brain
23. Tuberculosis, disseminated
24. Wasting syndrome due to HIV

New Face of HIV Non-AIDS Defining Events

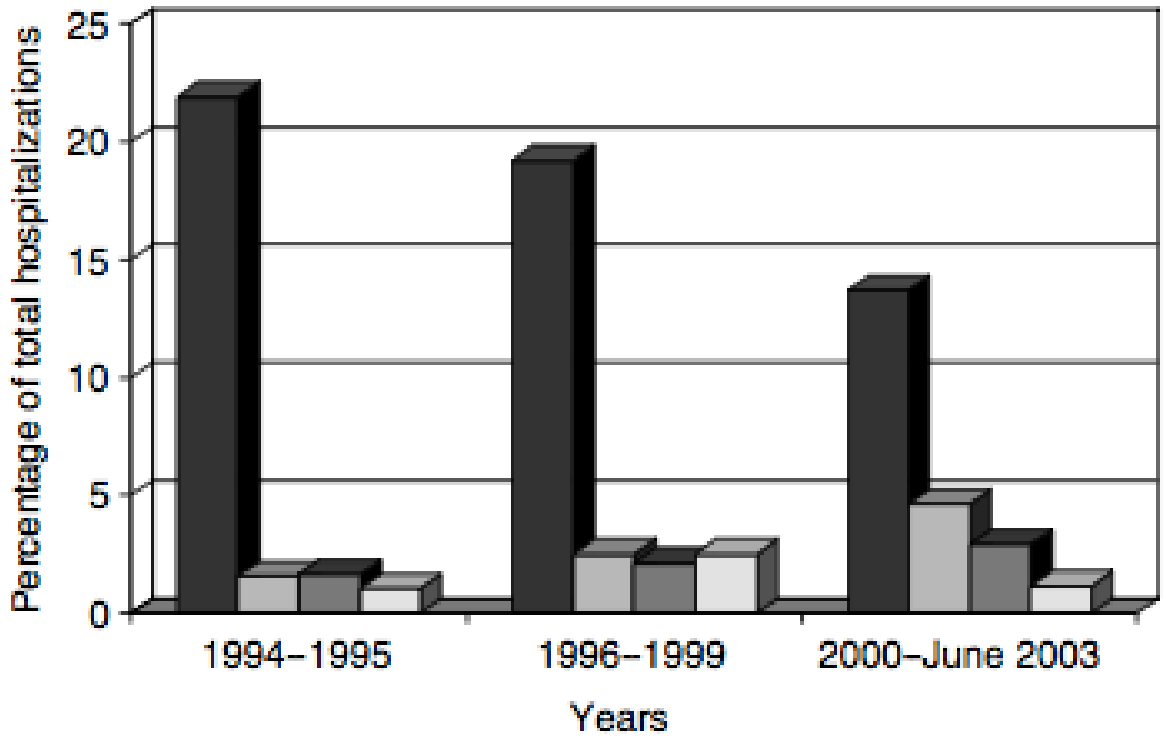


Fig. 2. Pulmonary, cardiovascular, and hepatic hospitalizations as percentage of total hospitalizations of HIV Outpatient Study (HOPS) participants, fourth quarter, 2003 update. ■ Total pulmonary diagnoses; ■ total cardiovascular diagnoses; ■ total hepatic diagnoses; □ total renal diagnoses.

Not everything is about OIs anymore…

- Veterans Aging Cohort Study Virtual Cohort
- 33,420 HIV-infected veterans
- 66,840 matched age, sex, race and ethnicity HIV-uninfected veterans.
- Adjusted for self-reported smoking.

Am J Respir Crit Care Med Vol 183. pp 388–395, 2011

Smoking

- Even after adjusting for smoking higher rates of COPD, lung cancer, pulmonary fibrosis, and pulmonary hypertension were found when compared with HIV uninfected individuals.

Am J Respir Crit Care Med Vol 183. pp 388–395, 2011

Smoking and HIV

- Life expectancy
  - Current smokers 62.6 years
  - Ex-smokers 69.1 years
  - Never smokers 78.4 years
- 12.3 life-years lost to smoking vs. 5.1 years lost to HIV infection
- Risk of death associated w/ smoking
  - 61.5% for those w/ HIV vs. 32.4% for HIV negative participants

Helleberg Clin Infect Dis, Dec 18,2012

Lung Cancer

- IRR for lung cancer was 1.7; 95% CI: 1.5–1.9 after adjusting for age, sex, race/ethnicity, smoking, baseline COPD and bacterial pneumonia.
- Current smokers IRR 6.3, 95% CI: 4.7– 8.4
- Former smokers IRR 3.0, 95% CI: 2.2–4.1.
- COPD was associated with increased lung cancer risk (IRR 1.9; 95% CI: 1.5–2.3)

Sigel AIDS 2012, Vol 26 No 8

HIV-Associated Neurocognitive Disorder (HAND)

- Spectrum→ ADC, HIV encephalopathy, HIV-D
- Nadir CD4 count predicts development
- High rates of mild neurocognitive impairment persist at all stages of HIV infection
- Pre-cART had more impairment in motor skills, cognitive speed, and verbal fluency
- cART era involves more memory (learning) and executive function impairment.
- Support for earlier Rx of HIV

J Neurovirol Heaton 2011

Epidemiology of HAND

- Observational study of 1555 HIV positive patients
- 52% had neuropyschologic impairment on testing.
- 33% had asymptomatic neurocognitive impairment.
- 12% had mild neurocognitive disorder.
- Only 2% for HIV-associated dementia.
- History of low nadir CD4 was a strong predictor of impairment.
- Lowest impairment rate on CART occurred in the subset with suppressed plasma viral loads and nadir CD4 ≥200.

Neurology. 2010 December 7; 75(23): 2087–2096. Heaton

Bone complications

- 67% of HIV-infected individuals had reduced BMD
- 15% had osteoporosis
- ART associated with 2-6% decrease in BMD over first 2 years
- HOPS → 5000 patients
  - 233 had incident fractures

- Risk factors:
  - Old age
  - Substance abuse
  - CD4+ nadir < 200
  - HCV infection
  - DM
  - Neuropathy

Young CID 2011

Summary

- Many treatment advances but lots to do.
- Crisis in the SE and in TN.
- Unique population with special needs!
- ADE remain a big part of what we do for those with low CD4 counts.
- There is a “new face” of HIV and people are dying of NADES.

Questions?