HUMAN IMMUNODEFICIENCY VIRUS 1

HIV-1

INTRODUCTION

- **HIV pandemic causes one million deaths a year worldwide (no longer in top ten)**
- **First AIDS cases were recognized clinically 1981**
  - **Kaposi's sarcoma and *Pneumocystis carinii* pneumonia in young homosexual men**
- **1983 HIV was isolated by Luc Montagnier and Robert Gallo**
- **Subsequently sequenced etc…..**

History

- HIV is a mutation of SIV which likely spread to humans from bushmeat in the 19th century.
- Small, remote, isolated populations prevented the spread. An individual would get sick and die without much chance to spread it around.
- The huge growth of trucking in Africa started in the 1950's caused spread to the cities through sexual contact of truckers, villagers, and urban populations.
- With air travel it spread globally in the 1970's.

PATHOGENESIS OF AIDS
how does HIV cause AIDS?

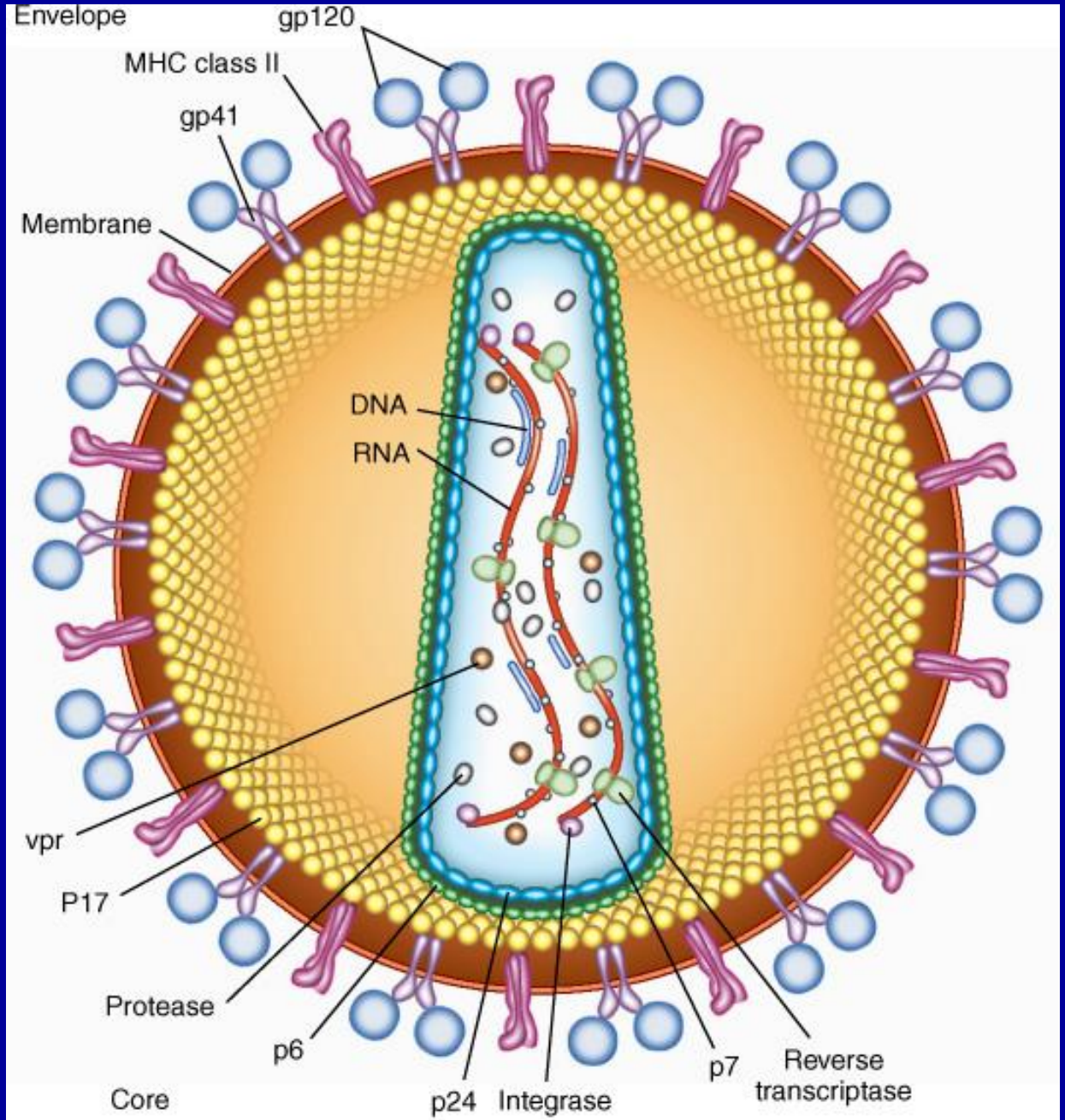
HIV: human immunodeficiency virus

HIV is a member of the lentivirus family, a subgroup of retroviruses, RNA viruses that replicate via a DNA intermediate

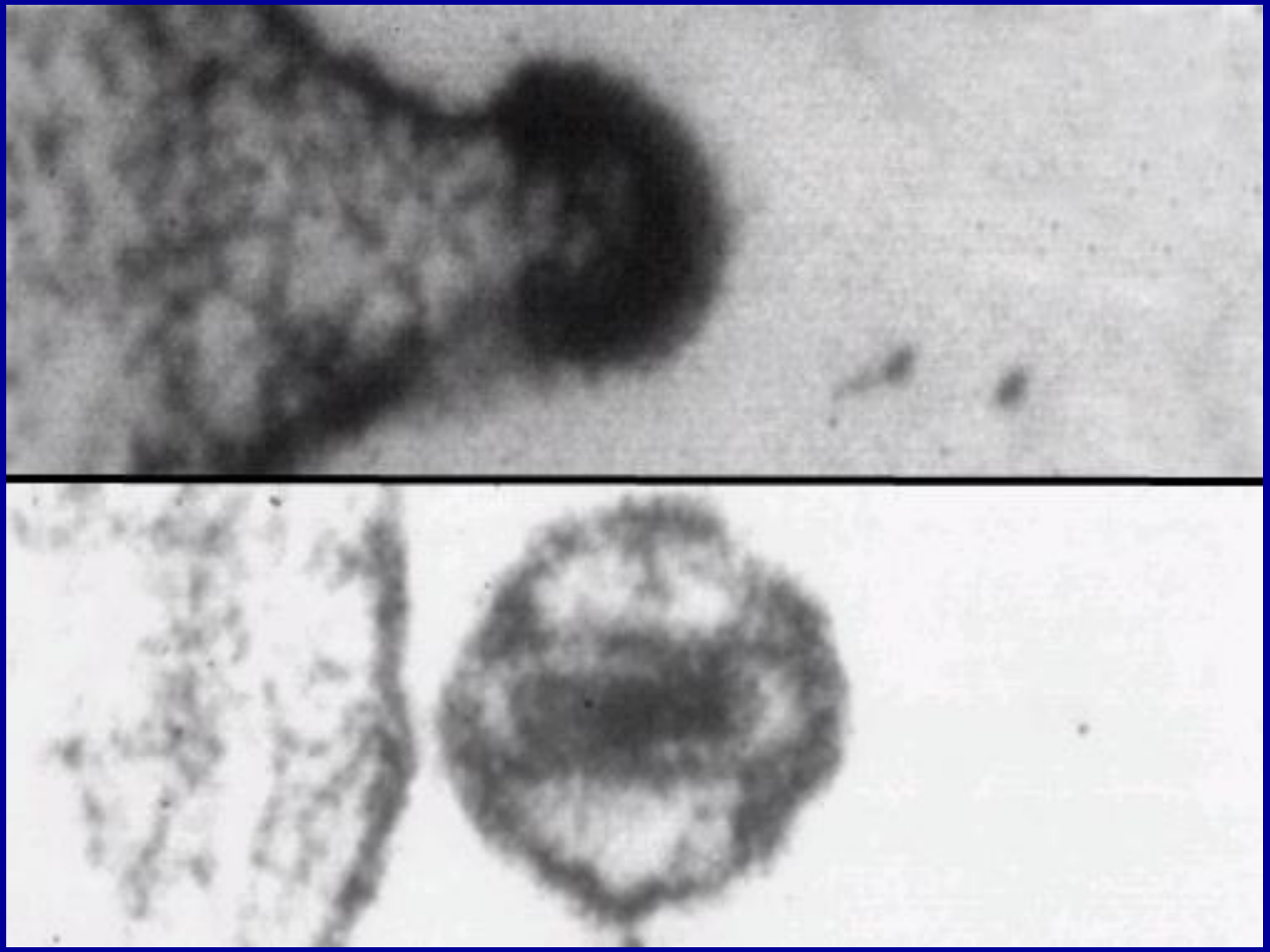
AIDS: acquired immunodeficiency syndrome

AIDS is defined by a loss of CD4 T lymphocytes (less than 200/cubic mm or the occurrence of opportunistic infections or cancers

VIRUS STRUCTURE



Courtesy of Edward C. Klatt, M.D., Department of Pathology, University of Utah.



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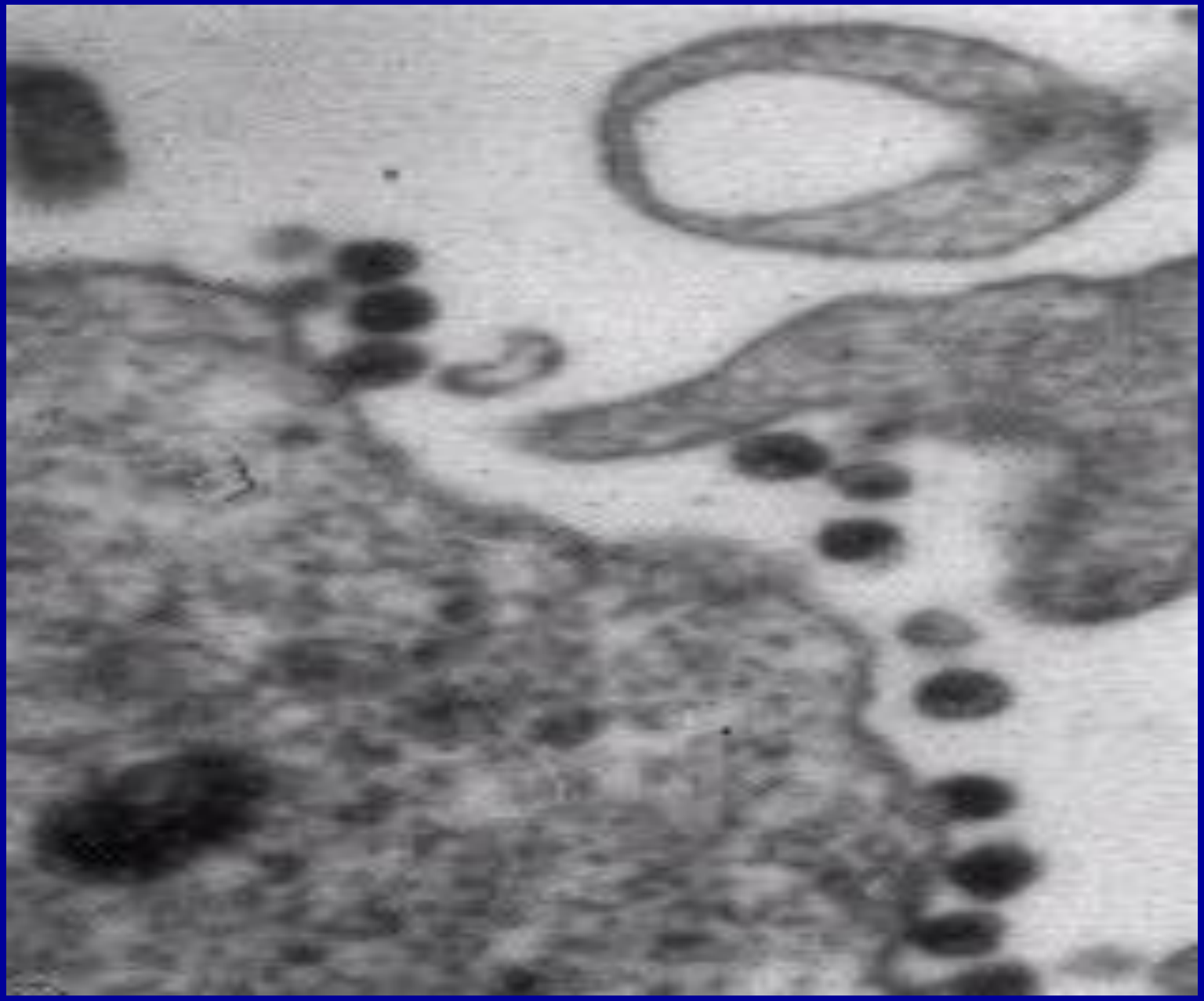

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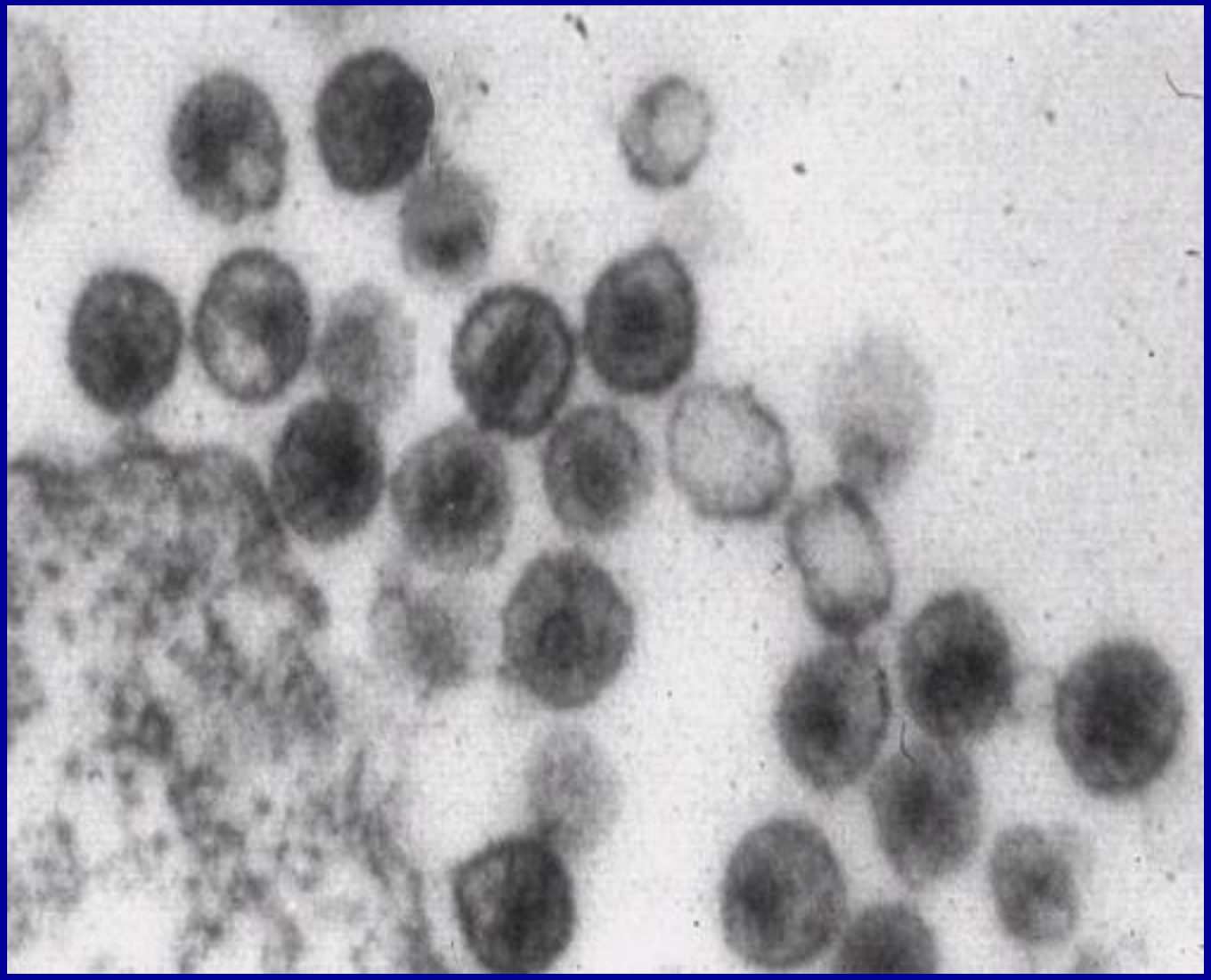
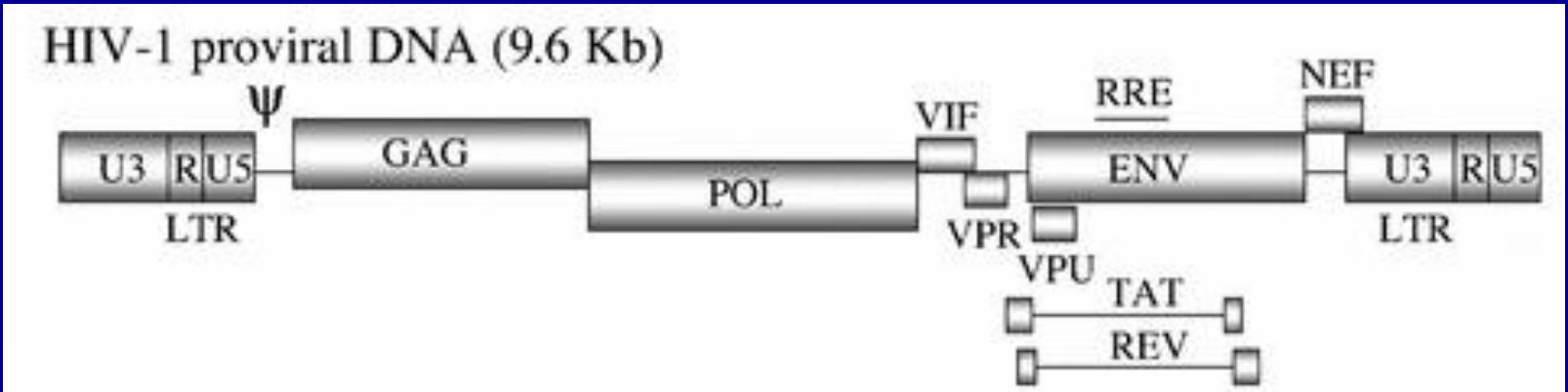
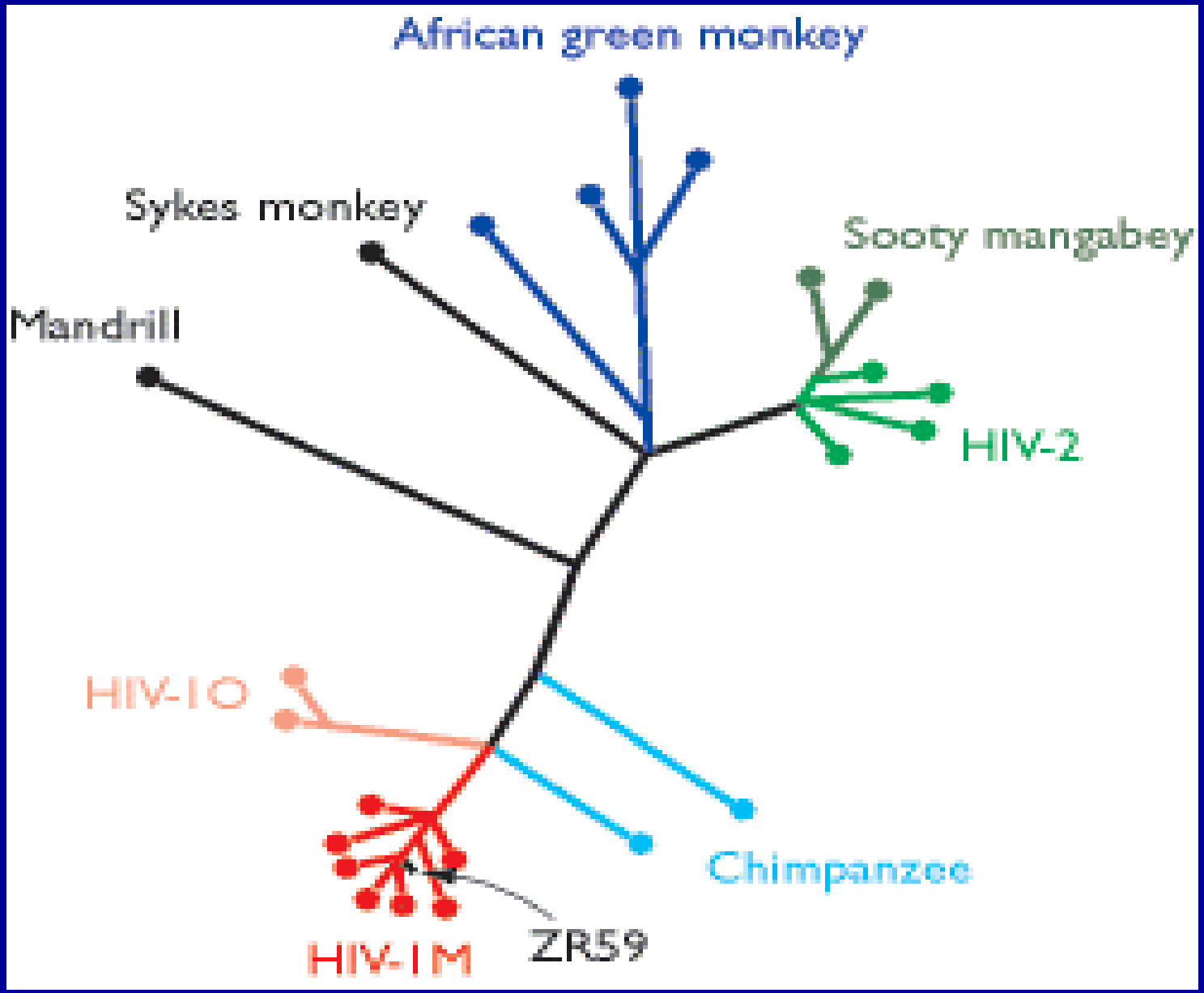


Courtesy of Edward C. Klatt, M.D., Department of Pathology, University of Utah

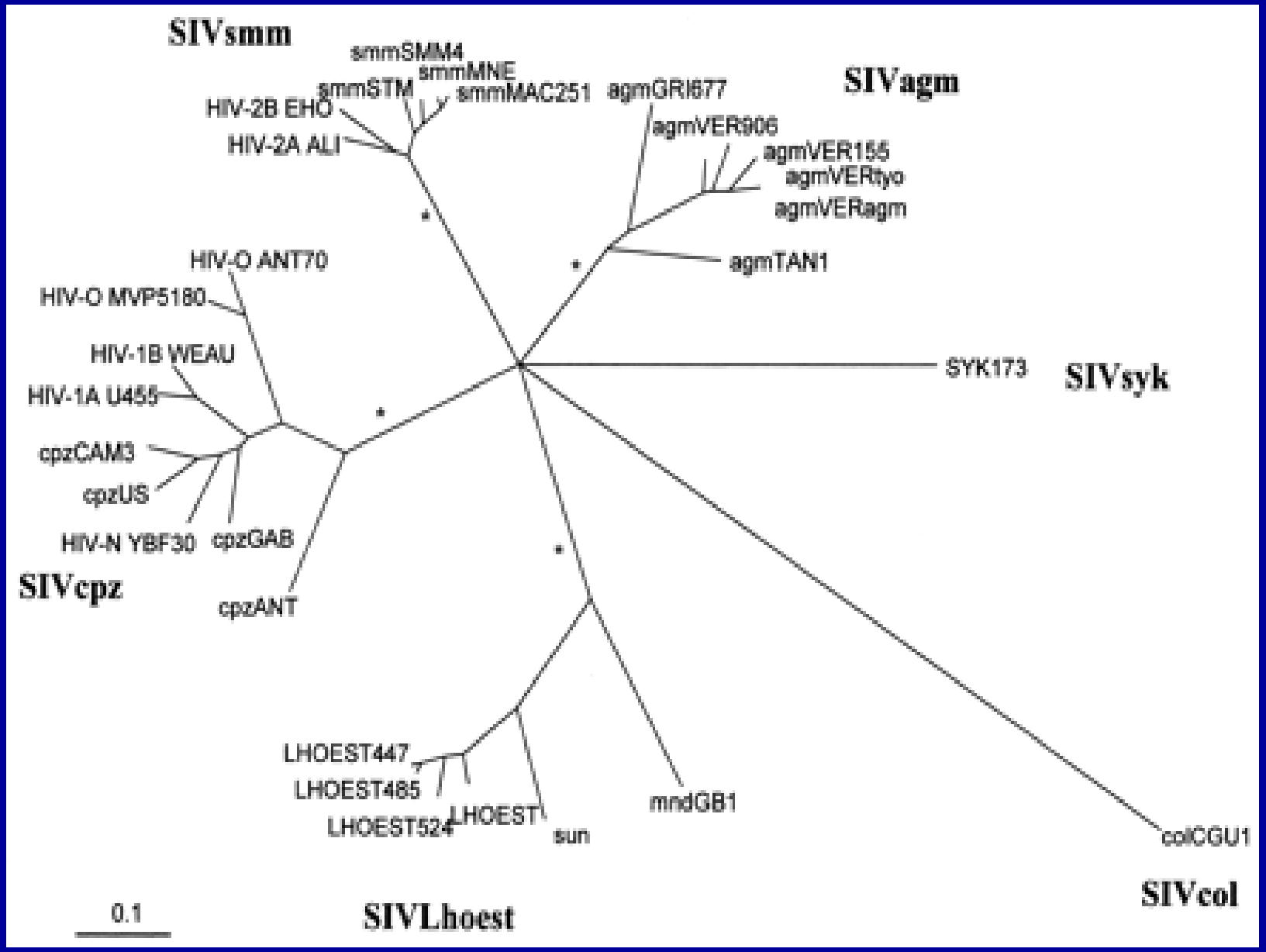
•This is the proto virus molecule. This giant protein molecule must be cut by protease to make viable virions. Protease inhibitors disrupt this process.



CLASSIFICATION: genotypes



Wain-Hobson (1998).



Mosaic Genomes of the Six Major Primate Lentivirus Lineages Revealed by Phylogenetic Analyses. Journal of Virology, July 2003, p. 7202-7213, Vol. 77, No. 13

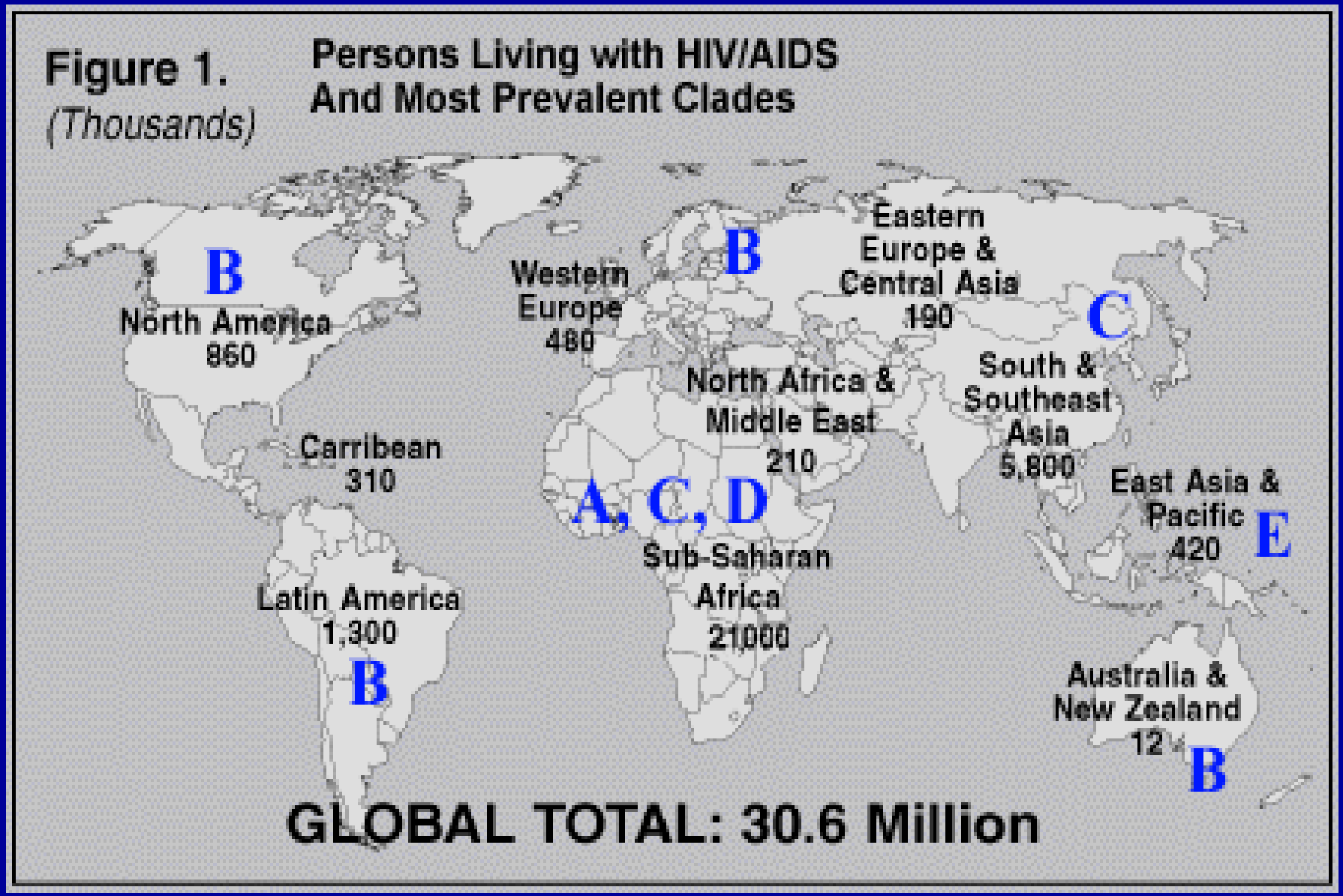
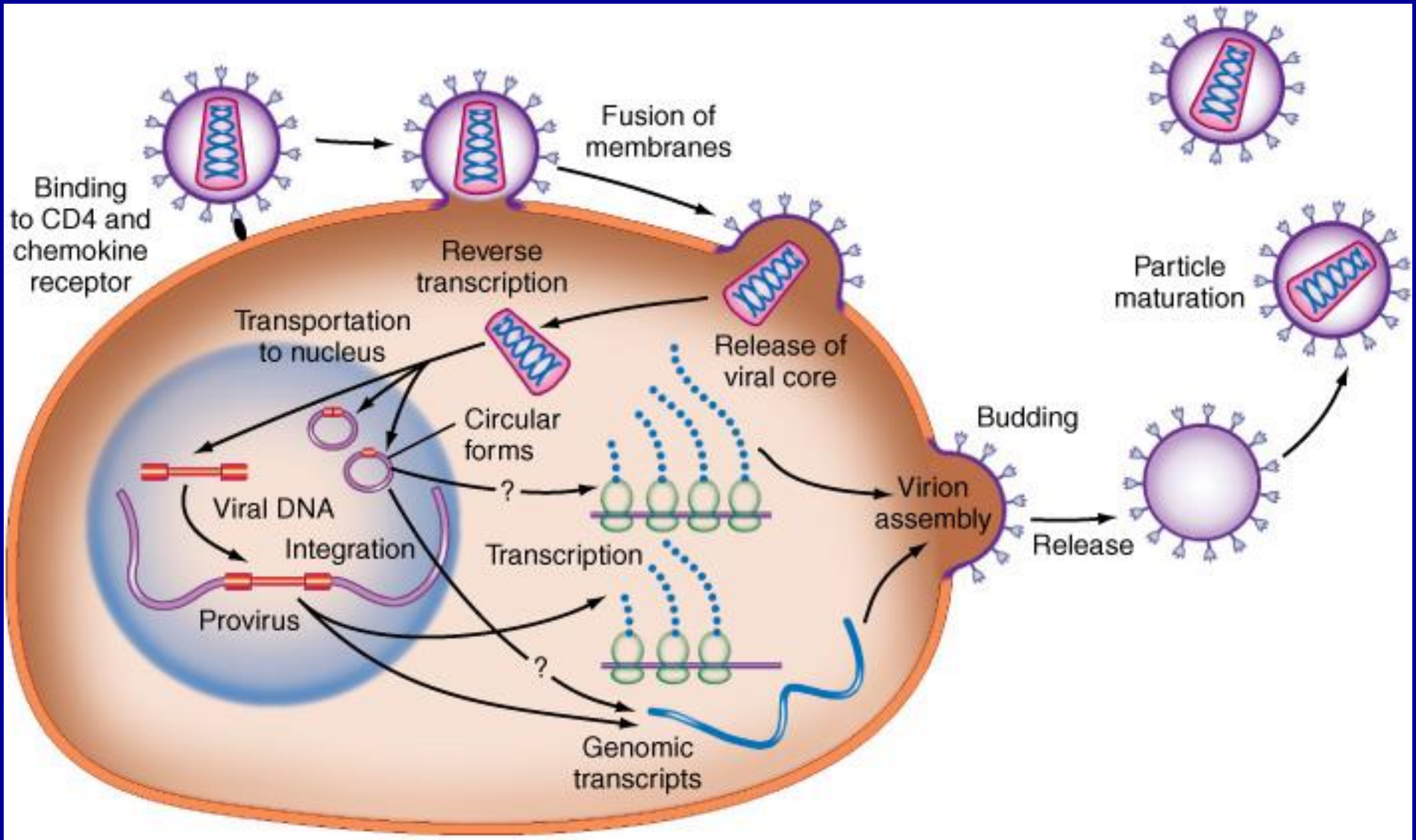


Figure 1.
(Thousands)
Persons Living with HIV/AIDS
And Most Prevalent Clades
B
North America
860
Carribean
310
Latin America
1,300
B
B
Western
Europe
480
Eastern
Europe &
Central Asia
190
C
North Africa &
Middle East
210
South &
Southeast
Asia
5,800
A, C, D
Sub-Saharan
Africa
21000
East Asia &
Pacific
420
E
Australia &
New Zealand
12
B
GLOBAL TOTAL: 30.6 Million

VIRUS LIFE CYCLE

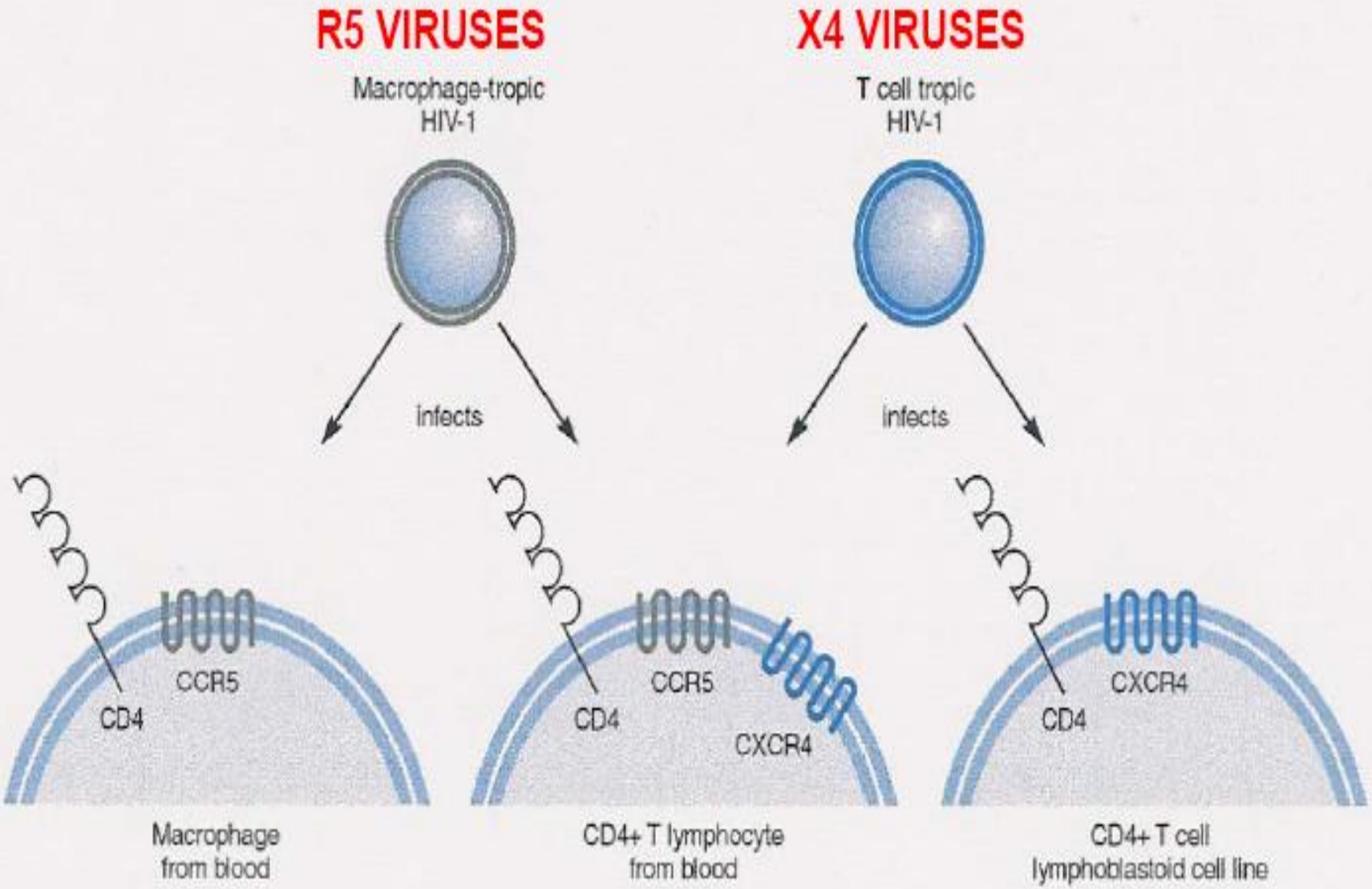


HIV infects cells that carry the receptor and co-receptor

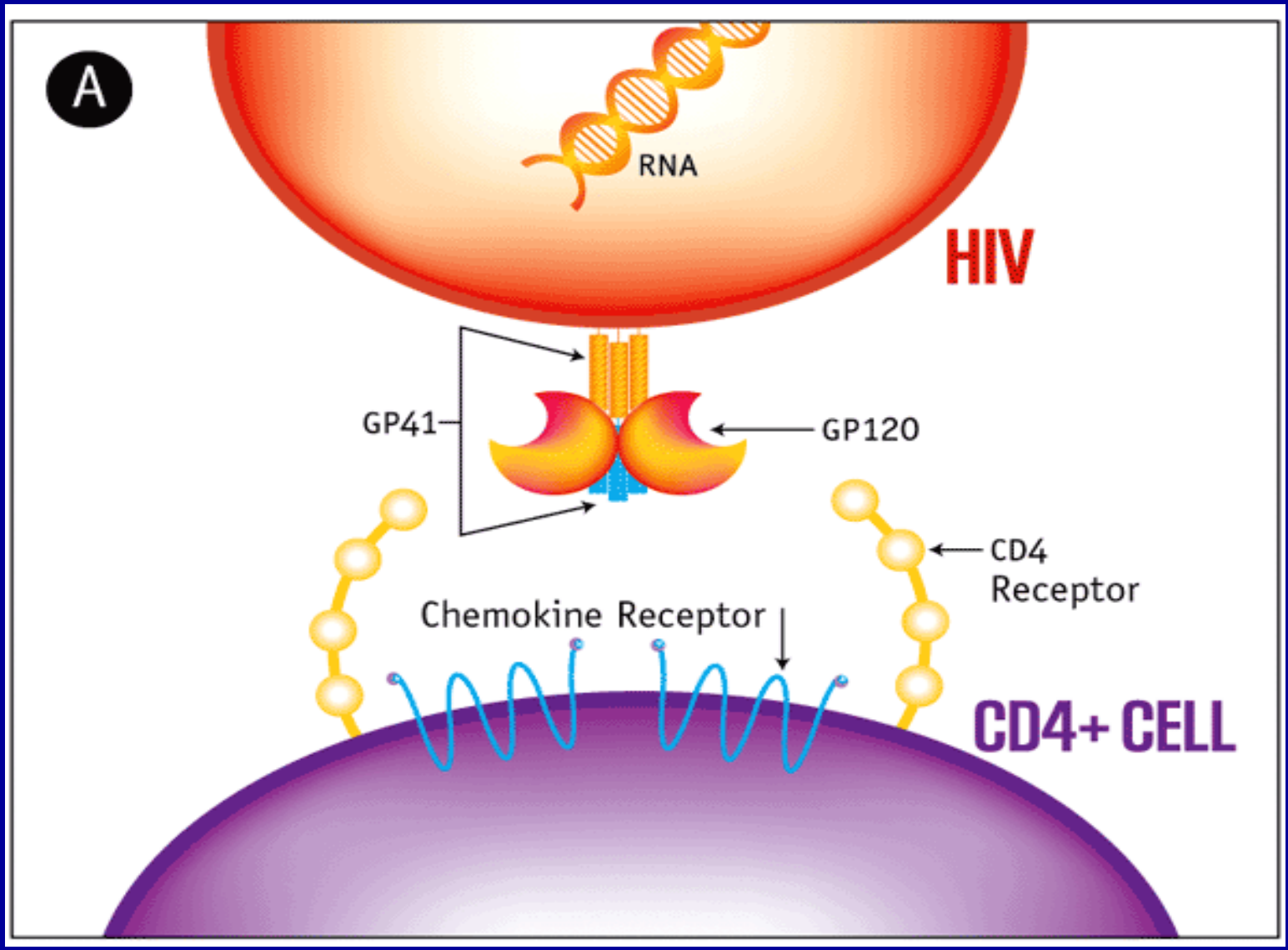
CD4: Expressed on the surface of CD4 T lymphocytes (helper T lymphocytes) and macrophages (including dendritic cells)

CCR5: Expressed on CD4+ T lymphocytes and on macrophages

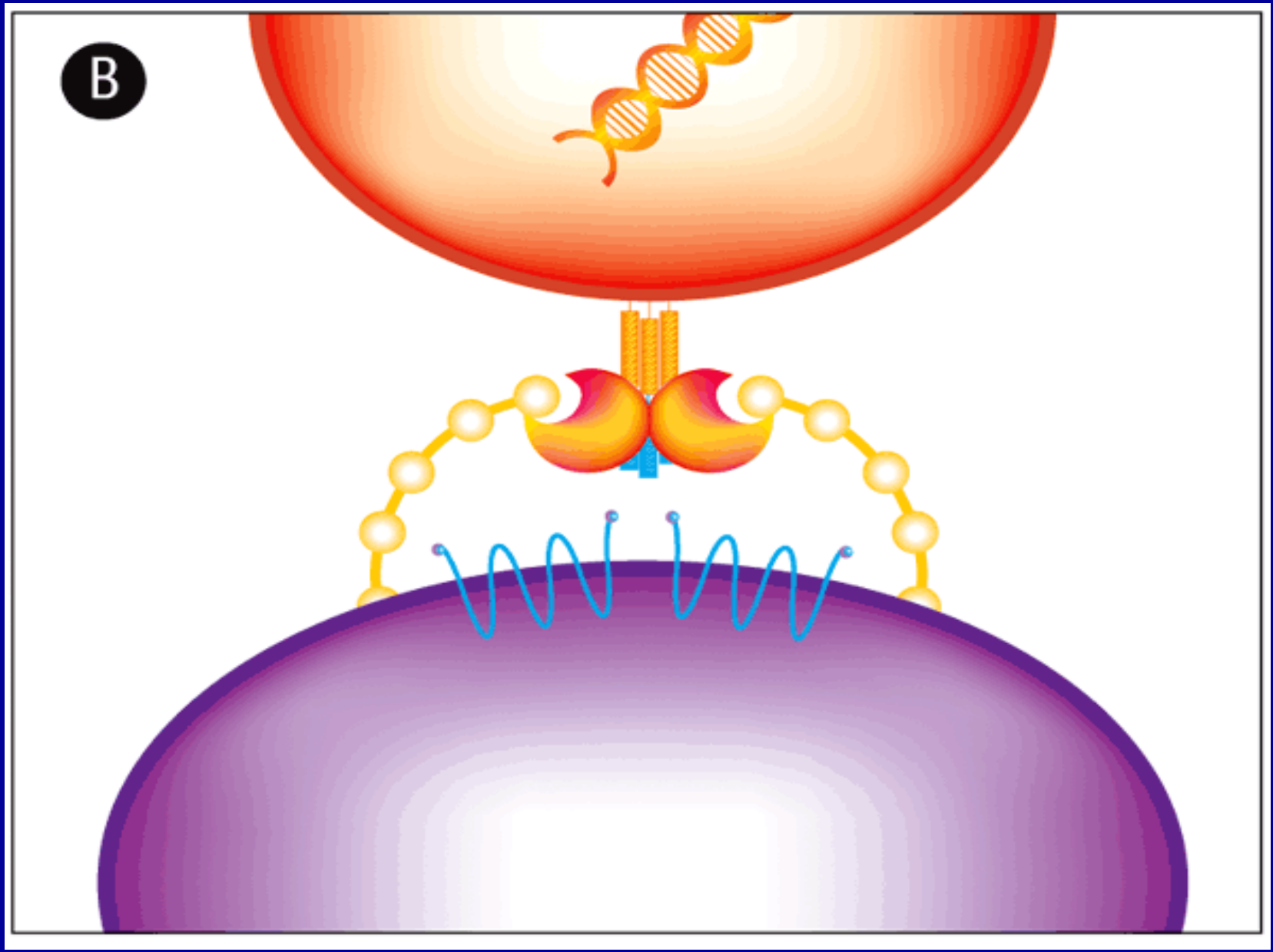
CXCR4: Expressed on CD4+ T lymphocytes and T cell lines


R5 VIRUSES
X4 VIRUSES
Macrophage-tropic HIV-1
T cell tropic HIV-1
infects
infects
CD4
CCR5
CD4
CCR5
CXCR4
CD4
CXCR4
Macrophage from blood
CD4+ T lymphocyte from blood
CD4+ T cell lymphoblastoid cell line

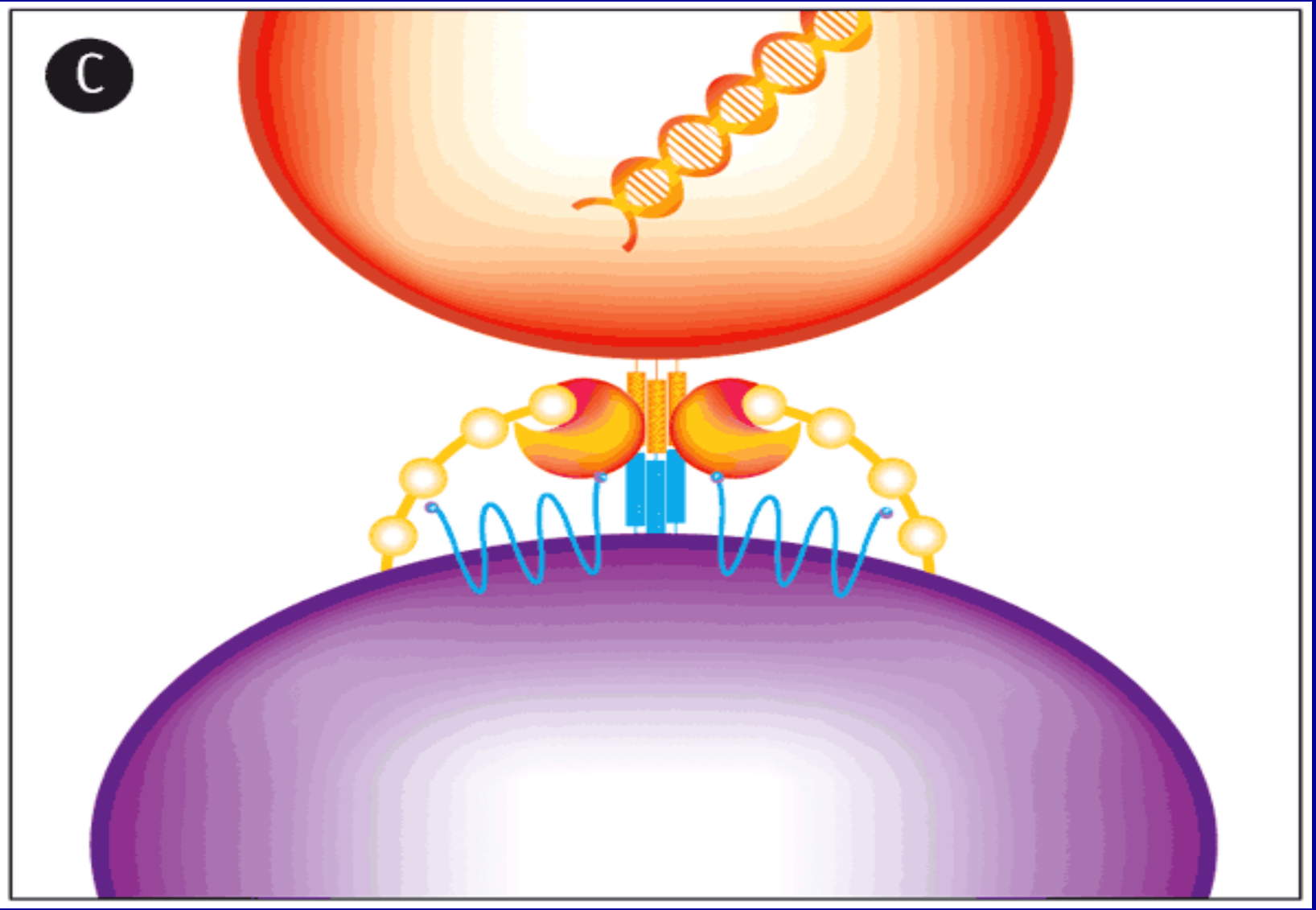
ENTRY

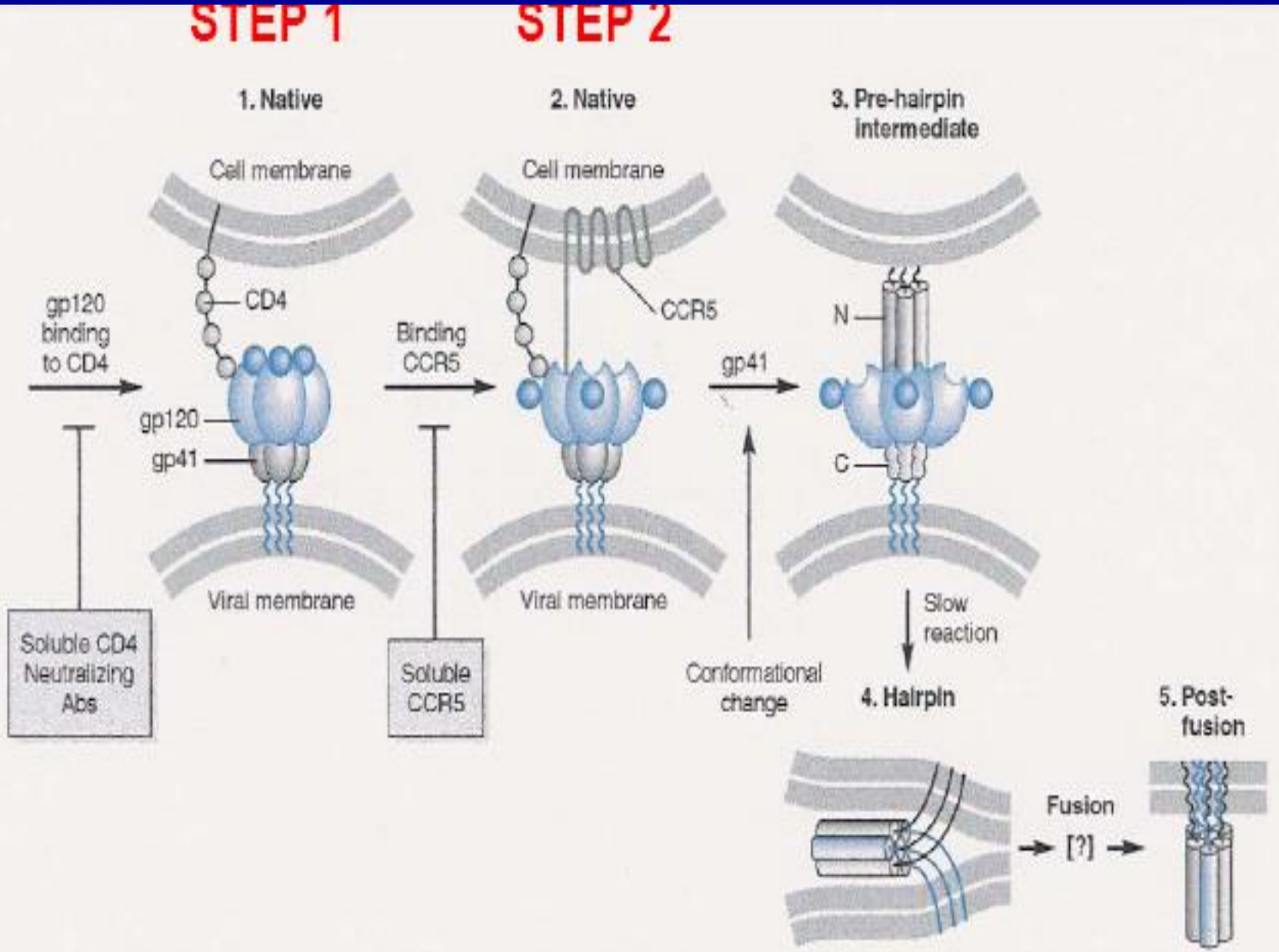

A
RNA
HIV
GP41
GP120
CD4
Receptor
Chemokine Receptor
CD4+ CELL

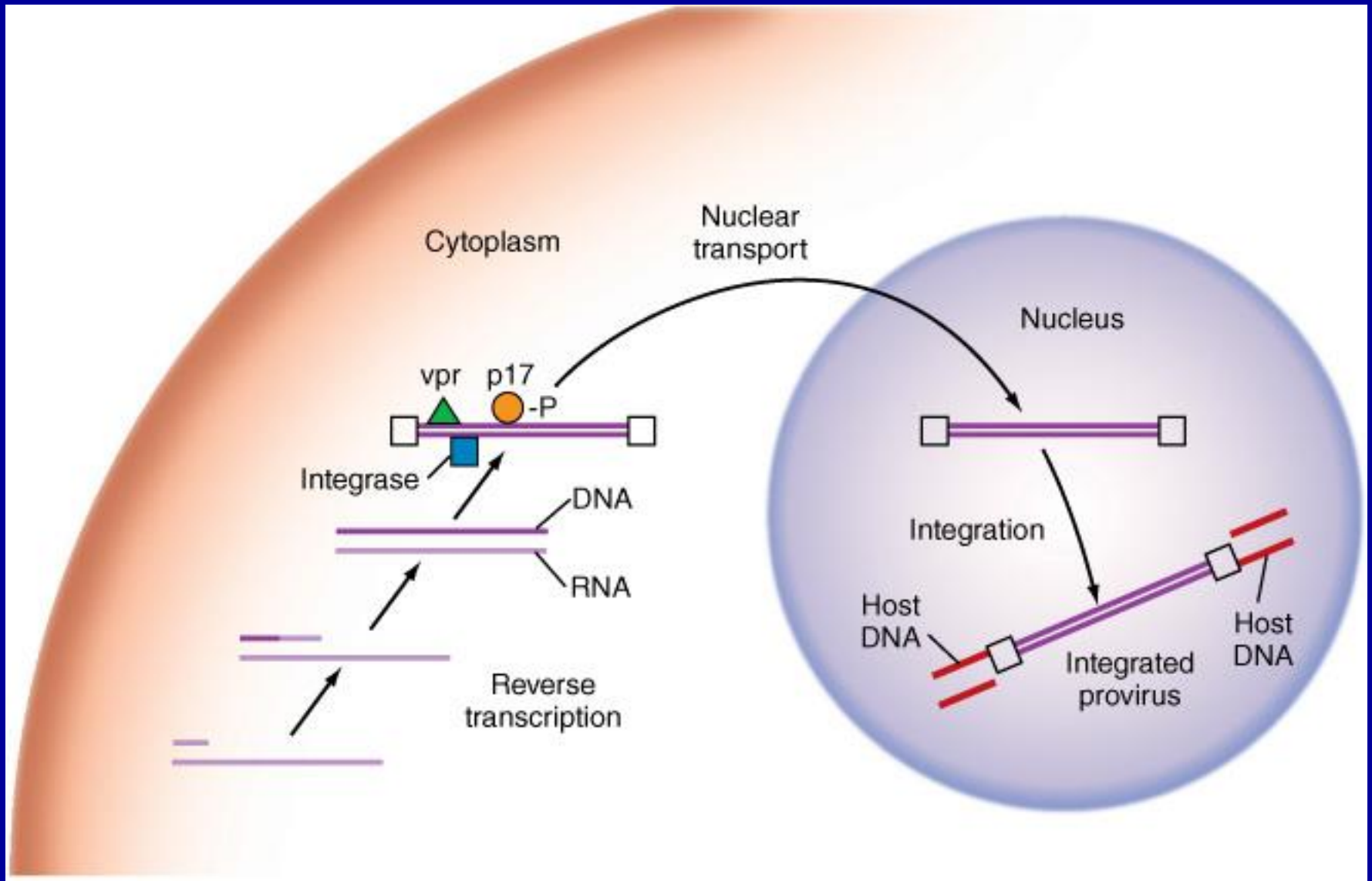
ENTRY



ENTRY

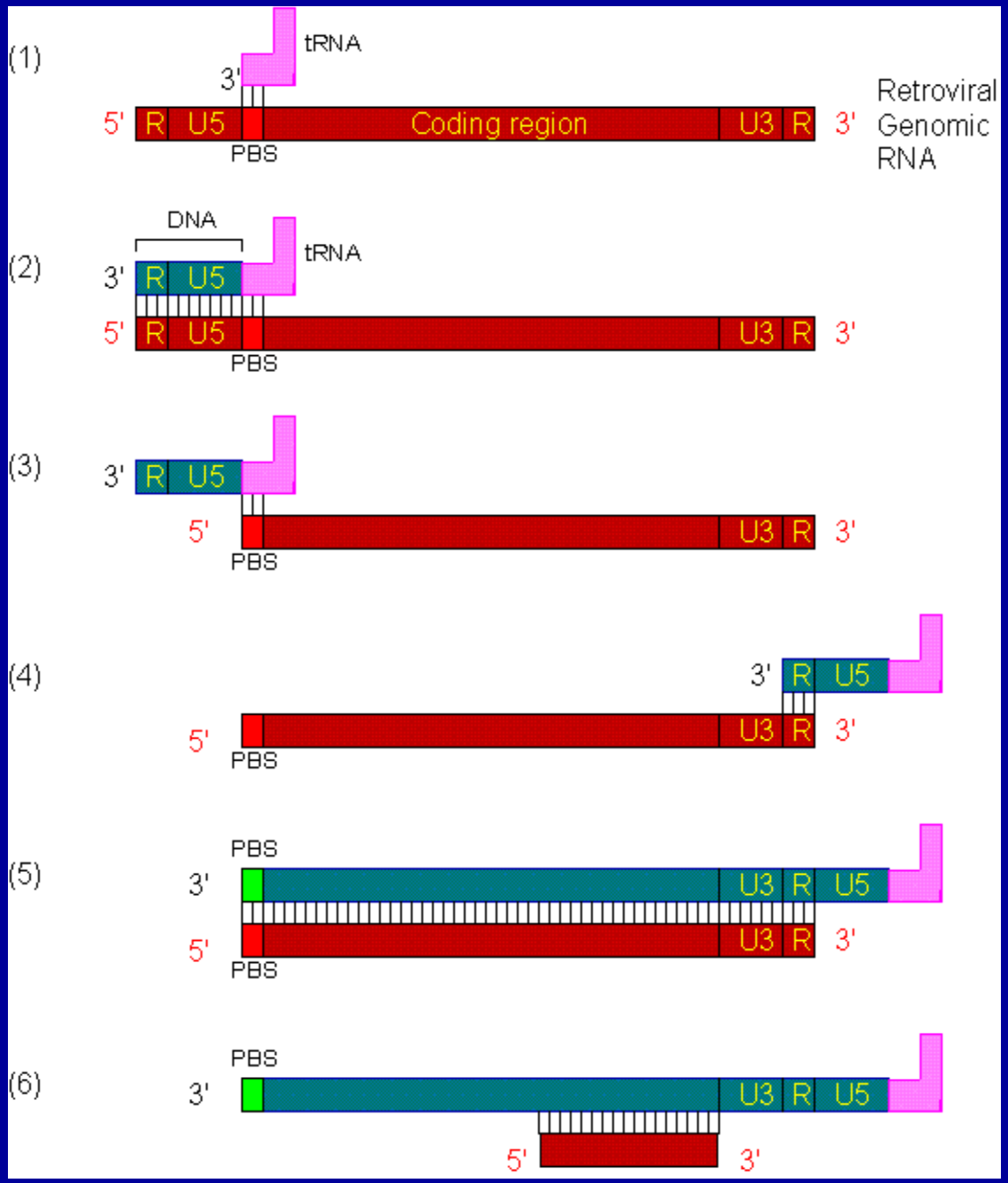


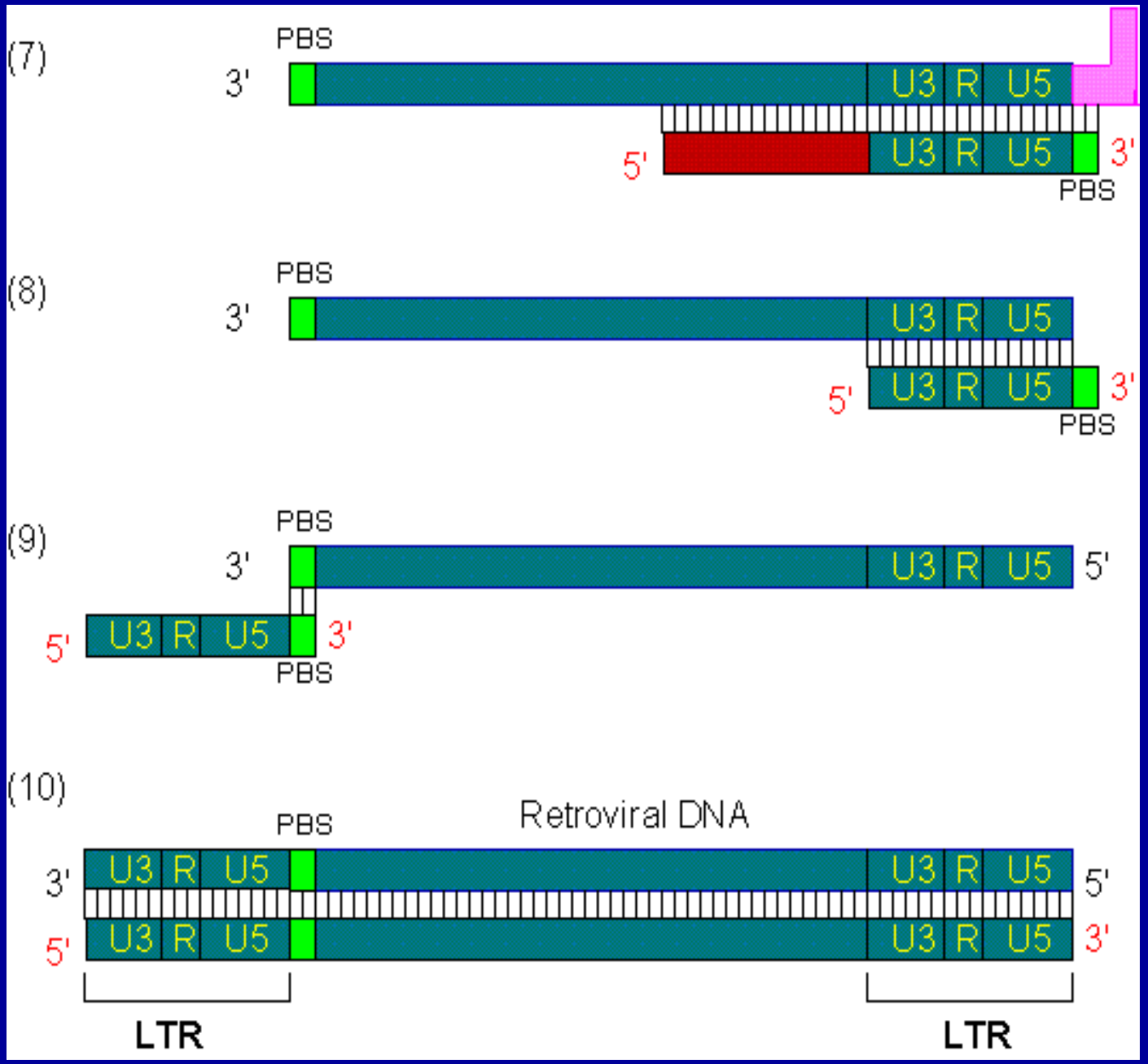

STEP 1
STEP 2
1. Native
2. Native
3. Pre-hairpin intermediate
Cell membrane
Cell membrane
gp120 binding to CD4
CD4
Binding CCR5
CCR5
gp41
N
gp120
gp41
C
Viral membrane
Viral membrane
Soluble CD4 Neutralizing Abs
Soluble CCR5
Conformational change
Slow reaction
4. Hairpin
5. Post-fusion
Fusion
[?]

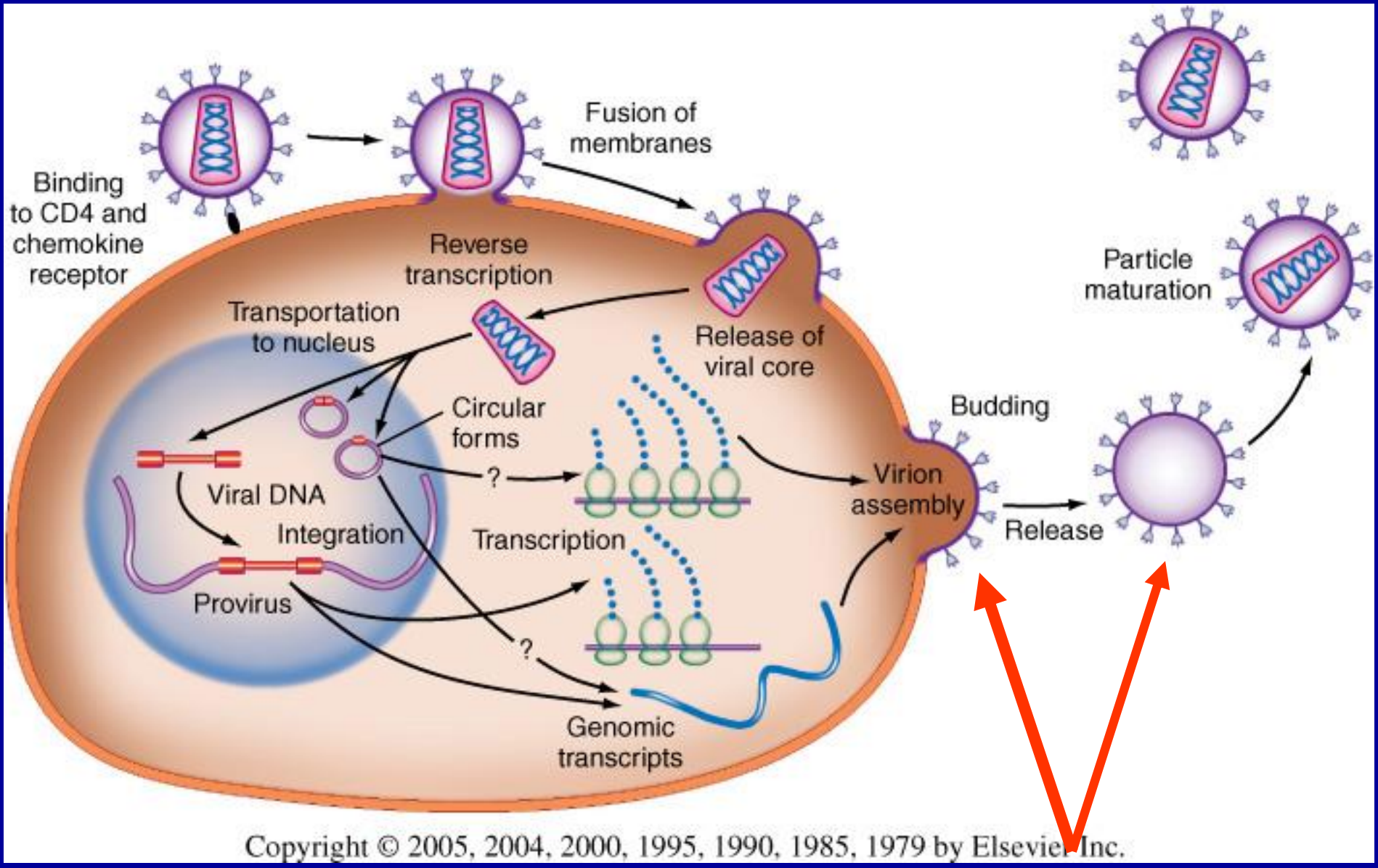


HIV Reverse Transcription

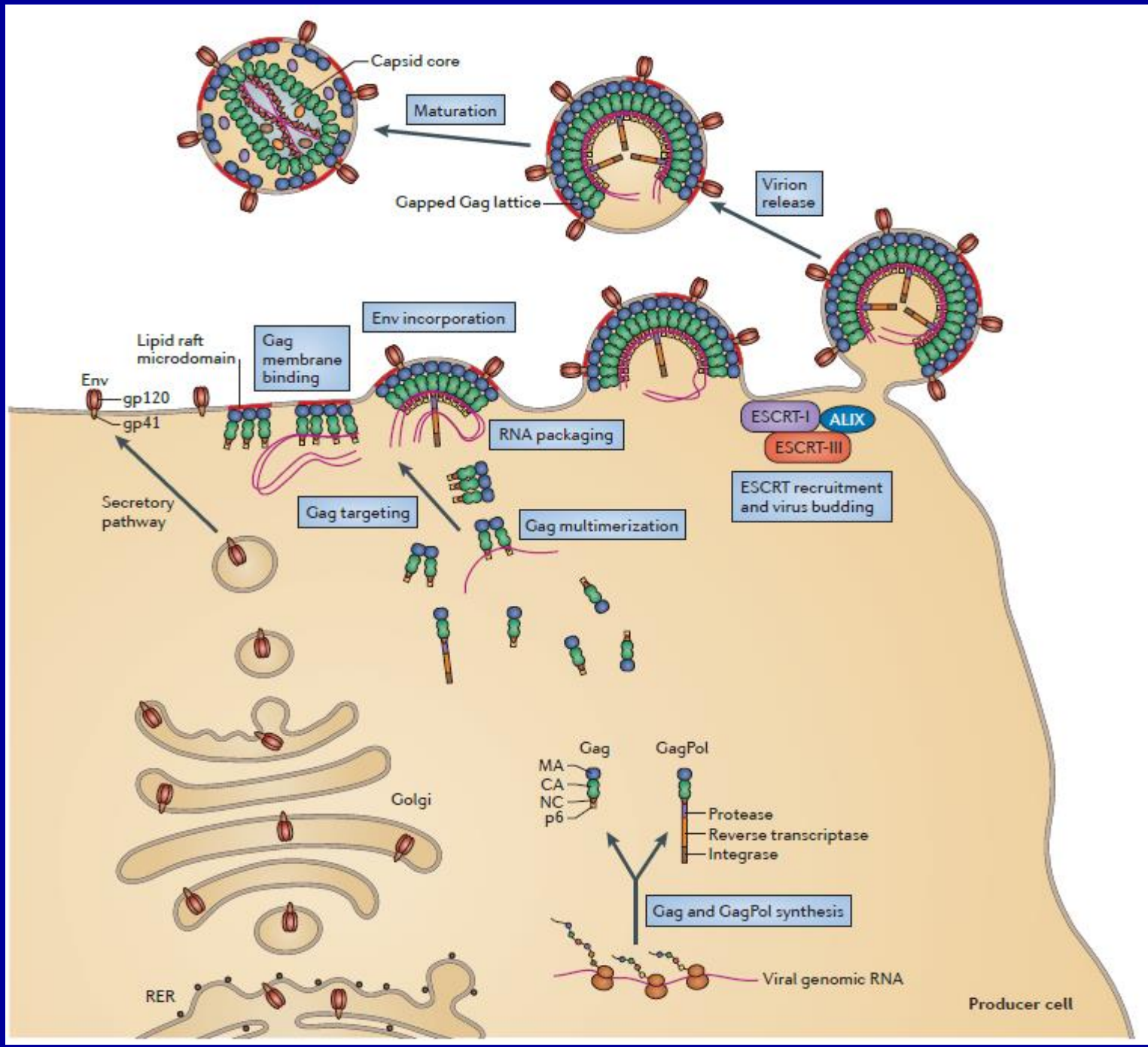
- HIV has high mutation rate during the virus replication
  - Due to the “jumping” and loose interaction between Reverse transcriptase template
  - Many mutations are non viable and don’t reproduce but some do making novel strains in a single host which rapidly evade host immune response and develop resistance to antiviral drugs
  - Old strains die out and are replaced with new


(1)
tRNA
3'
5'
R
U5
Coding region
U3
R
3'
PBS
Retroviral
Genomic
RNA
(2)
DNA
tRNA
3'
R
U5
5'
R
U5
U3
R
3'
PBS
(3)
3'
R
U5
5'
U3
R
3'
PBS
(4)
3'
R
U5
5'
U3
R
3'
PBS
(5)
PBS
3'
U3
R
U5
5'
U3
R
3'
PBS
(6)
PBS
3'
U3
R
U5
5'
3'

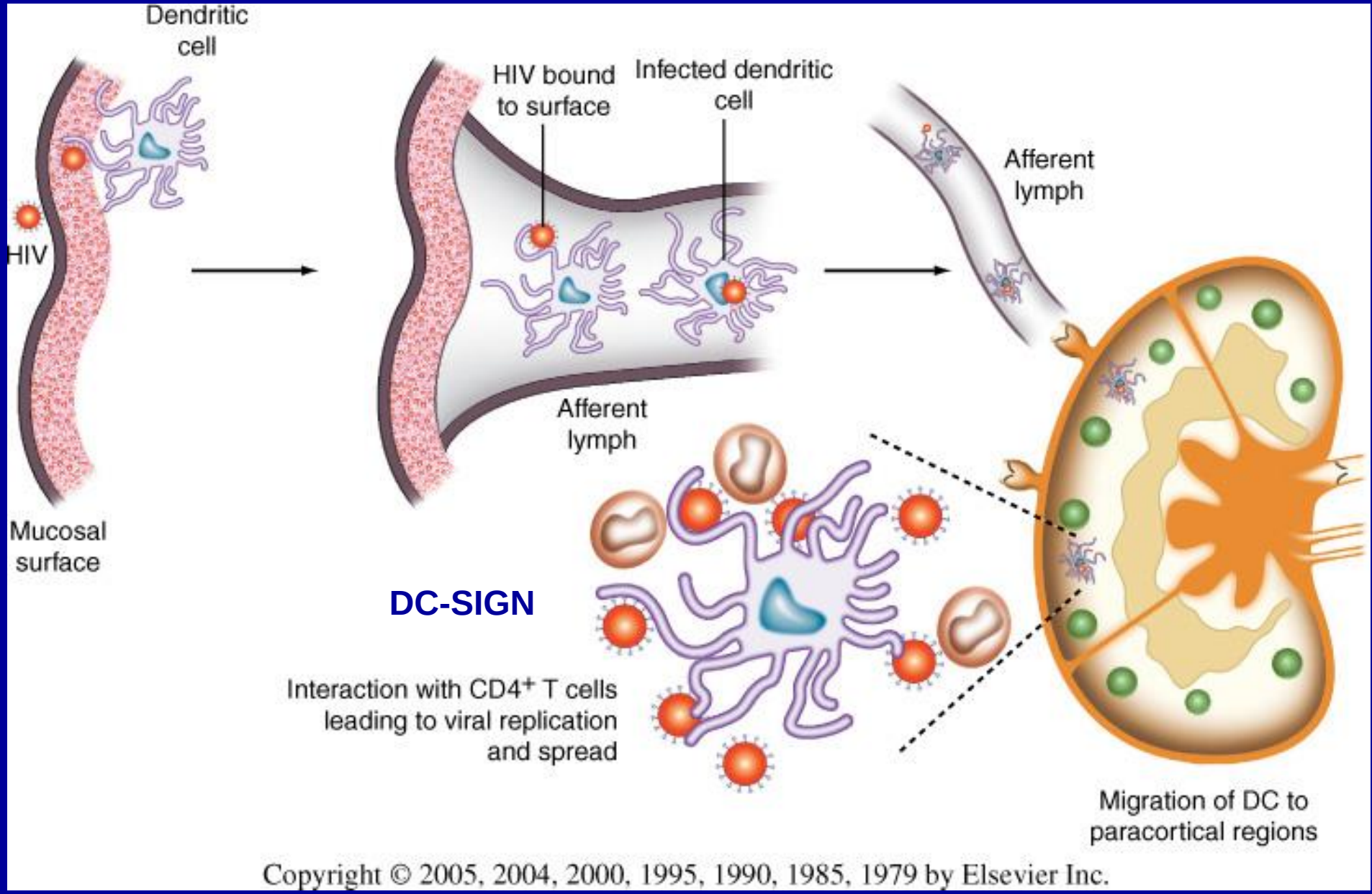

(7)
PBS
3'
U3
R
U5
5'
U3
R
U5
3'
PBS
(8)
PBS
3'
U3
R
U5
5'
U3
R
U5
3'
PBS
(9)
PBS
3'
U3
R
U5
5'
5'
U3
R
U5
3'
PBS
(10)
Retroviral DNA
PBS
3'
U3
R
U5
U3
R
U5
5'
5'
U3
R
U5
U3
R
U5
3'
LTR
LTR

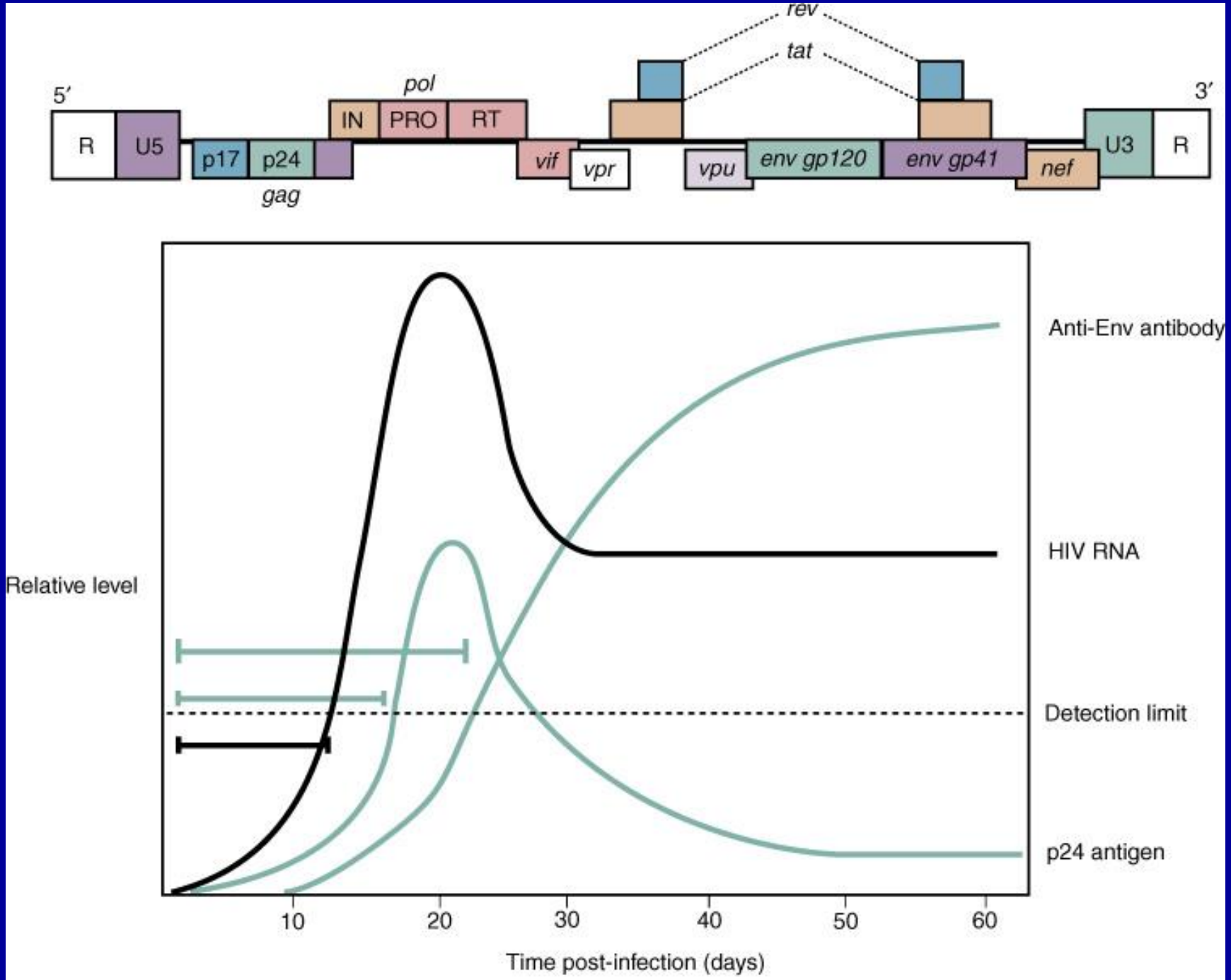


-Viral protease cleaves gag-pol polyprotein
-Protease inhibitors inhibit this action resulting the production of unmatured, noninfectious viral particles

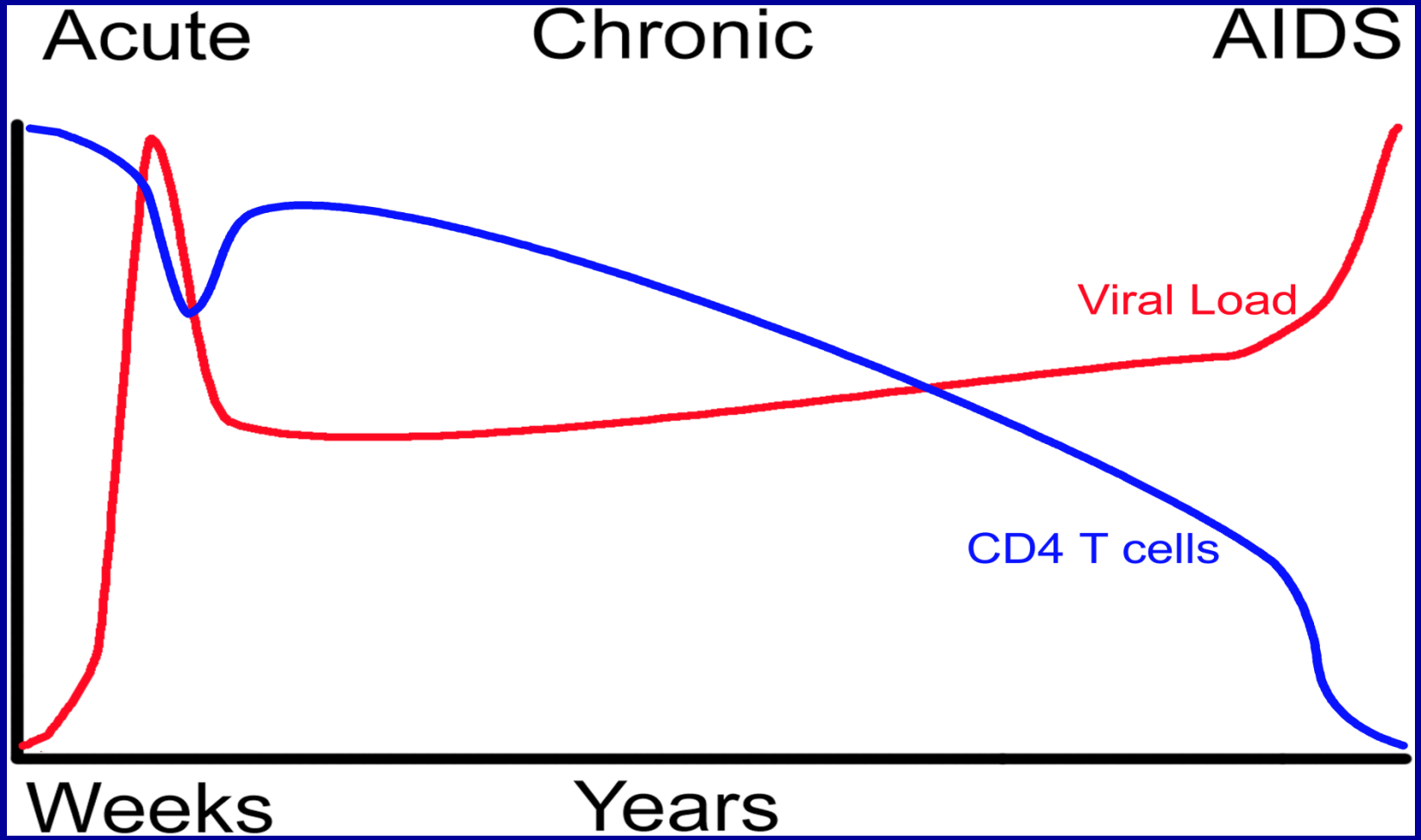

Capsid core
Maturation
Gapped Gag lattice
Virion release
Env incorporation
Lipid raft microdomain
Gag membrane binding
Env
gp120
gp41
RNA packaging
ESCRT-I
ALIX
ESCRT-III
ESCRT recruitment and virus budding
Secretory pathway
Gag targeting
Gag multimerization
Gag
GagPol
MA
CA
NC
p6
Protease
Reverse transcriptase
Integrase
Golgi
Gag and GagPol synthesis
Viral genomic RNA
RER
Producer cell

PATHOGENESIS

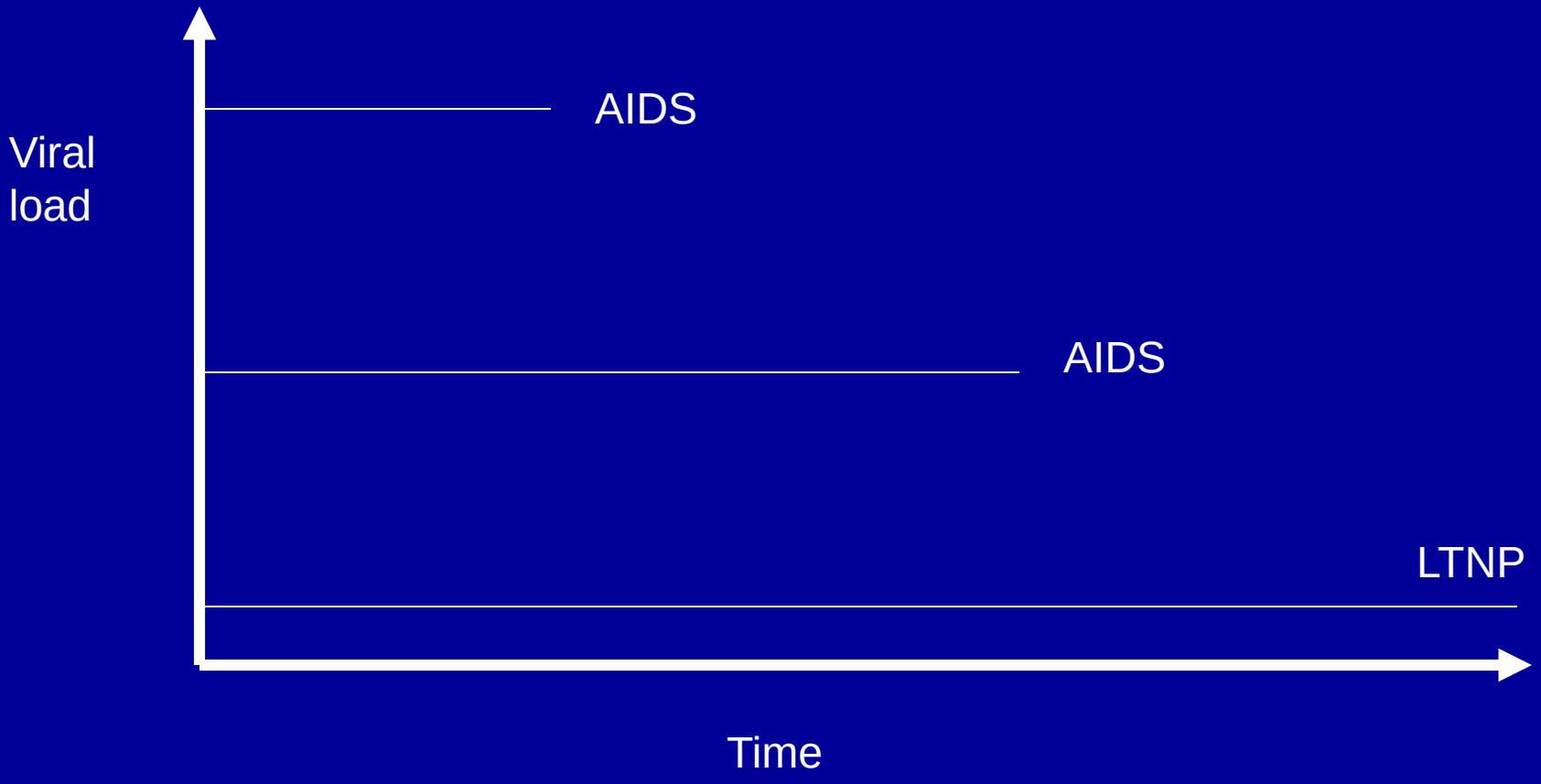




Natural history course of HIV infection



VIRAL LOAD



Viral Load

Plasma load	% who died in 6 yrs	Progressed
<500 copies/ml	0.9	5.4
501-3000	6.3	16.6
3001-10 000	18.1	31.7
10 001- 30 000	34.9	55.2
> 30 000	69.5	80.0

TABLE 116-2 Possible Mechanisms of Long-Term Nonprogression with Human Immunodeficiency Virus (HIV) Infection

Host genetic factors
Slow progressor HLA profile
Heterozygosity for 32-bp deletion in chemokine receptor CCR5
Mannose binding lectin alleles
Tumor necrosis factor e2 microsatellite alleles
Gc vitamin D–binding factor alleles
Host immune response factors
Effective CTL responses
Secretion of CD8 antiviral factor
Secretion of chemokines that block HIV entry co-receptors CCR5 (e.g., MIP-1α, MIP-1β, and RANTES) and CXCR4 (e.g., SDF-1)
Secretion of interleukin-16
Effective humoral immune response
Maintenance of functional lymphoid tissue architecture
Virologic factors
Infection with attenuated strains of HIV

MIP, macrophage inflammatory protein; RANTES, regulated on activation, normal T-cell expressed and secreted; SDF, stromal cell–derived factor.

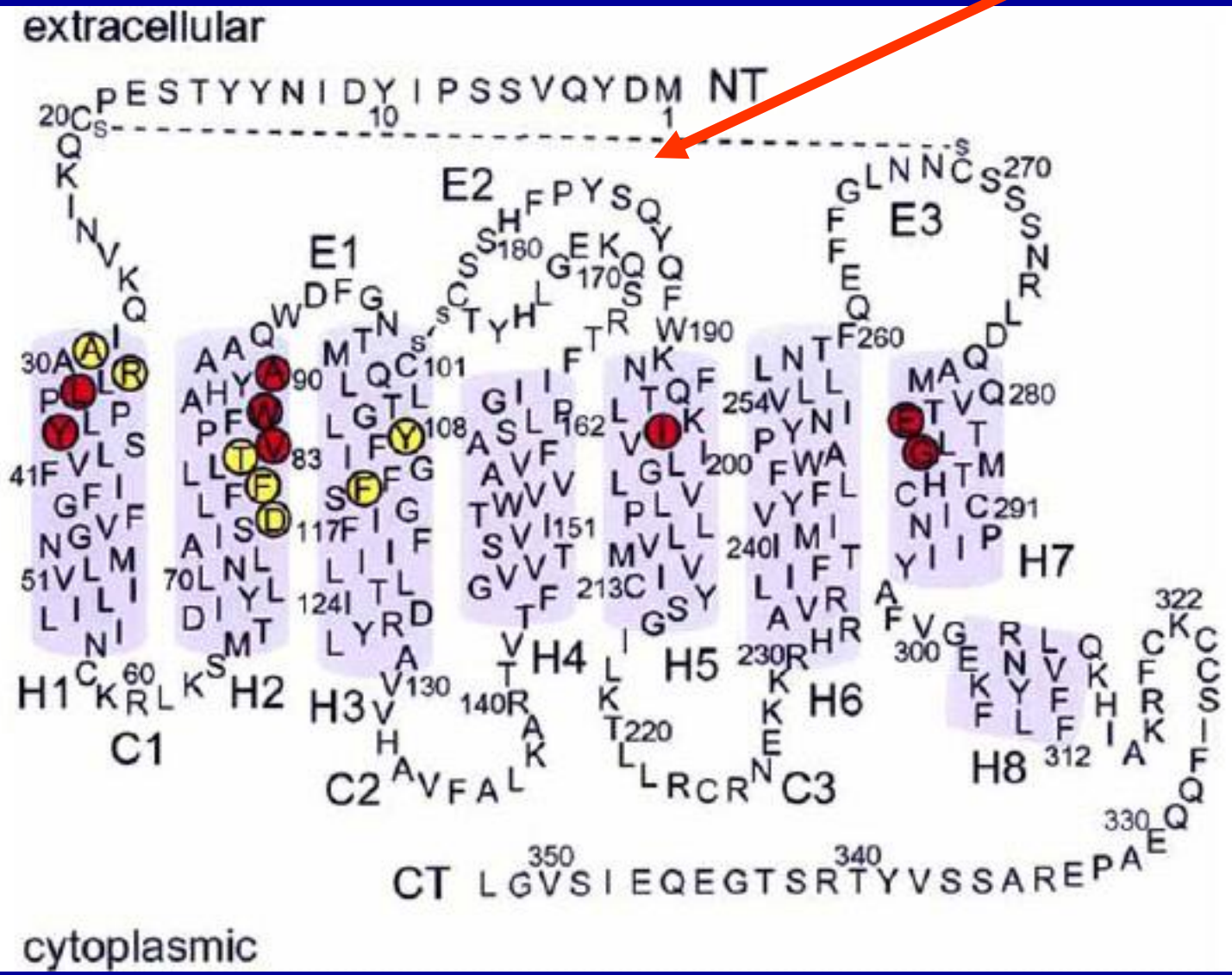
CCR5 and HIV infection

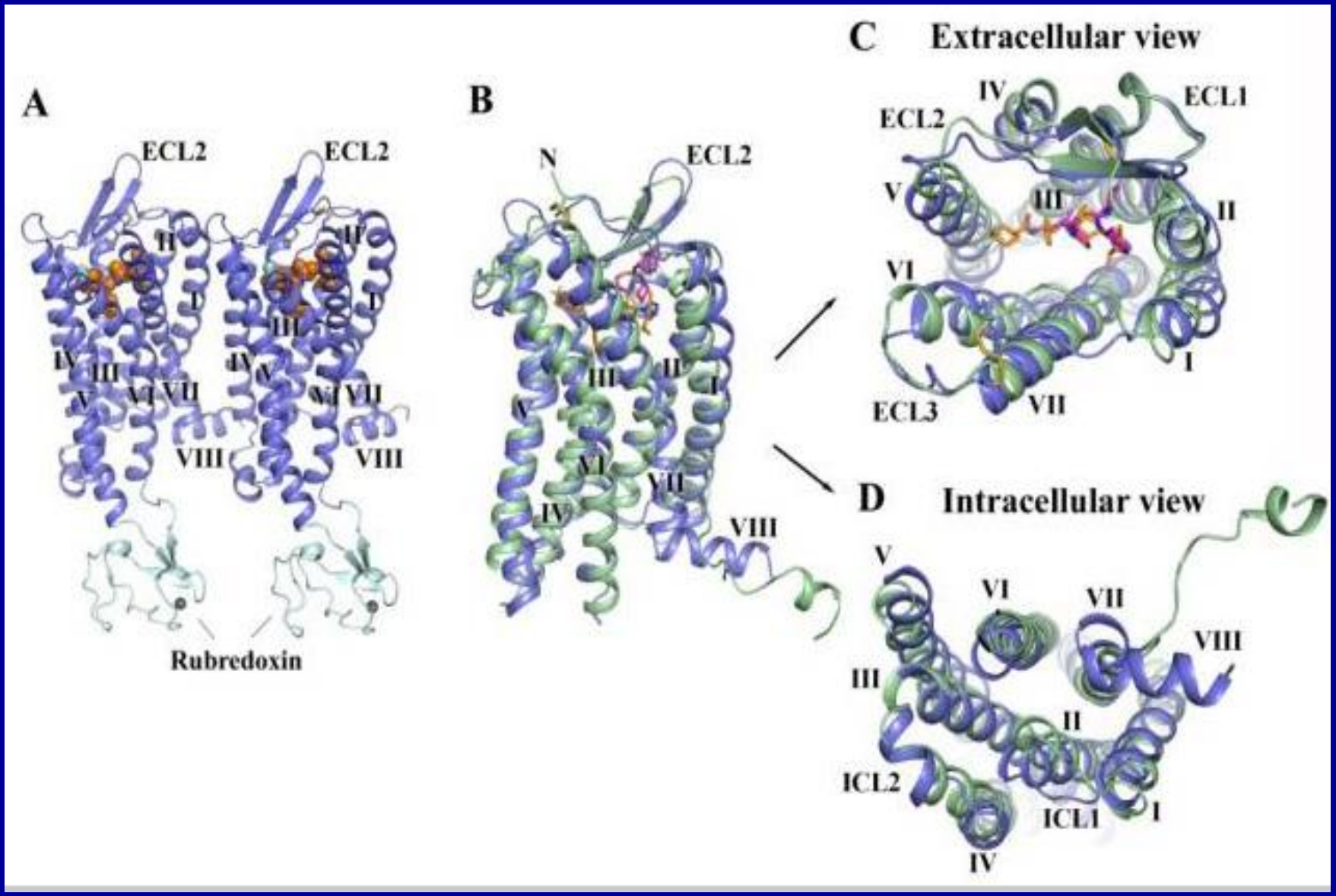
Receptor and co-receptor

- Early on it was recognized that CD4 was a receptor for HIV-1
- However, expression of CD4 in mouse cells did not permit HIV infection
- When mouse cells were fused with human cells these cells became infected
  - Additional receptor – coreceptor!!!!

- The coreceptors CXCR4 and CCR5

- A deletion of 32 base pairs was identified in the CCR5 gene (a mutation conferring immunity to HIV!)
  - CCR5-delta 32 protein is not expressed on the cell surface. HIV cannot attach!
  - HIV-1 infection in persons homozygous for mutation is extremely rare.


extracellular
NT
E1
E2
E3
H1
H2
H3
H4
H5
H6
H7
H8
C1
C2
C3
CT
cytoplasmic


A
ECL2
ECL2
II
II
I
I
III
III
IV
IV
V
VI
VII
VI
VII
VIII
VIII
Rubredoxin
B
N
ECL2
III
II
I
V
VI
VII
IV
VIII
C
Extracellular view
IV
ECL1
ECL2
V
III
II
VI
I
ECL3
VII
D
Intracellular view
V
VI
VII
VIII
III
II
ICL2
ICL1
I
IV

CCR5-delta 32

- **Allele is common in white population with the prevalence of 10-14%**
- **Approximately 1% of the white population are homozygous for this gene**
  - **Resistant for infection**
- **Heterozygous population**
  - **Has lower risk for HIV-1 infection**
  - **Attenuated disease course**
- **Subsequently, other mutations resulting in dysfunctional CCR5 protein has been identified in high risk seronegative populations. (High risk behavior without infection.)**
- **THUS, the availability of cell surface CCR5 is critical determinant of susceptibility to HIV infection and disease progression**

CCR5delta32 and immune function

- Persons who are homozygous for CCR5delta32 seem to have a normal life expectancy

- No apparent alteration in risks for infectious or immunological disorders
  - Redundancy of chemokines and their chemokine receptors
  - Can be compensated for by the other chemokine receptors for directing cellular trafficking and cellular activation

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

SUMMARY

Infection with the human immunodeficiency virus type 1 (HIV-1) requires the presence of a CD4 receptor and a chemokine receptor, principally chemokine receptor 5 (CCR5). Homozygosity for a 32-bp deletion in the *CCR5* allele provides resistance against HIV-1 acquisition. We transplanted stem cells from a donor who was homozygous for *CCR5* delta32 in a patient with acute myeloid leukemia and HIV-1 infection. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy. This outcome demonstrates the critical role *CCR5* plays in maintaining HIV-1 infection.

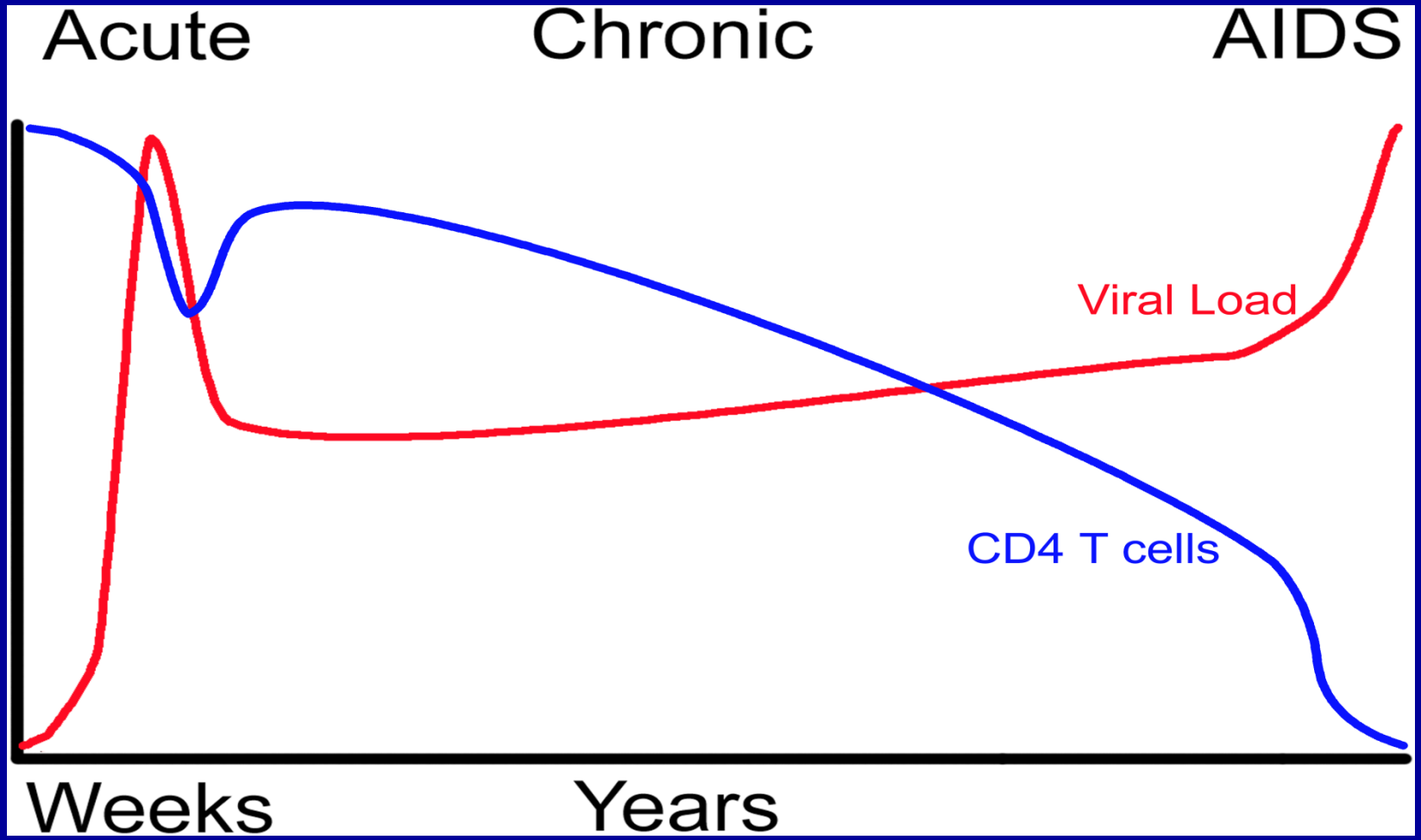
Therapy

- Two classes of CCR5 antagonists in development
  - antibody to CCR5
  - Small molecule inhibitors
    - FDA has proved: Maraviroc
    - Many others in clinical development

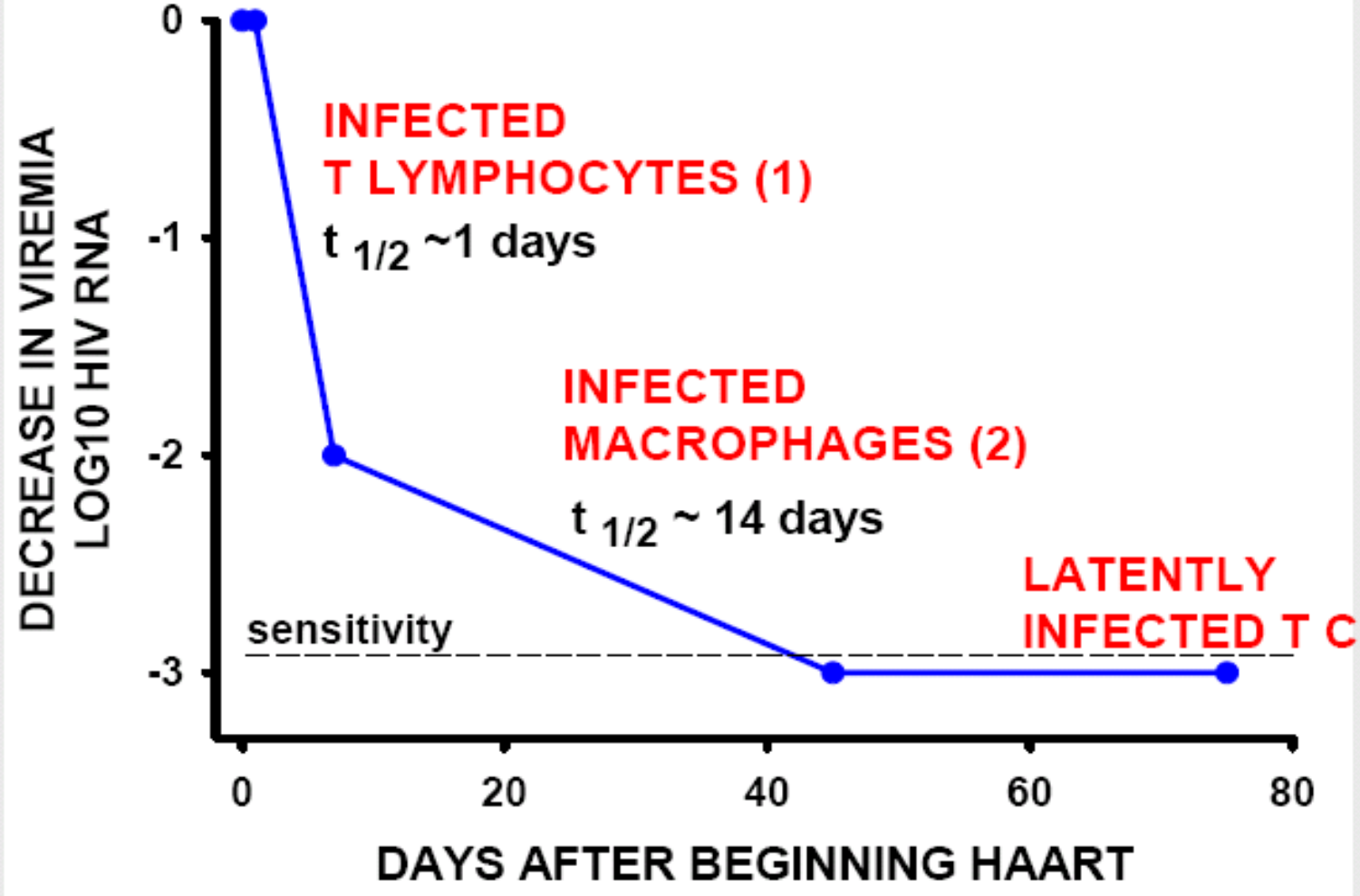
- Inhibit HIV binding

HIV-1 VIRAL DYNAMICS

Natural history course of HIV infection
Production of viral load



ANTI-RETROVIRAL TREATMENT SHOWS 3 DIFFERENT COMPARTMENTS



Why 3 levels of reduction?

- As antivirals take hold new infection goes down and infected cells die off.
- First the t cells with ½ life of 1 day
- Then macrophages with ½ life of 14 days.
- But latent T cells have ½ life of 44 months.
- Memory cells are the problem. The antivirals only work when the T cells are activated, often decades down the road.

Viral dynamics

- **Productive infections in CD4 T cells produce at least 10 new infectious viral particles per cell – capable to infect at least 10 other uninfected CD4 T cells**

- **Effective therapy should reduce the amount of infectious viral particles to less than one in relatively short time period (see phases of viral dynamics: phase 1 and 2)**

- **Why no cure for infected patients?**
  - **Low-level virus replication in sites where drugs are not efficiently penetrating**
  - **Latent HIV pool in resting memory CD4 T cells**

HIV Latency

- HIV exists in resting memory CD4 T cells – Third Phase in viral dynamics after administration of potent antiretroviral drugs
- **Memory cells** are long lived – half-live approximately 44 months
- The size of this latently infected cell pool is approximately "only" 10^5-10^6 latently infected cells/patient
- However, clearance of this latent reservoir is predicted to require the administration of anti-retroviral therapy for at least 60 years
- Approaches to activate and exhaust the latent reservoir are needed – not currently available!

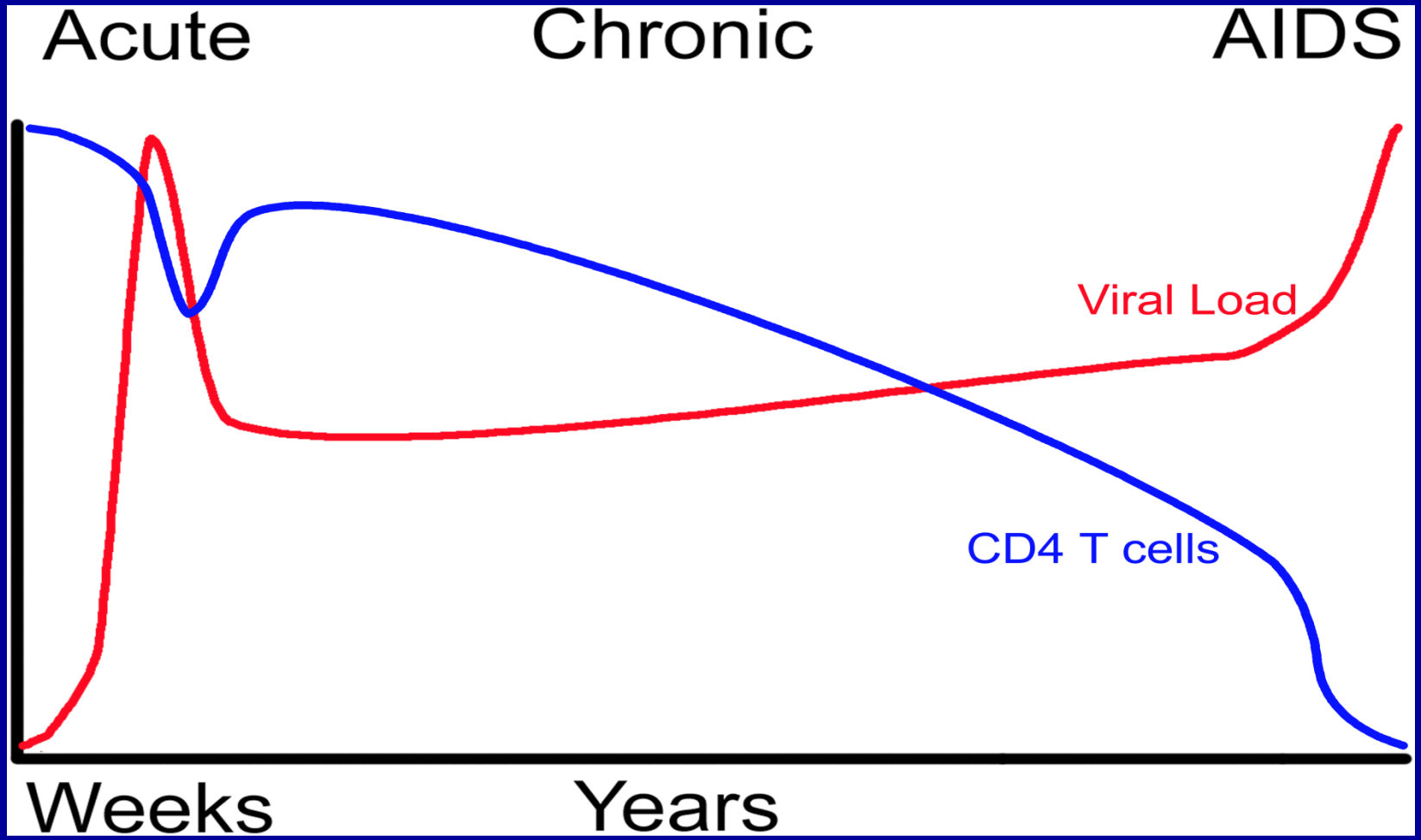
- **YOU NEED TO ACTIVATE EVERY LATENTLY INFECTED CELL IN HUMAN BODY TO BE ABLE TO CURE A PATIENT – OTHERWISE THE VIRAL LOAD REBOUNDS AFTER DISCONTINUATION THE THERAPY**

- **WITH CURRENT DRUG TREATMENTS - CURE IS IMPOSSIBLE**

HIV and CD4 T cell depletion

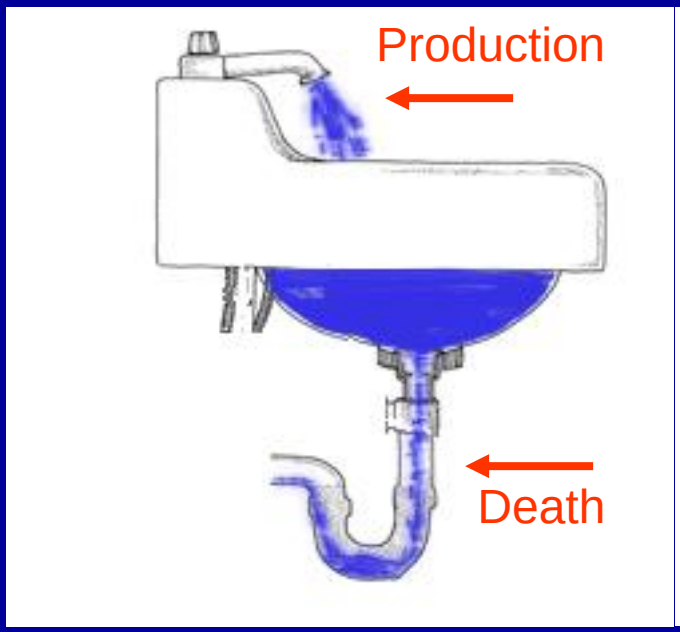
- HIV infects CD4 T cells resulting in high viral load in infected individuals
- This infection kills CD4 T cells
- Homeostasis: The body replaces killed cells by producing more CD4 + T cells.
- This continues until you run out of stem cells. Then T cell count drops and the opportunistic infections take their toll. Person goes from HIV + to AIDS.

Natural history course of HIV infection
Production of viral load



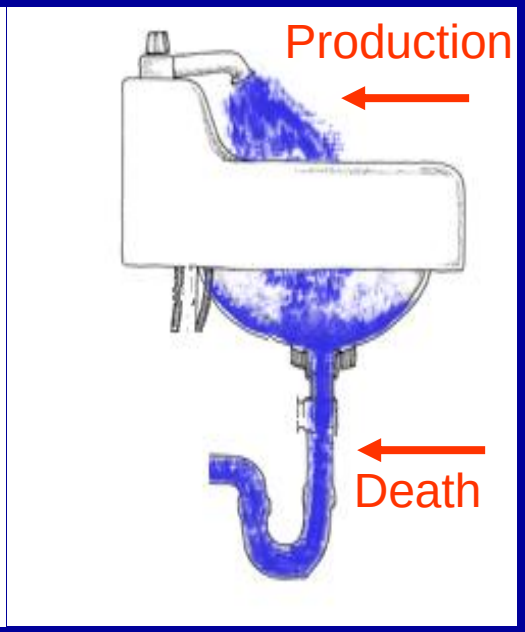
The Tap and Drain Model for CD4 T cells in HIV infection

Healthy



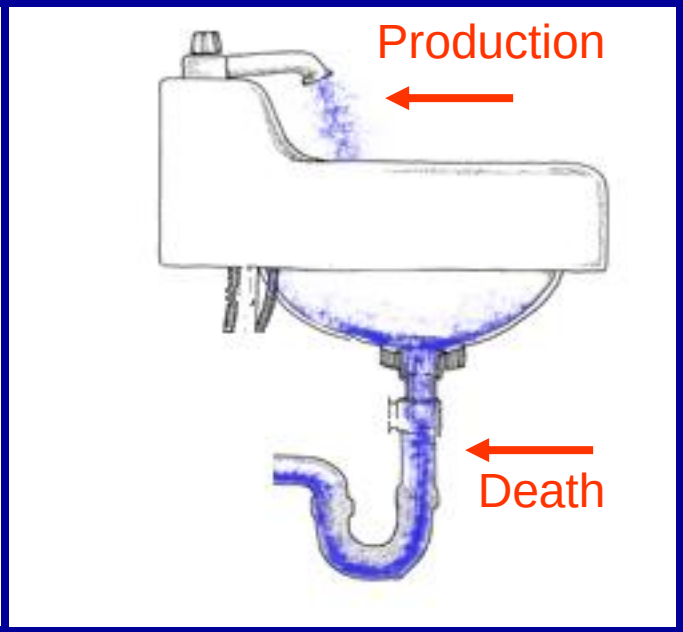
In homeostasis:
Production = Death

HIV



Due to an increase of death of CD4 cells, immune system increases the production:
“try to keep it in homeostasis”

AIDS



Production exhausted

From Dr. Daniel Douek
NIH

Table 7: Clinical Signs and Symptoms of Acute (Primary) HIV Infection[65]

Features (%)	Overall (n = 375)	Sex		Route of transmission	
		Male (n = 355)	Female (n = 23)	Sexual (n = 324)	Injection Drug Use (n = 34)
Fever	75	74	83	77	50
Fatigue	68	67	78	71	50
Myalgia	49	50	26	52	29
Skin rash	48	48	48	51	21
Headache	45	45	44	47	30
Pharyngitis	40	40	48	43	18
Cervical adenopathy	39	39	39	41	27
Arthralgia	30	30	26	28	26
Night sweats	28	28	22	30	27
Diarrhea	27	27	21	28	23

Aquired ImmunoDeficiency Syndrome

- A diagnosis of AIDS is conferred when the T cell count falls below 200 or major opportunistic infections appear:

- Pneumocystic Carinii Pneumonia (which we get all the time)
- Kaposi's Sacroma (caused by HHV-8 which most of us have.)
- Pelvic inflammatory disease
- Thrush(candida albicans which most of us have)
- Shingles (everyone in the room has the pathogen)
- A host of cancers; brain, cervical, lymphomas…

Treatment

- Most people who are HIV + are put on a protease inhibitor and 2 reverse transcriptase inhibitors. This keeps viremia low and T cell count close to normal.
- In most cases this allows for a normal life span but the meds must be changed as the virus mutates and/or the body rejects.
- Antivirals have many side effects and liver and kidney complications
- Suspected exposures are treated with heavy antivirals immediately
- PrEP – Truvada is recommended for people healthy people in intimate relationships with HIV+ partners or people who engage in high risk behavior. Decreases spread by 90%.
- The WHO has adopted “Treatment as containment.”
- Education and antiviral use has decreased the spread of HIV for many years.

Current ARV Medications

NRTI

- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (AZT, ZDV)

NNRTI

- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)
- Rilpivirine (RPV)

PI

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

Integrase Inhibitor (II)

- Raltegravir (RAL)
- Elvitegravir* (EVG)

Fusion Inhibitor

- Enfuvirtide (ENF, T-20)

CCR5 Antagonist

- Maraviroc (MVC)

Indicated Medication

The medication proven safe and effective, and currently approved by FDA for PrEP in healthy adults at risk of acquiring HIV infection, is the fixed-dose combination of TDF and FTC in a single daily dose (see Table 9). Therefore, TDF/FTC is the recommended medication that should be prescribed for PrEP for MSM, heterosexually active men and women, and IDU who meet recommended criteria. Because TDF alone has been proven effective in trials with IDU and heterosexually active men and women, it can be considered as an alternative regimen for these specific populations. As PrEP for MSM, TDF alone is not recommended because no trials have been done, so the efficacy of TDF alone for MSM is unknown.

Table 9: Recommended Oral PrEP Medications

Generic Name	Trade Name	Dose	Frequency	Common Side Effects[66]
Tenofovir disoproxil fumarate (TDF)	Viread	300 mg	Once a day	Nausea, flatulence
Emtricitabine (FTC)[a]	Emtriva	200 mg	Once a day	Rash, headache
TDF + FTC	Truvada	300mg/200 mg	Once a day	—

[a] Not recommended alone; only for use in combination with TDF.

In addition to the safety data obtained in PrEP clinical trials, data on drug interactions and longer-term toxicities have been obtained by studying the component drugs individually for their use in treatment of HIV-infected persons. Studies have also been done in small numbers of HIV-uninfected, healthy adults (see Table 10).

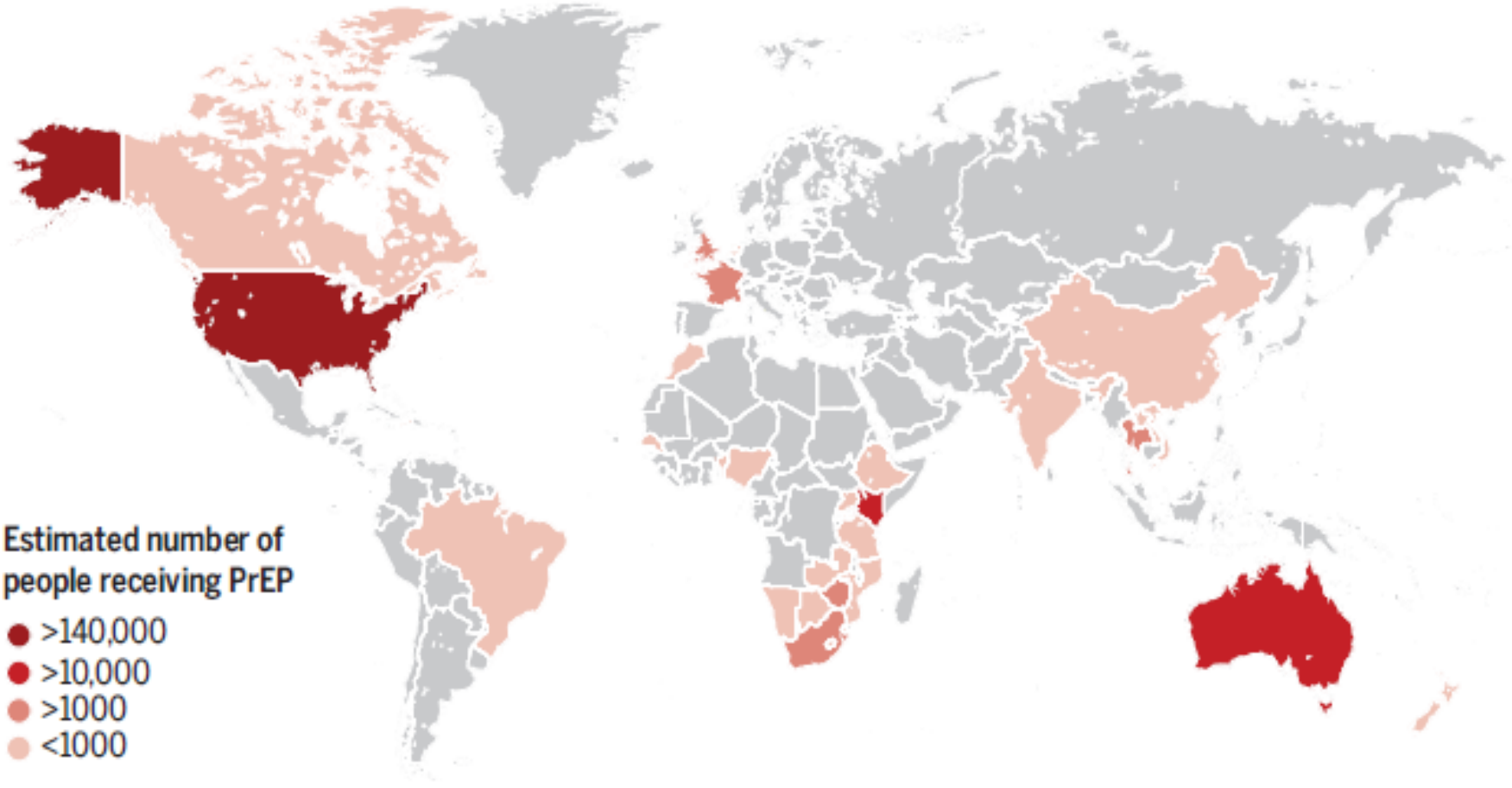
Table 1: Summary of Guidance for PrEP Use

	Men Who Have Sex with Men	Heterosexual Women and Men	Injection Drug Users
Detecting substantial risk of acquiring HIV infection	HIV-positive sexual partner Recent bacterial STI High number of sex partners History of inconsistent or no condom use Commercial sex work	HIV-positive sexual 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)
Clinically eligible	Documented negative HIV test result before prescribing PrEP No signs/symptoms of acute HIV infection Normal renal function; no contraindicated medications Documented hepatitis B virus infection and vaccination status		
Prescription	Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90-day supply		
Other services	Follow-up visits at least every 3 months to provide the following: HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment At 3 months and every 6 months thereafter, assess renal function Every 6 months, test for bacterial STIs		
	Do oral/rectal STI testing	Assess pregnancy intent Pregnancy test every 3 months	Access to clean needles/syringes and drug treatment services

STI: sexually transmitted infection

Poorly PrEPared

Only the United States, Australia, and Kenya aggressively promote pre-exposure prophylaxis (PrEP).



Researchers around the world are conducting 12 late-stage trials of HIV vaccines.

PUBLIC HEALTH

HIV-vaccine strategy sought

Therapies to prevent infection advance in a crowded field.

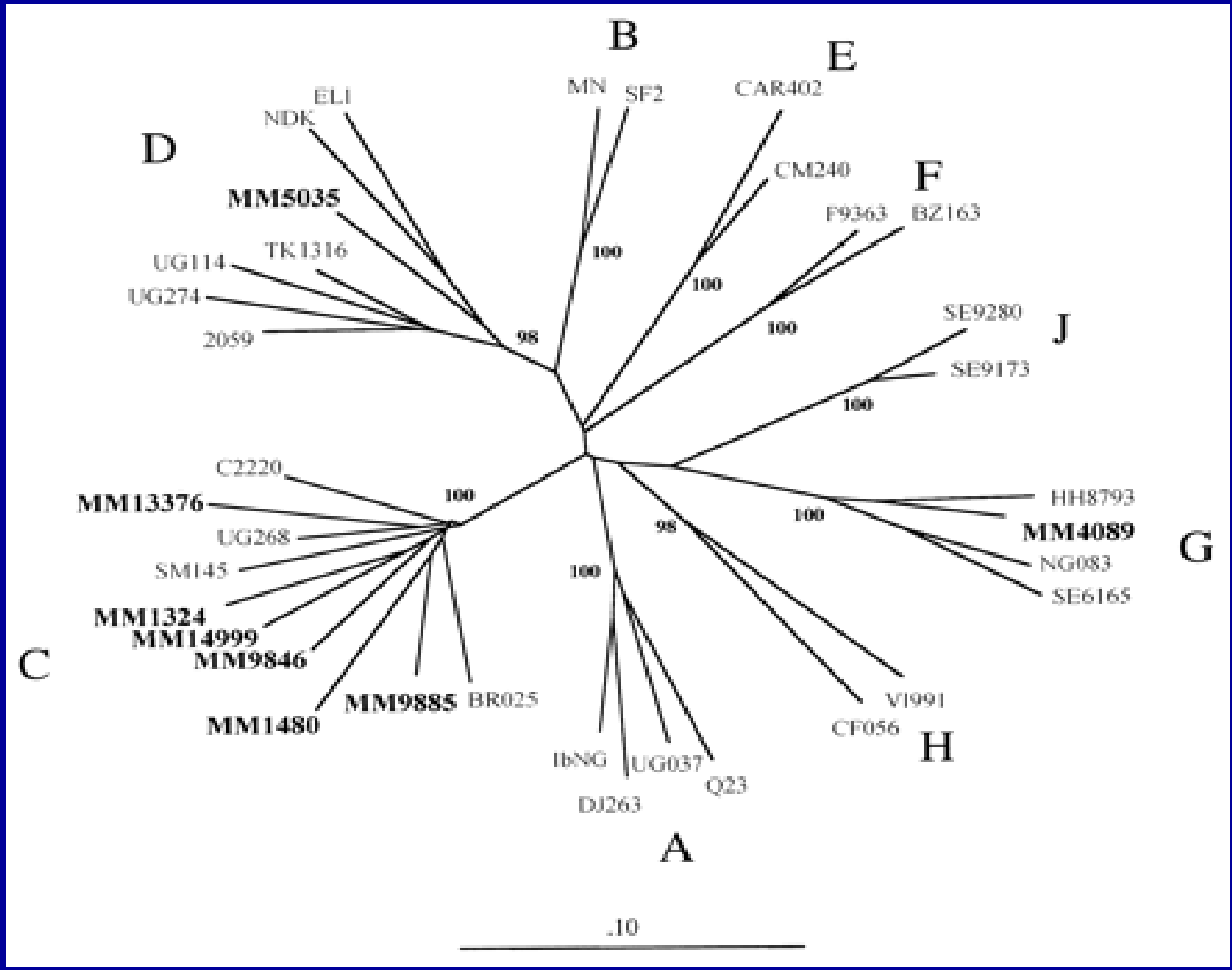
HIV VACCINES

NO VACCINES

HIV mutates a lot so it is difficult to make an antibody that will still work after mutation. A vaccine can stimulate the immune system to make an antibody that will work against one strain but not others. Even within one infected person HIV will mutate many times.

Also the most important antigen is hidden until after binding.

Work continues on multivalent vaccines.



Phylogenetic tree of HIV-1 envelope sequences in Nairobi women. Journal of Virology, May 1999, p. 4393-4403, Vol. 73, No. 5

EPIDEMIOLOGY WOLRDWIDE

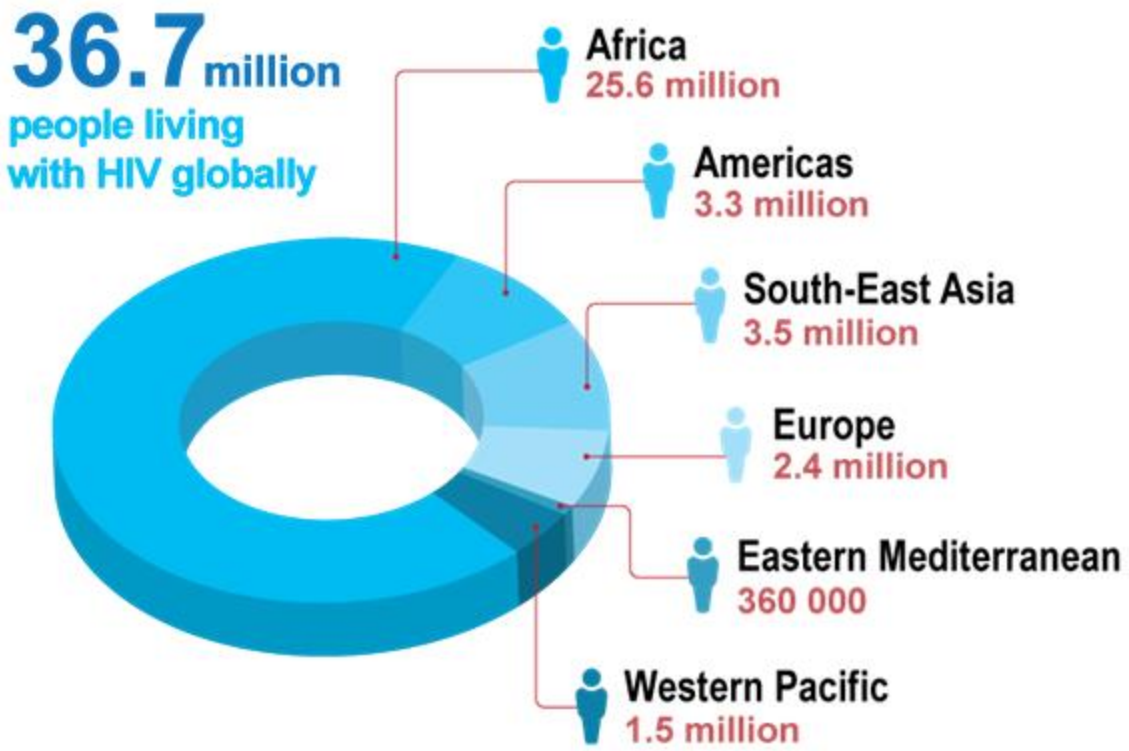
Summary of the global HIV epidemic (2016)

Number of people living with HIV in 2016	**Total**	36.7 million [30.8 million – 42.9 million]
	Adults	34.5 million [28.8 million – 40.2 million]
	Women	17.8 million [15.4 million – 20.3 million]
	Men	16.7 million [14.0 million – 19.5 million]
	Children (<15 years)	2.1 million [1.7 million – 2.6 million]
People newly infected with HIV in 2016	**Total**	1.8 million [1.6 million – 2.1 million]
	Adults	1.7 million [1.4 million – 1.9 million]
	Children (<15 years)	160 000 [100 000 – 220 000]
AIDS deaths in 2016	**Total**	1.0 million [830 000 – 1.2 million]
	Adults	890 000 [740 000 – 1.1 million]
	Children (<15 years)	120 000 [79 000 – 160 000]

Source: UNAIDS/WHO estimates.

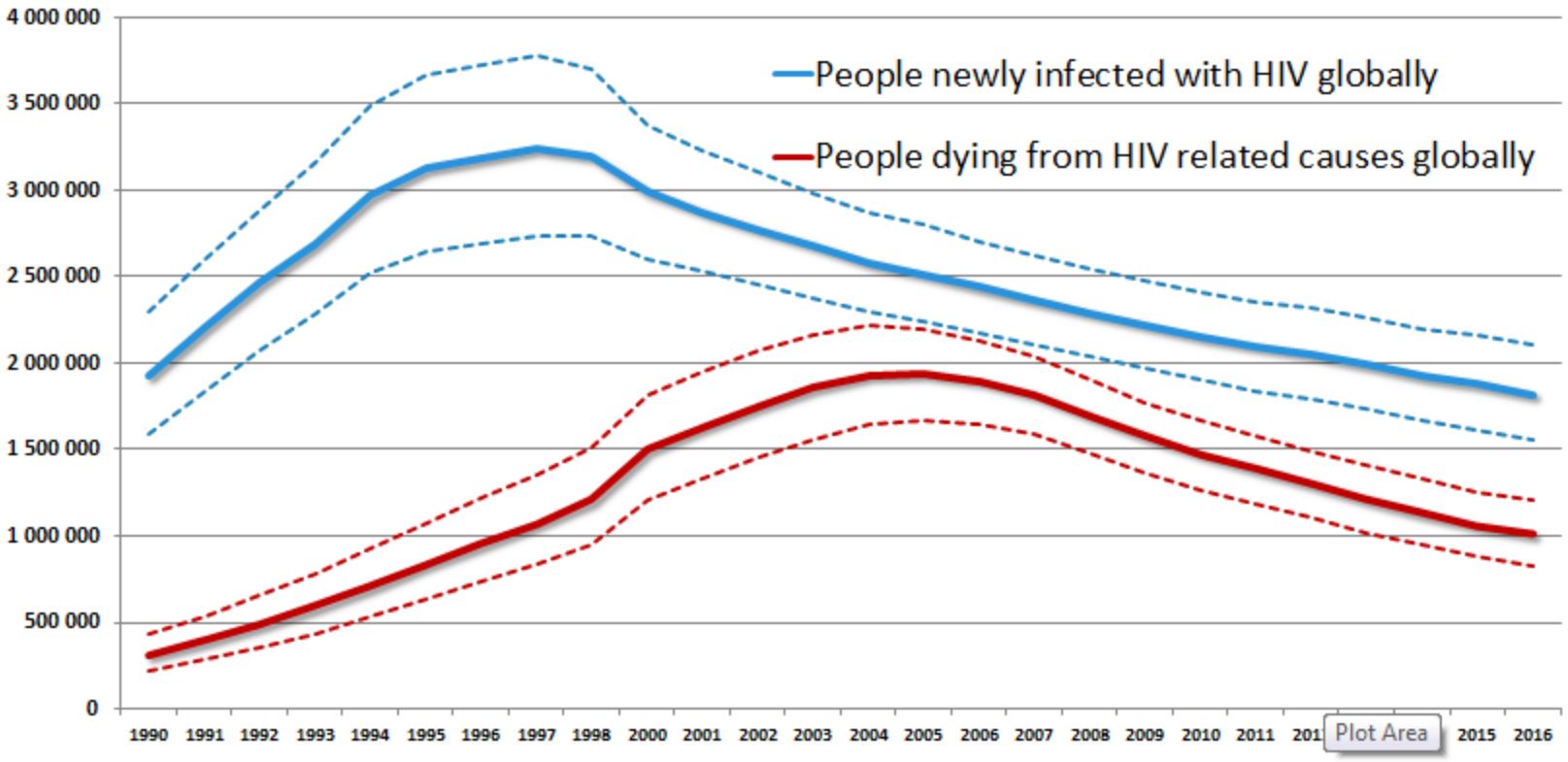
World Health Organization

People living with HIV by WHO region (2016)



World Health Organization

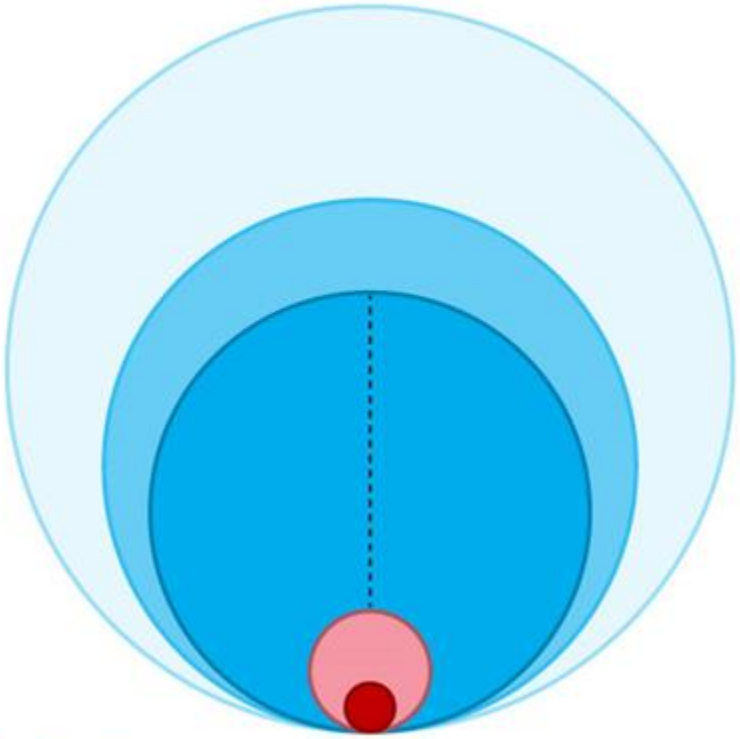
Decline in HIV incidence and mortality over time



Source: UNAIDS/WHO estimates.

World Health Organization

Number of people newly infected with HIV



2000 — 3.0 million

2010 — 2.2 million

2016 — 1.8 million

2020 — <500 000

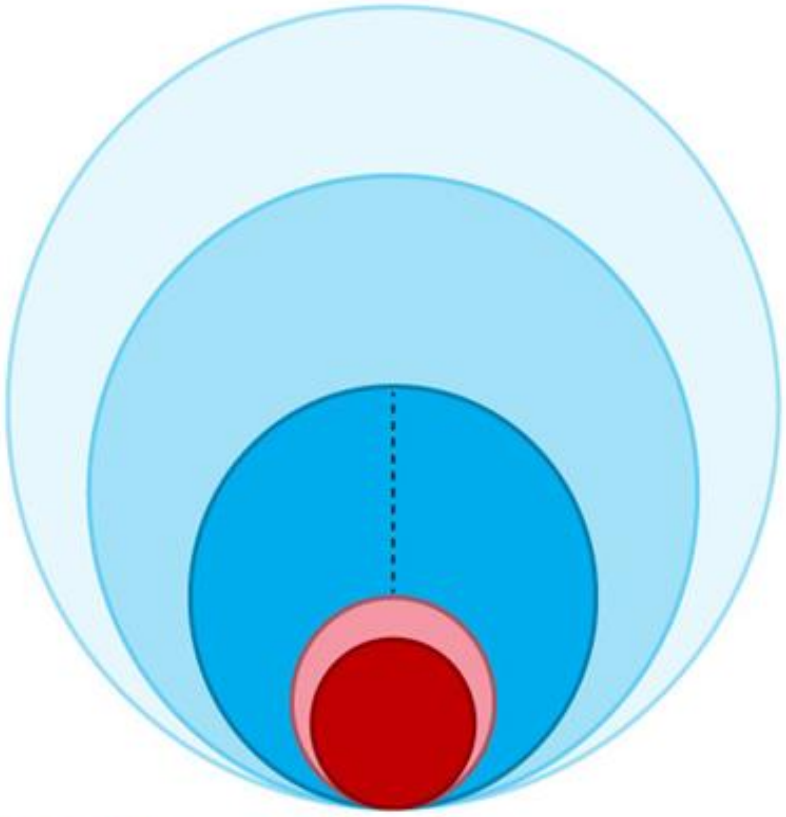
2030 — <200 000

Future targets

UNAIDS/WHO estimates

World Health Organization

Number of people dying from HIV



2005 — 1.9 million

2000 — 1.5 million

2016 — 1.0 million

2020 — <500 000

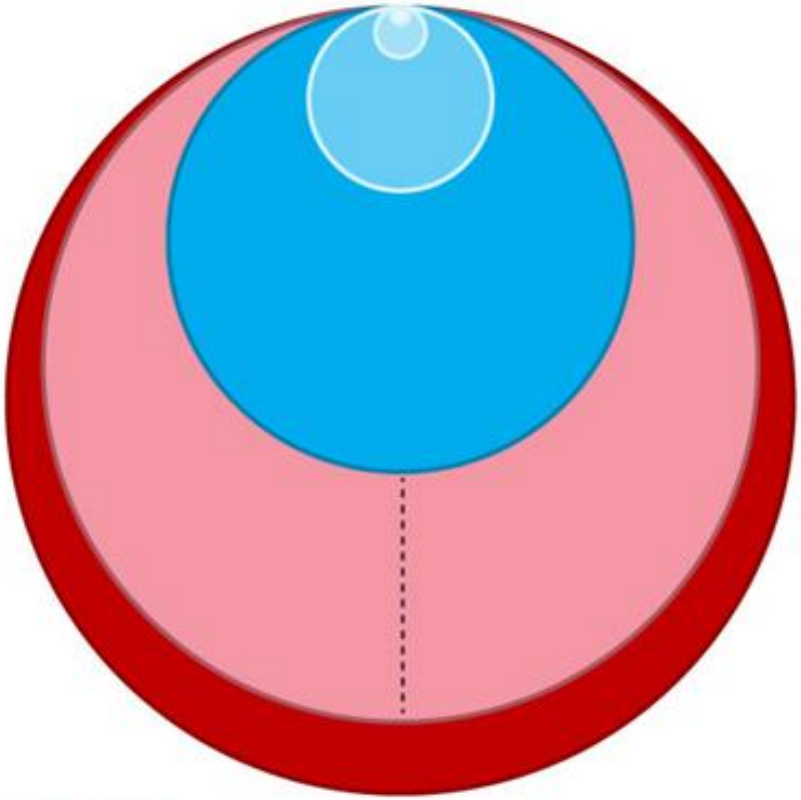
2030 — <400 000

Future targets

UNAIDS/WHO estimates

World Health Organization

Number of people receiving antiretroviral treatment



2000 — 685 000
2005 — 2.1 million
2010 — 7.7 million
2016 — 19.5 million
Mid-2017 — 20.9 million
2020 — ≈ 30 million
2030 — ≈ 33 million

Future targets

UNAIDS/WHO estimates

World Health Organization

EPIDEMIOLOGY IN USA

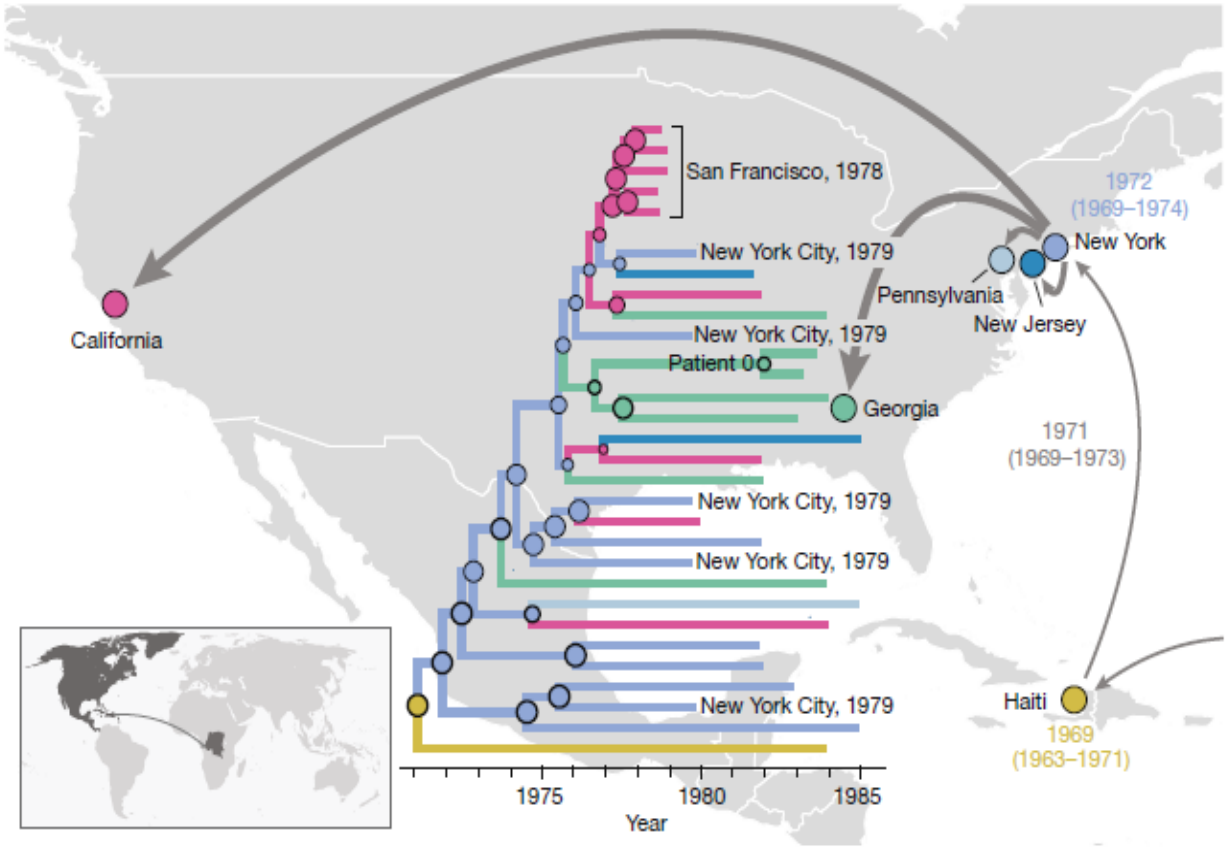
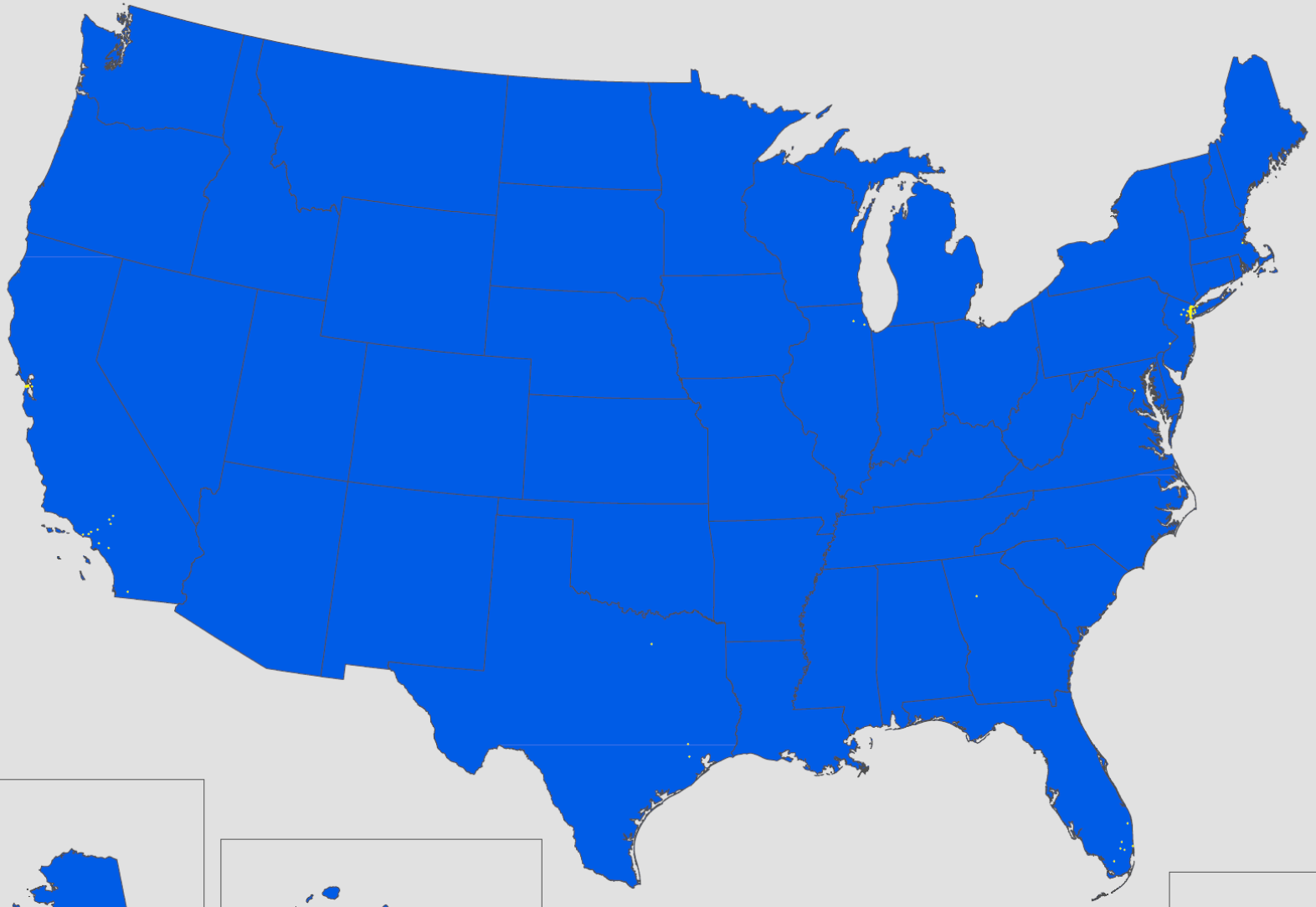
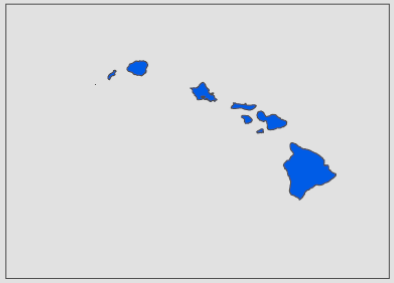


Figure 3 | The early patterns of HIV-1 subtype B spread in the Americas. The map summarizes the main patterns of spread inferred from the molecular clock phylogeographic analyses. The map inset shows the initial introduction of the subtype B lineage into the Caribbean from Africa. From there, the virus spreads first to NY and subsequently to different locations in the United States. The tree depicts the US clade, plus the most closely related basal Haiti strain, as inferred from the *'env* 74' analysis (Extended Data Fig. 5b). Tips of the clade correspond to the year of sampling. Tip branch colours reflect the actual sampling locations as indicated on the map; interior branches depict phylogenetically inferred locations using the same colour scheme. Diameters of internal node circles reflect posterior location probability values. Thick outer circles indicate internal nodes with posterior probability support >0.95. Thickness of the arrows reflects number of transitions inferred from this tree cluster. Mean dates and 95% credible intervals in yellow and blue represent the date estimates for the MRCA in the Caribbean and the US, respectively, based on the *env* 74 analysis. Date next to arrow between these locations represents the estimated timing of the corresponding jump. Patient 0 (represented by two sequences) and the earliest sequences from San Francisco (1978) and New York City (1979) are labelled. Maps made with Natural Earth.

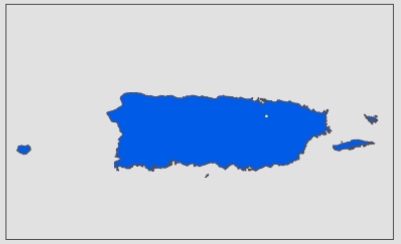
Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 1983 N = 4,782



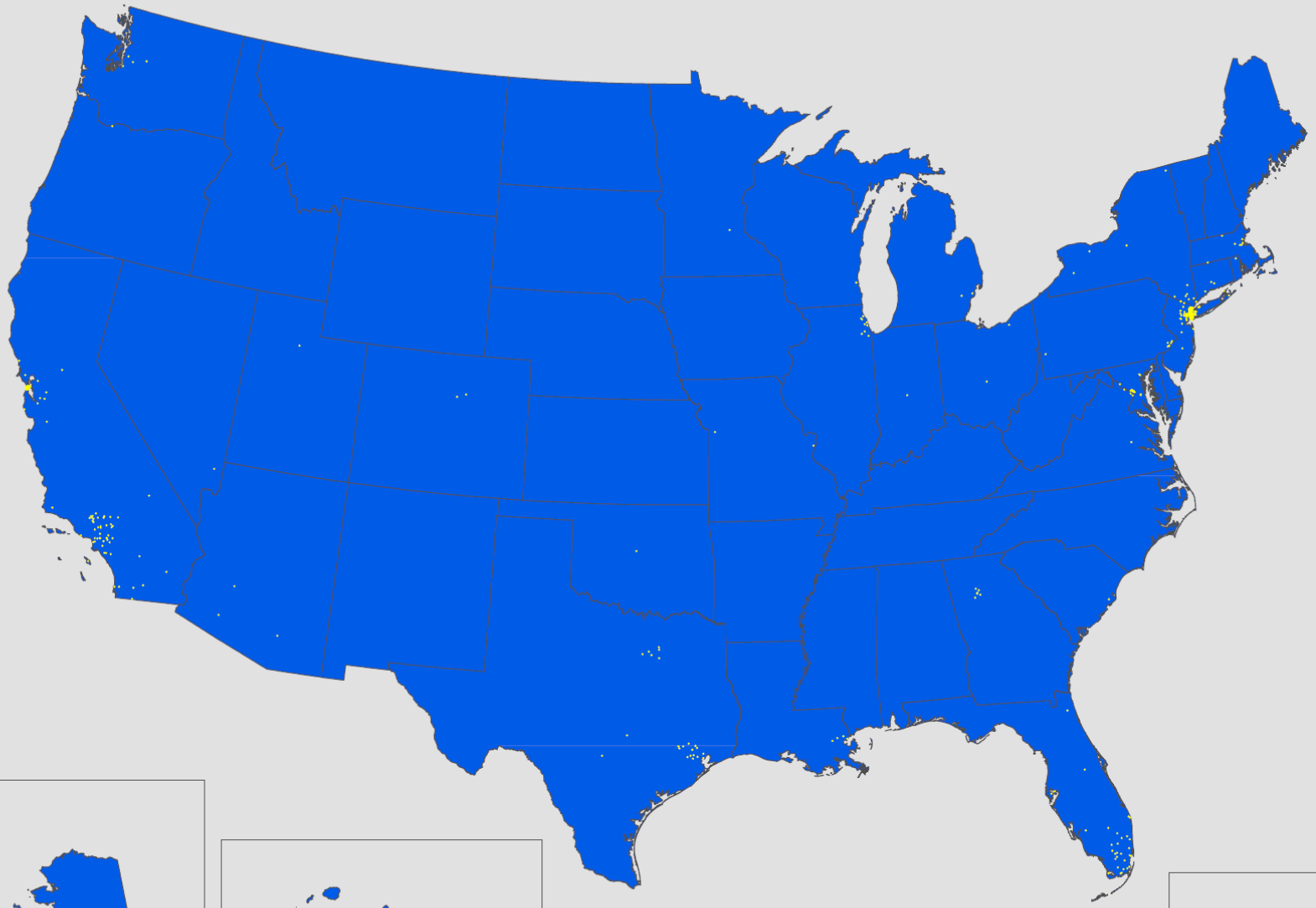


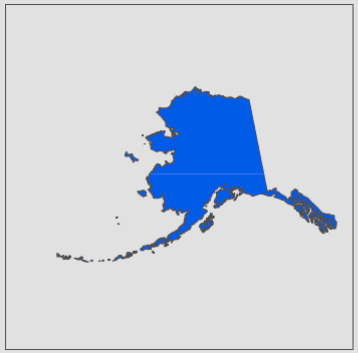
Each Dot Represents 50 Cases

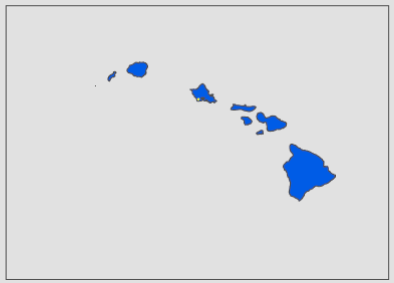
Note. Data have been adjusted for reporting delays. Data are presented for AIDS cases reported to CDC through June 2007. All data are provisional.



Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 1985 N = 23,109







Each Dot Represents 50 Cases

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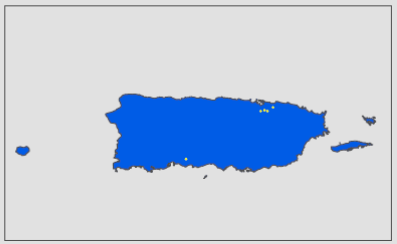
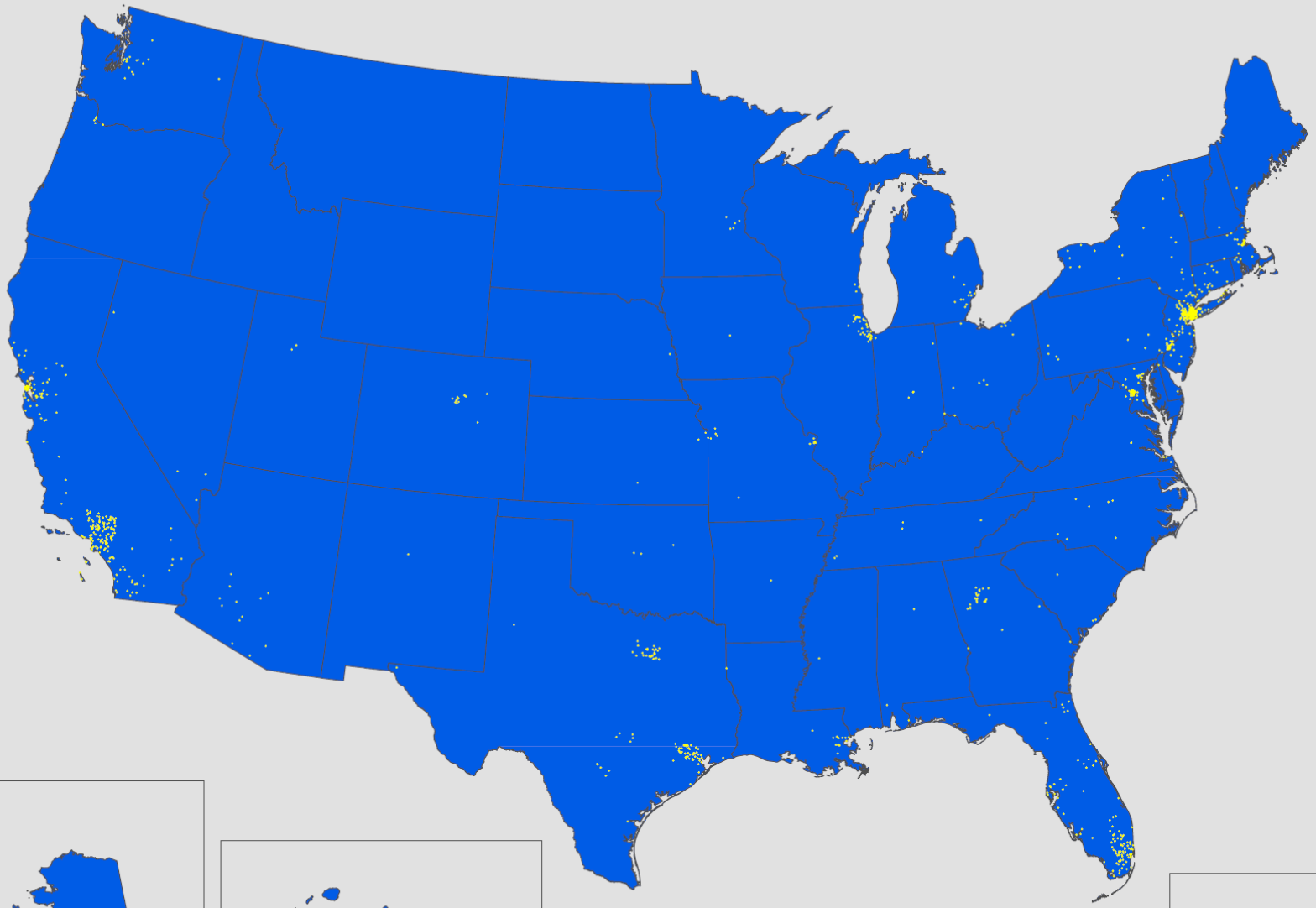


Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 1987 N = 71,136



Each Dot Represents 50 Cases

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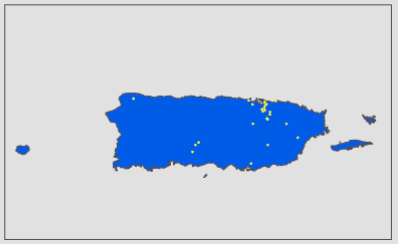
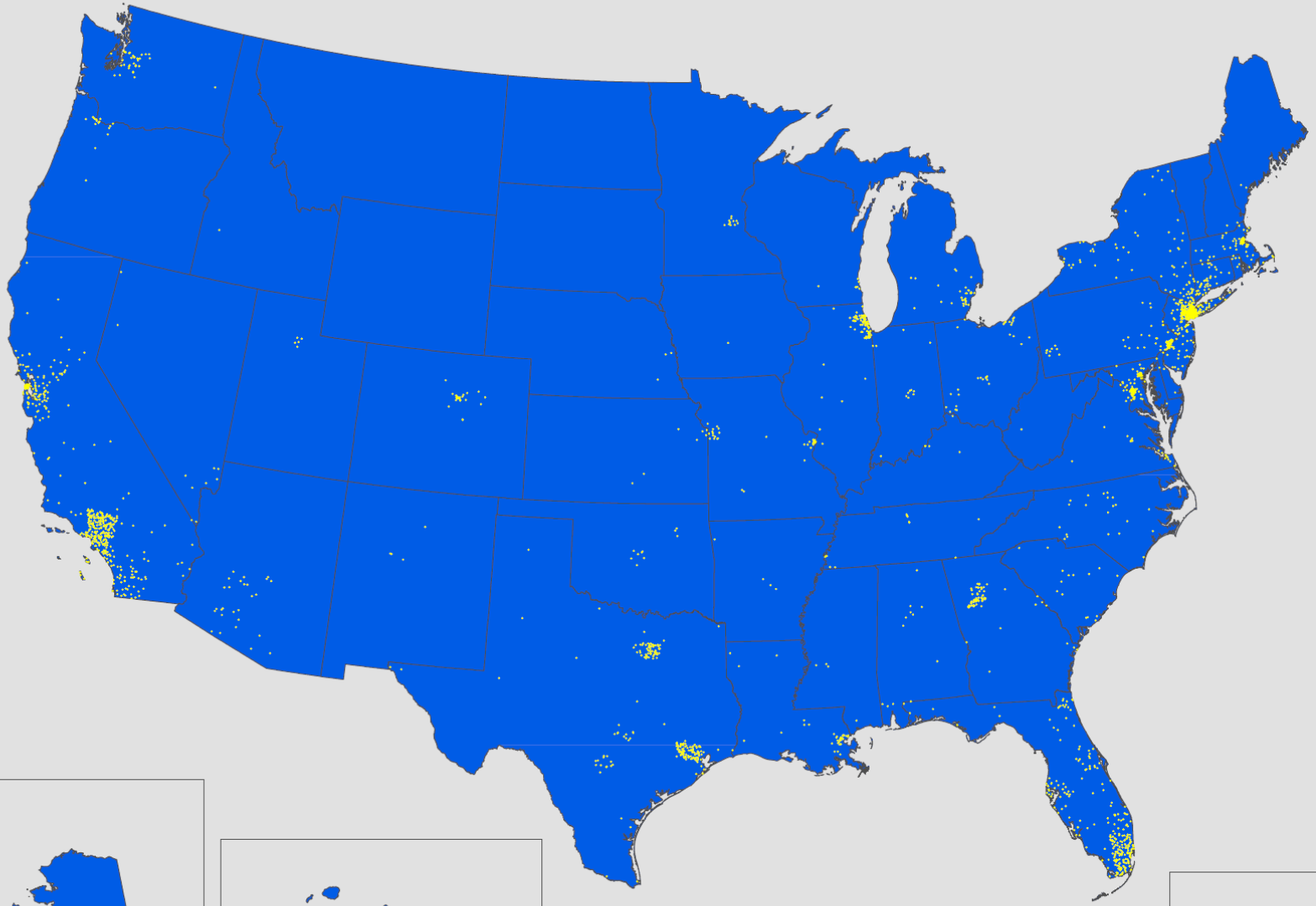
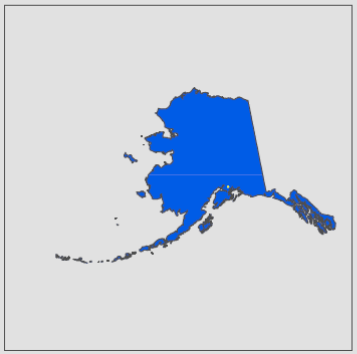
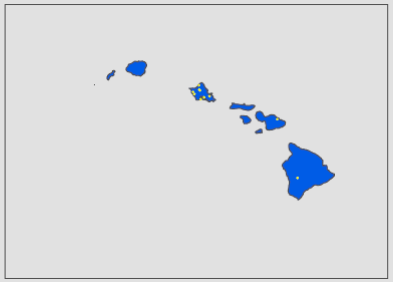


Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 1989 N = 149,523







Each Dot Represents 50 Cases

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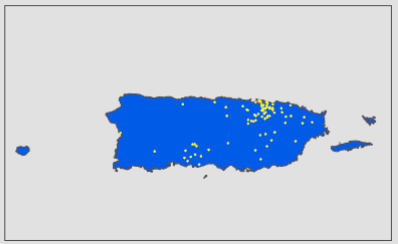
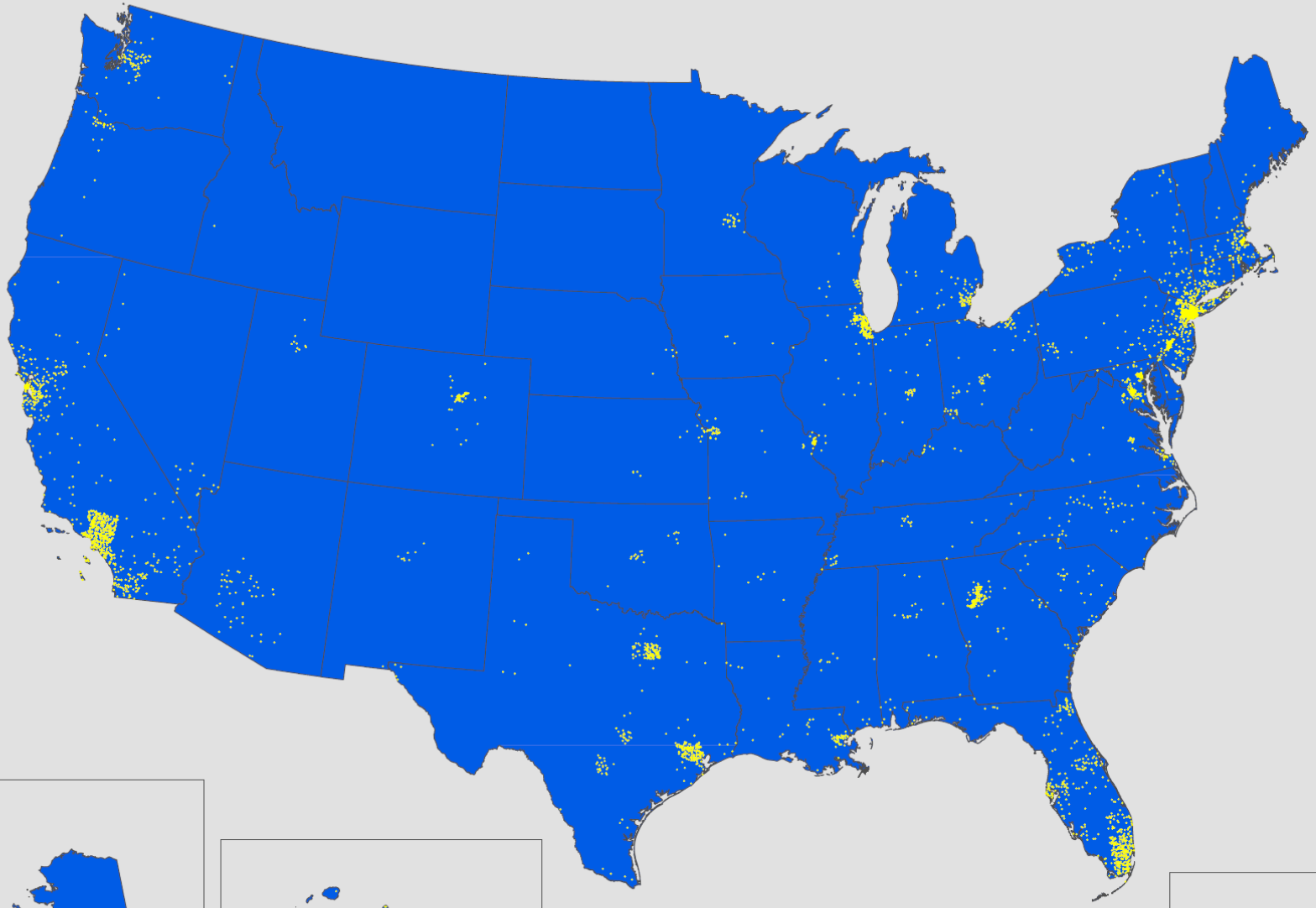
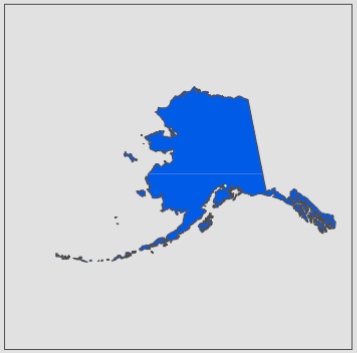
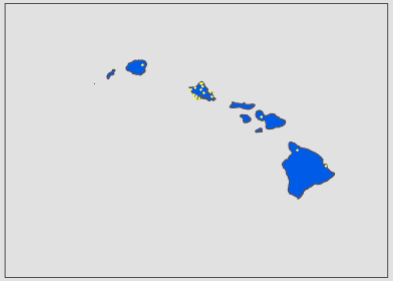


Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 1991 N = 257,674

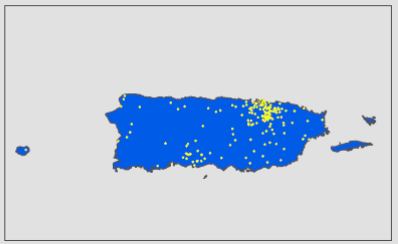




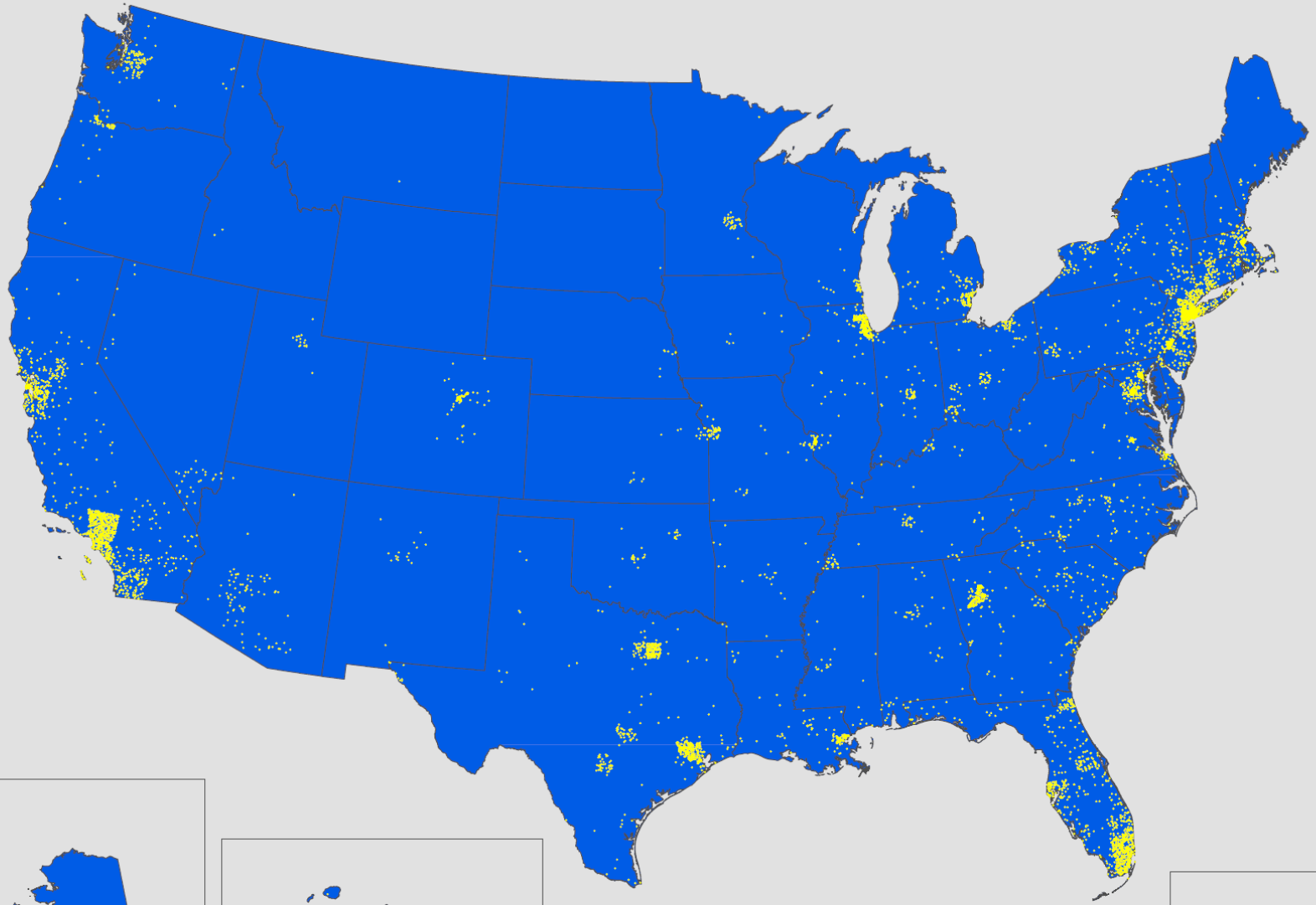


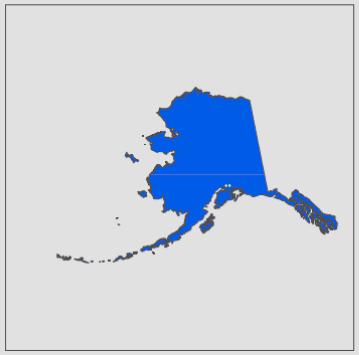
Each Dot Represents 50 Cases

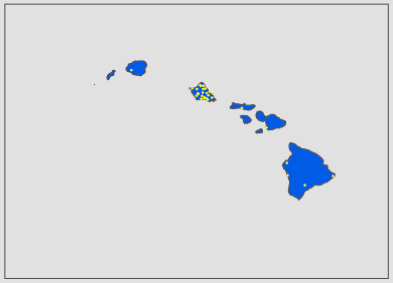
Note. Data have been adjusted for reporting delays. Data are presented for AIDS cases reported to CDC through June 2007. All data are provisional.



Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 1993 N = 413,102

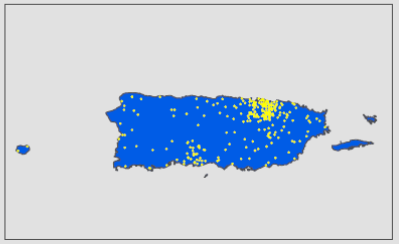




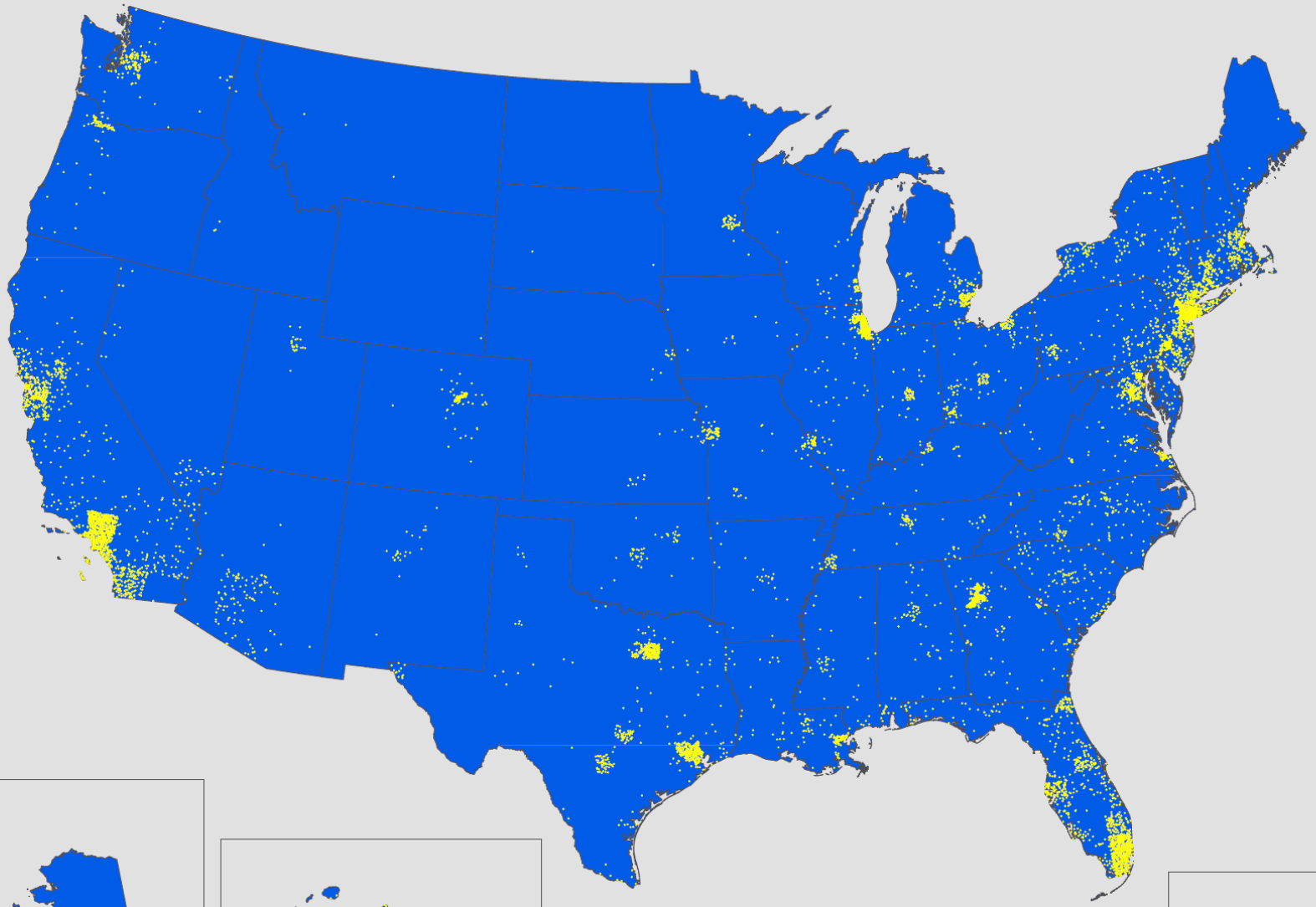


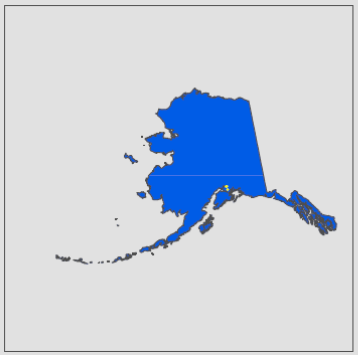
Each Dot Represents 50 Cases

Note. Data have been adjusted for reporting delays. Data are presented for AIDS cases reported to CDC through June 2007. All data are provisional.



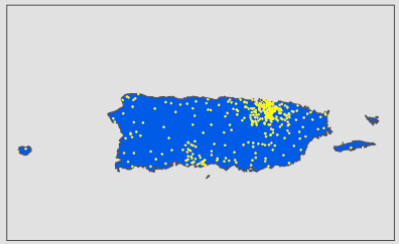
Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 1995 N = 551,750



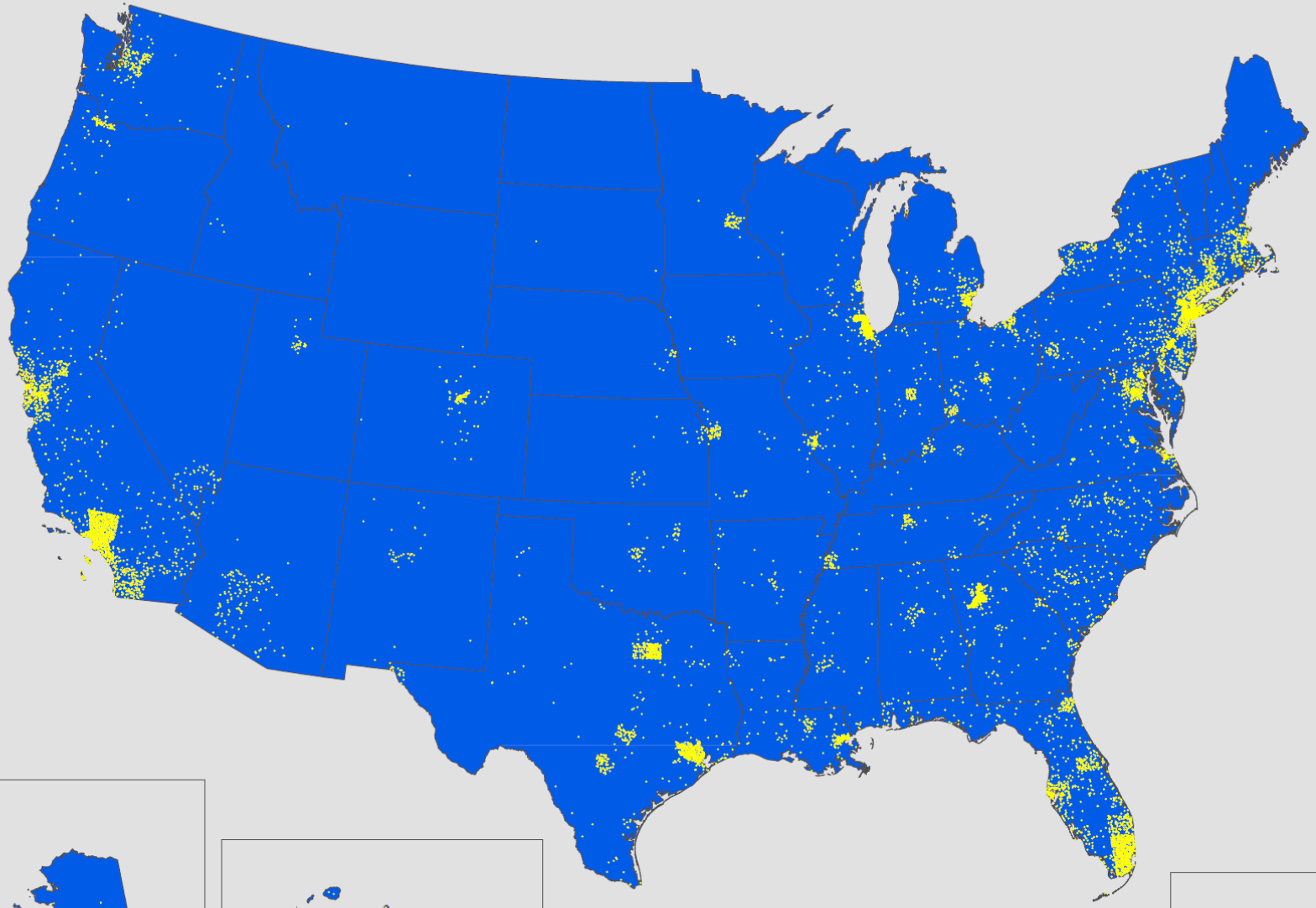


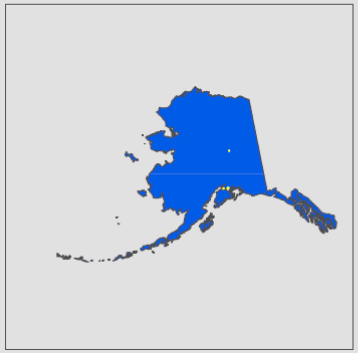
Each Dot Represents 50 Cases

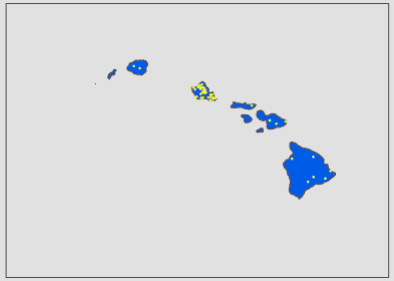
Note. Data have been adjusted for reporting delays. Data are presented for AIDS cases reported to CDC through June 2007. All data are provisional.



Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 1997 N = 660,102

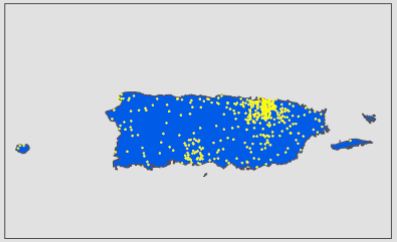




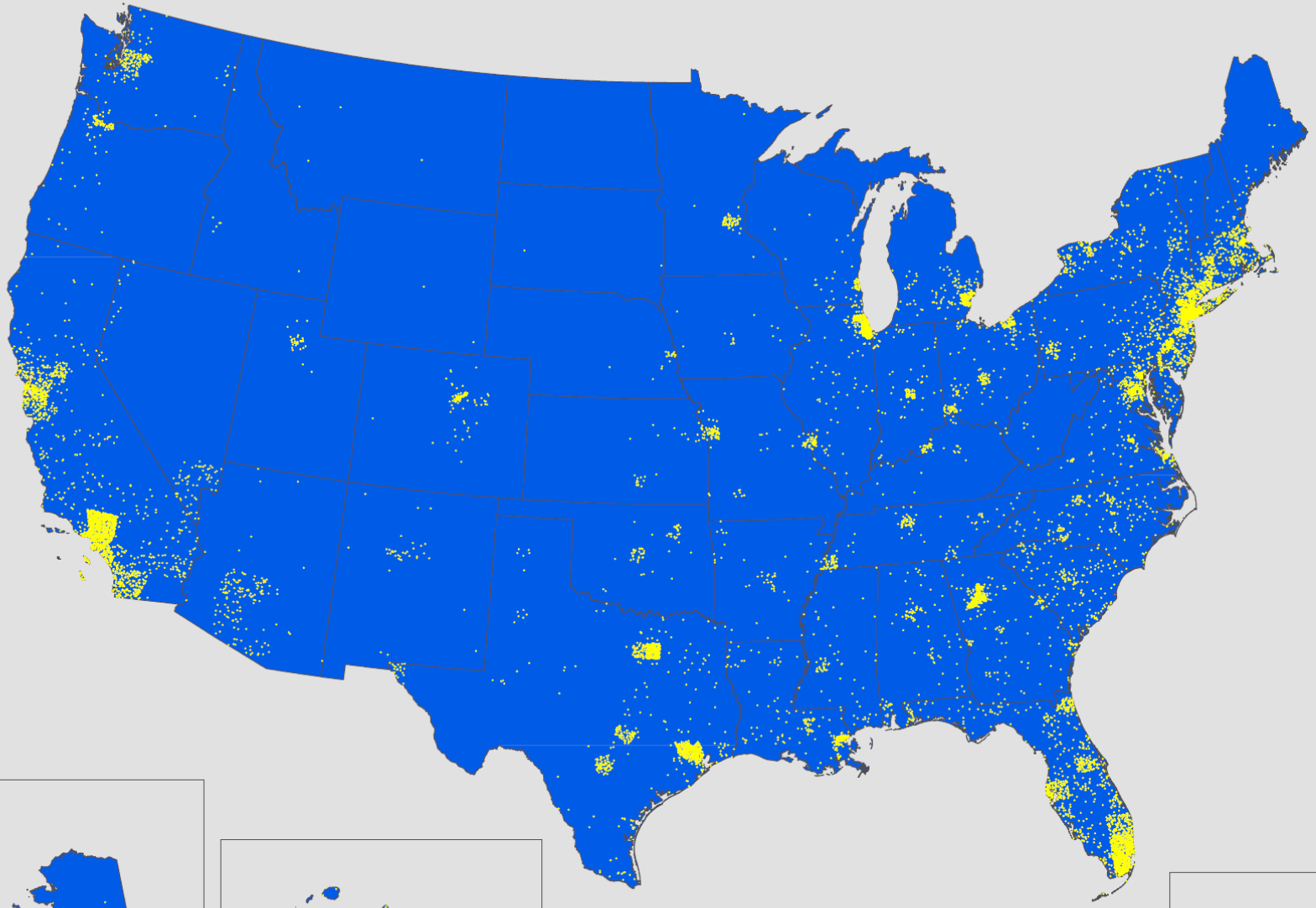


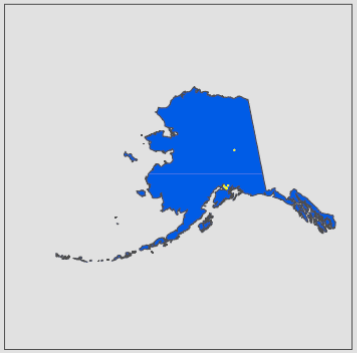
Each Dot Represents 50 Cases

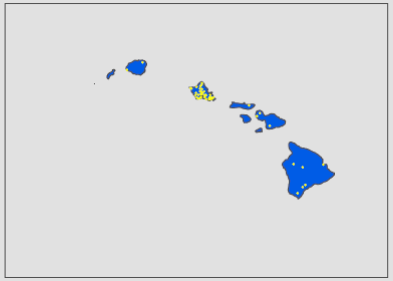
Note. Data have been adjusted for reporting delays. Data are presented for AIDS cases reported to CDC through June 2007. All data are provisional.



Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 1999 N = 741,488

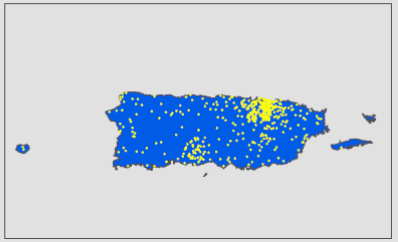




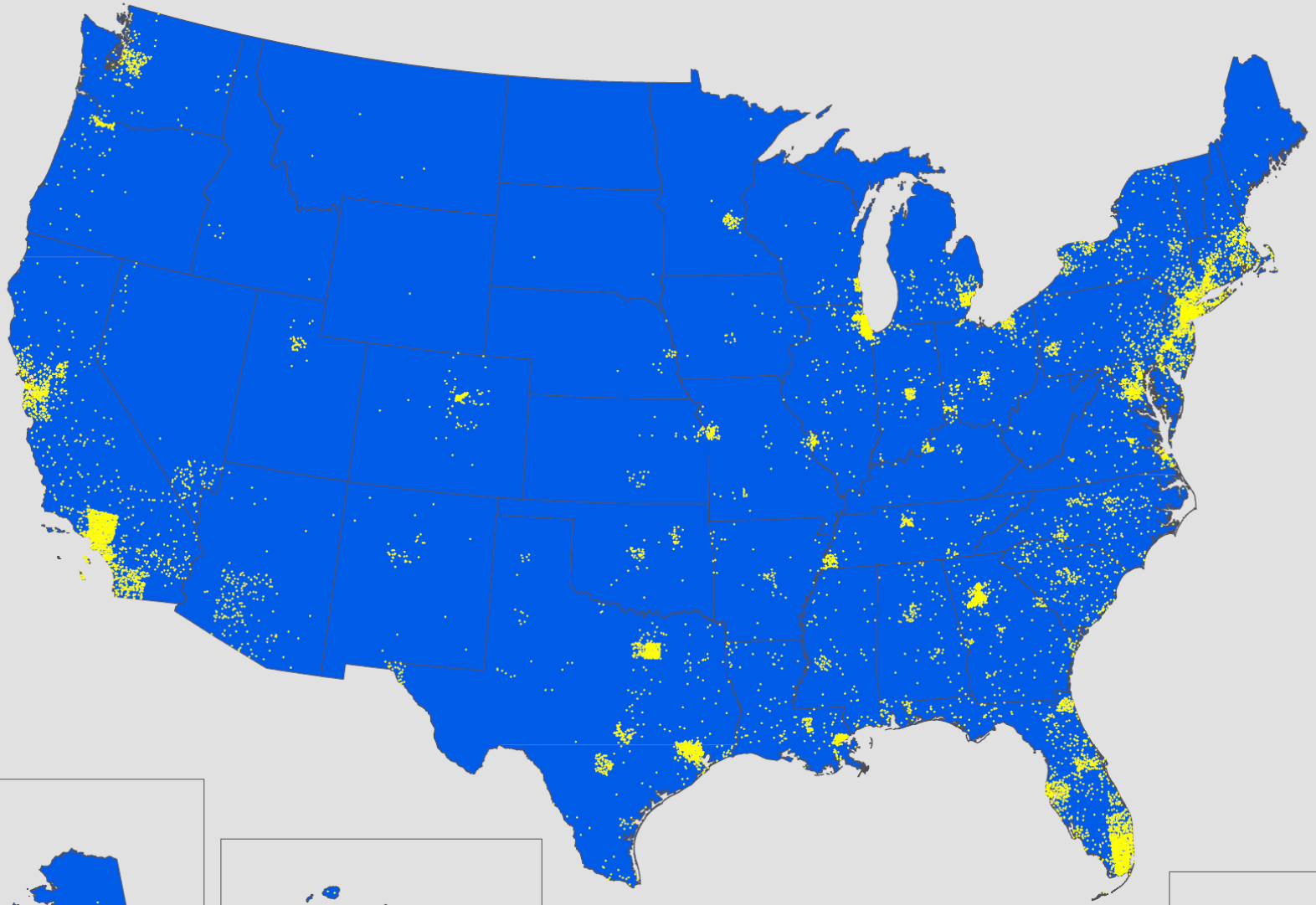


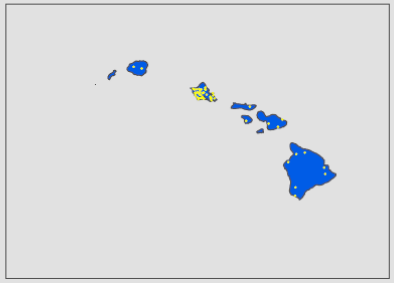
Each Dot Represents 50 Cases

Note. Data have been adjusted for reporting delays. Data are presented for AIDS cases reported to CDC through June 2007. All data are provisional.



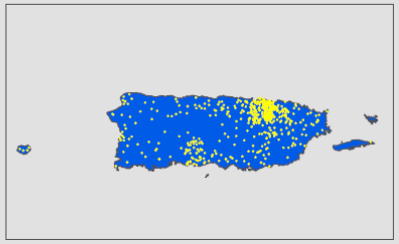
Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 2001 N = 820,513



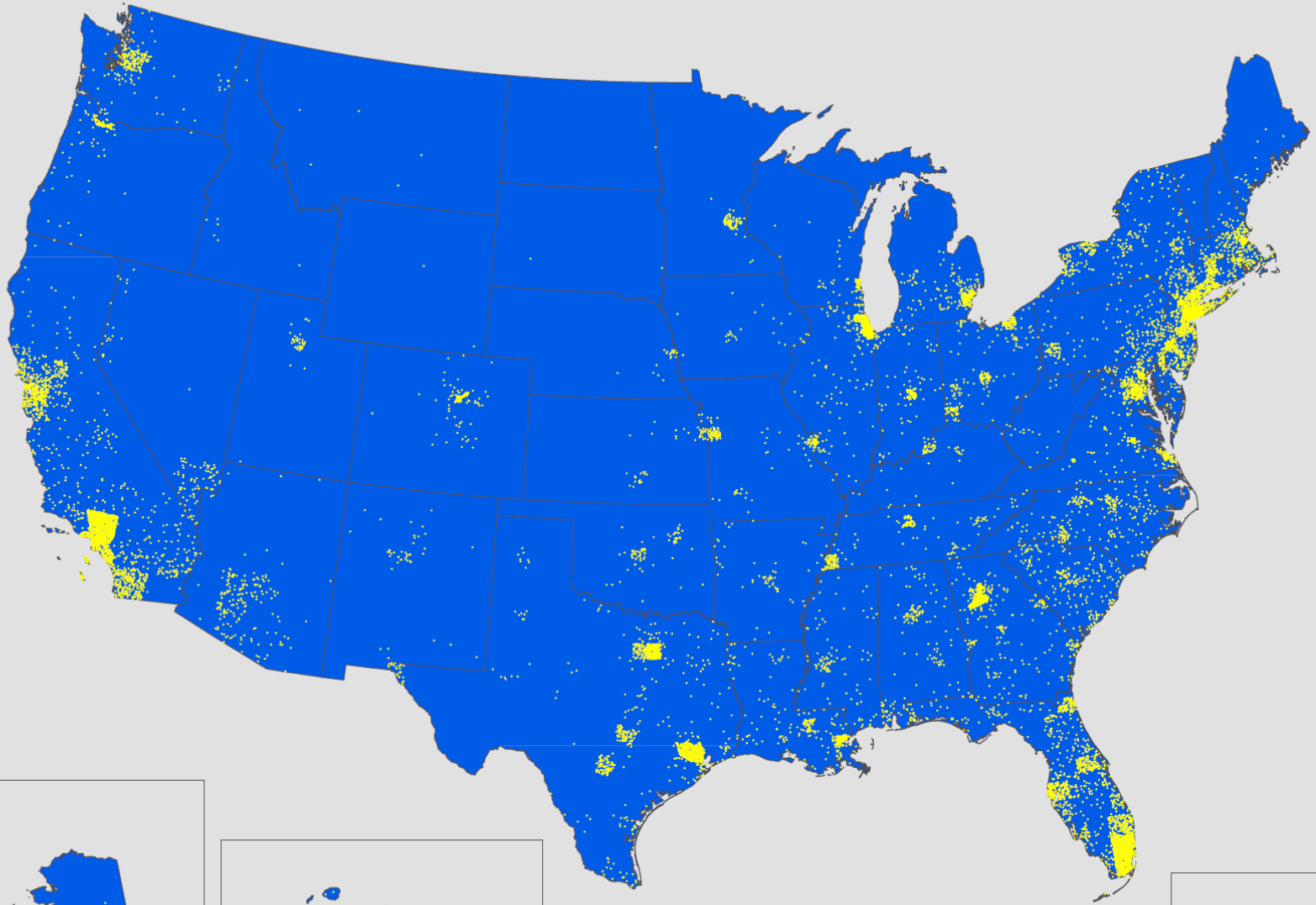


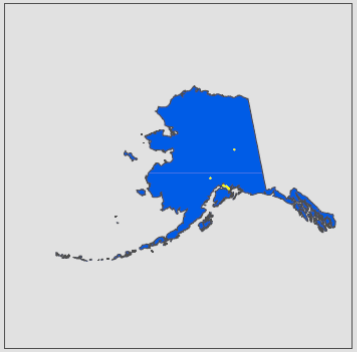
Each Dot Represents 50 Cases

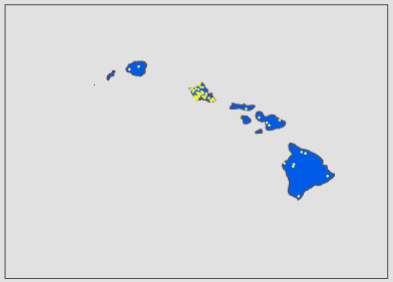
Note. Data have been adjusted for reporting delays. Data are presented for AIDS cases reported to CDC through June 2007. All data are provisional.



Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 2003 N = 899,238

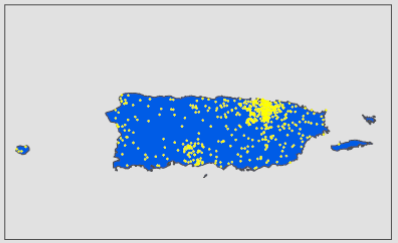




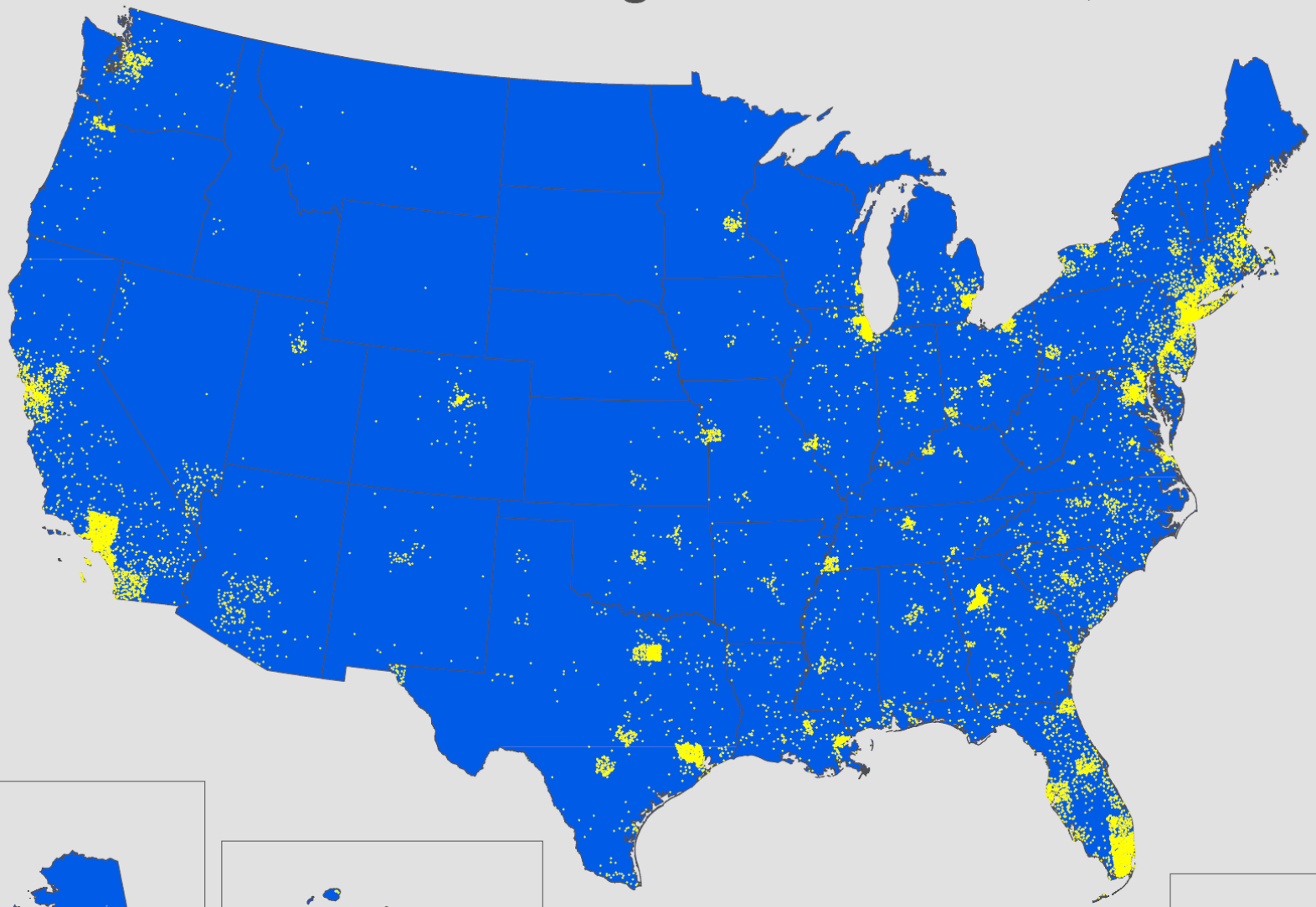


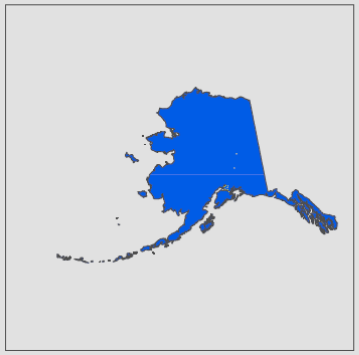
Each Dot Represents 50 Cases

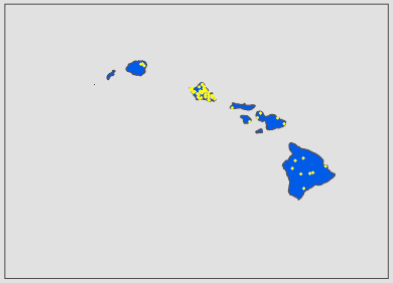
Note. Data have been adjusted for reporting delays. Data are presented for AIDS cases reported to CDC through June 2007. All data are provisional.



Estimated AIDS Cases in the United States and Puerto Rico
Cumulative through 2005 N = 975,350

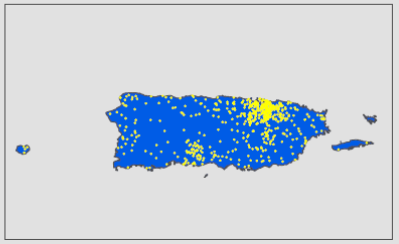




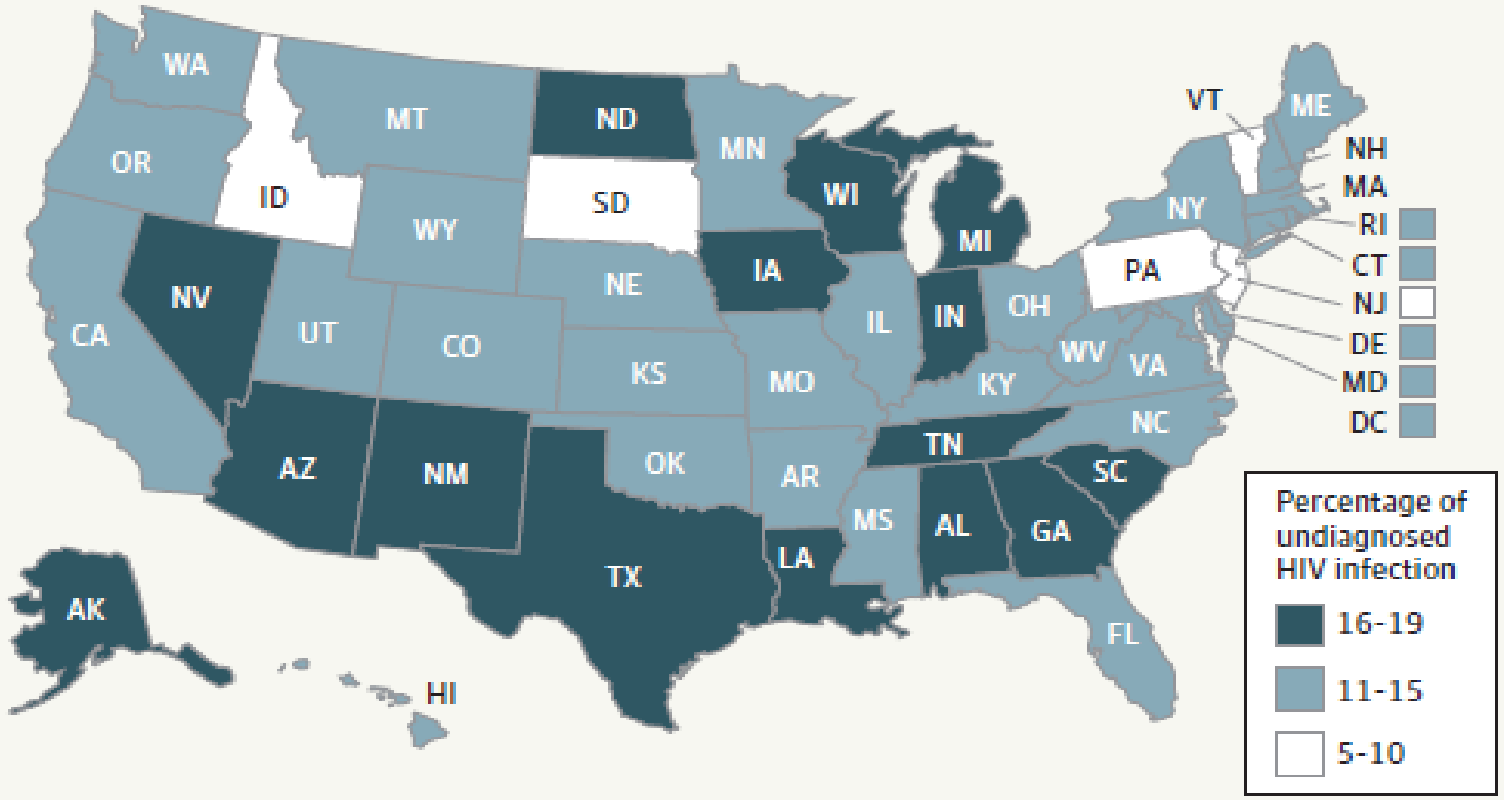


Each Dot Represents 50 Cases

Note. Data have been adjusted for reporting delays. Data are presented for AIDS cases reported to CDC through June 2007. All data are provisional.



Percentage of Undiagnosed Infections Among Persons Aged 13 Years or Older Living With Diagnosed or Undiagnosed HIV Infection, United States, 2015[a]



[a]Overall percentage of undiagnosed infections is 14.5%. Data were classified manually. Estimates were derived by using HIV surveillance data for persons aged 13 years or older at diagnosis in the 50 states and the District of Columbia.
Source: *MMWR Morb Mortal Wkly Rep*. 2017;66(47):1300-1306.

On average, the delay between infection and diagnosis of HIV was 3 years, but it varied more than 2-fold among segments of the population and more than 3-fold across states.