Update on HIV Infection: Ten Important Concepts

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Steven C. Johnson, M.D.
Professor of Medicine
Division of Infectious Diseases
University of Colorado School of Medicine

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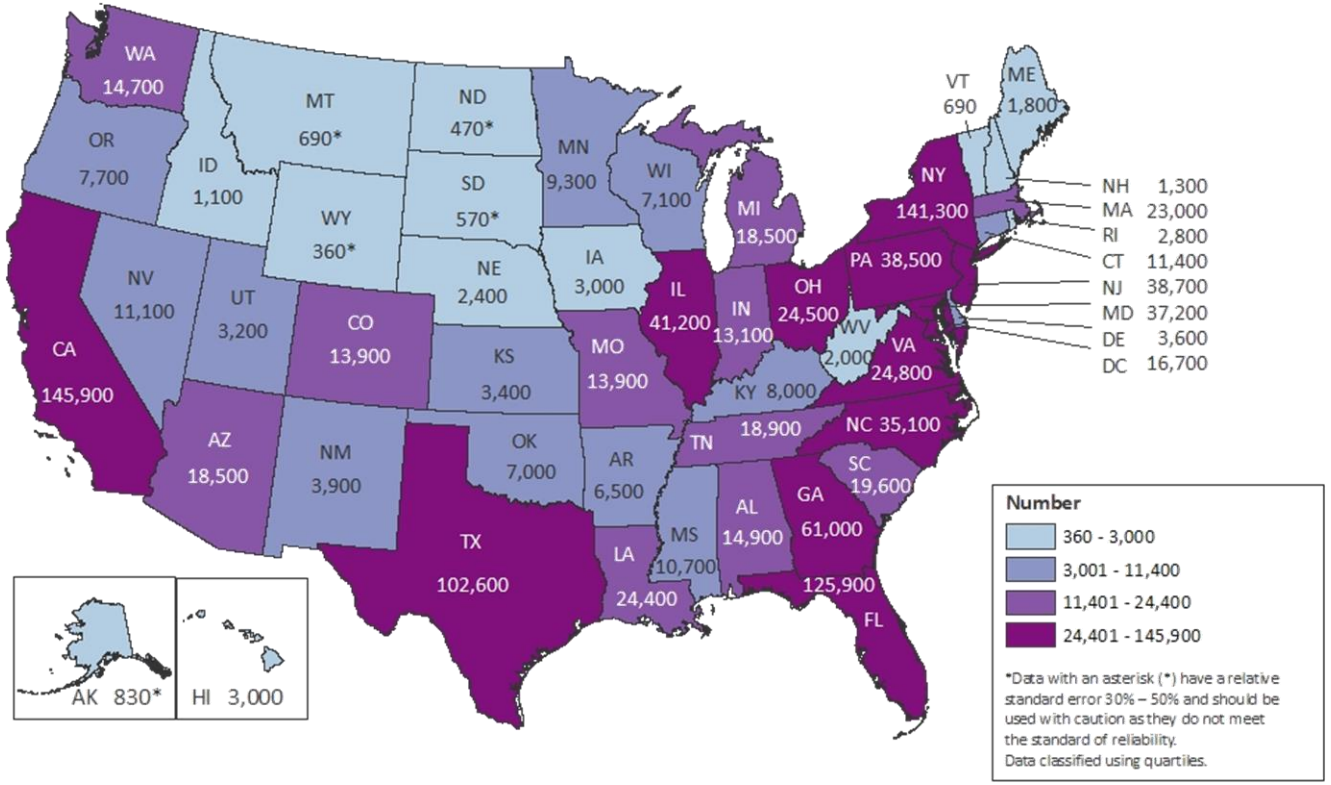
Learning Objectives

1. Review the epidemiology of HIV infection in the U.S.
2. Recognize recent advances in HIV testing
3. Learn the clinical manifestations of acute and chronic HIV infection
4. Understand current treatment approaches to HIV infection
5. Discuss the role of co-morbidities in HIV infection
6. Learn the benefits of pre-exposure prophylaxis (PrEP) in prevention of HIV infection

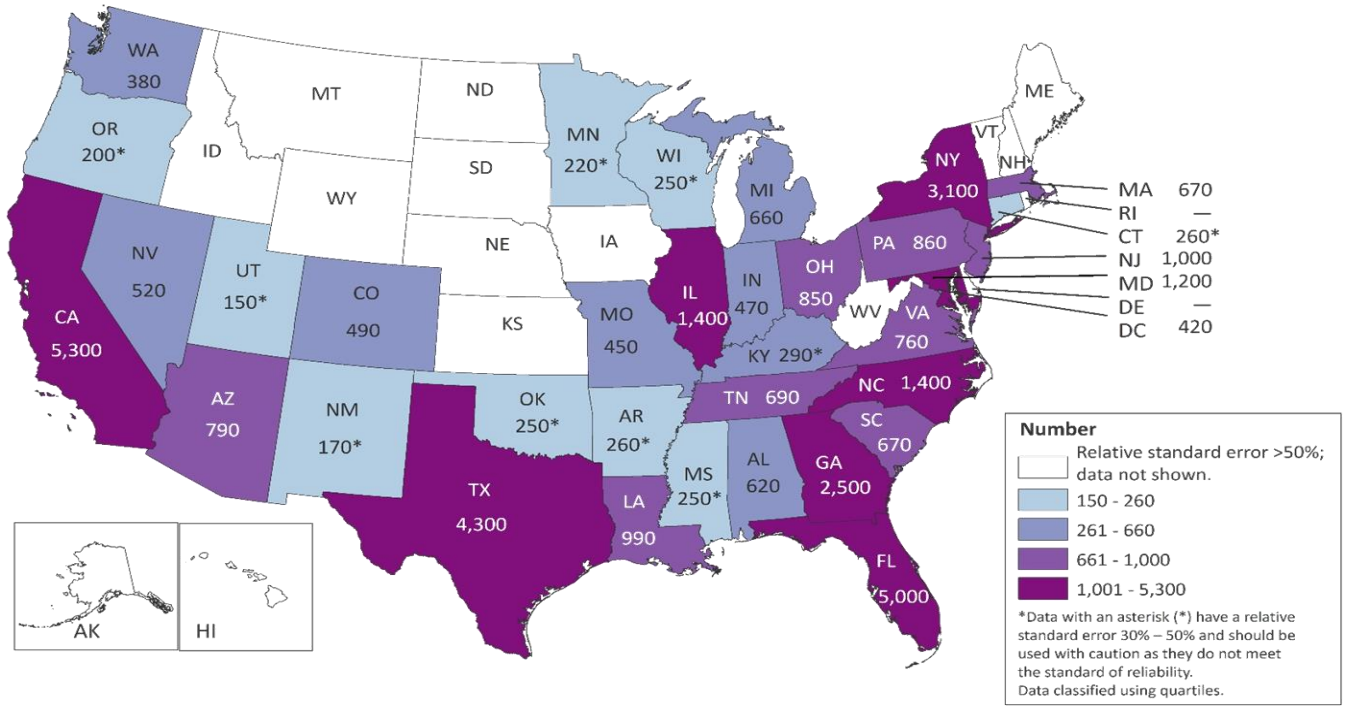
1. HIV infection is common in the U.S. affecting about 1 in 300 persons

Estimated HIV Prevalence among Persons Aged ≥13 years, by Area of Residence 2016—United States. Total = 1,140,400.



Note. Estimates were derived from a CD4 depletion model using HIV surveillance data. Estimates rounded to the nearest 100 for estimates >1,000 and to the nearest 10 for estimates ≤1,000 to reflect model uncertainty.

Estimated HIV Incidence among Persons Aged ≥13 Years, by Area of Residence 2016—United States. Total = 38,700.



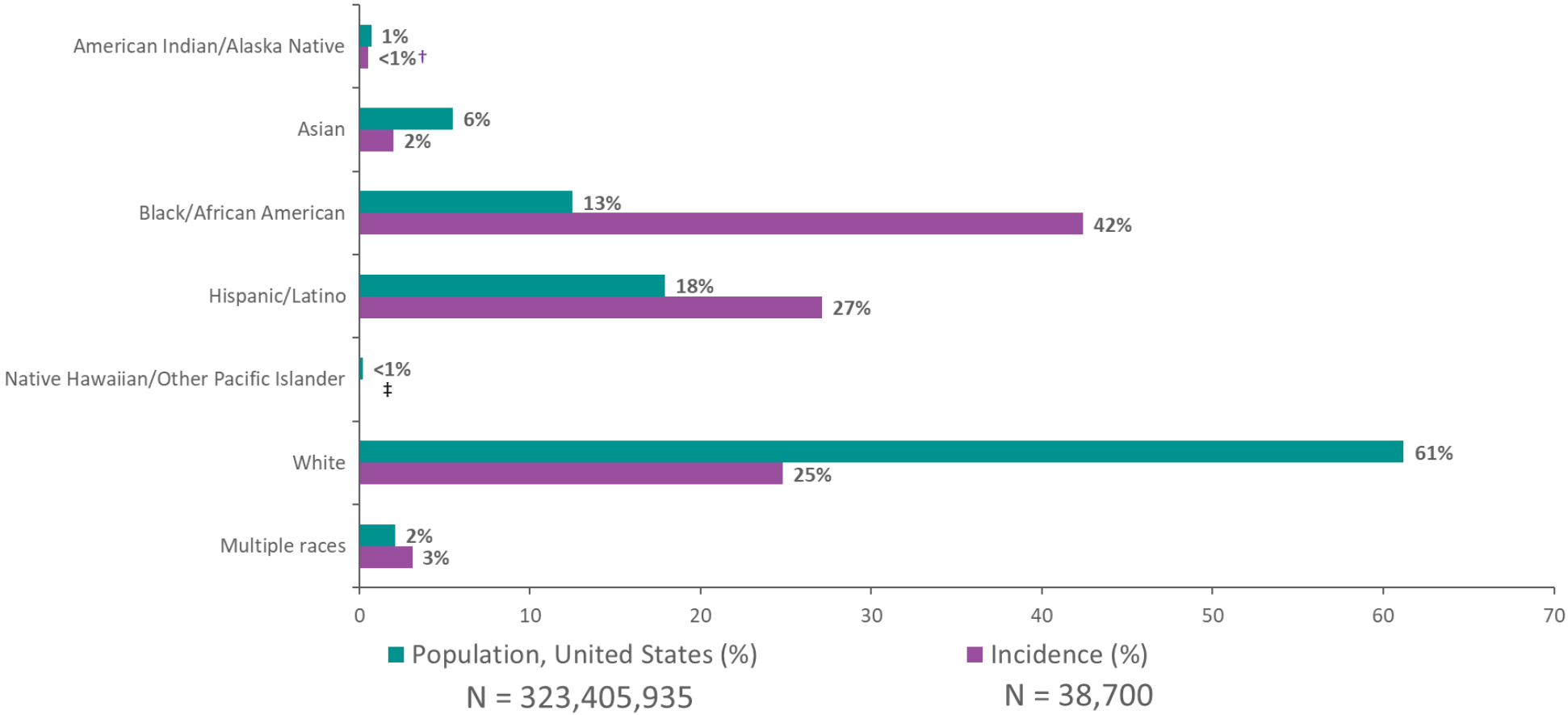
Note. Estimates were derived from a CD4 depletion model using HIV surveillance data. Estimates rounded to the nearest 100 for estimates >1,000 and to the nearest 10 for estimates ≤1,000 to reflect model uncertainty.

New HIV Infections Among Adult and Adolescents in the U.S. in 2017 (n = 38,739)

Transmission Category	Adult and Adolescent Males	Adult and Adolescent Females	Total
Male-to-male sexual contact	25,748	NA	25,748
Injection drug use	1,371	1,016	2,389
Male-to-male sex and IDU	1,252	NA	1,252
Heterosexual contact	2,829	6,341	9,170
Other (hemophilia, (transfusion, perinatal, risk not reported	37	44	81

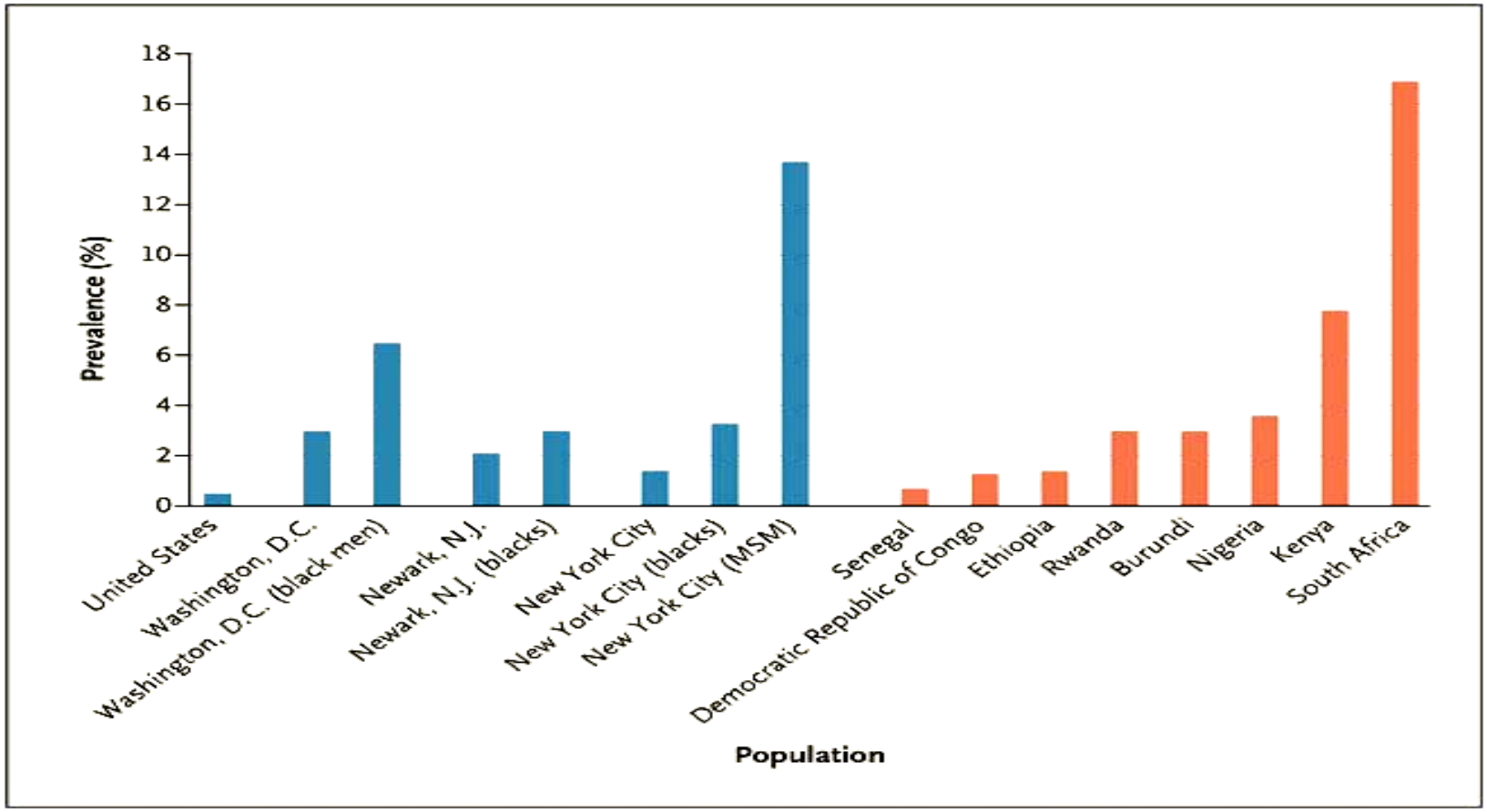
www.cdc.gov/hiv/statistics/overview/index.html

Estimated HIV Incidence and Population among Persons Aged ≥13 Years by Race/Ethnicity, 2016—United States



Note. Estimates were derived from a CD4 depletion model using HIV surveillance data. Hispanics/Latinos can be of any race.
† Estimate should be used with caution because it does not meet the standard of reliability.
‡ Incidence estimate is not provided for Native Hawaiians/other Pacific Islanders because it does not meet the minimum standard of reliability.

HIV Prevalence in Adults from Selected Countries in Sub-Saharan Africa and Subpopulations in the United States



El-Sadr W et al. N Engl J Med 2010;362:967-970

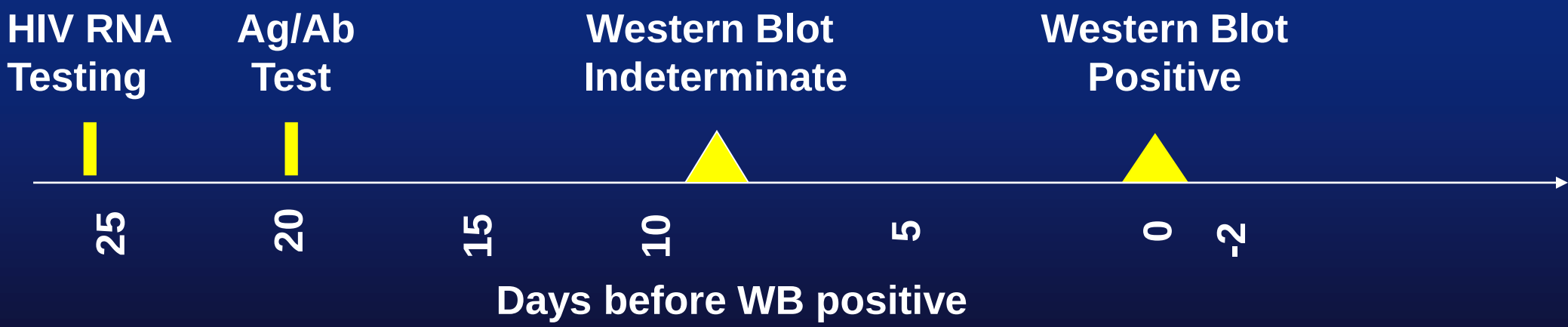
2. The CDC and the USPSTF currently recommend HIV testing for all adults and adolescents

Types of HIV Tests

- Prior HIV screening tests only detected antibody to HIV
- The currently recommended HIV screening test detects both p24 antigen, part of the virus, and HIV antibody
- Positive screening tests are confirmed with a second test, an HIV-1/HIV-2 antibody differentiation assay.
- Nucleic acid tests (NAT), usually HIV RNA testing, can be useful during acute or primary HIV infection, and to confirm indeterminate screening test results

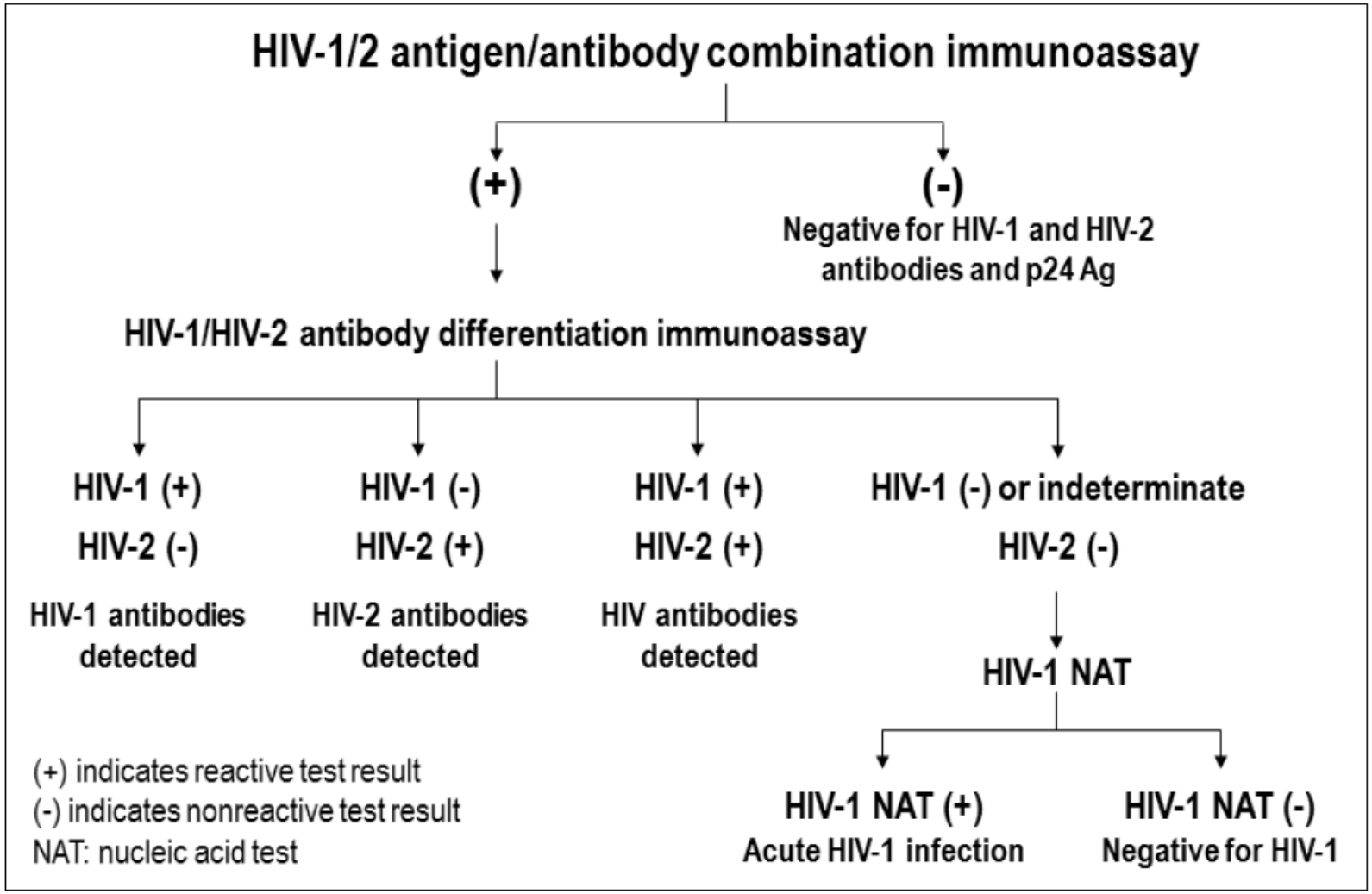
Sequence of Test Positivity Relative to the HIV Western Blot

Antigen-Antibody Screening Tests
Narrow the Serologic Window



Modified from Owen et al J Clin Micro 2008

Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens



www.cdc.gov

HIV Testing: What does the CDC recommend?

- In health care settings, HIV screening should be performed routinely in all patients aged 13-64 yrs
- Patients may decline (opt out) of testing
- General informed consent for medical care should suffice; a separate written informed consent for HIV testing is not necessary
- Rapid HIV tests are available to provide preliminary information within 20-30 minutes

CDC 2006;55:RR14

HIV Testing: What does the USPSTF recommend?

- The USPSTF recommends that clinicians screen all adolescents and adults aged 15 to 65 years for HIV infection. Younger adolescents and older adults who are at increased risk should also be screened. (Grade A recommendation)
- The USPSTF recommends that clinicians screen all pregnant women for HIV, including those who present in labor who are untested and whose HIV status is unknown. (Grade A recommendation)

Published On-Line at www.annals.org, April 30, 2013

Status of U.S. Testing Efforts

- Approximately 46% of nonelderly adults in the U.S. have ever been tested for HIV infection

- The CDC estimates that in 2016, 15% of persons living with HIV infection were unaware of their diagnosis

3. In the absence of treatment, HIV infection is a progressive illness usually leading to immunodeficiency and death

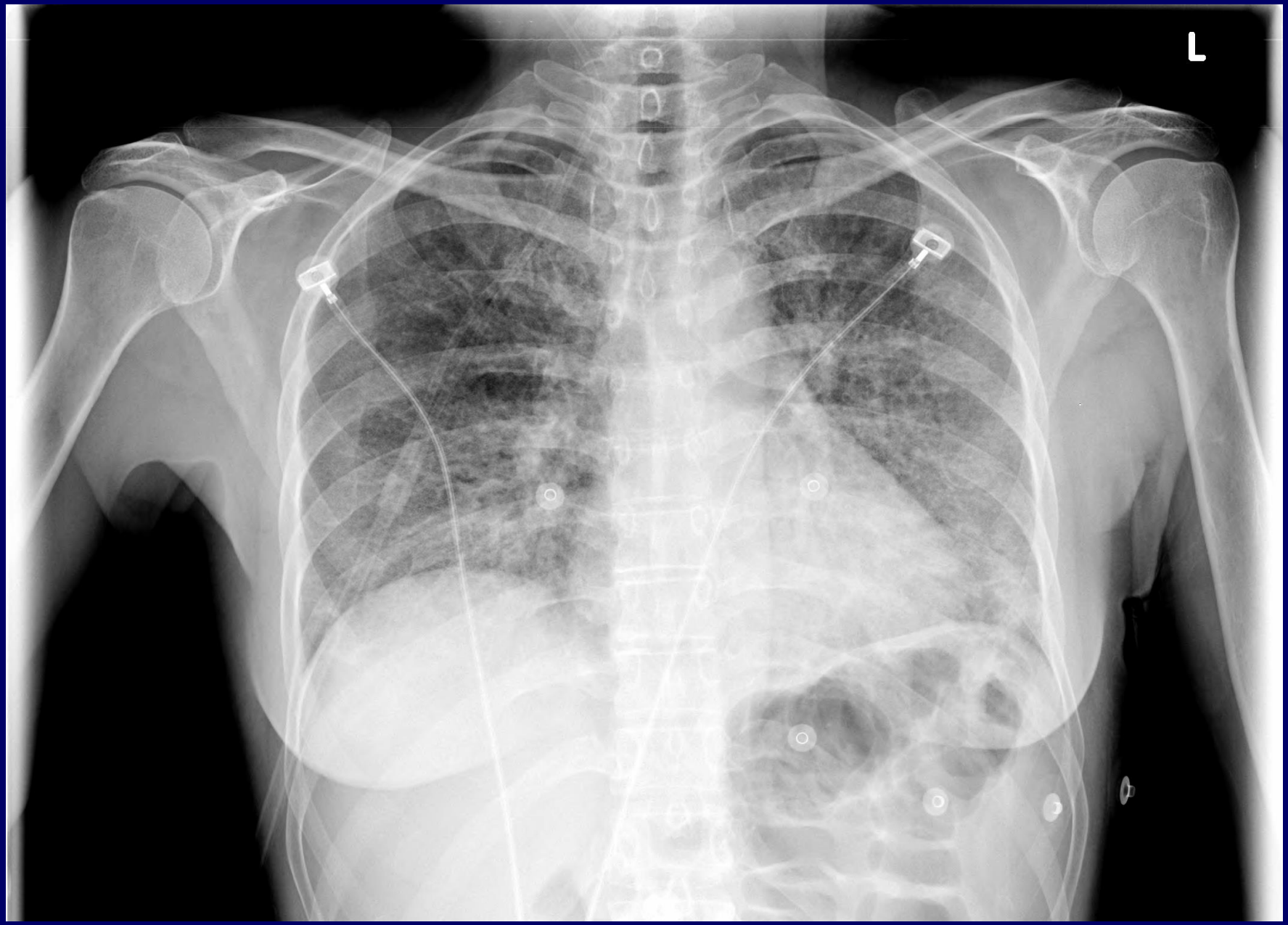
Case 1 - History

45 year old female

- Presented to the ER at the University of Colorado Hospital in 2008 with acutely worsening cough and shortness of breath
- She had noted several months of cough, fatigue, and shortness of breath
- PMH: no chronic medical problems, no alcohol or tobacco use
- Medications: none

Case 1 - Physical Exam

- Vital Signs: BP 114/64, P 95, R 20, T 37.4^{o} C
- Pulse oximetry: 64% on room air at rest
- HEENT: no oral lesions
- Lungs: diffuse rales and wheezing
- Cardiac: normal S1S2 without murmur
- Abdomen: soft, non-tender, no masses
- Extremities: cyanosis of nail beds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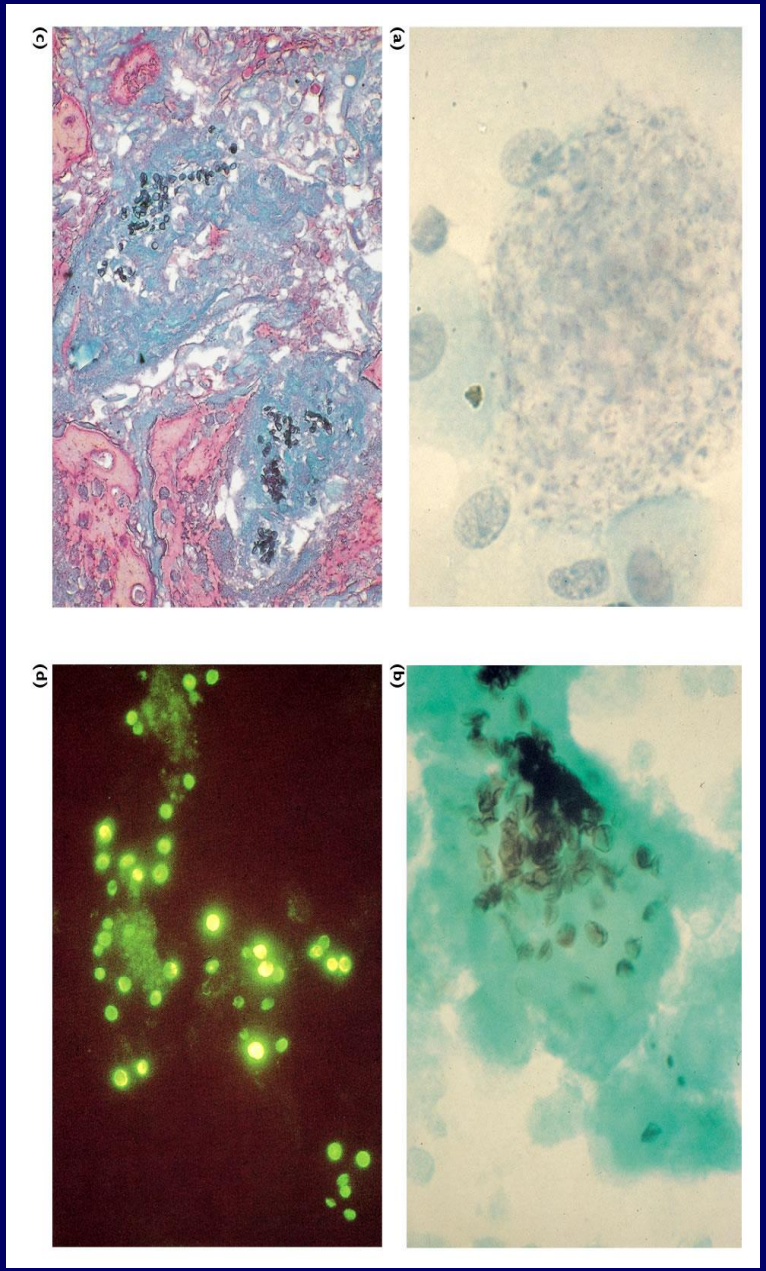
Case 1 - Labs and other Tests

- Chest x-ray: bilateral pneumonia
- No prior HIV testing; rapid HIV test was positive
- Sputum: PCP DFA +
- CD4 count 0 cells/mm^3, HIV RNA level 42,500 copies/mL
- Diagnosis: Pneumocystis pneumonia (PCP) complicating HIV/AIDS

Pneumocystis jirovecii in Respiratory Secretions

Key Laboratory Test: PCP DFA from sputum or bronchoscopy

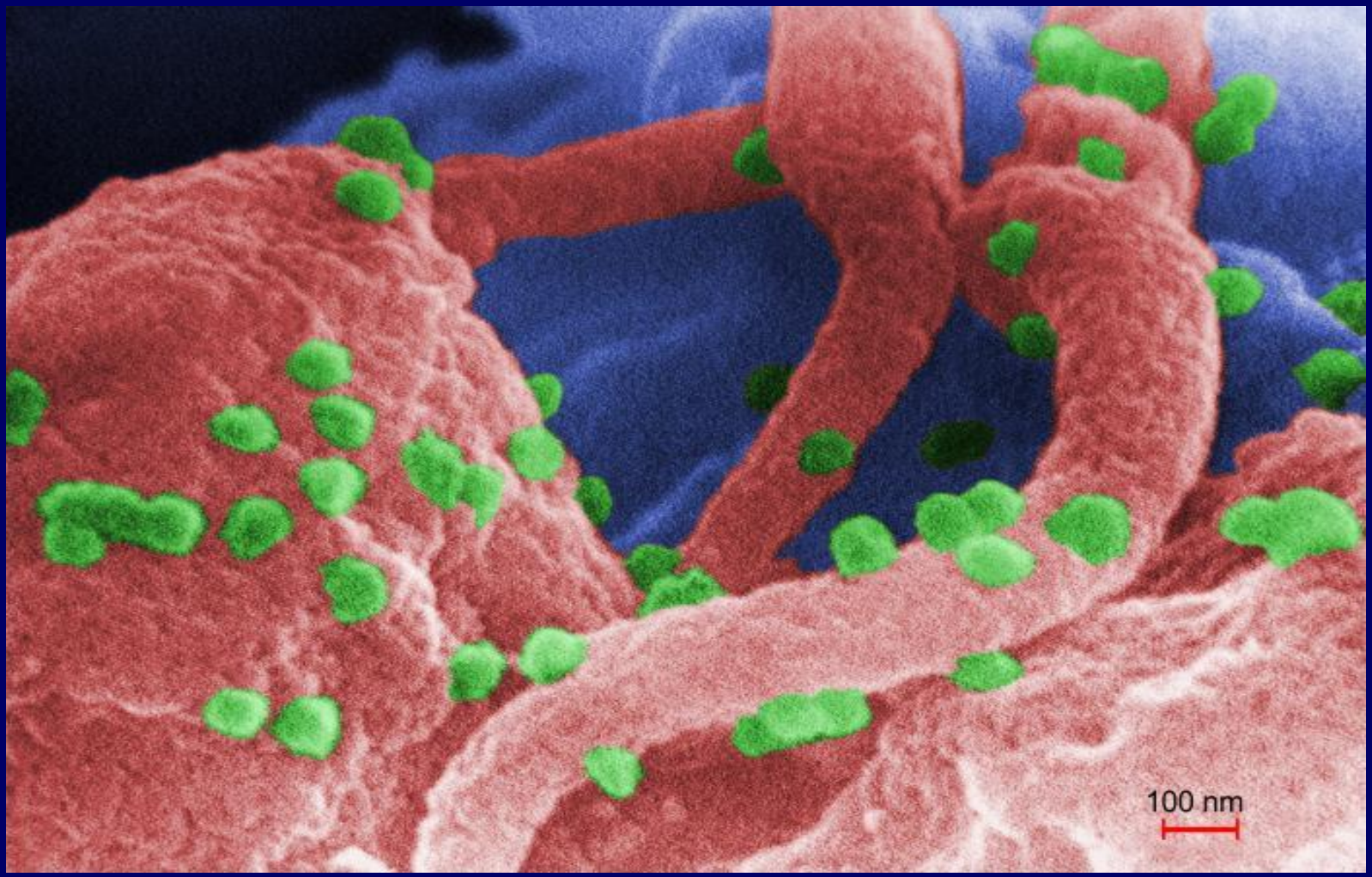
From Lipman, Baker, Johnson, An Atlas of Differential Diagnosis in HIV Disease



Case 1 - Clinical Course

- She responded to IV trim-sulfa and was discharged
- Presents to the clinic 1 week later and feels “120 percent” better
- Tolerating oral trimethoprim-sulfamethoxaxole and has 1 more week of PCP therapy
- CD4 count 0 cells/mm^3, HIV RNA level 42,500 copies/mL
- HIV genotyping: no significant mutations
- She is interested in starting antiretroviral therapy

HIV (in green) on the surface of the CD4 lymphocyte

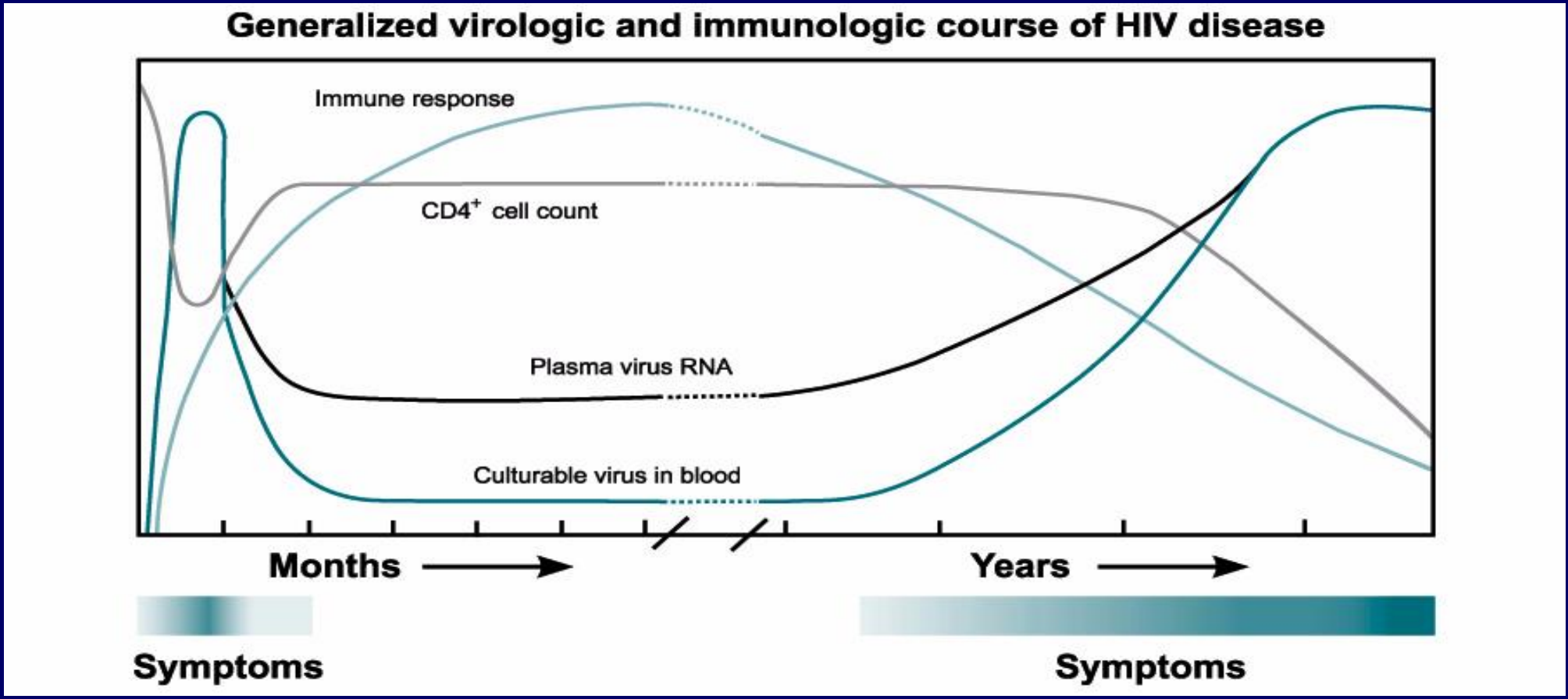


Source: CDC/Public Health Image Library

Markers of HIV disease and response to treatment

- CD4+ lymphocyte count
  - CD4+ lymphocytes are the main host cell for HIV
  - CD4+ lymphocyte count correlates with disease progression and risk of opportunistic illnesses
- Plasma HIV RNA level or Viral Load
  - Plasma viral load is a measure of the extent of ongoing replication in lymphoid tissue

Natural Course of Untreated HIV Infection



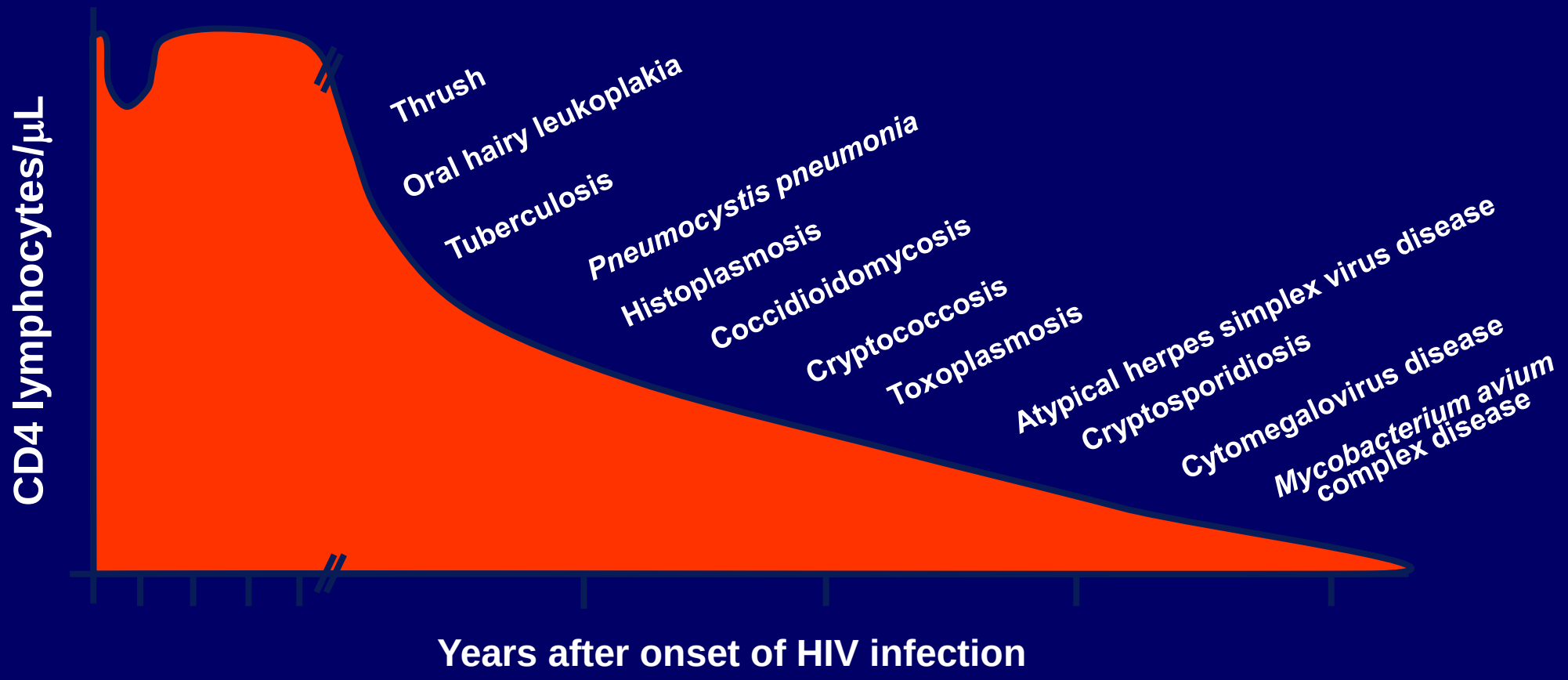
Acute HIV Infection

Advance HIV Infection/AIDS

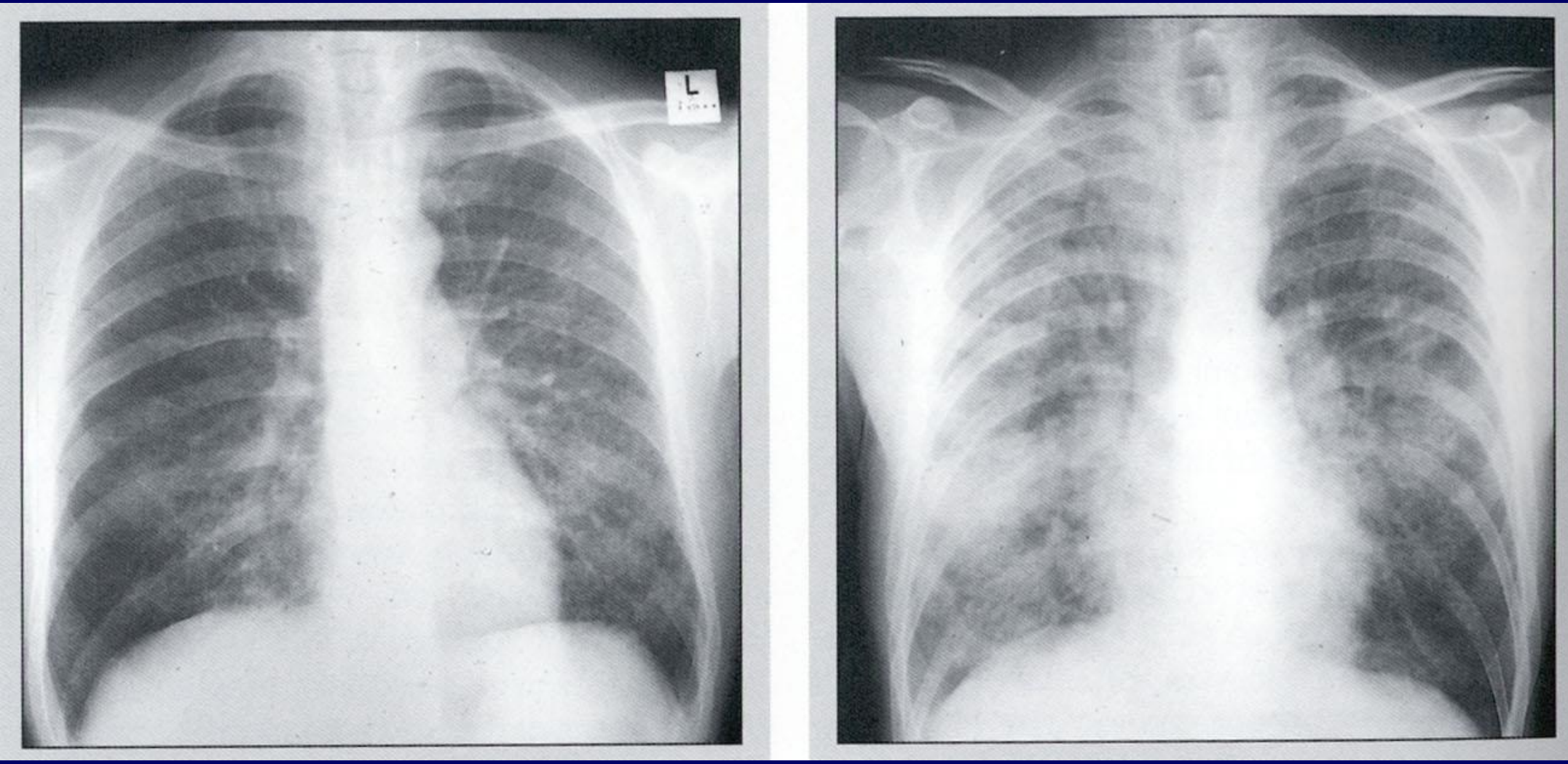
Opportunistic Infection

- An infection that takes advantage of the weakened immune system (the body's defense against infection) to cause an illness.
- Many of these infections only occur when the CD4 lymphocyte count is low (e.g. < 200 cells/mm^3).
- Restoring the CD4 count to more normal levels with the use of medications prevents these opportunistic infections from occurring.

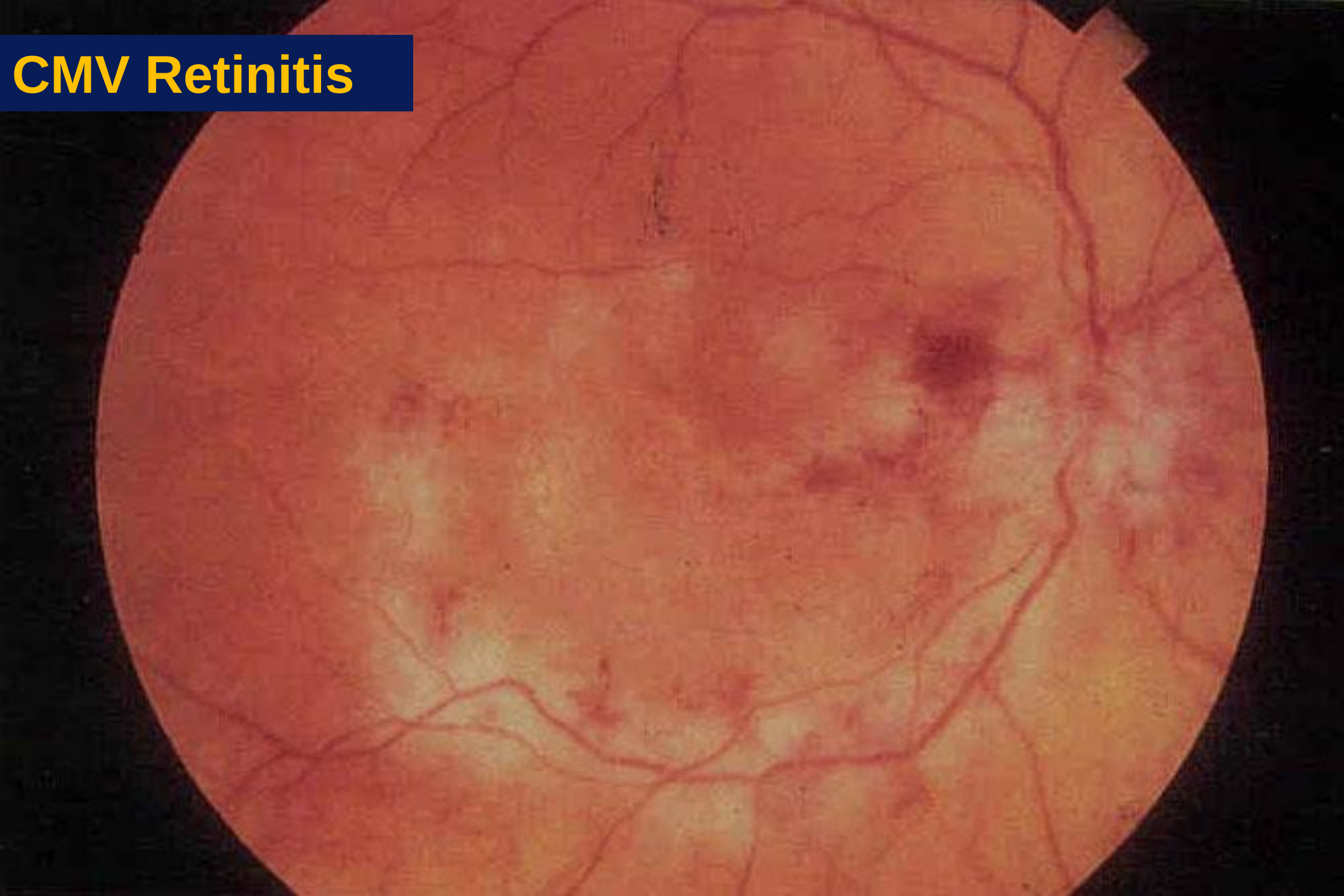
Natural History of HIV Infection



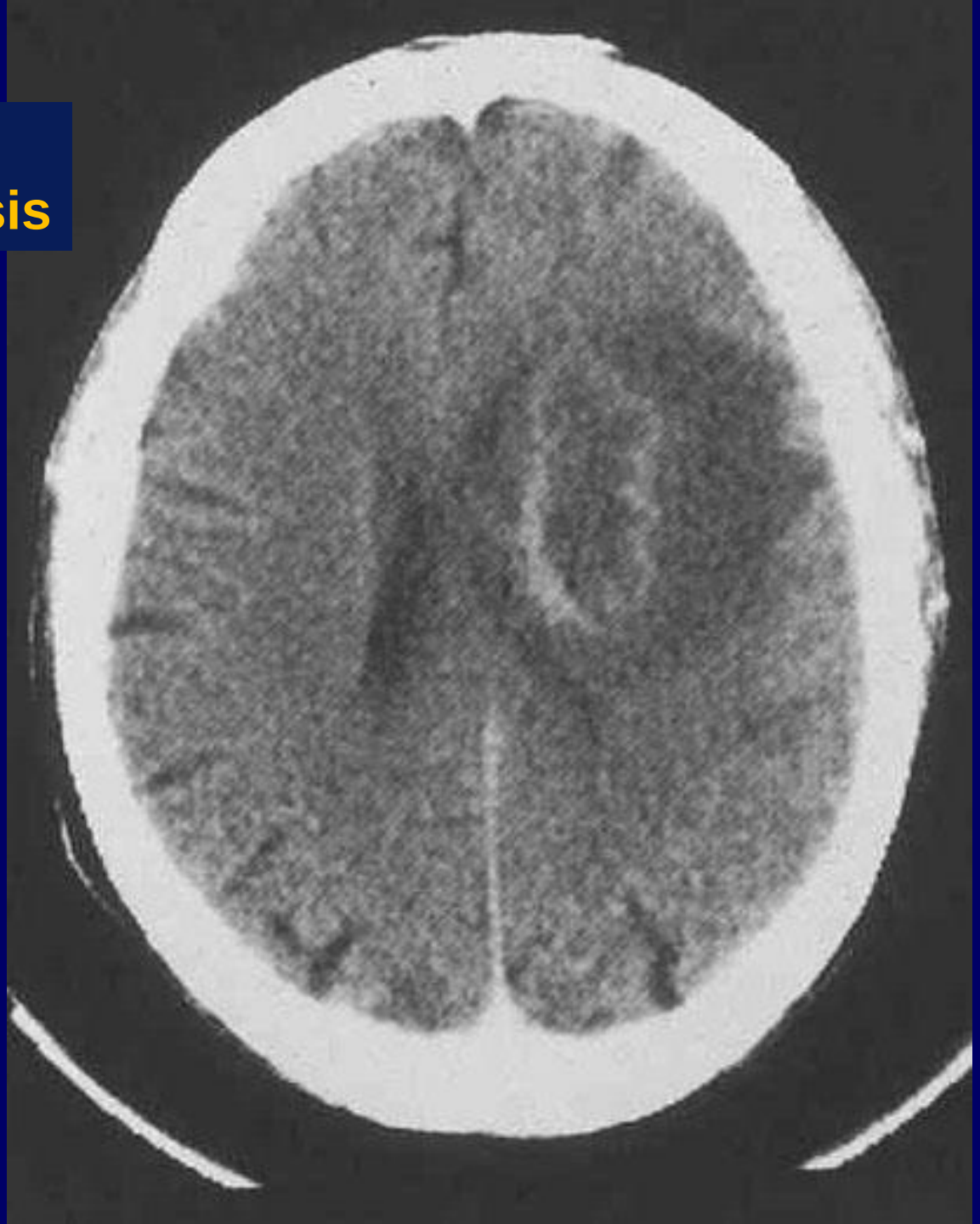
Pneumocystis Pneumonia (PCP)

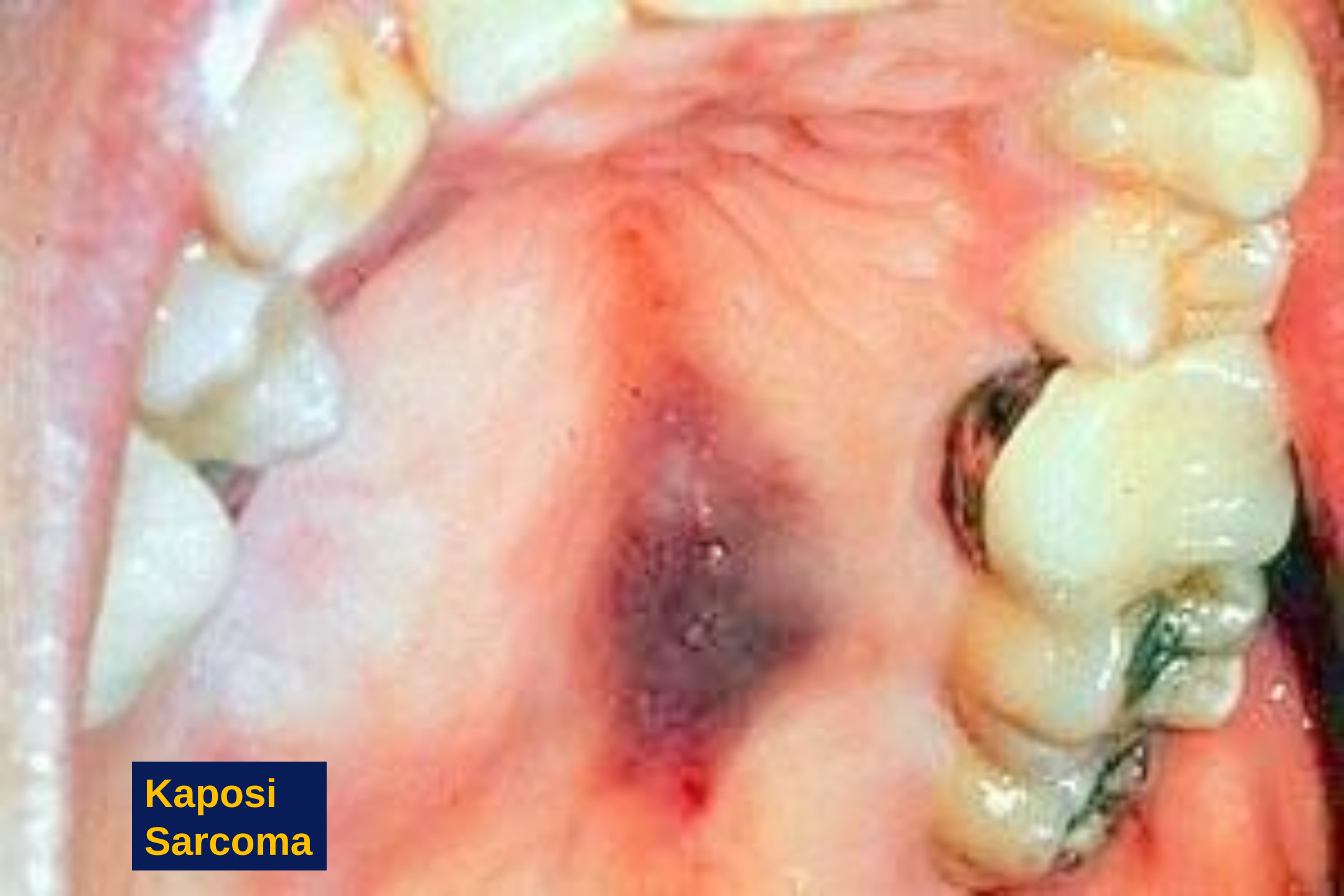


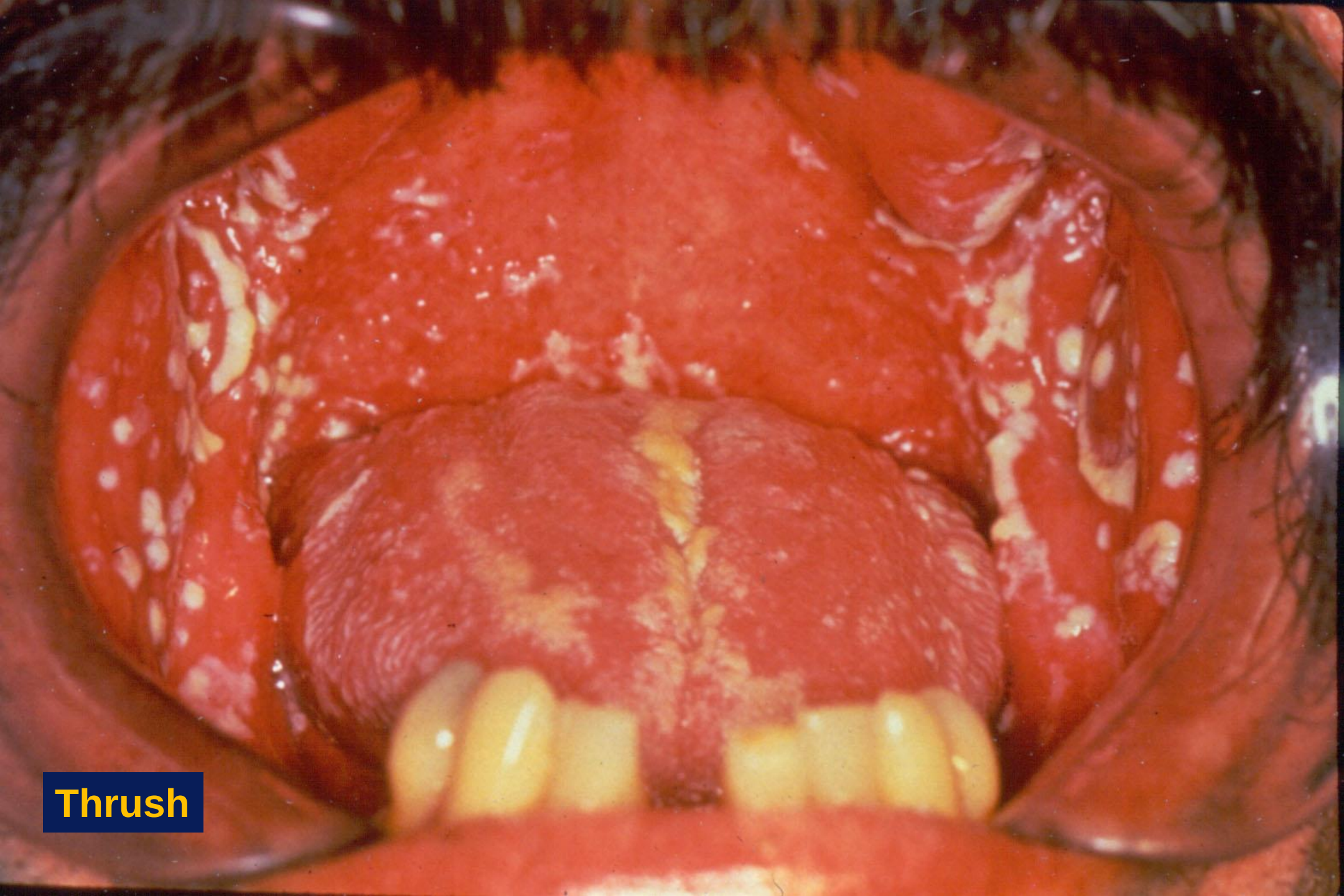
CMV Retinitis



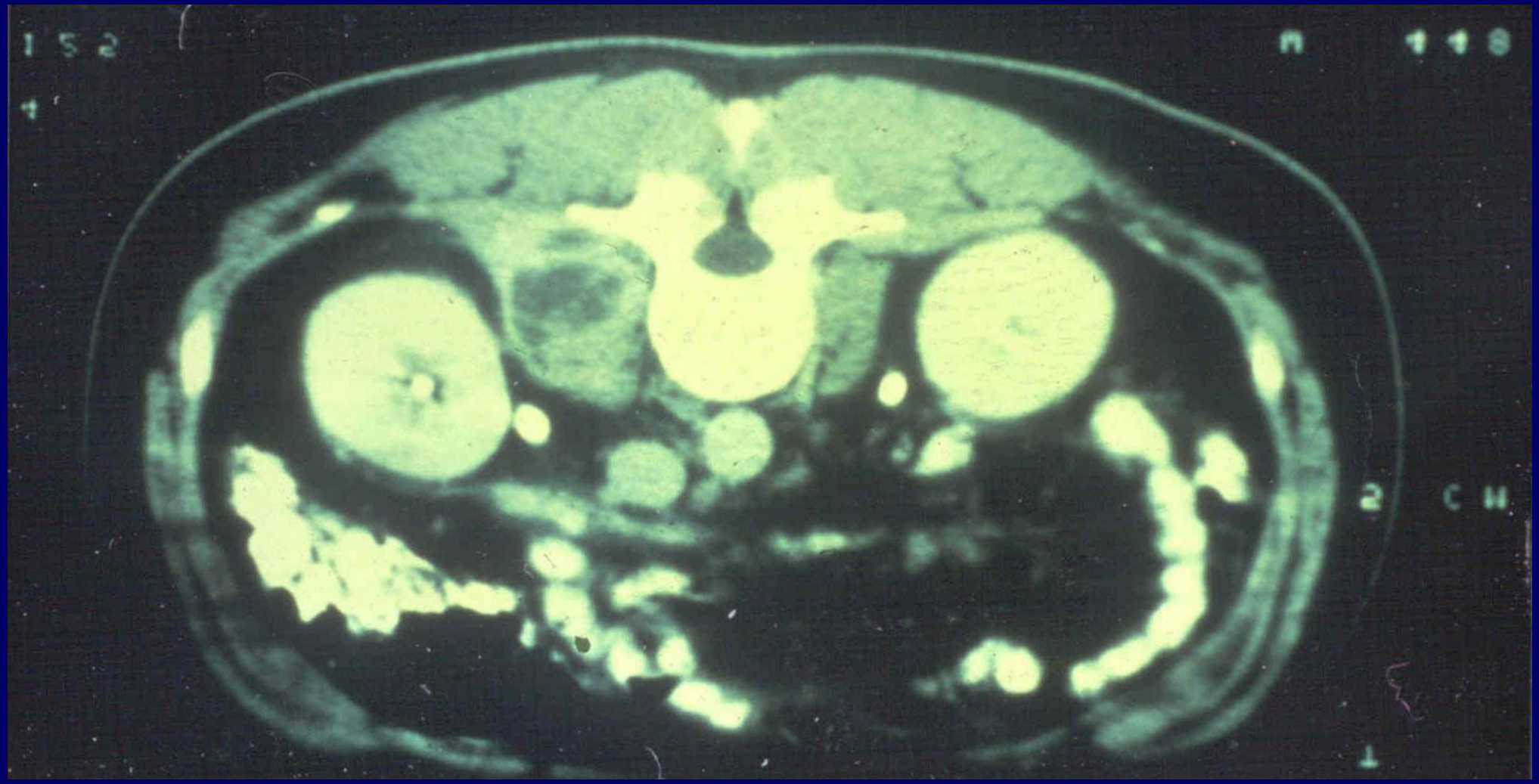
CNS Toxoplasmosis




Kaposi
Sarcoma


Thrush

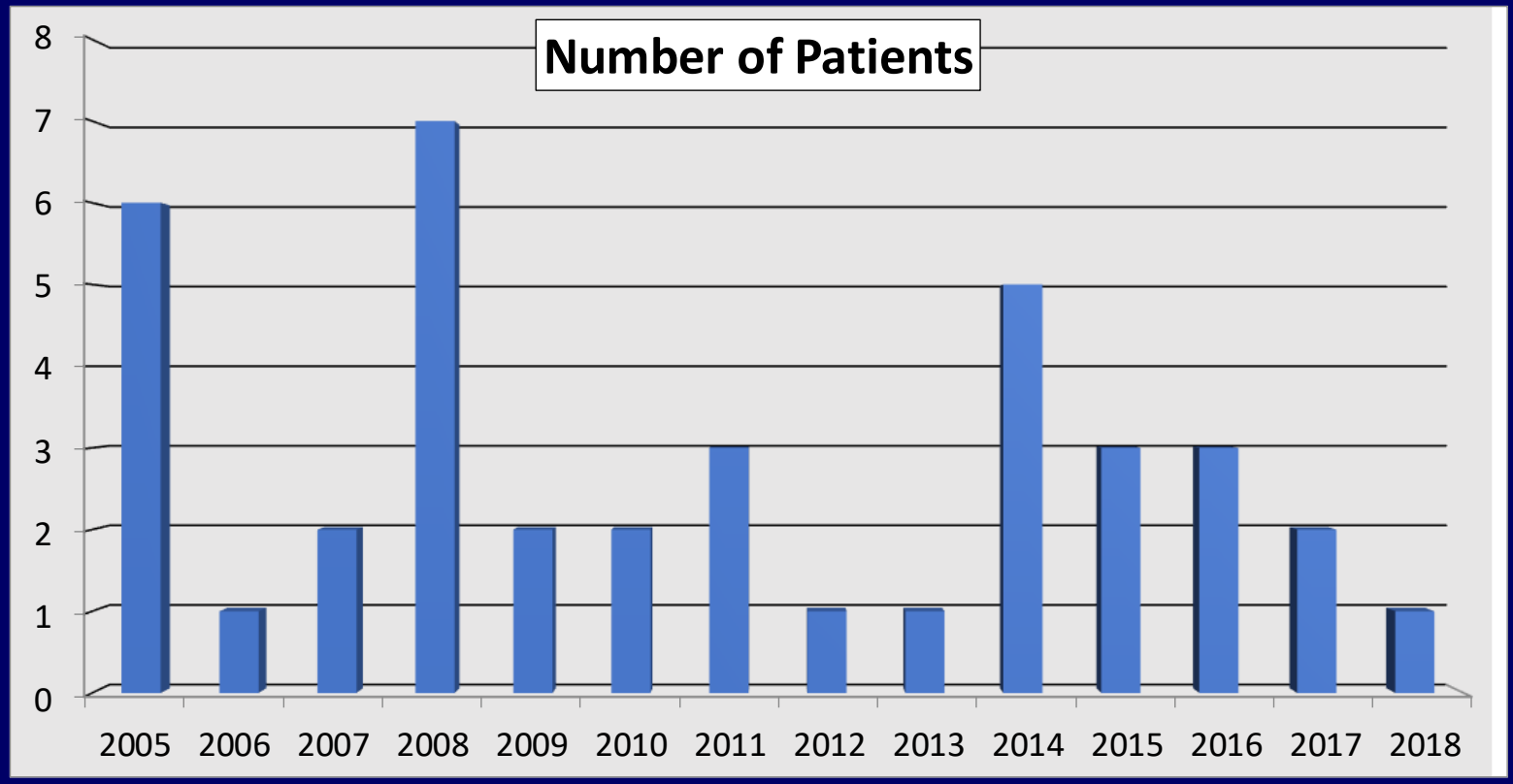
Tuberculous Psoas Abscess



Case 1 - Conclusion

- Enrolled in a clinical trial of fixed dose tenofovir/emtricitabine with the integrase inhibitor, raltegravir, primarily because of the costs of her insurance coverage
- Returned for follow-up 1 month later; doing well
- CD4 has increased to 24; HIV VL undetectable
- She has had subsequent years of follow up in our program and now has a normal CD4 count

Persons Presenting to the University of Colorado Hospital with PCP and a New HIV Diagnosis, 2005-2018



4. Recognition of Acute HIV Infection Can Provide Early Therapy and Reduce HIV Transmission

Case 2 - History

- A 27 year old male presented to the ER with a 2-week history of diarrhea, nausea, vomiting, headache, and fever
- PMH: unremarkable but worked as a Health Care Worker with neonates. On no medications.
- He denied recent travel, sick contacts, or sexual activity
- Social history: No tobacco or alcohol. Active duty Specialist in the Army

Case 2 - Physical Exam

- Vital Signs: BP 110/74, P 96, R 18, T 102^{o} F
- HEENT: photophobia noted during fundoscopic exam, shallow ulcers noted in the oral cavity
- Lungs: clear to auscultation
- Cardiac exam: S1S2 with 2/6 systolic murmur
- Abdomen: RLQ tenderness without rebound
- Skin, Lymph, and Neurologic exams: WNL

Case 2 - Labs and Other Tests

- Laboratory Data:
  - CBC: WBC 4600, HCT 38.5%, PLT 181K
  - Chem: BUN 18, Cr 0.9, AST 28, ALT 37
- Chest X-ray: WNL
- Serology: monospot negative, HIV antibody test negative
- Microbiology: blood, urine, and stool cultures collected

Case 2 - Clinical Course

- Blood, urine, and stool cultures negative
- Placed on IV antibiotics for possible enteric bacterial infection
- Persistent headache prompted an LP:
  - CSF WBC 17 (all mononuclear), CSF RBC 0
  - CSF protein elevated at 60, CSF glucose normal at 86
  - gram stain and bacterial culture negative
- MRI of head: WNL

Case 2 - Clinical Course

- One week into his hospitalization, elevated transaminases and an atypical lymphocytosis developed
- The patient gradually became somnolent and confused, and was comatose by hospital day 19
- An EEG revealed diffuse slow wave abnormalities
- Empiric IV acyclovir was started for possible HSV encephalitis
- A diagnostic test was done

Acute HIV Infection

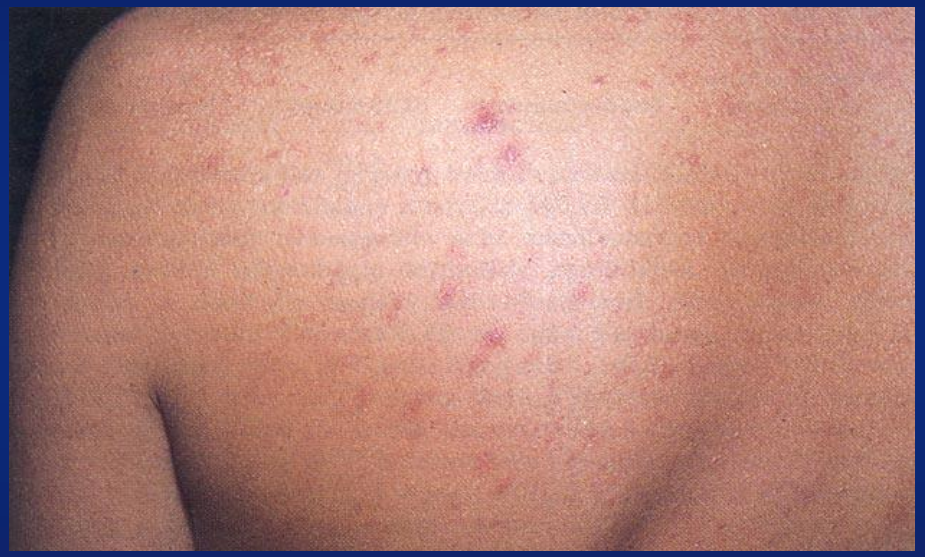
- Initial HIV infection is often associated with an acute febrile illness, a mononucleosis-like illness with or without aseptic meningitis
- Usually occurs 2-3 weeks after HIV exposure
- Occurs in > 50% of patients although is often unrecognized

Acute HIV Infection: signs and symptoms

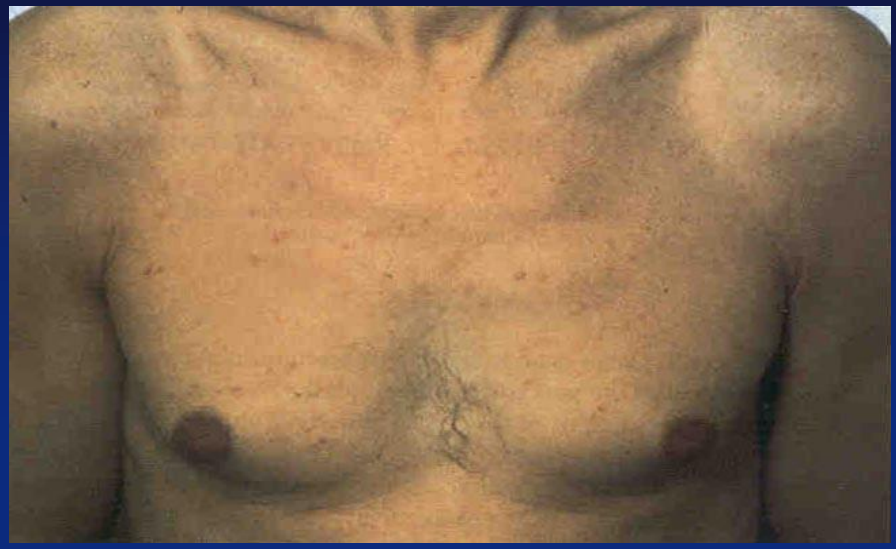
- fever 77%
- fatigue 66%
- maculopapular rash 56%
- myalgia 55%
- headache 51%
- pharyngitis 44%
- cervical nodes 39%
- arthralgia 31%
- oral ulcers 29%
- odynophagia 28%
- weight loss 24%
- diarrhea 23%
- oral candidiasis 17%
- photophobia 12%

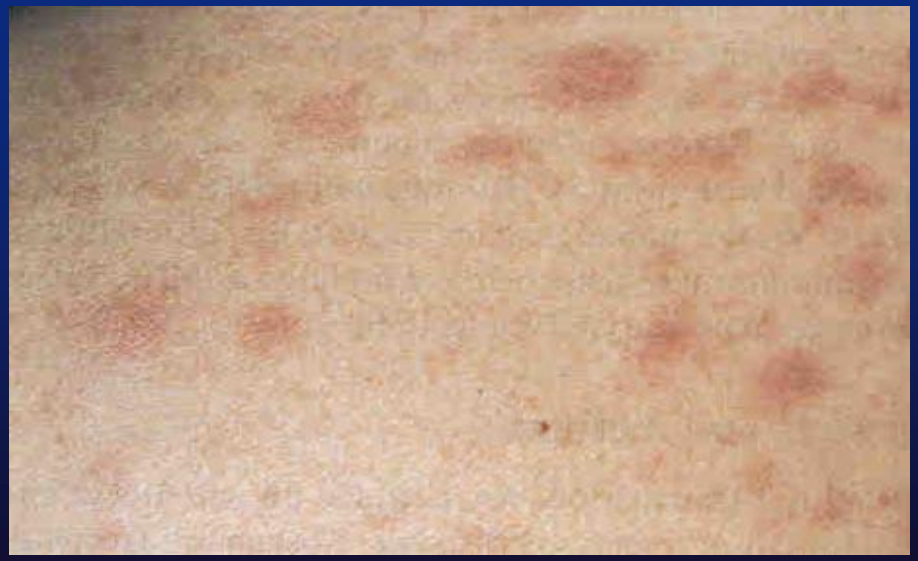
Clin Inf Dis 1997;24:965

Rash of Acute HIV Infection



Wantzin, et al. Br J Derm 1986;115:601





Lapins, et al. Br J Derm 1996;134:257

Slide courtesy of E. Connick, MD

Laboratory Aspects of Acute HIV Infection

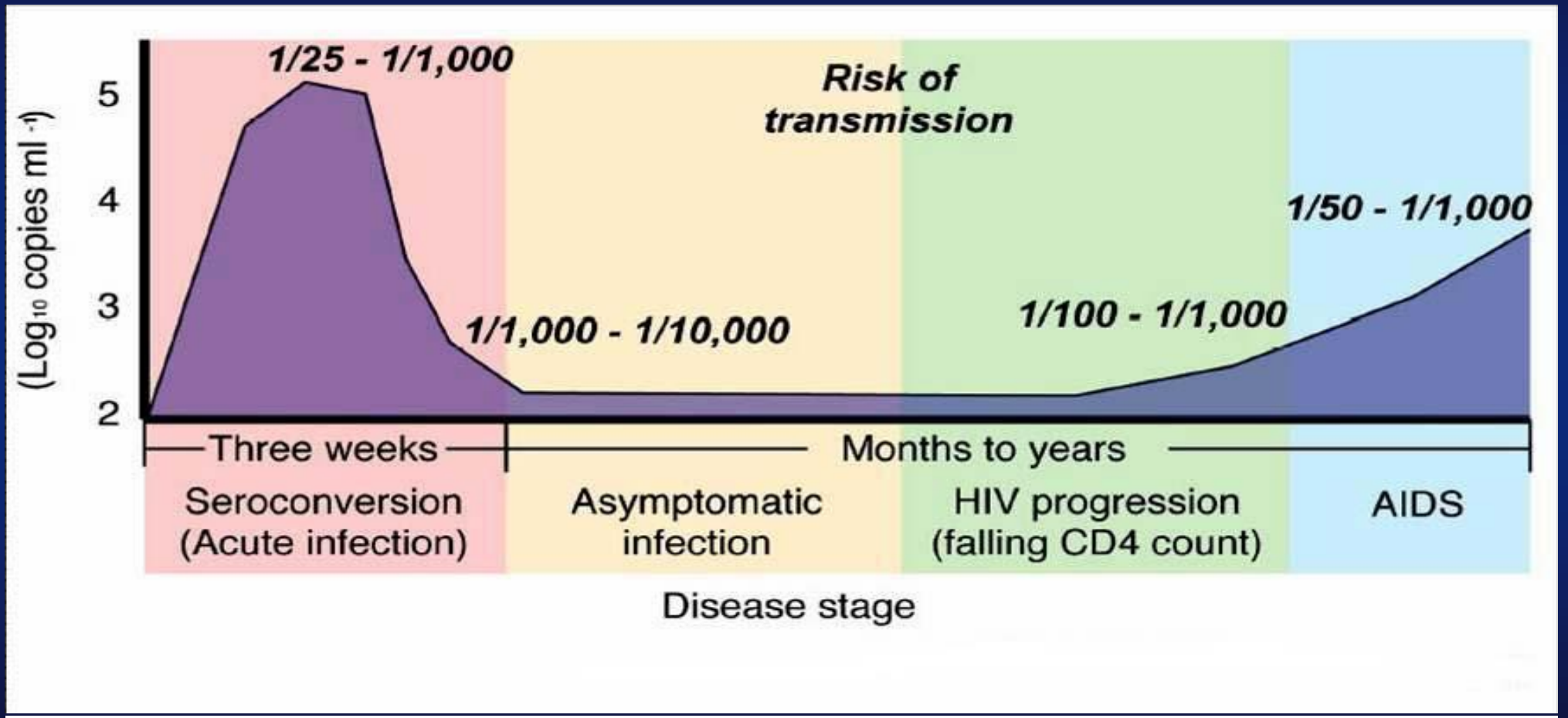
General lab testing

- Leukopenia with atypical lymphocytes
- Mildly elevated transaminases
- Evidence of aseptic meningitis on LP

HIV-specific lab testing

- Tests with only antibody may be negative
- Newer HIV screening tests use antibody and p24 antigen and will be positive earlier in infection
- HIV plasma RNA testing (AKA HIV viral load testing) will be the earliest positive test

The Risk of HIV Transmission Varies During the Course of HIV Infection



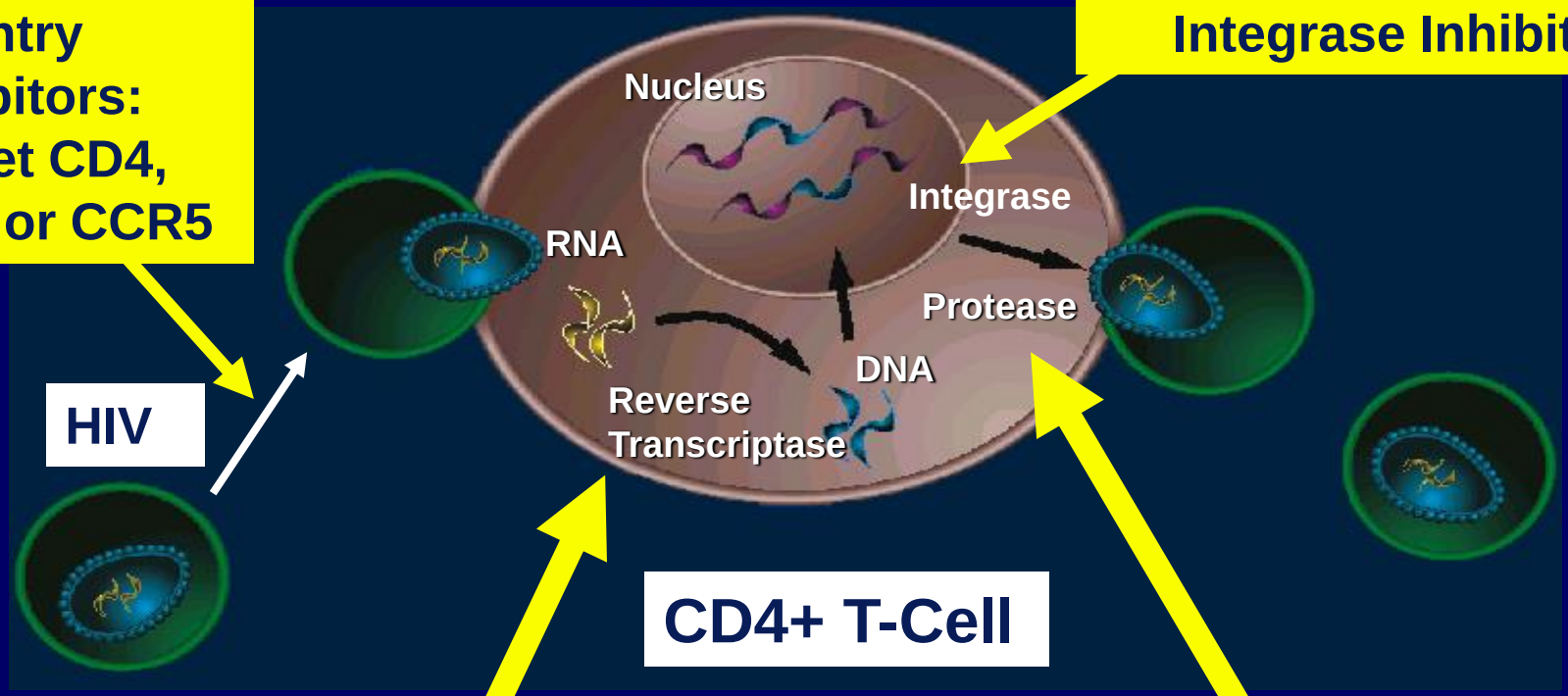
Acute "Early" HIV patients responsible for 8-43% of HIV transmission in serodiscordant couples (Pinkerton, AIDS Behavior, 2008)

Case 2 - Continued

- The patient recovered completely from his acute illness
- He now presents to the outpatient clinic
- He is feeling well and has few other medical problems
- He is on no medications
- He asks whether he should be on antiretroviral therapy

5. Antiretroviral therapy can either prevent or reverse the immunodeficiency seen with HIV infection

Targets for Antiretroviral Therapy



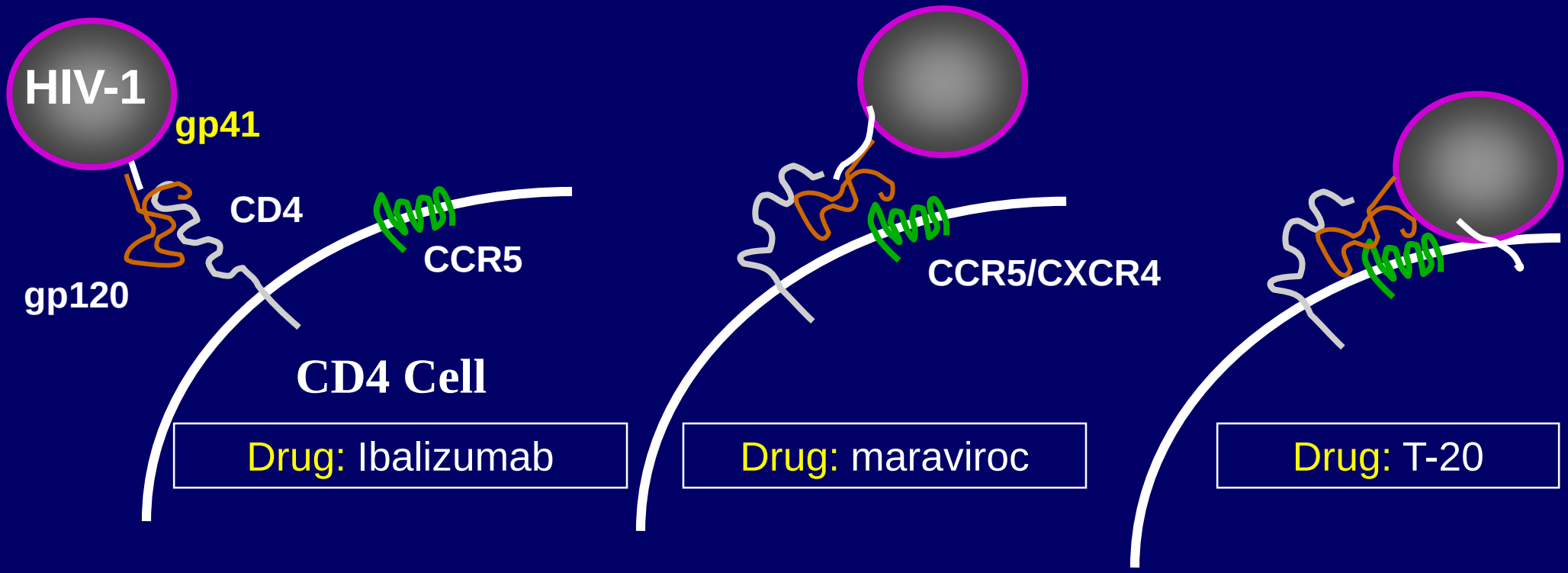
Entry Inhibitors: Target CD4, Fusion or CCR5

Integrase Inhibitors

Protease Inhibitors

Reverse Transcriptase Inhibitors: NRTIs (Nucleosides, Nucleotides) and NNRTIs

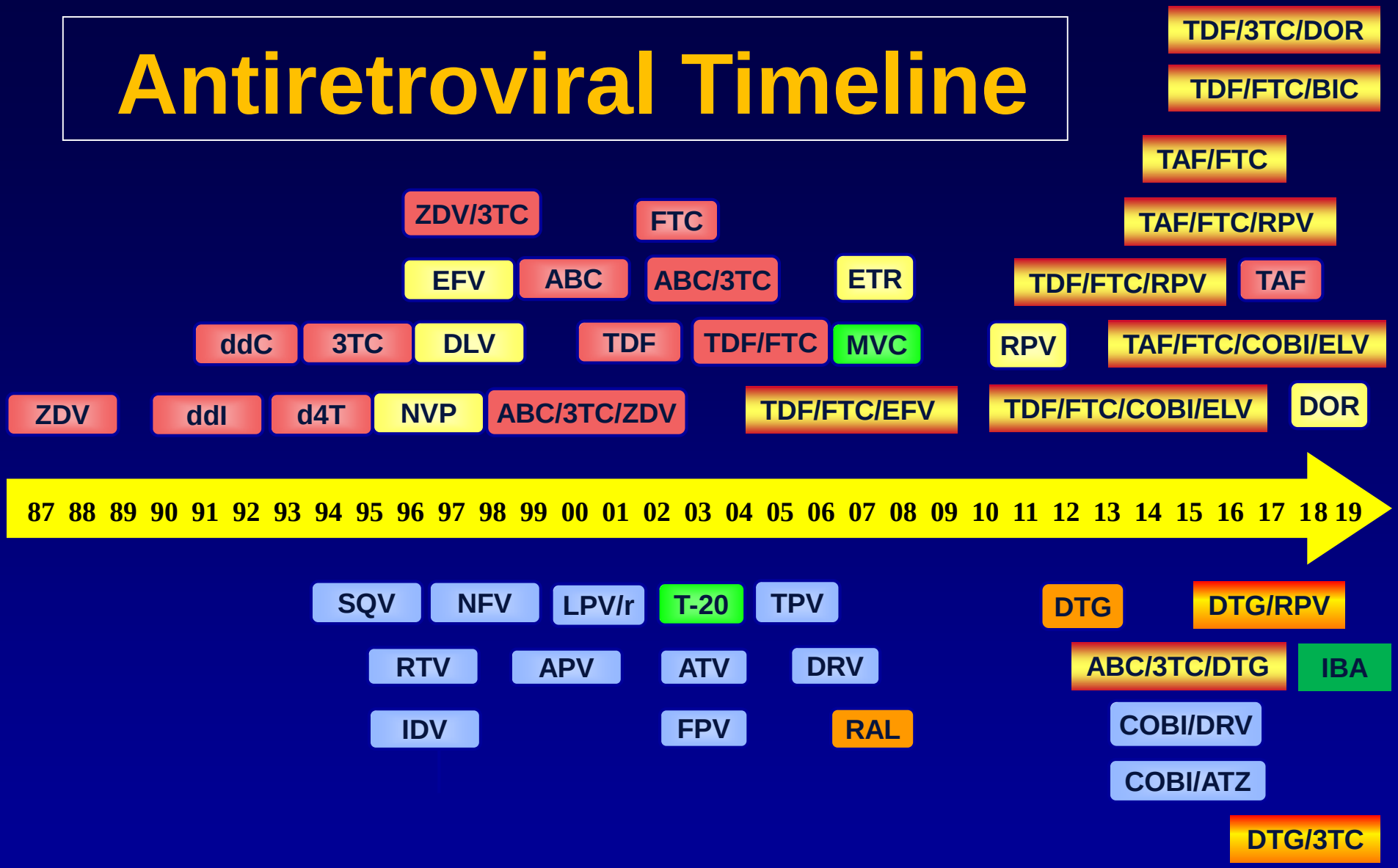
Three Steps of HIV-1 Entry



CD4 Binding → gp120 Conformational Change and Co-receptor Binding → gp41 Conformational Change/ Fusion

Slide courtesy of Thomas Campbell, MD

Antiretroviral Timeline



Nucleoside/nucleotide RTIs

Non-nucleoside RTIs

Entry Inhibitors

Protease Inhibitors

Integrase Inhibitors

Multi-class co-formulations

HIV Medication Chart

Combination Antiretrovirals

Atripla (EFV/TDF/FTC)

Biktarvy (BIC/TAF/FTC)

Combivir† (ZDV/3TC)

Complera (RPV/TDF/FTC)

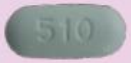
Delstrigo (DOR/TDF/3TC)

Descovy (TAF/FTC)

Dovato (DTG/3TC)

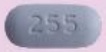
Epzicom† (ABC/3TC)

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)

Truvada (TDF/FTC)

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

Emtriva* (emtricitabine, FTC)

Epivir*† (lamivudine, 3TC)

Retrovir*† (zidovudine, ZDV)

Viread*† (tenofovir DF, TDF)

Ziagen*† (abacavir, ABC)

Vemlidy (tenofovir alafenamide, TAF)
FDA approved for HBV only

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Edurant (rilpivirine, RPV)

Intelence (etravirine, ETR)

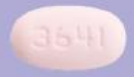
Pifeltro (doravirine, DOR)

Sustiva† (efavirenz, EFV)

Viramune*† (nevirapine, NVP)

Protease Inhibitors (PI)

Evotaz (ATV/COBI)



Kaletra* (lopinavir/ritonavir, LPV/RTV)

Lexiva* (fosamprenavir, FPV)

Prezcobix (DRV/COBI)

Prezista* (darunavir, DRV)

Reyataz*† (atazanavir, ATV)

Viracept* (nelfinavir, NFV)

Entry Inhibitors

Fuzeon (enfuvirtide, T-20)
Fusion Inhibitor

Selzentry (maraviroc, MVC)
CCR5 Antagonist

Trogarzo (ibalizumab, IBA)
Post-Attachment Inhibitor

Integrase Inhibitors (INSTI)

Isentress*▲ (raltegravir, RAL)

Isentress HD (raltegravir, RAL)

Tivicay (dolutegravir, DTG)

Boosting Agents

Norvir*† (ritonavir, RTV)

Tybost (cobicistat, COBI)

All pills shown in relative size/scale. *Medication brand names appear in bold. Generic names and commonly used abbreviations appear in parentheses.*

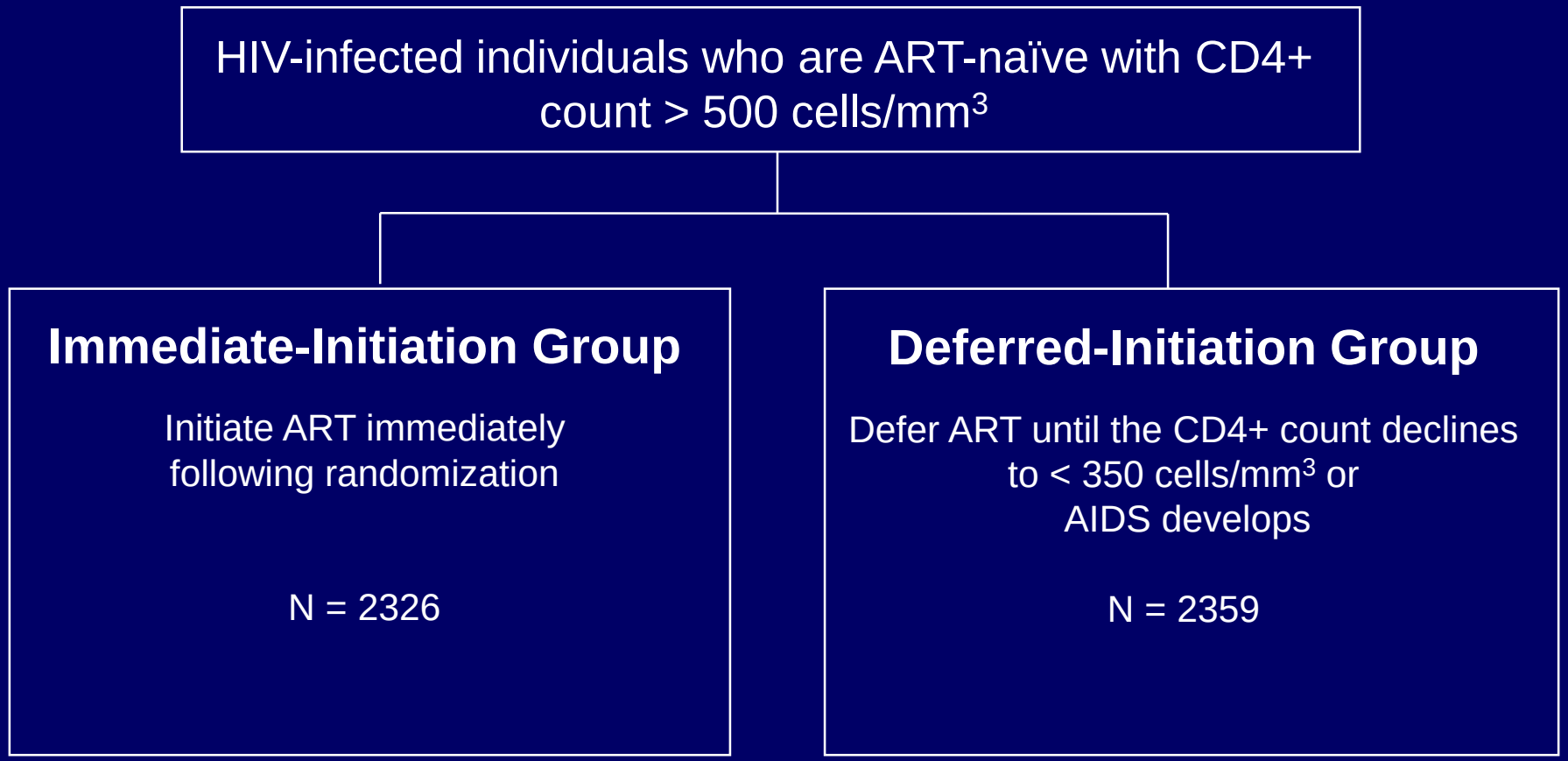
*Also available in liquid or powder form. †Generic formulation available. ▲Chewable form available.

6/19

Expected Response to Antiretroviral Therapy

- Reduction in plasma HIV-1 RNA levels (viral load), ideally to undetectable levels
- Increase in CD4 lymphocyte count
- Improvement of existing opportunistic complications
- Decreased mortality and morbidity
- Reduced HIV transmission

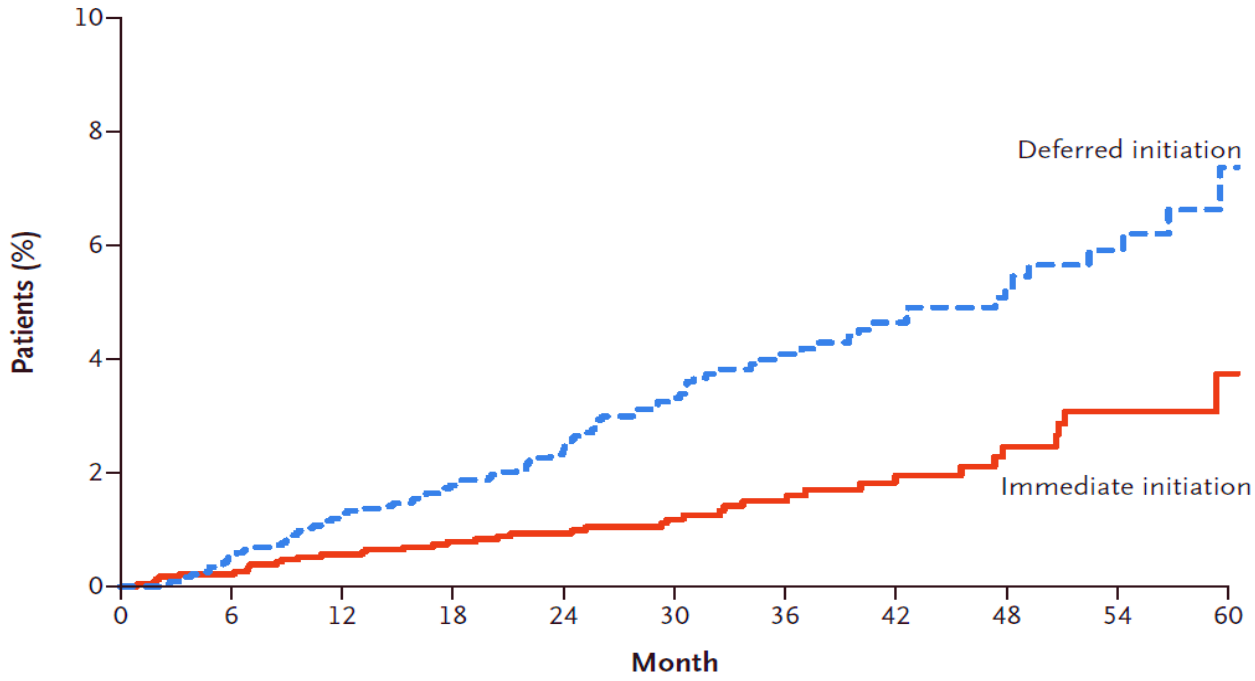
START Design



The INSIGHT START Study Group, N Engl J Med 2015; **DOI: 10.1056/NEJMoa1506816**

START Results: Time to First Event (AIDS, Serious Non-AIDS Event, or Death)

A Time to First Primary Event



No. at Risk											
Immediate initiation	2326	2302	2279	2163	1801	1437	1031	757	541	336	110
Deferred initiation	2359	2326	2281	2135	1803	1417	1021	729	520	334	103
Estimated Percentage											
Immediate initiation		0.2	0.6	0.8	0.9	1.2	1.5	2.0	2.5	3.1	3.7
Deferred initiation		0.5	1.2	1.8	2.4	3.3	4.1	4.6	5.3	5.9	7.4

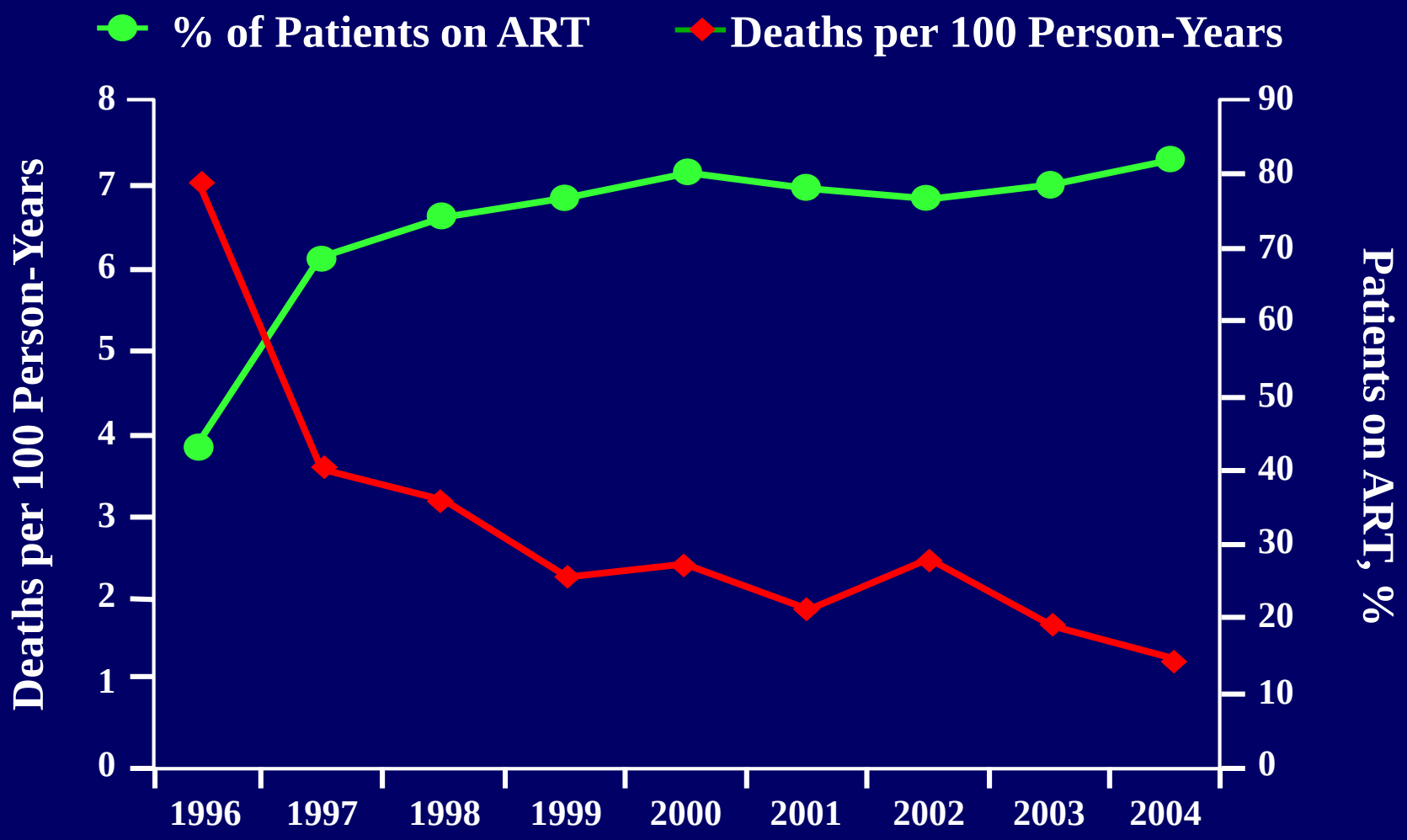
The INSIGHT START Study Group, N Engl J Med 2015; **DOI: 10.1056/NEJMoa1506816**

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents: When to Start

- **Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression.**
- ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV.
- Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence.

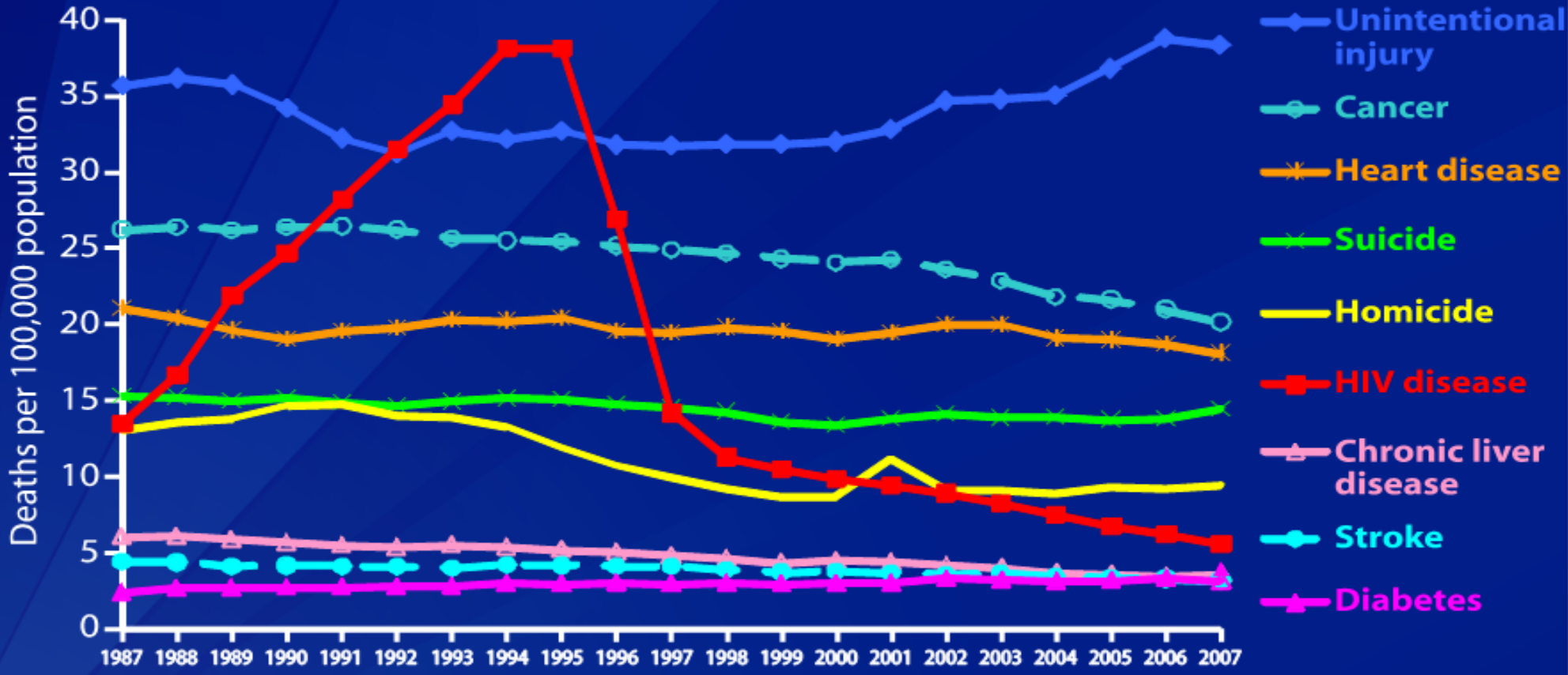
DHHS Guidelines, last updated July 10, 2019, available at www.aidsinfo.nih.gov

Effect of ART on Mortality Over Time



Palella FJ et al. J Acquir Immune Defic Syndr. 2006;43(1):27-34.

Trends in Annual Rates of Death due to the 9 Leading Causes among Persons 25–44 Years Old, United States, 1987–2007



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.

Recommended Initial Regimens for Most People with HIV

DHHS Guidelines[1]	IAS-USA Guidelines[2]
• Bictegravir/tenofovir alafenamide/emtricitabine • Dolutegravir/abacavir/lamivudine —**only** for persons who are HLA-B*5701-negative • Dolutegravir plus tenofovir/emtricitabine • Raltegravir plus tenofovir/emtricitabine	• Bictegravir/tenofovir alafenamide/emtricitabine • Dolutegravir/abacavir/lamivudine — **only** for persons who are HLA-B*5701-negative • Dolutegravir plus tenofovir alafenamide

1. DHHS Guidelines, July 10, 2019. 2. Saag MS, et al. JAMA 2018;320:379-396.

Baseline Laboratory Testing: General Tests

- CBC with differential: screening primarily for leukopenia, anemia, and thrombocytopenia
- Chemistry panel: screening primarily for renal disease, hyperglycemia, or evidence of hepatitis
- Fasting lipid panel: dyslipidemia can be a complication of HIV/AIDS as well as its treatment
- Urinalysis: to screen primarily for pyuria, hematuria, or proteinuria

Baseline Laboratory Testing: For HIV Staging and Preparation for Treatment

- CD4 lymphocyte count
- HIV RNA level (AKA HIV viral load)
- HIV resistance testing (HIV genotyping is preferred over HIV phenotyping)
- Other tests to consider
  - HLA B*5701 testing (if planning to use the drug abacavir)
  - HIV tropism testing (if planning to use the drug maraviroc)

Baseline Laboratory Testing: Screening for Co-Infections

- GC and Chlamydia (urine, throat, rectum, based on exposure)
- Hepatitis A: Total Hepatitis A antibody
- Hepatitis B:
  - Hepatitis B core antibody, surface antibody, and surface antigen
  - Hepatitis B DNA level (in selected circumstances)
- Hepatitis C:
  - Hepatitis C antibody
  - Hepatitis C RNA level (if HCV AB+ or suspect false negative)
- Syphilis: Treponemal antibody screen or RPR
- Toxoplasmosis: Toxoplasma IgG
- Tuberculosis: PPD or interferon gamma release assay

Recommendations on the Indications and Frequency of Viral Load and CD4 Count Monitoring

Clinical Scenario	Viral Load Monitoring	CD4 Count Monitoring
Before Initiating ART	At entry into care	At entry into care
After Initiating ART	2-4 weeks into ART; every 4-8 weeks until VL und	3 months after initiation of ART
During the first 2 years of ART	Every 3-4 months	Every 3-6 months
After 2 years, consistently suppressed, CD4 300-500	Every 6 months	Every 12 months
After 2 years, consistently suppressed, CD4 > 500	Every 6 months	Optional
Change in clinical status (e.g., new HIV clinical symptom or initiation of interferon, chronic systemic corticosteroids, or anti-neoplastic therapy)	Every 3 months	Perform CD4 count and repeat as clinically indicated

Modified from Table 4, DHHS guidelines, www.aidsinfo.nih.gov

Limitations of Antiretroviral Therapy

- Drug toxicity
- Drug interactions
- Drug resistance
- Need for adherence
- Cost
- Not curative

Hypersensitivity to Abacavir

- Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by signs or symptoms in 2 or more of the following groups:
  - (1) fever
  - (2) rash
  - (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)
  - (4) constitutional (including malaise, fatigue, or achiness)
  - (5) respiratory (including shortness of breath, cough, or sore throat)

HLA-B*5701 Testing

- Individuals who are HLA-B*5701 positive have approximately a 50% risk of an abacavir hypersensitivity reaction
- Individuals who are HLA-B*5701 negative have a less than 1% risk of an abacavir hypersensitivity reaction
- Testing for HLA-B*5701 is relatively inexpensive and is done once in the life of a patient
- Recommended prior to abacavir use in federal treatment guidelines

Dolutegravir Safety Alert

- Tsepamo: Neural tube defects were initially detected in 4 out of 429 (0.9%) of infants born to mothers who were on dolutegravir at the time of conception
- Recent data indicate a risk of approximately 0.3%. Ongoing studies will define the risk with more certainty.
- Dolutegravir appears to be safe when started after 12 weeks of pregnancy
- Women of child-bearing potential should be counseled about this finding
- There are no data on bictegravir, a compound similar in structure to dolutegravir
- Raltegravir appears to be safe in pregnancy

Current DHHS Guidelines Advice

DTG should not be prescribed for individuals:

- Who are pregnant and within 12 weeks post-conception **(AII)**; *or*
- Who are of childbearing potential and planning to become pregnant **(AII)**; *or*
- Who are of childbearing potential, sexually active, and not using effective contraception **(AIII)**.

www.aidsinfo.nih.gov. Last updated July 10, 2019

Drug Resistance

- Acquired drug resistance
  - Develops in a patient while on therapy
  - Prescribing errors can lead to resistance
  - Patient nonadherence can lead to resistance
- Primary drug resistance
  - Acquired from a patient with resistant virus
- Assessed by one of two technologies
  - HIV genotyping
  - HIV phenotyping

Drug-Drug Interactions

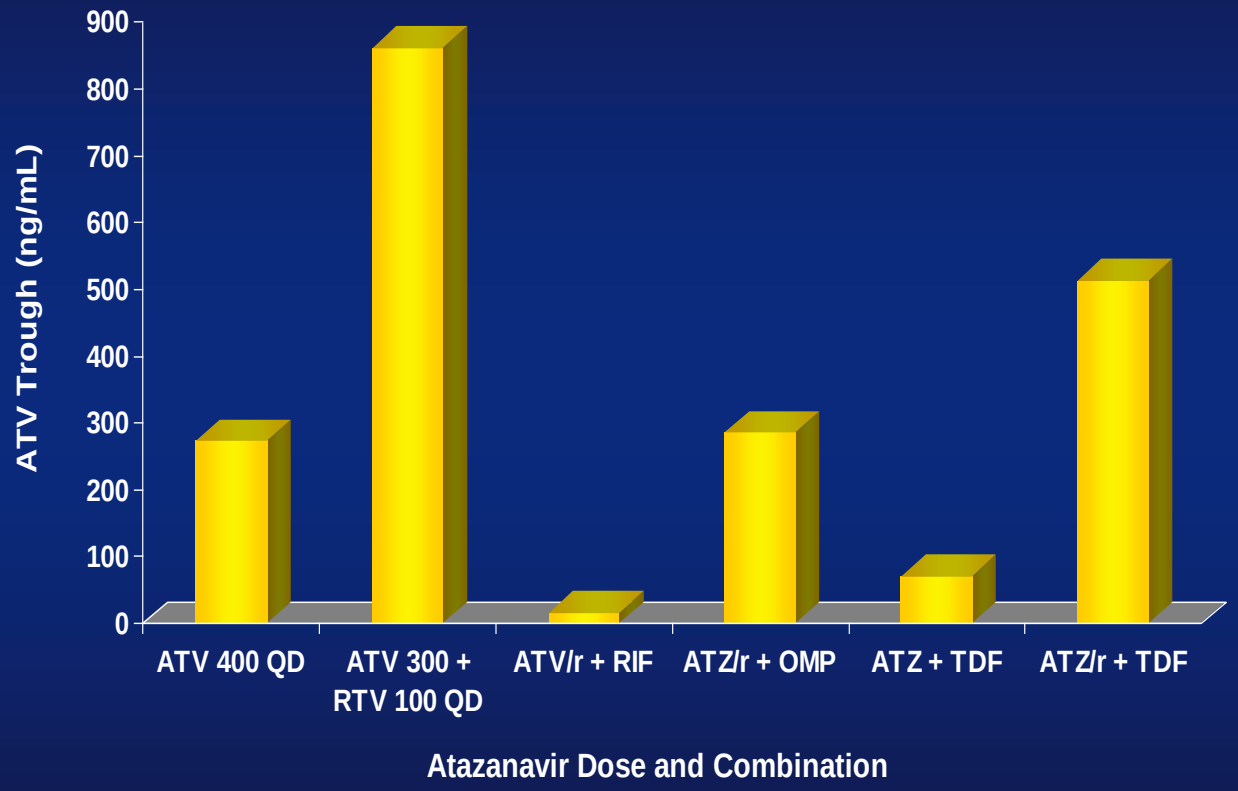
- Protease inhibitors, including atazanavir/ritonavir, darunavir/ritonavir, and lopinavir/ritonavir, inhibit cytochrome p450 enzymes and may lead to higher levels of co-administered drugs

- Nevirapine and efavirenz, through induction of cytochrome p450 enzymes, may reduce levels of co-administered drugs

- A number of other drug-drug interactions are important; many are reviewed in the DHHS antiretroviral treatment guidelines or through on-line drug interaction databases

www.aidsinfo.nih.gov

Drug-Drug Interactions With Atazanavir: Effect on Trough Concentrations



ATV = atazanavir, RTV or r = ritonavir, RIF = rifampin
OMP = omeprazole, TDF = tenofovir

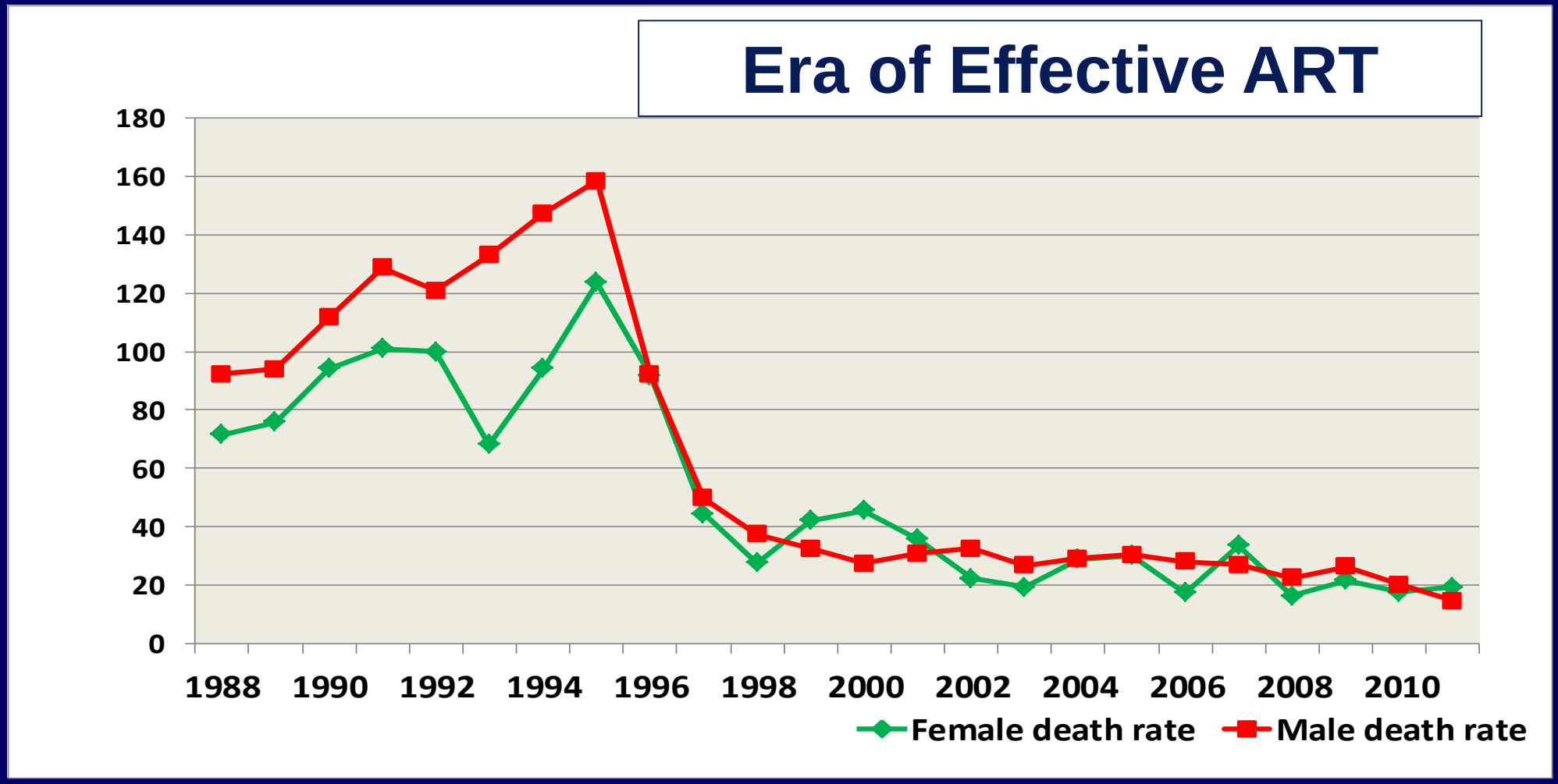
Some Additional Points About Antiretroviral Therapy

- At the present time, all persons living with HIV infection should be offered ART
- Great advances in safety, potency, and convenience have occurred over the last 20 years
- Despite the cost of therapy, ART is very cost-effective and comparable to many other interventions in medicine
- Maximizing use of antiretroviral therapy is one of the cornerstones in the prevention of HIV transmission

Questions So Far
And a Break

6. Persons living with HIV infection have the potential to live a normal lifespan

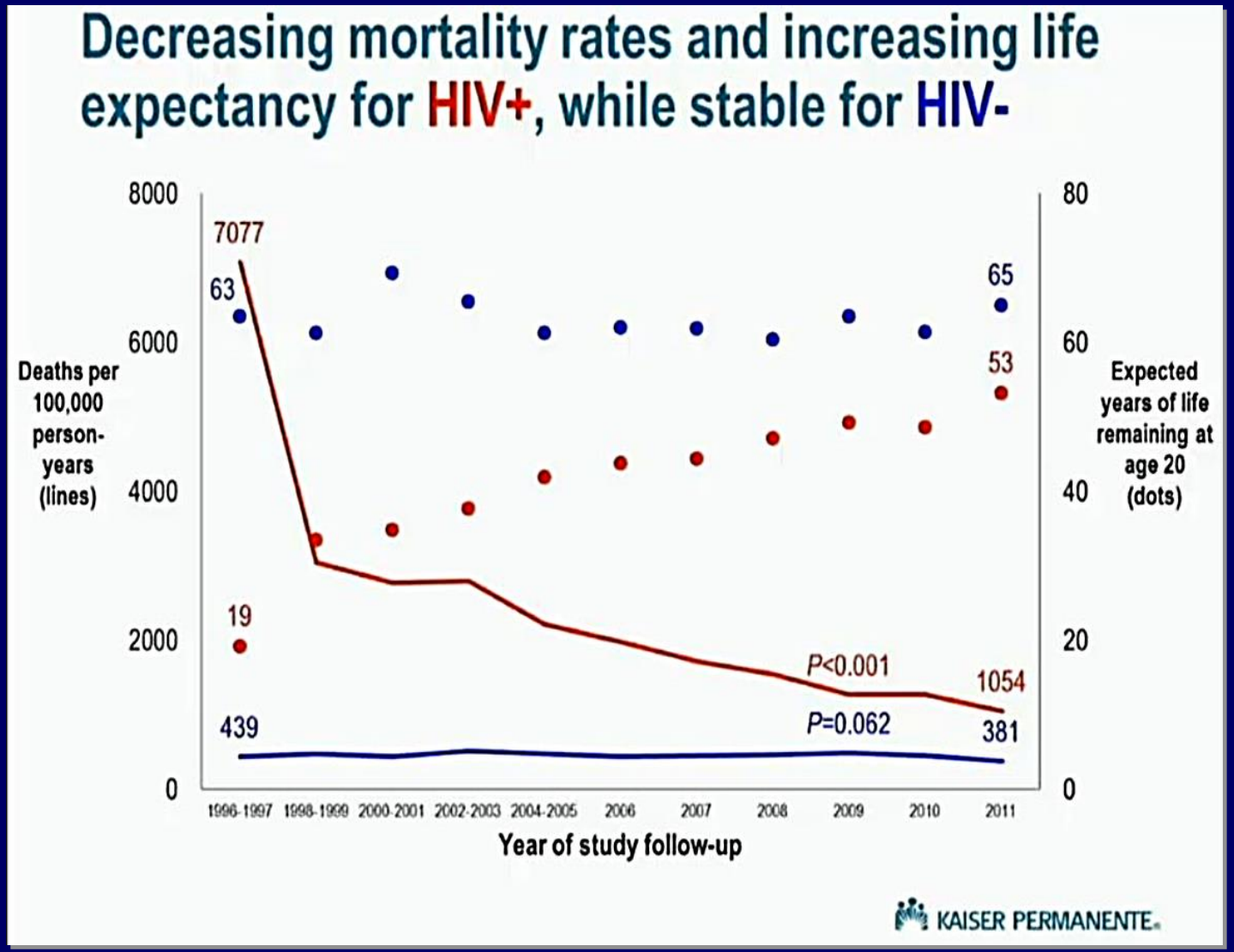
Trends in Annual Death Rate Among People Living with HIV by Gender, Colorado, 1988-2011, Deaths per 1000 persons



Source: CDPHE

HIV+ vs. HIV- Life Expectancy- Kaiser California

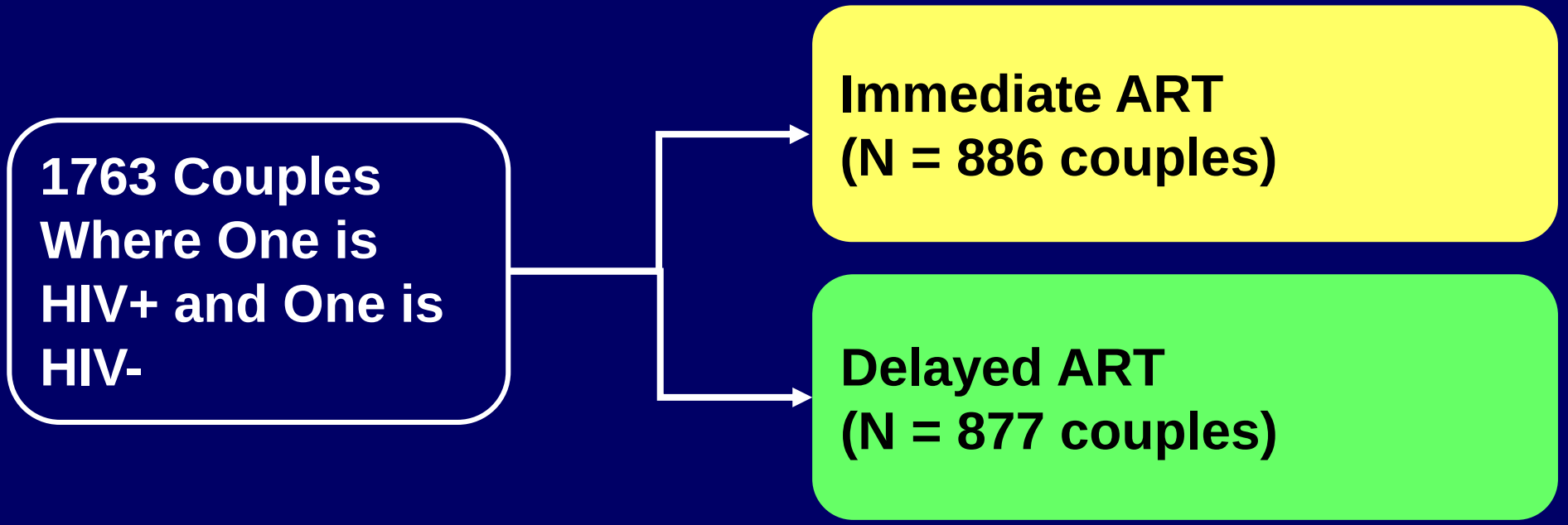
- Adults receiving care at Kaiser California
- 10:1 match HIV- to HIV+ for those seen between 1996 and 2011
- 24,768 HIV+, 257,600 HIV-, 91% male, ~25% white, ~35% ever smoked



Marcus J, et al. Abstract #54, CROI 2016, Boston, Massachusetts, February 22-25, 2016

7. Antiretroviral therapy in an HIV+ person can prevent HIV transmission to others

Clinical Trial HPTN 052



Cohen M, et al. NEJM 2011;365:493-505

Results: 96% Reduction in HIV Transmission

	Immediate Therapy	Delayed Therapy
Number of Couples	886	877
Number of HIV transmissions	4	35
HIV transmissions genetically linked	**1**	**27**
Rate of HIV transmission per 100 patient-years	0.1	1.7

Cohen M, et al. NEJM 2011;365:493-505

PARTNER2: HIV Transmission

- No linked transmissions documented in ~ 77,000 condomless sex acts when HIV-positive MSM partner suppressed to HIV-1 RNA < 200 copies/mL

Sexual Behavior Reported by HIV-Negative Partner	**Number of Linked Transmissions**	Upper 95% CI*	Condomless Sex Acts, n	Couple-Years Follow-up
Any sex	**0**	0.23†	76991	1596
Anal sex	**0**	0.24	70743	1546
Insertive anal sex	**0**	0.27	52572	1345
Receptive anal sex without ejaculation	**0**	0.43	23153	867
Receptive anal sex with ejaculation	**0**	0.57	20770	652
Any sex with an STI	**0**	2.74	6301	135

- Unlinked transmissions occurred in 15 initially HIV-negative MSM partners

*For rate of within-couple HIV transmission per 100 CYFU. †Compared with 0.84 for MSM and 0.46 for heterosexuals in PARTNER1.

Rodger A, et al. AIDS 2018. Abstract WEAX0104LB.

Slide source: Clinicalcareoptions.com

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents: When to Start

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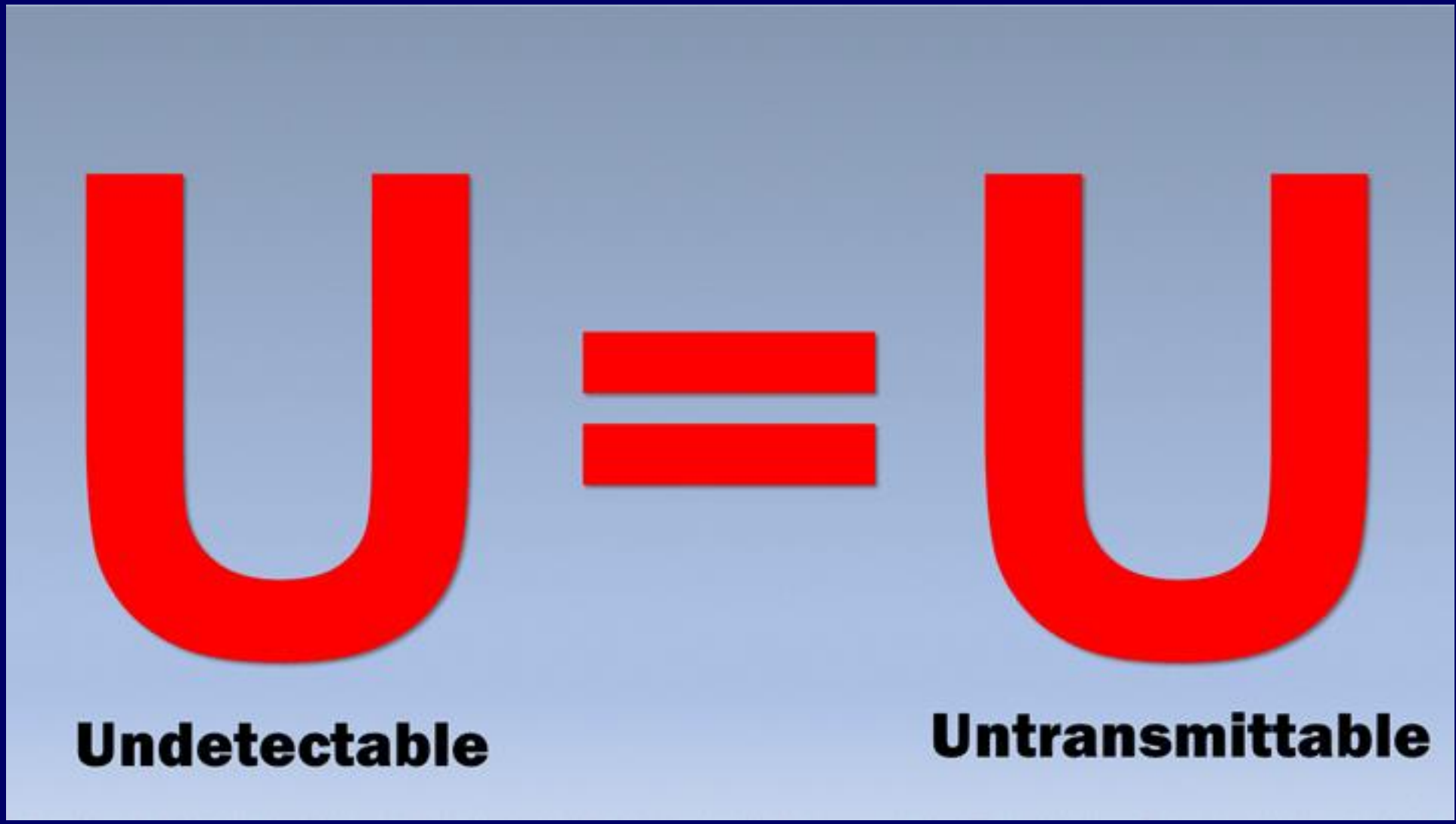
DHHS Guidelines, last updated July 10, 2019, available at www.aidsinfo.nih.gov

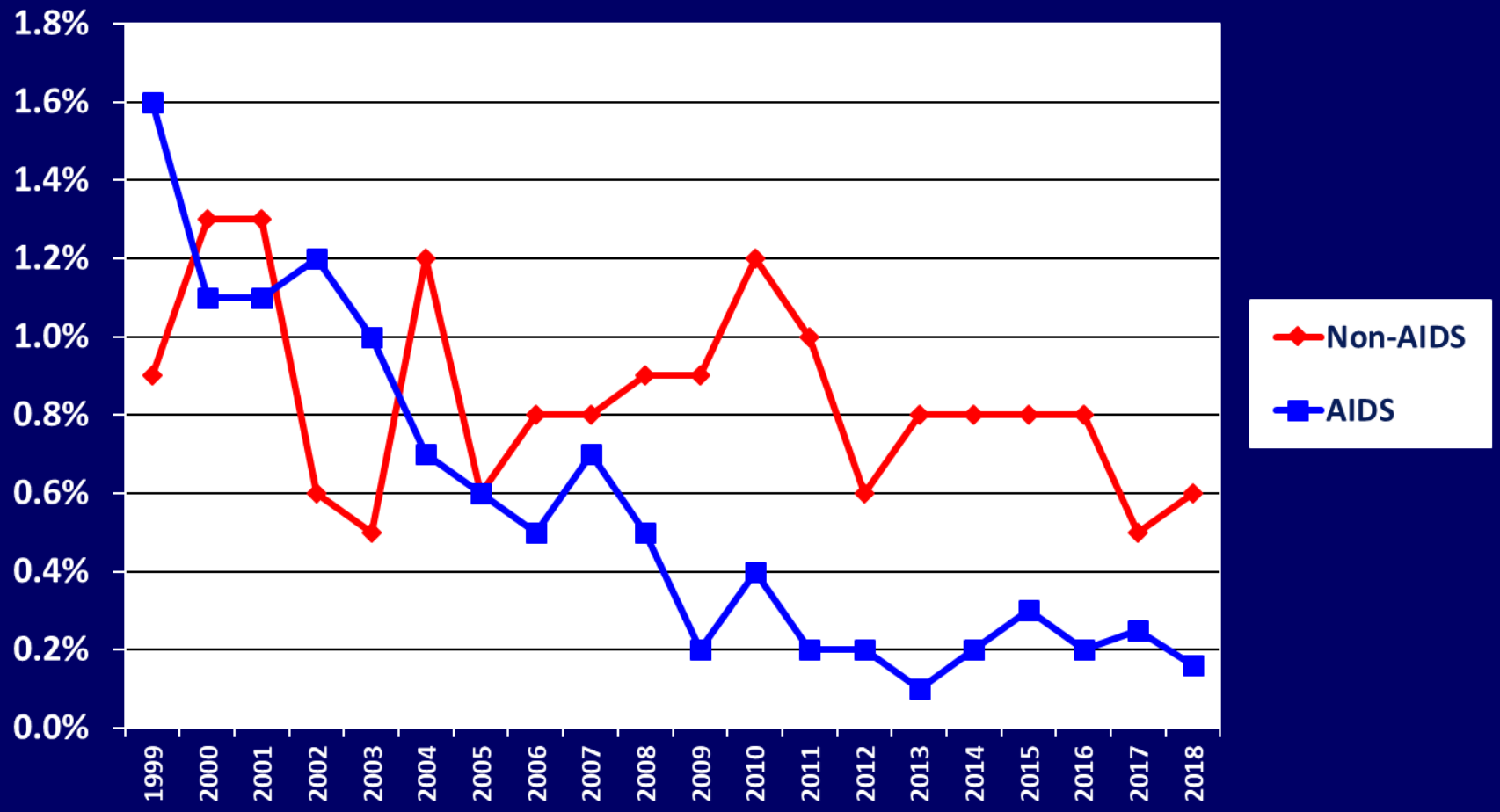

U = U
Undetectable
Untransmittable

8. Much of the Morbidity and Mortality in Persons with HIV Infection on ART are Related to Comorbidities

Treatment for Persons with HIV Infection

1. Antiretroviral therapy
2. Prevention/treatment of opportunistic infections
3. Treatment of AIDS and non-AIDS malignancies
4. Preventive vaccines (e.g. influenza, pneumococcal)
5. Treatment of co-infections (e.g. Hepatitis C)
6. Mental Health Care
7. Substance Abuse treatment and counseling
8. Treatment of illnesses unrelated to HIV infection
9. Age and gender-appropriate preventive health care

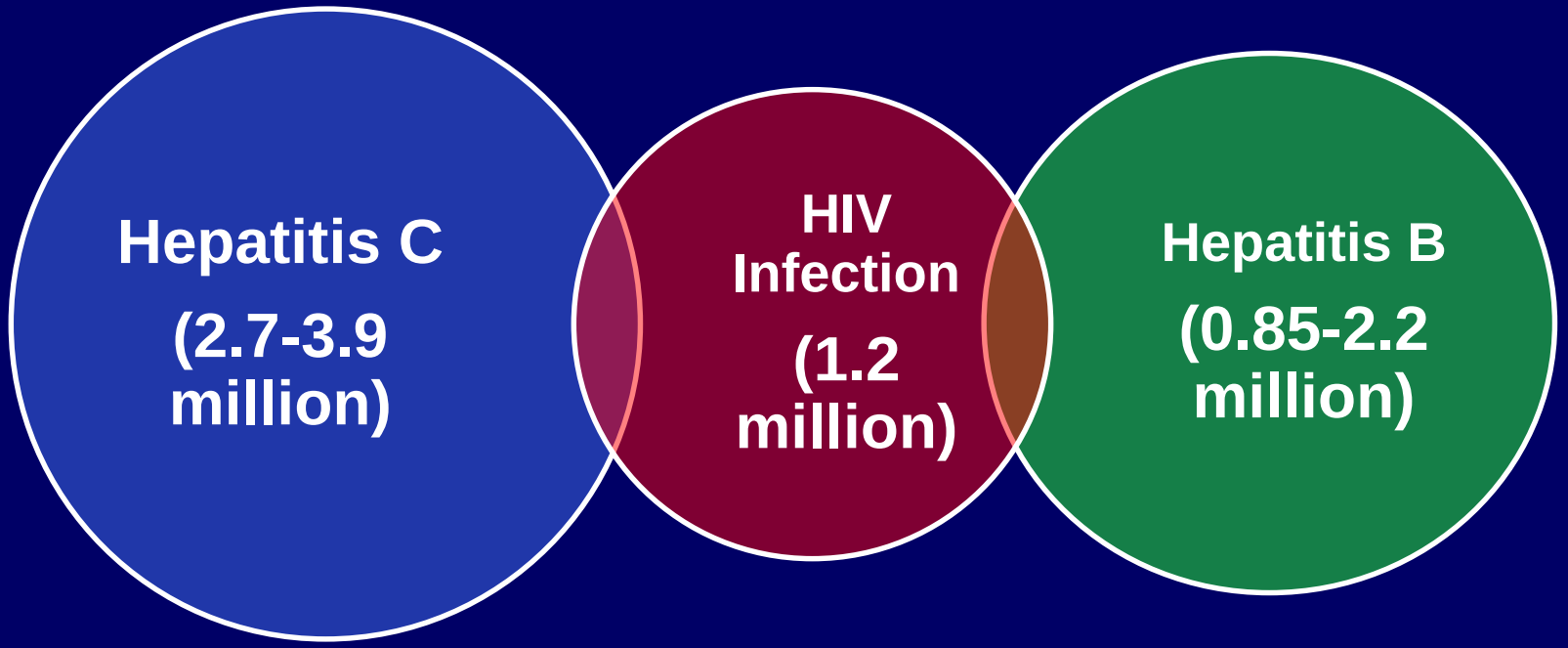
University of Colorado HIV/AIDS Clinical Program Mortality, 1999-2018



Common Co-Morbidities in HIV Infection

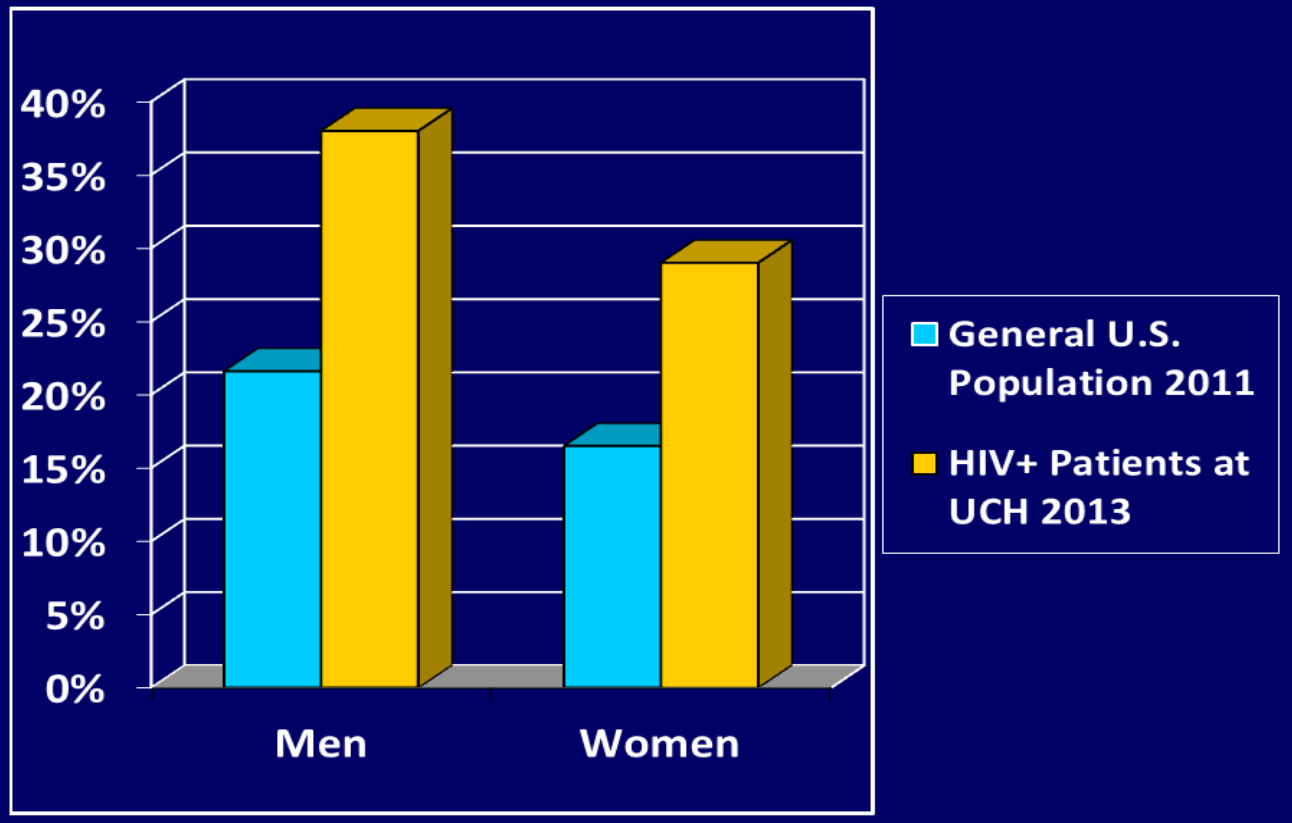
- Depression
- Bipolar Disease
- Alcohol use
- Tobacco use
- Other Drug use
- Human papillomavirus infection
- Hepatitis B
- Hepatitis C
- Syphilis
- Other STIs
- Tuberculosis
- Hyperlipidemia
- Diabetes mellitus
- Hypertension
- Heart disease
- Osteoporosis
- Non-AIDS cancers

HIV and Hepatitis B and C Co-infections are Common in the U.S.



150,000-300,000 HIV-HCV Co-Infected Persons in the U.S.

HIV+ Patients Smoke More than the General U.S. Population



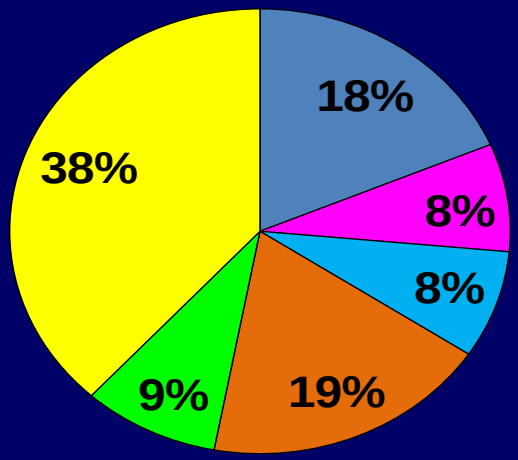
Morbidity and Mortality Weekly Report 2012;61(44):889–94
SBIRT Screening Data, University of Colorado HIV Program

Incidence of Non-AIDS Cancers among HIV + Persons Compared to General U.S. Population (Excludes Cervical Cancer which is AIDS-Defining)

Type of Cancer	Standardized Rate Ratio	95% CI
Anal Cancer	42.9	34.1 - 53.3
Vaginal Cancer	21	11.2 - 35.9
Hodgkin Lymphoma	14.7	11.6 – 18.2
Liver Cancer	7.7	5.7 – 10.1
Lung Cancer	3.3	2.8 – 3.9
Melanoma	2.6	1.9 – 3.6
Oropharyngeal Cancer	2.6	1.9 - 3.4
Leukemia	2.5	1.6 - 3.8
Colorectal Cancer	2.3	1.8 – 2.9
Renal Cancer	1.8	0.4 – 0.8

Patel P, et al. Ann Intern Med 2008;148:728-736

University of Colorado HIV/AIDS Clinical Program Mortality 2011-2015

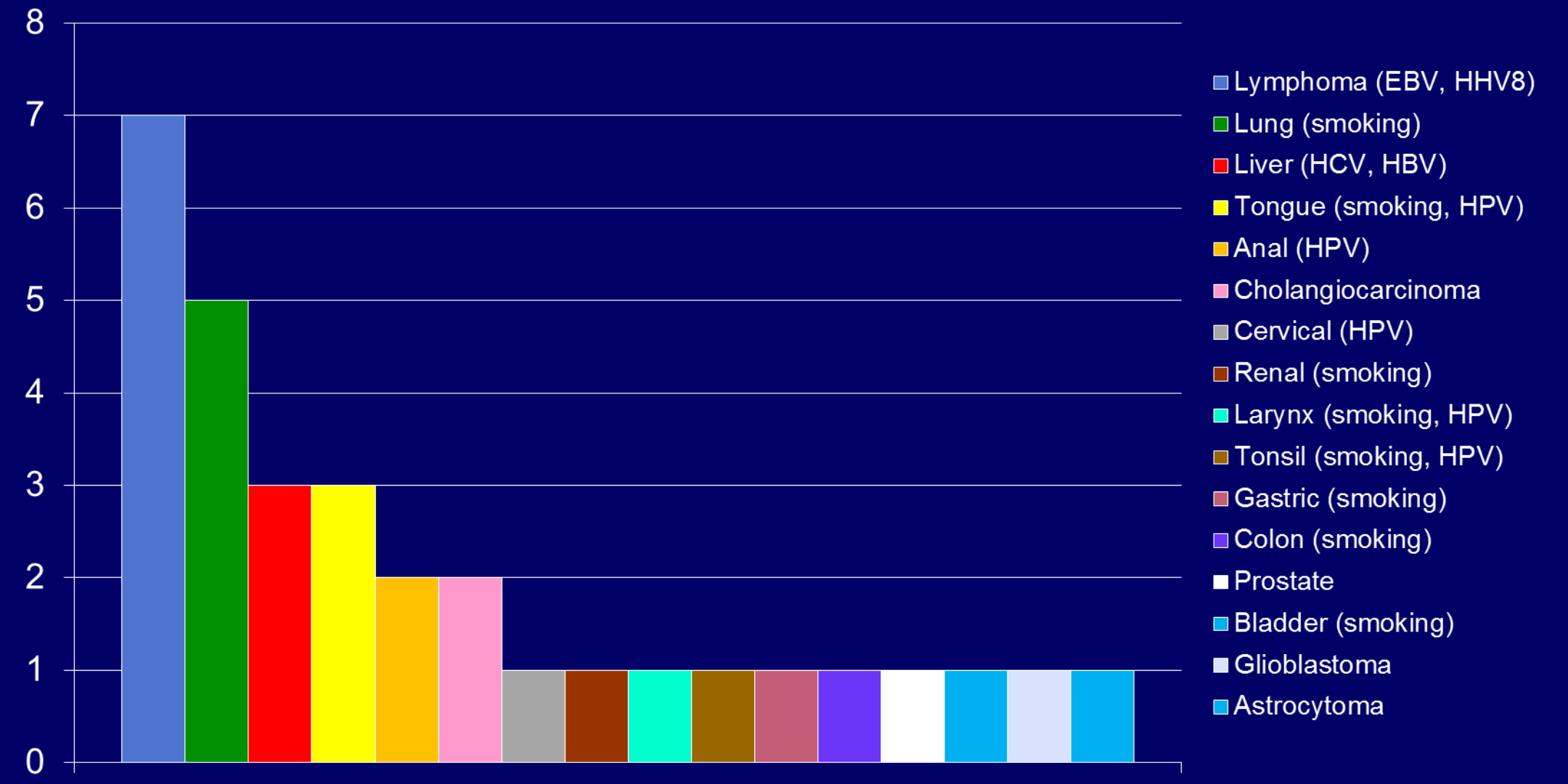


88 deaths over the last 5 years

Other*

- Sepsis
- Bee sting
- Murder
- MVA
- COPD
- Brain hemorrhage
- ESRD
- GI bleed
- Unknown

University of Colorado: Malignancy as a Cause of Death, 2010-2015; 32 cancer deaths out of 100 total deaths: Type of Cancer (Cofactors)



Strategies For Cancer Screening and Prevention in an HIV Program

Type of Cancer	Prevention Strategy
Lung cancer	Tobacco counseling, low dose chest CT scanning
Oral cancers	Oral exams
Anal cancer	Rectal exam, anal cytology, HPV testing
Prostate cancer	Rectal exam, PSA testing
Cervical cancer	Pelvic exam, cervical cytology, HPV testing
Colorectal cancer	Rectal exam, fecal occult blood testing, colonoscopy
Melanoma	Periodic skin exam, sun exposure counseling
Liver cancer	Hepatitis B vaccine, Hepatitis B and C treatment, abdominal ultrasound or CT scan for surveillance

HIV Adult Immunization Schedule by Vaccine and Age Group, September 2019

Vaccine	19-26 years	27-59 years	60-64 yrs	≥ 65 yrs
Influenza	1 dose annually			High dose
Td/Tdap	Substitute Tdap for Td once, then Td booster every 10 year.			
Varicella*	2 doses 3 months apart (if CD4 ≥ 200 and no immunity to Varicella)			
HPV	3 doses (0, 2 and 6 months)	27-45 (Discuss)		
Zoster Recombinant*			RZV: 2 doses, 0 and 2-6 months ≥ 50 yrs	
Zoster Live*			ZVL: 1 dose of ZVL > 60 (CD4 ≥ 200)	
MMR*	1 or 2 doses (if CD4 ≥ 200 and no immunity)			
PCV-13	1 dose, preferably prior to PPSV-23			
PPSV-23	2 doses 5 years apart, at least 8 weeks after PCV-13			1 dose
Hepatitis A	2 or 3 doses depending on the vaccine. 0 and 6-18 months). Check HAVAB after.			
Hepatitis B	2 or 3 doses depending on the vaccine. Check HBsAb after.			
Meningococcal Conjugate	If no prior vaccine, 2 doses of either MenACWY-D or MenACWY-CRM 8-12 weeks apart. Boost every 5 years.			

* Recombinant zoster vaccine is preferred over the live zoster vaccine. Live vaccines (MMR, Varicella, Zoster Live, and Yellow Fever) should not be given if CD4 < 200 cells mm^3. Oral typhoid and live flu vaccine are contraindicated in HIV.

After assessing age, immunity, and CD4 count. High dose flu vaccine is my recommendation.

9. Pre-Exposure Prophylaxis Can Dramatically Reduce the Risk of HIV Acquisition

Case 3 - History

42 year old male with HTN and asthma

- He is bisexual with multiple sexual partners
- He has a history of syphilis, Chlamydial infection, and gonorrhea
- He uses condoms at times
- He is not always aware of his partner's HIV status
- **Is he a good candidate for PrEP?**

Approaches to Prevent HIV Infection

In Clinical Practice

- Pre-exposure prophylaxis (PrEP)
- Post-exposure prophylaxis (PEP)
- Treatment as prevention (TasP)
- Diagnosis and treatment of sexually transmitted infections
- Prevention of mother-to-child transmission of HIV
- Voluntary male circumcision
- Blood safety
- Injection safety including needles exchange
- Condoms

Under study: Vaccines, Microbicides, HIV cure

Pre-Exposure Prophylaxis (PrEP)

- An HIV-negative person takes a combination of HIV medications to prevent acquisition of HIV infection
- Demonstrated effectiveness in a number of clinical trials
- Approved agent: tenofovir-emtricitabine
- Currently a strong national and global emphasis on using PrEP in HIV prevention

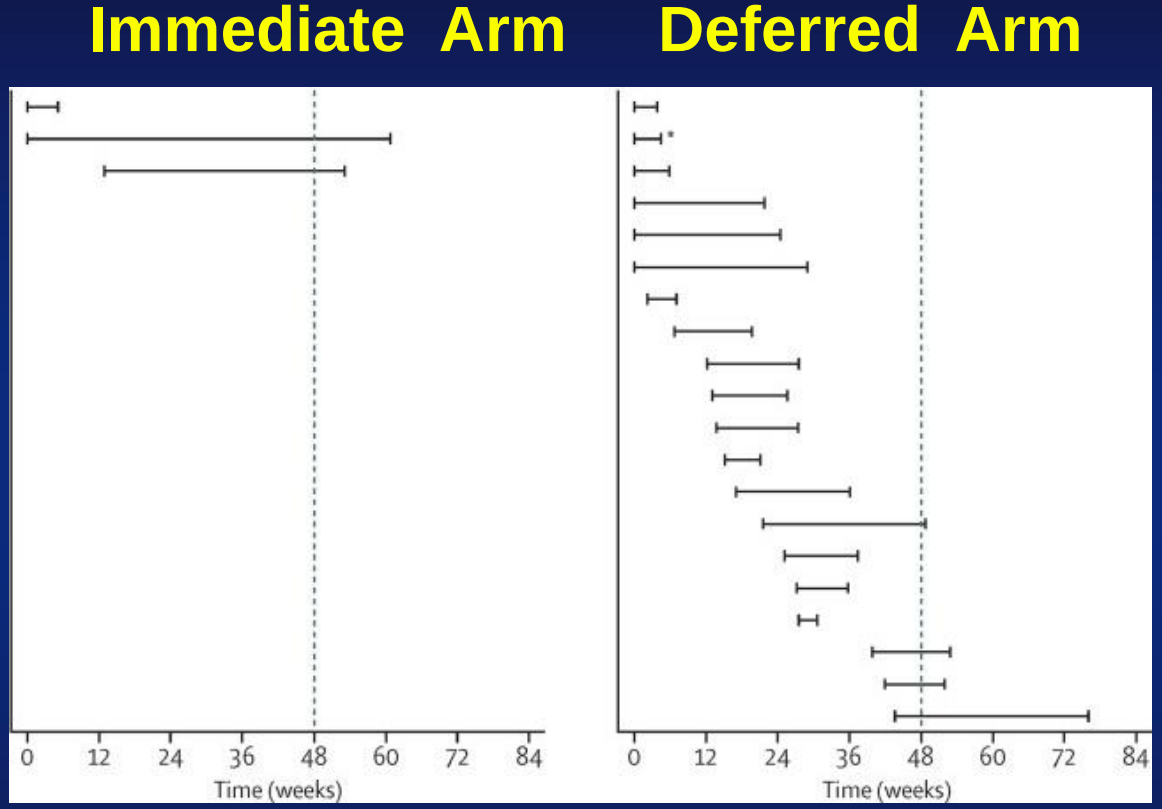
PrEP Studies: HIV transmission risk lowest when participants took PrEP consistently

Study	Reduction in risk of HIV infection overall	Reduction in risk of HIV infection when detectable levels of medication in the blood
iPrEx	44%	>90%
TDF2	62%	---
Partners PrEP	75%	90%
BTS	49%	74%

Adapted from summary of research at http://www.cdc.gov/hiv/prevention/research/prep/

Immediate vs. Deferred PrEP – PROUD Study

- Tested the use of TDF/FTC among high risk MSM at 13 clinics in England. Subjects started TDF/FTC or deferred for 1 year.
- 544 men were randomized
- There were 3 infections in the immediate arm, 20 in the deferred arm (86% efficacy)



McCormack et al, Lancet 2016;387:53-60.

What is PrEP and Who is Eligible?

- TDF/FTC for PrEP is the one-tablet, once-daily medication used in combination with safer sex practices to reduce the risk of sexually acquired HIV in uninfected adults at high risk

MSM	Heterosexual Women and Men	IDUs
• HIV-positive sex partner • Recent bacterial STI • High number of sex partners • History of inconsistent or no condom use • Commercial sex work	• HIV-positive sex partner • Recent bacterial STI • High number of sex partners • History of inconsistent or no condom use • Commercial sex work • In high-prevalence area or network	• HIV-positive injecting partner • Sharing injection equipment • Recent drug treatment (but currently injecting)

CDC. PrEP for the Prevention of HIV Infection in the US, 2014: A Clinical Practice Guideline. May 2014. www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf.

CDC Guidance on PrEP for HIV Prevention: Prescription and Monitoring

	MSM	Heterosexual Women and Men	IDUs
Prescription	• TDF/FTC (300/200 mg) QD; daily, continuing, oral dose, ≤ 90-day supply		
	• TDF alone can be considered as an alternative regimen in IDUs and heterosexually active adults		
	• Other ARVs, coitally timed PrEP, or other noncontinuous daily use is not recommended		
Other Services	• Follow-up visits at least every 3 months to provide HIV test, adherence counseling, behavioral risk reduction support, AE assessment, STI evaluation • At 3 months and every 6 months thereafter, assess renal function • Every 6 months, test for bacterial STIs		
	• Do oral/rectal/urethral testing for chlamydia and gonorrhea and test for syphilis at least annually or every 3–6 months, if at increased risk	• Assess pregnancy intent • Pregnancy test every 3 months	• Access to clean needles/syringes and drug treatment services

Case 3 – Follow up

- He initiated therapy with tenofovir DF-emtricitabine 1 tablet daily
- He has received the Hepatitis B vaccine and is immune
- He agrees to regular follow up for HIV testing, other STI testing, and assessment of TDF-FTC adherence and toxicity
- He remains HIV-negative 7 years into PrEP

10. New Approaches to HIV Treatment Include 2 drugs, Parenteral Therapy, and a Search for the Cure

New Antiretroviral Agents 2018-2019

Brand Name	Components	Comments
Biktarvy	Bictegravir-FTC-TAF	Single tablet regimen (STR)
Cimduo	3TC-TDF	Generic combination
Delstrigo	Doravirine-3TC-TDF	New STR with NNRTI
Dovato	Dolutegravir-3TC	New STR with 2 drugs
Pifeltro	Doravirine	New NNRTI
Symfi	Efavirenz-3TC-TDF	Generic STR with efavirenz
Symfi Lo	Efavirenz 400-3TC-TDF	STR with lower dose of EFV
Symtuza	Darunavir-COBI-FTC-TAF	First PI-based STR
Temixys	3TC-TDF	Generic combination
Trogarzo	Ibalizumab-uiyk	IV monoclonal antibody

Areas of Study in HIV Treatment and Prevention

- 2-drug antiretroviral therapy
- Parenteral antiretroviral therapy
- New agents for drug-resistant HIV
- Co-morbidity management
- New agents for Pre-Exposure Prophylaxis
- HIV vaccine
- HIV cure

Why a 2-drug regimen?

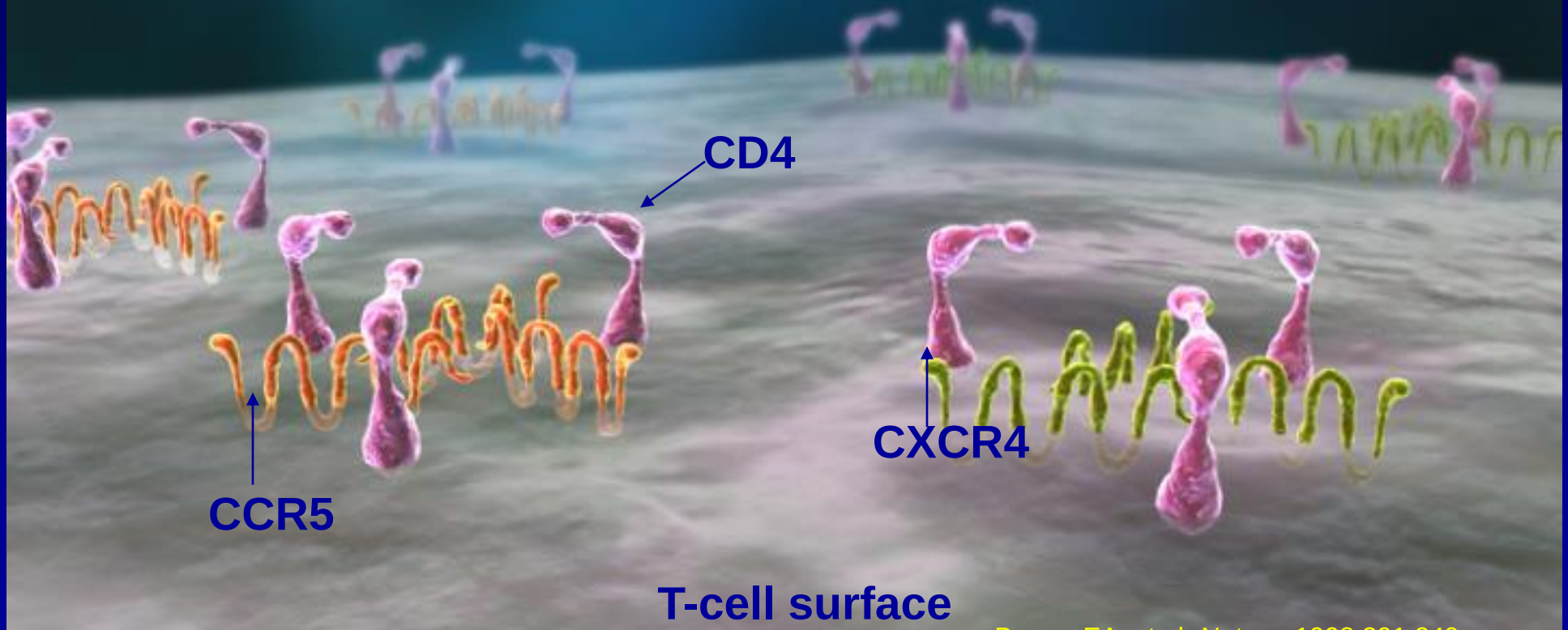
- “As much as needed, as little as possible”
- Reduce potential impact of long-term exposure to multiple ARVs
- Clinical profile of newer agents suggests that 2-drug ART might be potent and sufficient
- Potential for reduced drug interactions
- Lower cost

Selected 2-Drug Regimens Approved or Under Study

- Dolutegravir + Rilpivirine
- Dolutegravir + 3TC
- Cabotegravir + Rilpivirine (by injection)
- Dolutegravir + boosted darunavir
- Raltegravir + boosted darunavir
- Boosted darunavir + 3TC

Who is this person?

To enter a cell, HIV uses the CD4 receptor and a co-receptor, either CCR5 or CXCR4



Berger EA, et al. *Nature*. 1998;391:240.

The Berlin Patient

- HIV+ patient with leukemia.
- Treated with chemotherapy and two stem cell transplants.
- Transplanted stem cells were from a CCR5 Δ 32/CCR5 Δ 32 donor.
- Patient is now off antiretroviral therapy and has no detectable HIV infection.
- 10 years out, he appears to be cured.

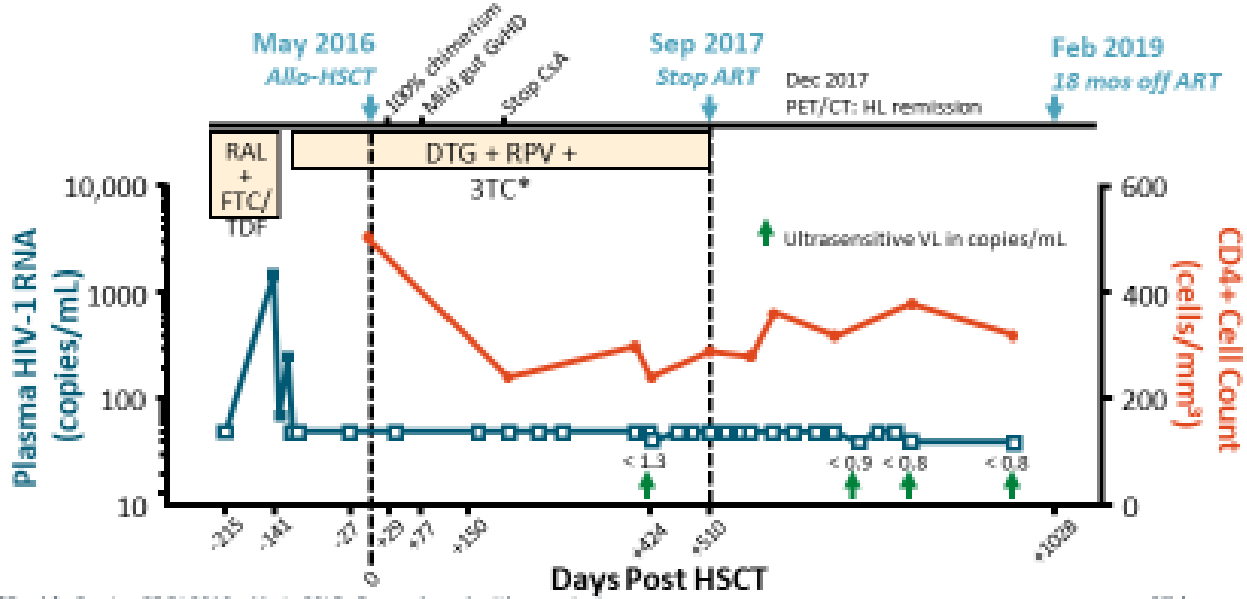
The London Patient

- 2003 HIV diagnosis – preserved CD4
- 2013 Stage IVb Hodgkin lymphoma
  - Atripla started → viral load suppressed
  - Changed to TDF/FTC/RAL
- Failed multiple chemotherapies, failed mobilization for auto-SCT
- Donor registry search for allo-HSCT
  - Unrelated 9/10 HLA high-resolution match
  - Donor homozygous CCR5-Δ32 mutation

Gupta, et al. Abstract 29, CROI 2019, March 4-7, 2019, Seattle, Washington

Second Apparent Case of HIV Cure: Timeline of Allo-HSCT and Viral Load Measures

- Patient has experienced 18-mos HIV "remission" without ART following allo-HSCT
  - Adaptive immune responses declining or absent after transplant



Gupta. Nature. 2019;[Epub]. Gupta. CROI 2019. Abstr 29LB. Reproduced with permission.

Slide credit: clinicaloptions.com

Gupta, et al. Abstract 29, CROI 2019, March 4-7, 2019, Seattle, Washington

The Dusseldorf patient

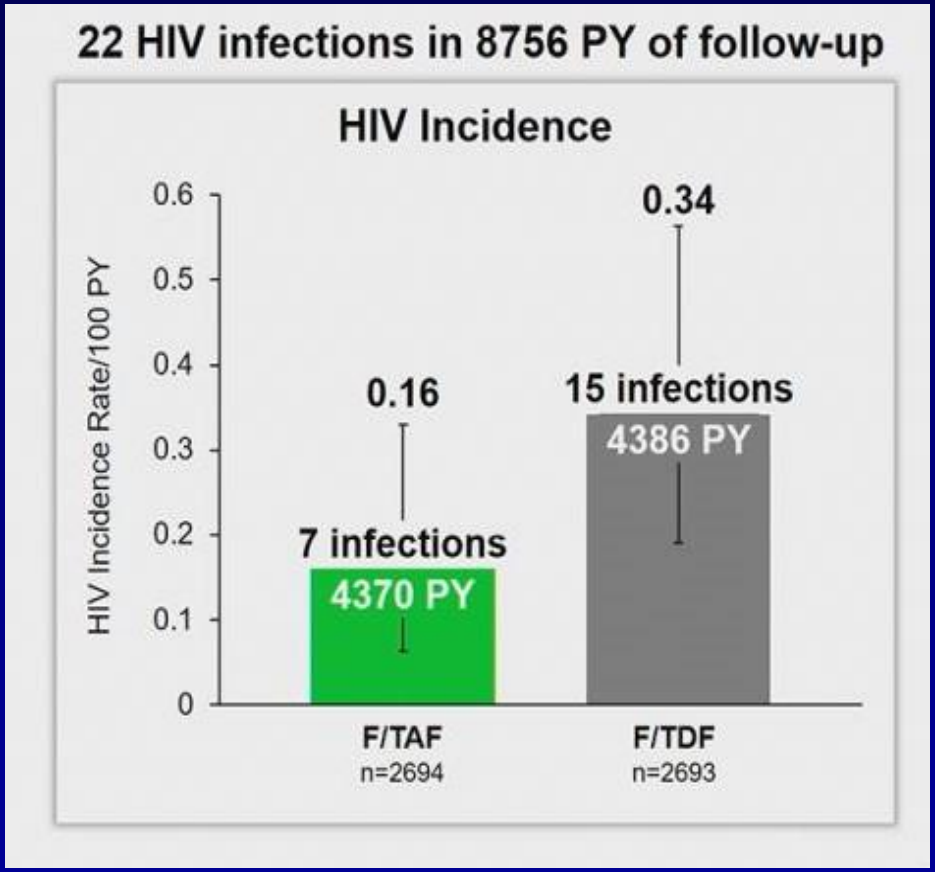
- AML in second remission
- HSCT with homozygous donor CCR5-Δ32 mutation 2/2013
- Also undetectable plasma viral load, proviral viral load; bone marrow, ileum and rectal biopsies all negative for HIV infection
- Stopped ART in 11/2018 with a negative HIV viral load so far

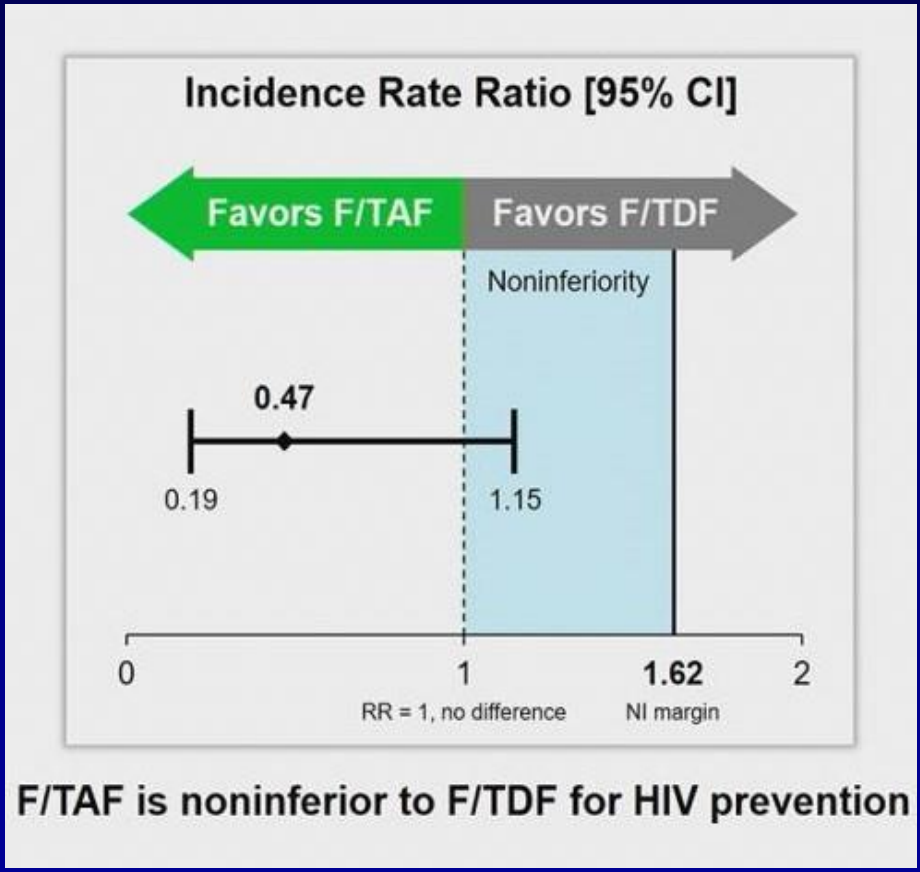
Jensen, et al. Abstract 394, CROI 2019, March 4-7, 2019, Seattle, Washington

Selected Investigational Antiretroviral Agents

Agent	Mechanism	Potential Benefit
Fostemsavir	Attachment Inhibitor	Use in resistant virus
GSK2838232	Maturation inhibitor	Use in resistant virus
GS-6207	Capsid inhibitor	Picomolar potency, T1/2 long Possible q12wk dosing
PGT 121	Monoclonal Ab targeting HIV envelope	May be injection q 6 mos
MK-8591	Nucleoside RT translocation inhibitor	Long acting. Use in resistant virus. Co-formulations.
Cabotegravir (long-acting and oral)	Integrase inhibitor	Possible monthly injection
TMC278 LA (long-acting rilpivirine)	NNRTI	Possible monthly injection

DISCOVER Results: TAF/FTC for PrEP





Hare, et al. Abstract 104, CROI 2019, March 4-7, 2019, Seattle, Washington

Summary

1. HIV infection is common in the U.S.
2. Guidelines recommend HIV testing for essentially all adults
3. Current antiretroviral agents are remarkable in their ability to either prevent or repair immunodeficiency
4. Co-morbidities play the major role in current morbidity and mortality among HIV+ persons who are on ART
5. Pre-exposure prophylaxis (PrEP) is very effective in preventing HIV acquisition

Useful Internet Resources

- www.aidsinfo.nih.gov: The definitive guidelines on ART, OI management, PrEP, and perinatal HIV management
- www.iasusa.org: Alternative ART guidelines, charts of resistance mutations, other HIV content
- www.hcvguidelines.org: Updated HCV treatment guidelines
- www.idsociety.org: Multiple guidelines on HIV management including primary care guidelines
- www.hiv-druginteractions.org: Excellent site on drug interactions from the University of Liverpool
- www.aidsinfonet.org: Excellent fact sheets on a variety of HIV issues

Questions and Discussions