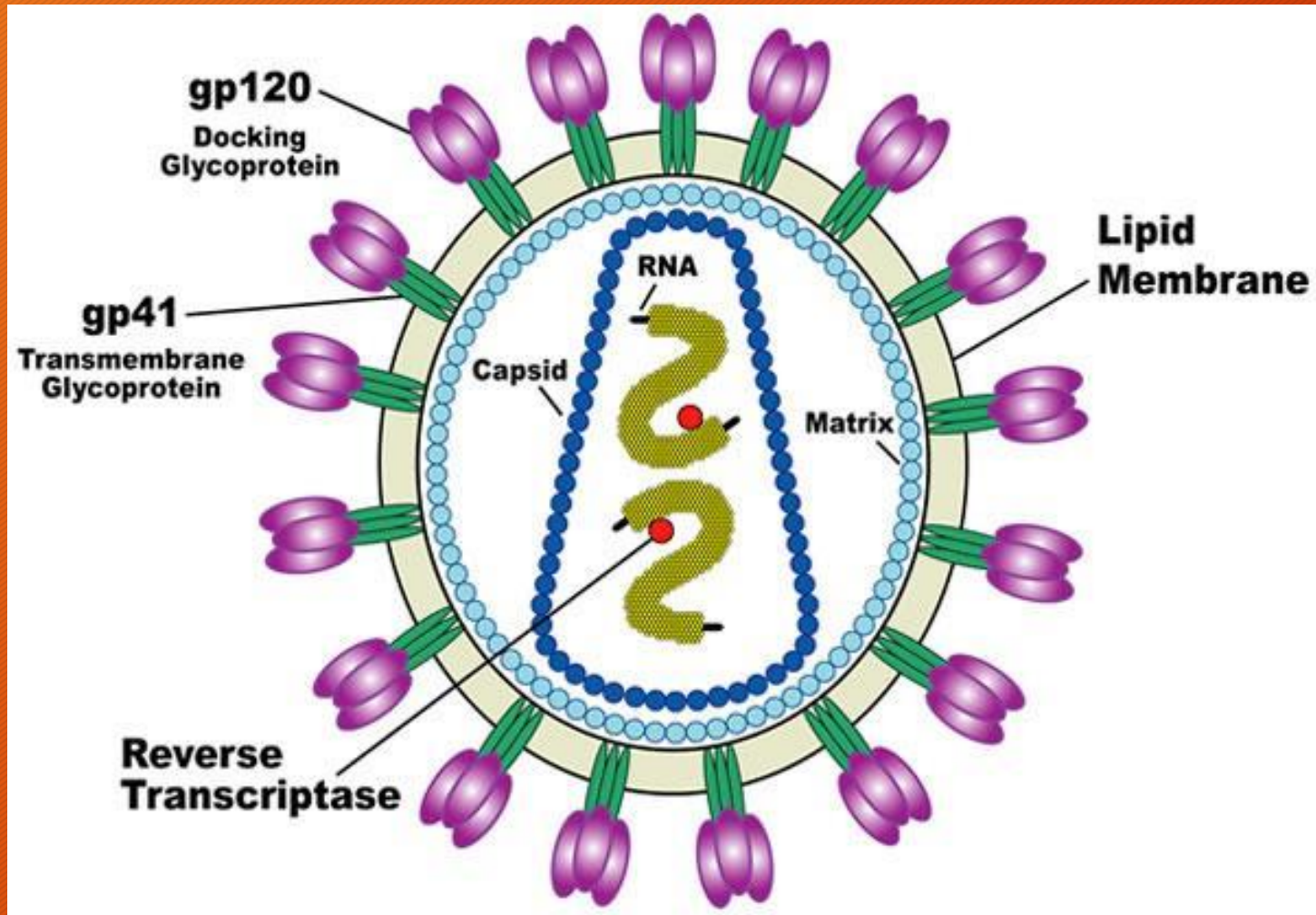
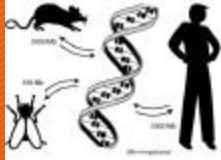


HIV: Past, Present and Future

- Columbus, December 7, 2018
- Global Infectious Disease Initiative Yearly Meeting

Jeffrey L. Stephens, MD, FACP, FIDSA
Professor and Chair Department of Medicine
Mercer University School of Medicine
Navicent Health Medical Center
Macon, GA

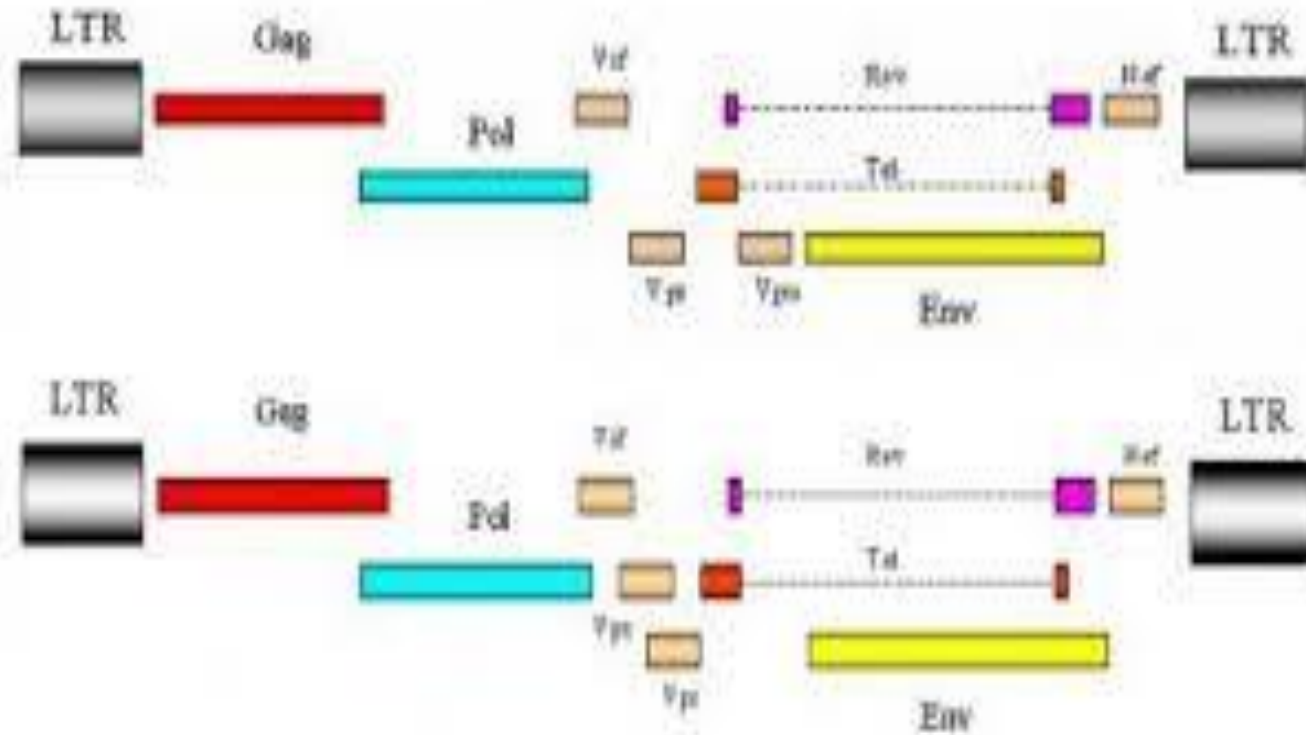




GENERAL GENOMIC COMPARISONS

Organism	Genome Size (Bases)	Estimated Genes
Human (<i>Homo sapiens</i>)	3 billion	30,000
Laboratory mouse (<i>M. musculus</i>)	2.6 billion	30,000
Thale cress (<i>A. thaliana</i>)	100 million	25,000
Roundworm (<i>C. elegans</i>)	97 million	19,000
Fruit fly (<i>D. melanogaster</i>)	137 million	13,000
Yeast (<i>S. cerevisiae</i>)	12.1 million	6,000
Bacterium (<i>E. coli</i>)	4.6 million	3,200
Human immunodeficiency virus (HIV)	9700	9





Genome layouts of HIV-1 (upper) and HIV-2 (lower)

2015

2015

HERV-K

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DEN

HIV₀

1992

100

10⁵

10

10

10

 10^2

Years from present

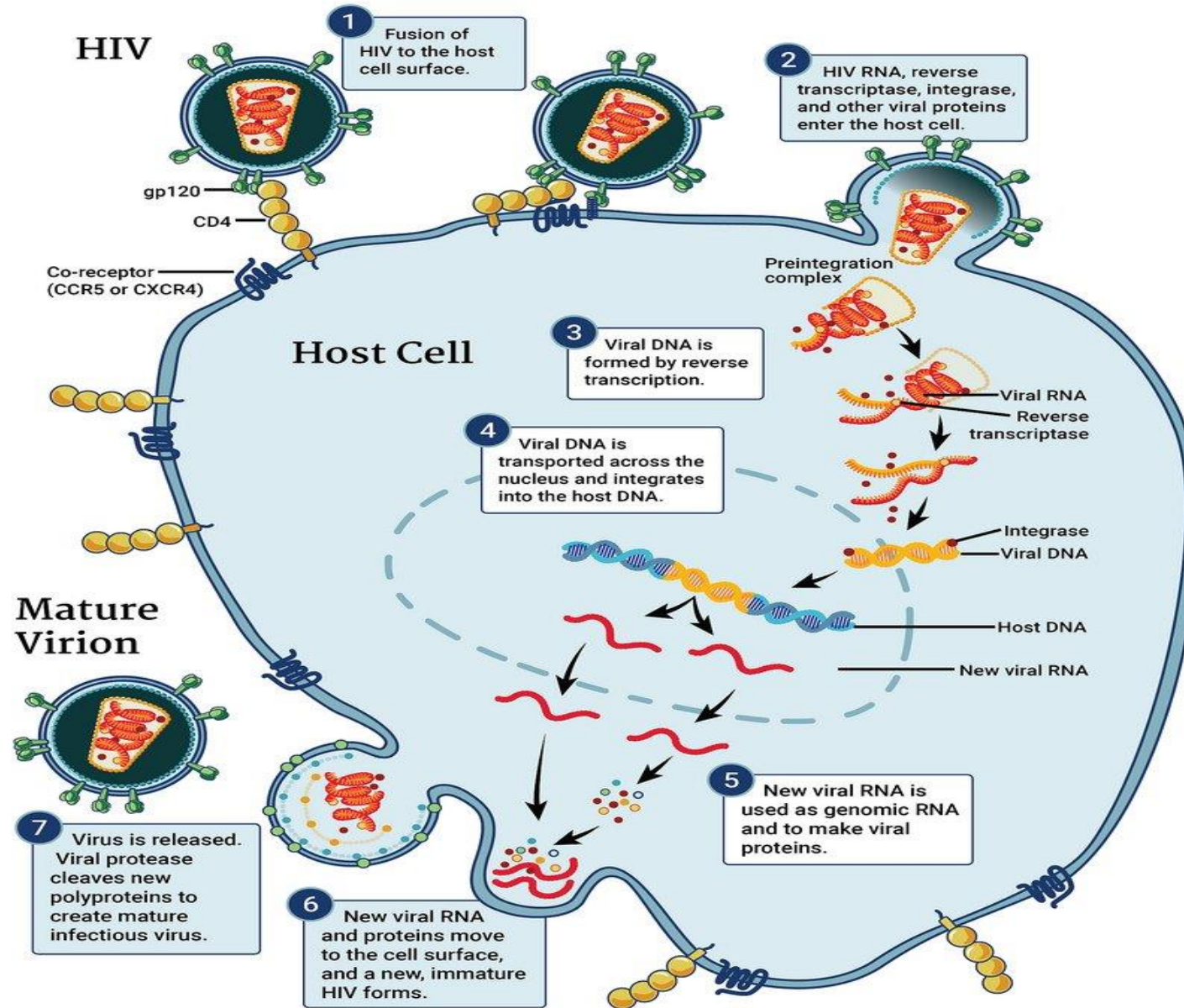
other
hominoids

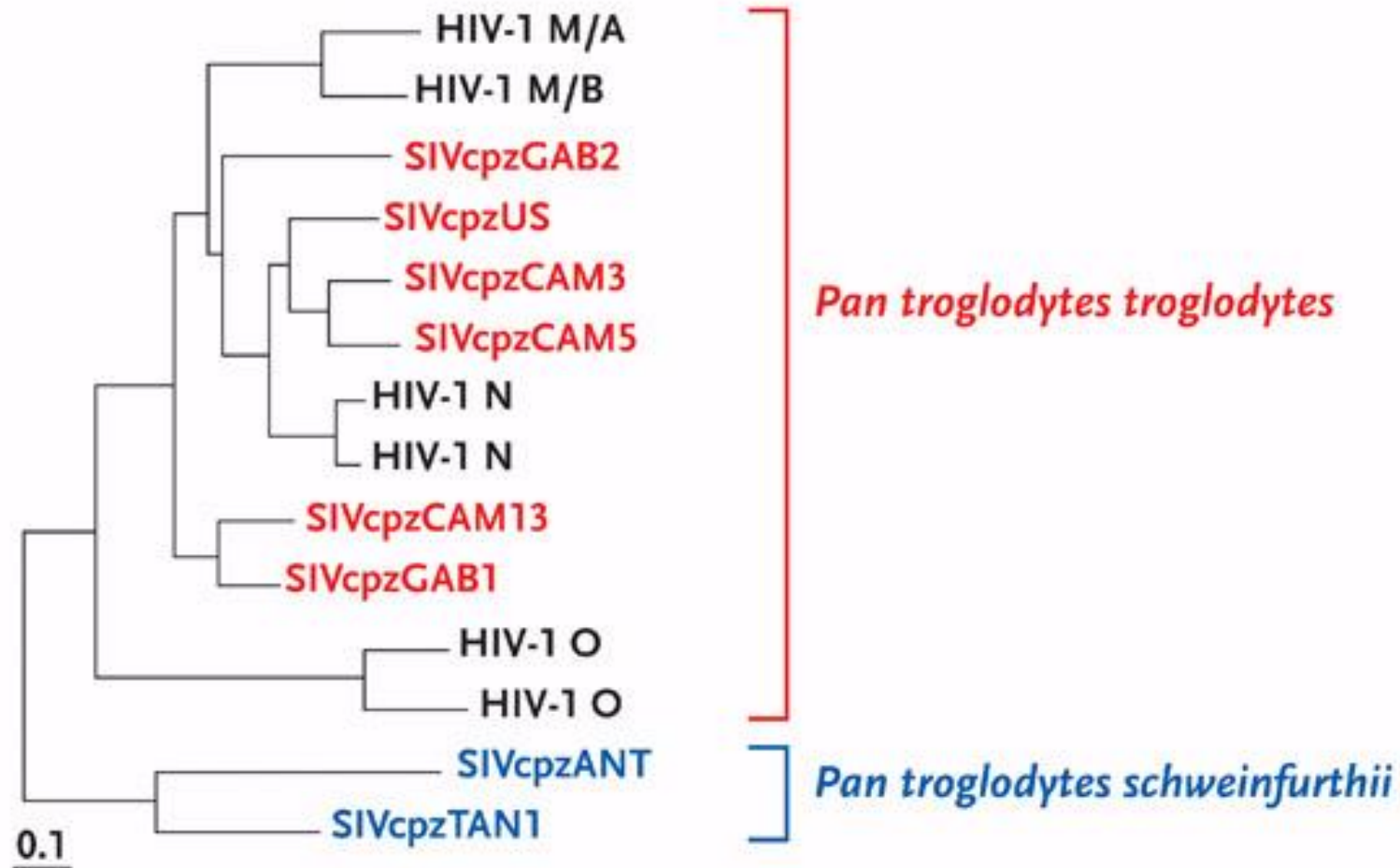
old world
monkeys

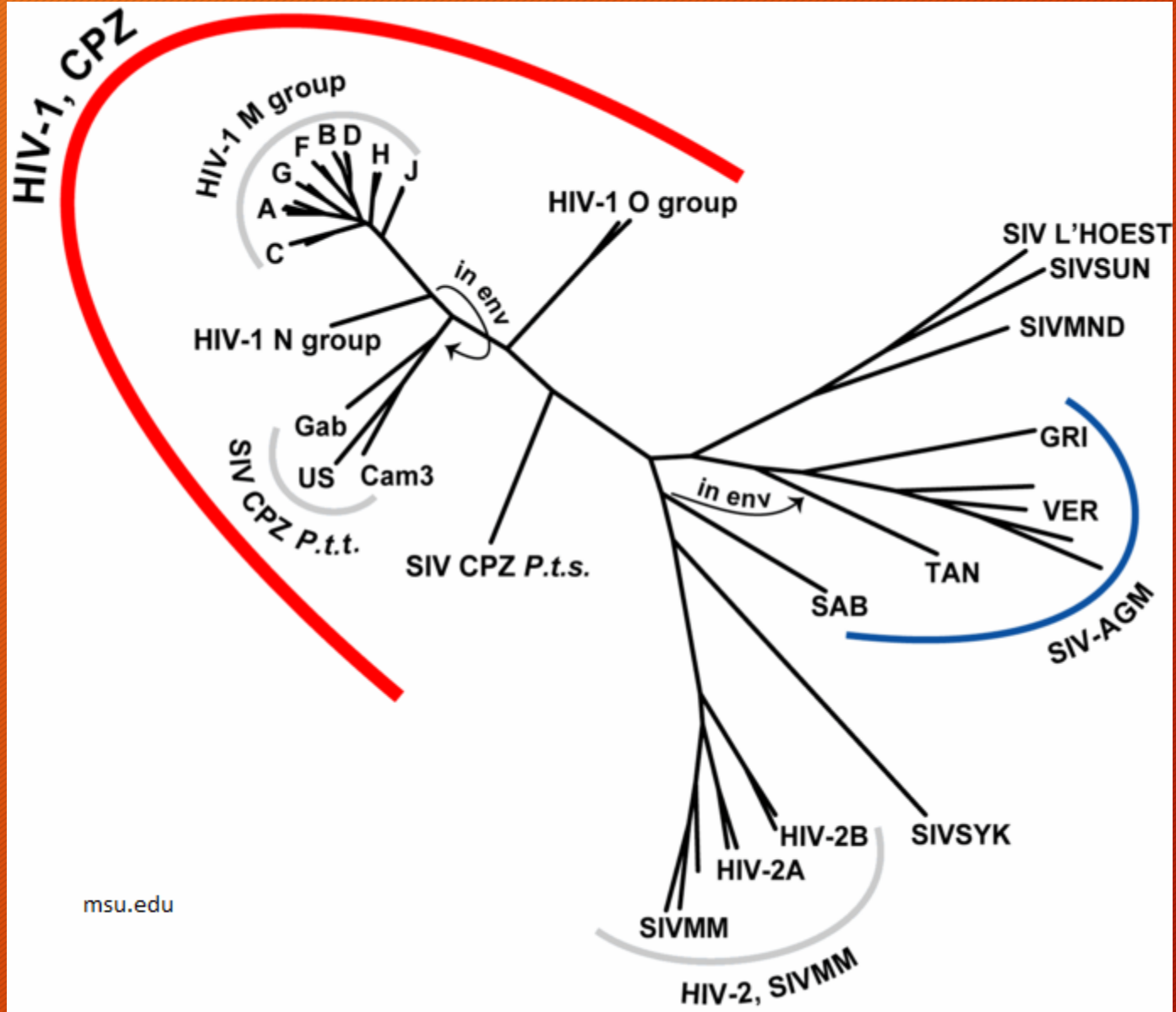
new world
monkeys

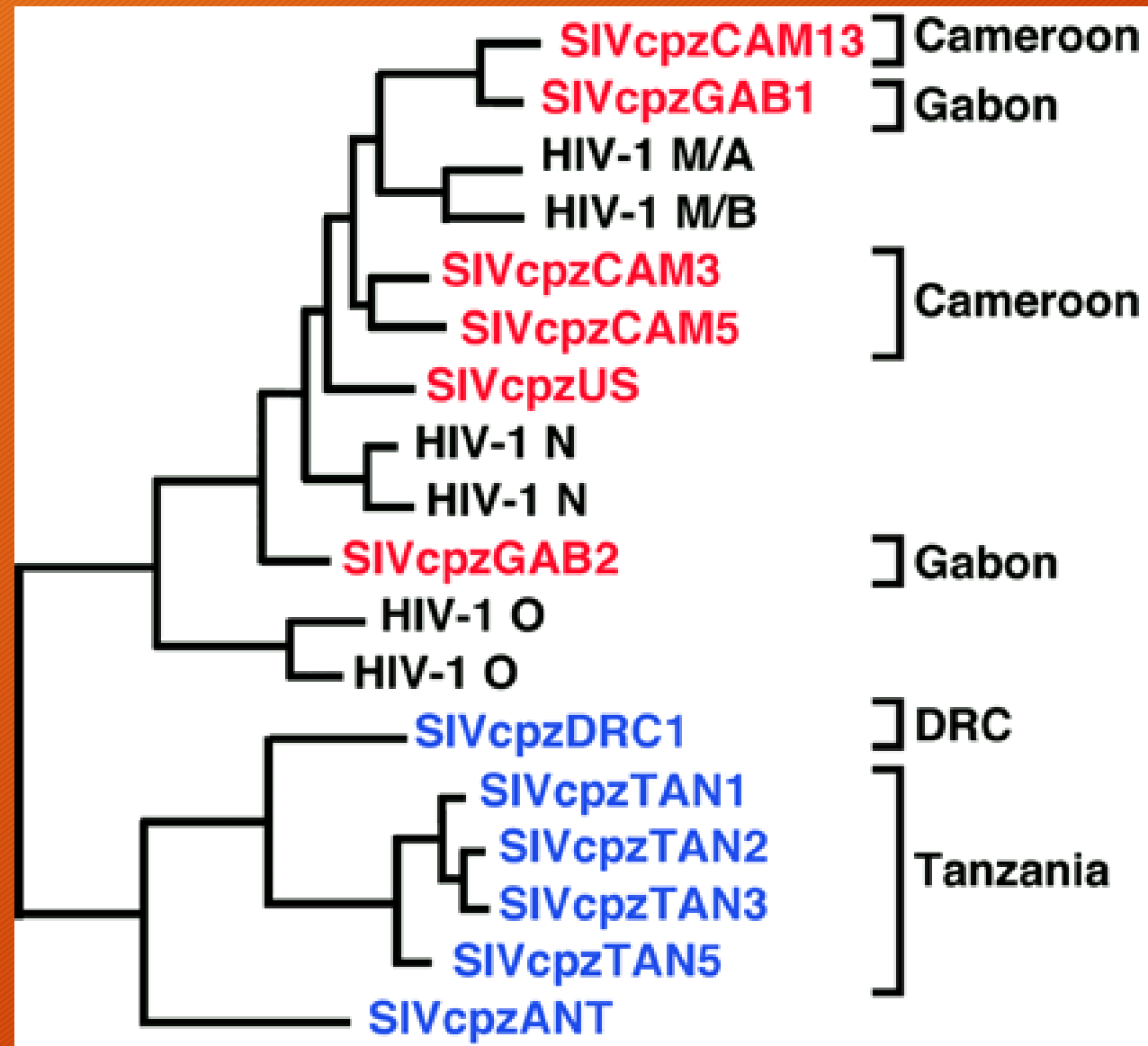
30 25 20 15 10 5

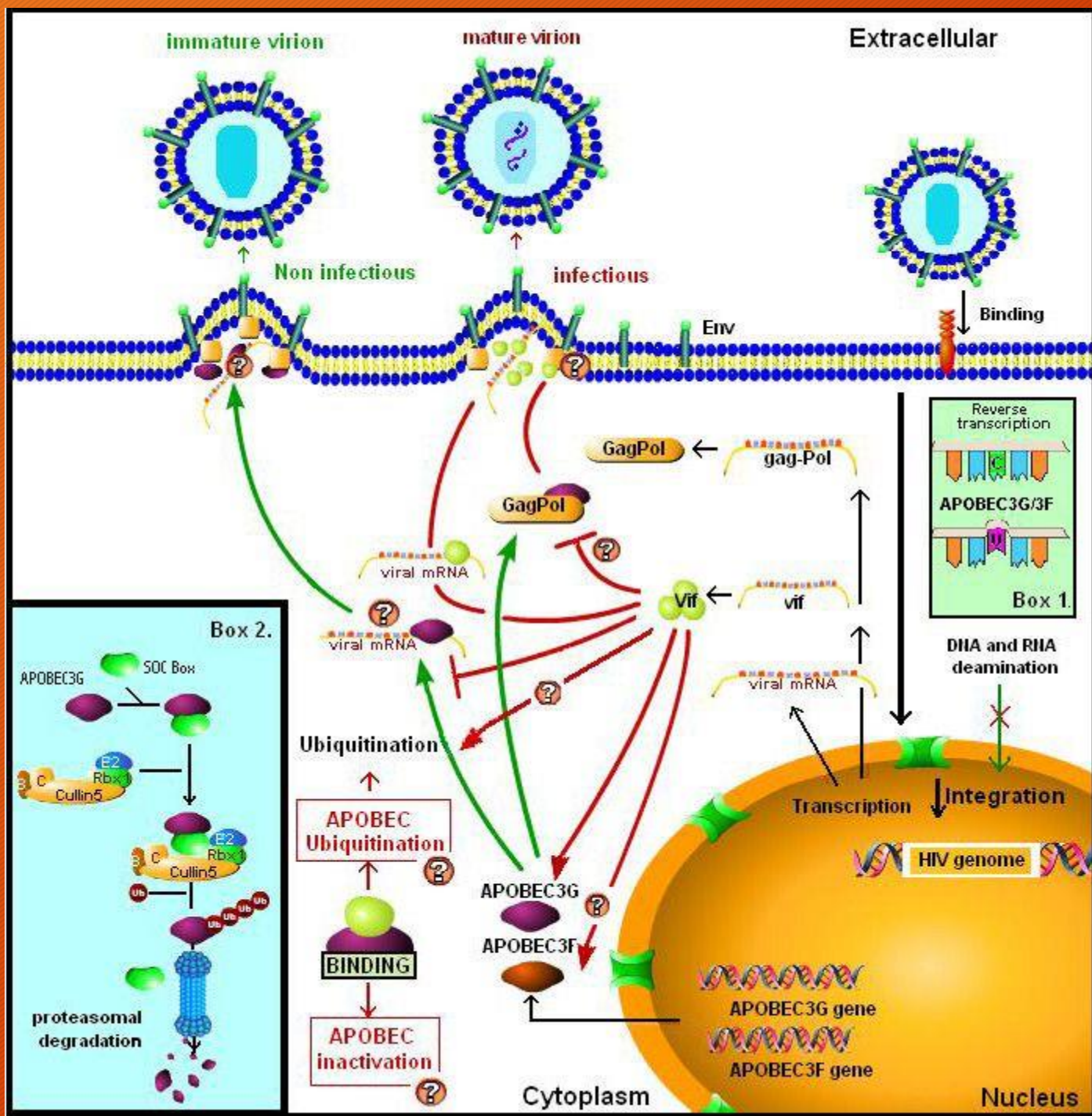
mya

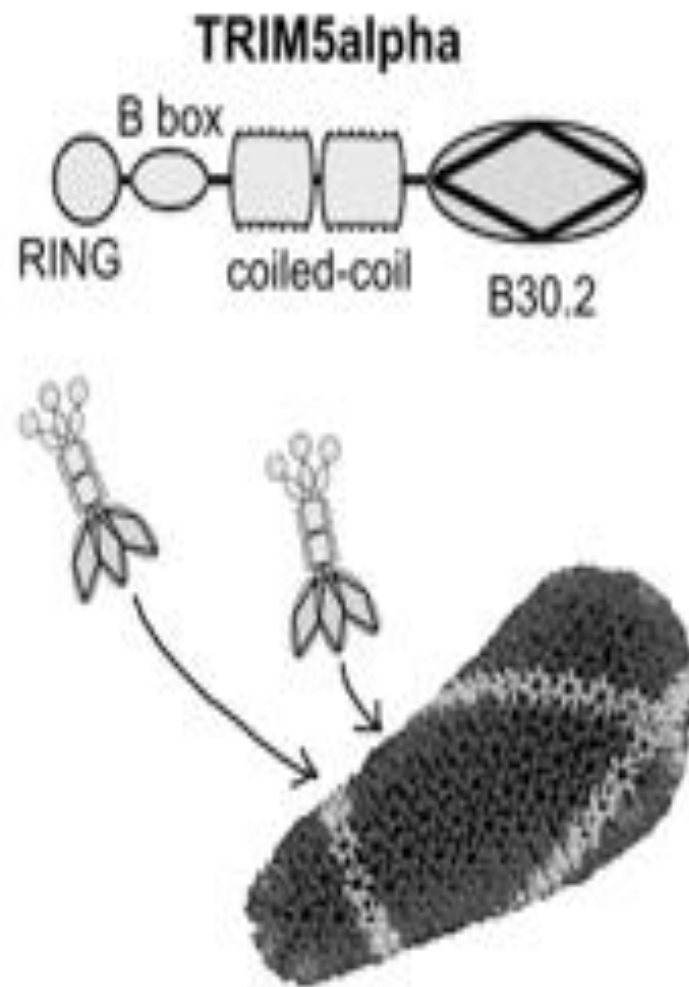
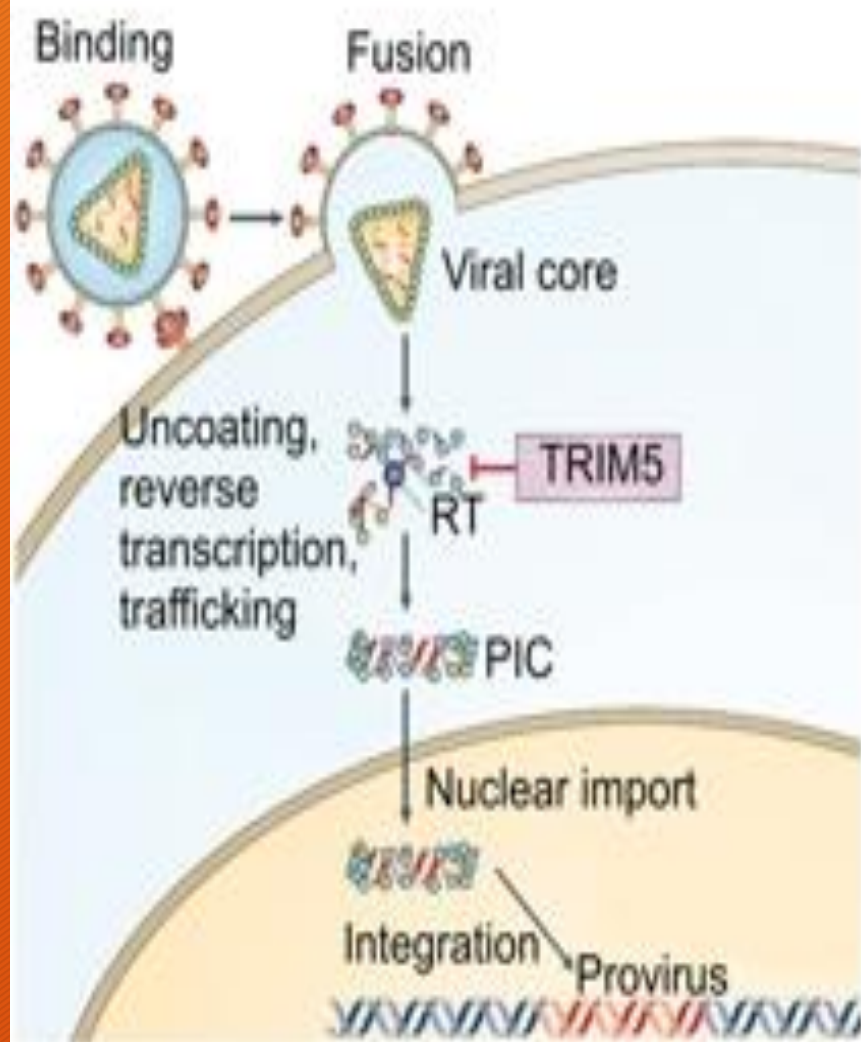


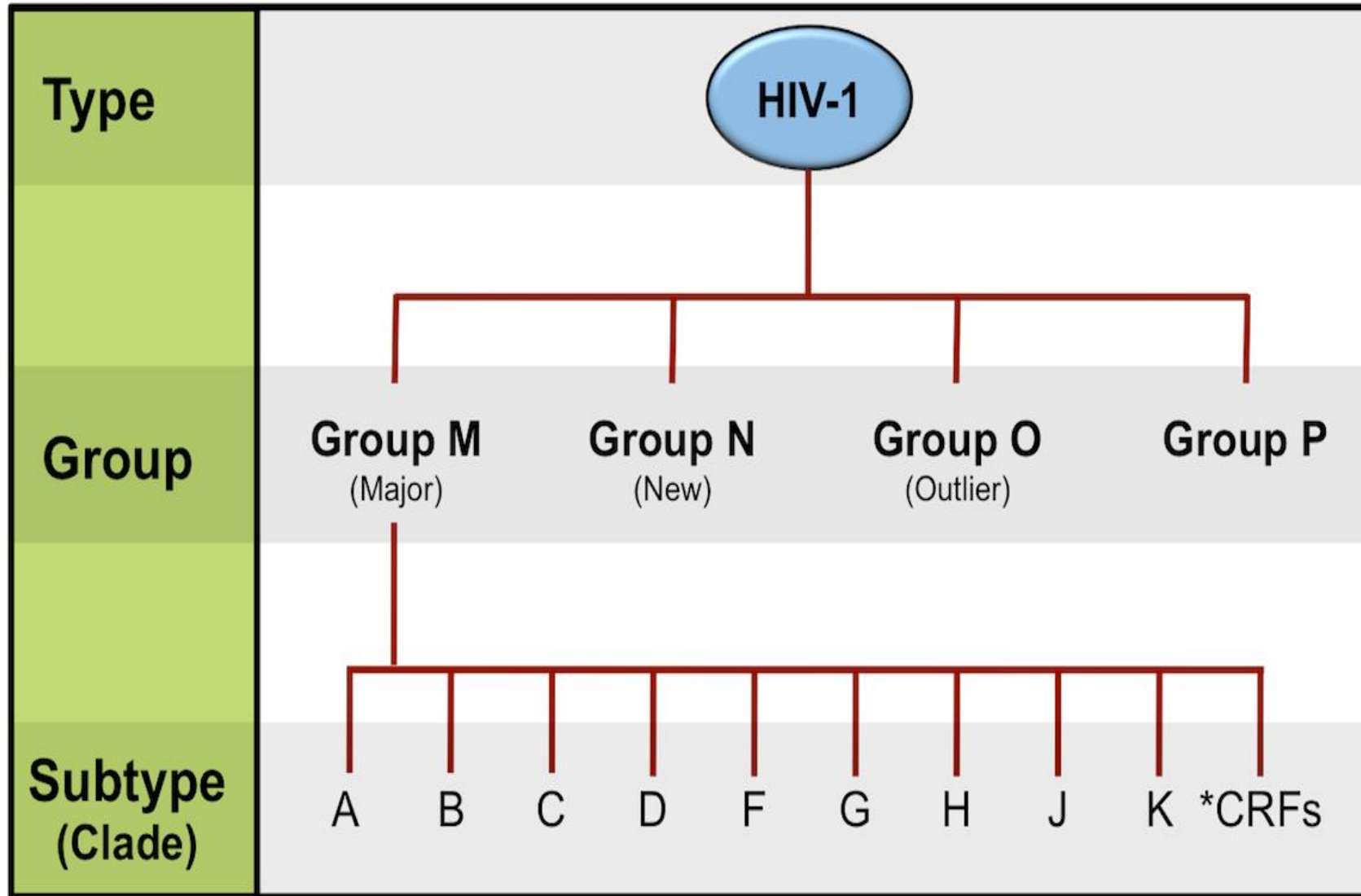




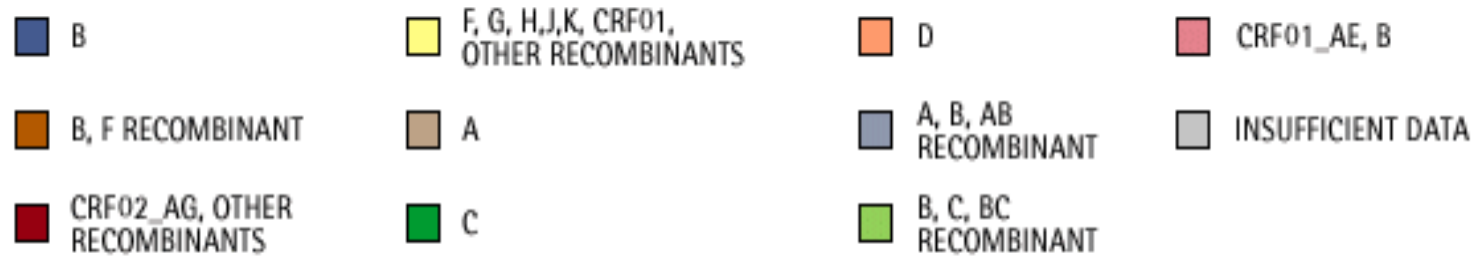
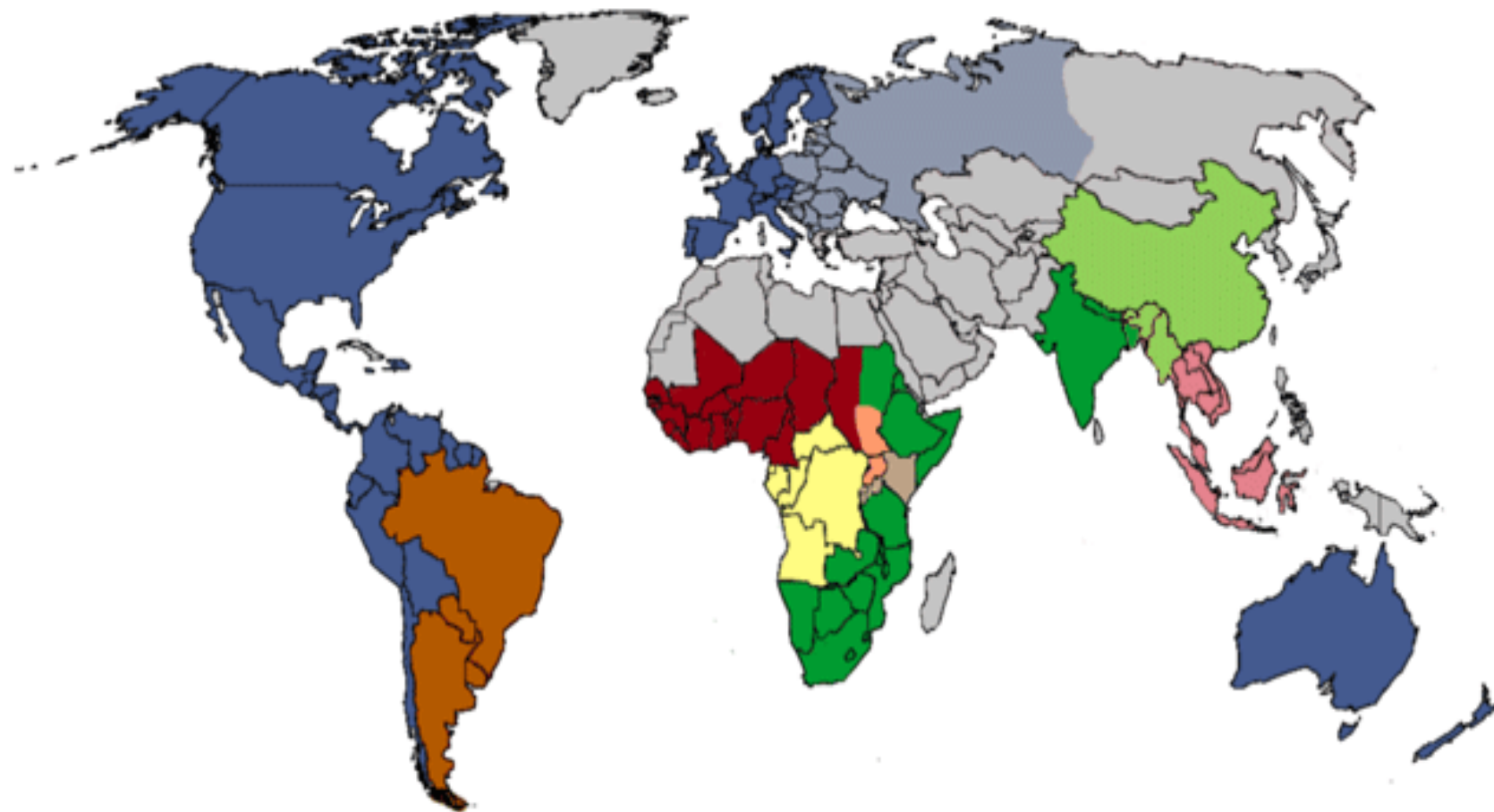








*CRFs = Circulating Recombinant Forms





CENTERS FOR DISEASE CONTROL

June 5, 1981 / Vol. 30 / No. 21

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

	Epidemiologic Notes and Reports
249	Dengue Type 4 Infections in U.S. Travelers to the Caribbean
250	<i>Pneumocystis Pneumonia</i> — Los Angeles
	Current Trends
252	Measles — United States, First 20 Weeks
253	Risk Factor Prevalence Survey — Utah
258	Surveillance of Childhood Lead Poisoning — United States
	International Notes
261	Quarantine Measures

Pneumocystis Pneumonia — Los Angeles

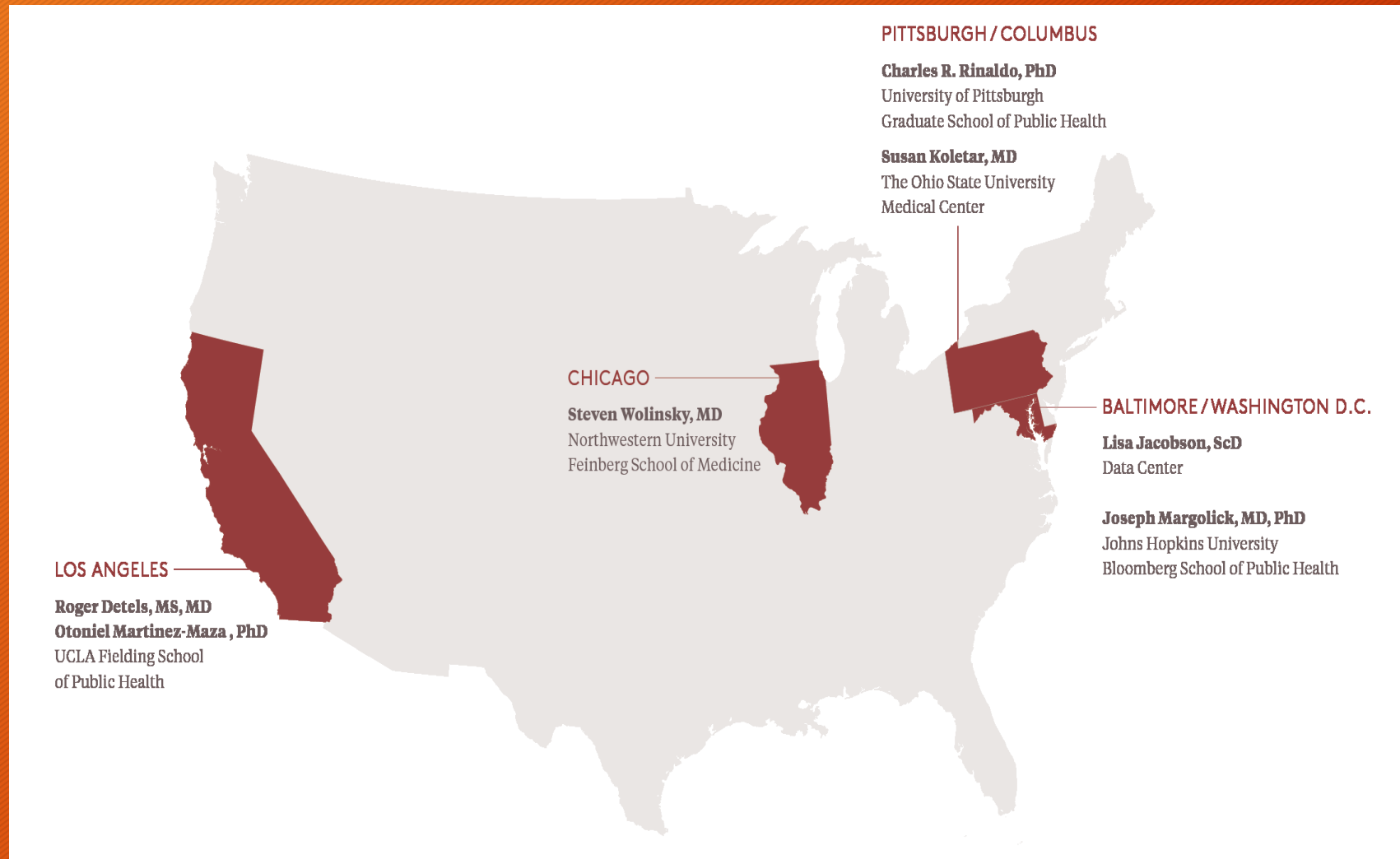
In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with

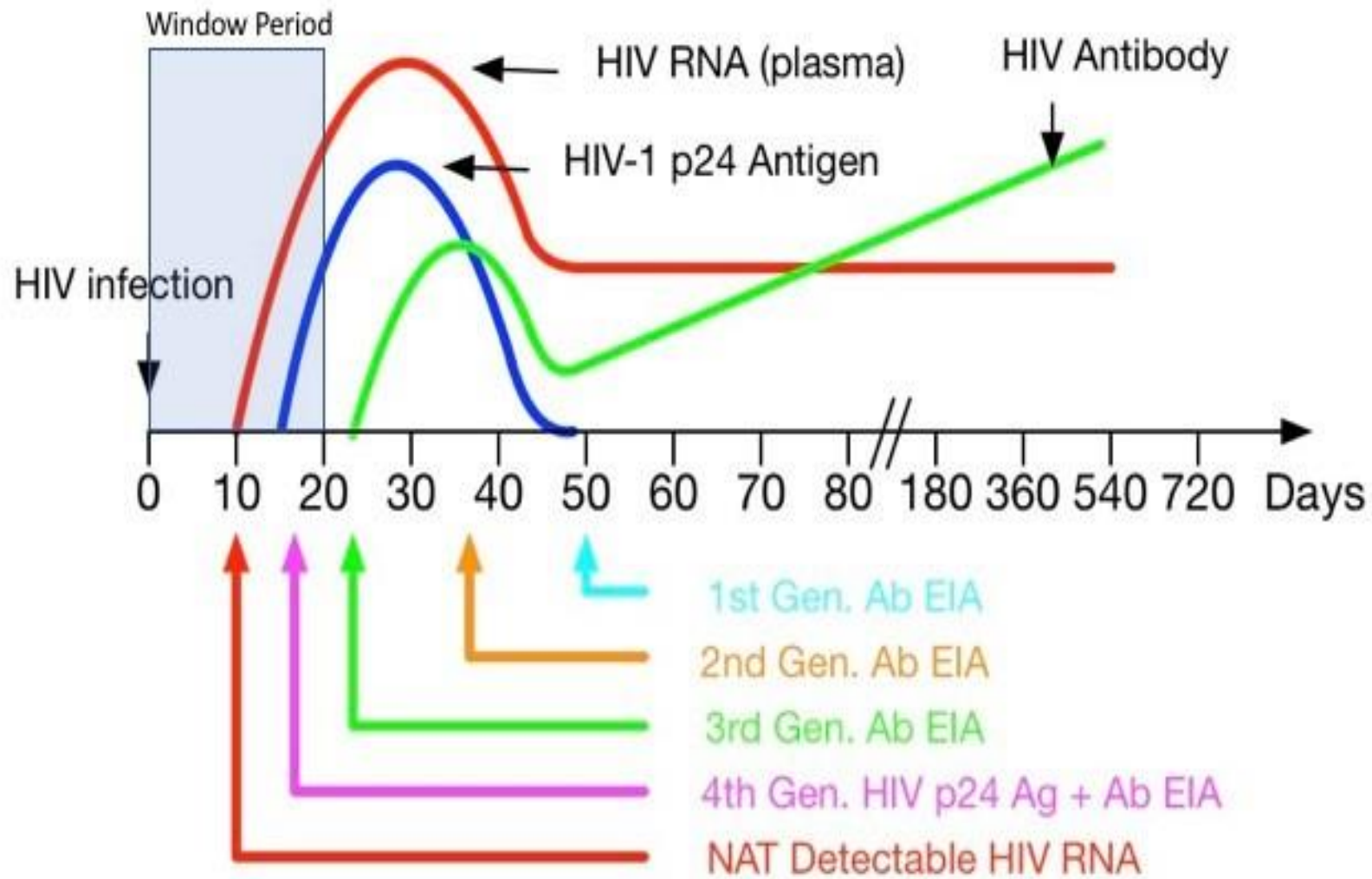


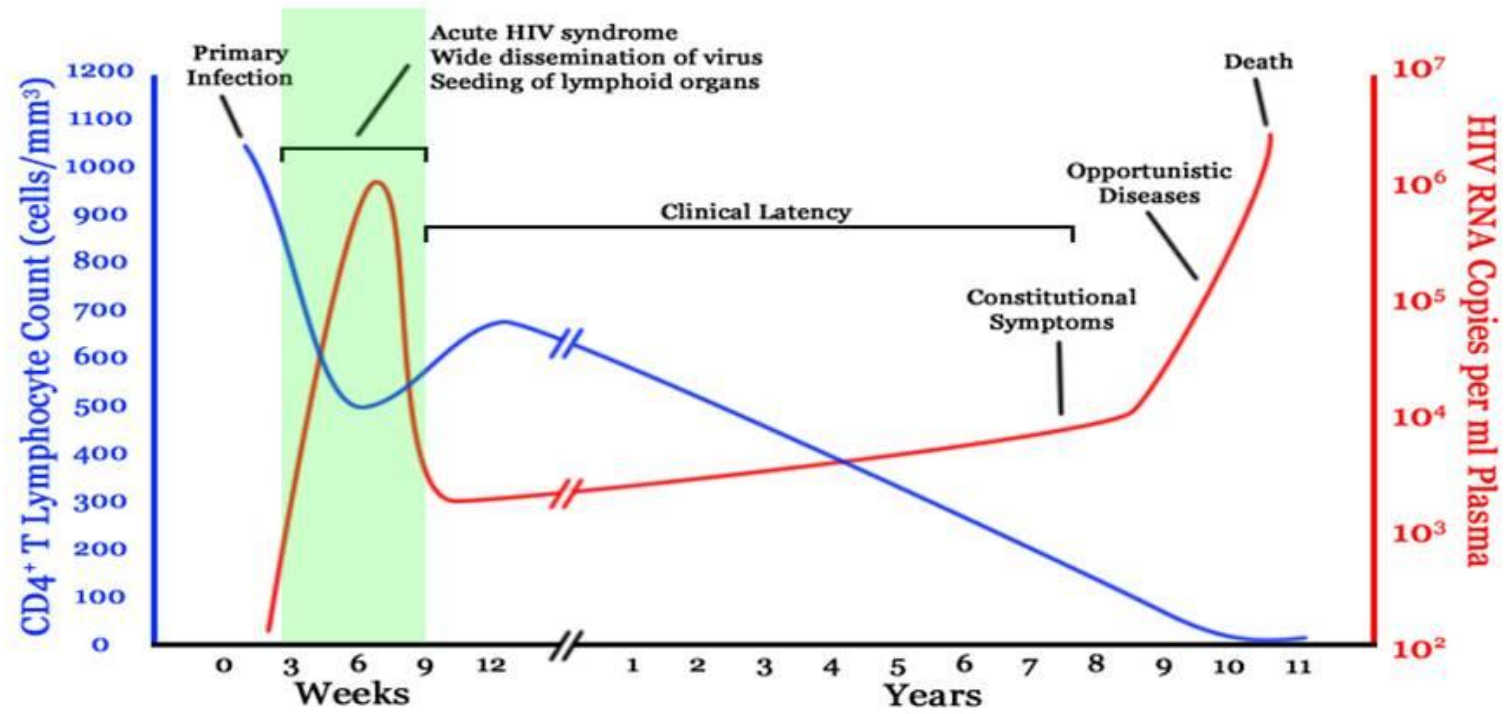
MACS

MULTICENTER AIDS
COHORT STUDY

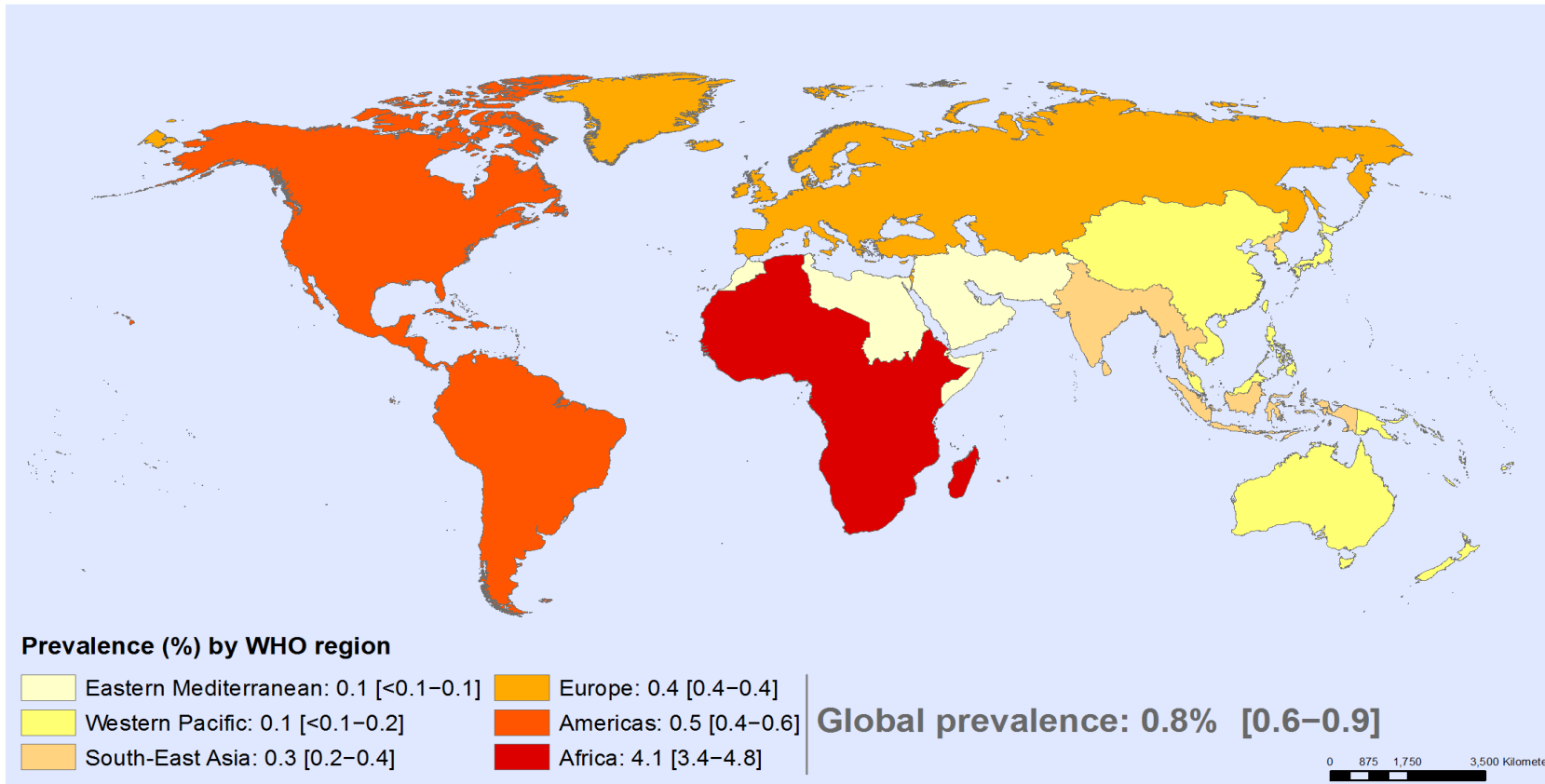








Prevalence of HIV among adults aged 15 to 49, 2017 By WHO region








The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

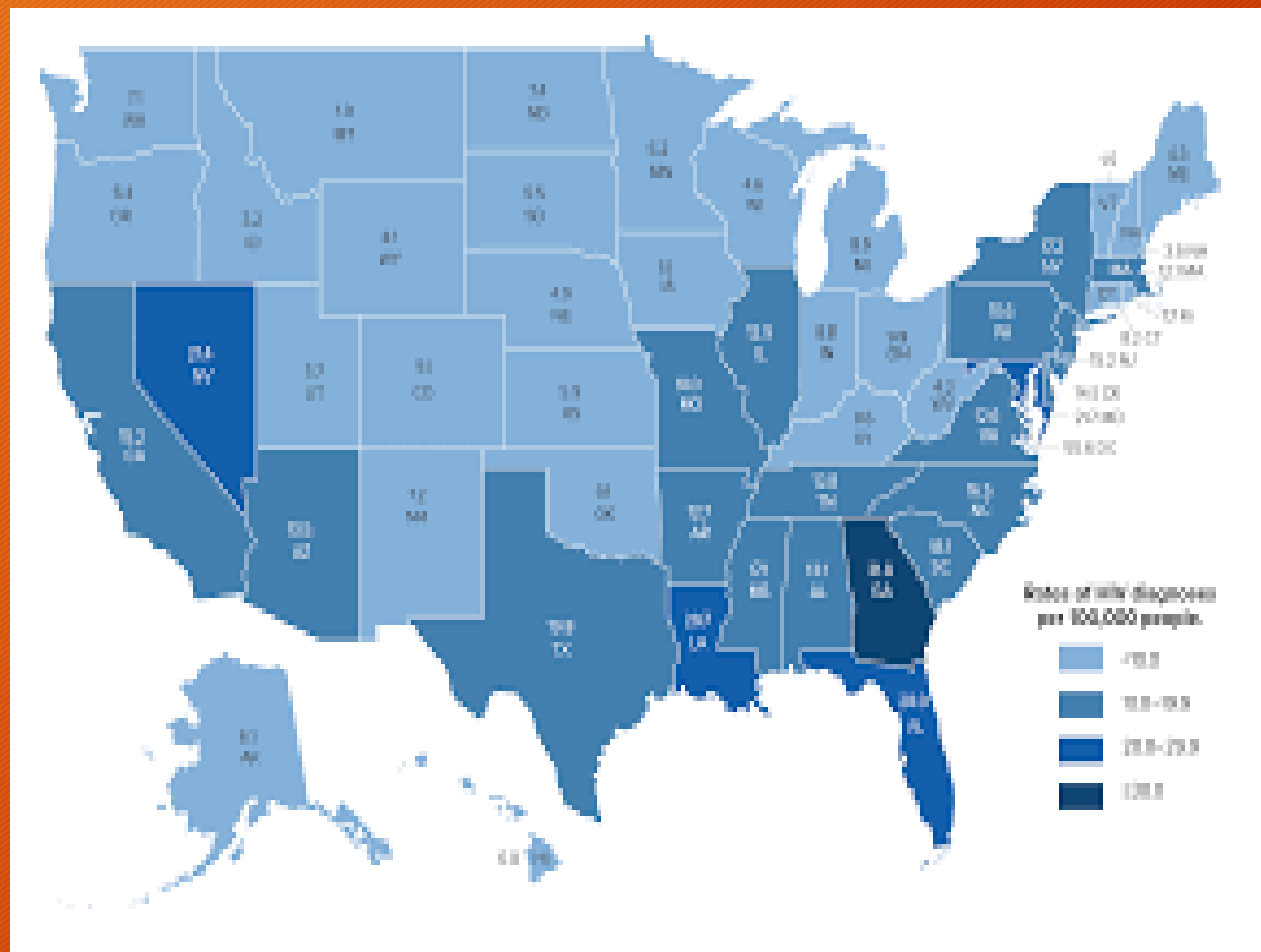


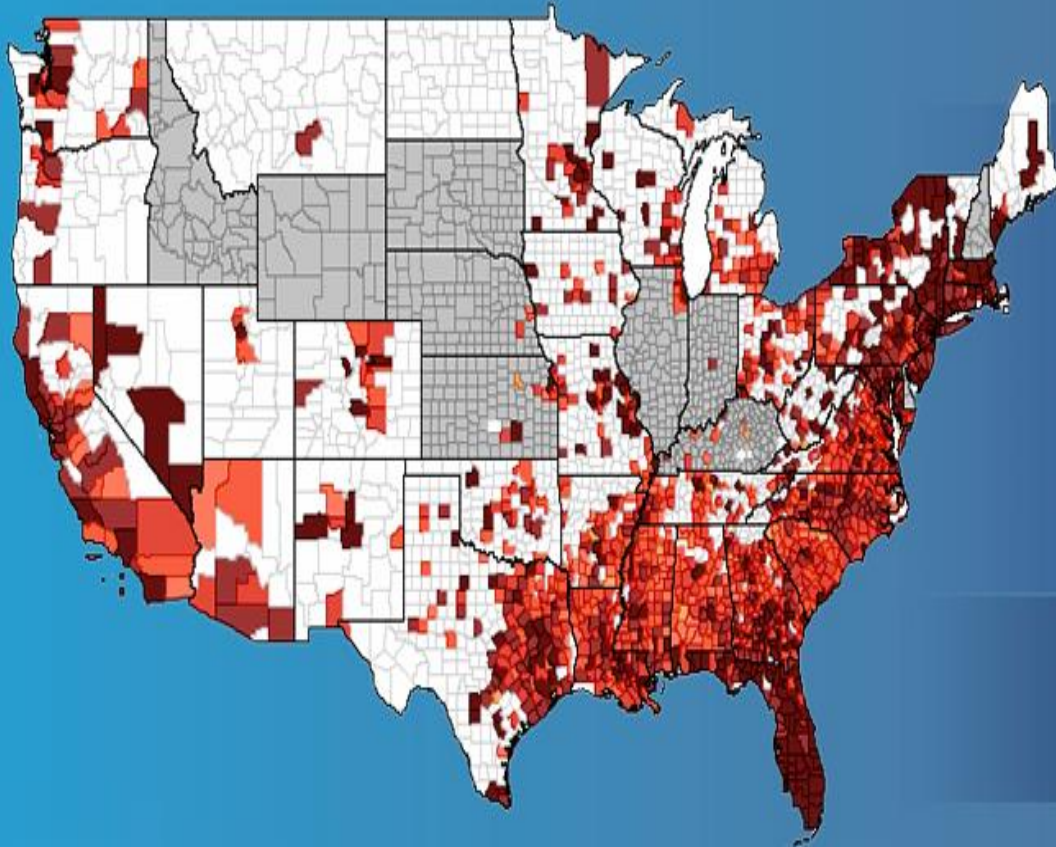
© WHO 2018. All rights reserved.

Summary of the global HIV epidemic (2017)

	People living with HIV in 2017	People newly infected with HIV in 2017	HIV-related deaths 2017
 Total	36.9 million [31.1 million – 43.9 million]	1.8 million [1.4 million – 2.4 million]	940 000 [670 000 – 1.3 million]
 Adults	35.1 million [29.6 million – 41.7 million]	1.6 million [1.3 million – 2.1 million]	830 000 [590 000 – 1.2 million]
 Women	18.2 million [15.6 million – 21.4 million]	–	–
 Men	16.8 million [13.9 million – 20.4 million]	–	–
 Children (<15 years)	1.8 million [1.3 million – 2.4 million]	180 000 [110 000 – 260 000]	110 000 [63 000 – 160 000]

Source: UNAIDS/WHO estimates





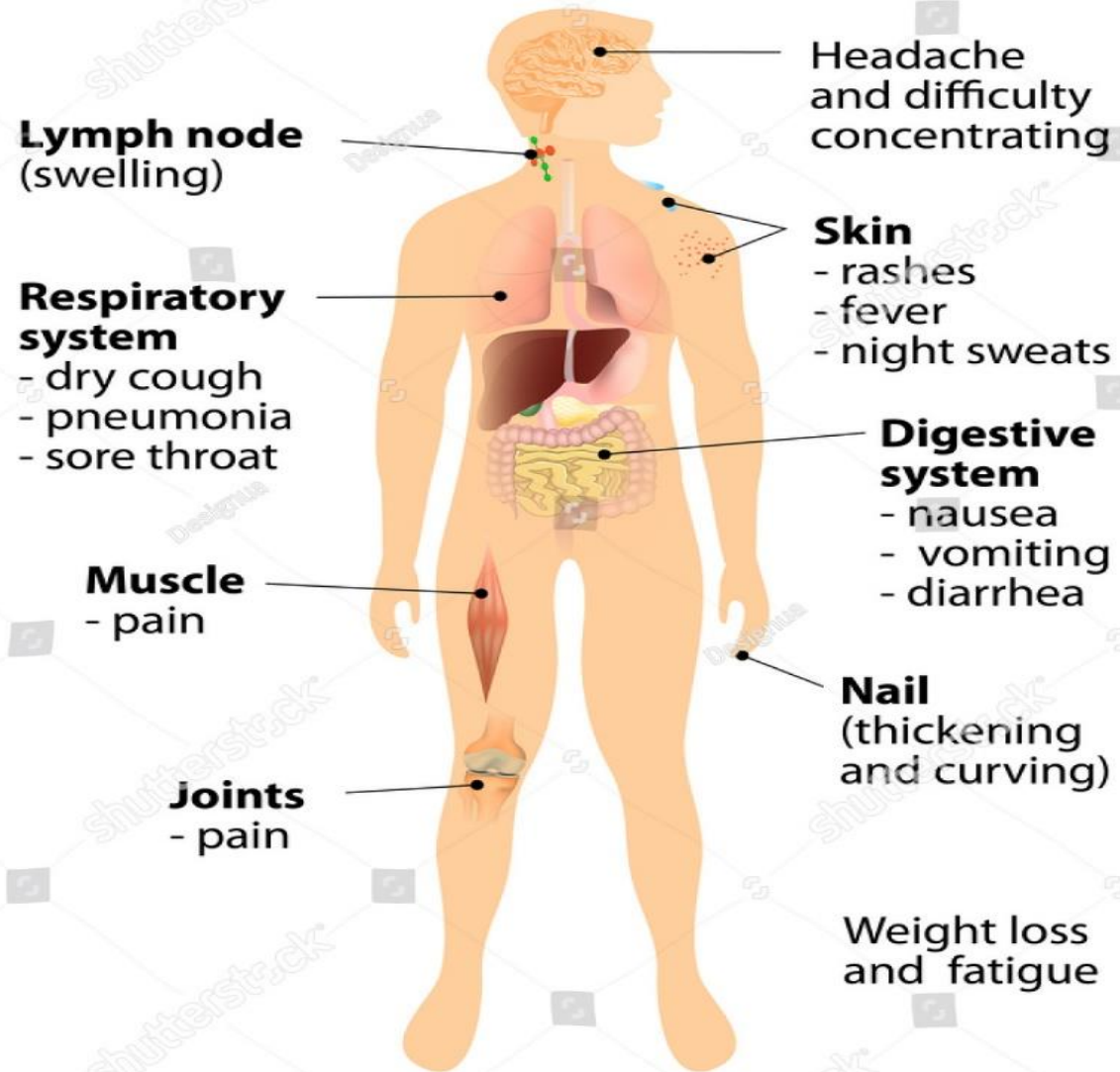
AFRICAN AMERICANS
make up **12%** of the
U.S. population but
accounted for **40%** of
people living with
diagnosed HIV in 2014.

**THAT'S MORE THAN
390,000 PEOPLE.**

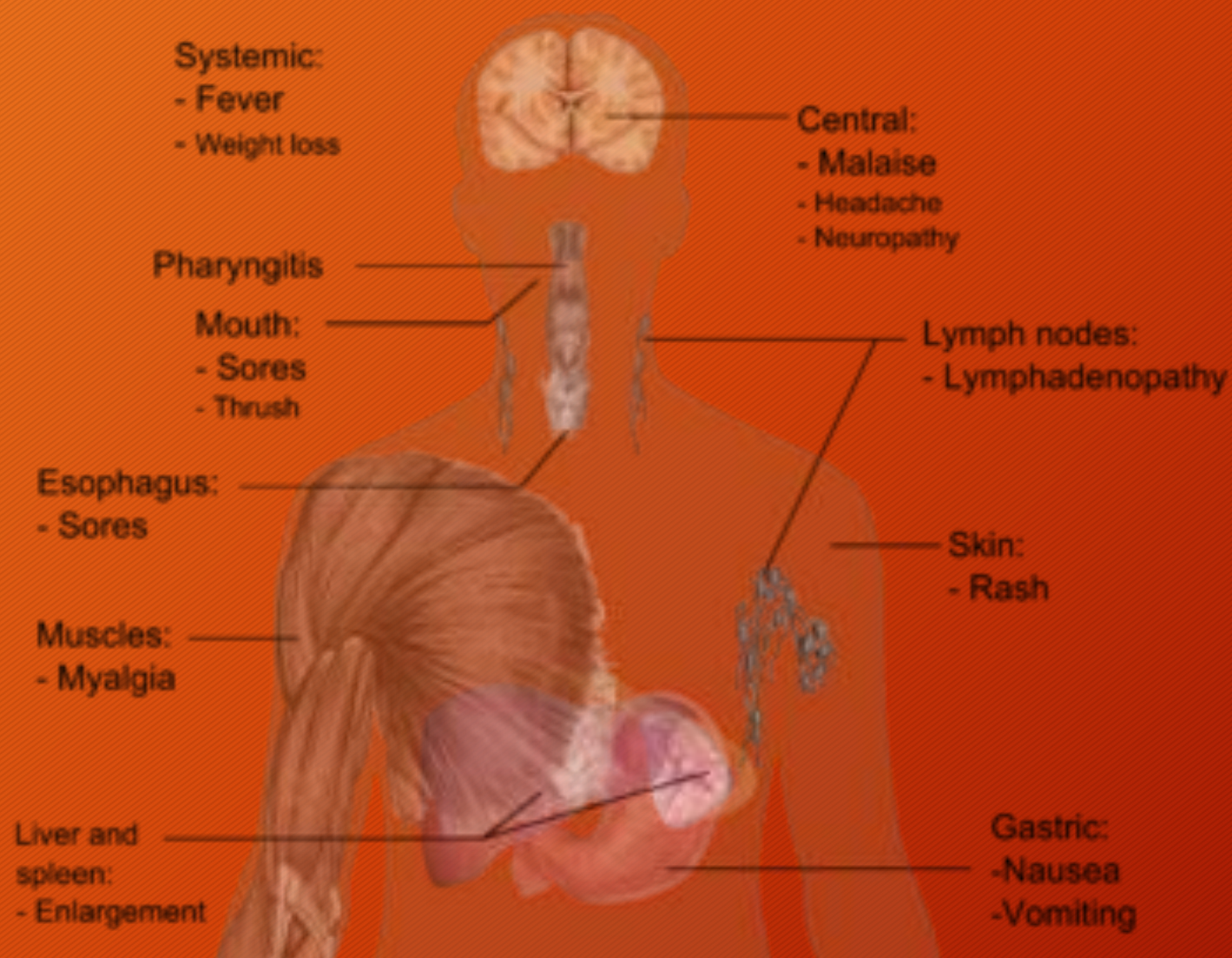
RATES OF BLACK PERSONS LIVING WITH DIAGNOSED HIV, 2014

0-50	51-75	76-100	101-125	126-200	201-325	326-475	476-675	676-1000	1001+
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Symptoms of HIV infection



Main symptoms of Acute HIV infection



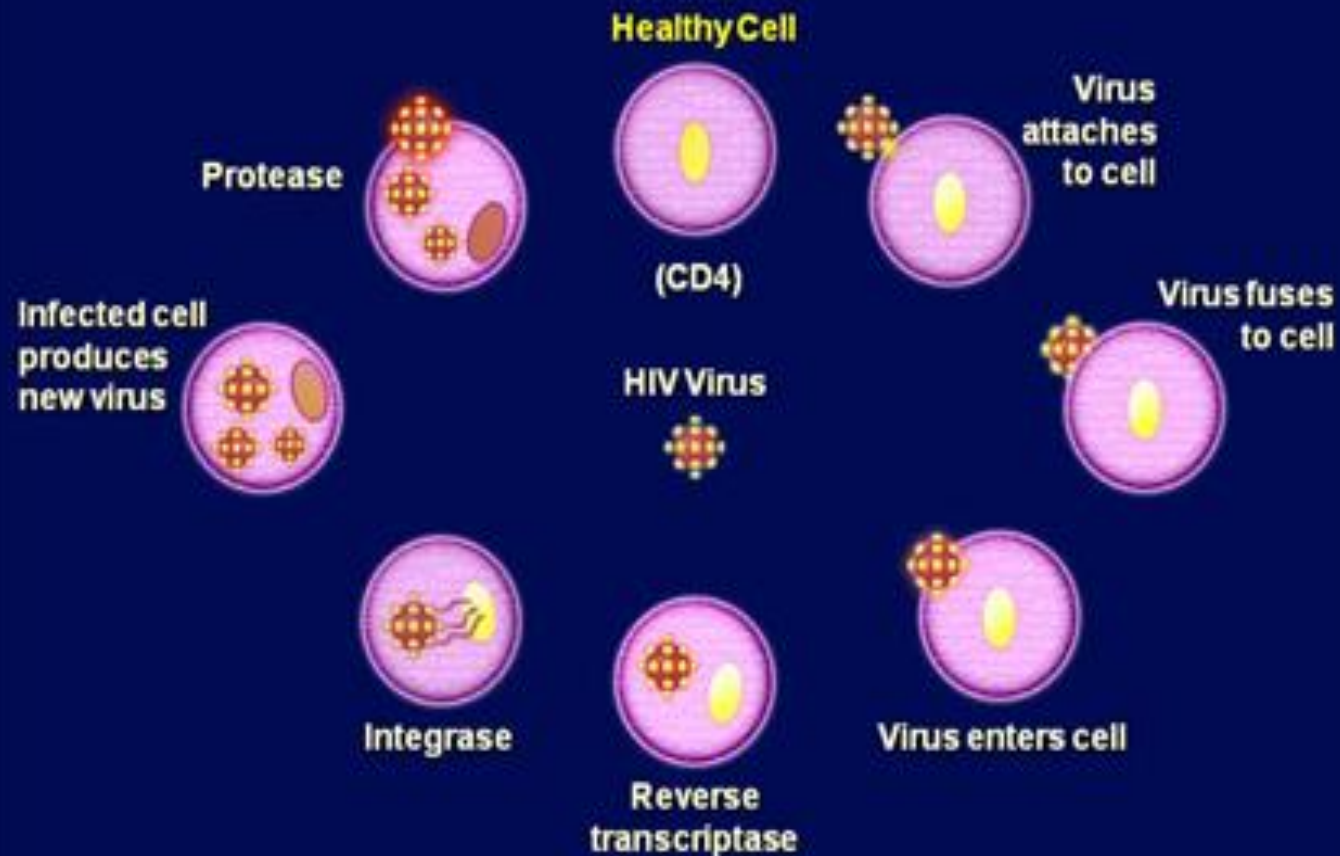
Classification System-HIV/AIDS

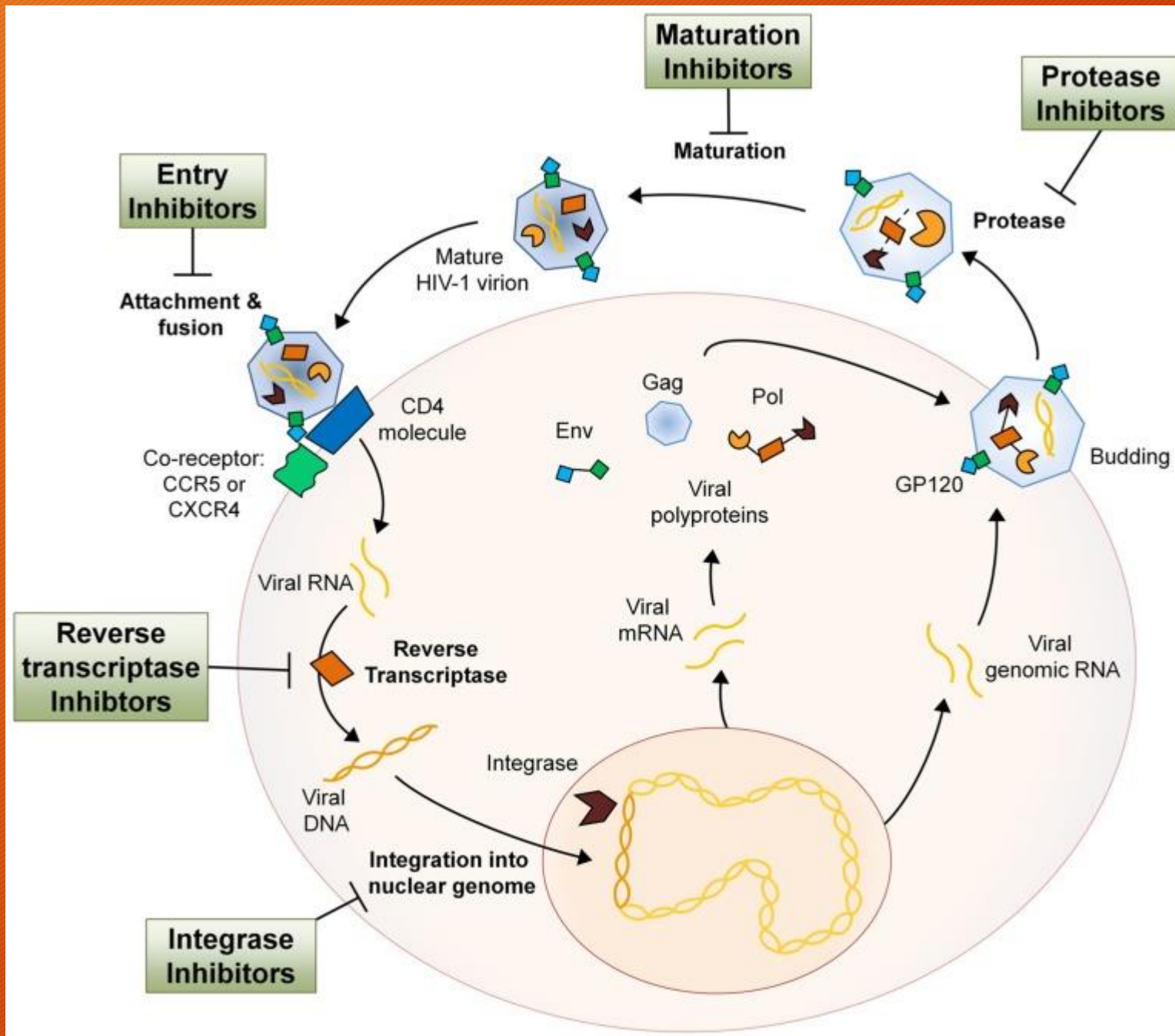
Adolescents & Adults

CD4 T-CELL COUNTS CATEGORY	CLINICAL CATEGORY A (asymptomatic)	CLINICAL CATEGORY B (not A or C category)	CLINICAL CATEGORY C (AIDS indicator condition)
1 ≥500/mm ³	A1	B1	C1
2 200-499/mm ³	A2	B2	C2
3 <200/mm ³	A3	B3	C3

CDC, 1993

Targets for HIV Meds





Antiretroviral therapy for HIV infection

In the 1990s



Up to 20 pills daily, taken at different intervals throughout the day

Today



As little as 1 pill per day, delivering multiple drugs

FDA Approval of HIV Medicines

'80-'84	1981 First AIDS cases reported in the United States			
'85-'89	1987 Zidovudine (NRTI)			
'90-'94	1991 Didanosine (NRTI)	1992 Zalcitabine (NRTI)	1994 Stavudine (NRTI)	
'95-'99	1995 Lamivudine (NRTI) Saquinavir (PI)	1996 Indinavir (PI) Nevirapine (NNRTI) Ritonavir (PI)	1997 Combivir (FDC) Delavirdine (NNRTI) Nelfinavir (PI)	1998 Abacavir (NRTI) Efavirenz (NNRTI)
'00-'04	2000 Didanosine EC (NRTI) Kaletra (FDC) Trizivir (FDC)	2001 Tenofovir DF (NRTI)	2003 Atazanavir (PI) Emtricitabine (NRTI) Enfuvirtide (FI) Fosamprenavir (PI)	2004 Epzicom (FDC) Truvada (FDC)
'05-'09	2005 Tipranavir (PI)	2006 Atripla (FDC) Darunavir (PI)	2007 Maraviroc (CA) Raltegravir (INSTI)	2008 Etravirine (NNRTI)
'10-'14	2011 Complera (FDC) Nevirapine XR (NNRTI) Rilpivirine (NNRTI)	2012 Stribild (FDC)	2013 Dolutegravir (INSTI)	2014 Cobicistat (PE) Elvitegravir (INSTI) Triumeq (FDC)
'15-'18	2015 Evotaz (FDC) Genvoya (FDC) Prezcobix (FDC)	2016 Descovy (FDC) Odefsey (FDC)	2017 Juluca (FDC)	2018 Biktarvy (FDC) Cimduo (FDC) Delstrigo (FDC) Doravirine (NNRTI) Ibalizumab (PAI) Symfi (FDC) Symfi Lo (FDC) Symtuza (FDC)

Drug Class Abbreviations:

CA: CCR5 Antagonist; **FDC:** Fixed-Dose Combination; **FI:** Fusion Inhibitor; **INSTI:** Integrase Inhibitor; **NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitor; **NRTI:** Nucleoside Reverse Transcriptase Inhibitor; **PE:** Pharmacokinetic Enhancer; **PI:** Protease Inhibitor; **PAI:** Post-Attachment Inhibitor

Note: Drugs in gray are not available in the United States and/or are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines. These drugs may still be used in fixed-dose combination formulations.

地址: 廣東省廣州市東莞道 10 號 5 樓 505 室 電話: 020-83333333

Intuitive (SPV) spiders showed for both how they are able to tell
 judgement and those who are not. This spider refers to the computer
 manual system, including with strong and strong variations.

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[illegible]

DHHS, IAS-USA Guidelines: Recommended Regimens for First-line ART

Class	DHHS ^[1]	IAS-USA ^{*[2]}
INSTI	<ul style="list-style-type: none">▪ BIC/TAF/FTC▪ DTG/ABC/3TC▪ DTG + (TAF or TDF)/FTC▪ EVG/COBI/(TAF or TDF)/FTC▪ RAL + (TAF or TDF)/FTC	<ul style="list-style-type: none">▪ DTG/ABC/3TC▪ DTG + TAF/FTC▪ EVG/COBI/TAF/FTC▪ RAL + TAF/FTC

Bold text identifies single-tablet regimens. *IAS-USA guidelines not updated since the approval of BIC/TAF/FTC.

- Recommendations may differ based on BL HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, and osteoporosis status
- With FDA approval of 1200-mg RAL,^[3] all options now available QD (except in pregnancy)

1. DHHS guidelines. March 2018. 2. Günthard HF, et al. JAMA. 2016;316:191-210. 3. Raltegravir [package insert]. 2018.



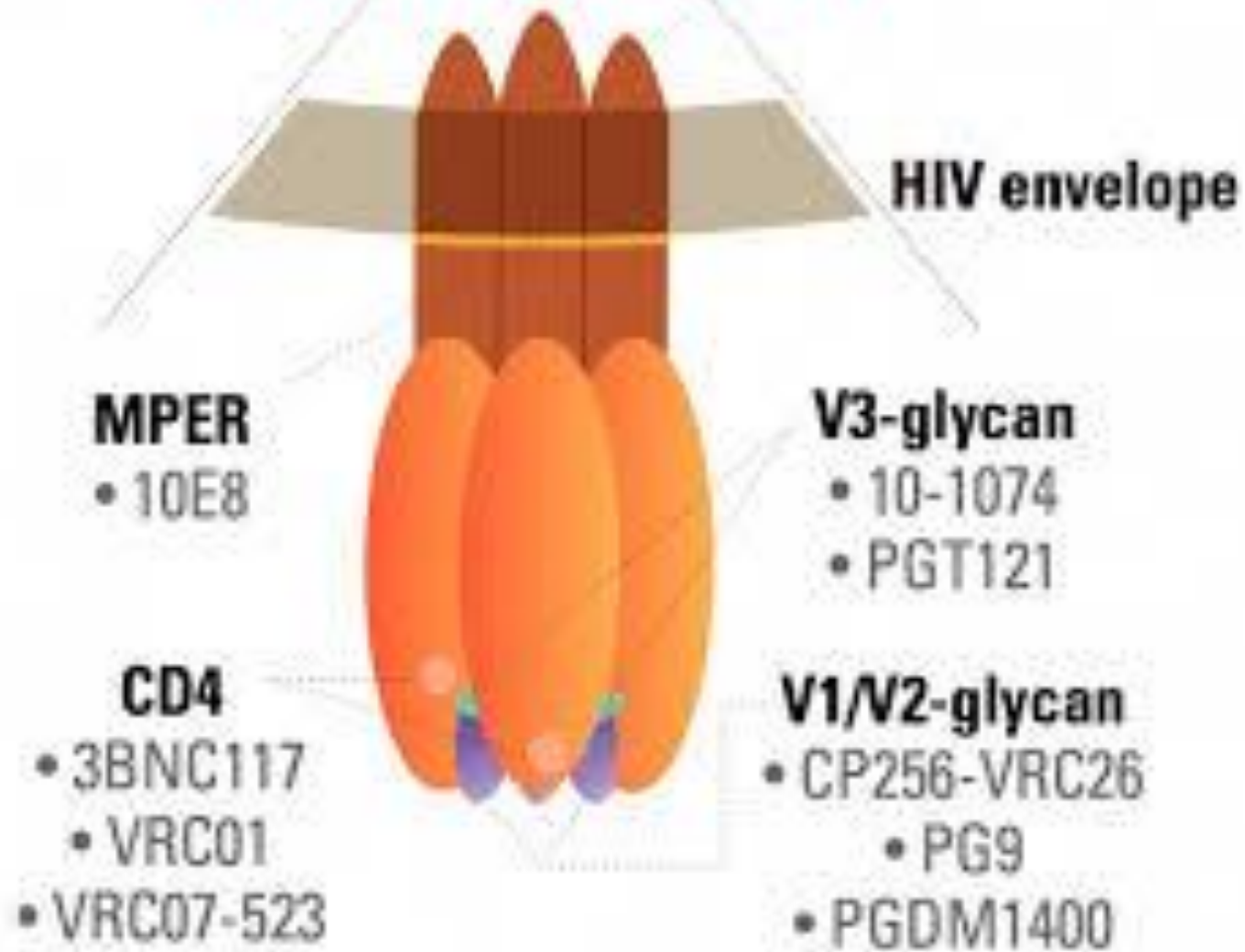
Slide credit: clinicaloptions.com



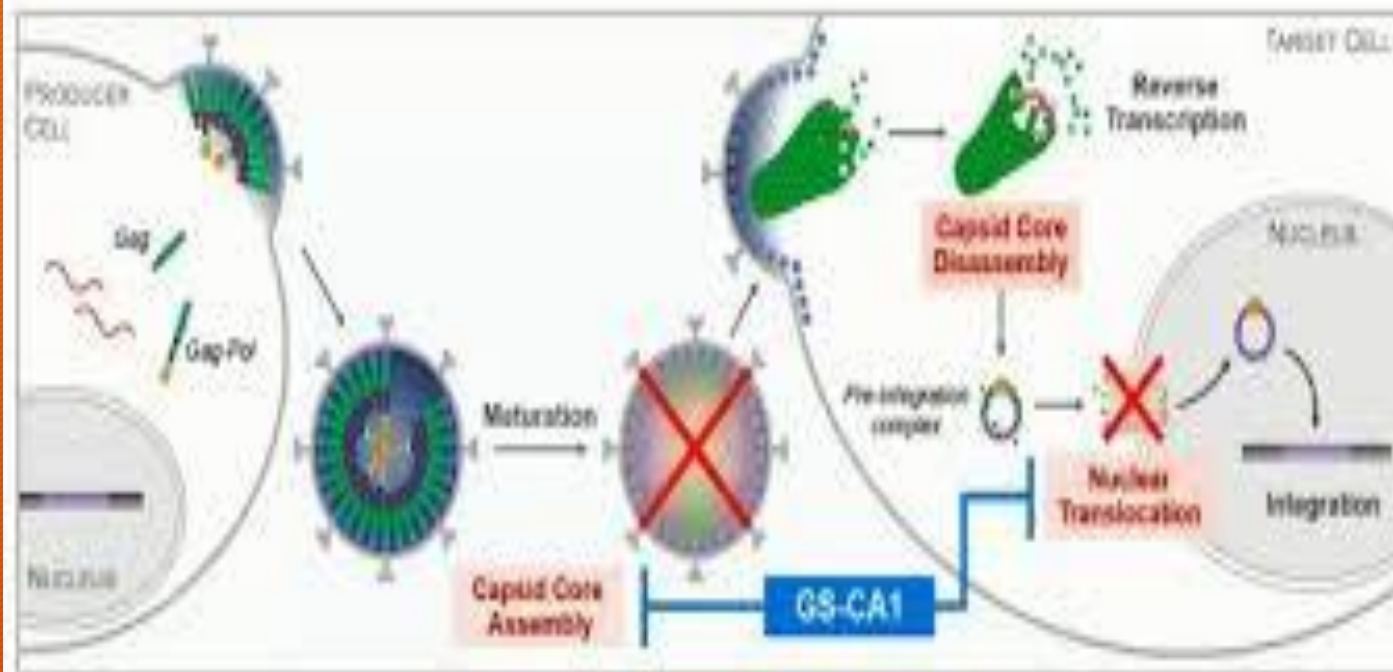
NOW APPROVED

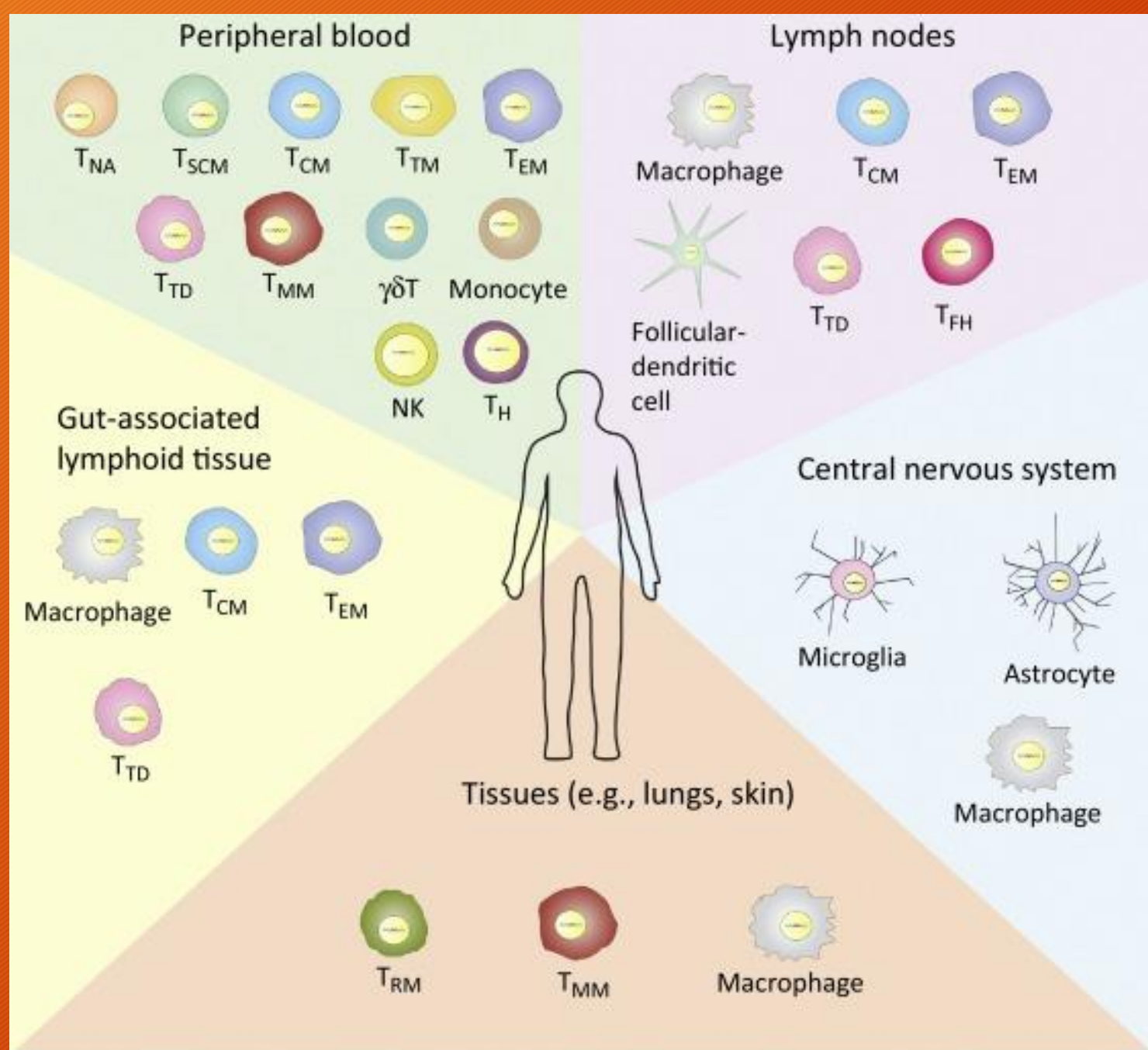
 **THERA**
LABORATORIES

bNAb Targets on HIV



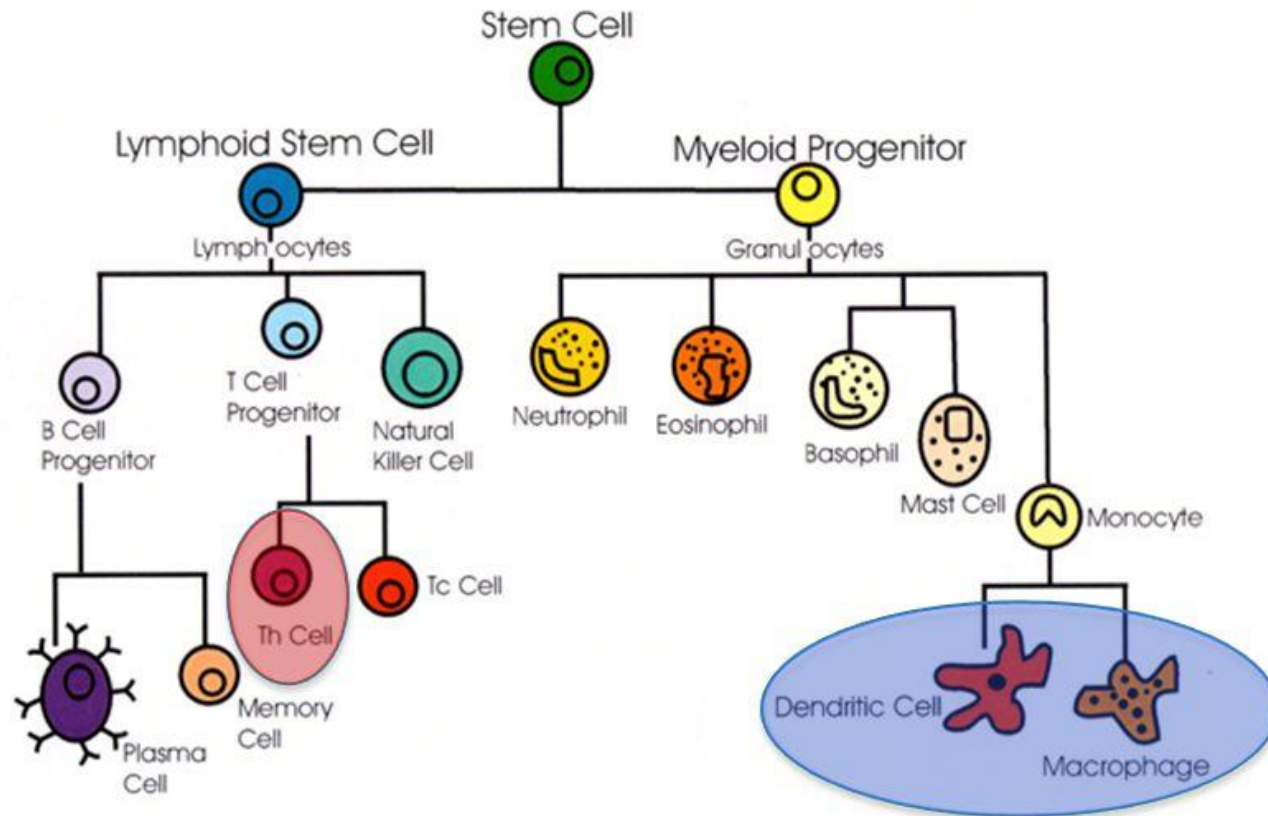
GS-CA1 Mode of Action Summary





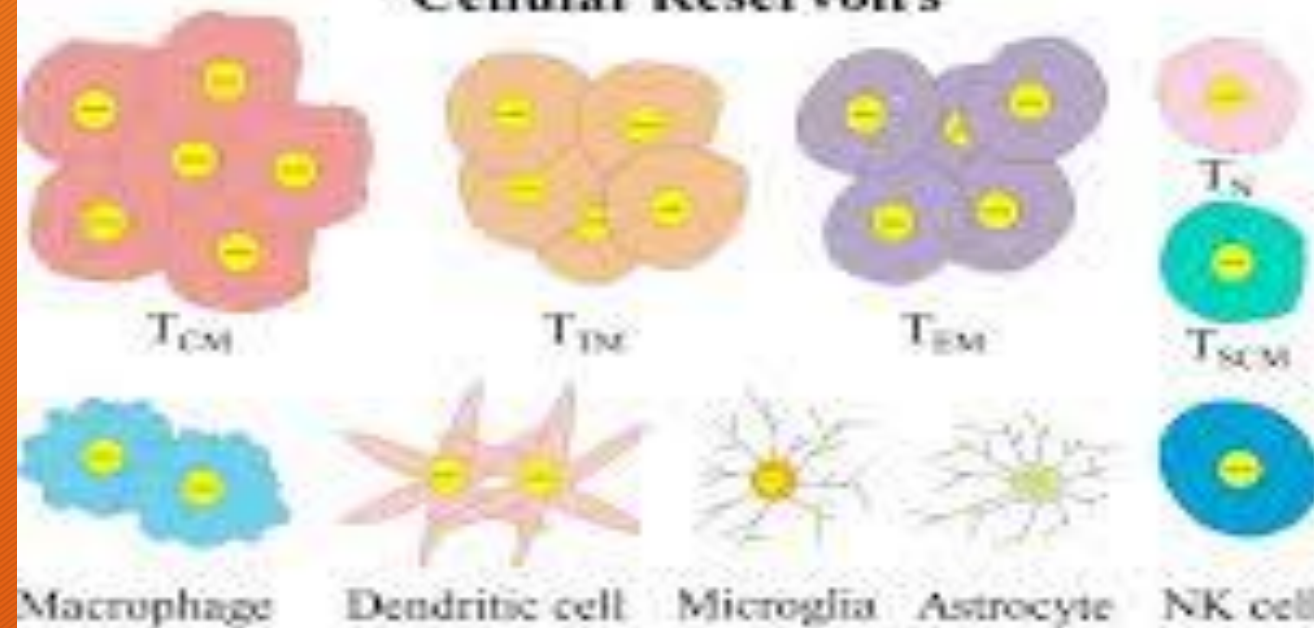
Where is the HIV reservoir?

Cells of the Immune System



From <http://textbookofbacteriology.net>

Cellular Reservoirs



Anatomical Reservoirs





**The only
man cured
of HIV.
Timothy Ray
Brown**

Examples of strategies currently in human studies

MINIMIZE RESERVOIR

Limit reservoir with early treatment

Antiretroviral therapy
Broadly neutralizing antibodies

SHOCK

Reactivating latently- infected cells

Inhibit histone deacetylase
Inhibit bromodomain
extraterminal
Activate toll-like receptors
Activate protein kinase C

KILL

Viral clearance by the immune system

Broadly neutralizing antibodies
Therapeutic HIV vaccines
Anti programmed cell
death (PD)1
Anti PD ligand 1

HIV RESISTANT CELLS

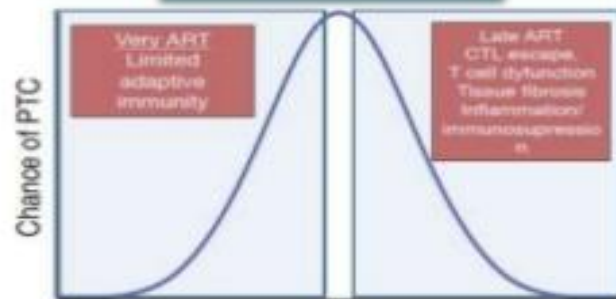
Transfusing cells without CCR5 gene

Gene-editing therapy
Bone marrow or cord blood transplantation

Combination
Cure

HIV Cure strategies: Lessons from Long-term control in human and NHP

To limit the
establishment of the
reservoir



To reduce the size of
the reservoir

Render
uninfected
cells resistant
to HIV

Deplete
infected cells

Flush out the
latent
reservoir

**Strategies to optimize innate and
adaptive immune functions to:**

- *facilitate clearance of infected cells*
- *enhance immune control*

Eradication Cure

- Timothy Ray Brown (Berlin Patient)

**Eradication
Cure**
No functional HIV-1
remaining in the body

Hybrid Cure

- Reduce reservoir size and diversity with “kick”
- Enhance immune responses with “kill”

**Hybrid
Cure**
Reduced functional
reservoirs & improve
immune control
without ART

**Functional
Cure**
Control of HIV
without ART or
deleterious
immunologic effects

Functional Cure

- Elite controllers
- VISCONTI Post-ART controllers
- Host cell modification

Approaches to HIV cure	
Gene therapy	<p>Knockdown of proteins required for HIV replication. For example, CCR5</p> <p>Overexpression of restriction factors. For example, Human: Rhesus chimeric TRIM5a</p> <p>Engineered T-cell receptors. For example, Third-generation chimeric antigen receptors</p>
Immune based	<p>Therapeutic vaccination</p> <p>Cytokine therapy. For example, 1h7, IL15</p> <p>Anti-inflammatory agents</p> <p>Growth hormone</p>
HIV reactivation	<p>HDAC inhibitors—For example, SAHA</p> <p>TLR agonists</p> <p>PKC activation</p>
Cytotoxic approaches	<p>Autologous stem-cell transplant</p> <p>Allogeneic stem-cell transplant</p>

90-90-90

An ambitious treatment target
to help end the AIDS epidemic



HIV is

- A chronic manageable disease
- Unclear as to pathophysiology
- Drugs are good to great
- Access/adherence remain an issue

HIV is

- Functional cure maybe possible
- Viral cure unlikely
- Epidemic is beginning to wane