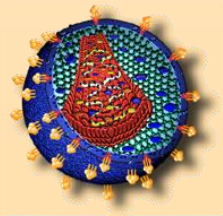
Retroviruses

TRACO

September 26, 2016

Frank Maldarelli



HIV Dynamics and Replication Program

NCI–Frederick

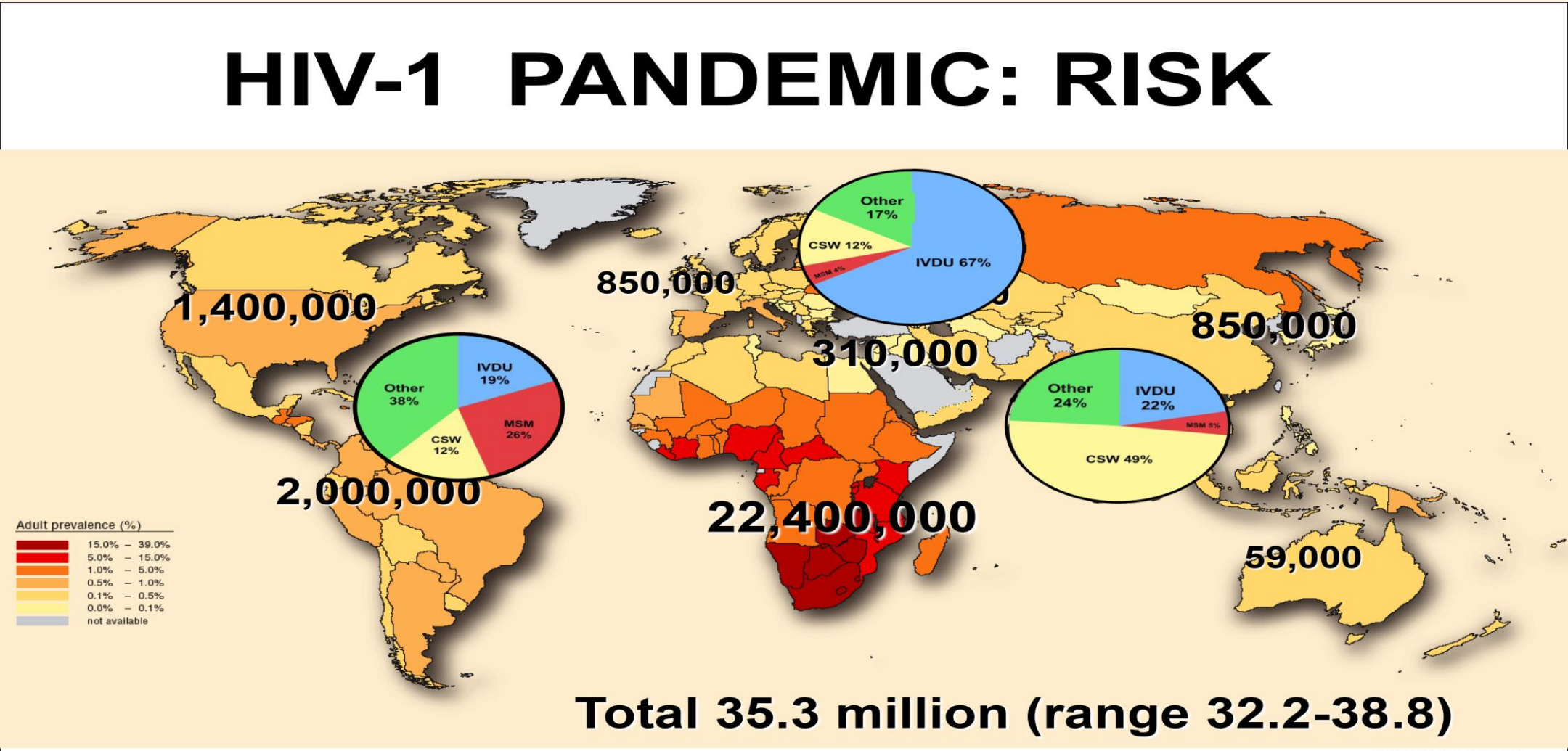
NATIONAL CANCER INSTITUTE

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

Retroviruses

- Introduction
- Molecular Biology/Replication
- Retroviruses in Human Populations
- Emergence/Spread
- Lessons

HIV-1 Pandemic: Risk



UNAIDS,2012

Retroviruses

- Molecular Biology/Replication

Retroviruses

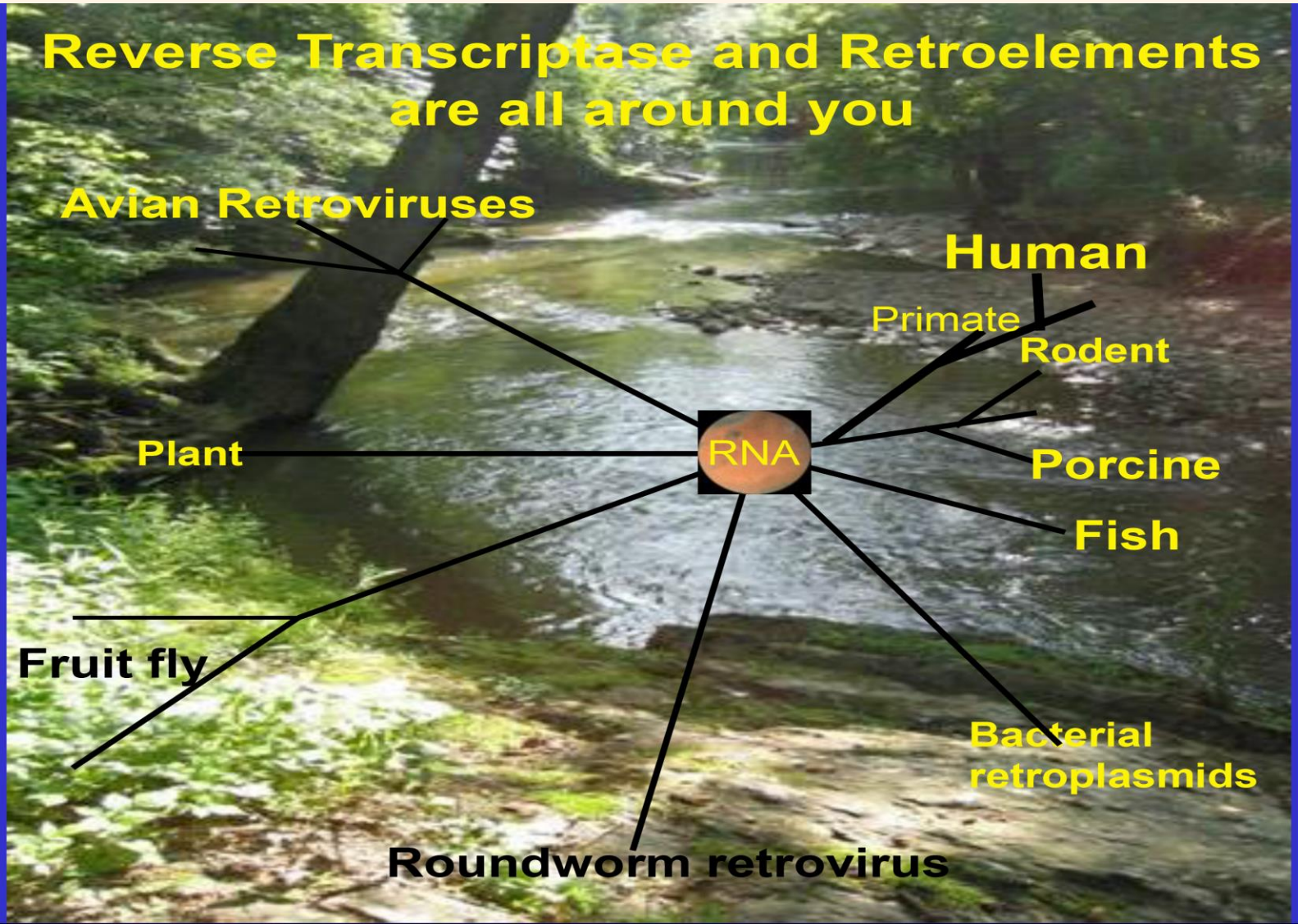
Retroviruses

A group of RNA viruses that replicate via a DNA intermediate using Reverse Transcriptase.

A different paradigm for replication

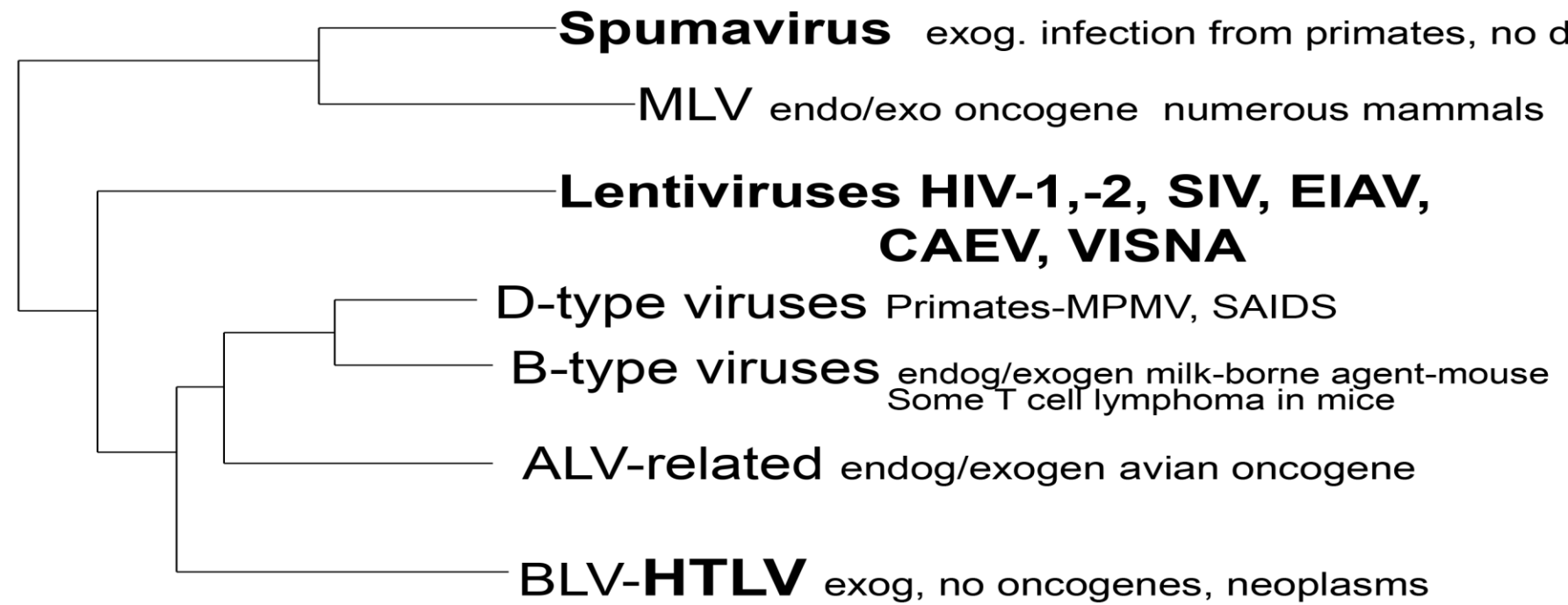
Transition from RNA World?

Retroelements



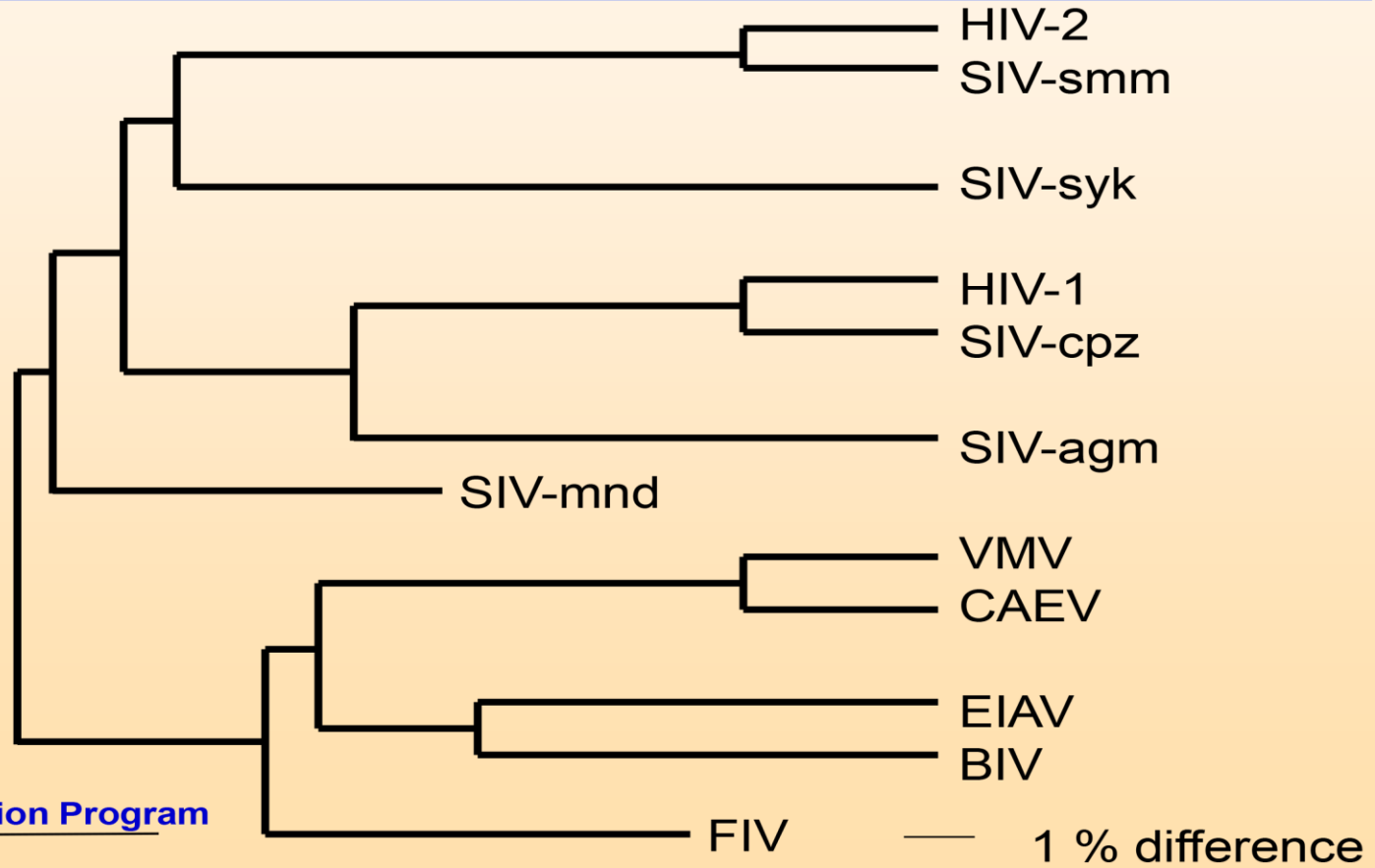
Retrovirus classification

Retroviruses
Classification by RT Sequence into Seven Families



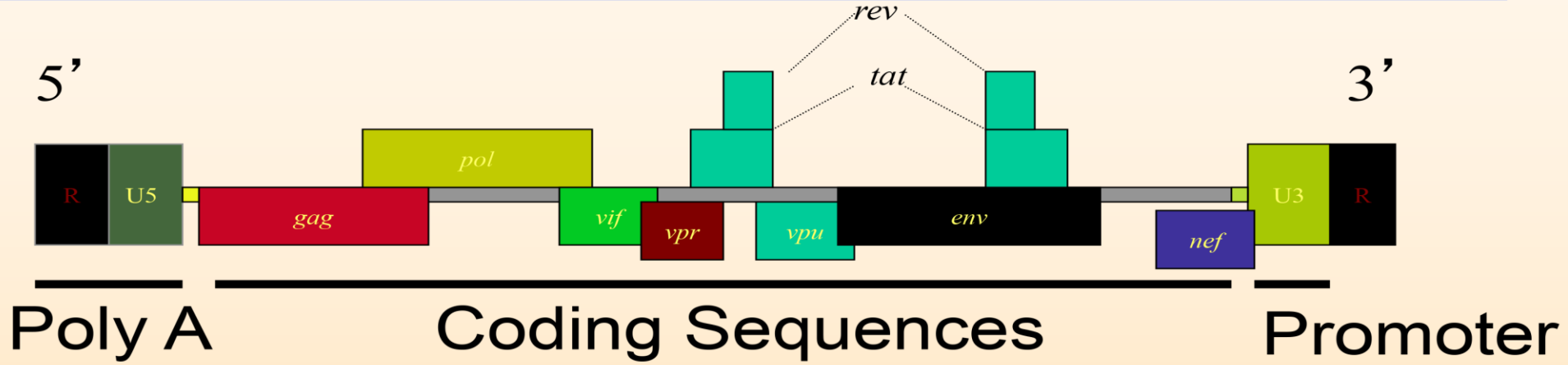
Lentivirus Relationships

Lentivirus Relationships



Retrovirus conventions

Retroviruses Conventions

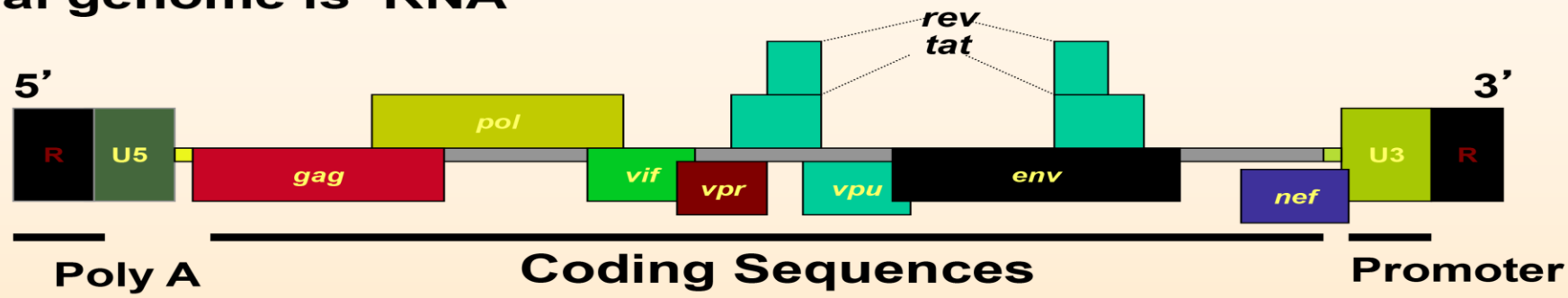


Names of genes in lower case *italics*, e.g., *pol, env*
Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120

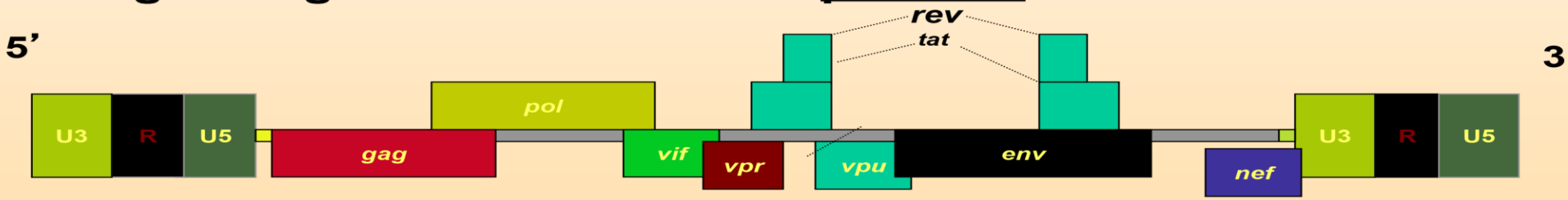
Retrovirus

Retroviruses Conventions

The viral genome is RNA



The integrated genome is called the provirus



Names of genes in lower case *italics*, e.g., *pol, env*
Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120

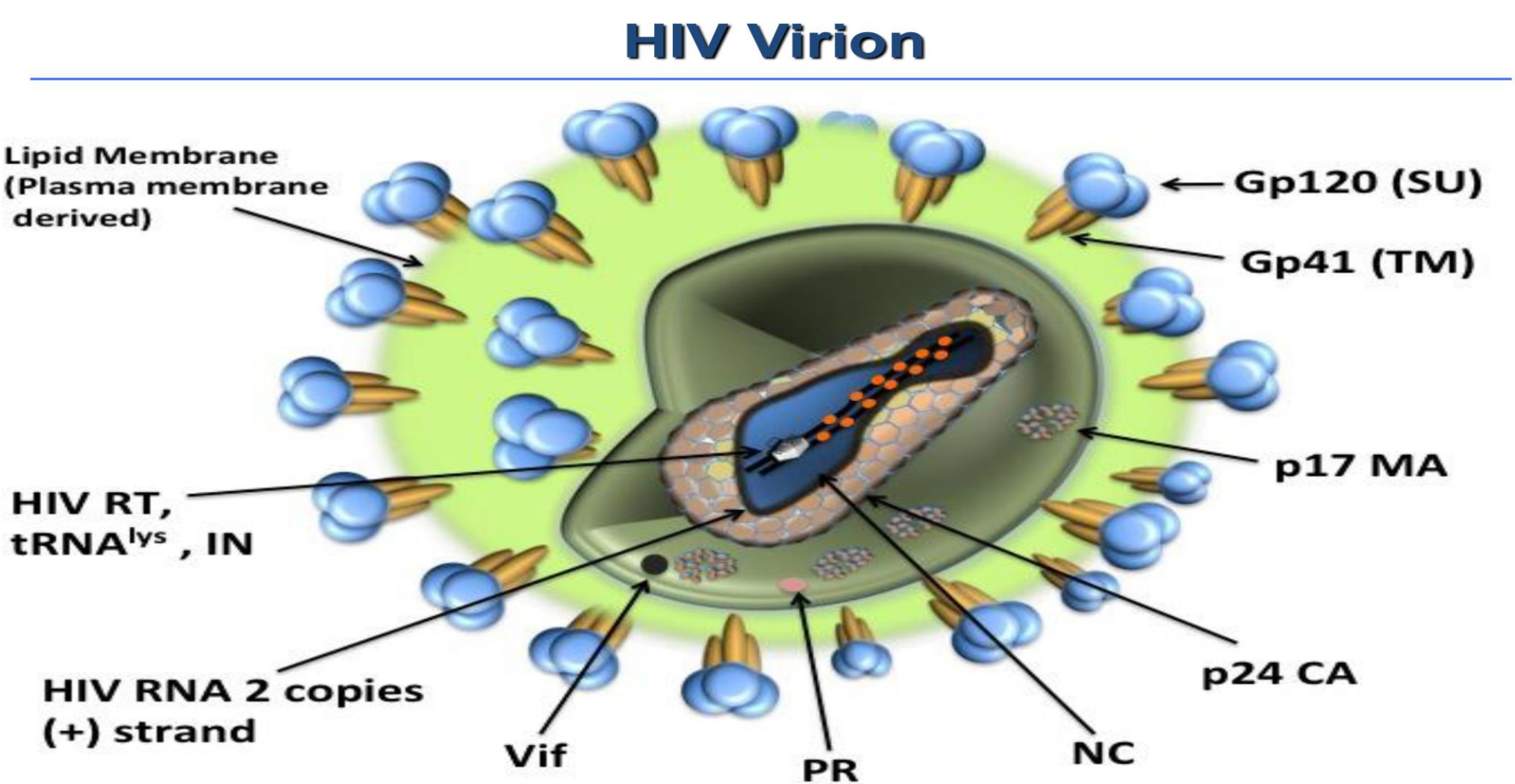
Retroviruses

Retroviruses Glossary

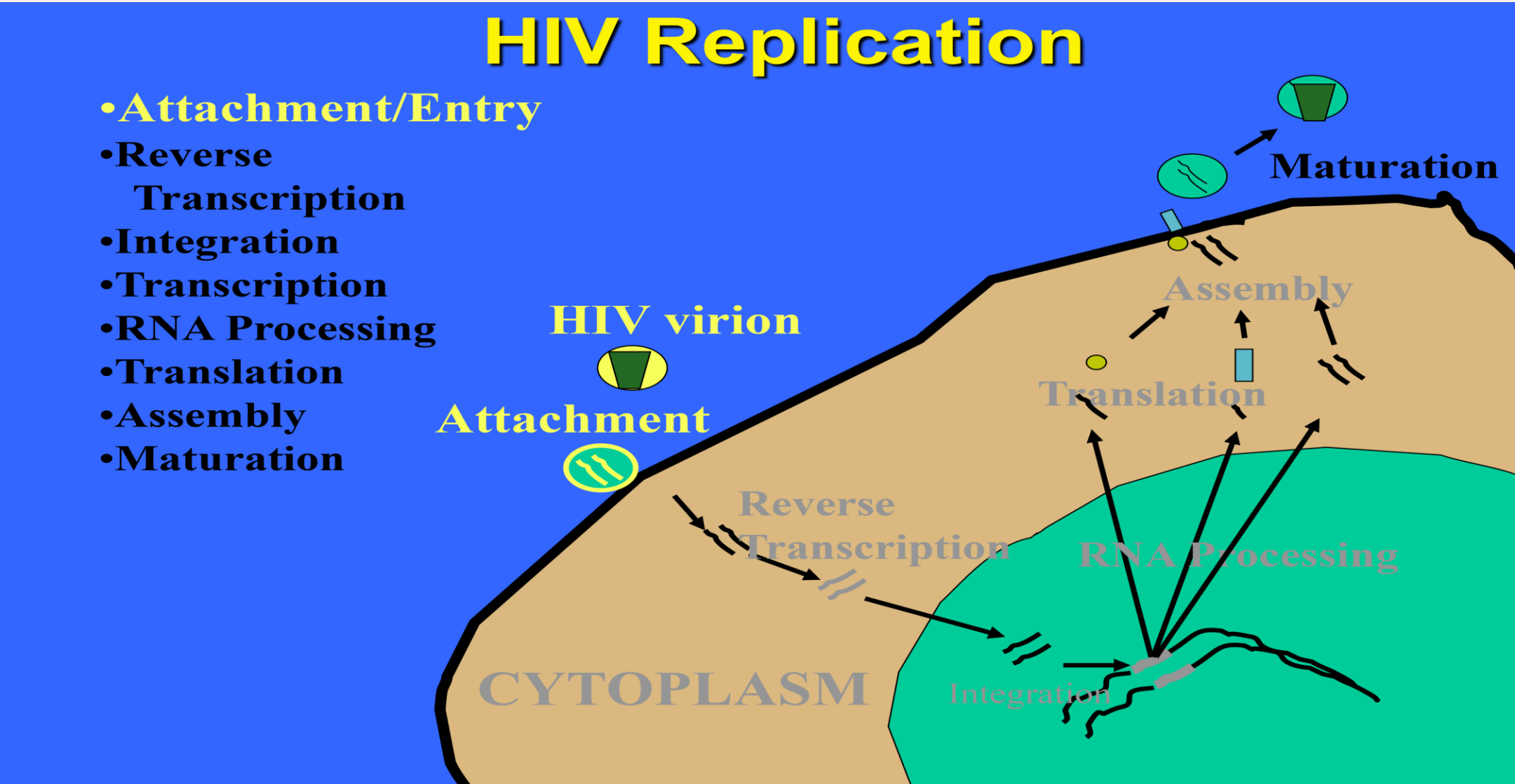
- *gag: group antigen*
- *pol: polymerase*
- *env: envelope*
- *tat: Transactivator*
- *rev:Regulator of Expression of Virion proteins*

- U3: unique sequence in 3' region
- U5: Unique sequence in 5' region
- R: Repeat sequence
- PBS Primer binding site for initiation of RT
- Ppt: polypurine tract primer for RT
- TAR: Tat activating sequence
- RRE: Rev responsive element
- Provirus: copy of retrovirus that is integrated into host genome

HIV virion


HIV Virion
Lipid Membrane
(Plasma membrane
derived)
Gp120 (SU)
Gp41 (TM)
p17 MA
HIV RT,
tRNA^lys , IN
p24 CA
HIV RNA 2 copies
(+) strand
Vif
PR
NC

HIV replication



HIV attachment and Entry

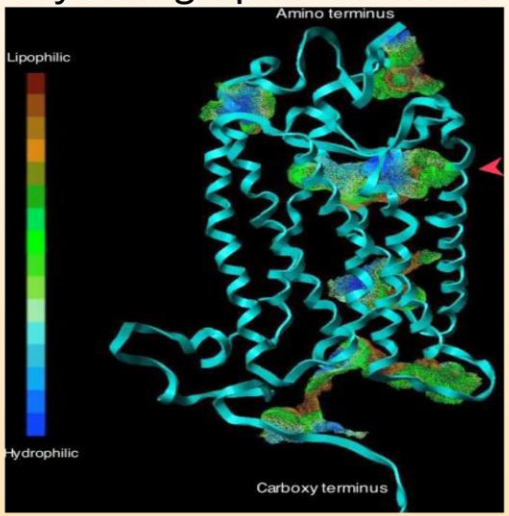
HIV Attachment and Entry

- **Virus Factors**
  - Attachment: Env glycoprotein gp120
  - Entry: Env glycoprotein gp41
- **Host Cell Factors**
  - Receptor
    - CD4
  - Co-receptor (major)
    - CXCR4
    - CCR5

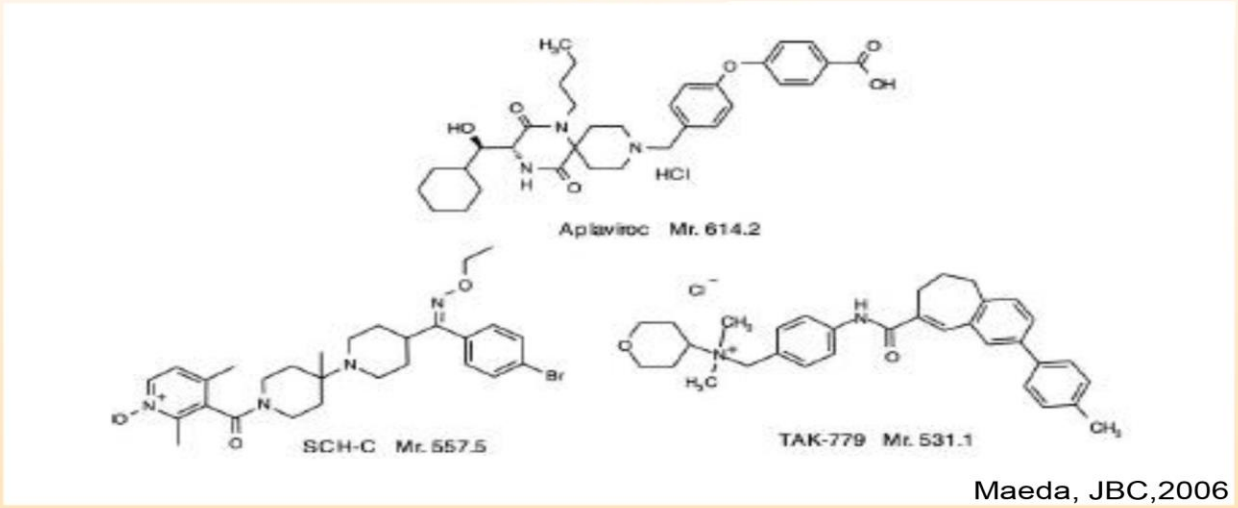
HIV coreceptor blockade

HIV Coreceptor Blockade

Crystallographic Structure



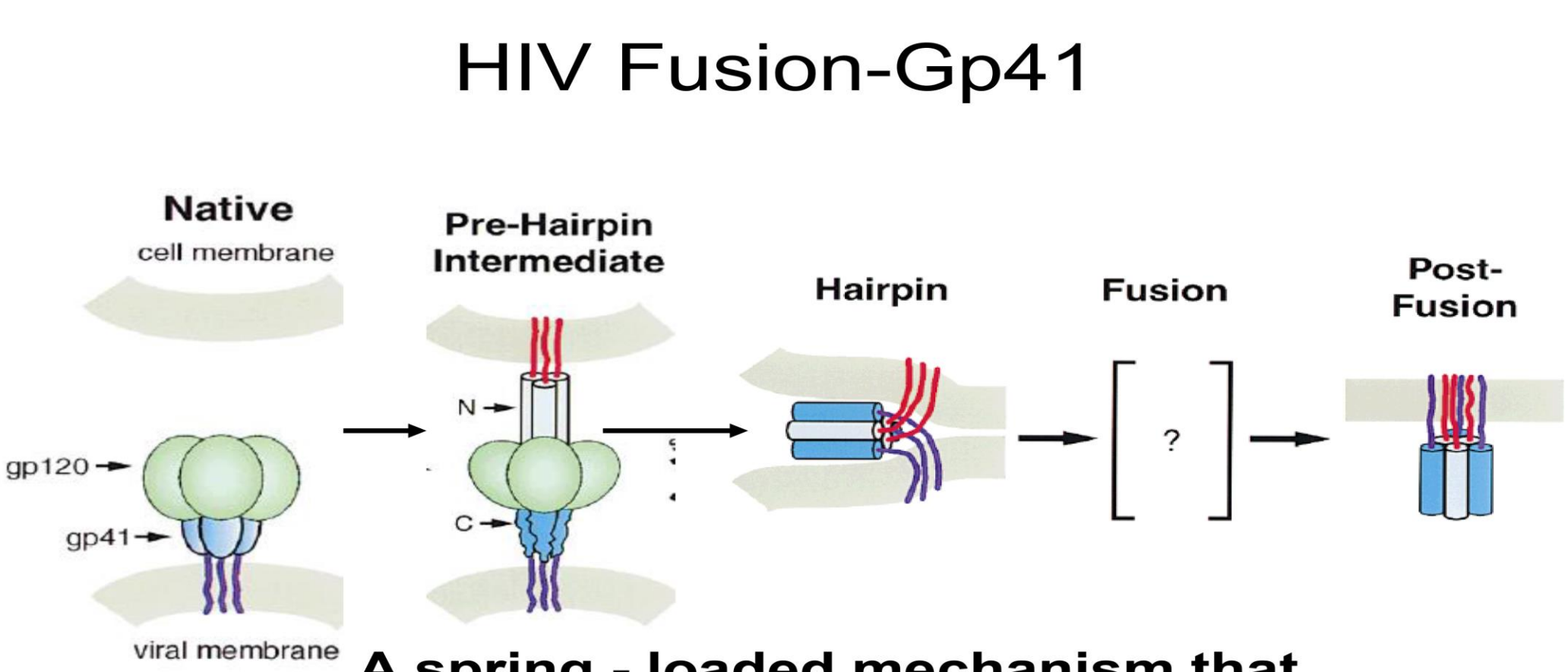
Model Inhibitors



Maeda, JBC,2006

- Multiple binding domains predicted
  - Binding disrupts structure generally
  - Does not require blocking CCR5-gp120 interaction
  - Potential for simultaneous inhibition
- Resistance emerges by reducing affinity for drug

HIV Fusion-Gp41



A spring - loaded mechanism that drives the membranes together to overcome a high energy barrier to

HIV gp41

HIV gp41

Coiled coil in a hydrophobic cavity

Spring-loaded mechanism

T-20

D amino acid interacting (PS Kim)

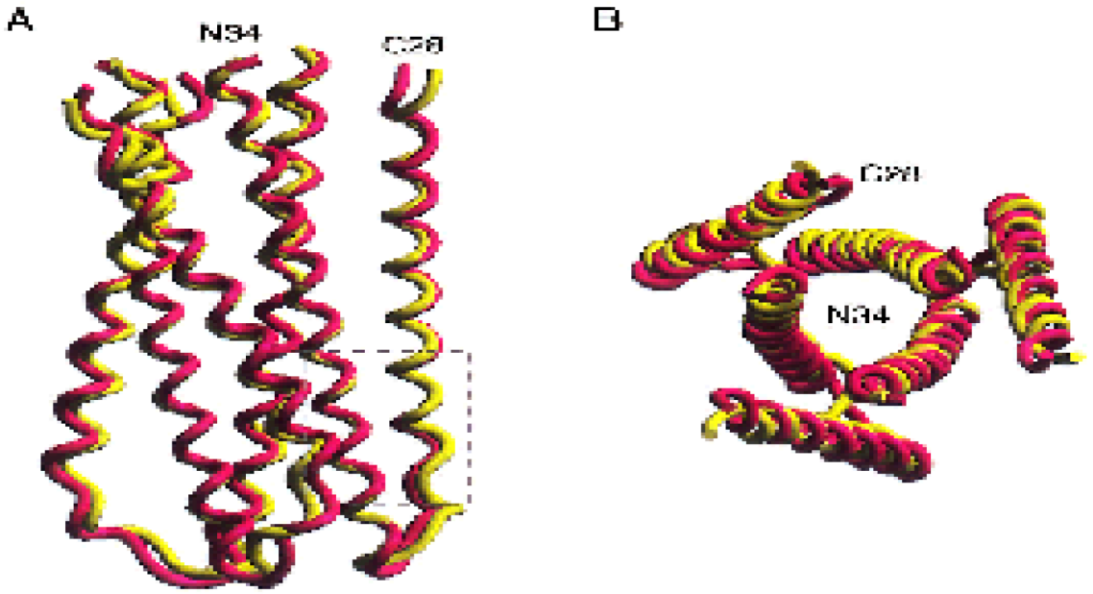
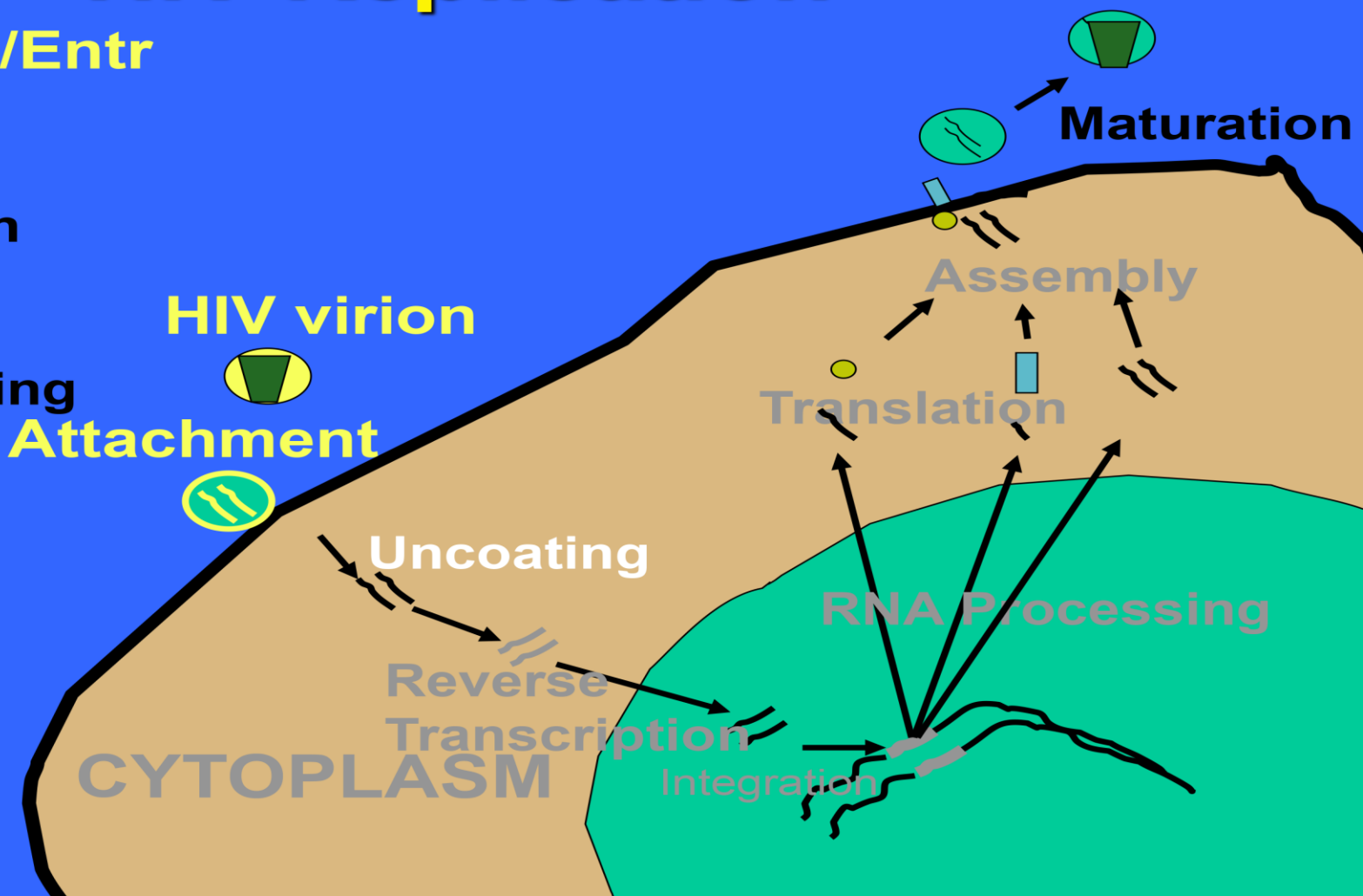


FIG. 4. Overall views of the mutant L568A and W571R cores. (A) Side view. The amino termini of N34 and the carboxyl termini of C28 are at the top. Helices in L568A (yellow) and W571R (pink) were used for the superposition. The bottom of the central N34-coiled-coil surface contains three symmetry-related hydrophobic cavities (one is outlined by the box). (B) View from the top, looking down the threefold axis of the trimer. The same color coding as in panel A is used. Figures were

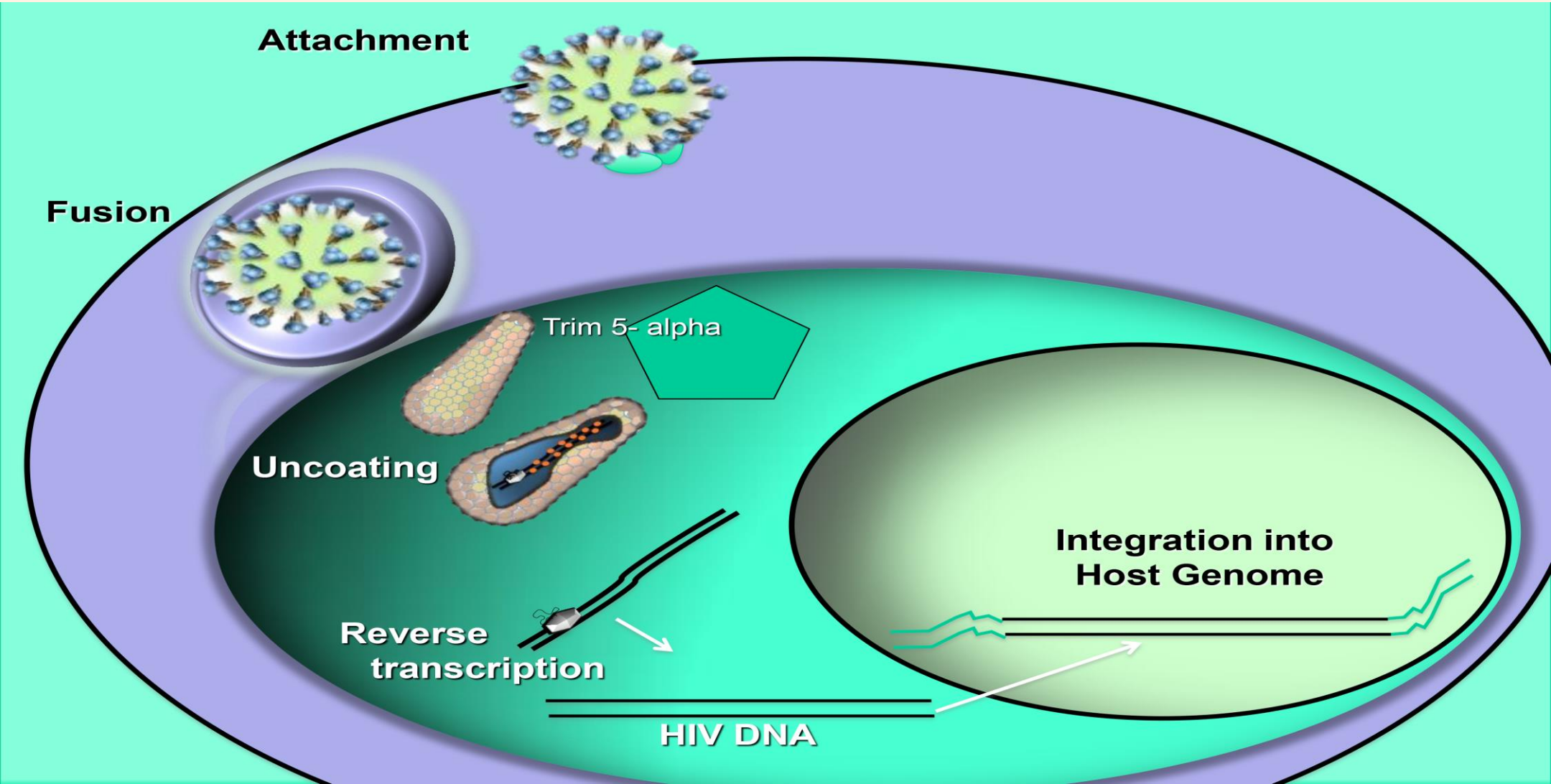
Uncoating

HIV Replication

- Attachment/Entry
- Reverse Transcription
- Integration
- Transcription
- RNA Processing
- Translation
- Assembly
- Maturation



Uncoating


Attachment
Fusion
Trim 5- alpha
Uncoating
Integration into
Host Genome
Reverse
transcription
HIV DNA

Post-Entry Events

HIV Post – Entry Events

- Uncoating is a fundamental step in virus replication
  - Restricts replication
  - Source of host range restriction
- Requires interactions between viral and cellular factors
- Virus
  - Gag
- Cell
  - Trim 5 – alpha

Post entry events

HIV Post – Entry Events

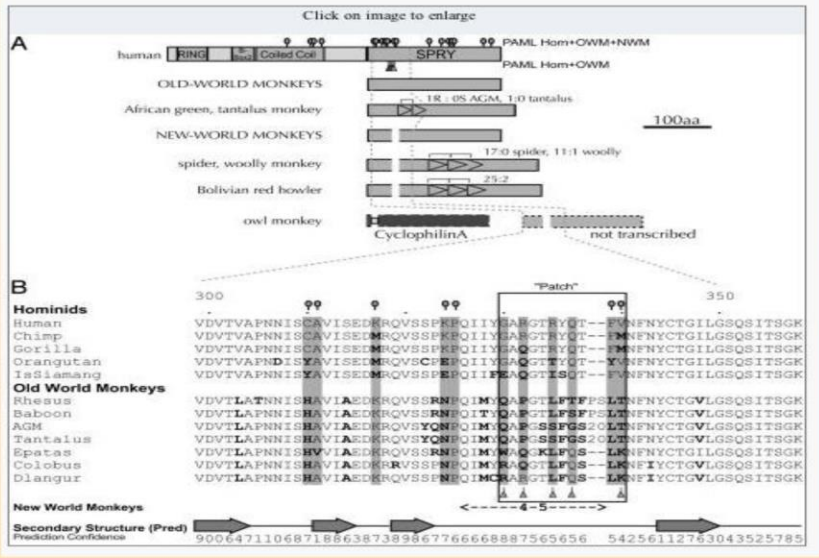
Host Trim5 Alpha

VIRUS	Human	Chimp	Monkey
HIV	Infection	Infection	NO INFECTION
SIV Chimp	INFECTION	Infection	Poor infection
SIV Monkey	INFECTION	Poor infection	Infection

Trim 5-alpha

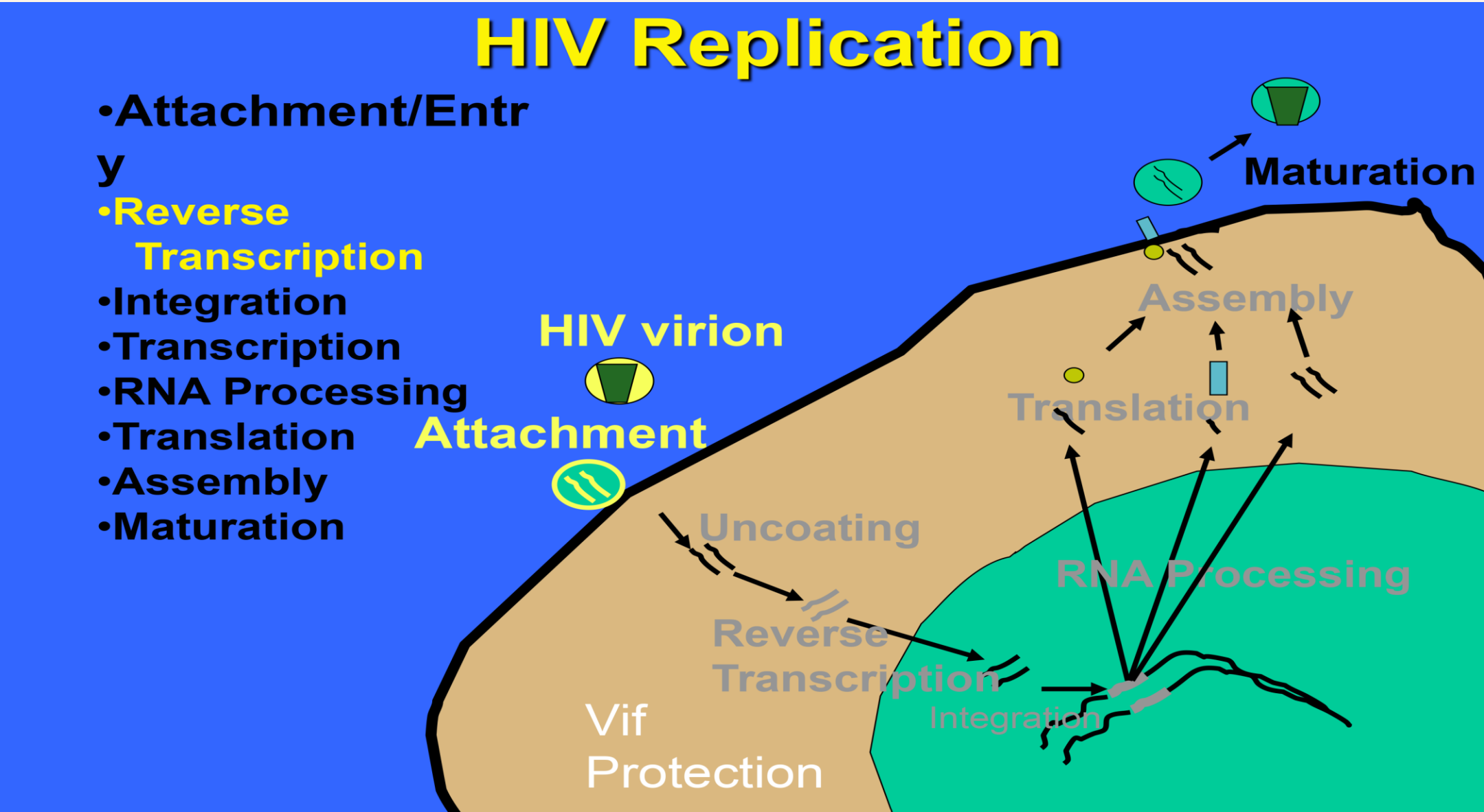
Positive Selection in Trim 5-alpha

- Trim 5 alpha undergoes genetic change faster than many genes
- Working hypothesis
  - human populations undergo waves of pandemics
  - Humans that survive have trim 5alpha variant that excludes infection



Generals are Always Fighting The Last War
Evolution can solve this problem but it will take time

HIV replication



Enzymatic Activities

Reverse Transcriptase Enzymatic Activities

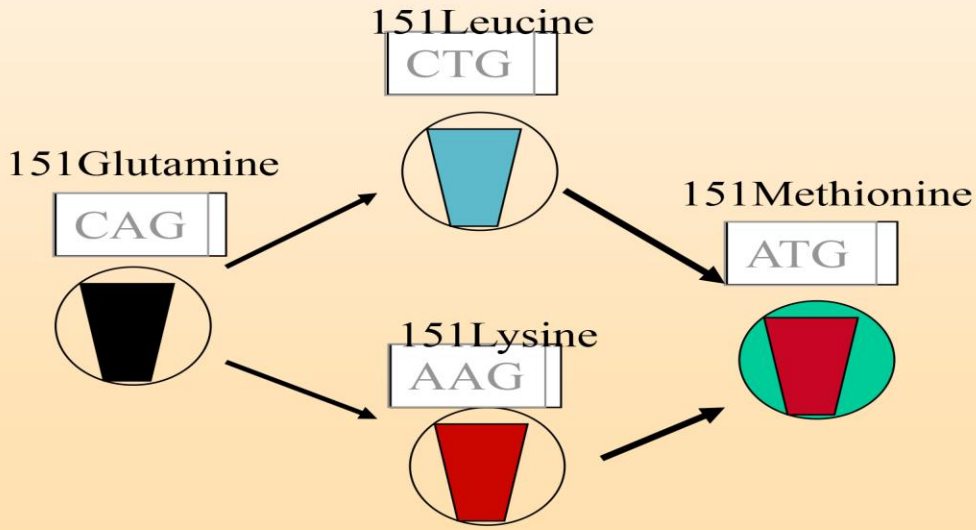
- RNA-dependent DNA Polymerase
- RNase H
- DNA-dependent DNA Polymerase
- Error rate on order of 1-4 / 100,000 bases synthesized
- Recombination occurs during reverse transcription permitting reassortment of sequences
- Replication rapid and error prone

MUTANTS ARE LIKELY TO EXIST PRIOR TO THE THERAPY

Error-Prone replication

Error-Prone HIV Replication is a Pathogenic Determinant

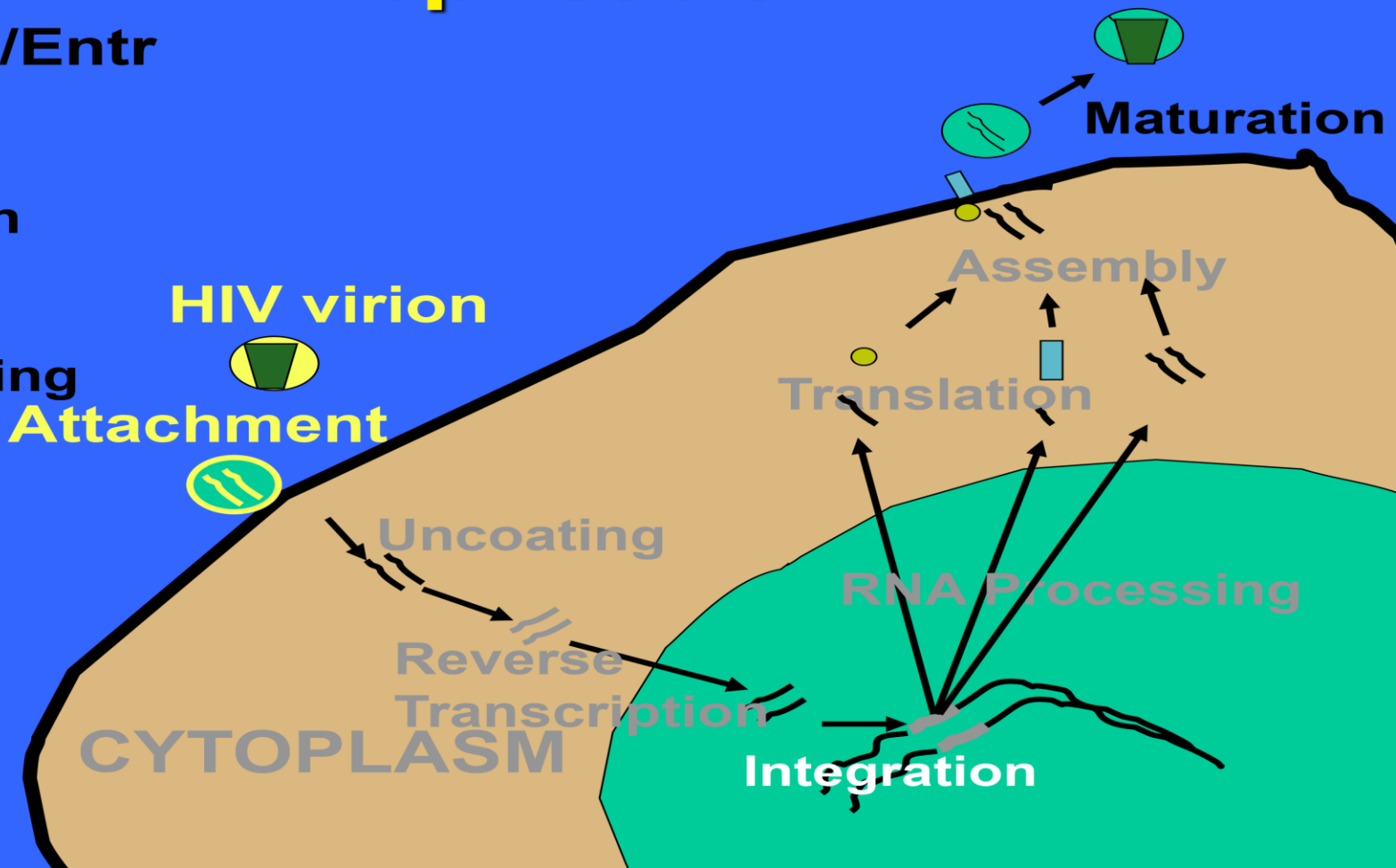
- Each round of HIV replication generates numerous mutants.
- The ability of the mutants to replicate (viral "fitness") may vary greatly.
- The virus population can respond rapidly to a selective pressure



Integration

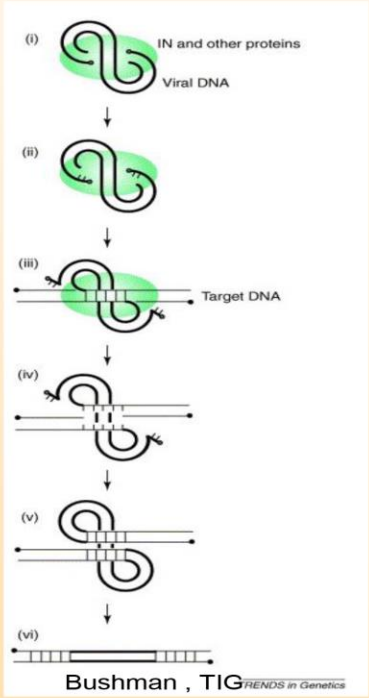
HIV Replication

- Attachment/Entry
- Reverse Transcription
- Integration
- Transcription
- RNA Processing
- Translation
- Assembly
- Maturation

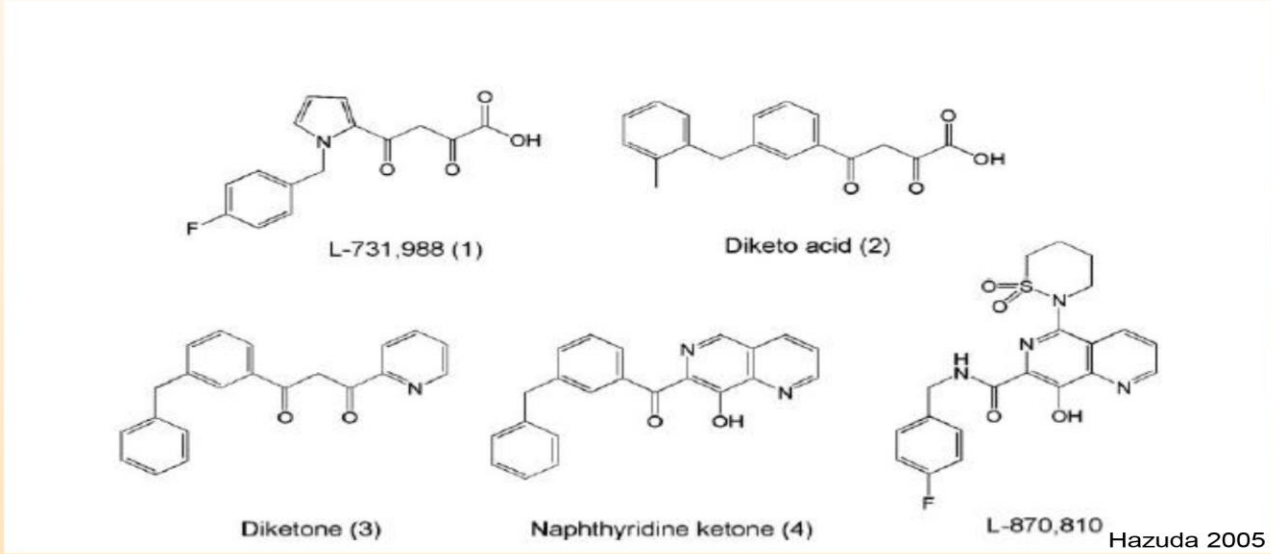


Integration

Integration

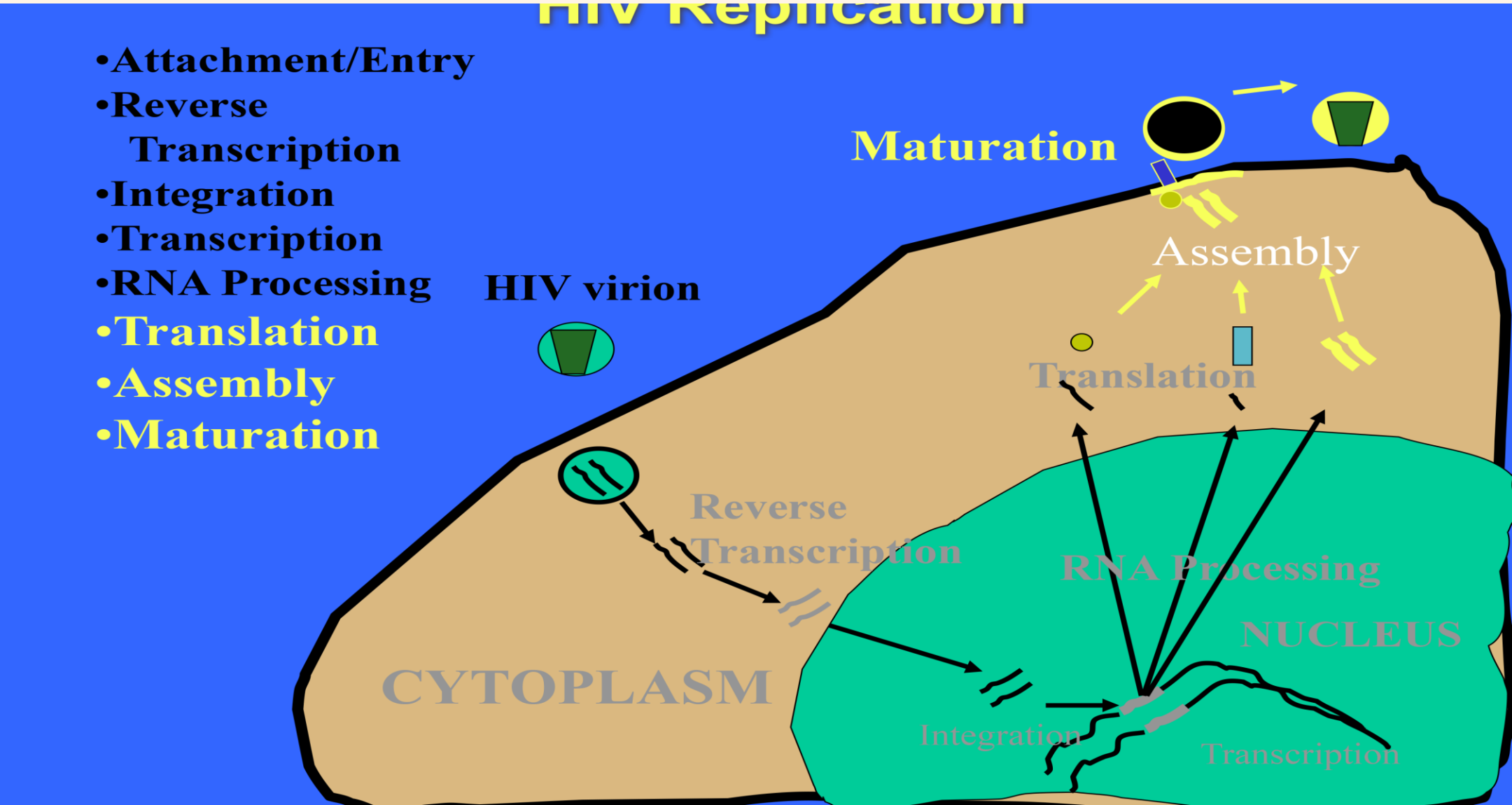


Multistep reaction



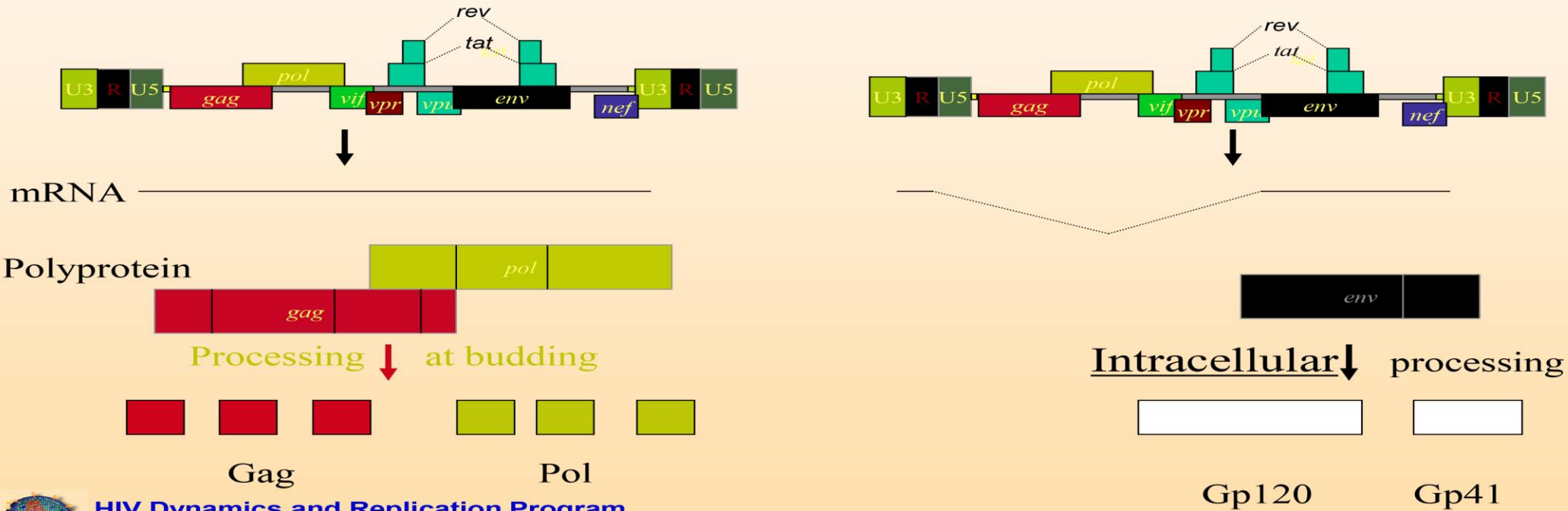
Strong inhibitors

Maturation


HIV Replication
•Attachment/Entry
•Reverse Transcription
•Integration
•Transcription
•RNA Processing
•Translation
•Assembly
•Maturation
Maturation
Assembly
HIV virion
Translation
Reverse Transcription
RNA Processing
NUCLEUS
CYTOPLASM
Integration
Transcription

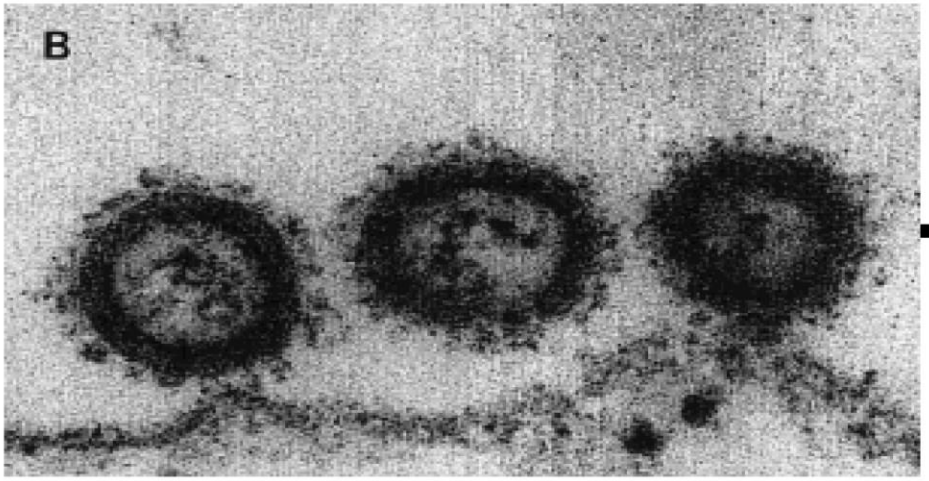
Translation

Translation of HIV *gag/pol* and *env* Paradigm: Process Polyprotein Precursors

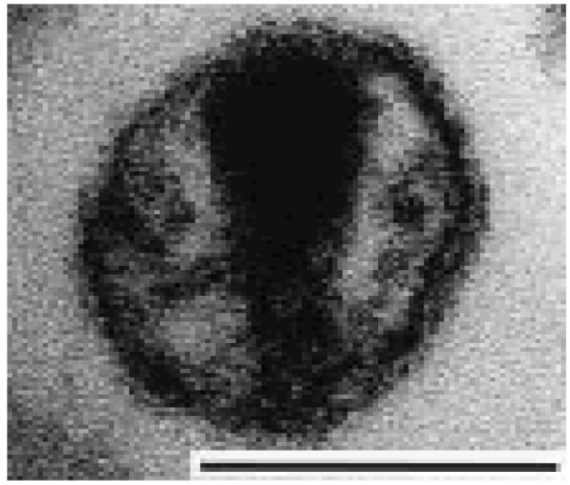


HIV Particle Maturation

HIV Particle Maturation



HIV
Protease



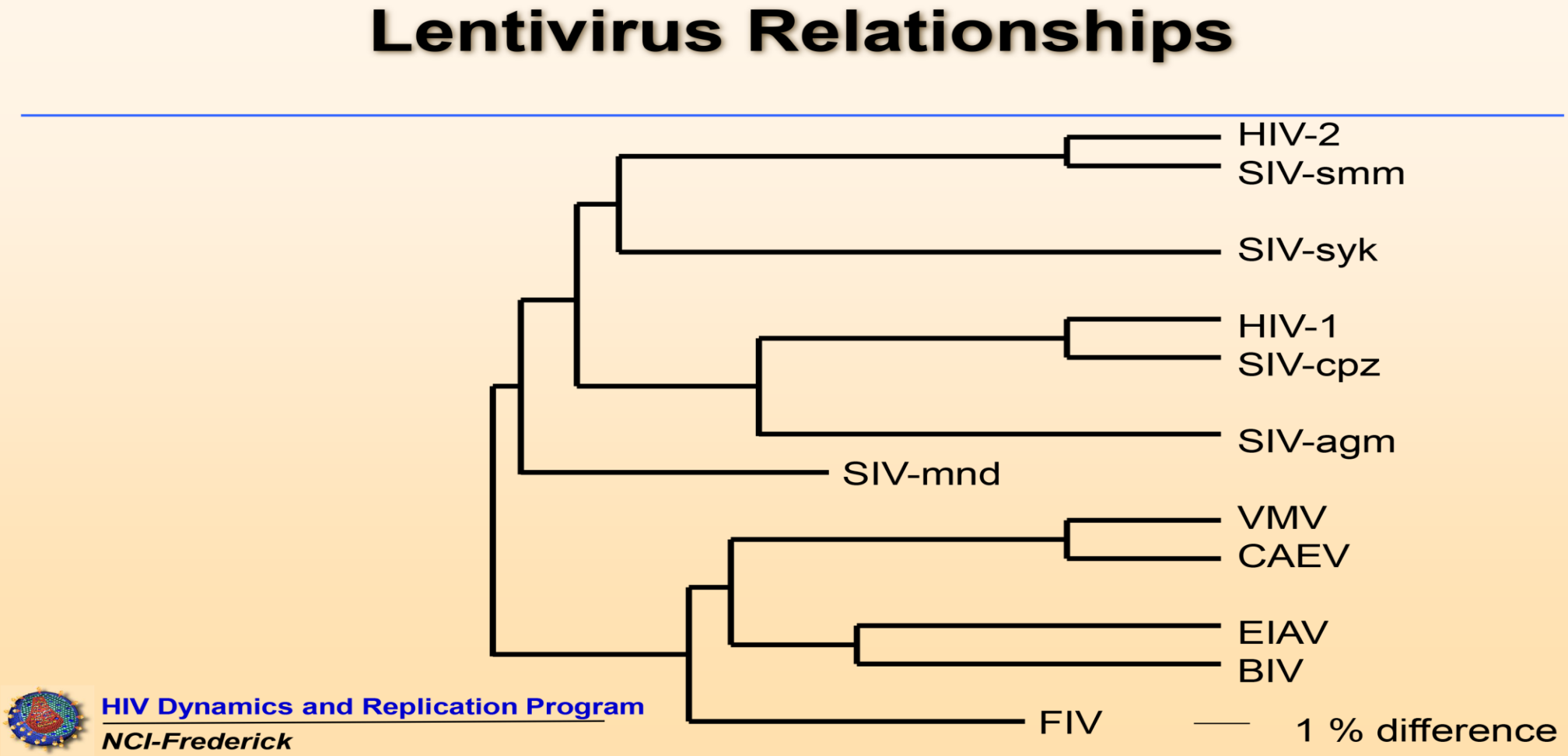
Immature Particle
Noninfectious

Mature Particle
Infectious

Retroviruses

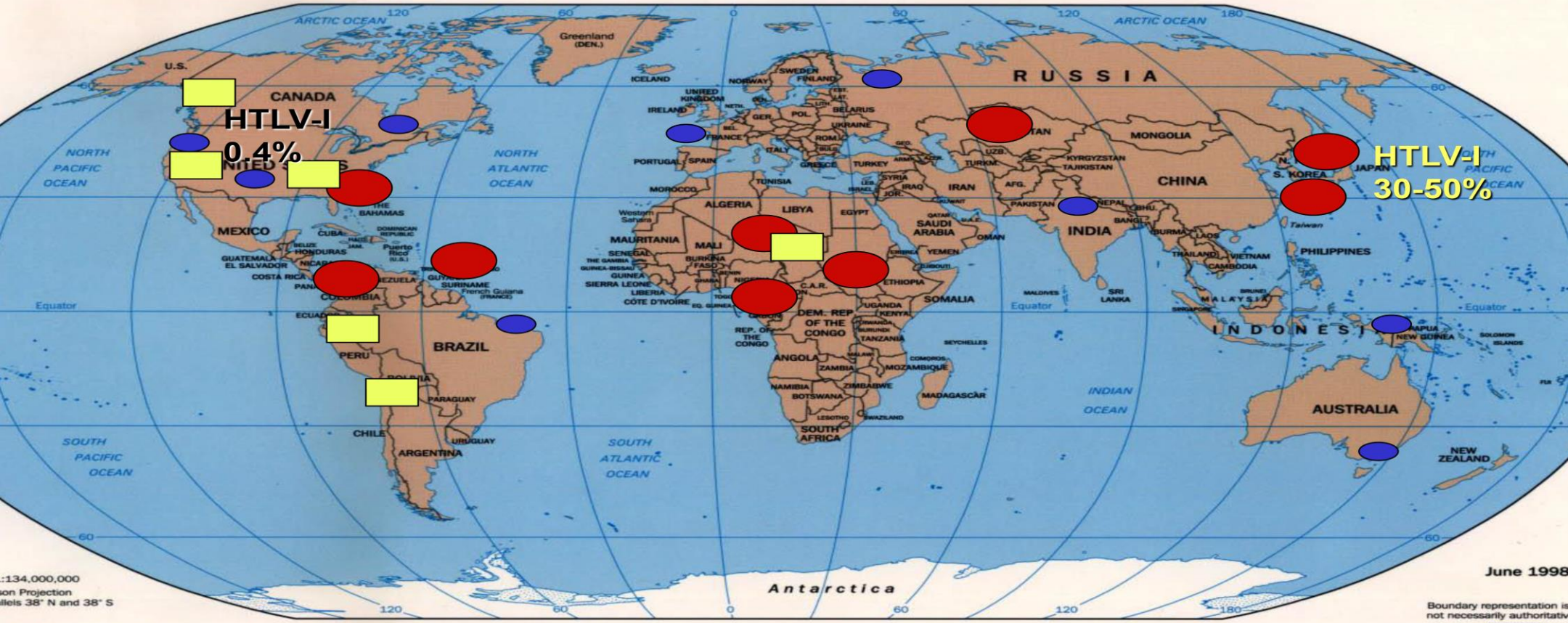
- **Retroviruses in Human Populations**

Lentivirus relationships



HTLV distribution

HTLV DISTRIBUTION



HTLV-I Sporadic
HTLV-I High endemicity

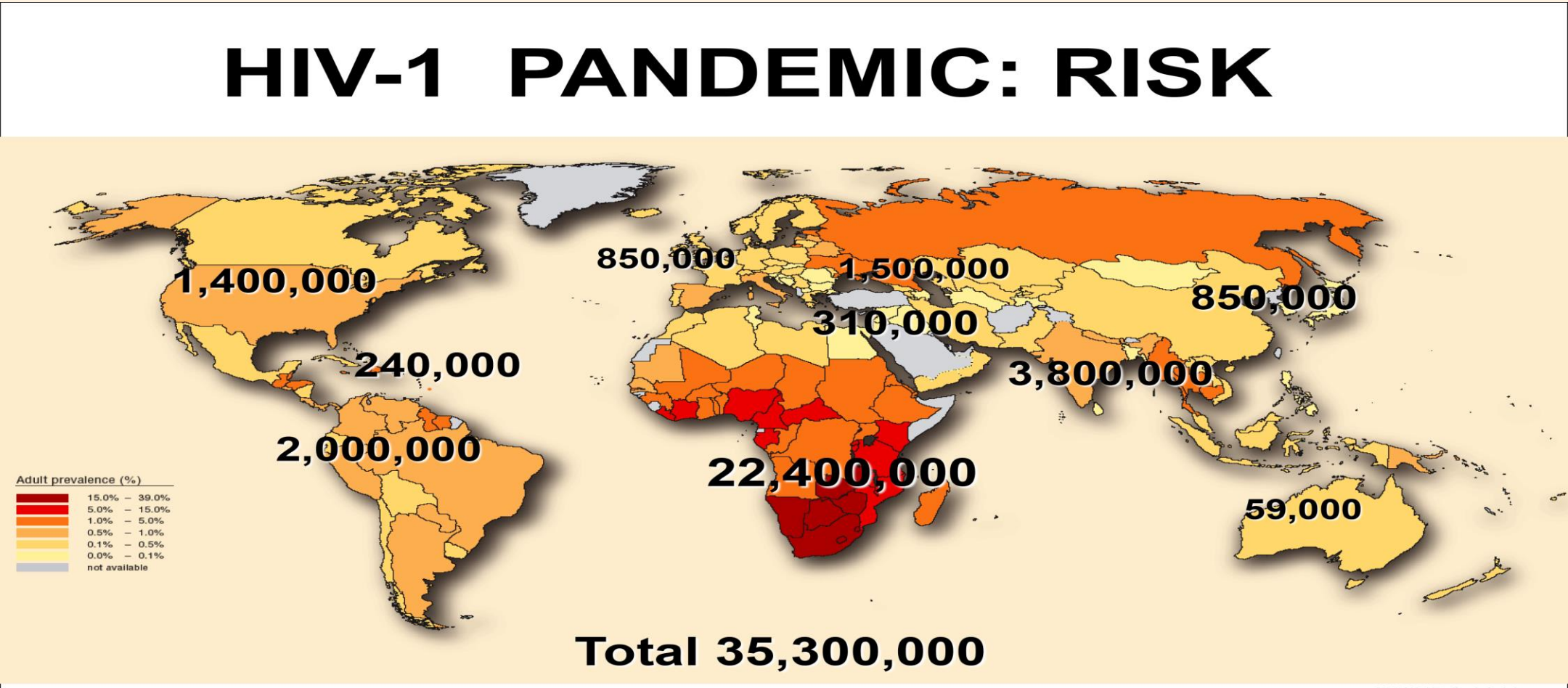
HTLV-II Endemic (Amerindian and Pygmy tribes)

HTLV-I ATL

HTLV-I ATL

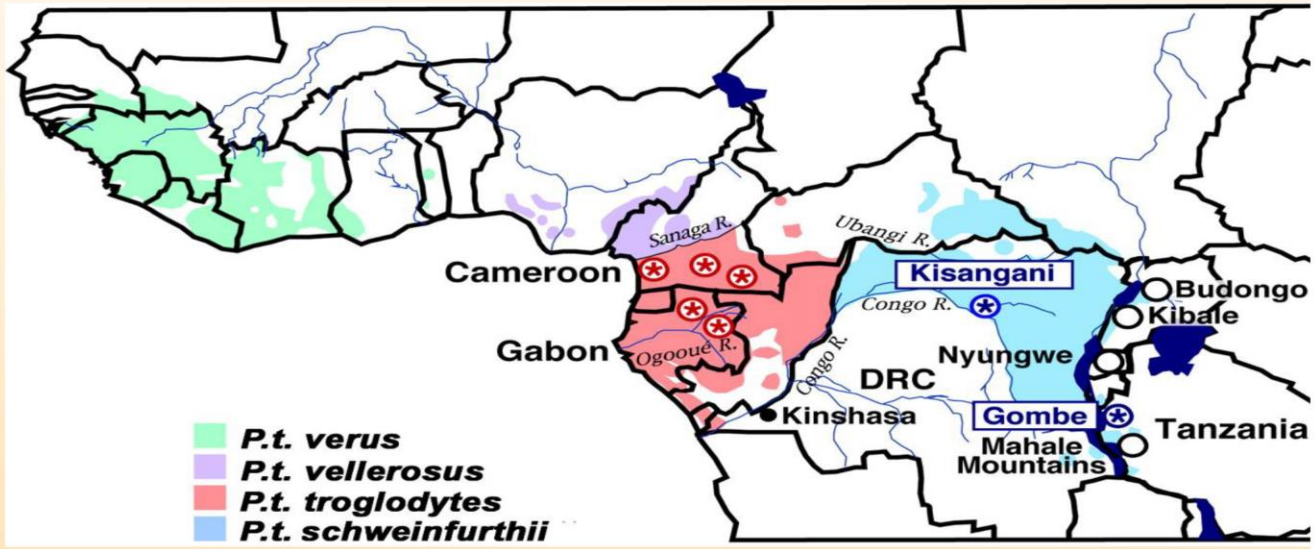
- Long Latency (>30 years)
  - Small pediatric series in SA
- Epidemiology
  - Approximately 1% of HTLV- I infected adults
- Associated syndromes
  - Infectious
    - TB, MAC, Leprosy
    - PCP
    - Strongyloides
    - Scabies esp. Norwegian scabies
  - Noninfectious-hypercalcemia+lytic bone lesions
- Therapy-Chemotherapy, Ifn, anti-Tac

HIV-1 pandemic risk



Higher Primate Origins of HIV-1

Higher Primate Origins of HIV-1



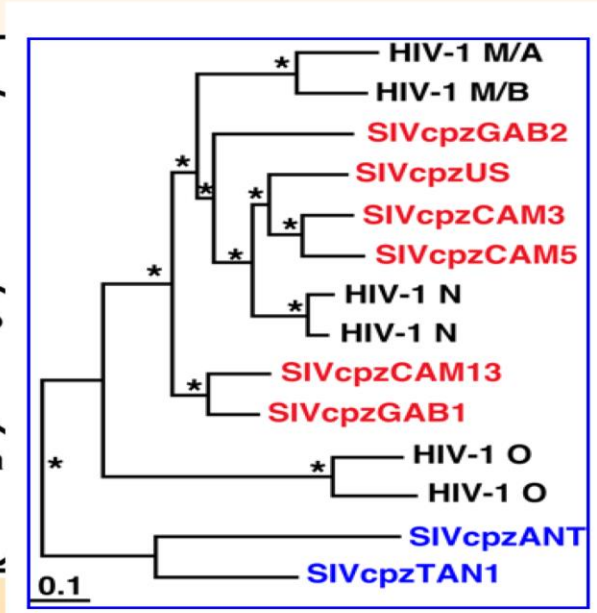
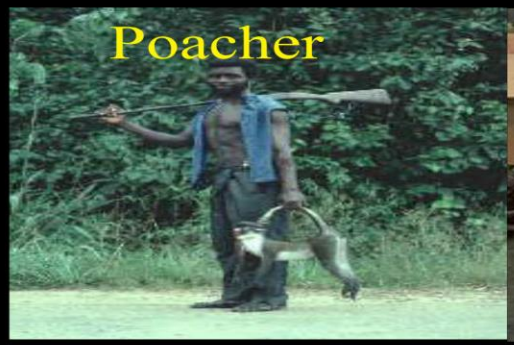


FIG. 2. Evolutionary relationships of SIVcpz and HIV-1 strains based on maximum-likelihood phylogenetic analyses of full-length envelope protein sequences (adapted from ref. 10). SIVcpz strains from *P. t. troglodytes* and *P. t. schweinfurthii* are highlighted in red and blue, respectively. Representative strains of HIV-1 groups M, N, and O were included for comparison. Asterisks indicate internal branches with estimated posterior probabilities of 95% or higher. The scale bar denotes 10% replacements per site.

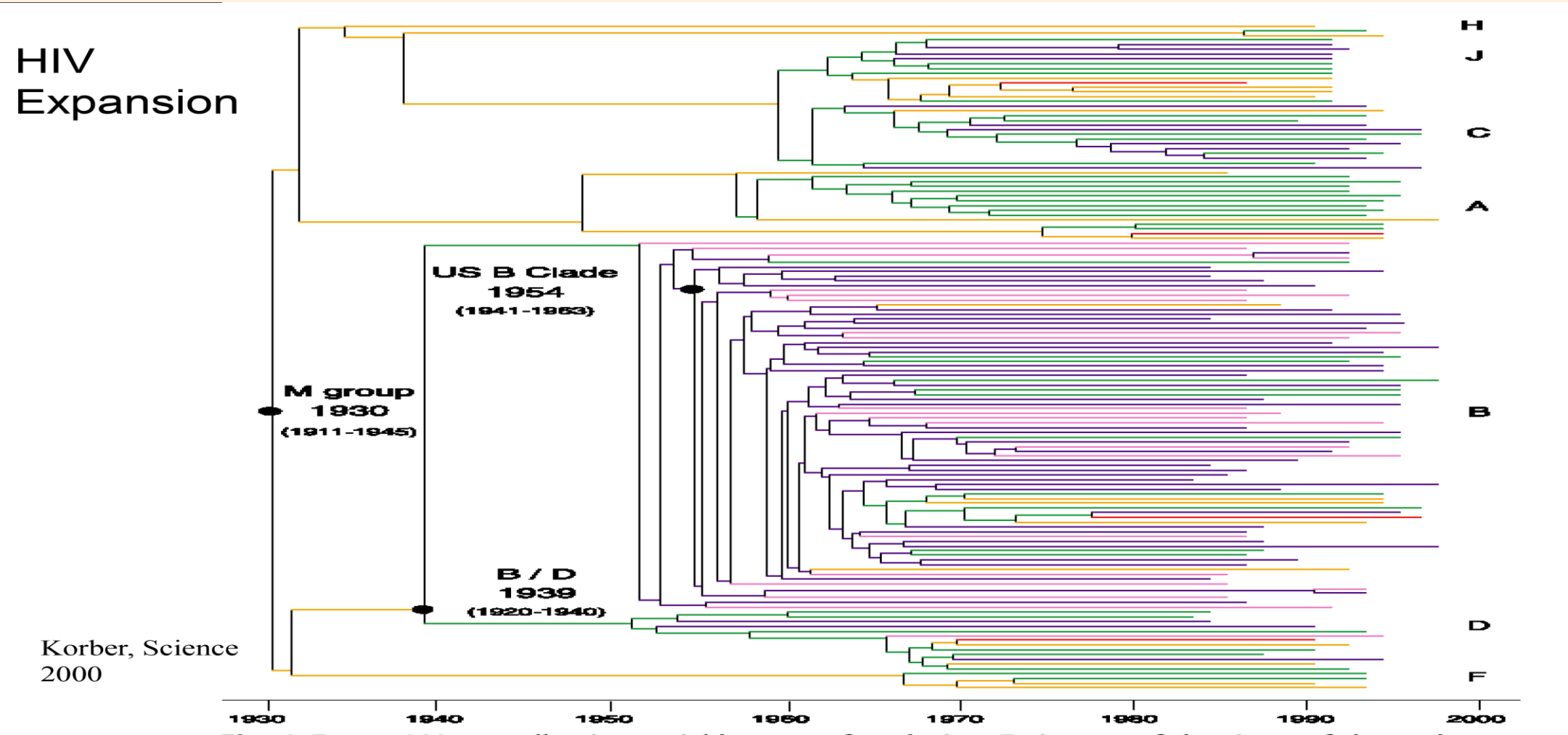
Hahn and coworkers JV 2005

Bushmeat trade in Africa

Bushmeat Trade in Central and West Africa



HIV expansion



Korber, Science 2000

HIV Spread

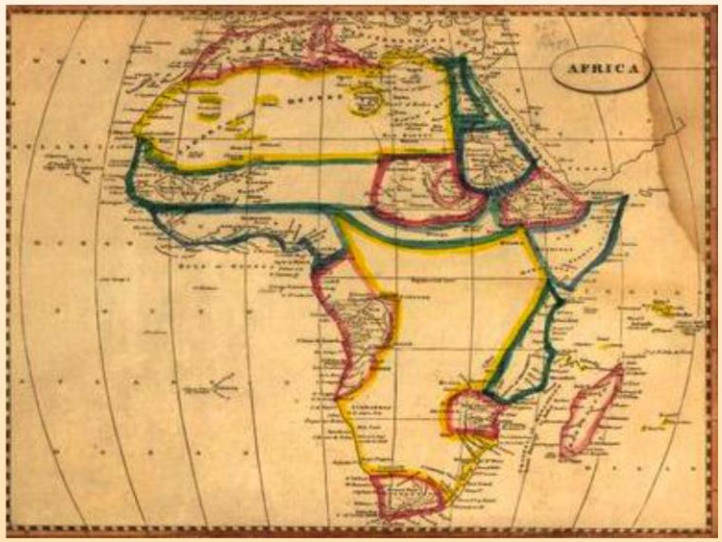
HIV Spread

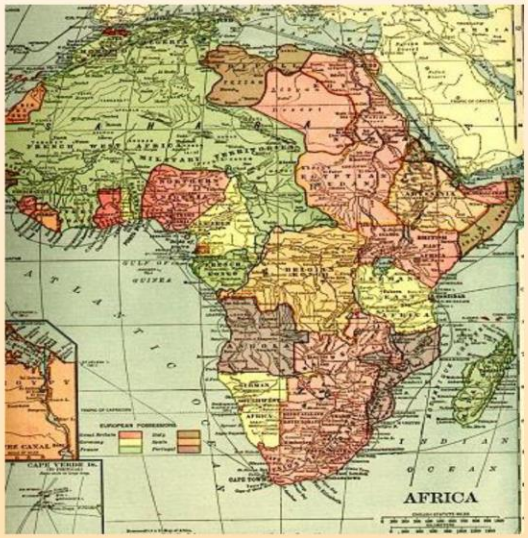
- Biologic
  - Blood and body fluid
  - Iatrogenic
    - Blood transfusion
    - Vaccination – needles not vaccine
  - Mother to Child
- Non-Biologic
  - Political
  - Economic
  - Multiple Epidemics

HIV spread

HIV Spread

- **Modes of Transmission**
  Political

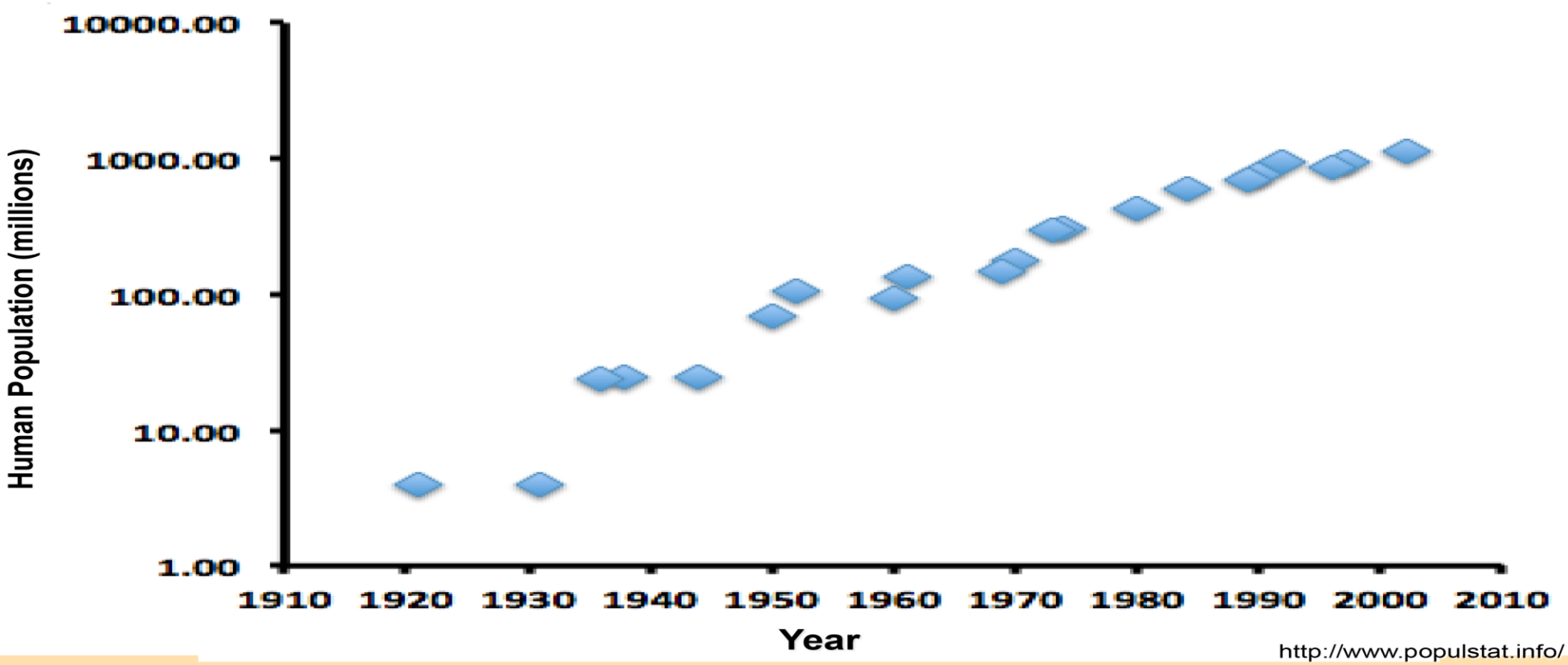




Consequences of large political upheaval are population movement and potential for malnutrition and immunodeficiency

HIV and population expansion

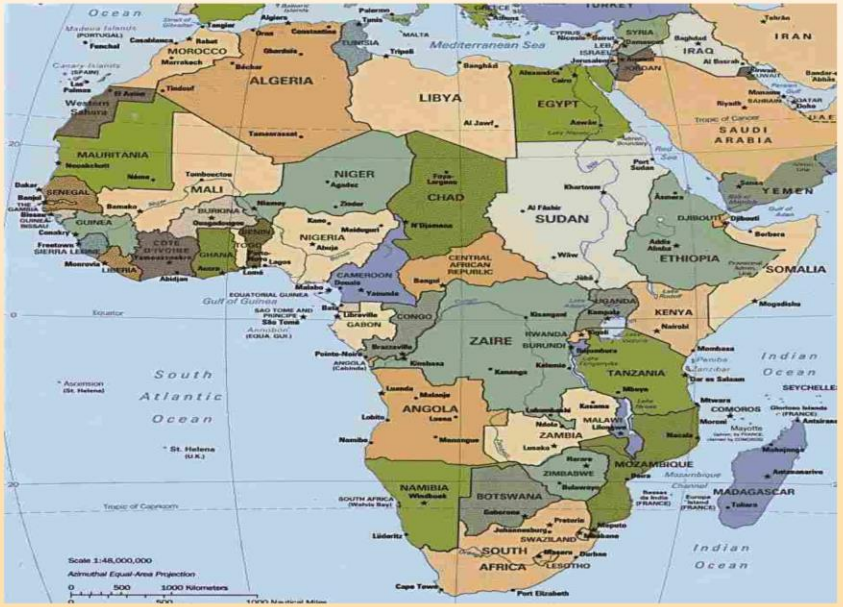
Zoonotic Transmission of HIV Coincides with Population Expansion in Africa



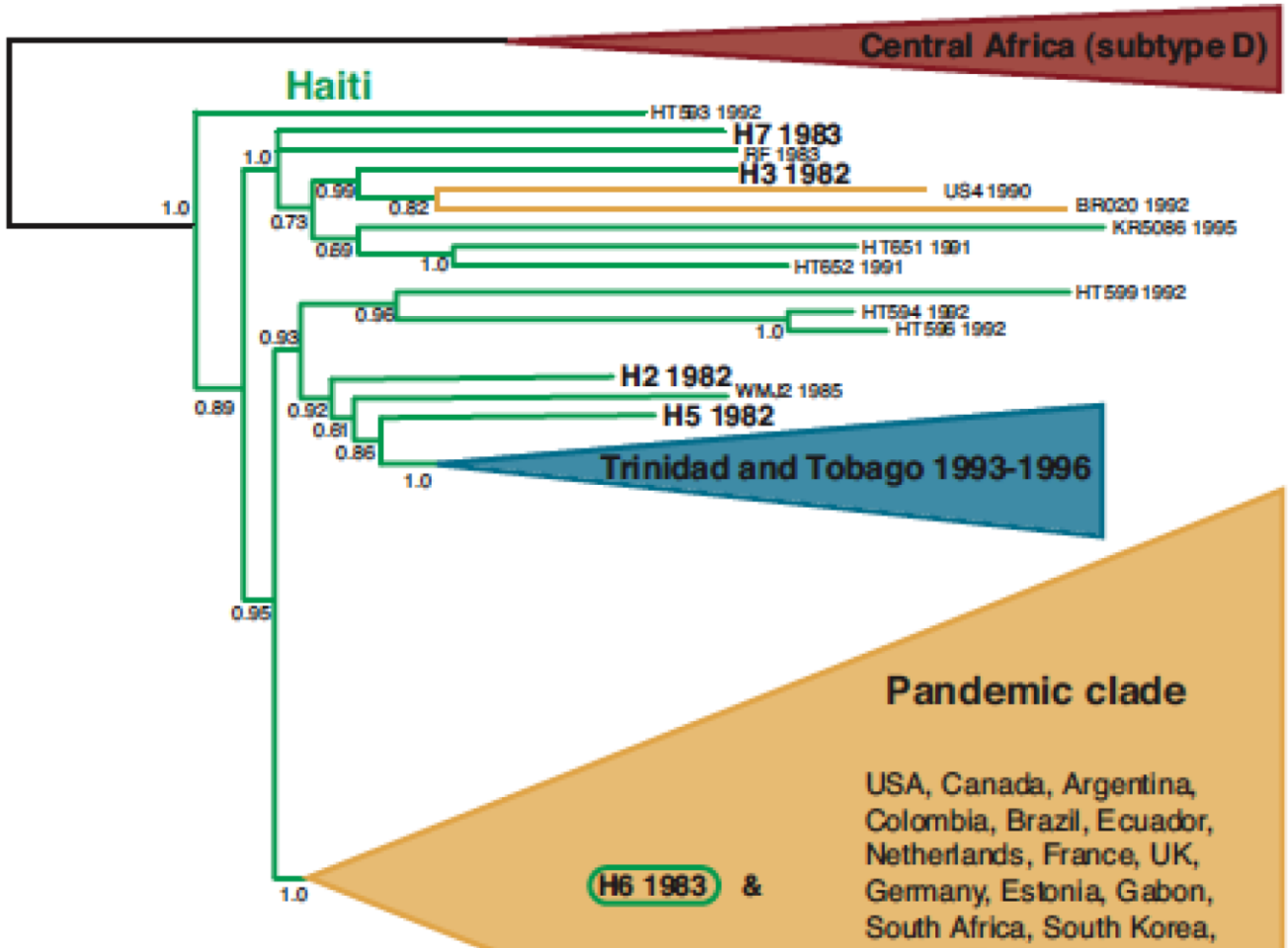
HIV spread

HIV Spread

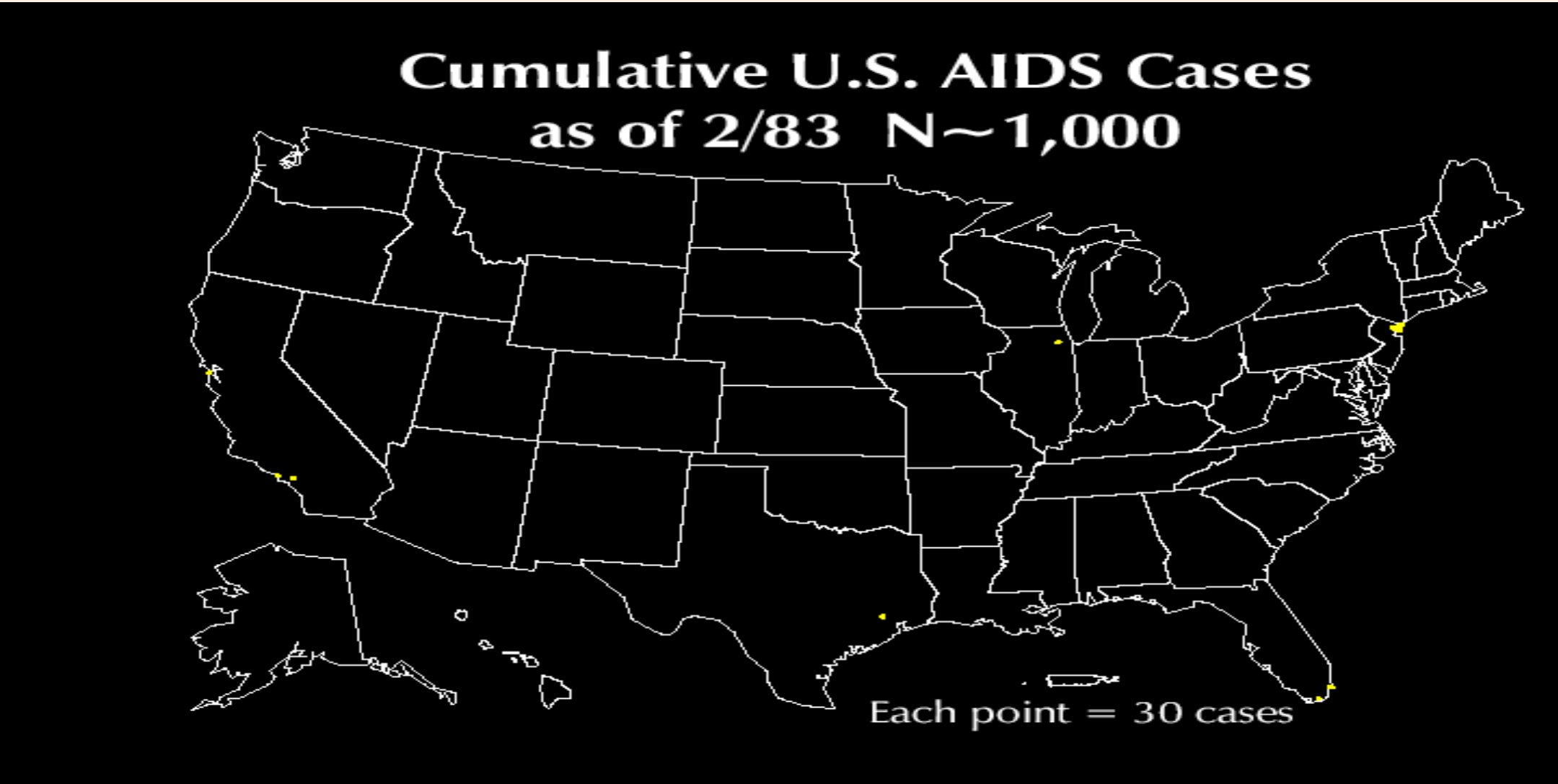
- **Modes of Transmission**
  Trans Africa Highway



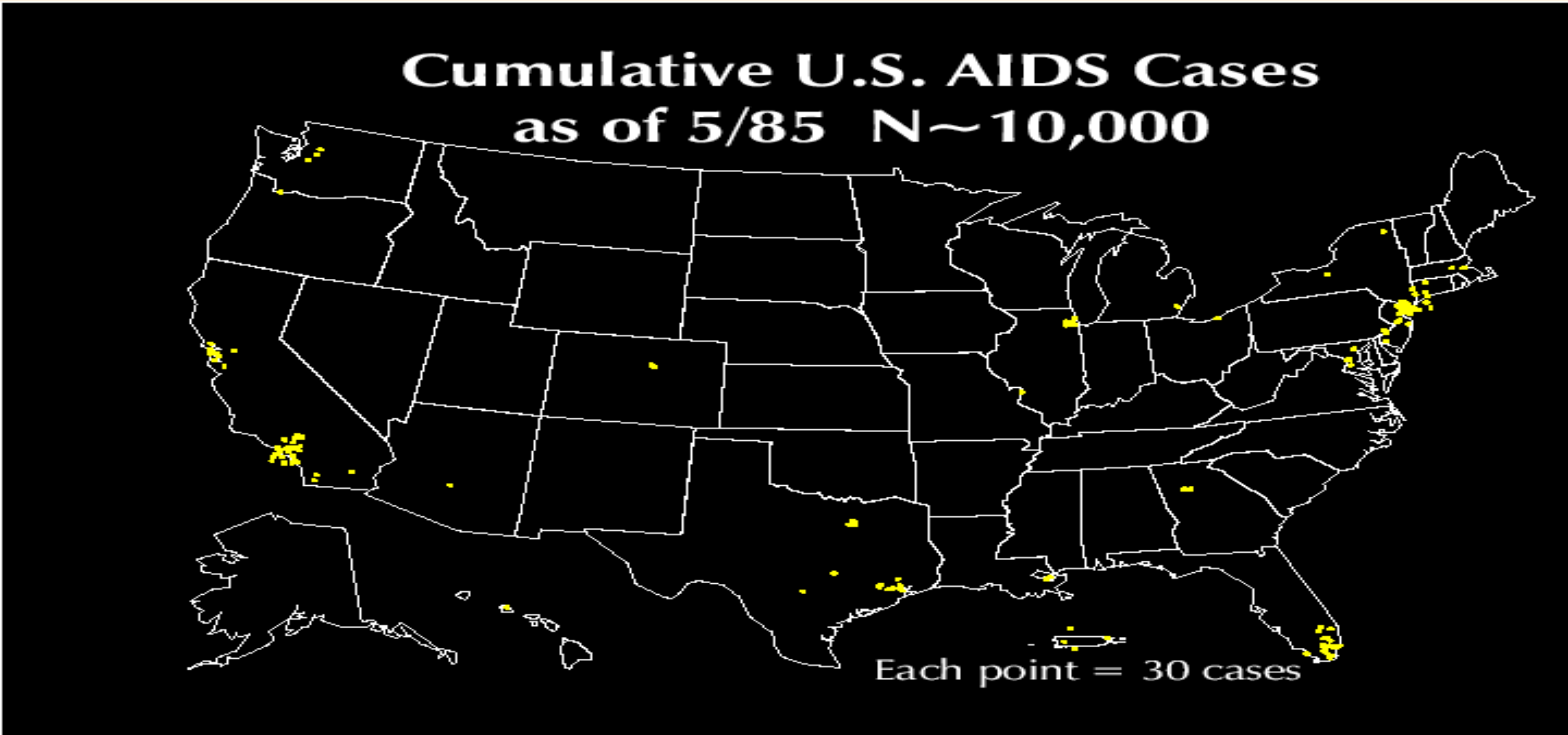
HIV evolution



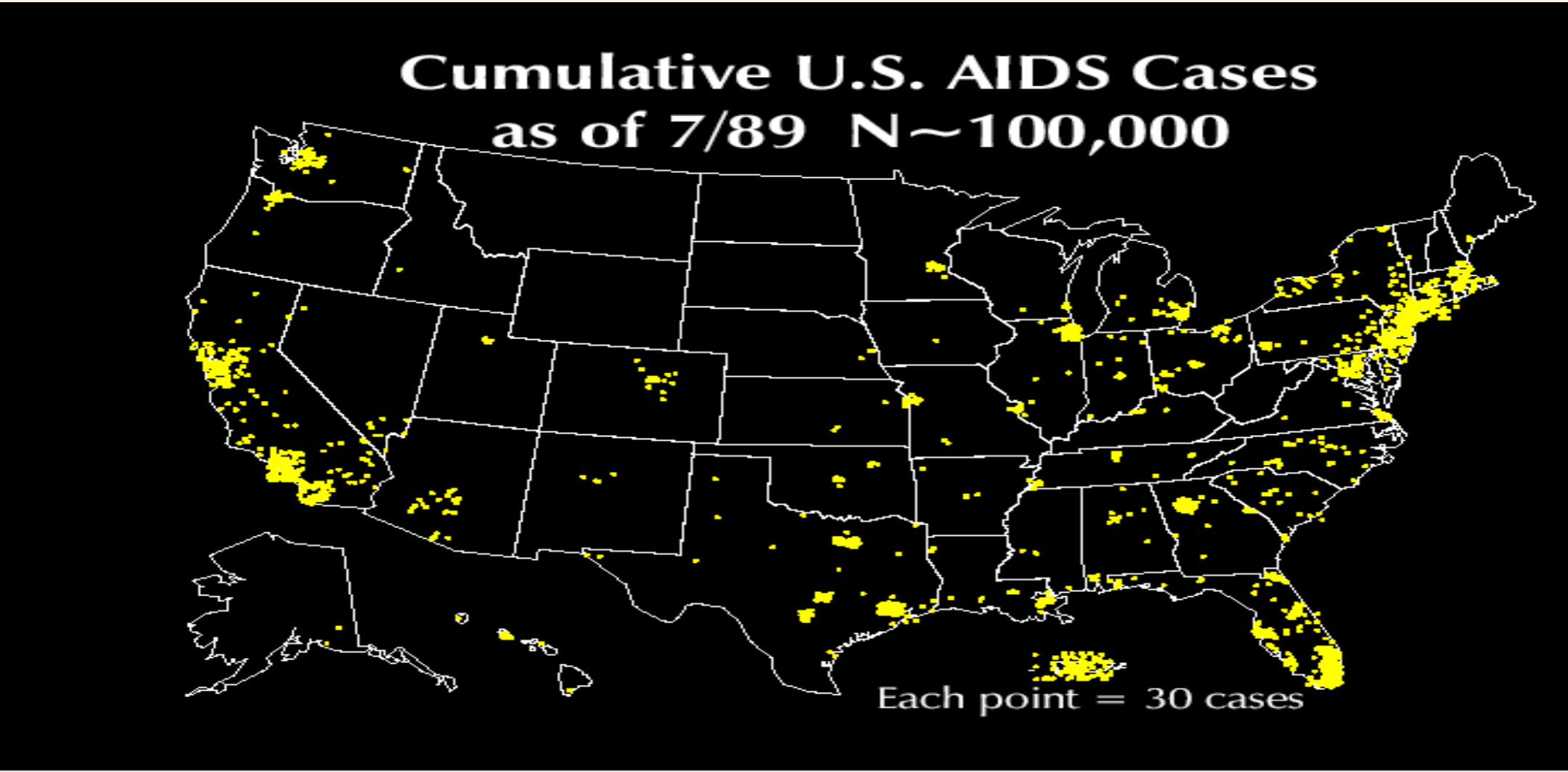
Cumulative U.S. AIDs cases as of 2/83 N = 1000



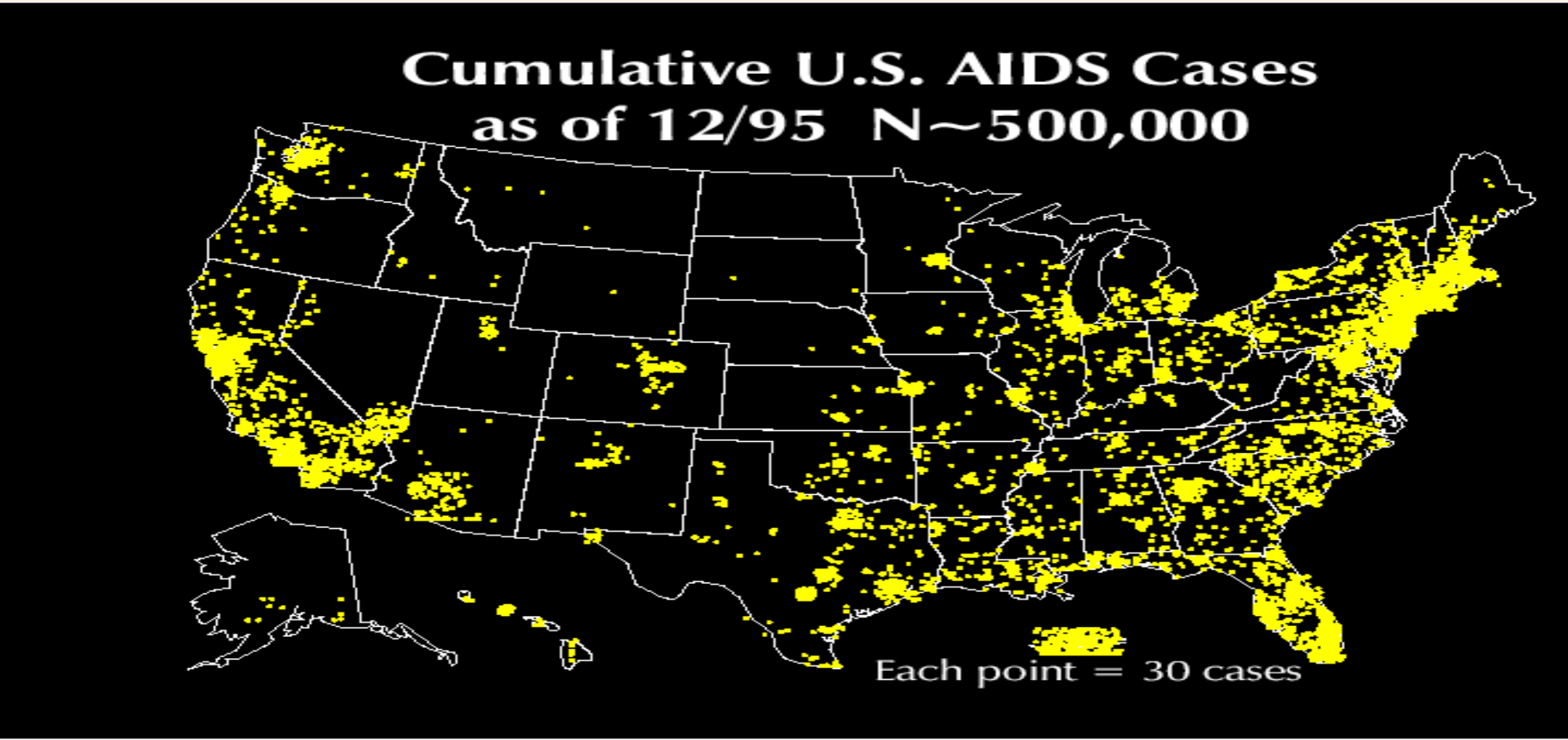
Cumulative U.S. AIDs cases as of 5/85 N = 10000



Cumulative AIDs cases as of 7/89 N = 100000



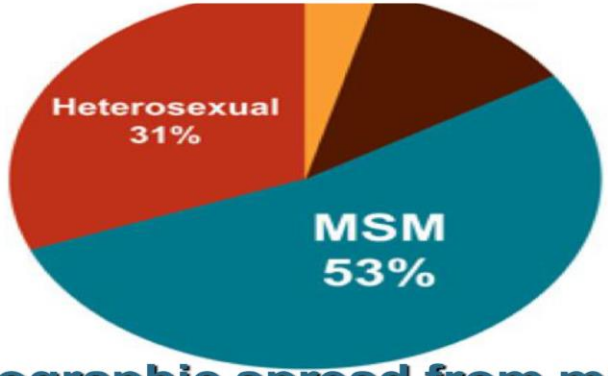
Cumulative AIDs cases as of 12/95 N = 500000

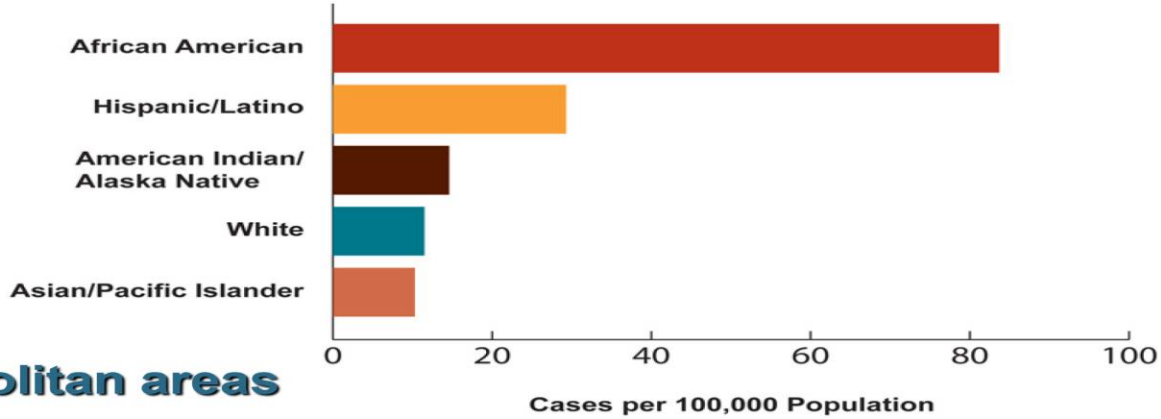


New cases of AIDS

New cases of HIV/AIDS—USA

Estimates of New HIV Infections in the United States, 2006, By Transmission Category



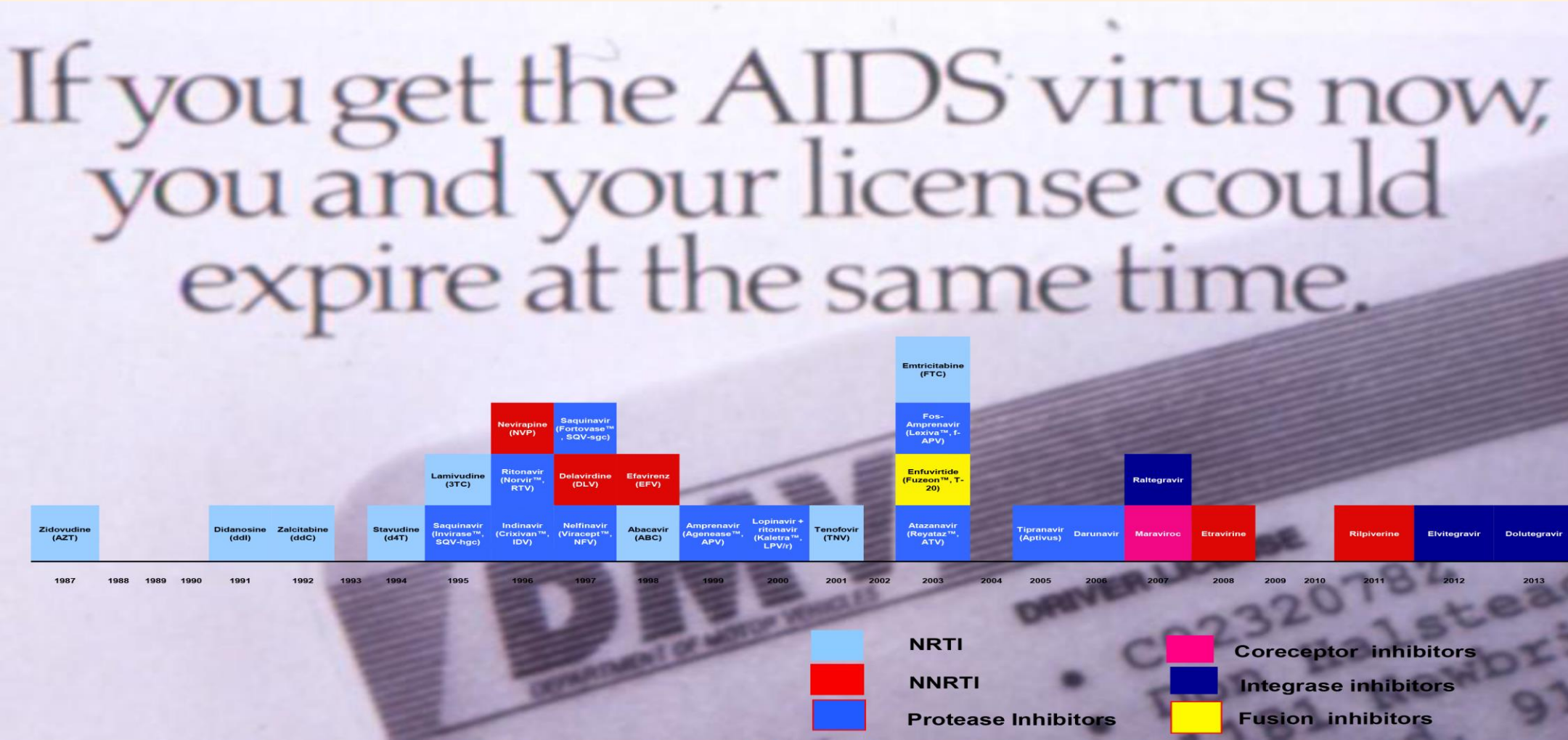


JAMA 2008

- **Geographic spread from metropolitan areas**
  - **~12% of cases in locations with population <50,000**
- **Women**
  - **comprise > 25% of all AIDS cases**
- **Age**
  - **11% of AIDS cases are 50+ years old**
  - **c.50% of persons living with HIV are >50 yo**

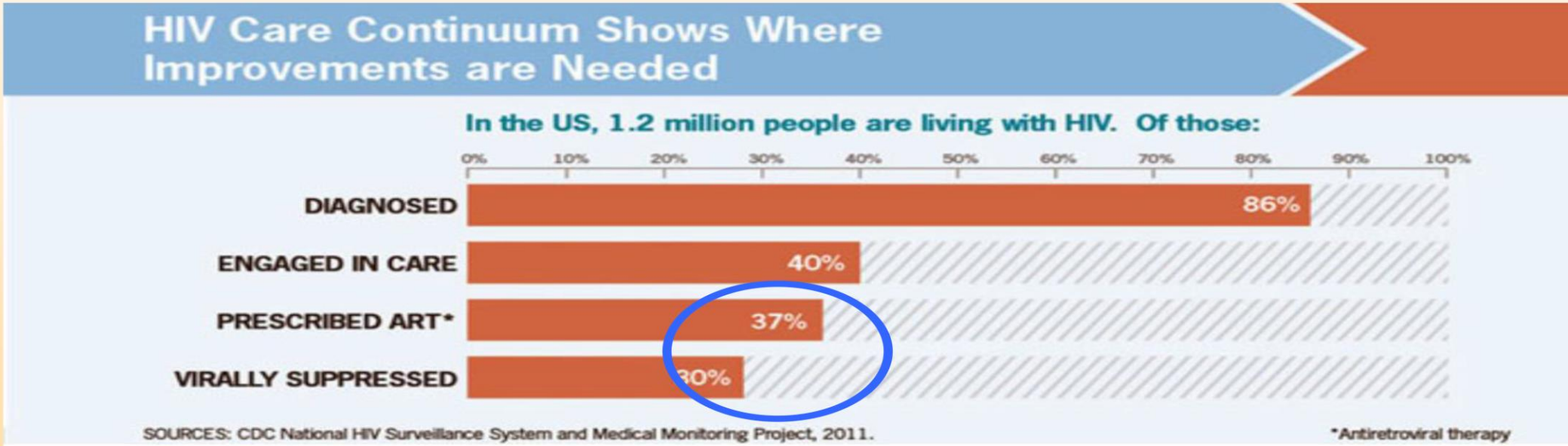
HIV Therapy and Beyond

AIDS drugs


If you get the AIDS virus now, you and your license could expire at the same time.
Zidovudine (AZT)
Didanosine (ddI)
Zalcitabine (ddC)
Stavudine (d4T)
Lamivudine (3TC)
Saquinavir (Invirase™, SQV-hgc)
Nevirapine (NVP)
Ritonavir (Norvir™, RTV)
Indinavir (Crixivan™, IDV)
Saquinavir (Fortovase™, SQV-sgc)
Delavirdine (DLV)
Nelfinavir (Viracept™, NFV)
Efavirenz (EFV)
Abacavir (ABC)
Amprenavir (Agenease™, APV)
Lopinavir + ritonavir (Kaletra™, LPV/r)
Tenofovir (TNV)
Emtricitabine (FTC)
Fos-Amprenavir (Lexiva™, f-APV)
Enfuvirtide (Fuzeon™, T-20)
Atazanavir (Reyataz™, ATV)
Raltegravir
Tipranavir (Aptivus)
Darunavir
Maraviroc
Etravirine
Rilpiverine
Elvitegravir
Dolutegravir
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
NRTI
NNRTI
Protease Inhibitors
Coreceptor inhibitors
Integrase inhibitors
Fusion inhibitors

Gardner Continuum of Care

Gardner Continuum of Care



Key Advances in HIV Therapy

- PrEP
  - Adherent prophylaxis is effective
- SMART Study
  - Continuous therapy essential to avoid AIDS and other complications
- START Study
  - Earlier therapy is initiated, greater preservation of therapy

Next Advances in HIV Therapy

- Vaccines
- Cures

Retroviruses

- **Lessons**

Summary

Summary

- Viruses are bad and should be avoided
- Except when they save the planet
- And maybe if it saves you from the next virus
- Epidemics are not single events
- Epidemics evolve
- Antivirals are useful
  - Instituted as early as possible
  - Adherence is essential