THE NATURAL HISTORY OF HIV INFECTION

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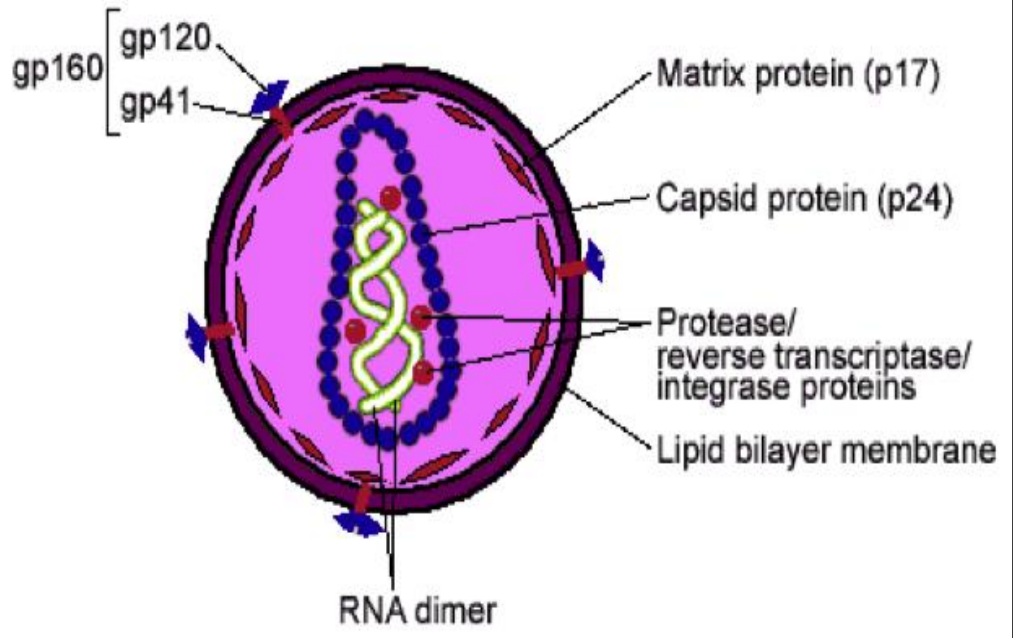
Learning Objectives

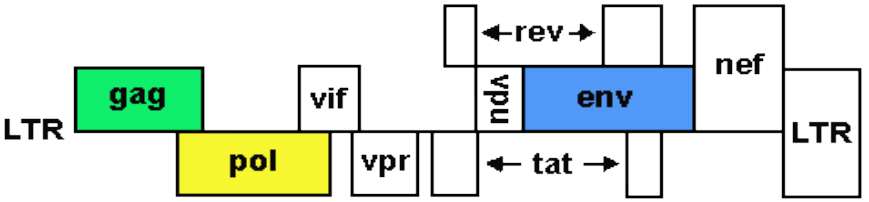
- Be able to teach your patients how antiretroviral drugs interrupt the viral life cycle to decrease viral load
- Be able to screen for and recognize primary HIV infection
- I do not intend to discuss any non-FDA-approved or investigational uses of any products/devices during this presentation.

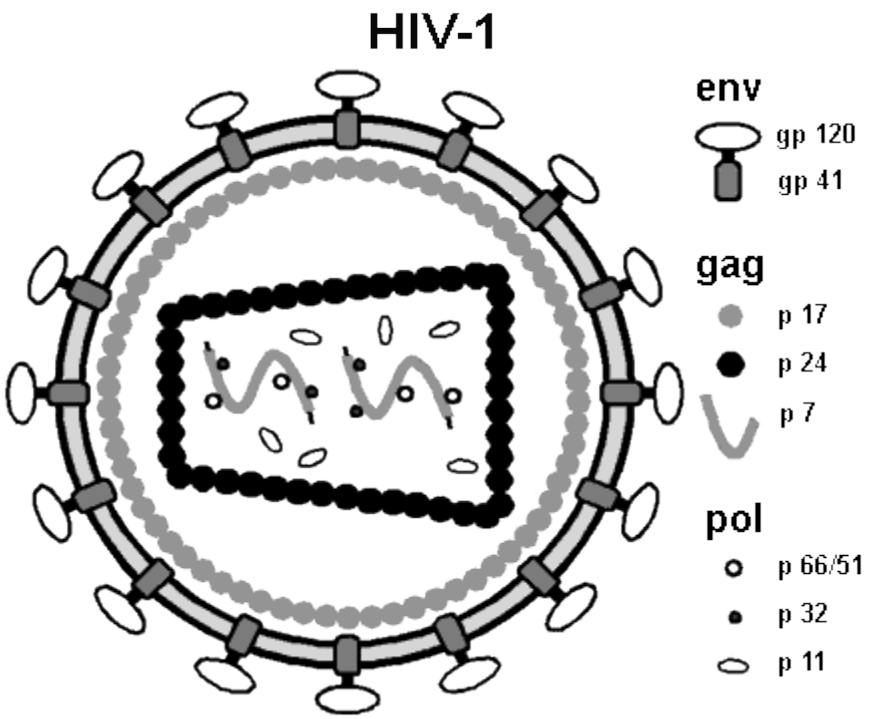
The Basics

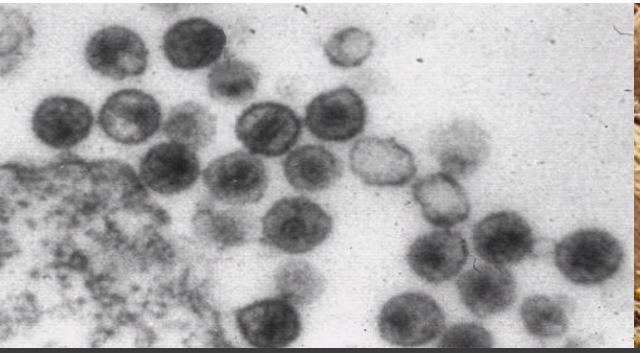
- Anatomy of HIV
- HIV Replication: Life Cycle Events
- Primary HIV Infection
- Chronic Infection
- AIDS

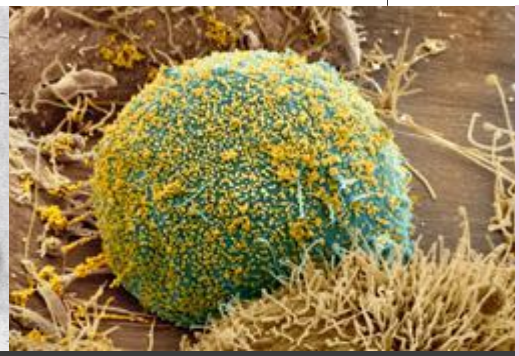
Anatomy of HIV



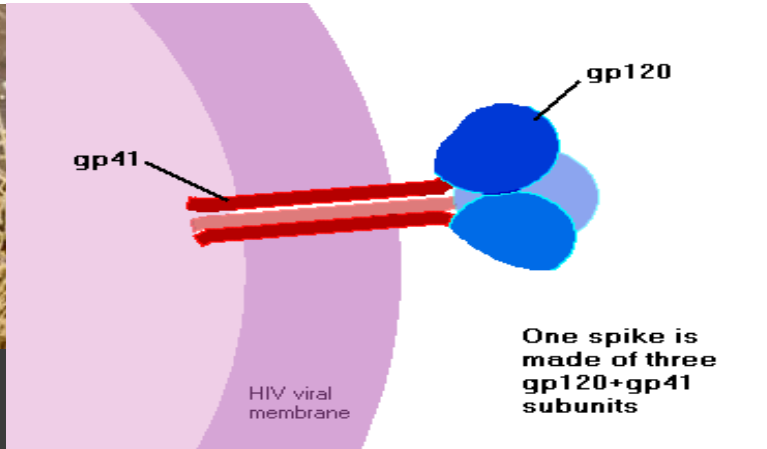








library.med.utah.edu/WebPath/TUTORIAL/AIDS/AIDS002
www.mcld.co.uk/hiv



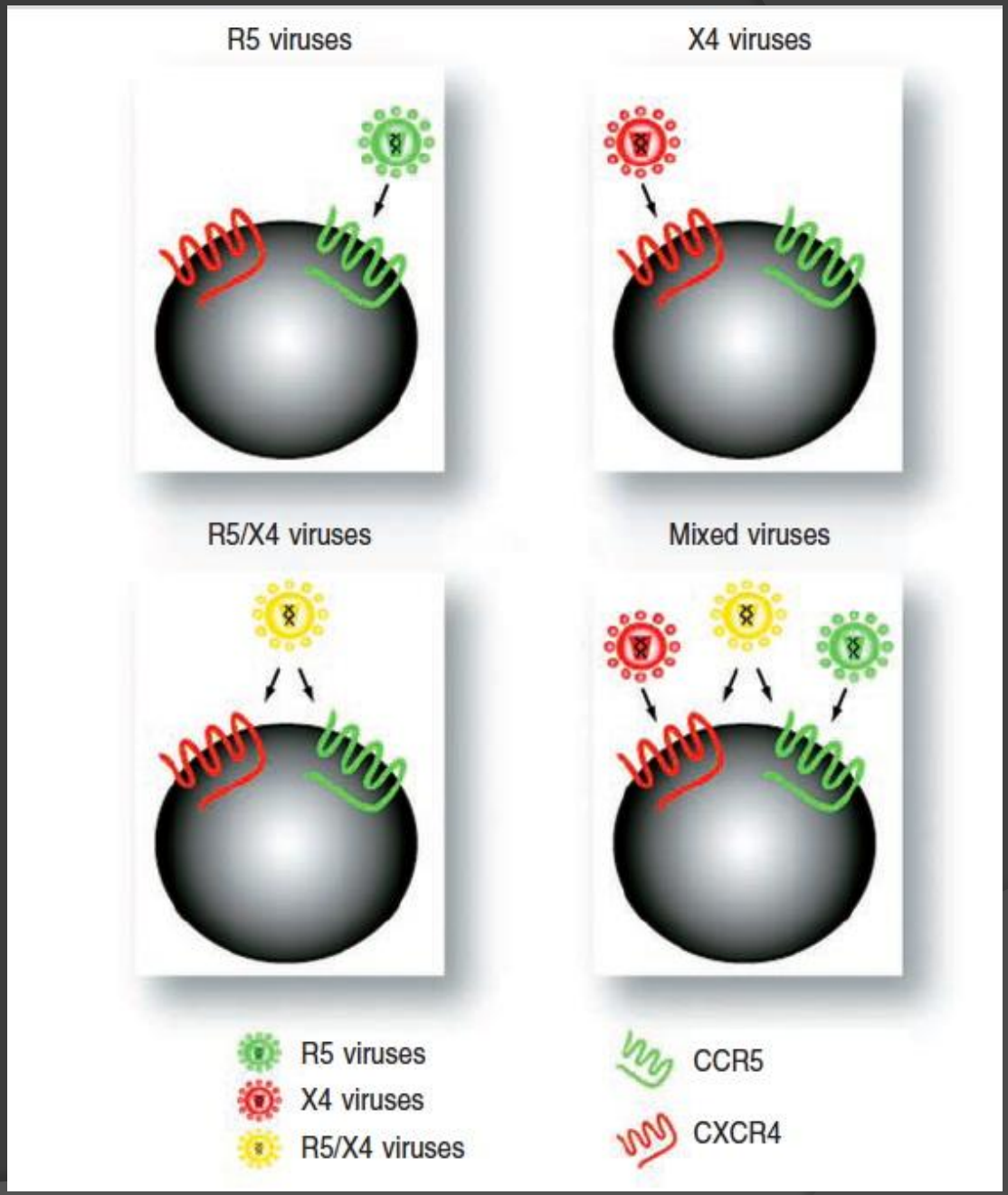
Co-Receptor Tropism and Viral Entry

CCR5 =
M tropic = NSI

CXCR4 =
T tropic = SI
(associated with CD4+ depletion)

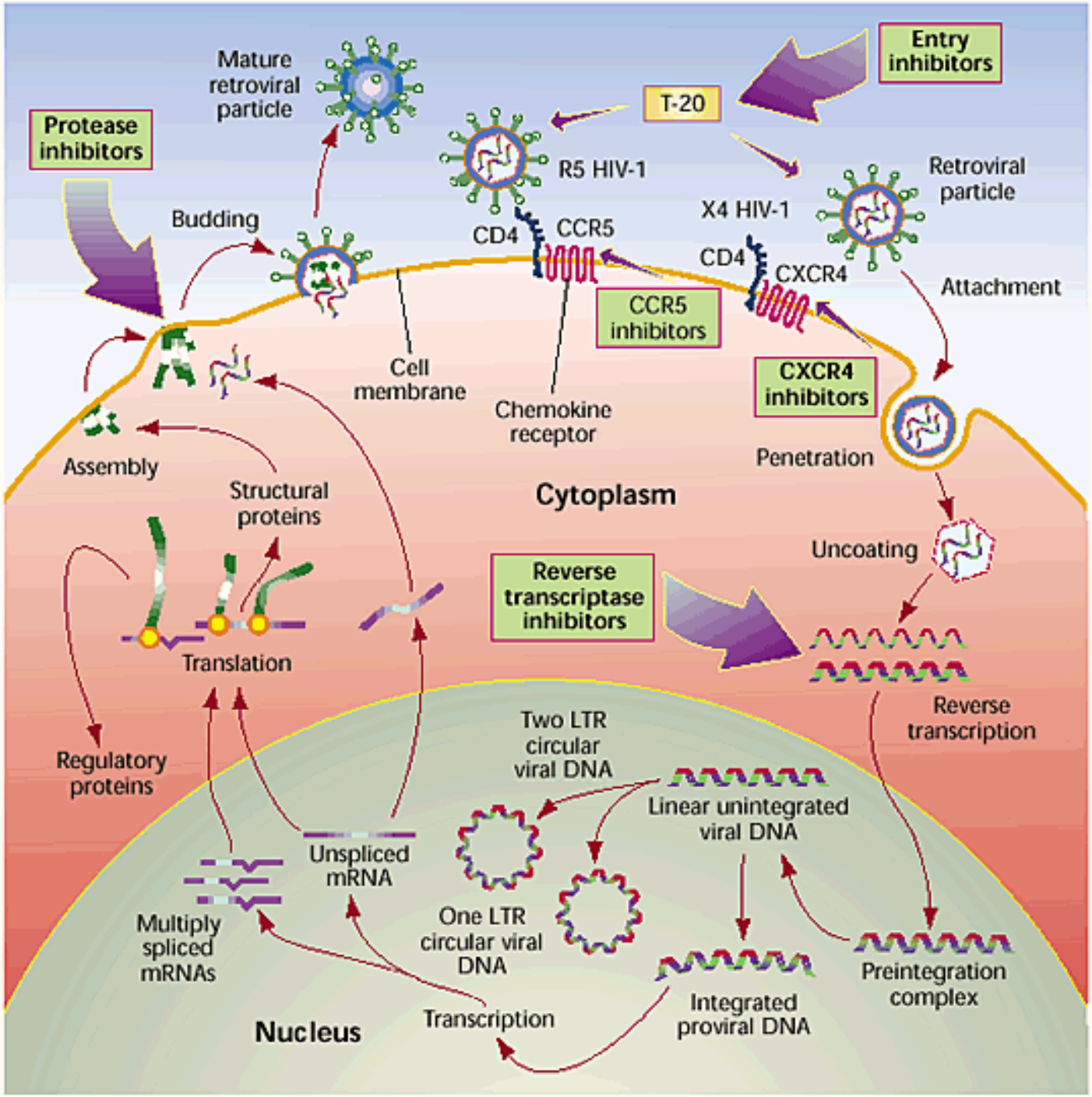
R5/X4 (Dual)

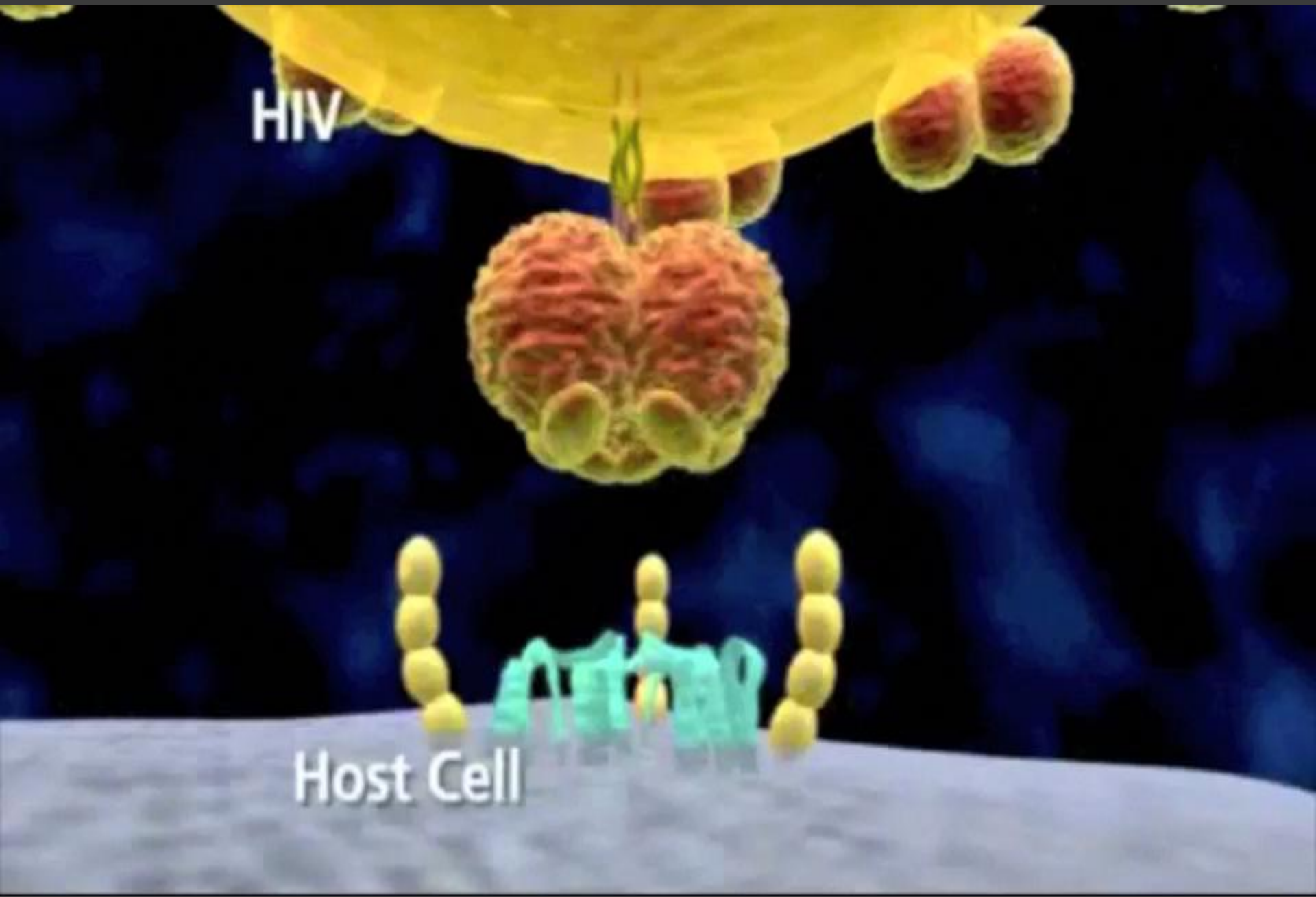
Mixed



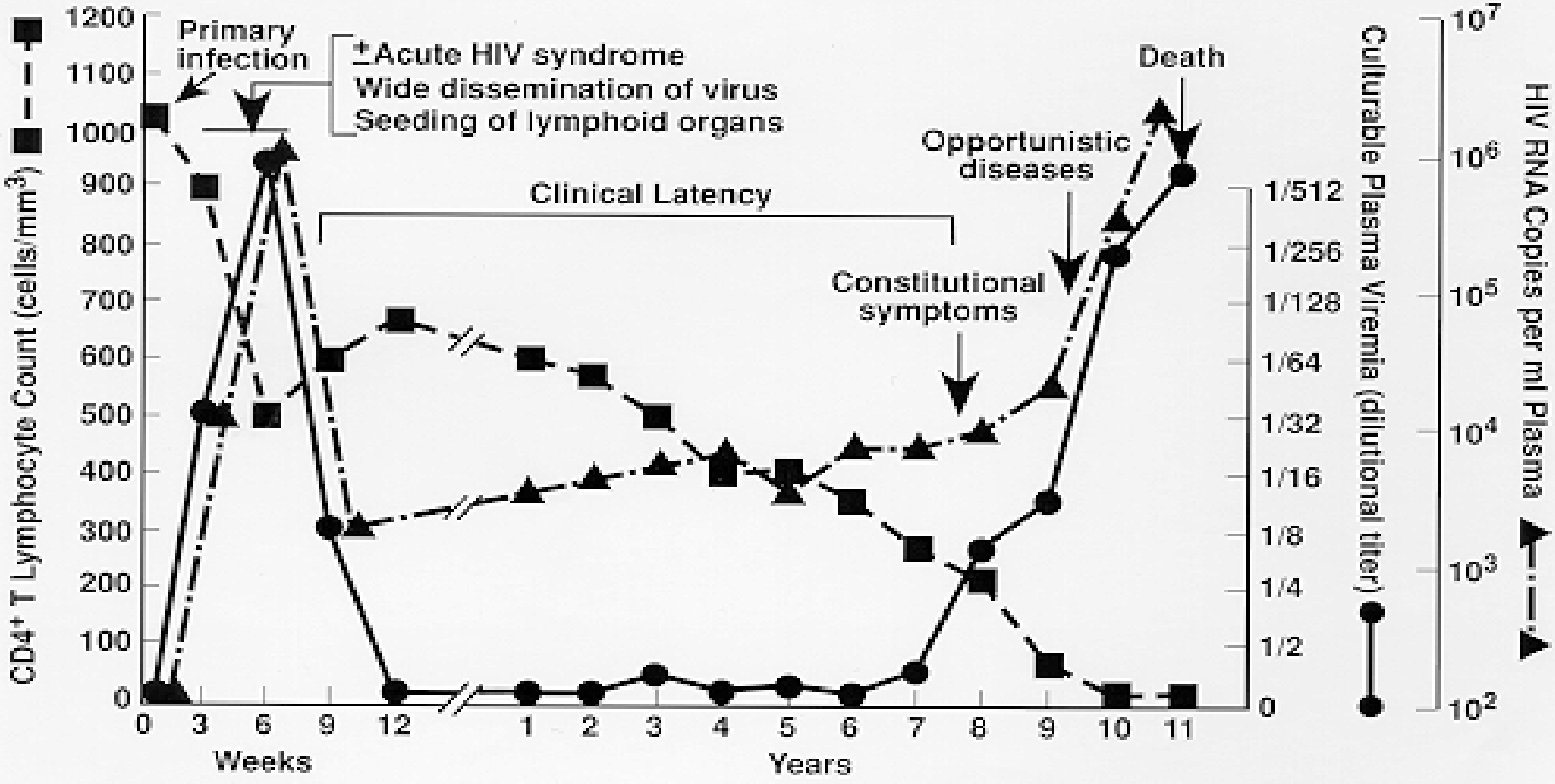
Weber J, et al. AIDS Reviews 2006; 8:60-77

HIV Life Cycle




HIV
Host Cell

Natural History of HIV Infection



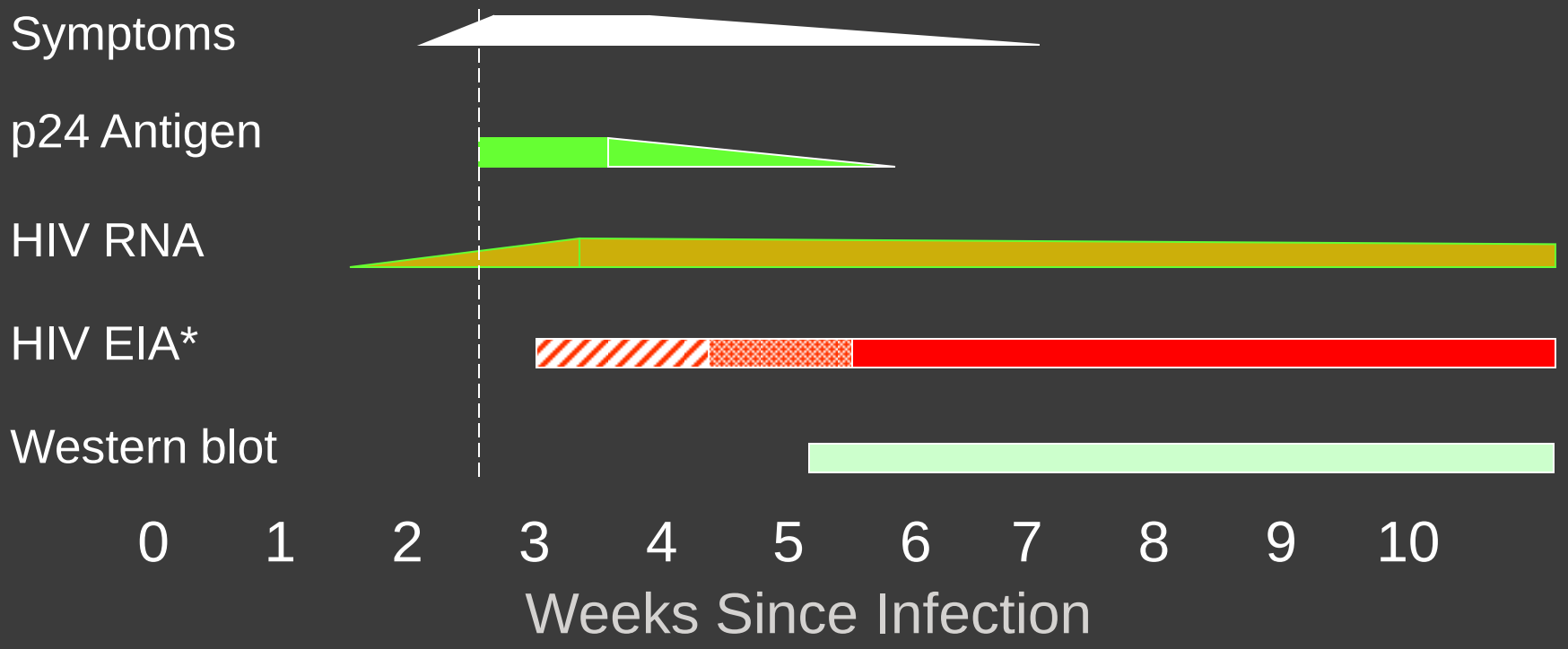
Pantaleo G, NEJM. 1993;328:327-35

Primary HIV Infection

- May be symptomatic or asymptomatic
  - Symptoms correlate with faster progression[1]
- Commonly missed by medical professionals
- Antibodies usually appear 2-4 wks later
- Viral loads: up to 100 million copies/ml
  - VL predicts disease progression rate[2]
  - VL in source correlates with VL in recipient[3]
  - Extremely infectious
- Virus “seeds” reservoirs very rapidly to establish chronic infection, currently irreversible

[1]Lavreys, CID 2002:35:77-81 & CID 2006: 42:1333-9
[2]Mellors J, Annals Int Med 1995:122:573-9 [3]Hecht F, AIDS 2010:24:DOI:10,1097

Detection of HIV by Diagnostic Tests



**3rd generation, IgM-sensitive EIA*

**2nd generation EIA*

**viral lysate EIA*

After Fiebig et al, AIDS 2003; 17(13):1871-9

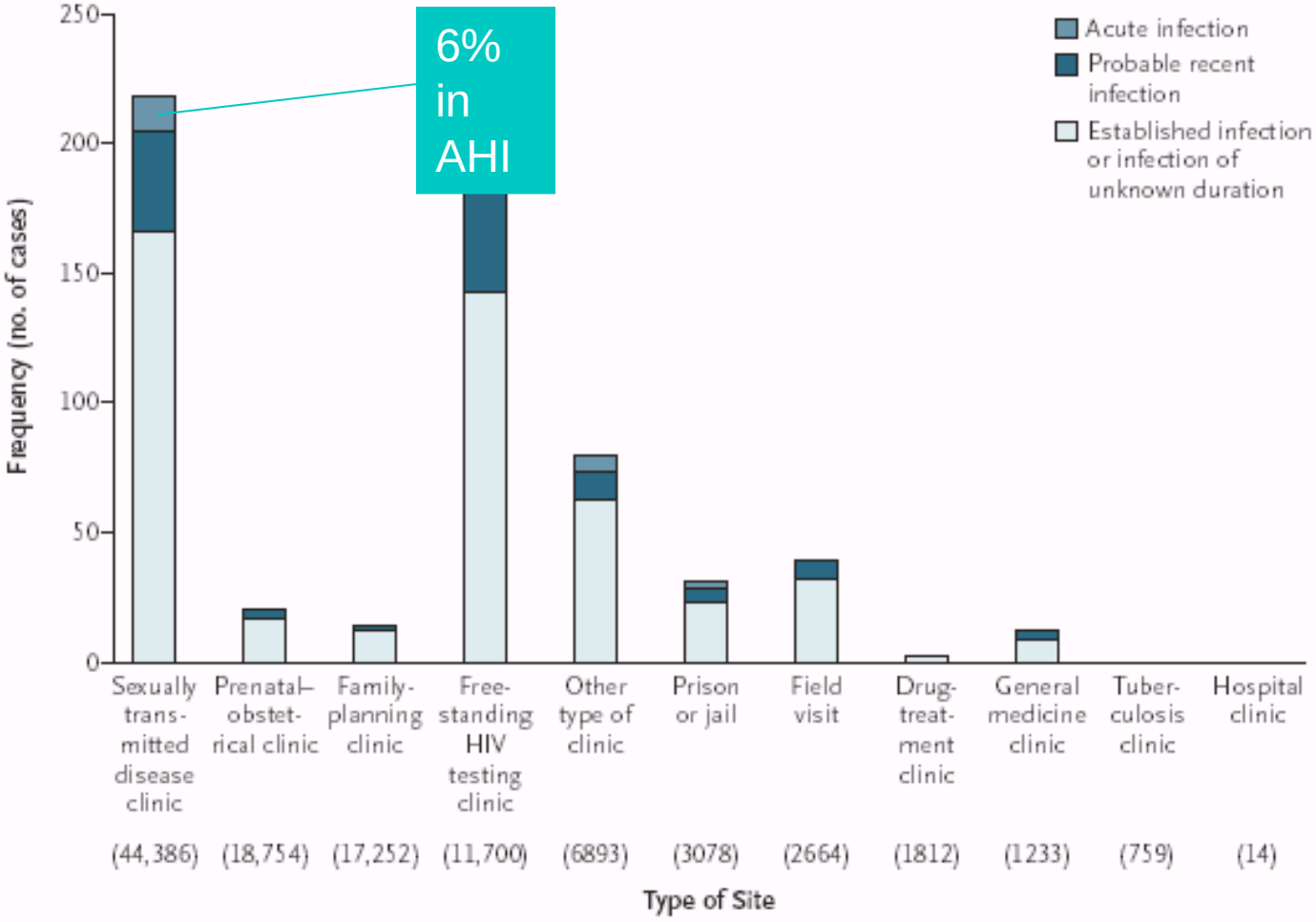


Figure 3. Frequency of Newly Diagnosed HIV Infections in North Carolina, November 1, 2002, through October 31, 2003, According to Type of Testing Site and Stage of Disease.

All sites were publicly funded and provided confidential HIV testing. The numbers in parentheses are the population at risk. Data regarding type of site were missing for 705 persons.

Pilcher C, et al. NEJM 352:1873-1883

Primary Infection: Clinical

- Incubation period: days to weeks after HIV infection
- Usually appears as “flu-like” syndrome with lymphadenopathy, lasting 7-14 days
- Fever/rash followed by pharyngitis/ulcers should raise s

Fever – 80%	Myalgia – 49%
Malaise – 68%	Fever & rash – 46%
Arthralgia – 54%	Oral ulcers – 37%
Loss of appetite – 54%	Weight loss > 2.5kg – 32%
Rash – 51%	

*Hecht, et al. AIDS 2002, 16:1119-29.

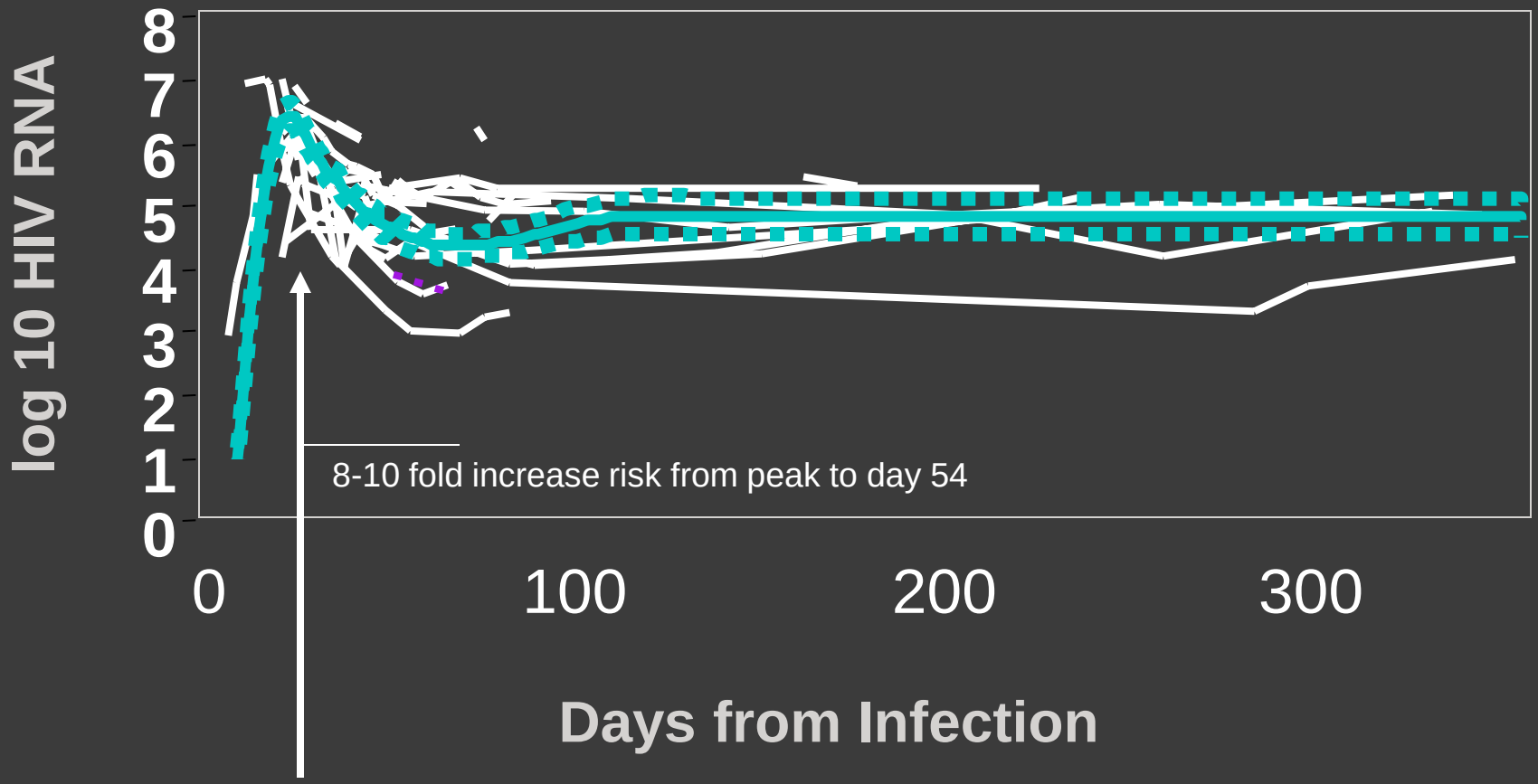
Infectivity During Acute Infection: UNC Cohort

- Viral load in semen paralleled that of plasma
- Peak occurred ~ 20 days post infection
- Viral set point occurred at 54 days post infection
- Risk of heterosexual transmission increased 8-10 fold between day 20 and day 54
- During the first 2 months of infection, 7-24% of partners would likely be infected

Pilcher, et al JID 2004 189(10):1785-92

Blood viral load in acute HIV (n=171)

Average fitted curve, with 95% confidence intervals



Pilcher, et al JID 2004
189(10):1785-92

Cellular Immune Response: CD8+

- Rapid, broad CD8+ T-cell expansion
- HIV-1-specific cytotoxic CD8+ T-cells (CTLs) kill HIV-infected cells
  - Direct cytolysis (MHC class I-restricted)
  - Indirect via cytokines (IFN-g), chemokines (RANTES), pro-inflammatory proteins (MIP1a & MIP1b)
  - Strength and breadth correlates with viral control and rate of disease progression*
- Rapid selection of virus with CTL epitope mutations = viral escape from CTL control

*Panteleo G, PNAS 1997: 94(1):254-8; Musey L, NEJM 1997:337(18):1267-74

Cellular Immune Response: CD8+

- High immune activation is associated with earlier mortality
  - Increased expression of T-cell activation markers (such as CD38+ and HLA-DR)[1]
  - Increased Ki-67 (proliferation marker)[2]
  - Increased plasma LPS
- Decreased levels of IL-7 receptor, a T-cell homeostasis marker (CD127)[2]
- Early depletion of naïve CD8+ cells[2]

[1]Panteleo G, PNAS 1997: 94(1):254-8 [2]Ganesan, JID 2010: 201:272-84

Cellular Immune Response: CD4+

- CD4+ T-cell count declines transiently, then rebounds, but usually not to normal levels
- Decline may be dramatic and, rarely, be associated with OIs
- Strong initial CD4+ T-cell proliferative response to Gag but impaired early
- Impaired number and function of central memory (CM) CD4+ cells
  - Accelerated differentiation into effector CD4+ cells
  - T-cell exhaustion

Immune Response: Humoral

- Antibodies are, generally, not primary mechanisms of HIV control
- Neutralizing antibodies (NAb)
  - May be helpful in controlling viremia
  - NAb titers inversely proportional to VL
  - Do not prevent disease progression in absence of strong cellular response

Role of Genetic Factors

- CCR5 deletion of 32 base pairs (CCR5delt32)[1]
  - Homozygotes do not express CCR5 and show high levels of resistance to HIV infection
  - Heterozygotes show lower viral setpoints and slower progression of disease
- HLA Class I alleles[2]
  - HLA-B57 associated with better viral control and lower frequency of symptomatic acute infection
  - HLA-B27 associated with strong CTL response, lower viral setpoint, slower progression of disease
  - HLA-B35 associates with more rapid progression[3]

[1]Liu R, Cell 1996: 86(3):367-77

[2]Kaslow RA, Nat Med. 1996: 2(4):405-11

[3]Itescu S, AIDS 1992: 5(1):37-45

The “Elite” Controllers[1]

- Definition: HIV-1 RNA < 50 copies/ml and ART naive
- Immune correlates
  - Strong HIV-1 specific responses
    - CD4+ proliferative responses to p24
    - CD8+ IFN-gamma production
    - Broad Gag- and Pol-specific CTL responses
  - Neutralizing antibodies not strongly protective
- Genetic correlates
  - HLA, chemokine receptor deletion, TLR polymorphism
- Viral correlates
  - Defective *nef* - long terminal repeat deletions
  - Decreased viral replicative fitness in some cases[2]

[1]Dyer W, Retrovirology 2008:5:112

[2]Kirchoff F, NEJM 1995 ;332(4):228-32

Chronic Infection

- Time from infection to AIDS may average 10 years in some settings (SF, 1980's)[1]
- "Clinical latency" is a virologically and immunologically active period[2]
  - Continuous HIV replication
  - Continuous CD4 depletion
  - Continuous viral evolution

[1]Bacchetti P, Moss Nature. 1989: 338(6212):251-3

[2]Pantaleo G, Nature 1993: 362:355-358

Relationship Between CD4+, HIV-1 RNA & Progression to AIDS

CD4 cell count/μL	Viral load copies/mL	% AIDS progression in men	
		over 3 years	over 9 years
<200	<10,000	14%	64%
	10,000-30,000	50%	90%
	>30,000	86%	100%
200-350	<10,000	7%	66%
	10,000-30,000	36%	85%
	>30,000	64%	93%
>350	<10,000	7%	54%
	10,000-30,000	15%	74%
	>30,000	40%	85%

Mellors JW, Science. 1996;272:1167-70

The Inflammatory Response to HIV: A Silent Killer

- The immune response includes
  - Increased T-cell activation
  - Secretion of pro-inflammatory agents
  - Increases in markers of inflammation (d-dimer, IL-6, hsCRP) – 65-70% higher in HIV-infected[1]
- Inflammatory cascade correlates with increased morbidity and mortality[2]
  - Association with cardiovascular disease, non-AIDS mortality, even at high CD4+ counts
  - Mitigated by antiretroviral therapy

[1]Baker J, JID 2010: 201(2): 285-292 [2]SMART, NEJM 2006: 355; 2283-96

“Non-AIDS” Morbidity and Mortality

- “Non-AIDS” events are an increasing cause of morbidity & mortality
  - Cardiovascular, renal, hepatic disease[1]
  - Malignancies: anal, vaginal, liver, lung, Hodgkin’s lymphoma, melanoma, oropharyngeal, leukemia, colorectal, renal[2]
- All-cause mortality is higher for Non-AIDS than AIDS events (6-month mortality)[3]
  - AIDS event = 4.7%
  - Non-AIDS event = 13.4%

[1]SMART, NEJM 2006: 355; 2283-96

[2]Patel P, Annals 2008:148:728-736 [3]Neuhaus J, AIDS 2010: 24(5):697-706

Hypothesis: HIV and Non-AIDS Disease Risk

Magnitude of absolute risk ↑ depends on other factors

Neaton J, IAS 2007: MOSY202

Adjusted Odds Ratios Associated with a 0.15 µg/mL Increase in D-dimer

Event	No. Events	Adj. OR	95% CI	P-value
All Deaths	74	1.23	1.07-1.42	.004
Major CVD	59	1.12	1.01-1.24	.04
AIDS	75	1.40	1.19-1.66	.0001

Neaton J , IAS 2007: MOSY202

AIDS: 1993 Case Definition

- CD4 $^{+}$ cell count <200 cells/µL, or
- CD4 $^{+}$ cells account for <14% of all lymphocytes, or
- Has been diagnosed with one or more specified AIDS-defining illnesses

Centers for Disease Control. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mort Wkly Rep 1992; 41(RR-17):1-19.

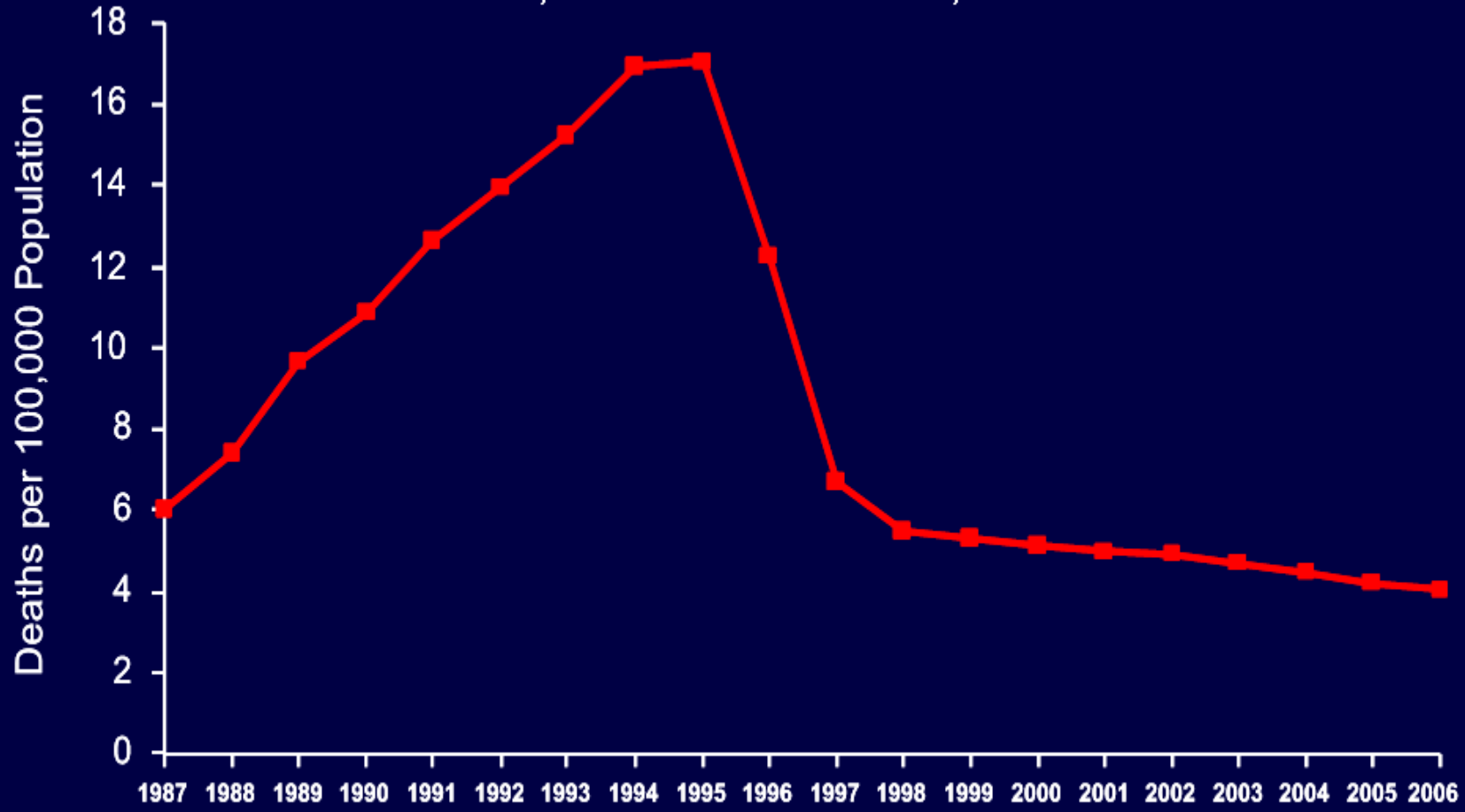
AIDS: 1993 Case Definition

Candidiasis of bronchi, trachea, or lungs	HSV: chronic ulcer(s) (>1-month) or bronchitis, pneumonitis, or esophagitis	Mycobacterium tuberculosis, any site (pulmonary *or extrapulmonary #)
Candidiasis, esophageal	Histoplasmosis, disseminated	Mycobacterium, other species, or unidentified species, disseminated
Cervical cancer, invasive	Isosporiasis, chronic intestinal (>1-month duration)	Pneumocystis jiroveci (formerly carinii) pneumonia
Coccidioidomycosis, disseminated	Kaposi sarcoma	Pneumonia, recurrent
Cryptococcosis, extrapulmonary	Lymphoma, Burkitt	Progressive multifocal leukoencephalopathy
Cryptosporidiosis, chronic intestinal (>1-month)	Lymphoma, immunoblastic	Salmonella septicemia, recurrent
CMV disease (other than liver, spleen, or lymph nodes); CMV retinitis	Lymphoma, primary, of brain (primary central nervous system lymphoma)	Toxoplasmosis of brain (encephalitis)
Encephalopathy, HIV related	Mycobacterium avium complex or disease caused by M kansasii, disseminated	Wasting syndrome caused by HIV infection

Centers for Disease Control. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mort Wkly Rep 1992; 41(RR-17):1-19.

GOOD NEWS…

Trends in Annual Age-Adjusted* Rate of Death due to HIV Disease, United States, 1987–2006



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.
*Standard: age distribution of 2000 US population

AND BAD NEWS!

The median CD4+ count at entry to care = 327 cells/μL in the NA-ACCORD cohort (2007) is below the level at which all current guidelines recommend beginning antiretroviral treatment !

Althoff K, CID 2010:50:1512-20

Therefore…

TEST, LINK TO CARE, TREAT!