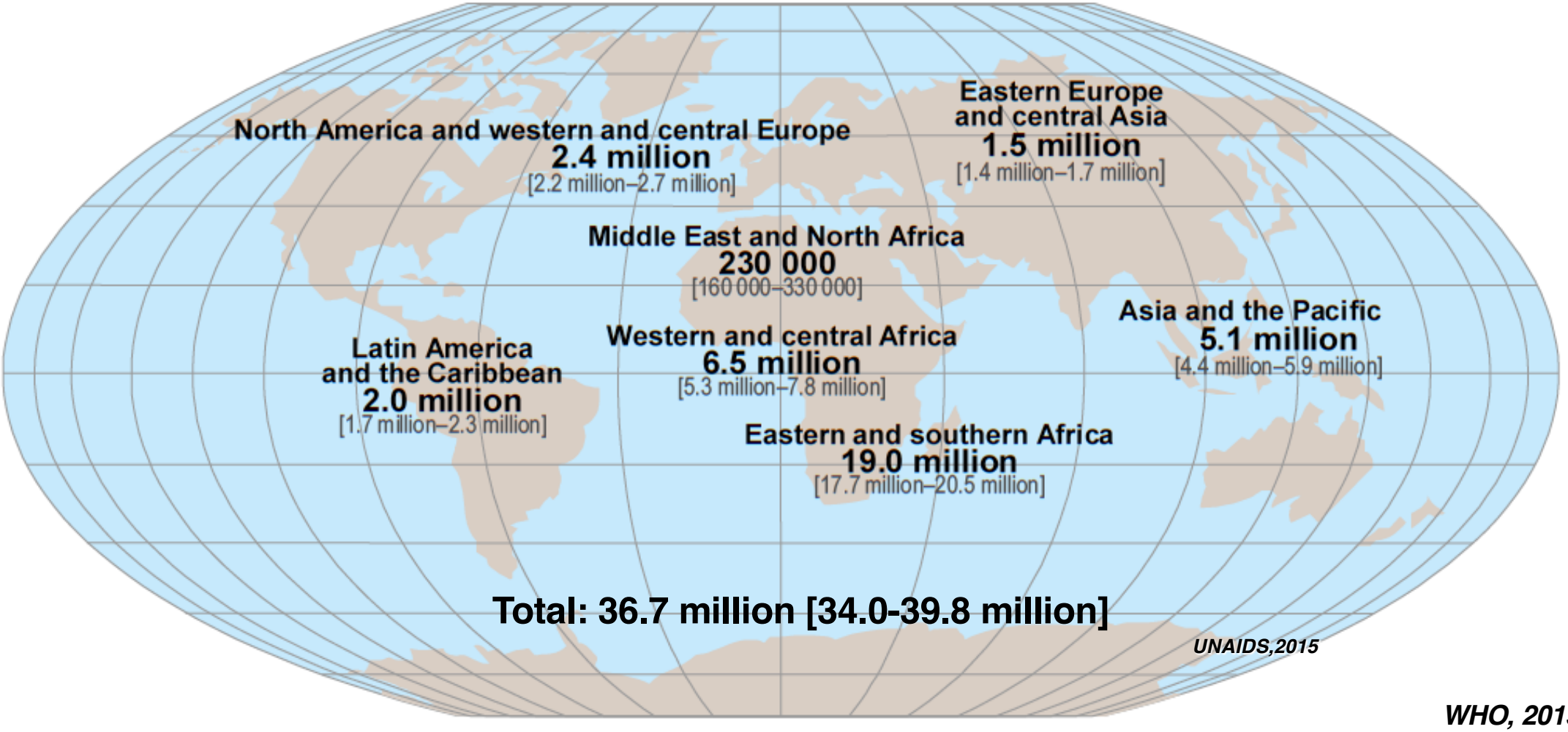
Retroviruses

TRACO
Frank Maldarelli
HIV Dynamics and Replication Program
NCI

Retroviruses

- Introduction
- Molecular Biology/Replication
- Retroviruses in Human Populations
- Emergence/Spread
- HIV Therapy and Beyond
- Lessons

The Disease is Widespread: Global Burden of HIV-1 Infection



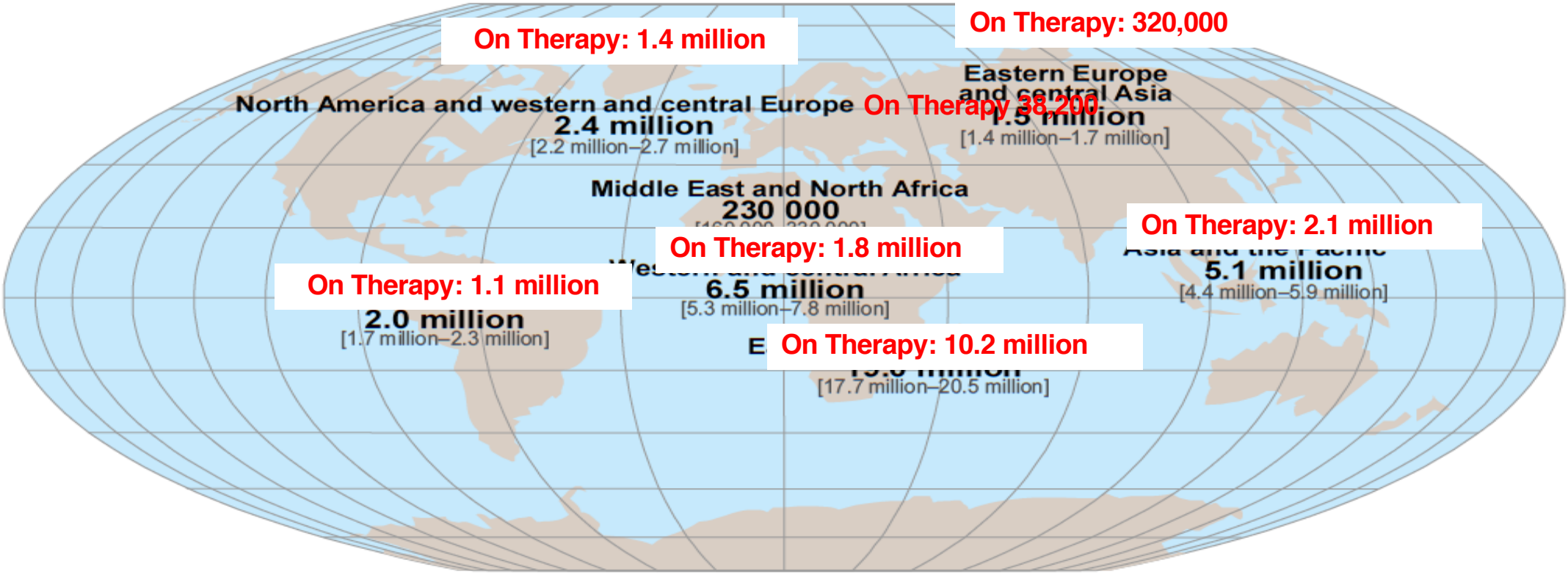
UNAIDS,2015

WHO, 201

Total: 36.7 million [34.0 million–39.8 million]

Global Burden of HIV-1 Infection

People undergoing antiretroviral therapy: 17 million



The Need is Great

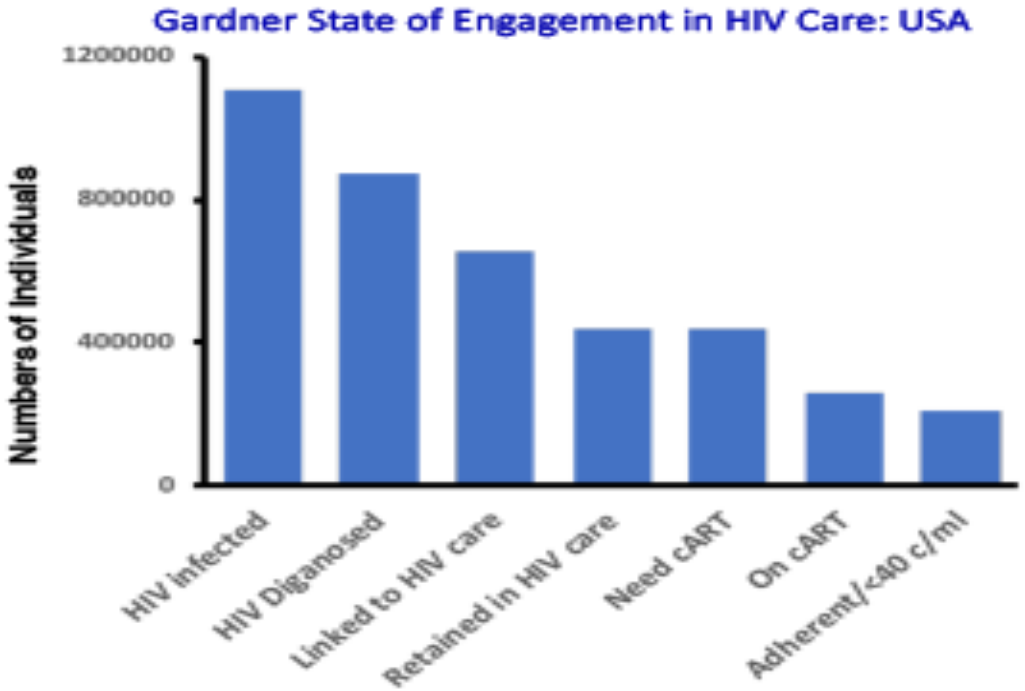
The Need is Great:
HIV is a Challenge on Numerous Levels

HIV Infection - USA

HIV Prevalence is INCREASING

New cases of HIV diagnosed=38,000

Deaths from HIV = 6465



Retroviruses

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

Office of AIDS research

The Need is Great:
Research Priorities Office of AIDS Research 2018

Distinct Areas

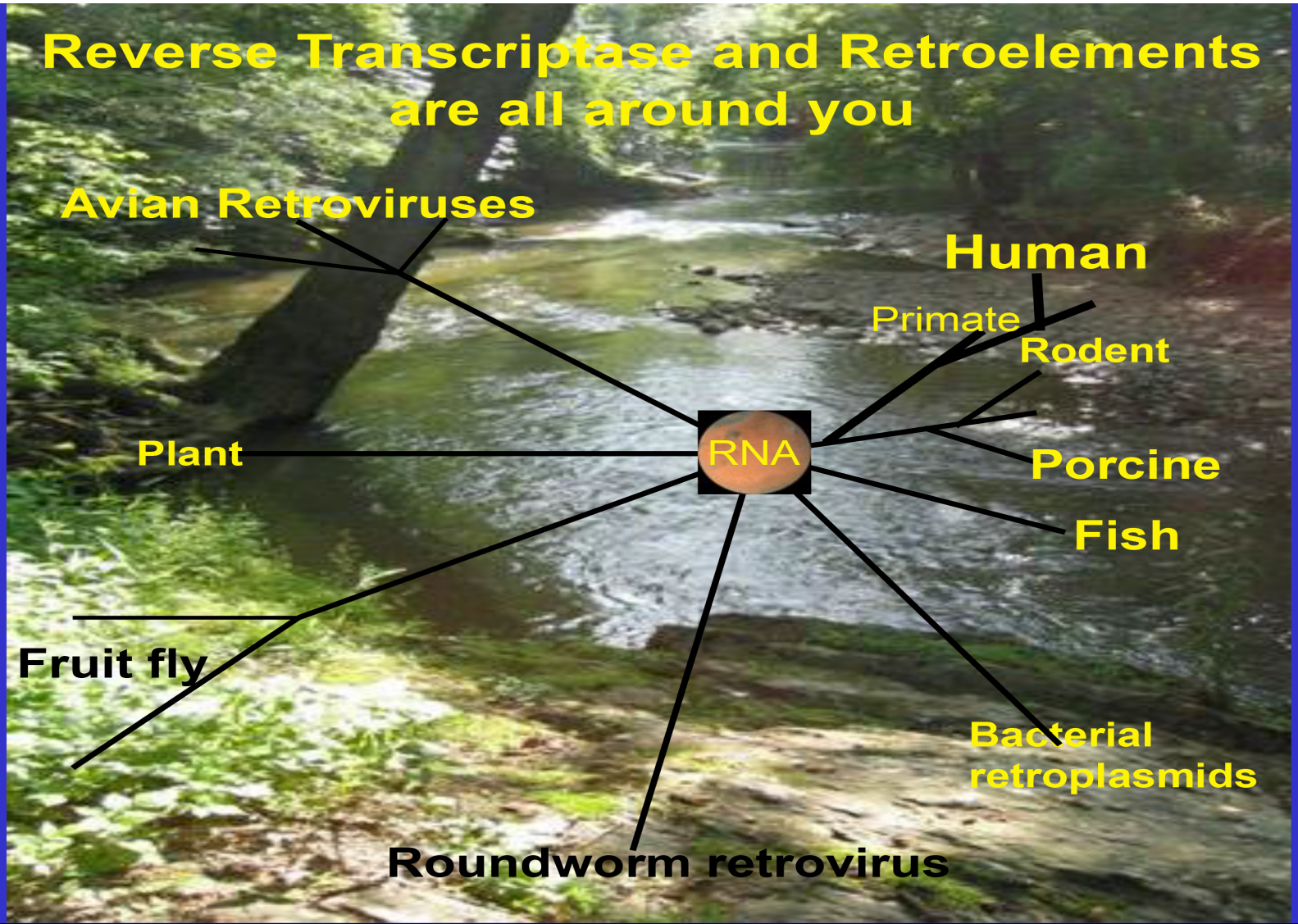
Cut across disciplines

Specific Goals

Retroviruses

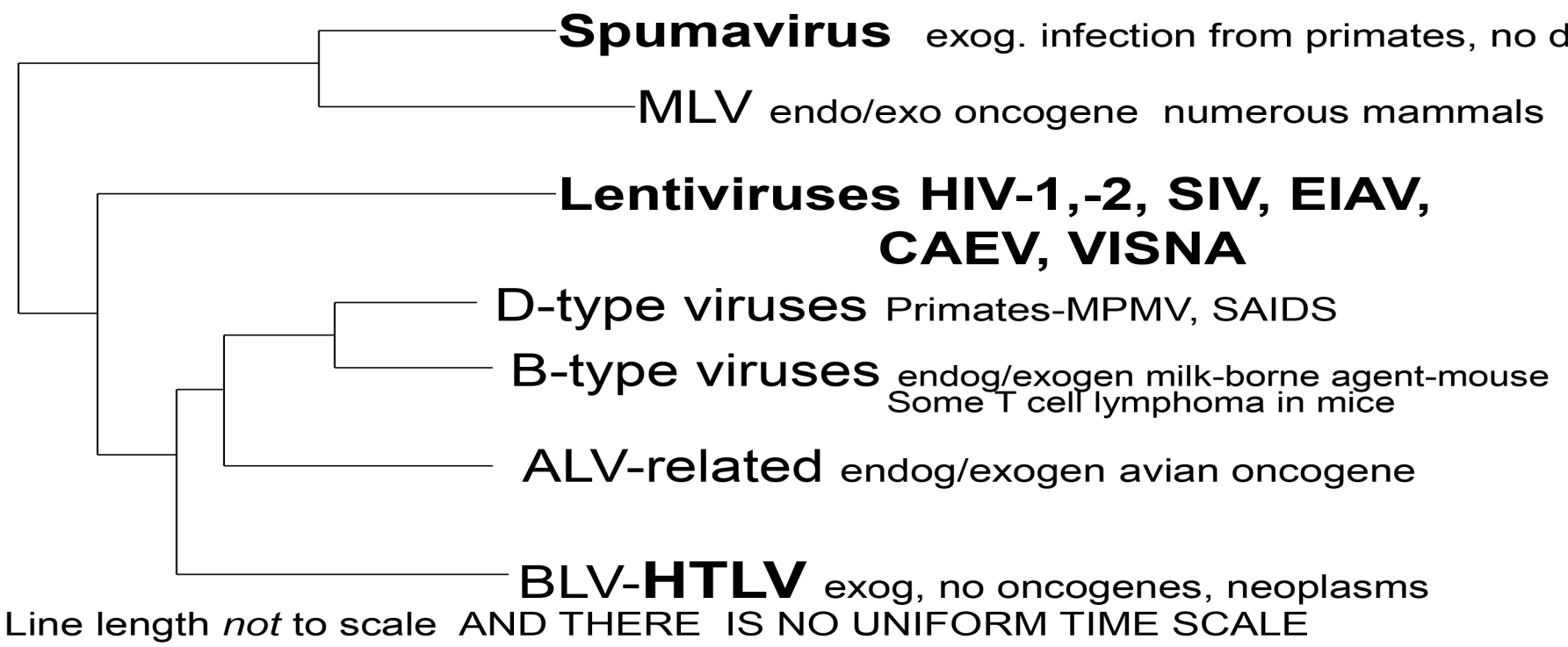
A group of RNA viruses that replicate via a DNA intermediate using Reverse Transcriptase.

Retroelements

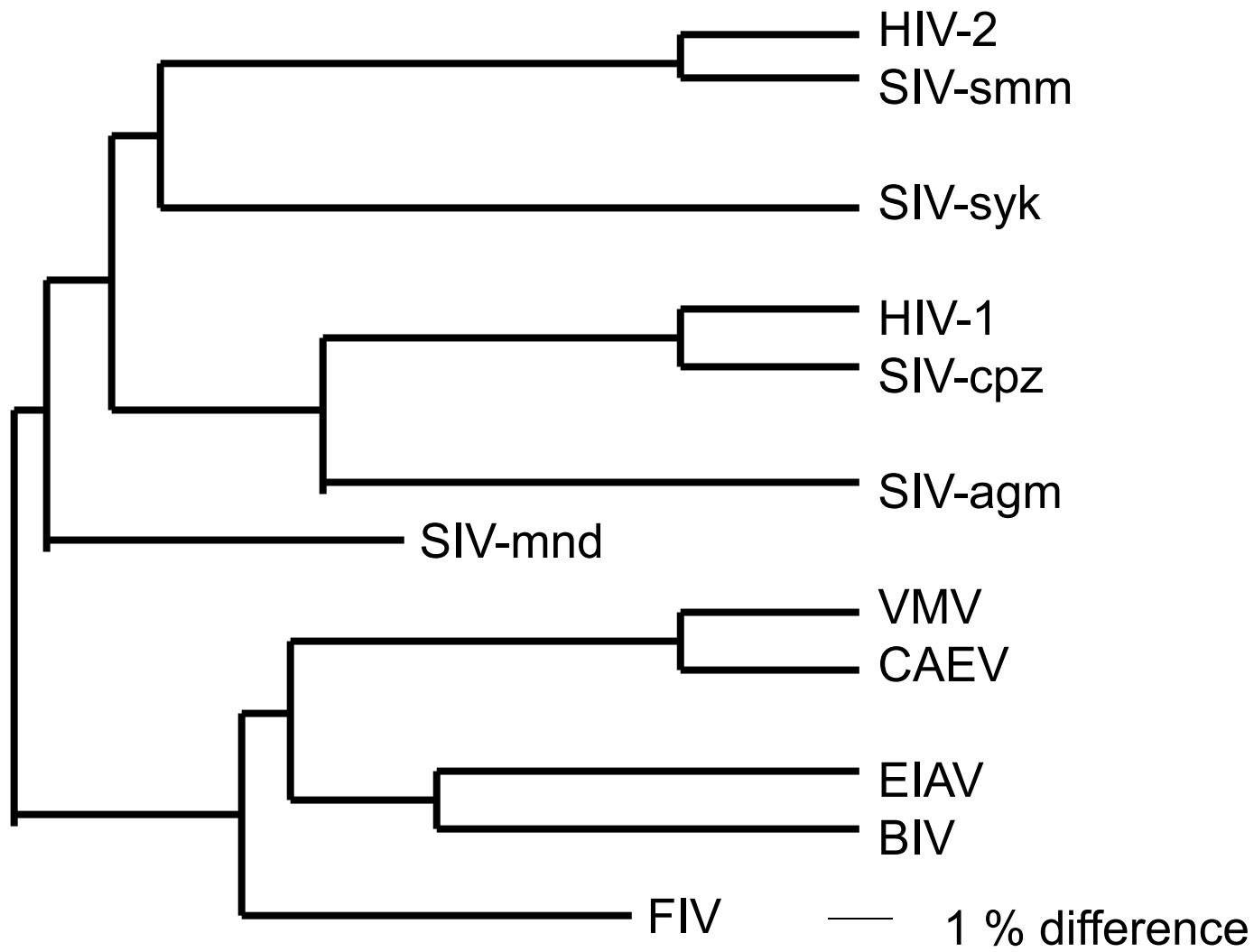


Retrovirus classification

Retroviruses
Classification by RT Sequence into Seven Families

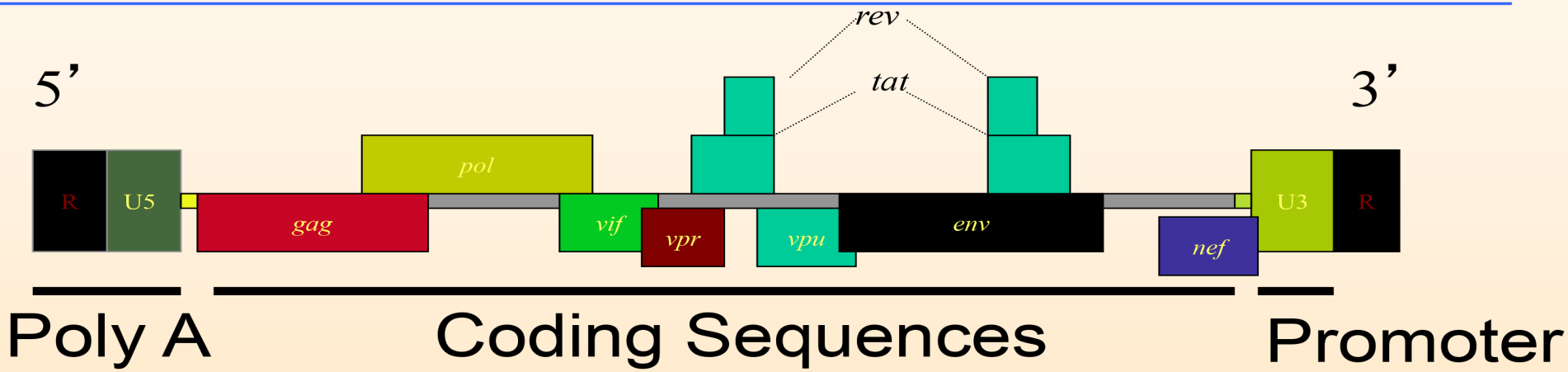


Lentivirus Relationships



Retrovirus conventions

Retroviruses Conventions

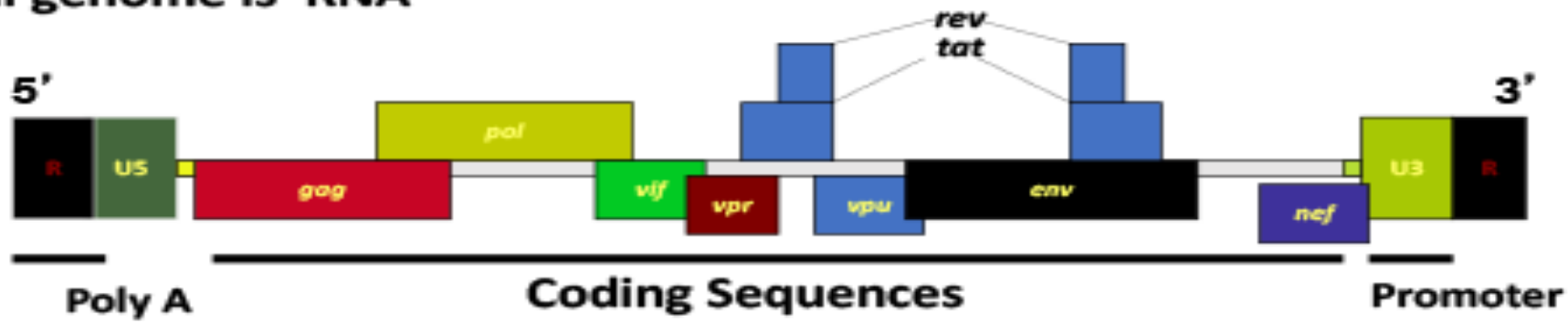


Names of genes in lower case *italics*, e.g., *pol, env*
Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120

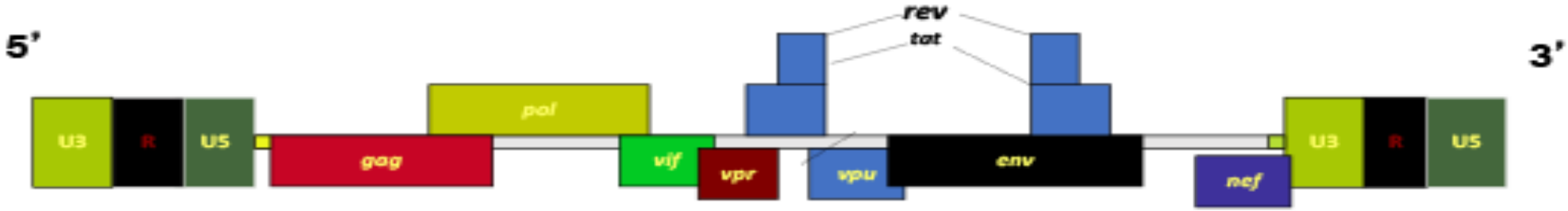
Retrovirus conventions

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*

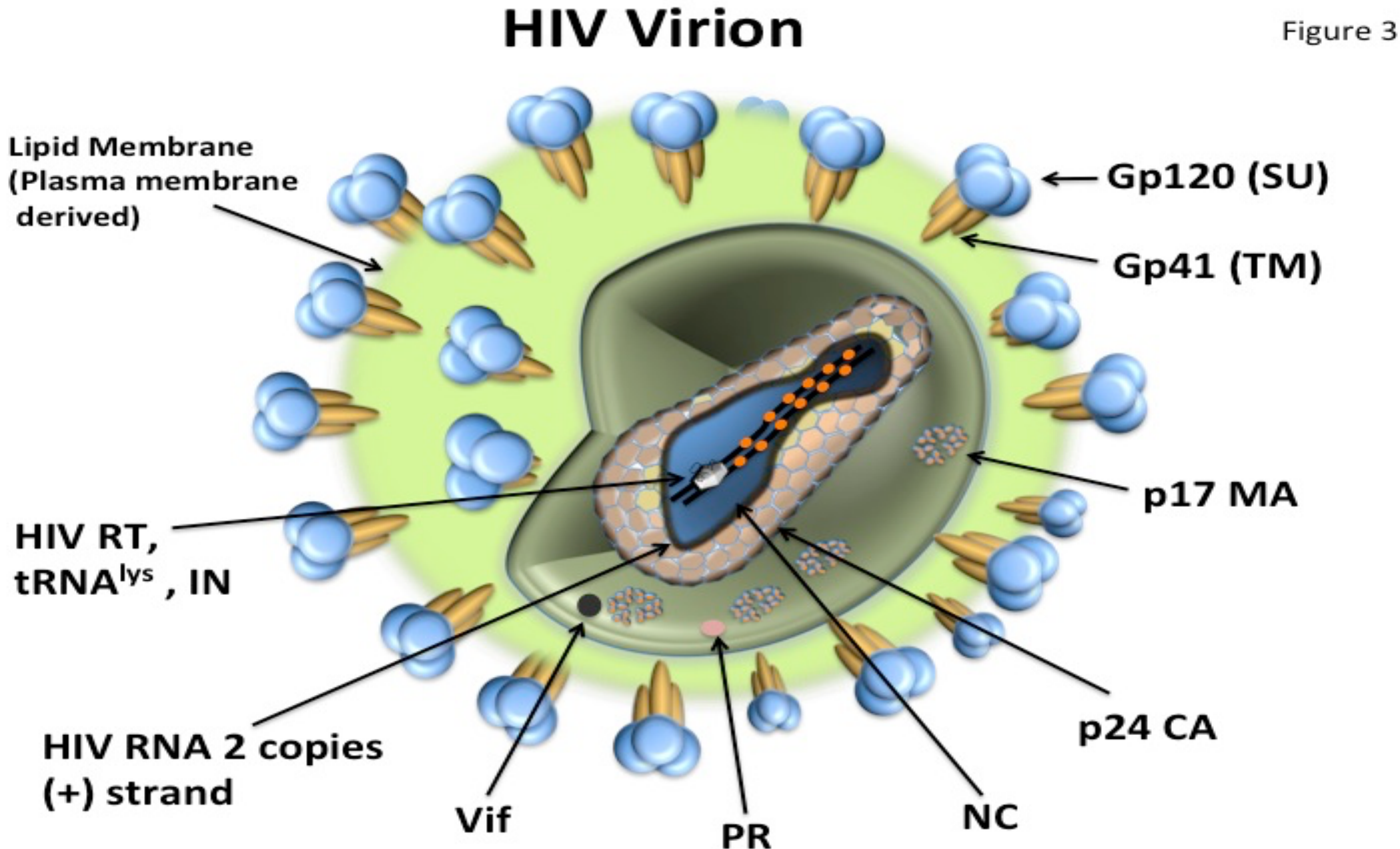
Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120

Retroviruses Glossary

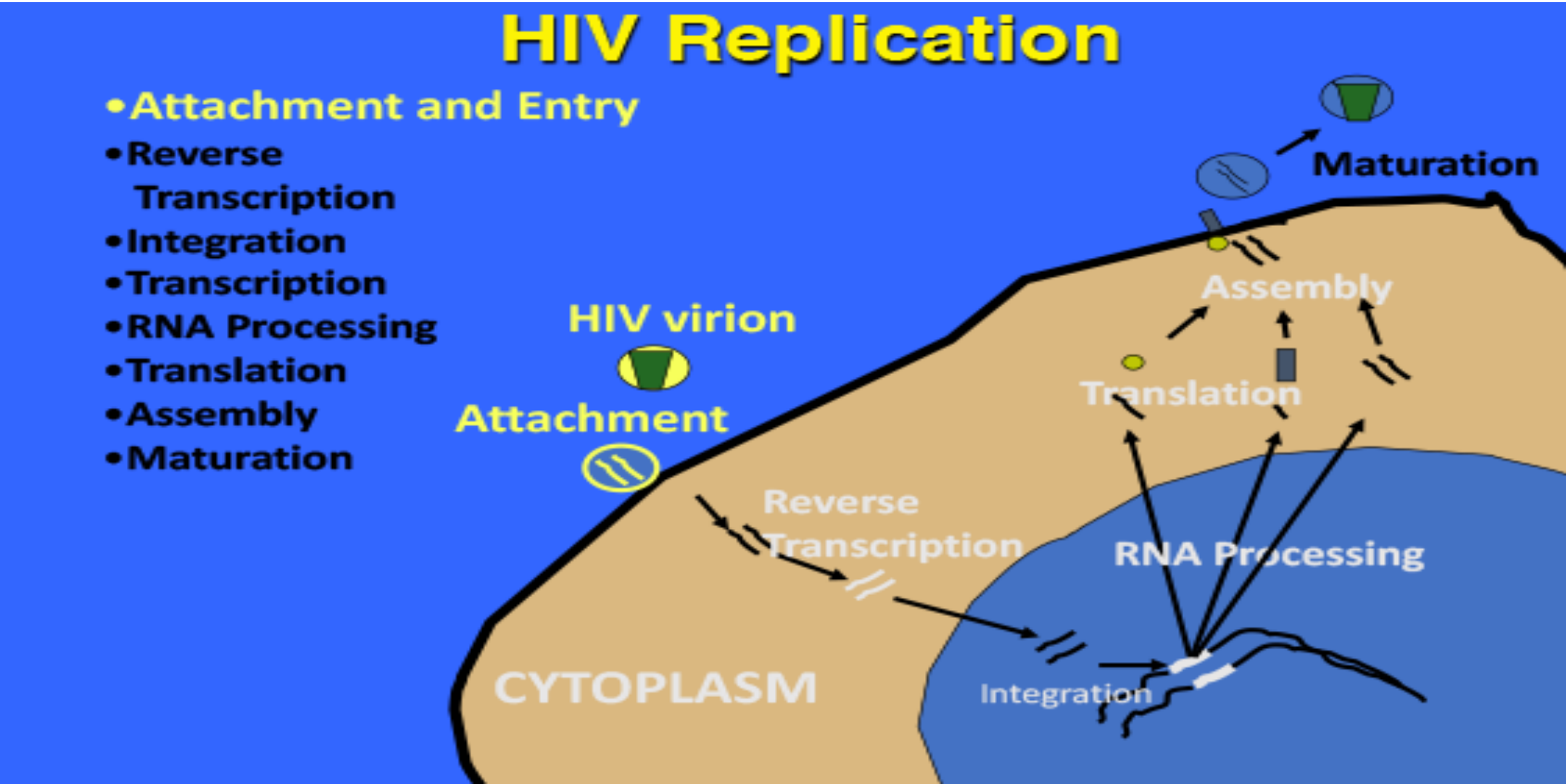
- *gag: group antigen*
- *pol: polymerase*
- *env: envelope*
- *tat: Transactivator*
- *rev:Regulator of Expression of Virion proteins*

- 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
Figure 3
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



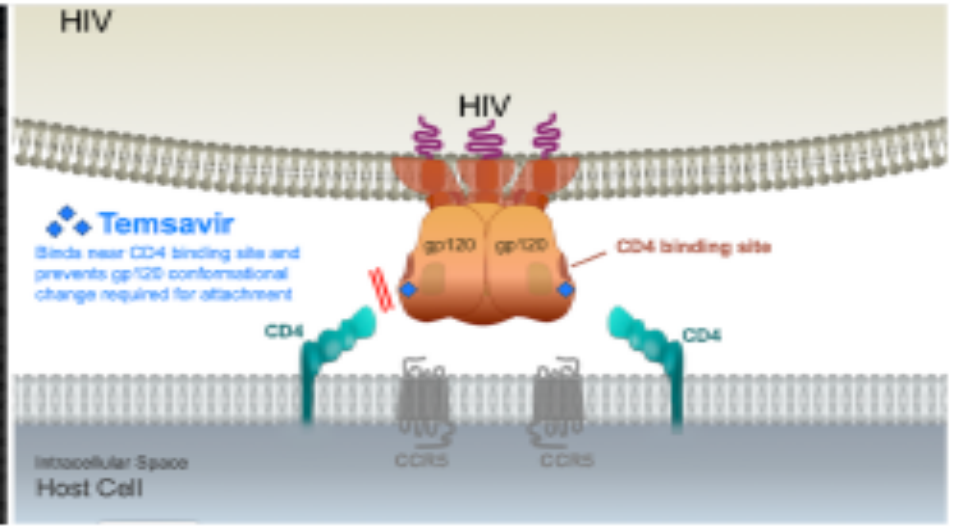
HIV Attachment and Entry

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

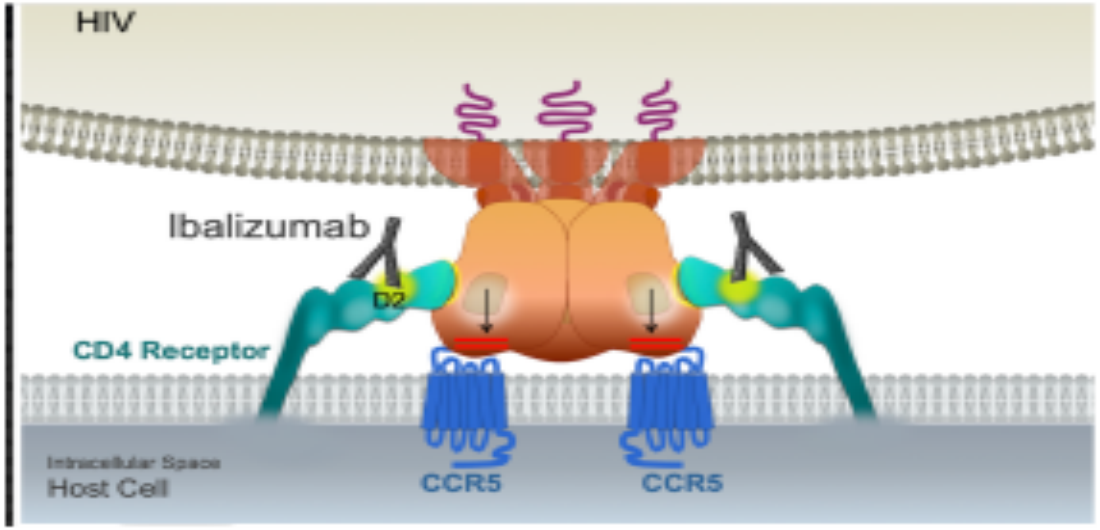
HIV receptor blockade

Blocking the HIV Receptor: Ibalizumab and Fostemsavir

Fostemsavir



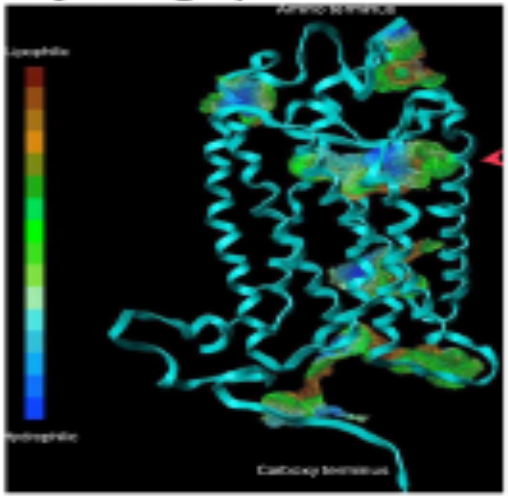
Ibalizumab

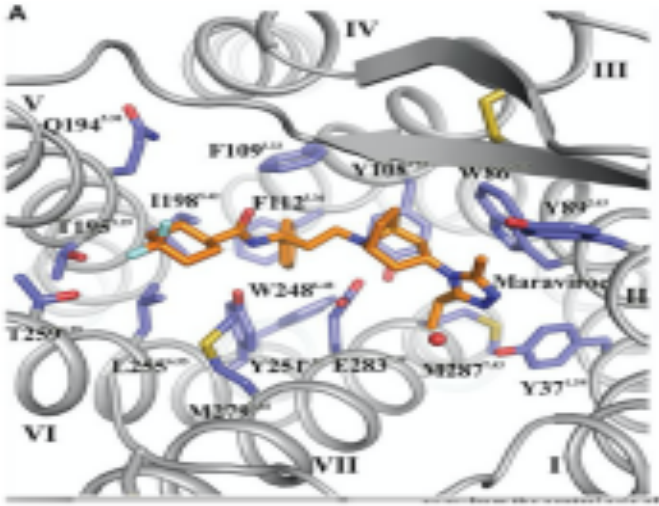


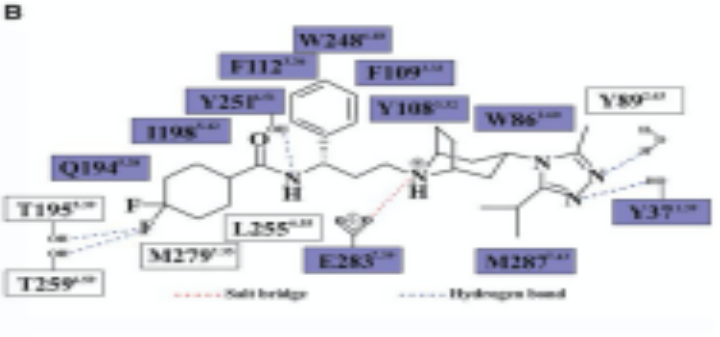
Blocking the HIV coreceptor

Blaocing the HIV Coreceptor: Maraviroc

Crystallographic Structure

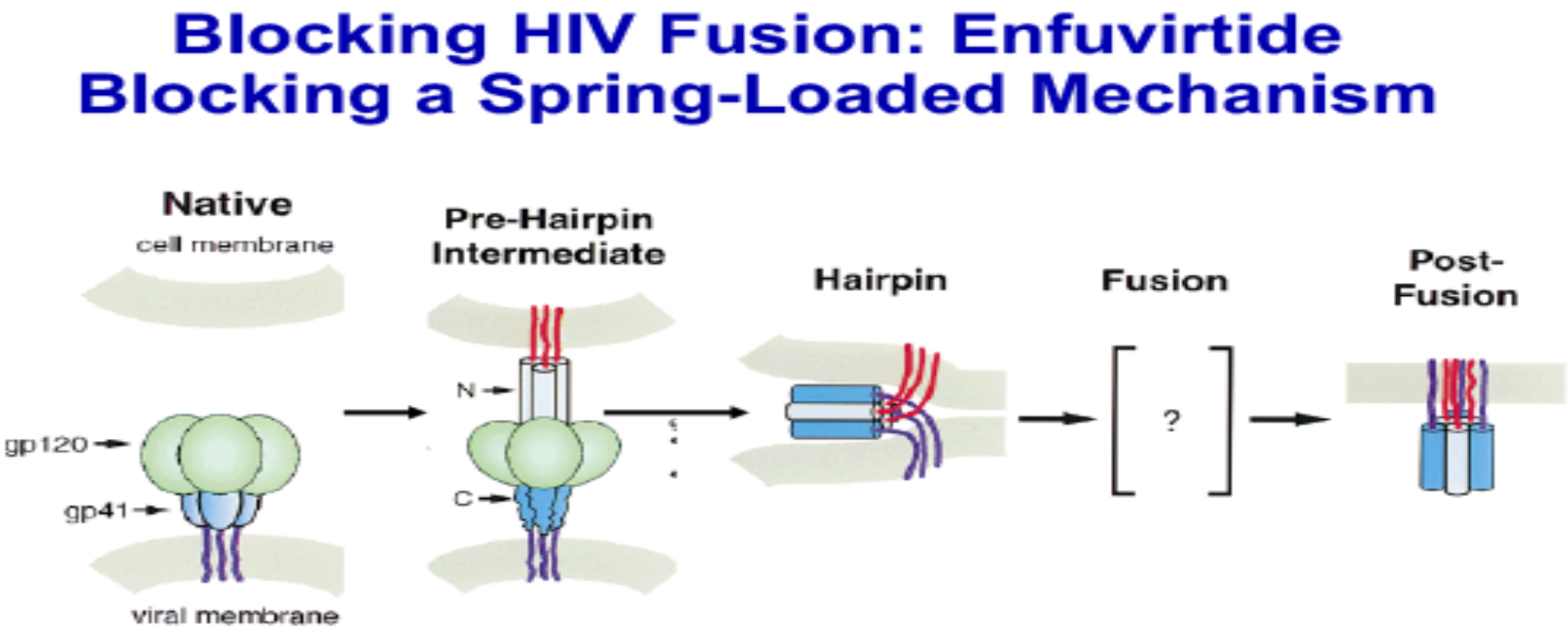




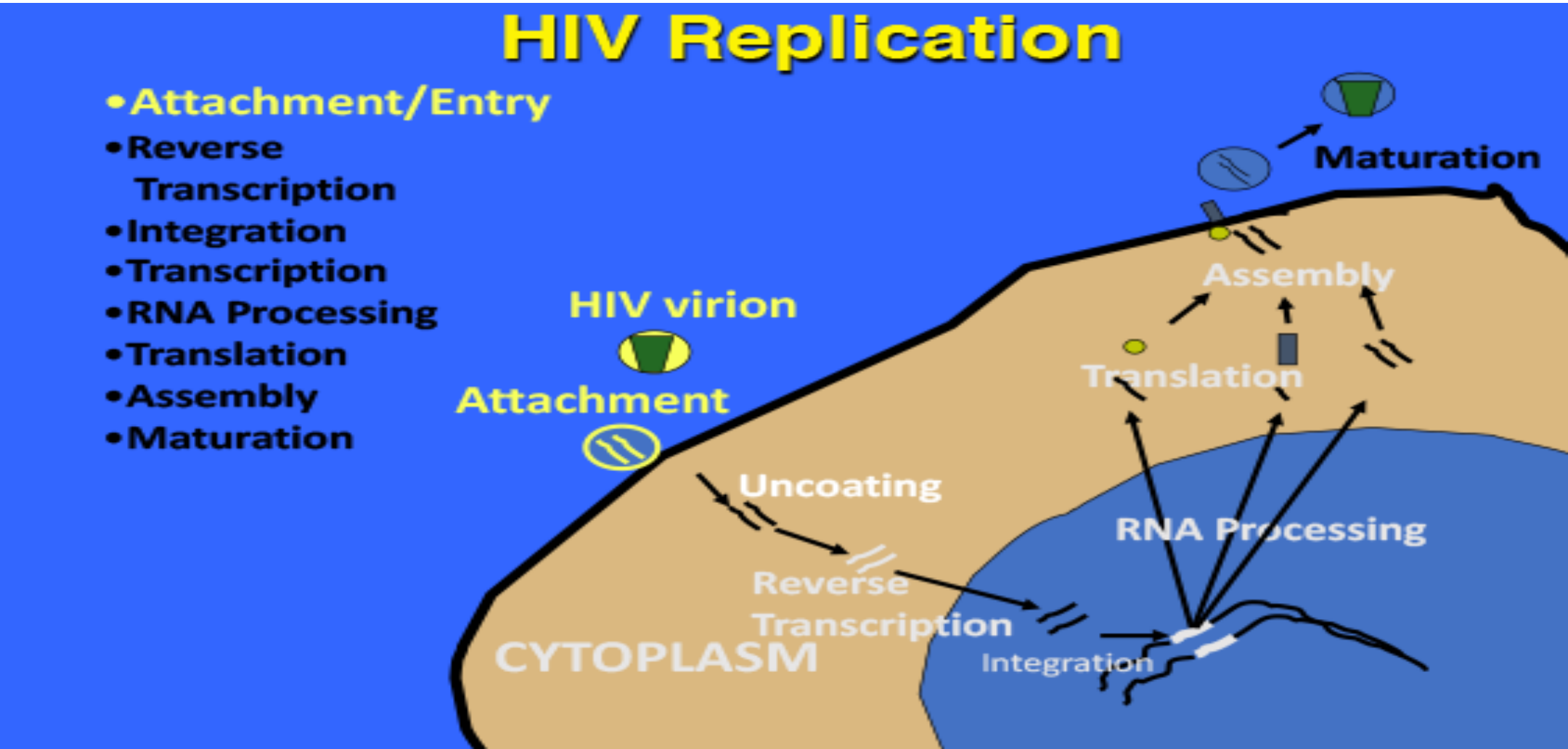


- Multiple binding domains predicted
  - Binding disrupts structure generally
  - Does not require blocking CCR5-gp120 interaction
  - Potential for simultaneous inhibition
- Resistance emerges by reducing affinity for drug

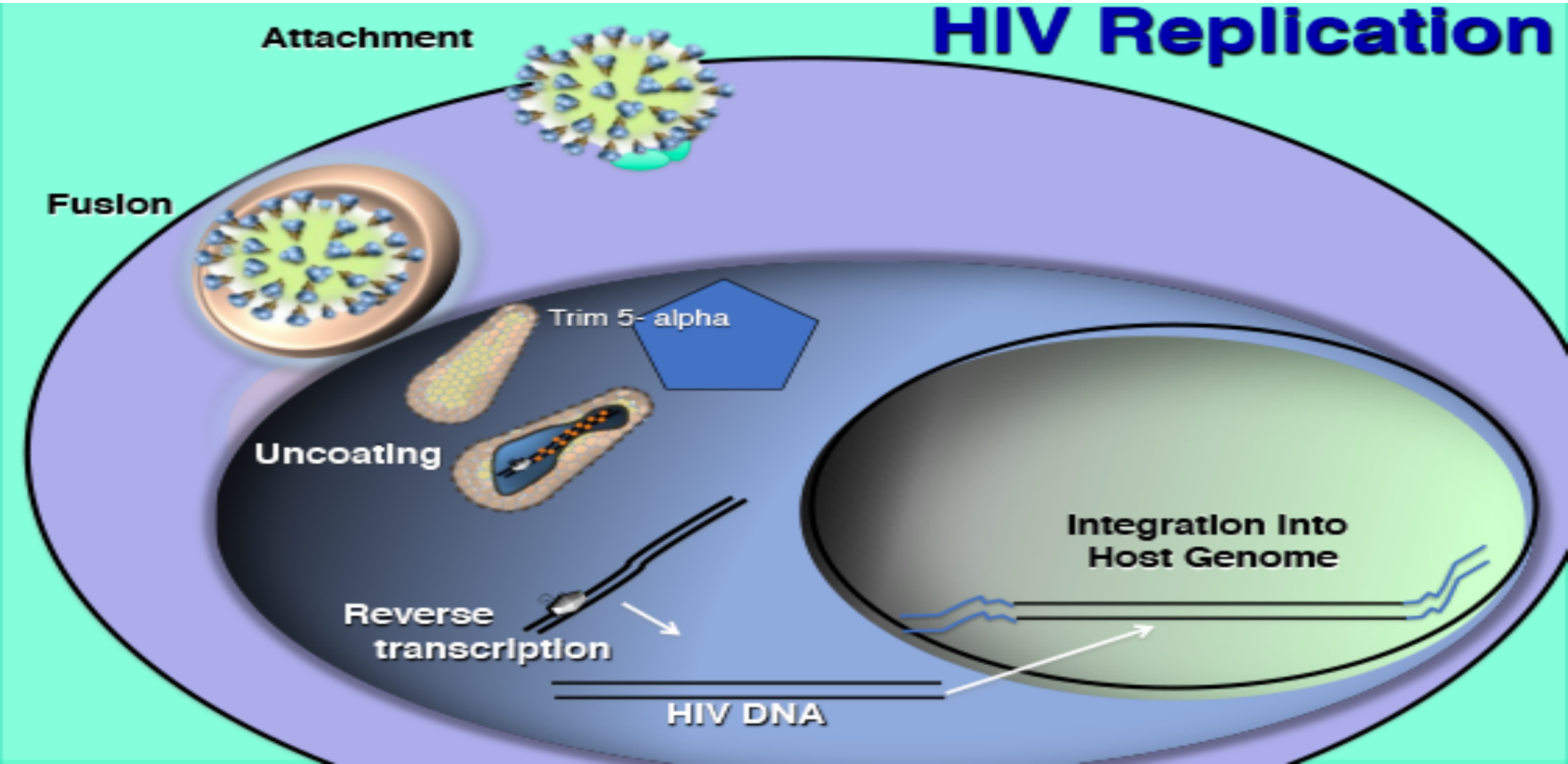
Blocking HIV Fusion



HIV replication



HIV replication



HIV 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

HIV Post-Entry events

HIV Post – Entry Events

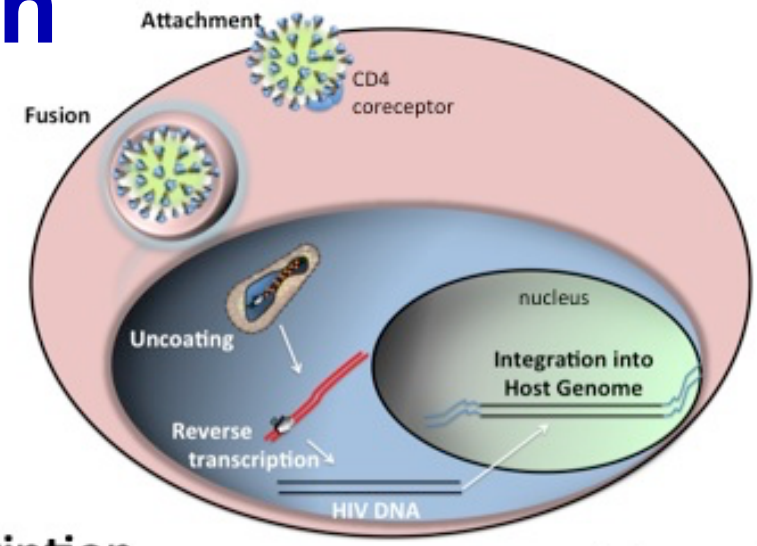
Host Trim5 Alpha

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

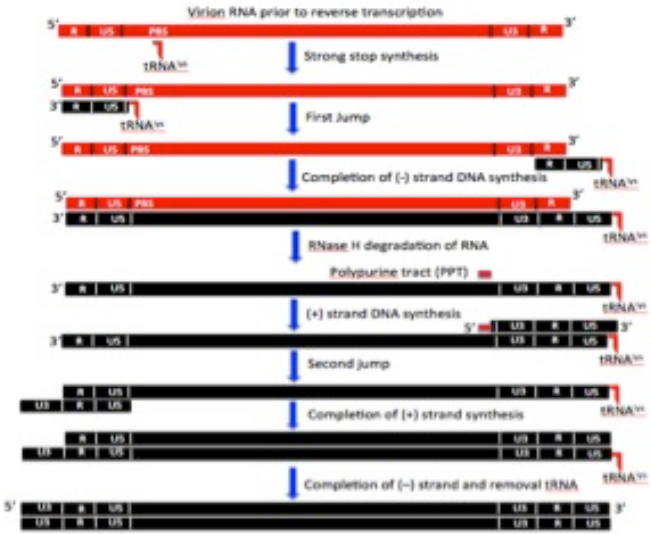
Positive Selection in Trim 5-alpha

- 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

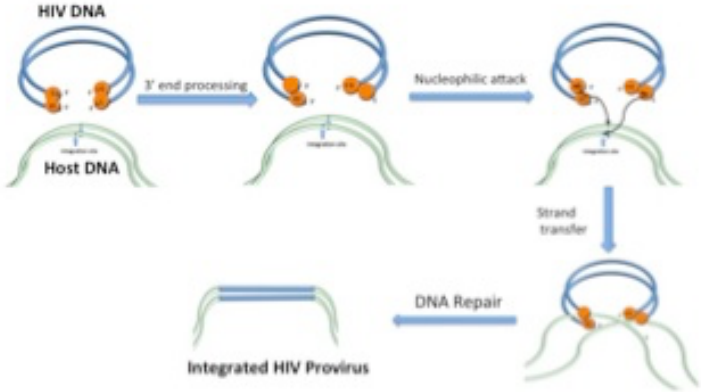
HIV Reverse Transcription and Integration



Reverse Transcription



Integration



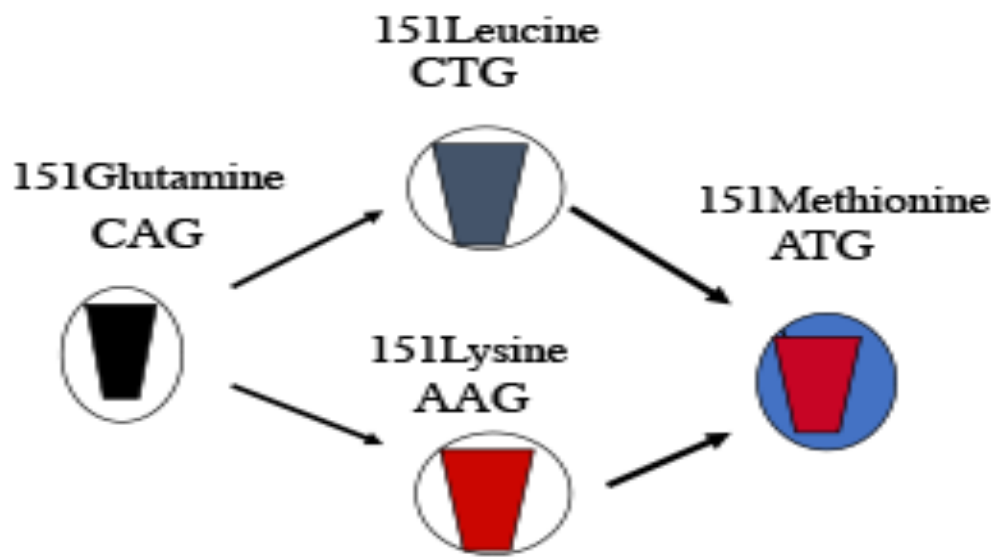
Reverse Transcriptase Enzymatic Activities

- 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

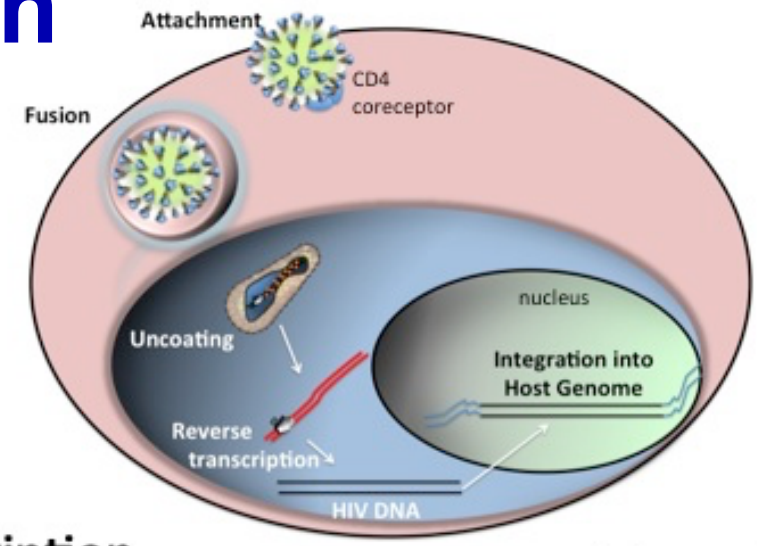
Error-Prone HIV replication

Error-Prone HIV Replication is a Pathogenic Determinant

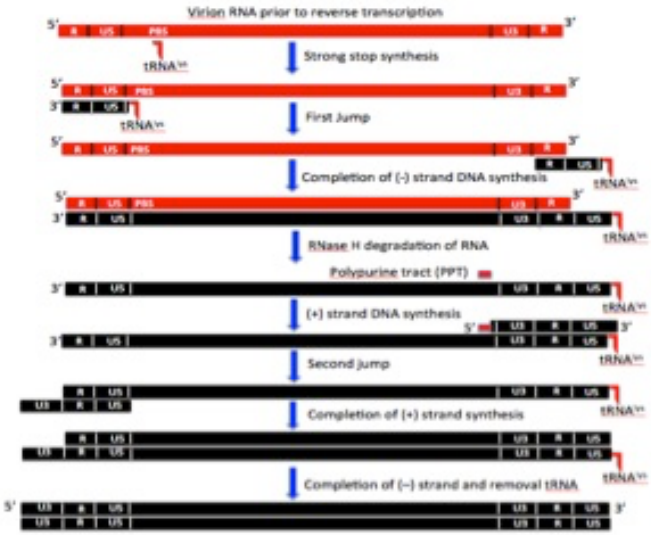
- Each round of HIV replication generates numerous mutants.
- The ability of the mutants to replicate (viral "fitness") may vary greatly.
- The virus population can respond rapidly to a selective pressure



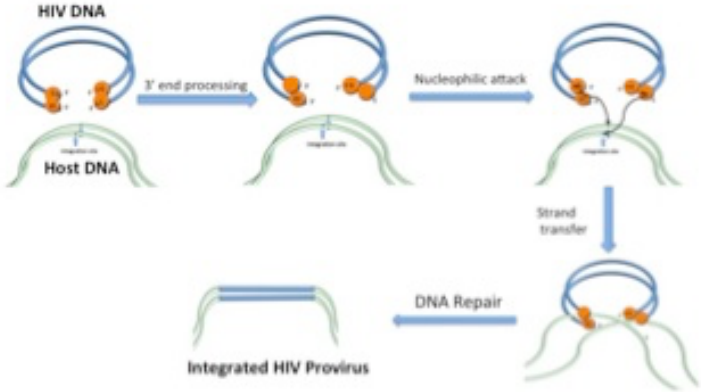
HIV Reverse Transcription and Integration



Reverse Transcription

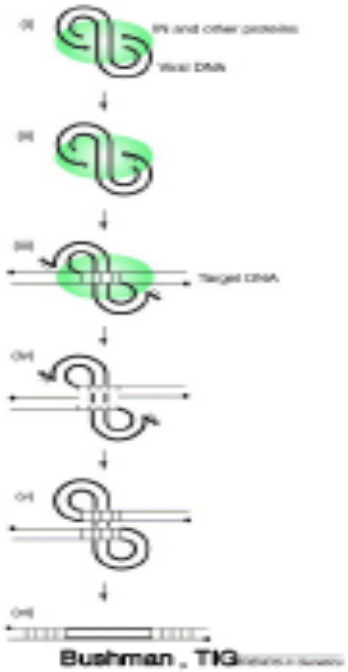


Integration

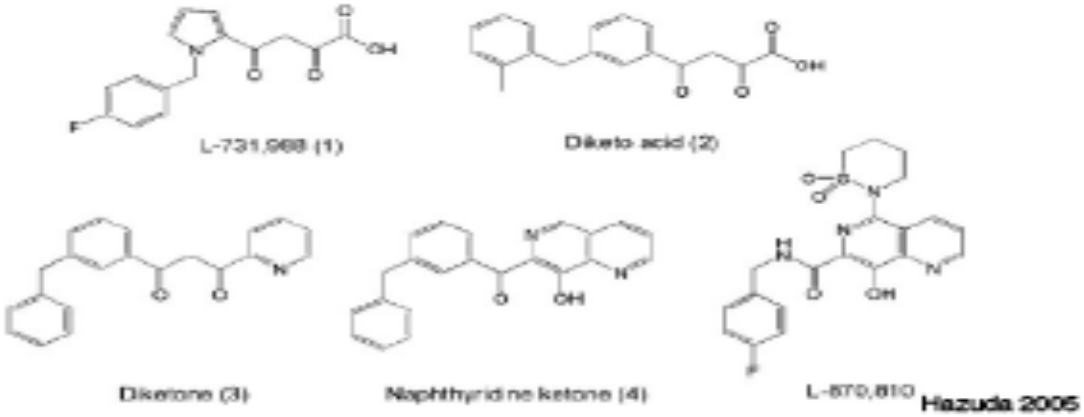


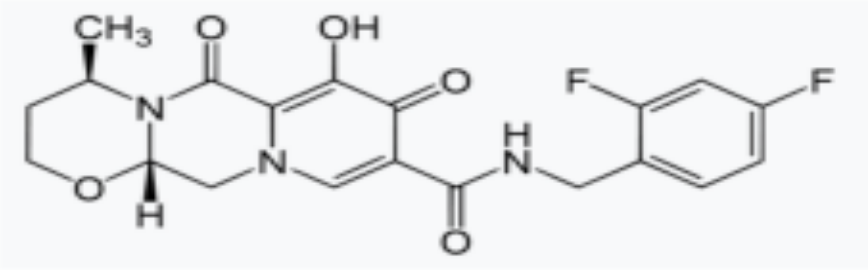
Integration

Integration



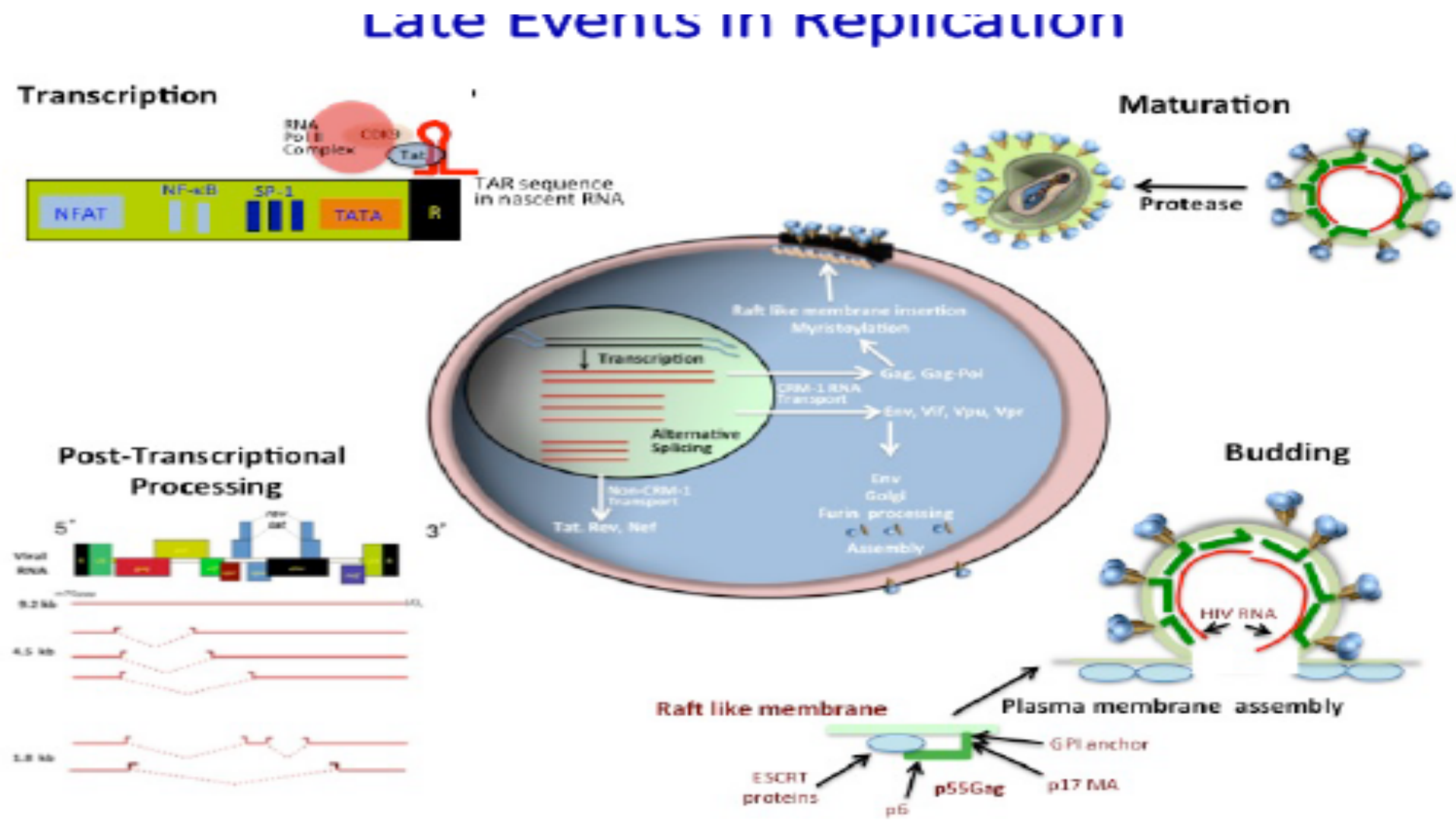
Multistep reaction





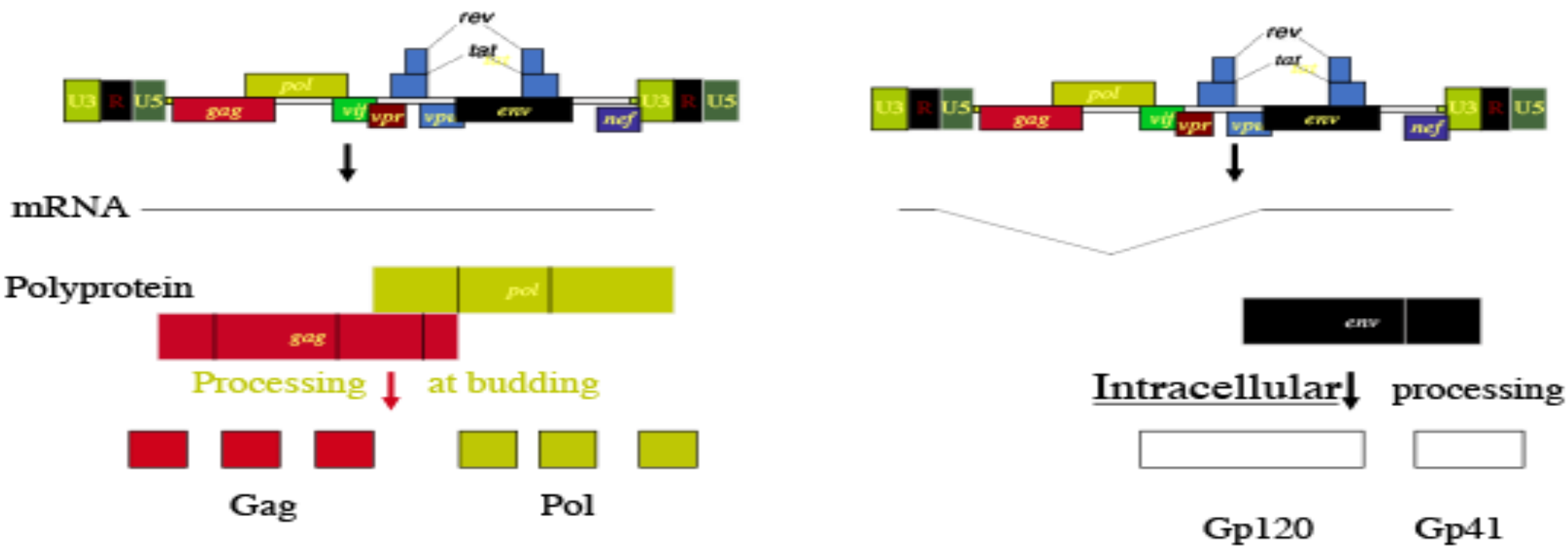
Dolutegravir

Late events


Late Events in Replication
Transcription
RNA Pol II Complex
CDK9
Tat
TAR sequence in nascent RNA
NFAT
NF-κB
SP-1
TATA
R
Maturation
Protease
Raft like membrane insertion
Myristoylation
Transcription
Gag, Gag-Pol
CRM-1 RNA Transport
Env, Vif, Vpu, Vpr
Alternative Splicing
Non-CRM-1 Transport
Tat, Rev, Nef
Env
Golgi
Furin processing
Assembly
Post-Transcriptional Processing
5'
3'
Viral RNA
9.2 kb
4.5 kb
1.8 kb
Budding
HIV RNA
Raft like membrane
Plasma membrane assembly
GPI anchor
ESCRT proteins
p6
p55Gag
p17 MA

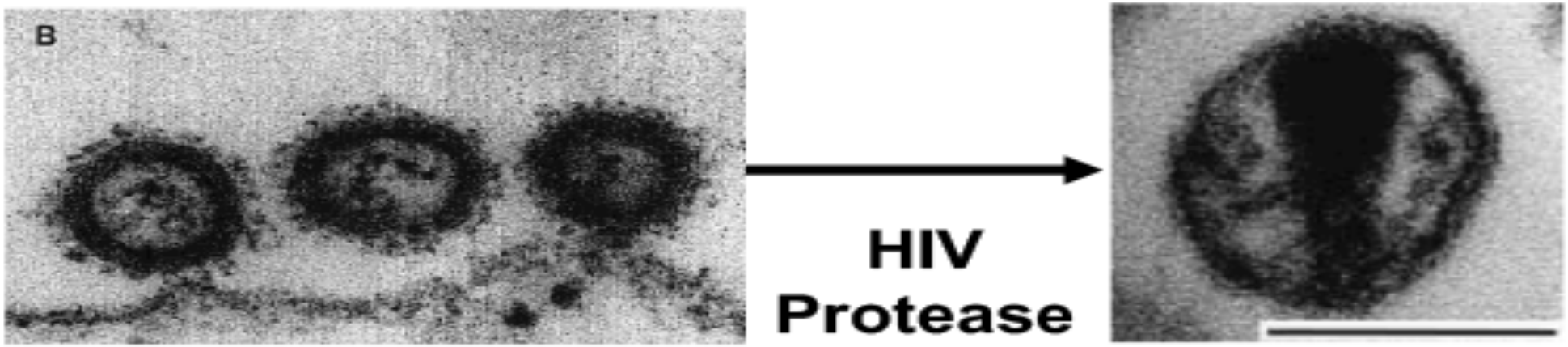
Translation

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



HIV particle maturation

HIV Particle Maturation



Immature Particle
Noninfectious

Mature Particle
Infectious

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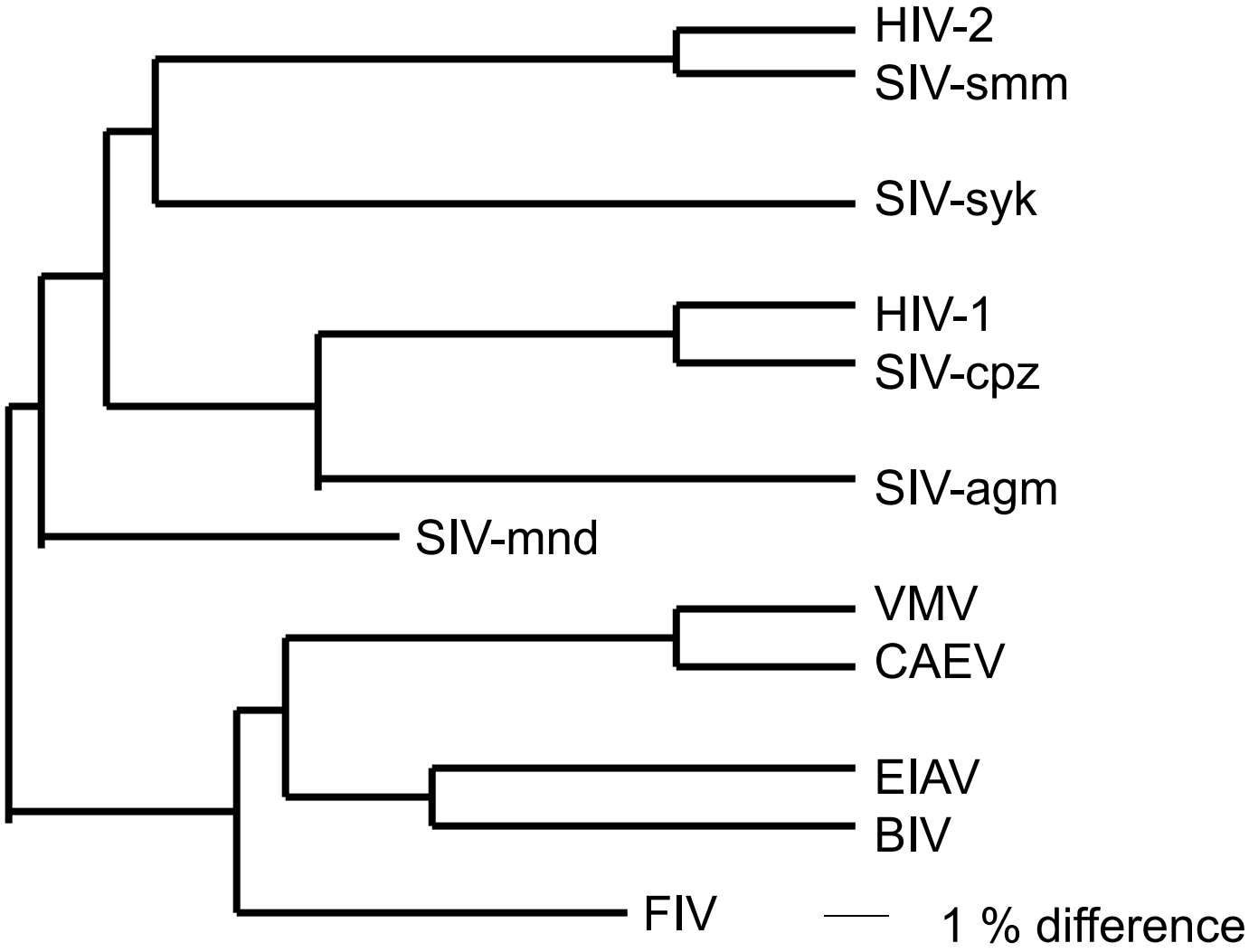
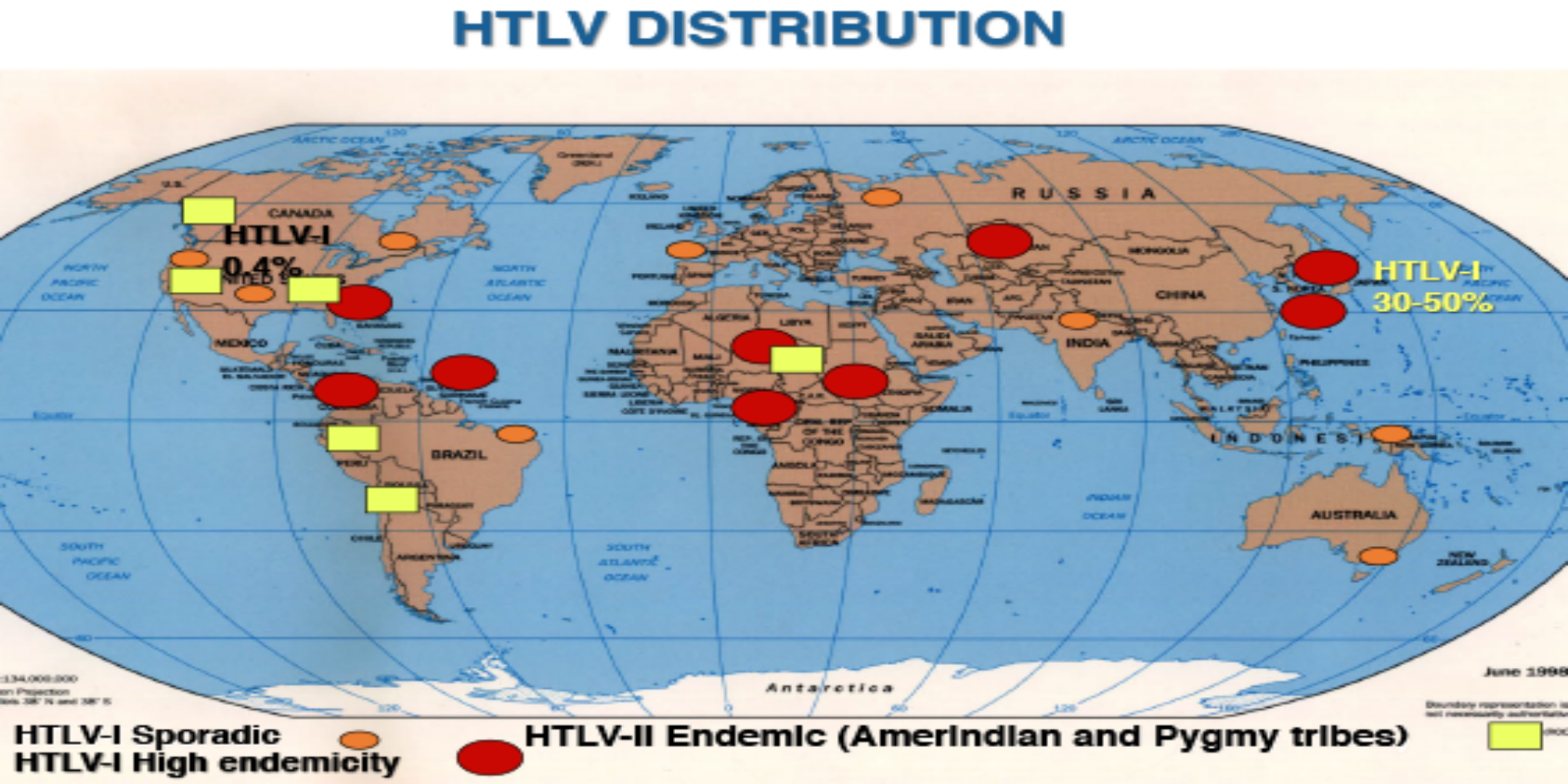
Lentivirus Relationships



HTLV distribution

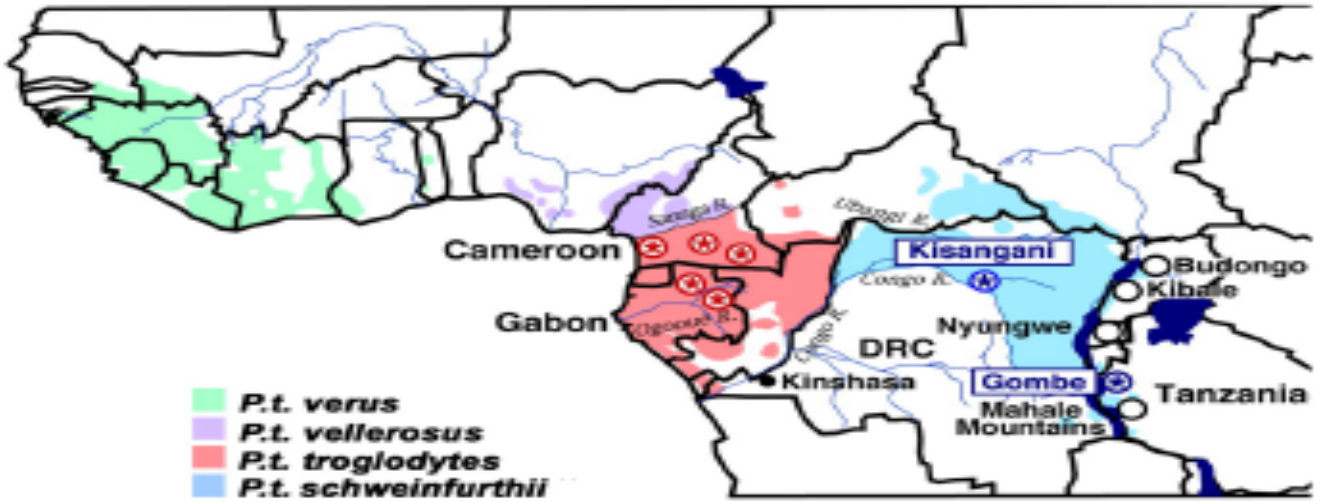


HTLV-I ATL

- 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 origins

Higher Primate Origins of HIV-1



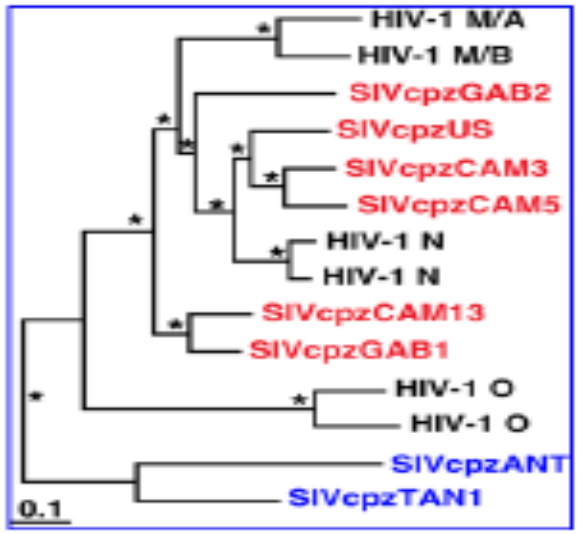


FIG. 2. Evolutionary relationships of SIVcpz and HIV-1 strains based on maximum-likelihood phylogenetic analyses of full-length envelope protein sequences (adapted from ref. 10). SIVcpz strains from *P. t. troglodytes* and *P. t. schweinfurthii* are highlighted in red and blue, respectively. Representative 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

Bushmeat Trade in Central and West Africa

Potential opportunities for Zoonotic Events

Phylogenetic Analyses Date Introduction to Late 1800's-Early 1900's

BUT WHY THEN?

HIV Spread

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

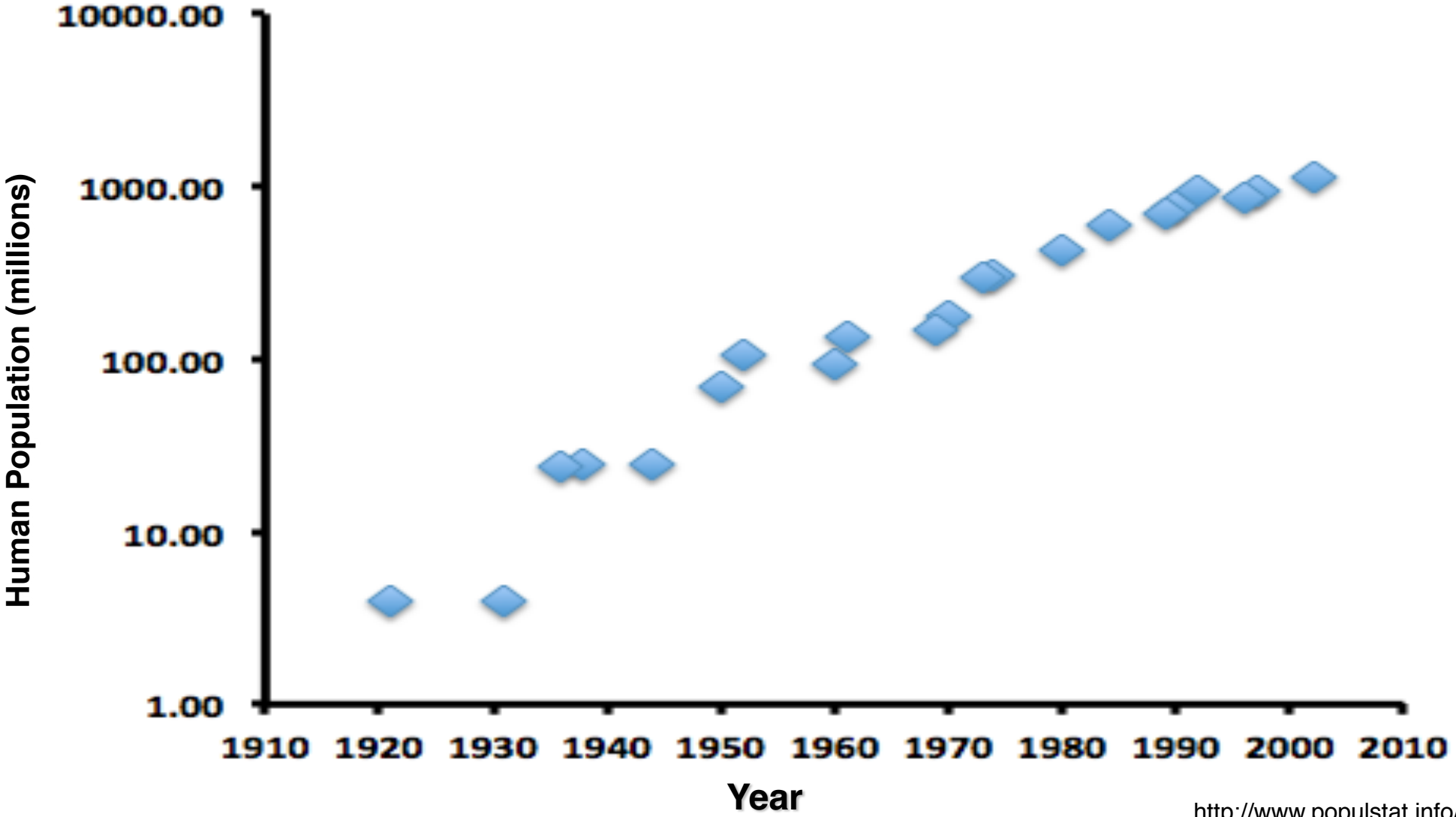
HIV spread

HIV Spread

- **Modes of Transmission**
  - **Political**

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

Zoonotic Transmission of HIV Coincides with Population Expansion in Africa



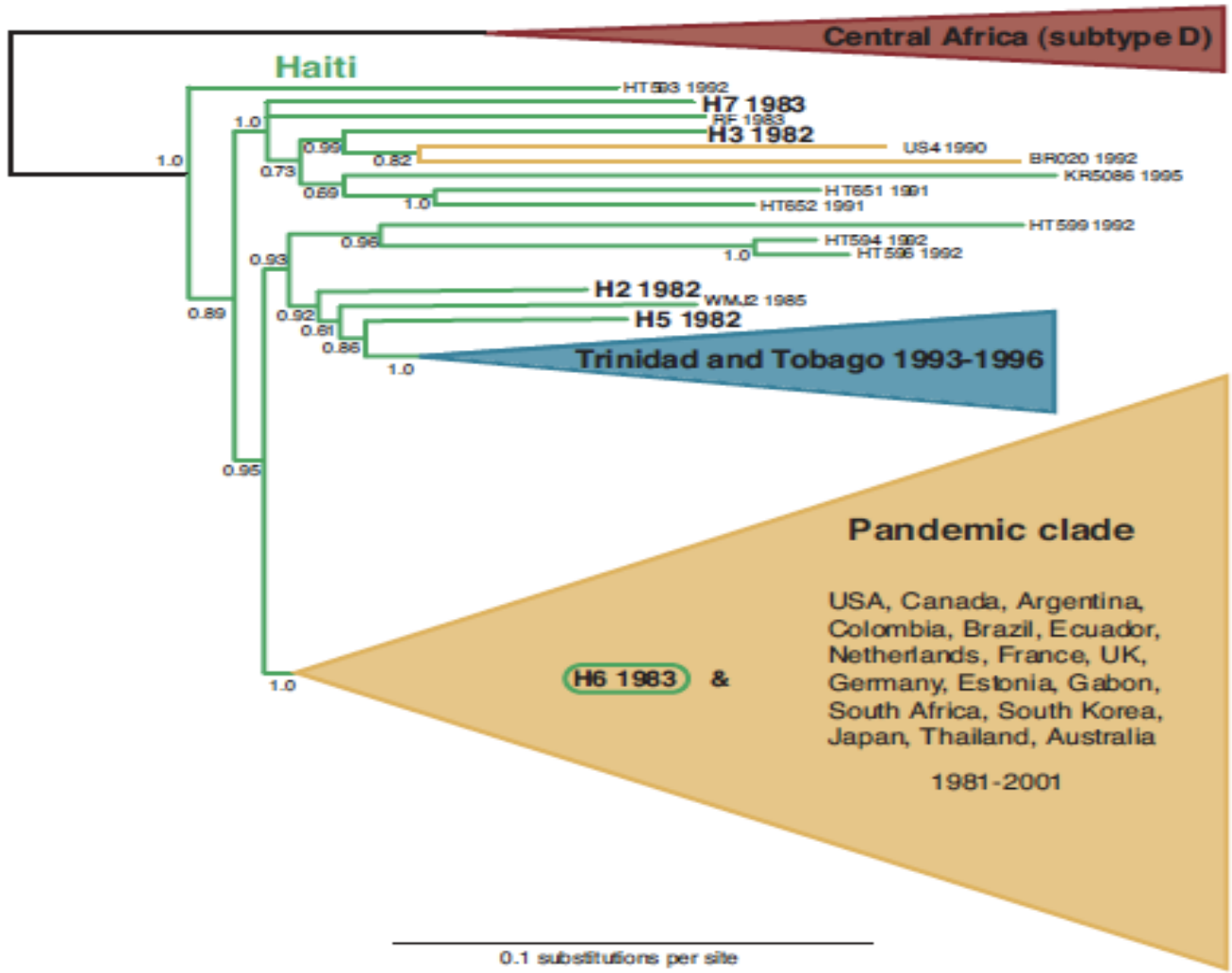
http://www.populstat.info/

HIV spread

HIV Spread

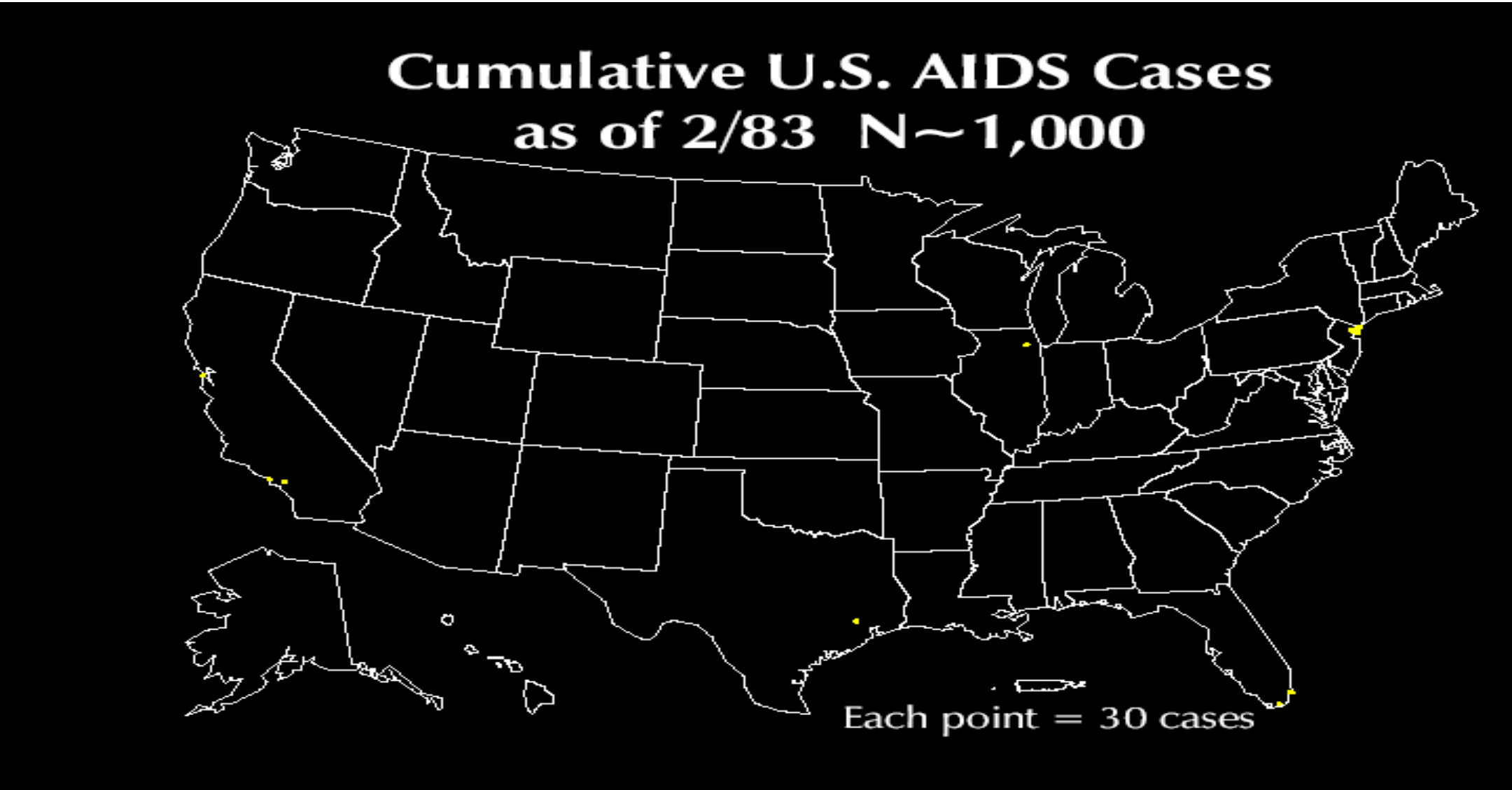
- **Modes of Transmission**
  - **Trans Africa Highway**

HIV Spread

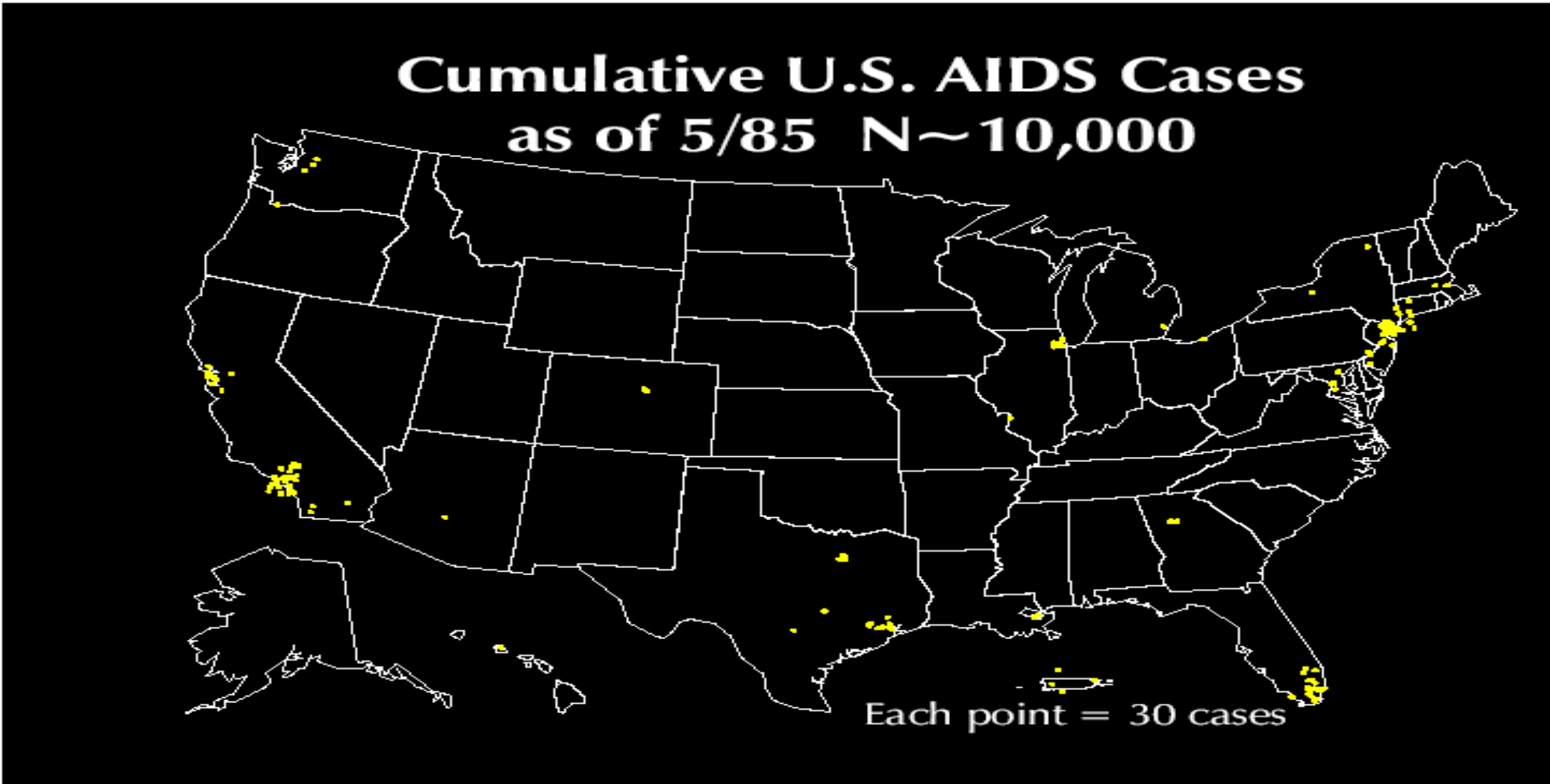


Worobey et al.

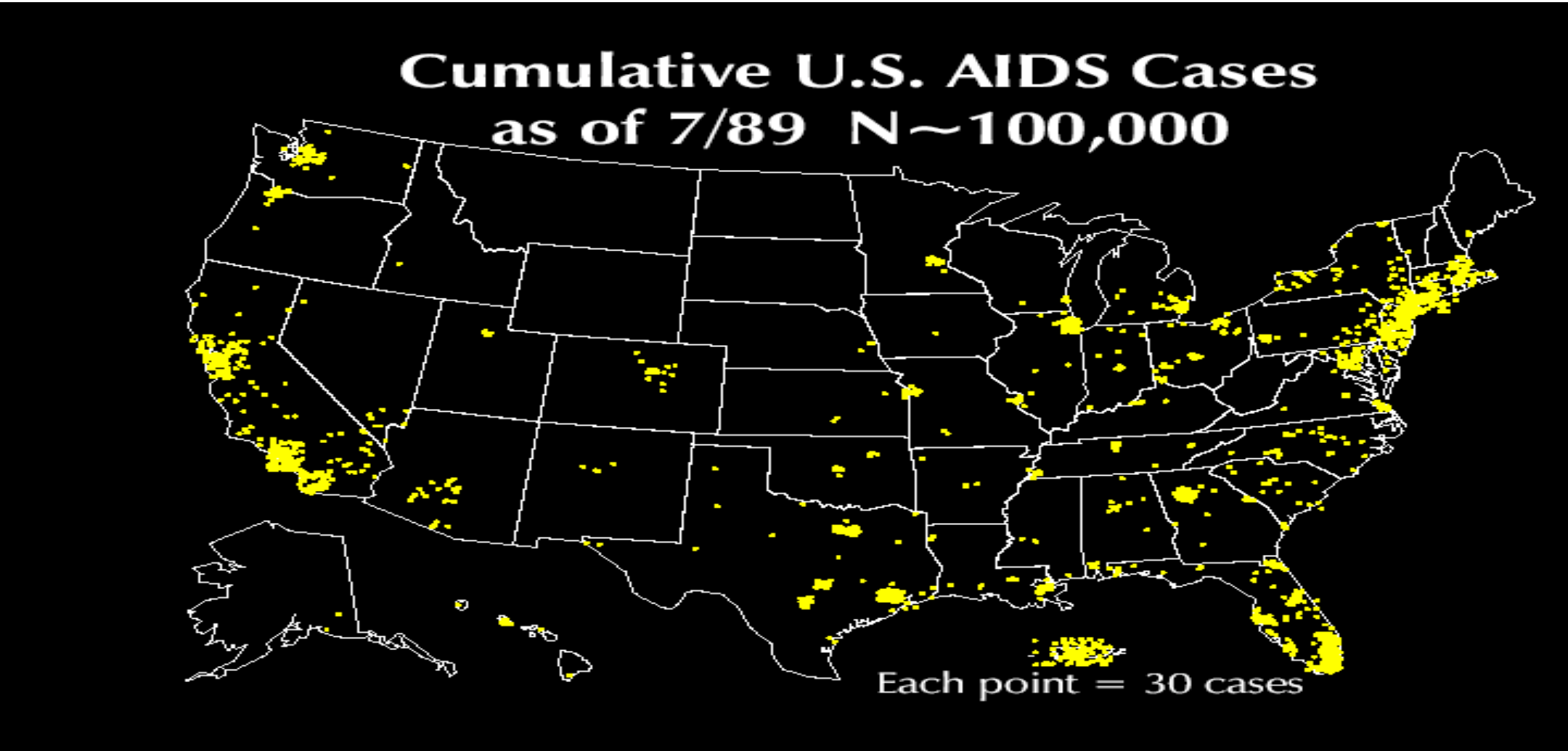
AIDS in 1983



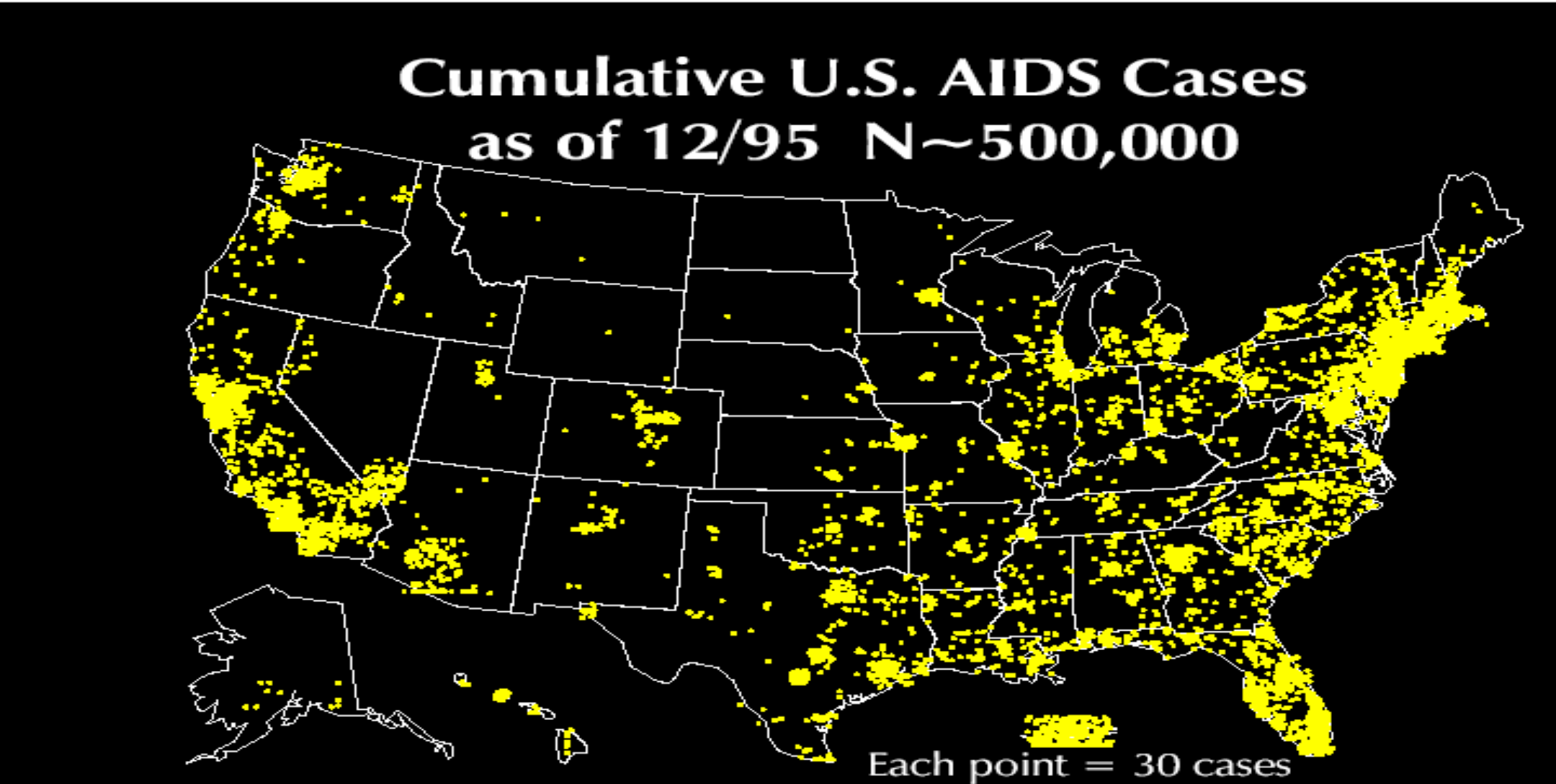
AIDS in 1985


Cumulative U.S. AIDS Cases
as of 5/85 N~10,000
Each point = 30 cases

AIDS in 1989


Cumulative U.S. AIDS Cases
as of 7/89 N~100,000
Each point = 30 cases

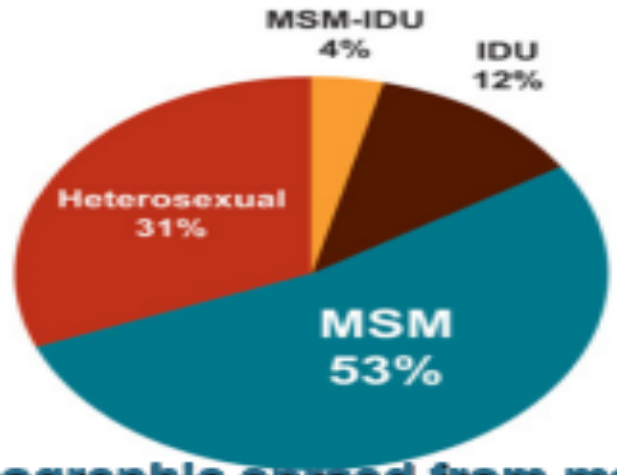
AIDS in 1995

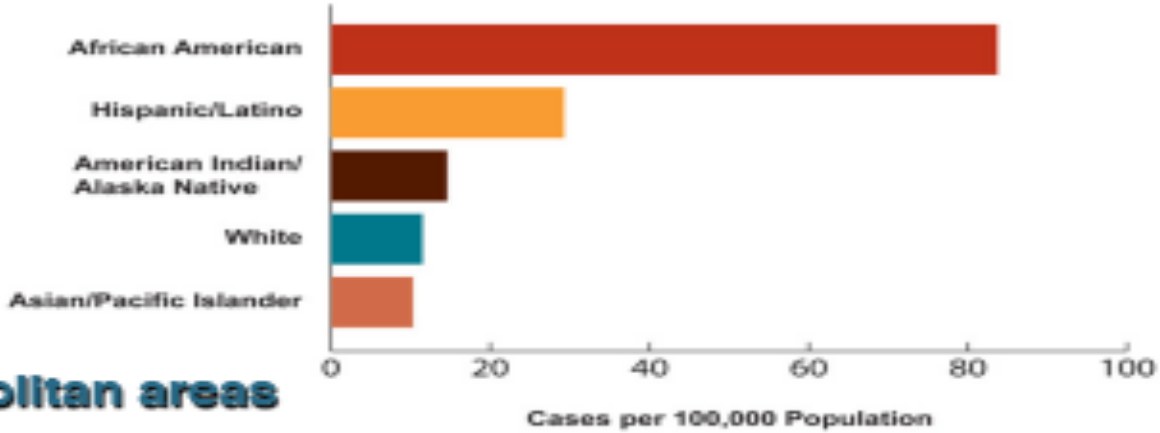

Cumulative U.S. AIDS Cases
as of 12/95 N~500,000
Each point = 30 cases

New cases of HIV/AIDS

New cases of HIV/AIDS—USA

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



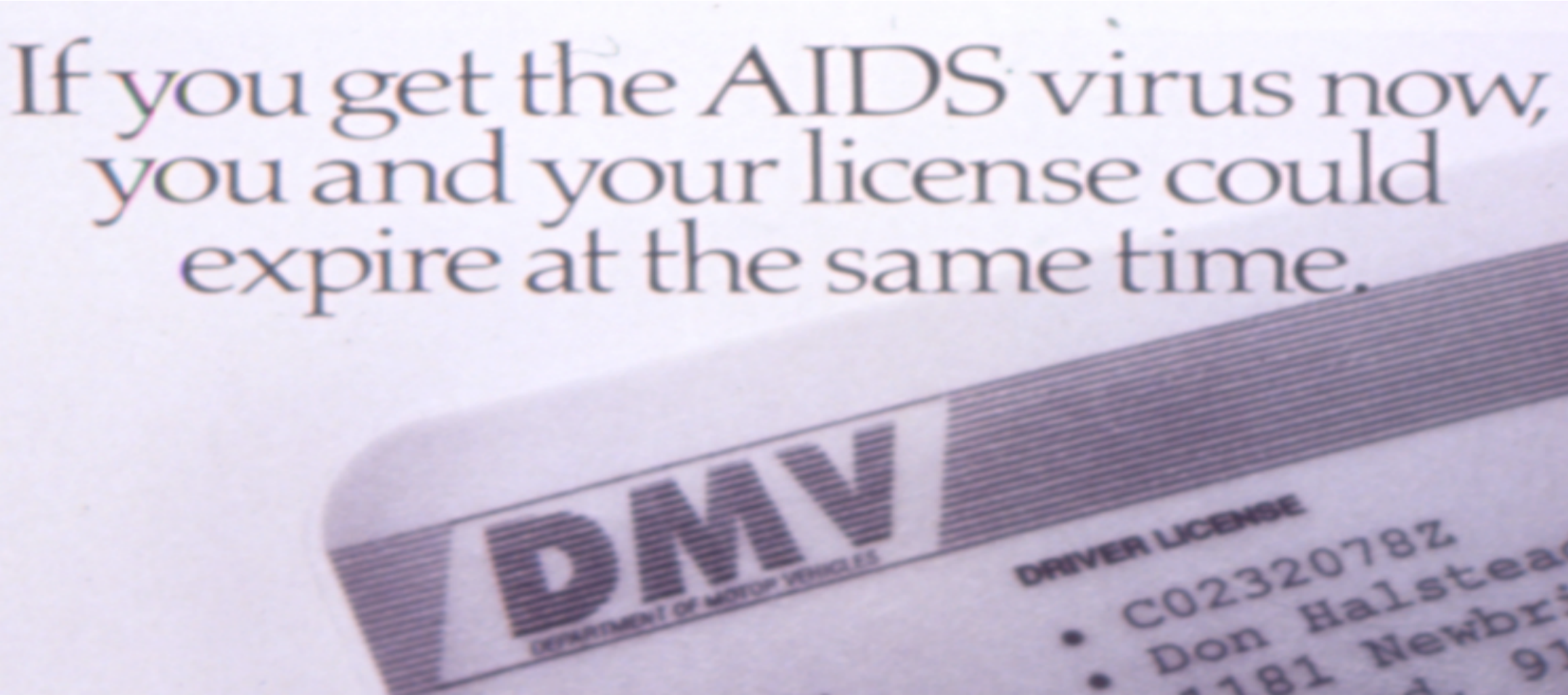


JAMA 2008

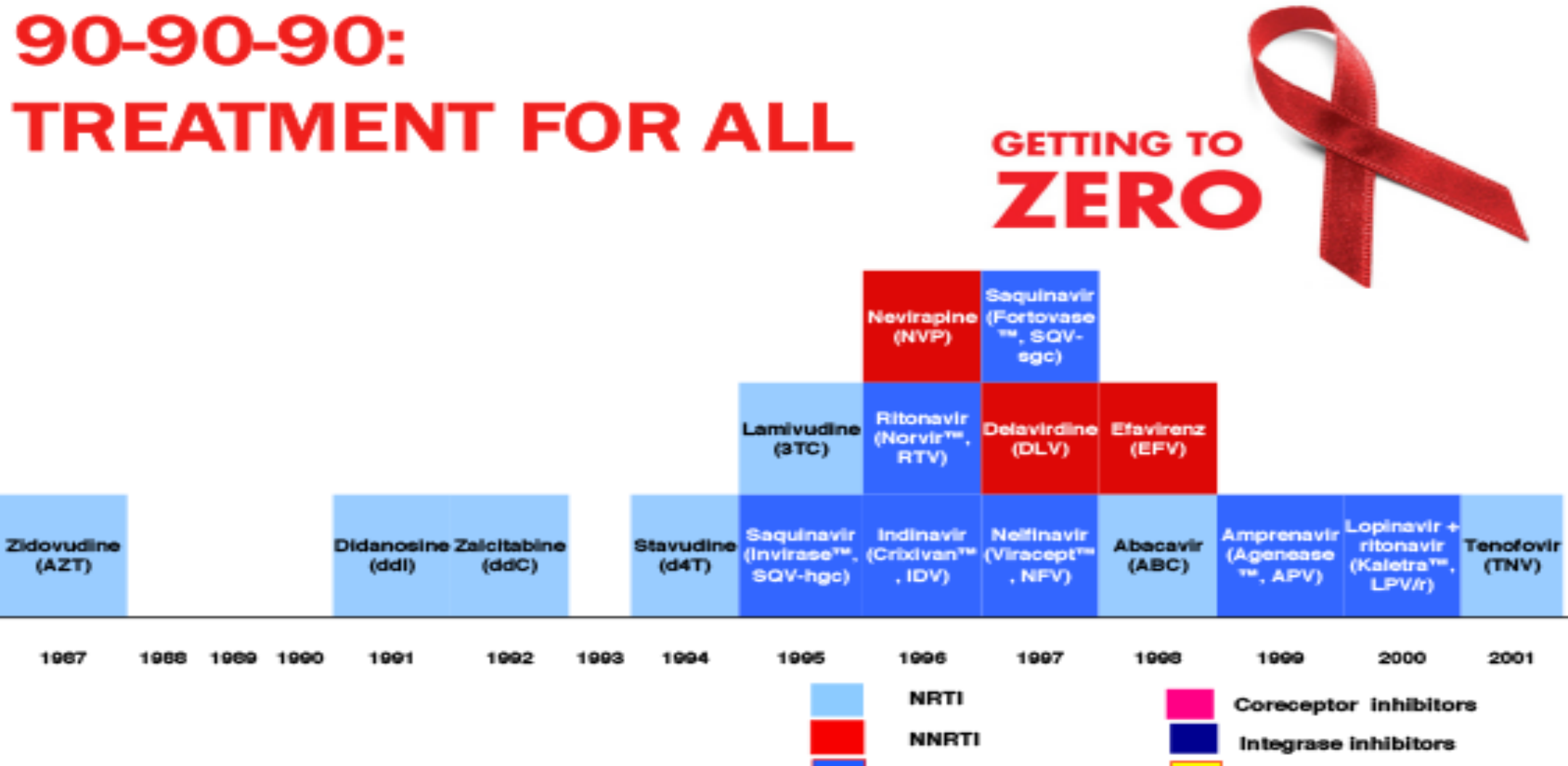
- Geographic spread from metropolitan areas
  - ~12% of cases in locations with population <50,000
- Women
  - comprise > 25% of all AIDS cases
- Age
  - 11% of AIDS cases are 50+ years old
  - c.50% of persons living with HIV are >50 yo

HIV Therapy and Beyond

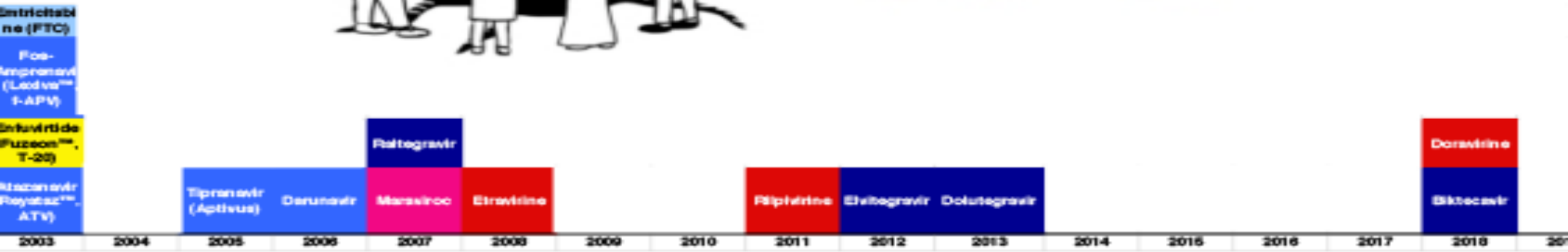
Expiration


If you get the AIDS virus now,
you and your license could
expire at the same time.
DMV
DRIVER LICENSE
C02320782
Don Halstea

Treatment for all



Worlds AIDS day



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
- CoviD-19

Lessons

- 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
- Detailed understanding of replication leads to new therapy
- Antivirals are useful
  - Instituted as early as possible
  - Adherence is essential