

# **Retroviruses**

**TRACO**

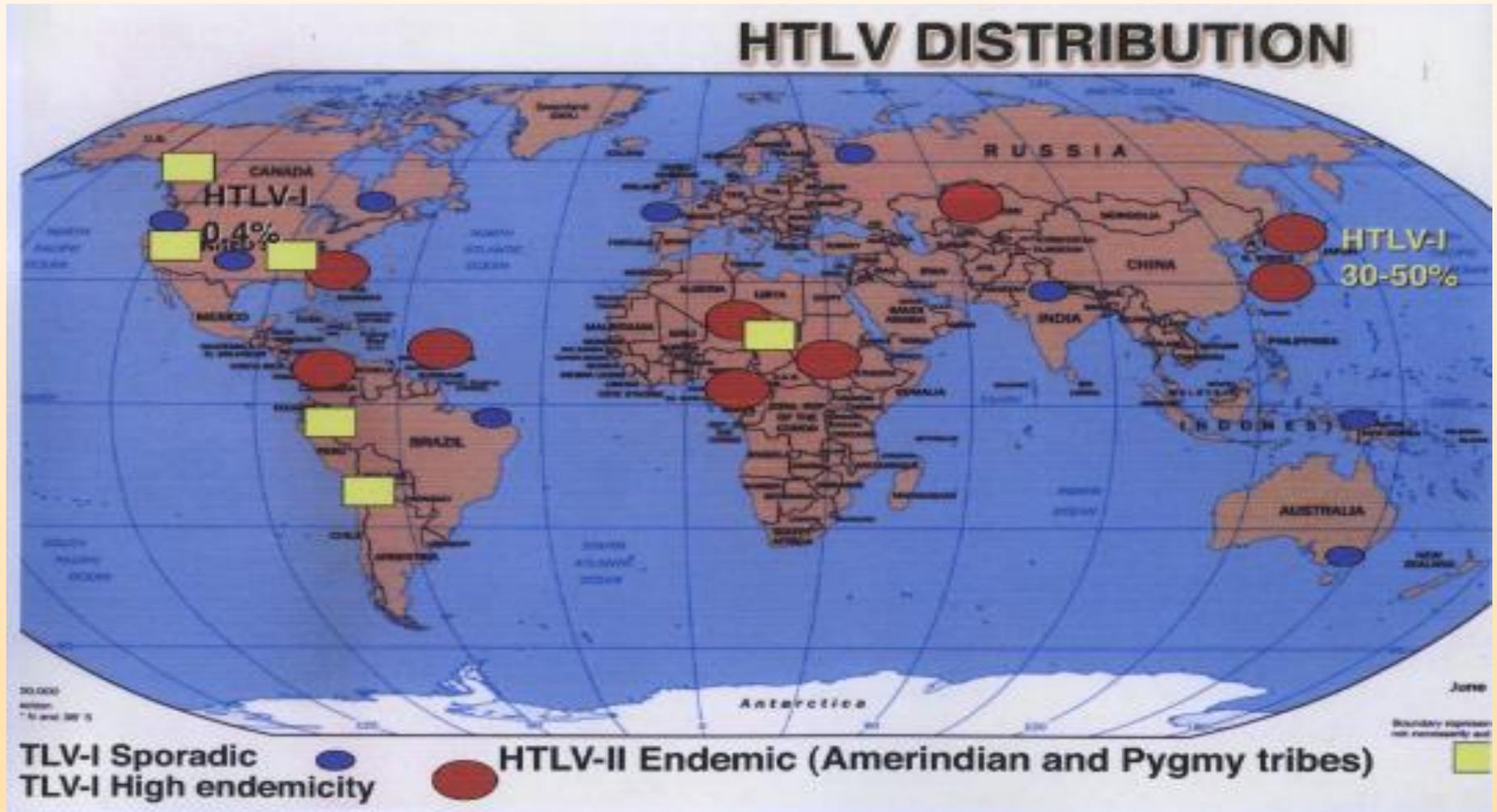
**October 15, 2014**

**Frank Maldarelli**

# **Retroviruses**

- **Introduction**
- **Molecular Biology/Replication**
- **Emergence/Spread**
- **Lessons**

# HTLV Distribution



# HIV-1 Pandemic

**HIV-1 PANDEMIC: Total 33.2 Million cases**  
with 1.4 M in N. America, 1.7 M in S. America, 0.7 M in Europe,  
0.9 M in Russia, 0.5 M in the Middle East, 24.7 M in Africa, 2.5 M  
in asia, 0.7 M in China and 0.08 M in Australia



**HIV Drug Resistance Program**

*NCI-Frederick*

# Retroviruses

## Molecular Biology/Replication



**HIV Drug Resistance Program**

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# Retroviruses

- **A group of RNA viruses that replicate via a DNA intermediate using Reverse Transcriptase. A different paradigm for replication. Transition from a RNA world.**



# Reverse Transcriptase and Retro elements are all around you.



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# **Retroviruses Classification by RT Sequence into Seven Families**

**Spumavirus** exog. infection from primates, no disease

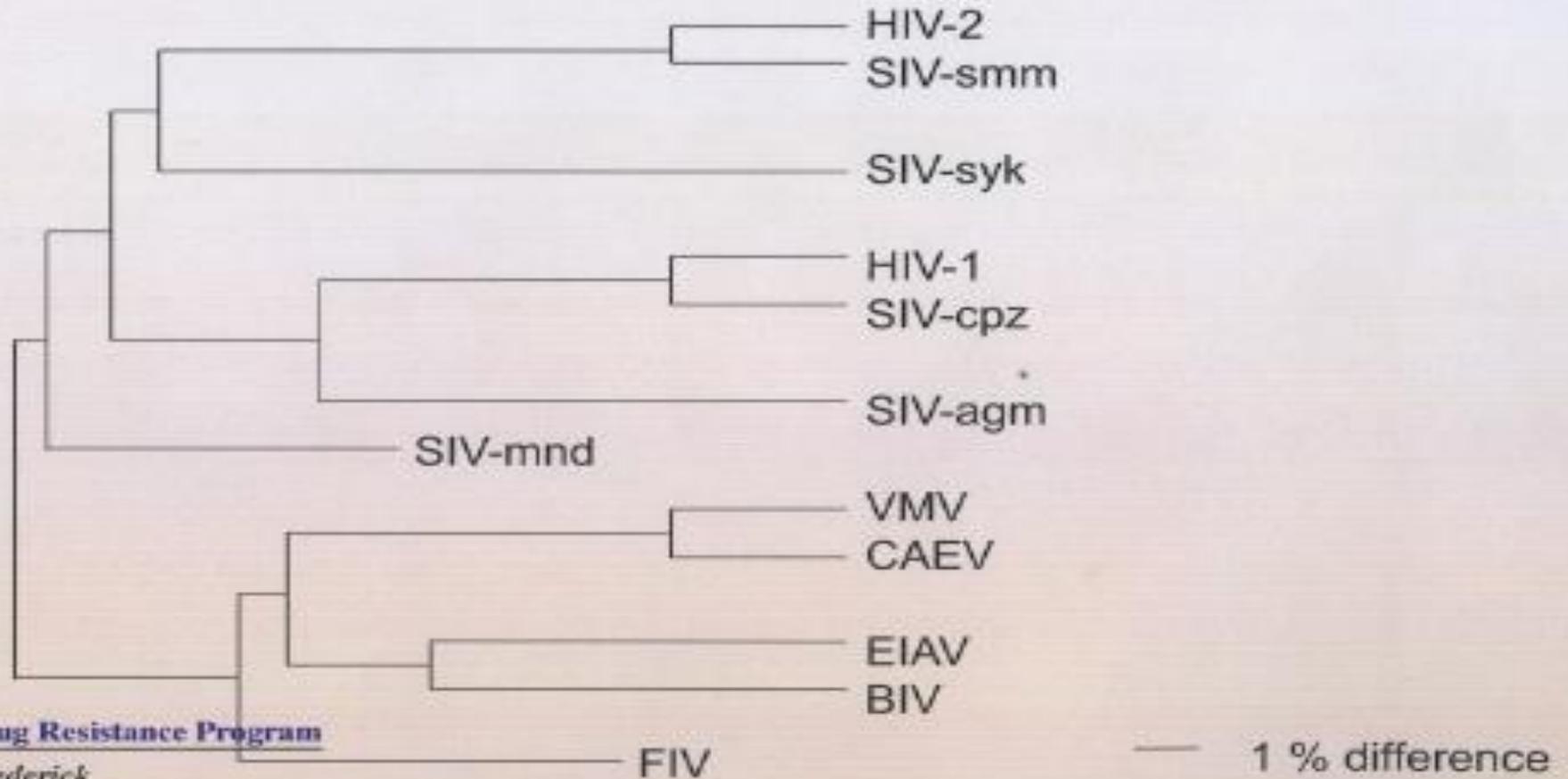
is closely related to MLV endo/exo oncogene numerous mammals and **XMRV ASSOCIATED Prostate CA. Lentiviruses HIV-1,-2, SIV, EIAV, CAEV, VISNA is distantly related.**

D-type viruses Primates-MPMV, SAIDS

**is closely related to** B-type viruses endog/exogen milk-borne agent-mouse and ALV-related endog/exogen avian oncogene. **BLV-HTLV** exog, no oncogenes, neoplasms are distantly related.

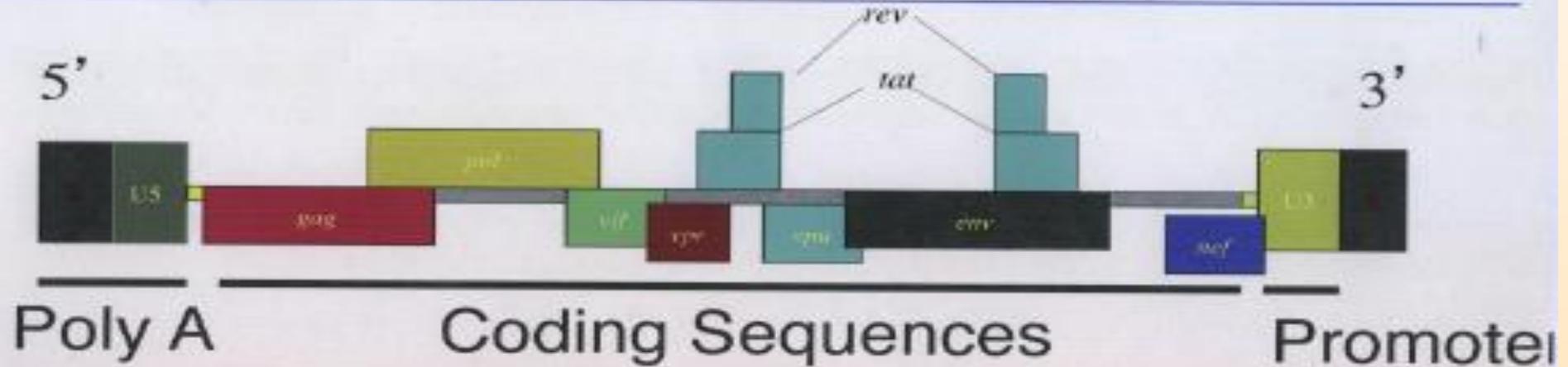
# Lentivirus Relationships

## Lentivirus Relationships



# Retroviruses Conventions

## Retroviruses Conventions



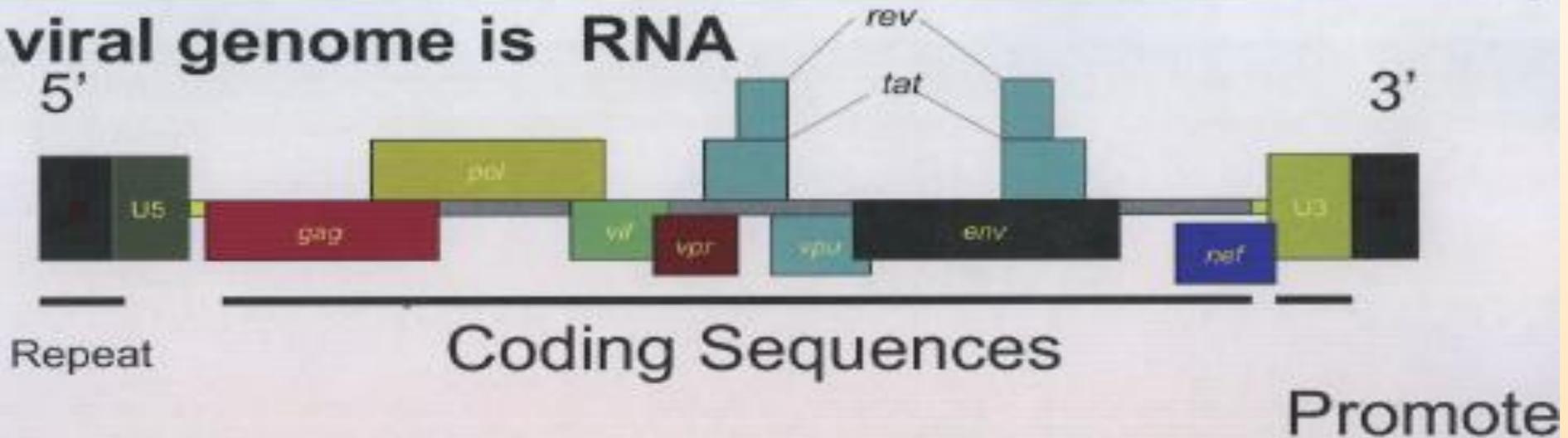
**Names of genes in lower case *italics*, e.g., *pol*, *env***  
**Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120**



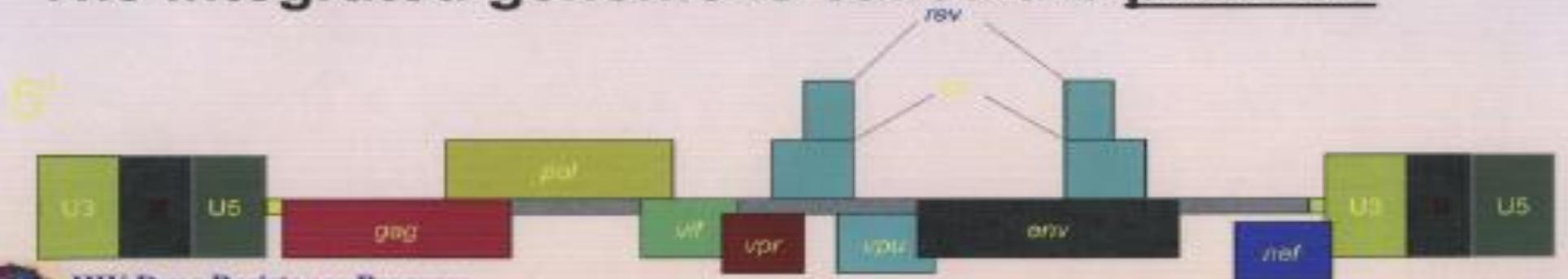
# Retrovirus Conventions

## Retroviruses Conventions

The viral genome is RNA



The integrated genome is called the provirus



# Retroviruses Glossary

## Retroviruses Glossary

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- ***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**

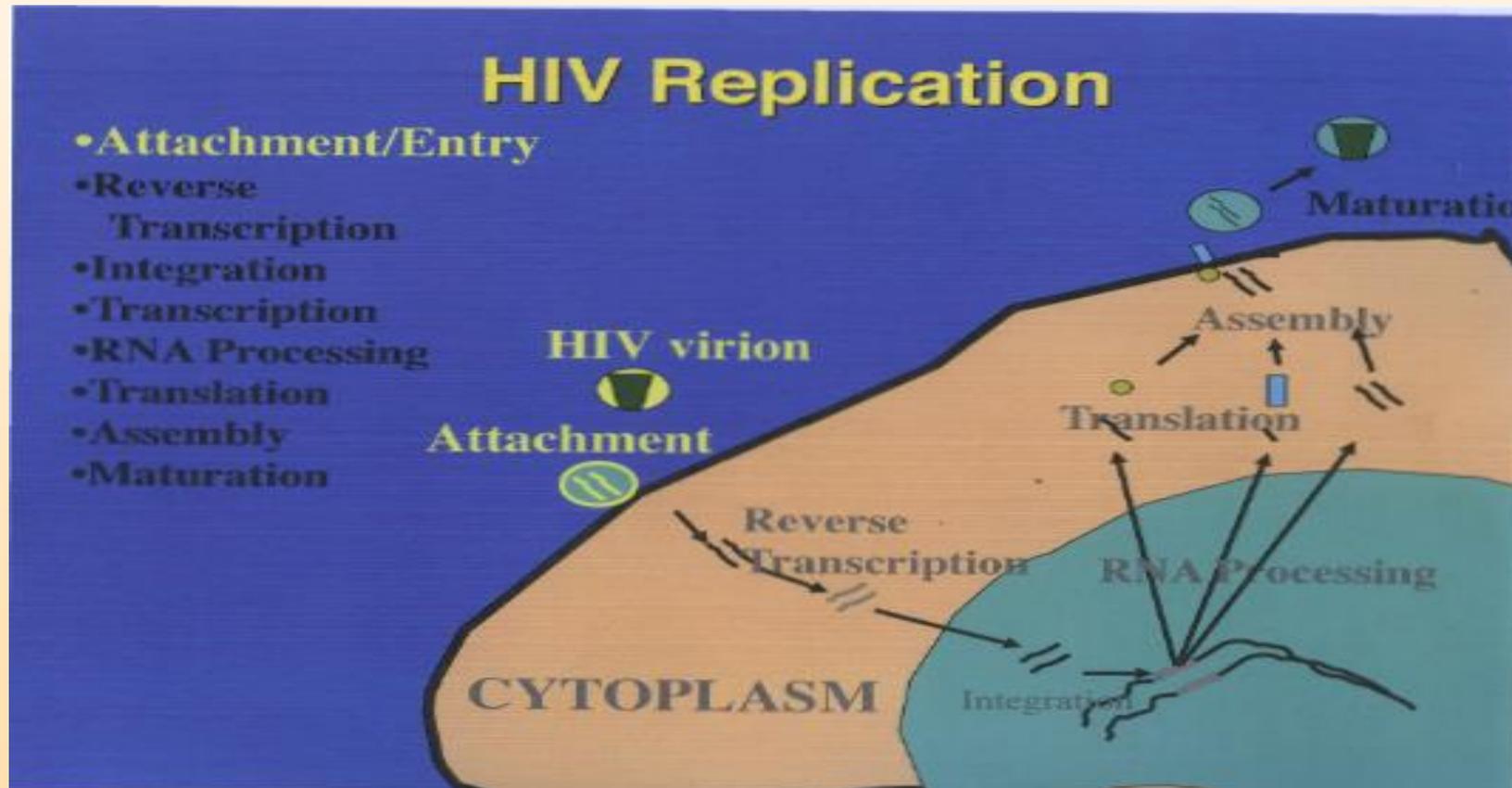


# Retrovirus glossary

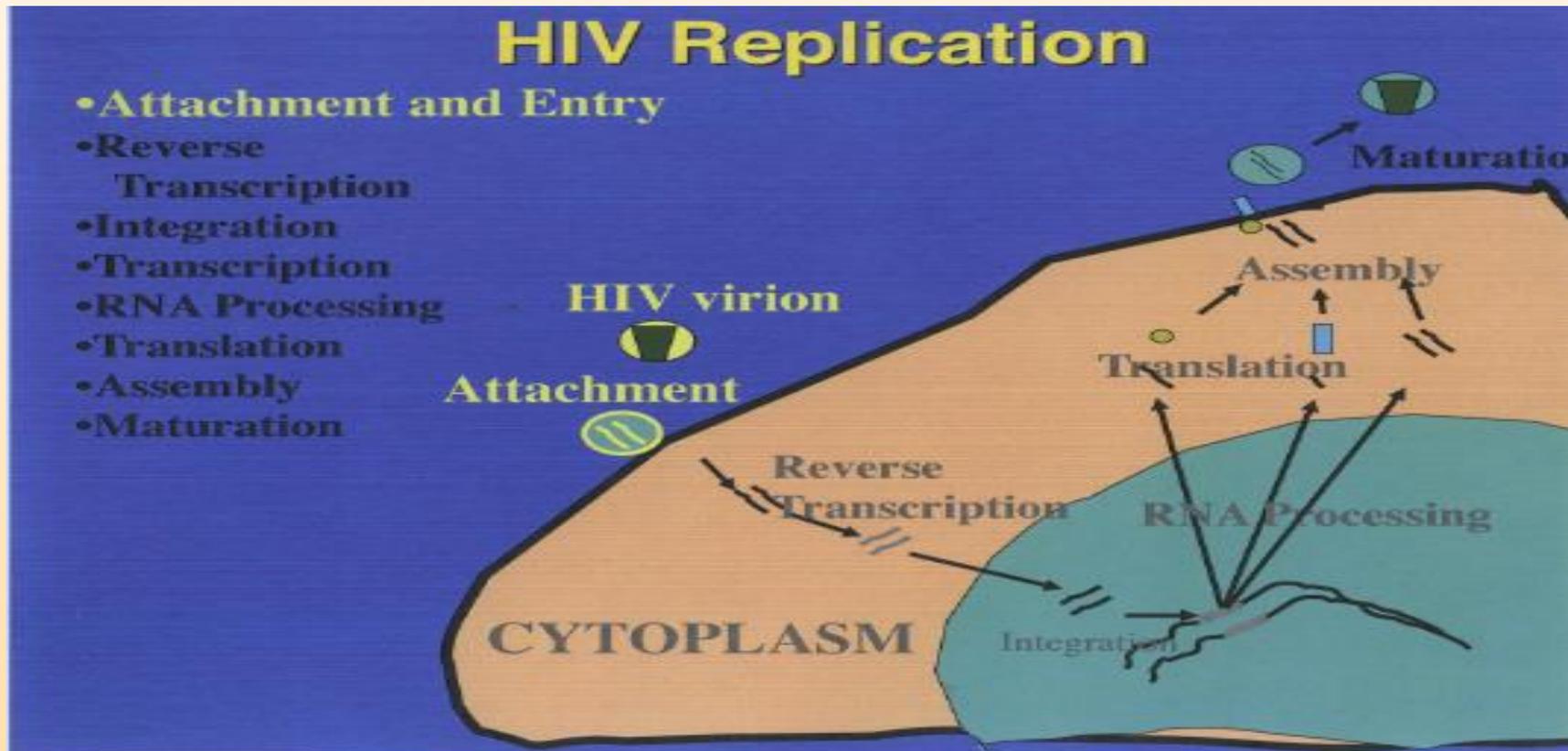
- ***gag: Group antiGen***
- ***pol: pOlymerase***
- ***env: eNvelope***
- ***tat: Transactivator***
- ***rev: Regulator of Expression of Virion proteins***
- **U3: unique sequence in 3' region**
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- **PBS Primer binding site for initiation of RT**
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- **Provirus: copy of retrovirus that is integrated into host genome**



# HIV replication, attachment



# HIV attachment



# HIV attachment and Entry

- **Virus Factors**

**Attachment: Env glycoprotein gp120**

**Entry: Env glycoprotein gp41**

- **Host Cell Factors**

**Receptor: CD4**

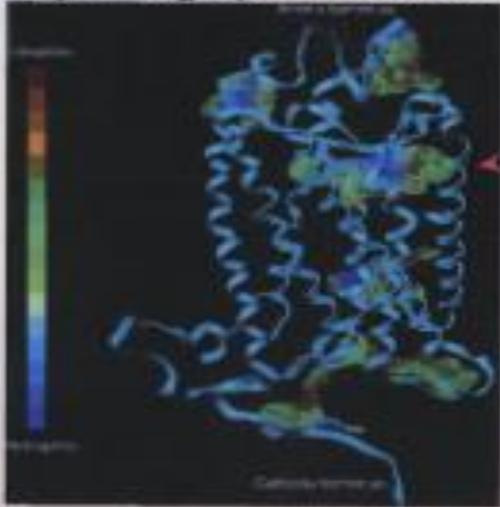
**Co-receptor: CXCR4, CCR5**



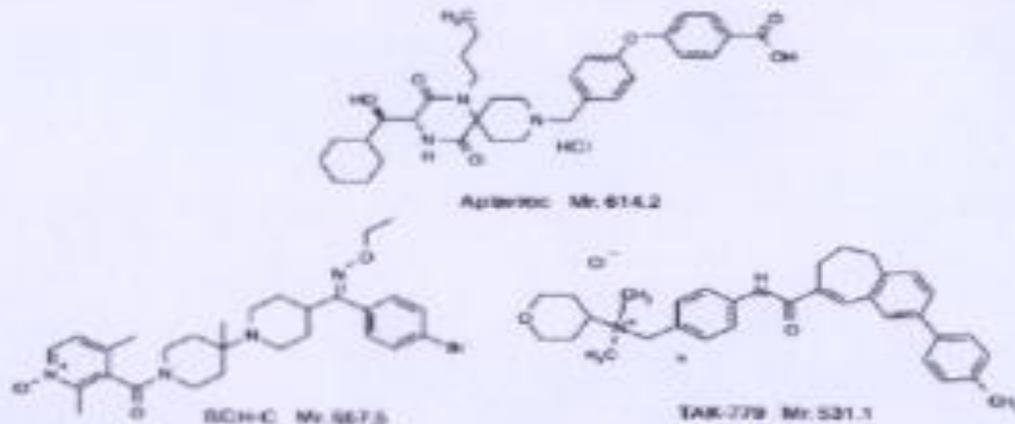
# HIV coreceptor blockade

## HIV Coreceptor Blockade

Crystallographic Structure



Model Inhibitors



Maeda, JBC, 2008

- 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

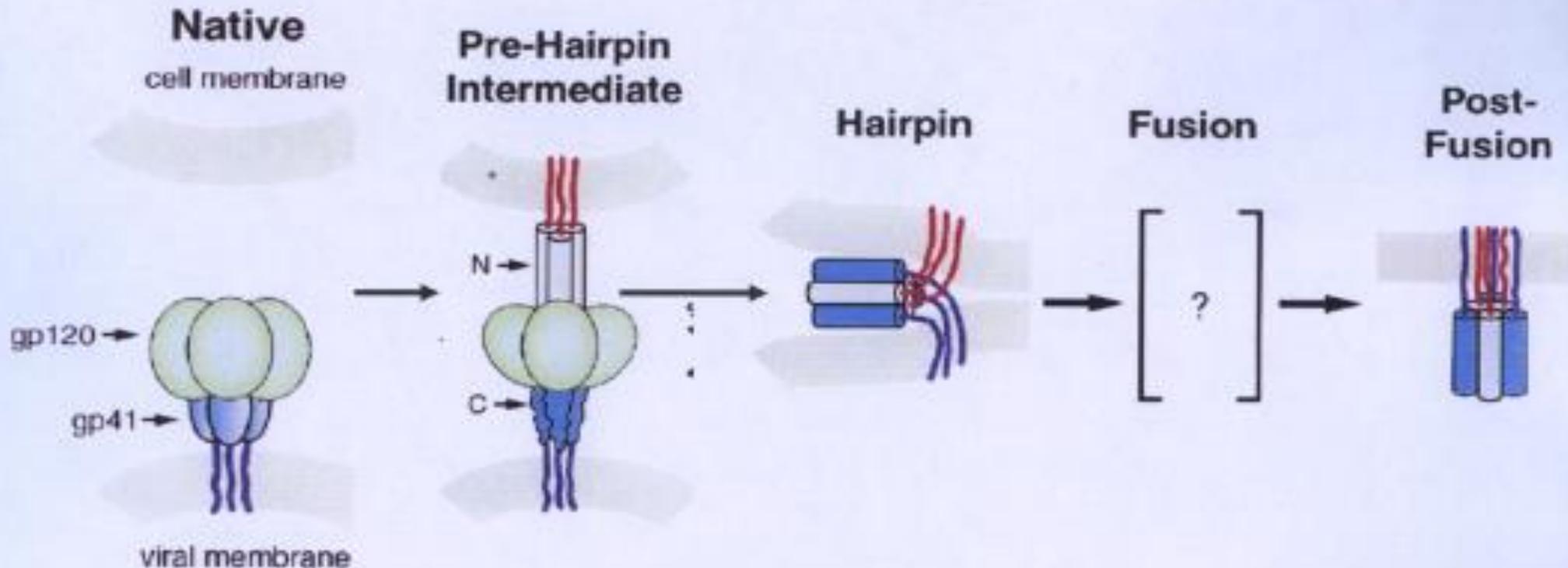


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# HIV Fusion-Gp41

**HIV Fusion-Gp41. A spring - loaded mechanism that drives the membranes together to overcome a high energy barrier to fusion**



# HIV gp41

## HIV gp41

Coiled coil in a hydrophobic cavity  
Spring-loaded mechanism

T-20

D amino acid interacting (PS Kim)

8542 JI ET AL.

J. Virol.

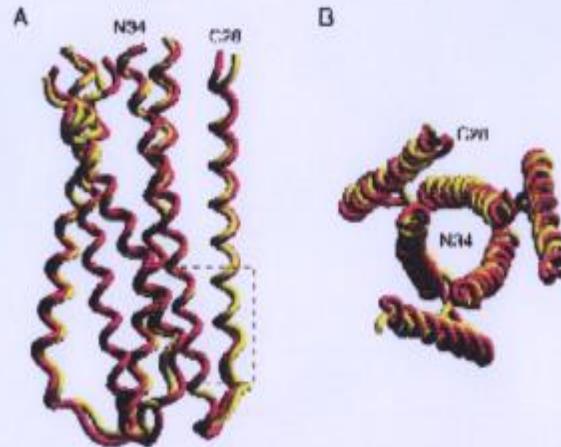


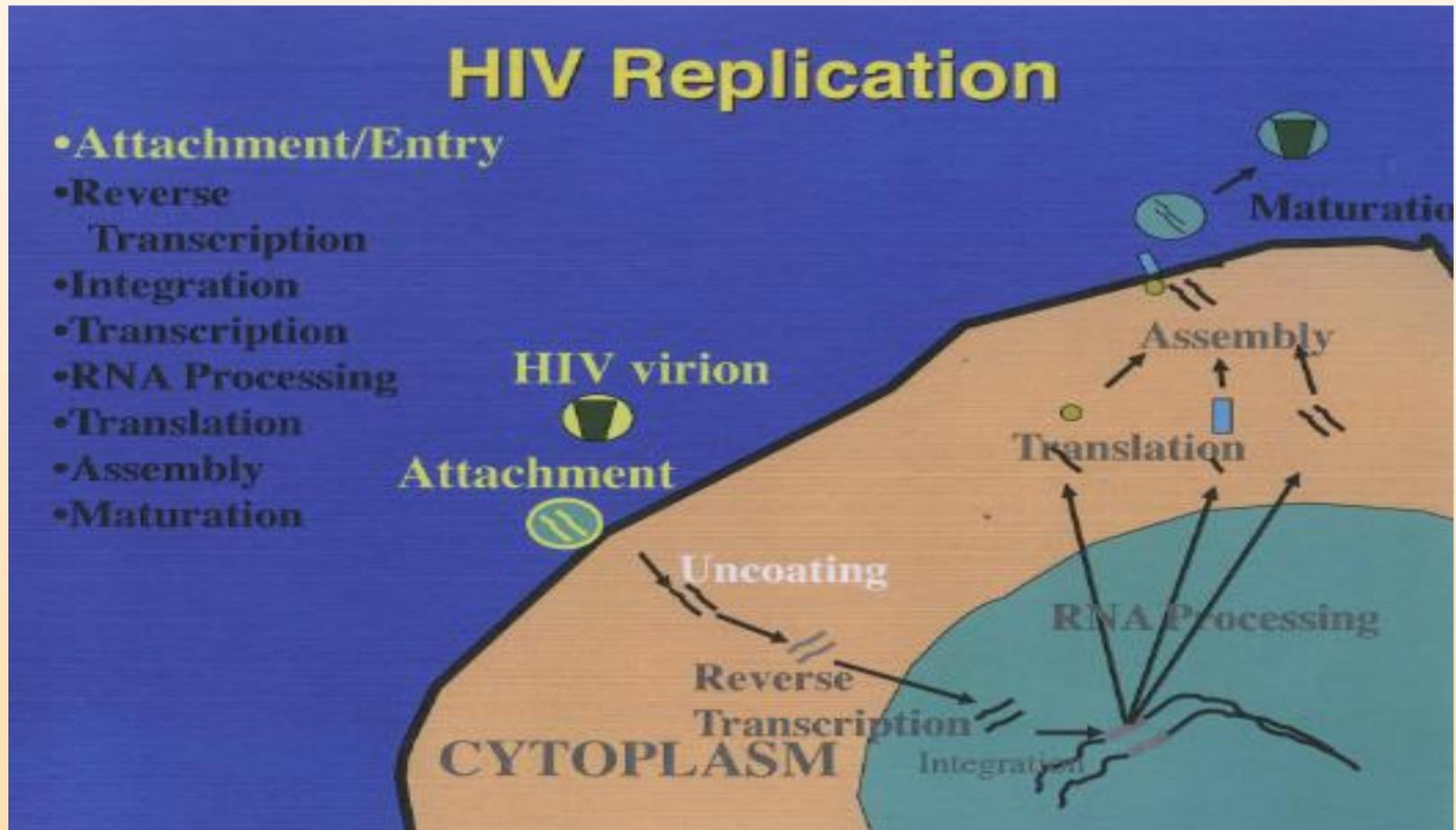
FIG. 4. Overall views of the mutant L396A and W378R coiled coils. (A) Side view. The amino termini of N34 and the carboxyl termini of C28 are at the top. Helices in L396A (yellow) and W378R (pink) were used for the superposition. The bottom of the central N34 coiled coil nucleus contains three mutually-related 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 generated with the program RIBBON (21).



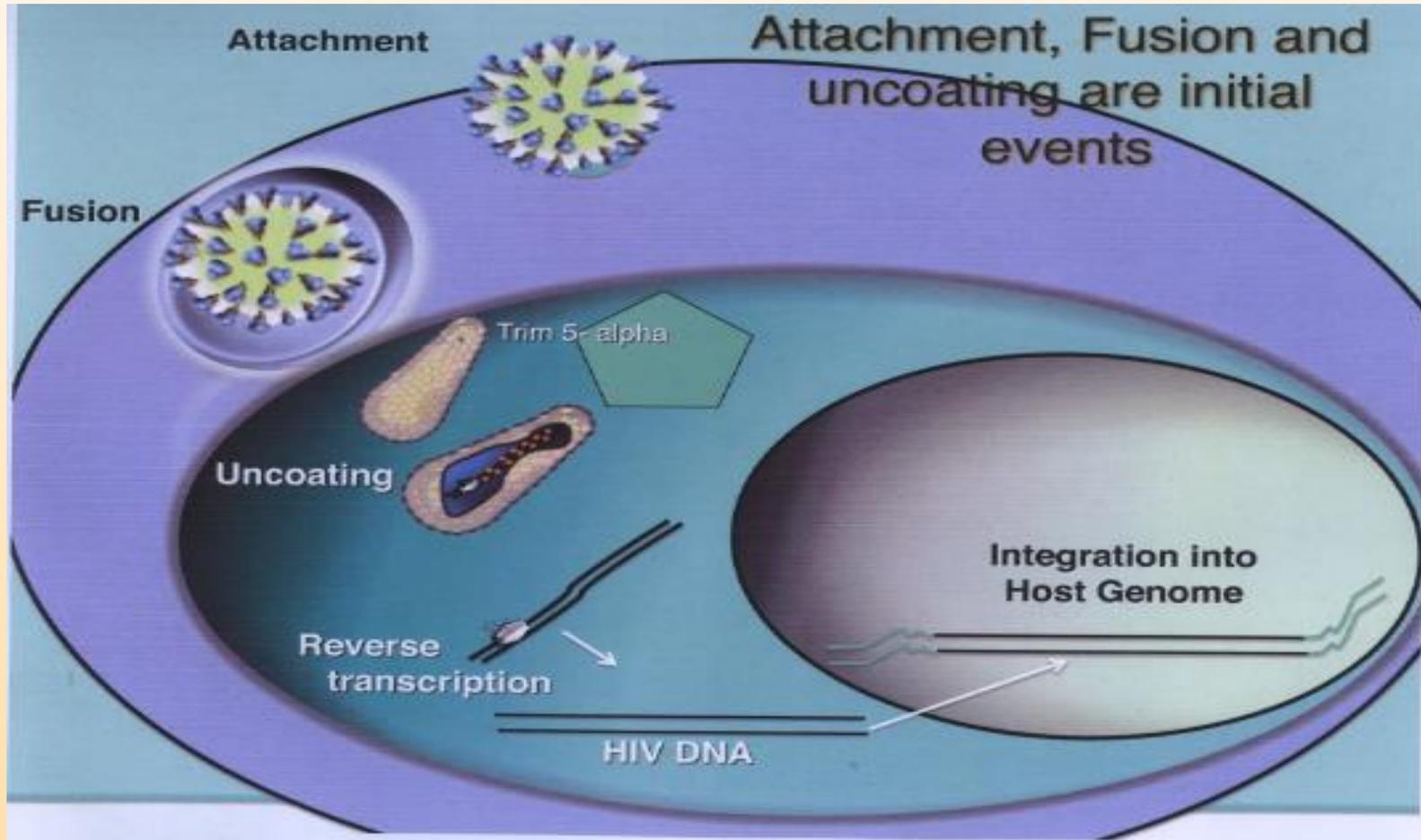
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# HIV replication



# HIV fusion



# HIV Post-Entry Events

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



# HIV Post-entry events

Host Trim 5 alpha

HIV infects the human and chimp but not the monkey

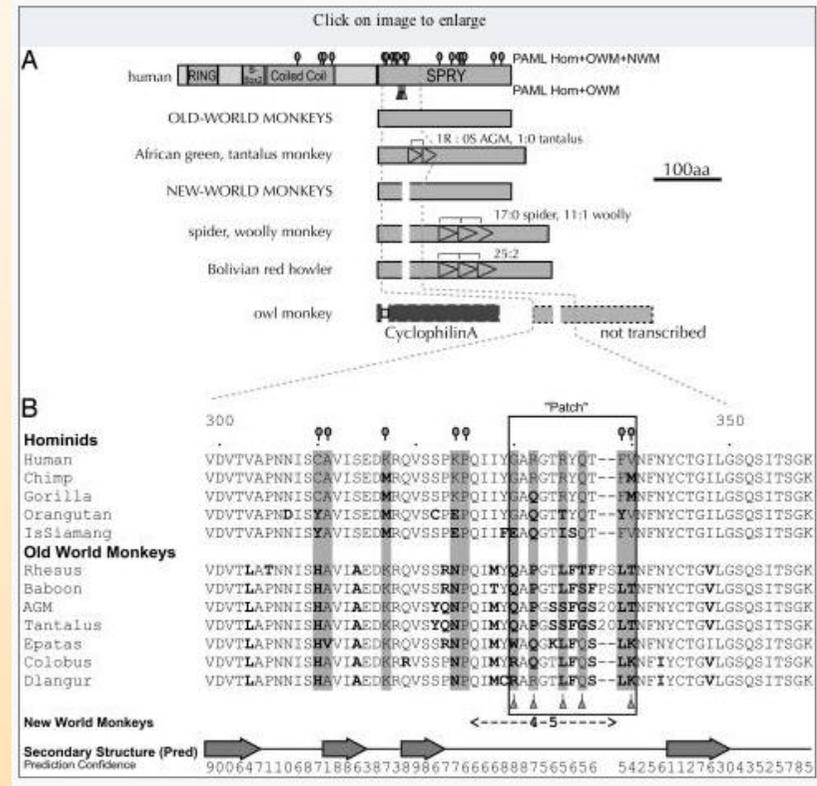
SIV Chimp infects the human and chimp but not the monkey

SIV monkey infects the human and monkey but not the chimp

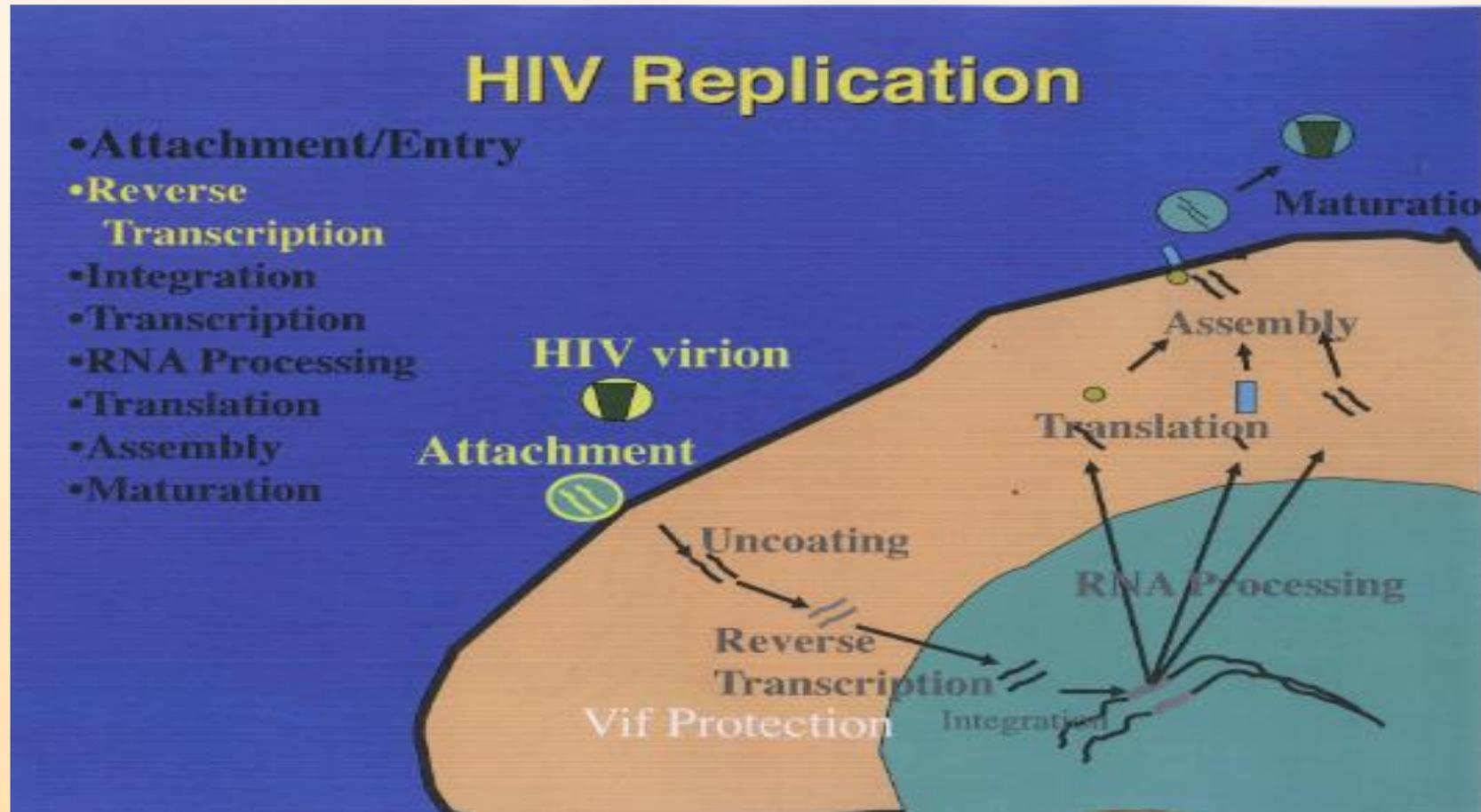


# Positive Selection in Trim 5-alpha

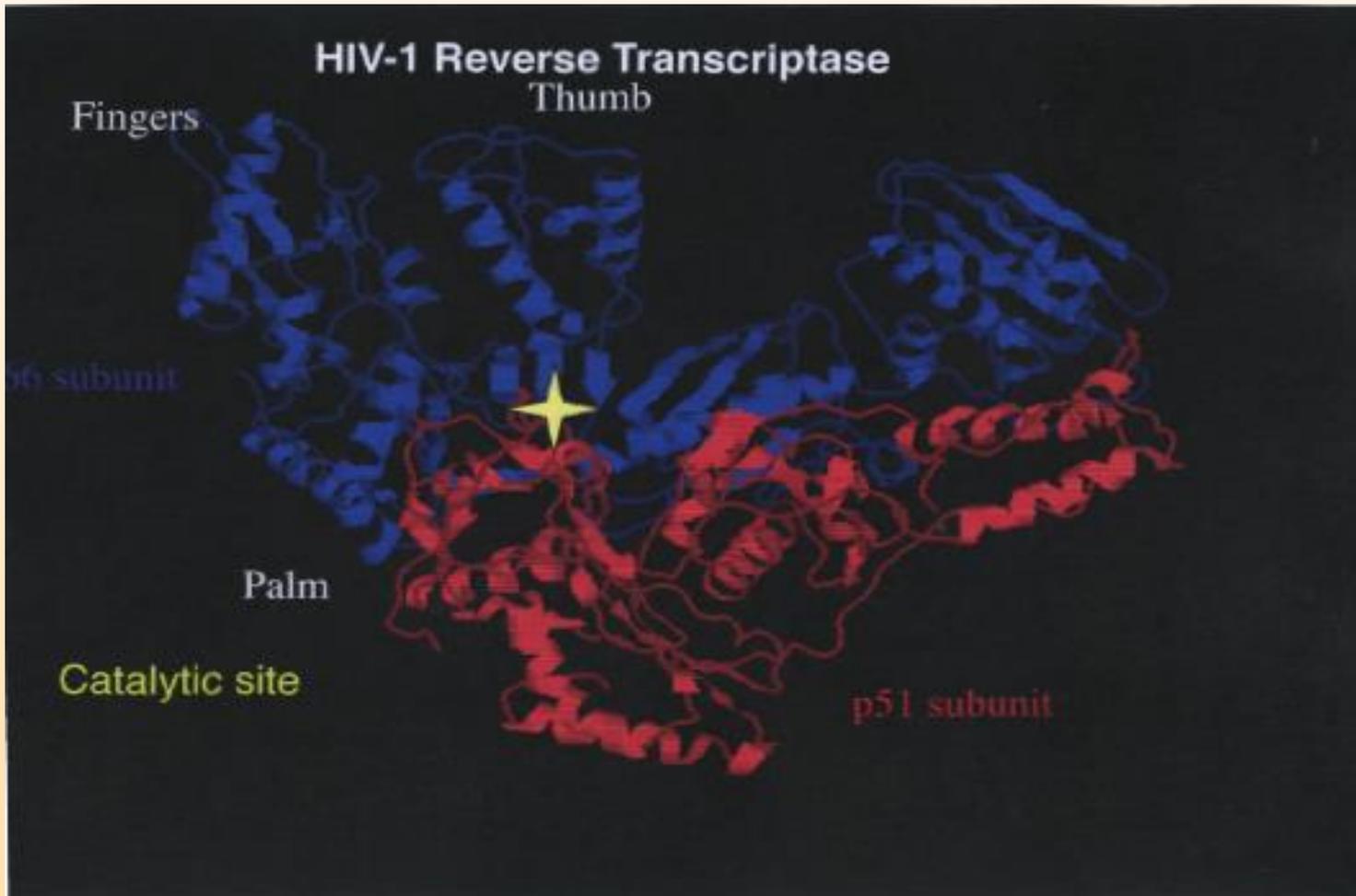
- Trim 5 alpha undergoes genetic change faster than many genes
- Working hypothesis
  - human populations undergo waves of pandemics
  - Humans that survive have trim 5alpha variant that excludes infection



# HIV uncoating



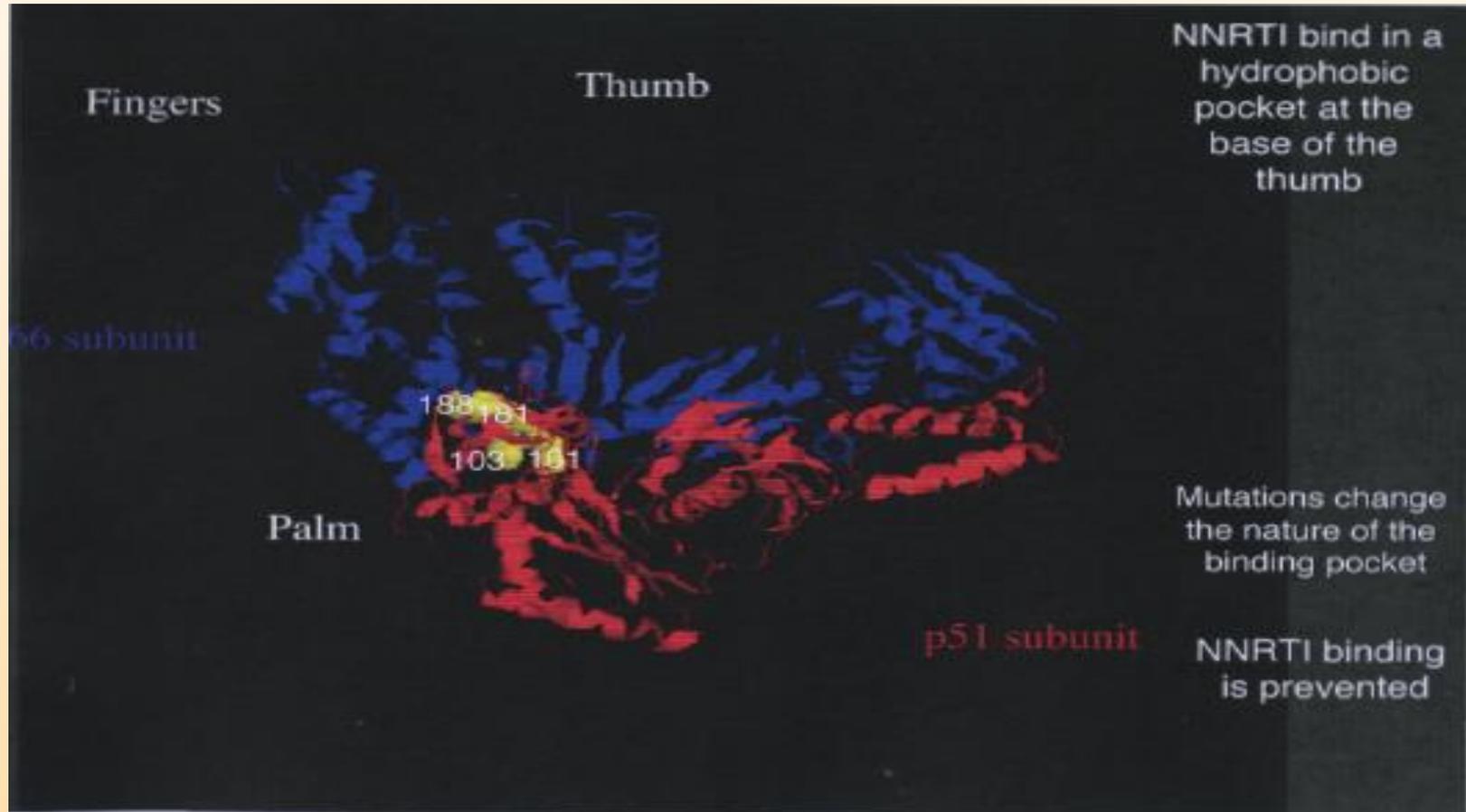
# Reverse Transcriptase



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# Reverse Transcriptase



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# Reverse Transcriptase Enzymatic Activities

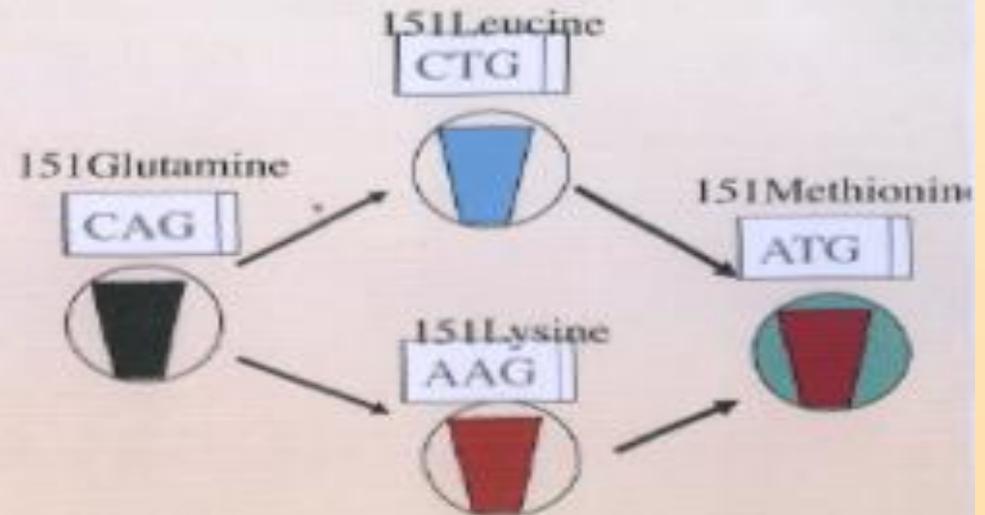
- **RNA-dependent DNA polymerases**
- **RNase H**
- **DNA-dependent DNA polymerases**
- **Error rate of 1/100,000 bases synthesized**
- **Recombination occurs during reverse transcription permitting reassortment of sequences**
- **Replication rapid and error prone**



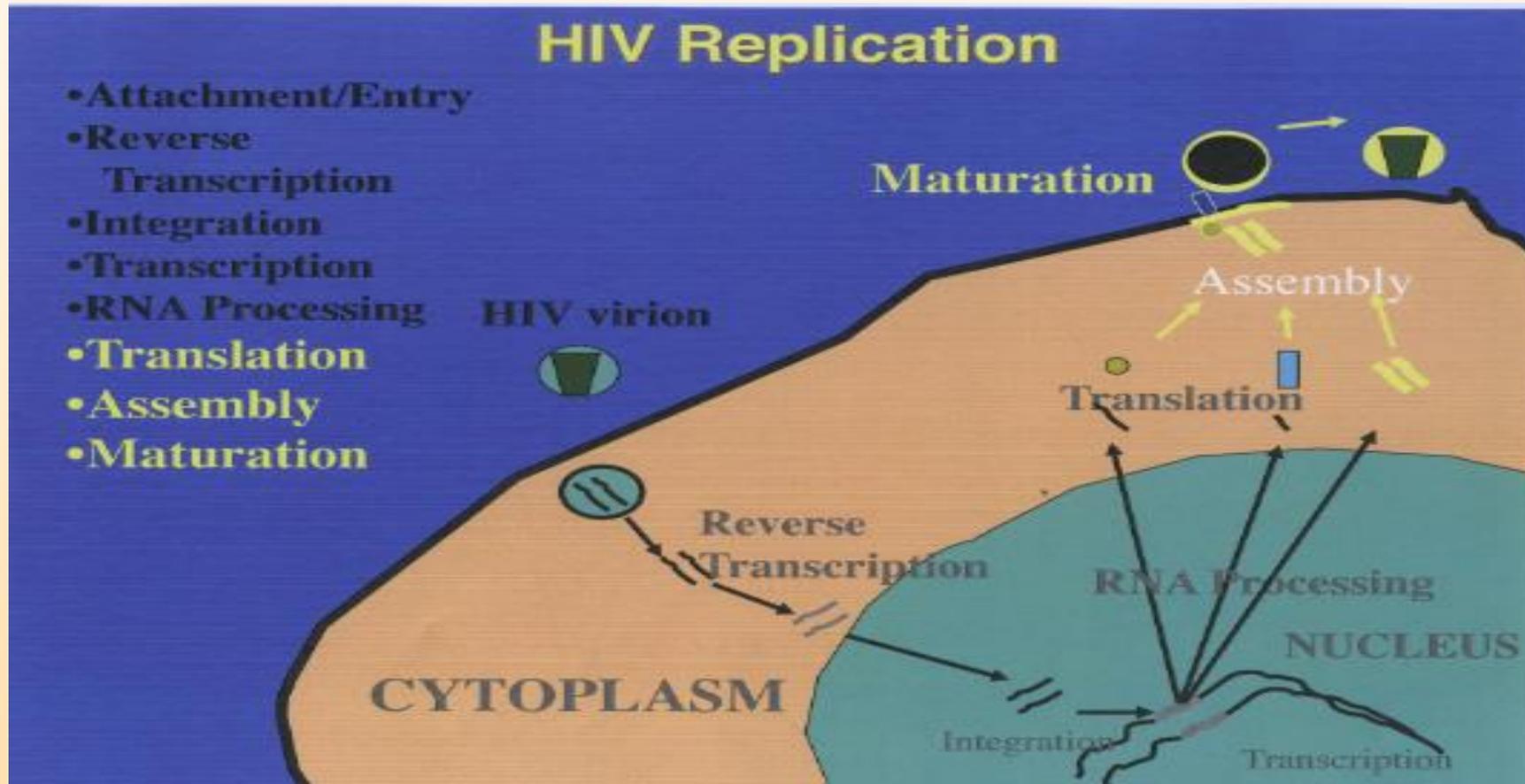
# Error-Prone HIV replication

## 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

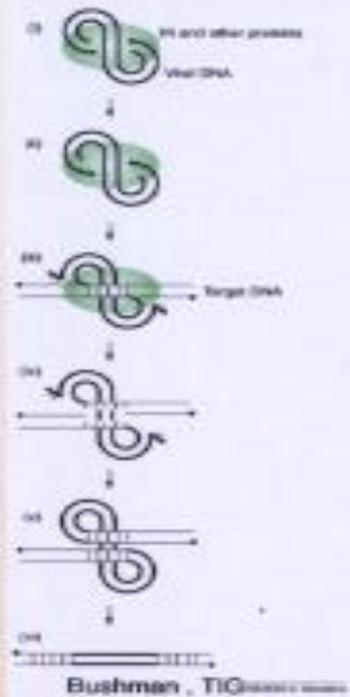


# HIV integration

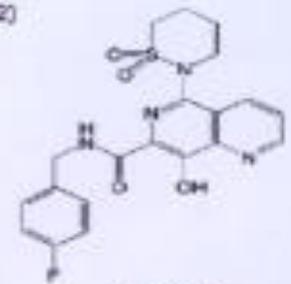
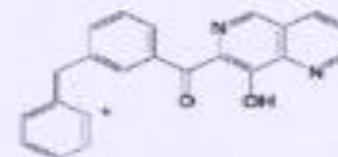
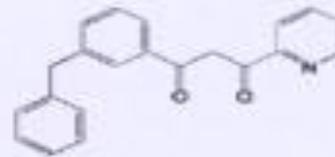
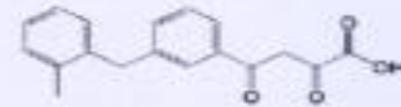
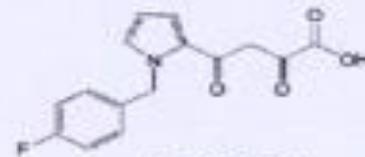


# HIV Translation

## Integration



Multistep reaction



Hazuda 2X

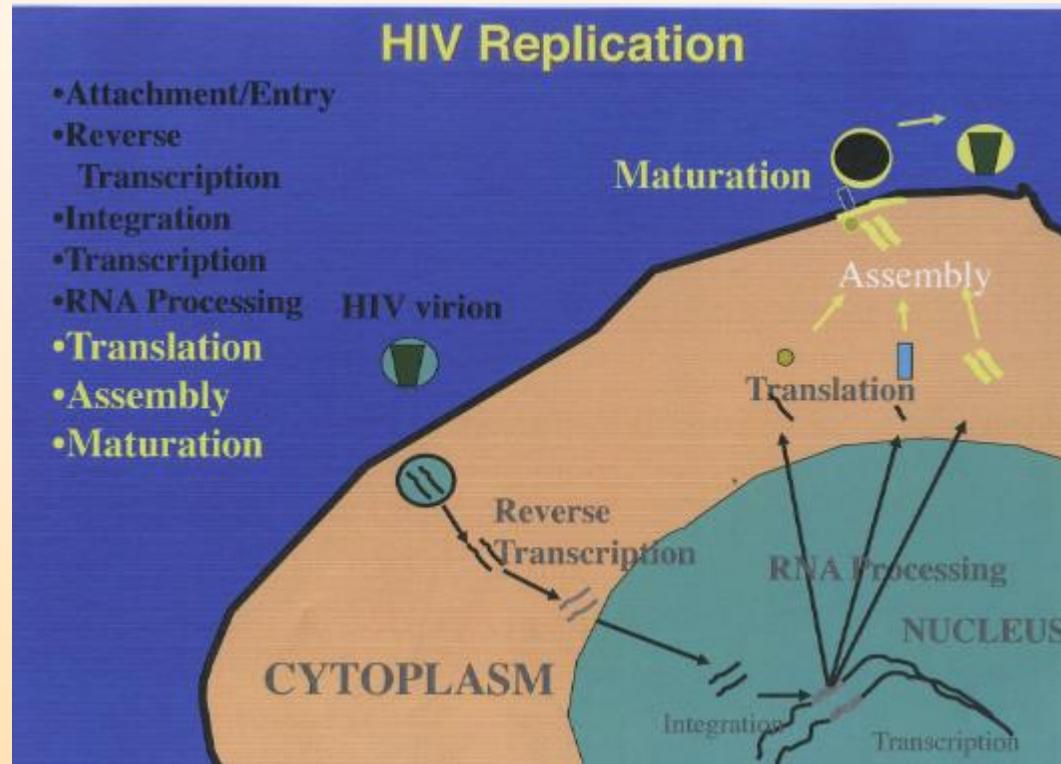
Strong inhibitors



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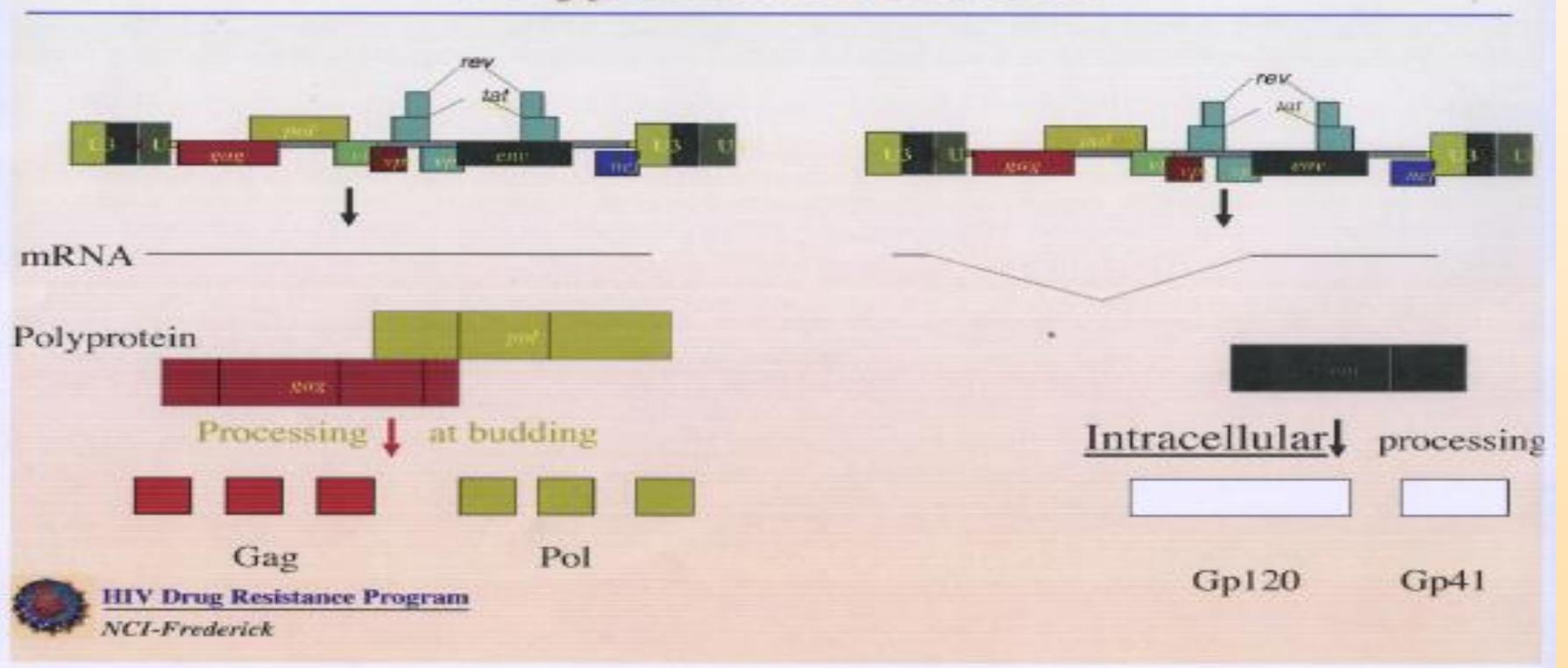
NCI-Frederick

# HIV Translation



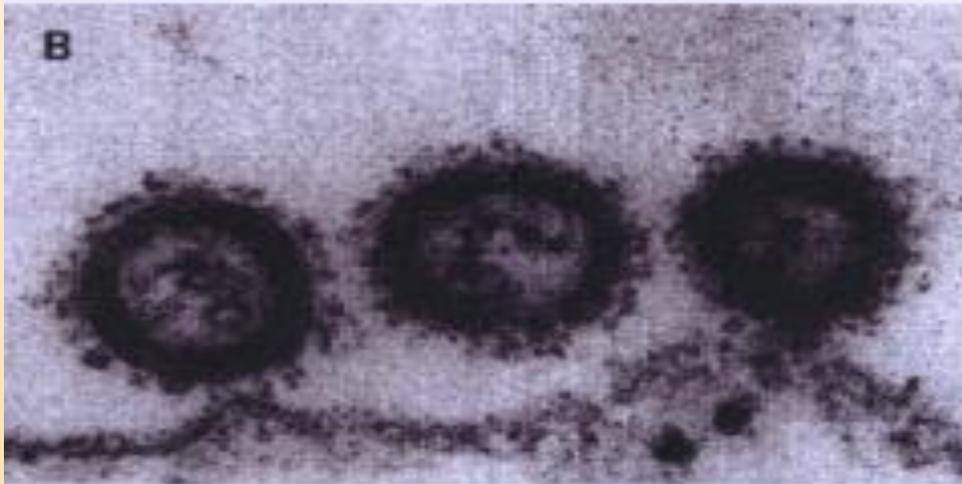
# Translation of HIV gag/pol and env paradigm: Process Polyprotein Precursors

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



# HIV Particle Maturation

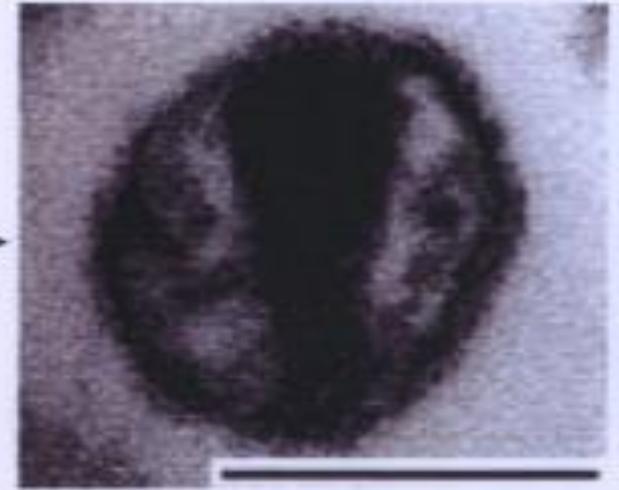
## HIV Particle Maturation



**Immature Particle**  
**Noninfectious**

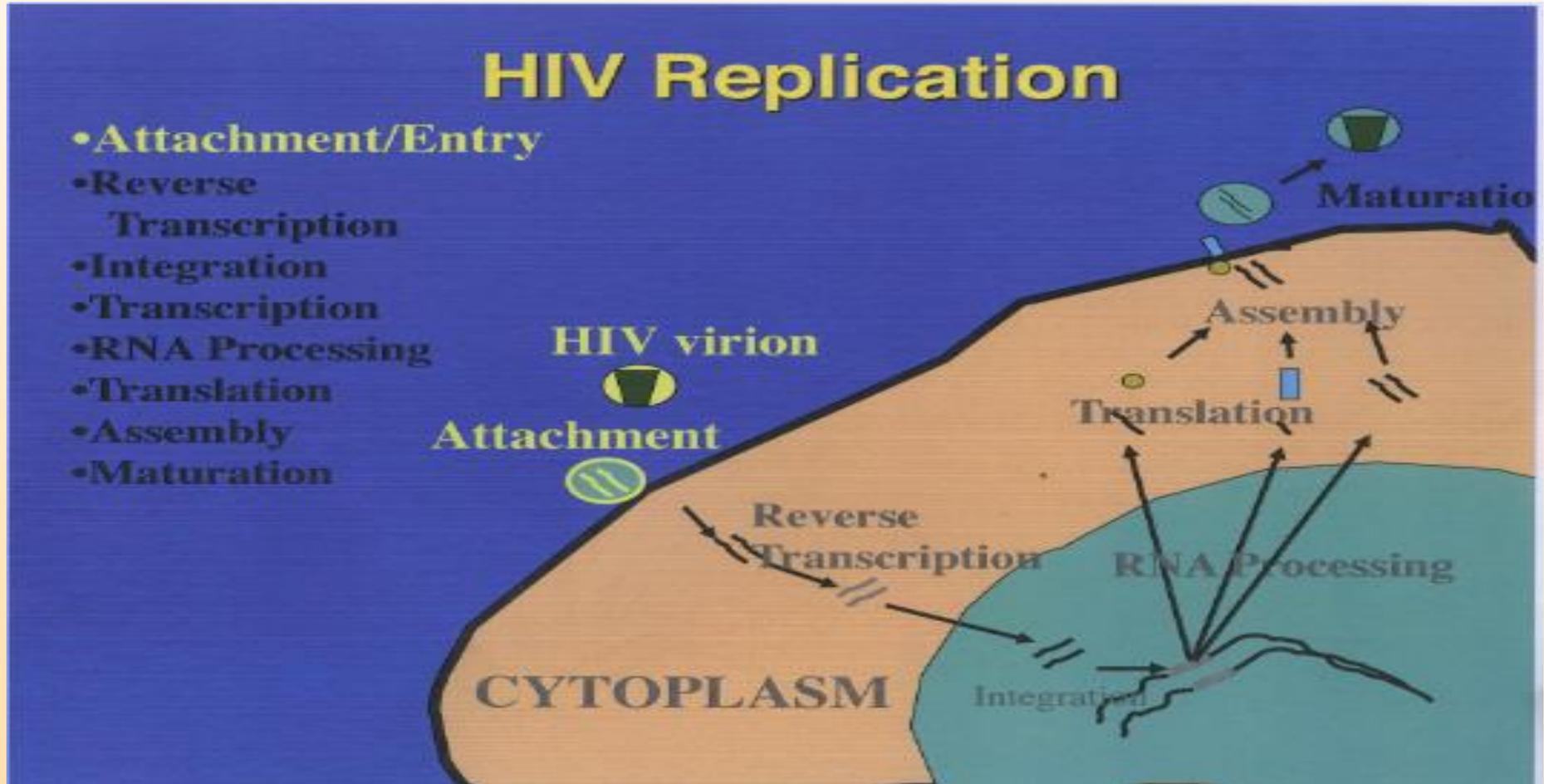


**HIV**  
**Protease**



**Mature Particle**  
**Infectious**

# HIV maturation



# **Retroviruses**

## **Emergence/Spread**

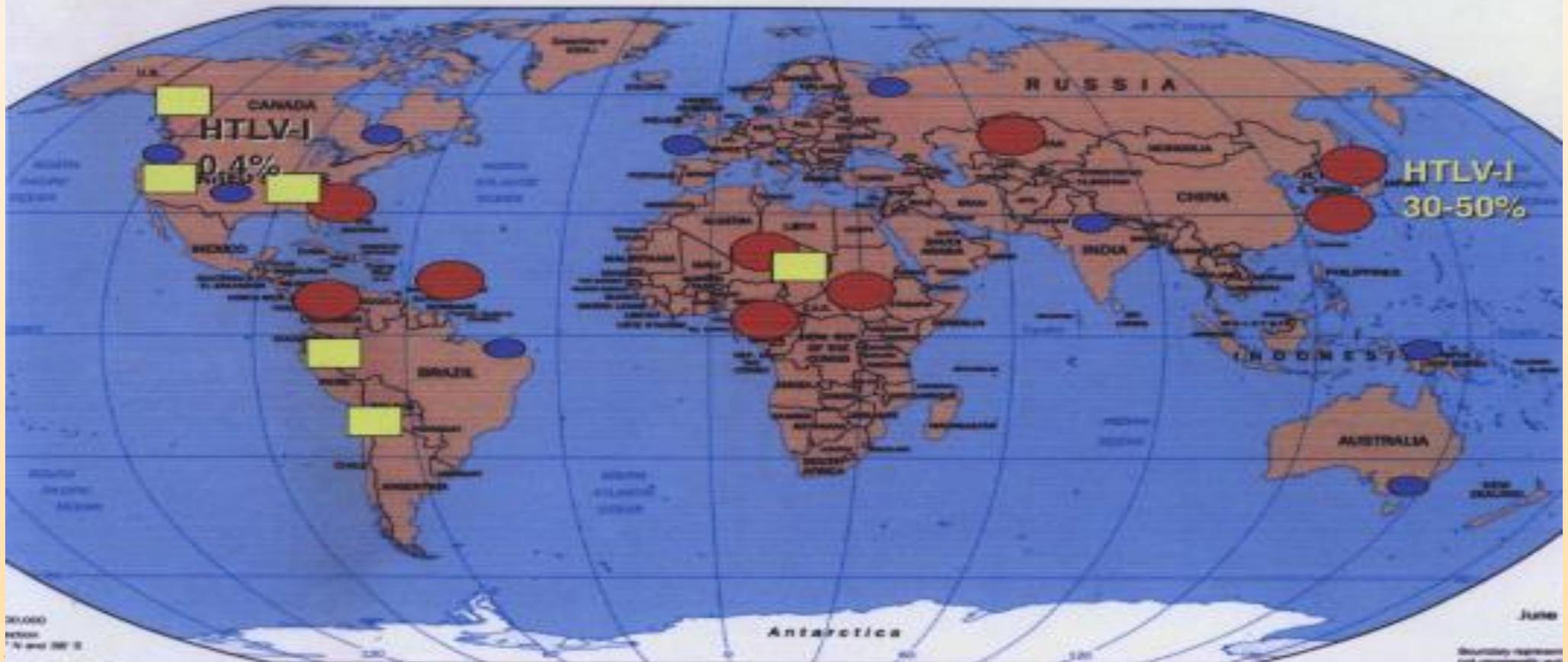
# Lentivirus Relationships

- **HIV-2 is closely related to SIV-smm, whereas SIV-syk is distantly related**
- **HIV-1 and SiV-cpz are closely related whereas SIV-agm and SIV-mnd are distantly related**
- **VMV and CAEV are closely related whereas EIAV and FIV are distantly related.**



# HTLV distribution

## HTLV DISTRIBUTION



TLV-I Sporadic  
TLV-I High endemicity



HTLV-II Endemic (Amerindian and Pygmy tribes)



# 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



**22.4 M cases in Africa**

**2.4 M cases in Europe**

**4.6 M cases in Asia**

**1.6 M cases in North America**

**2.0 M cases in South America**

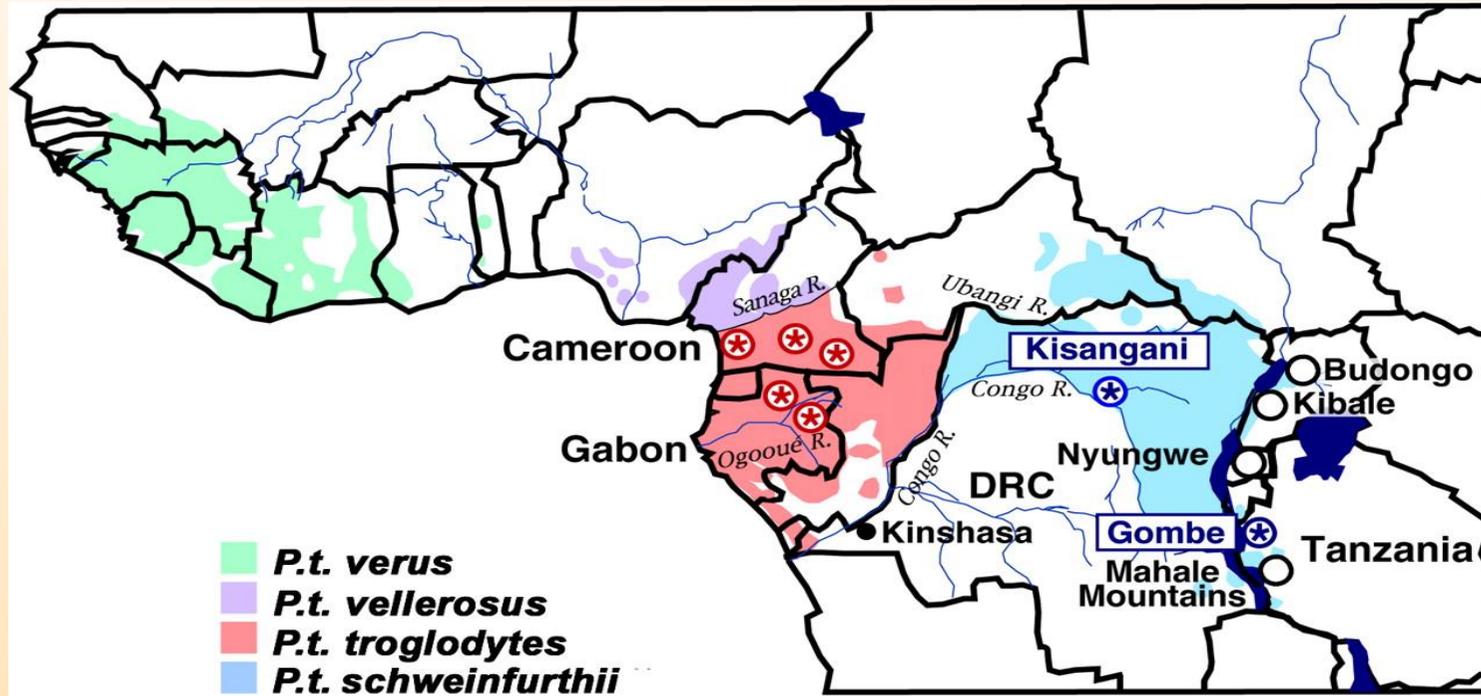
**33.0 M cases in the world**



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# Higher Primate Origins of HIV-1



# Bushmeat Trade in Central and West Africa

Bushmeat Trade in Central and West Africa



# HIV evolution

**M originated in 1930,**

**H originated in 1935,**

**B originated in 1941,**

**C originated in 1949,**

**D originated in 1950,**

**J originated in 1951 and**

**F originated in 1966**



# 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**



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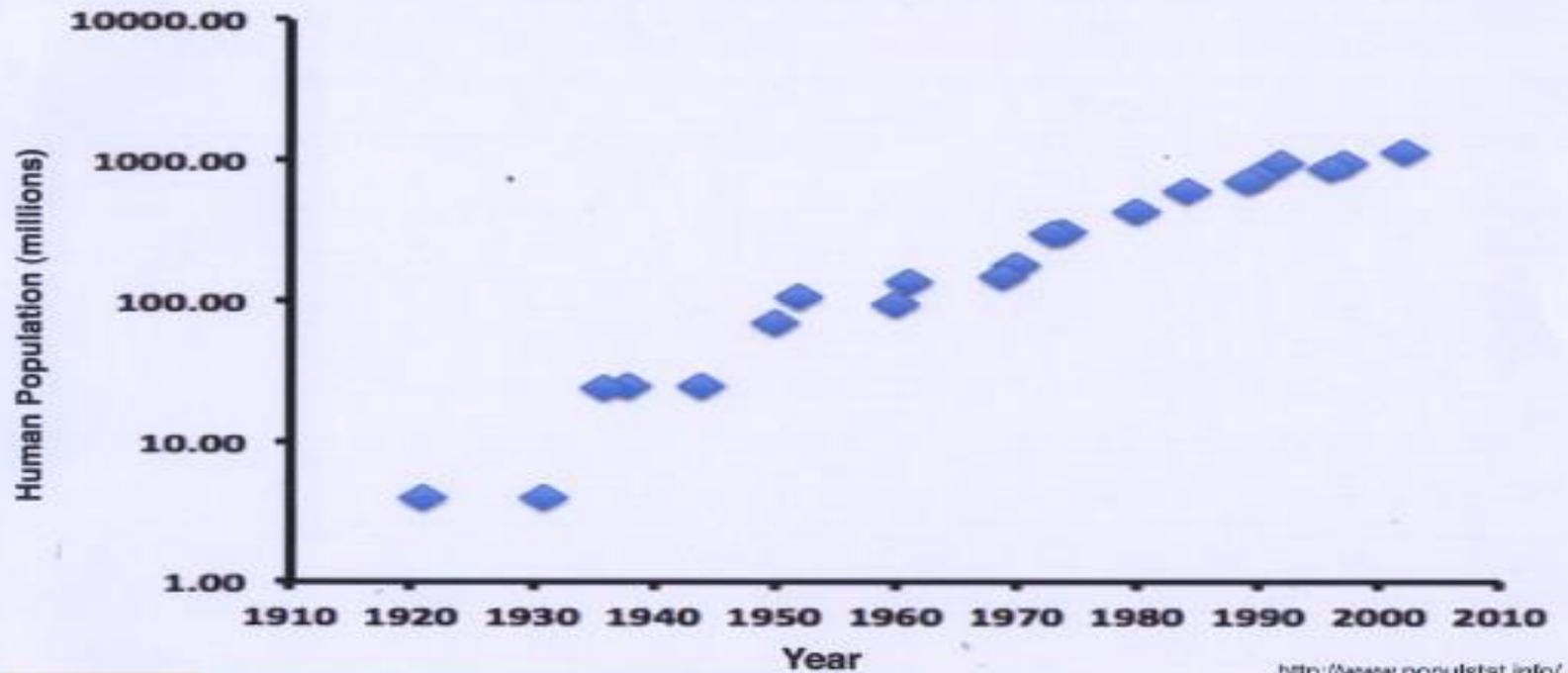


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# Zoonotic Transmission

## Zoonotic Transmission of HIV Coincides with Population Expansion in Africa



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# HIV spread

## HIV Spread

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



HIV Drug Resistance Program

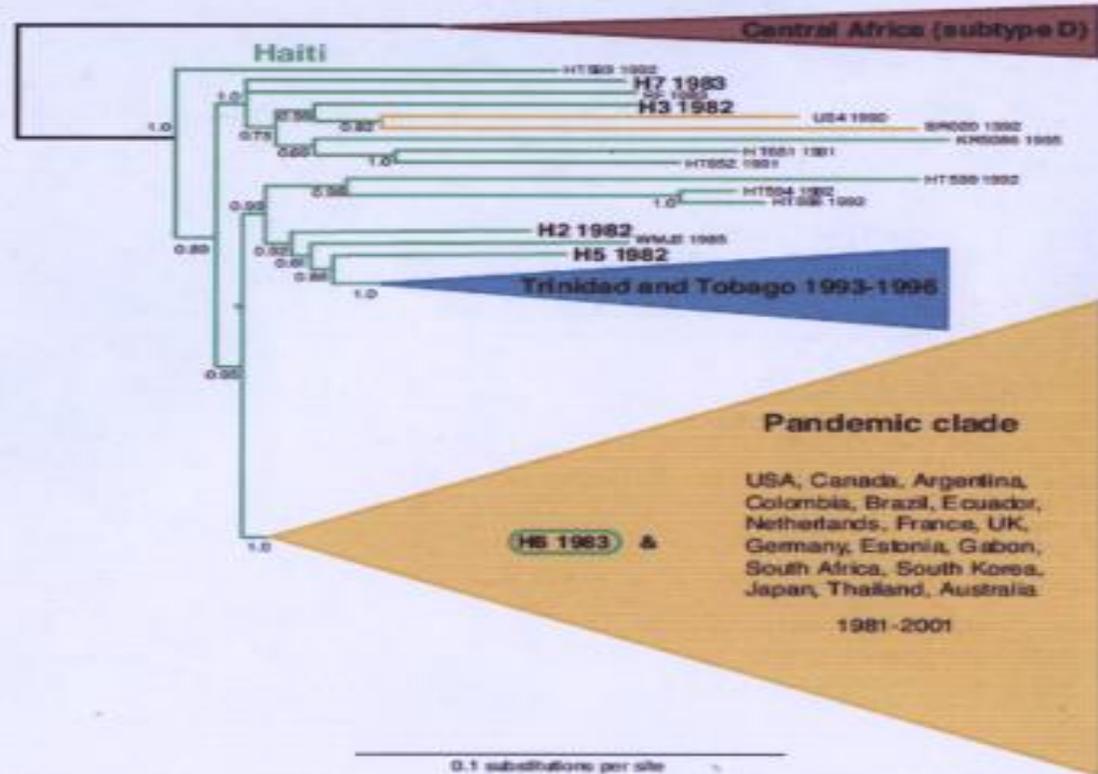
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# Spread of non B subtypes 2003

## Spread of Non B Subtypes 2003



# Evolution of AIDS



Worobey et al.

Fig. 1. The abridged majority-rule consensus tree summarizing the results from the MrBayes analysis of complete env genes. The branch lengths represent the mean value observed for that branch among the postburnin sampled trees. Posterior probabilities are indicated for each node. As expected under a "Haiti-first model" the non-Haitian CRF01\_A3 strains are phylogenetically nested within an older and more diverse range of Haitian CRF01\_A3 variants. The 11 sequences of th



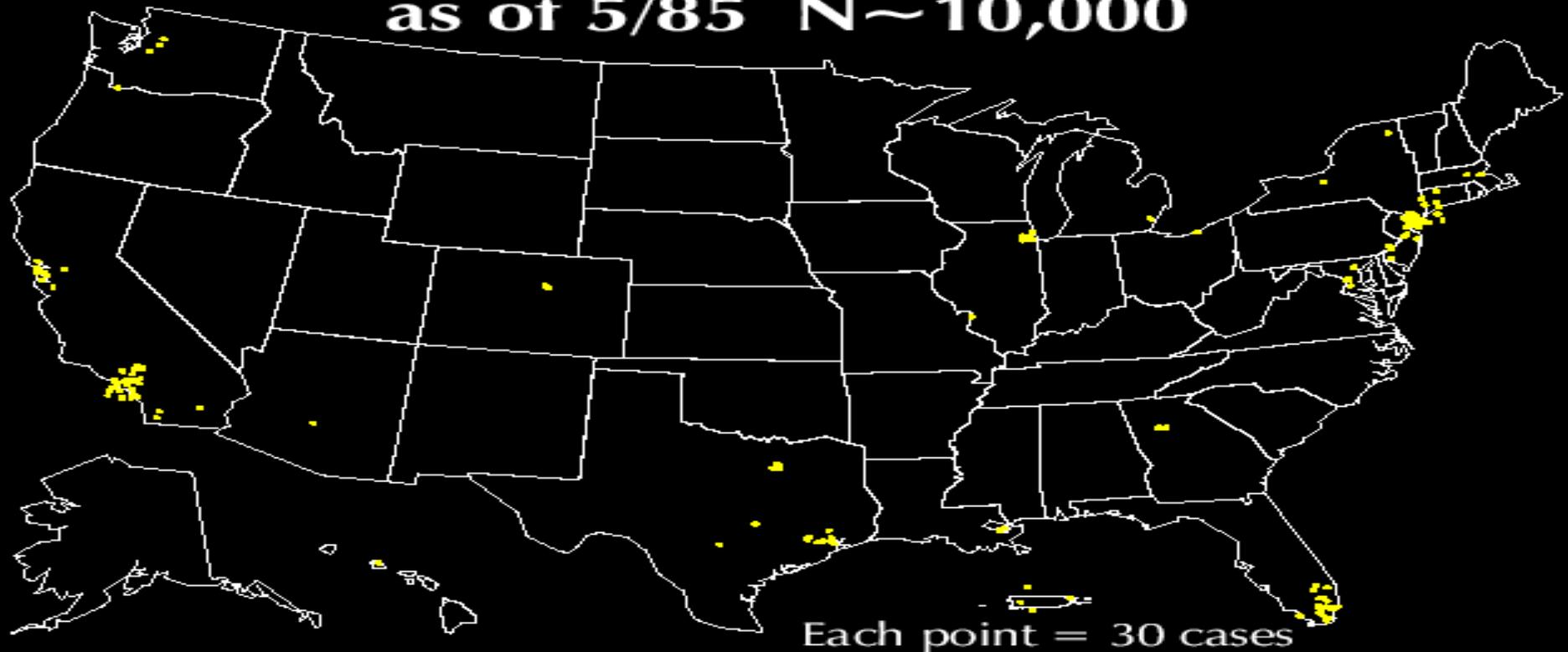
# Cumulative U.S. AIDS cases as of 2/83 N = 1000

**Cumulative U.S. AIDS Cases  
as of 2/83 N~1,000**



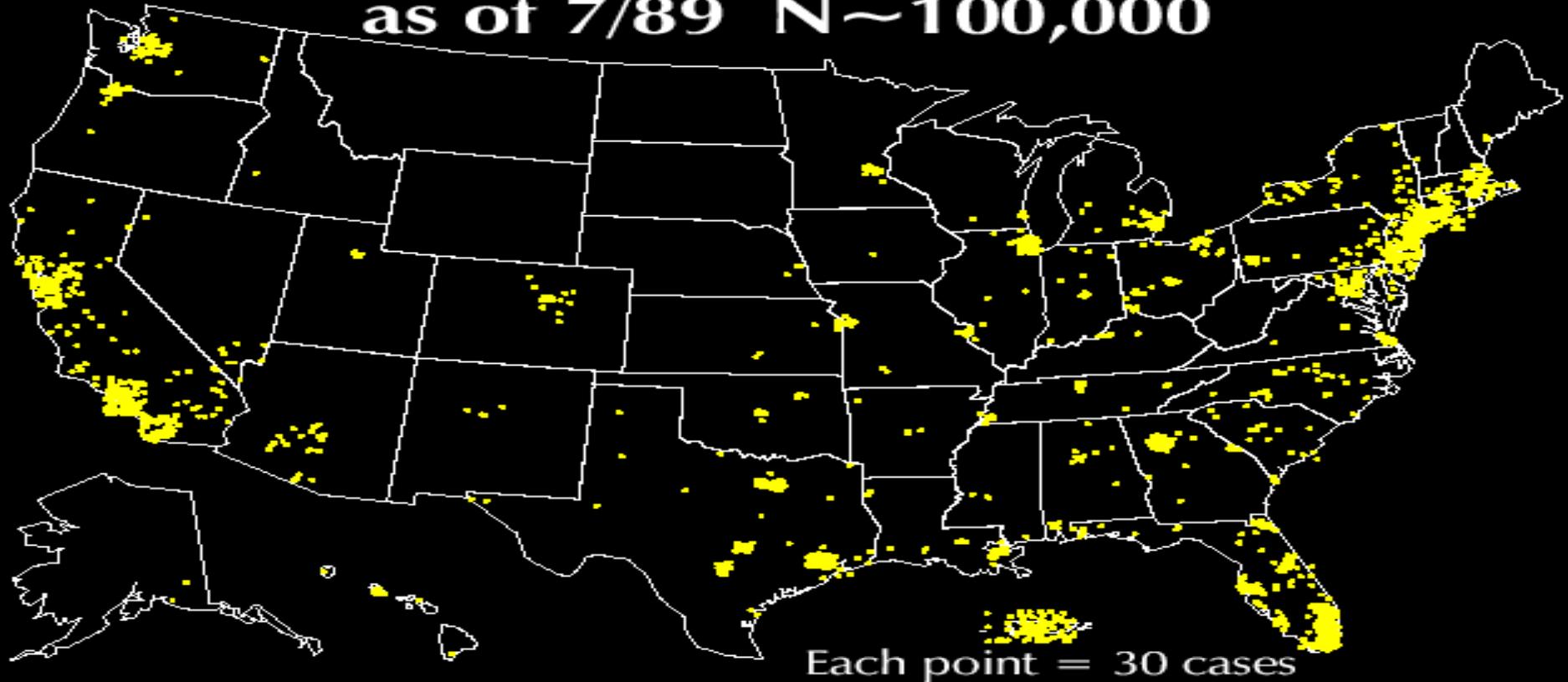
# Cumulative U.S. AIDS cases as of 5/85 N = 10000

**Cumulative U.S. AIDS Cases  
as of 5/85 N~10,000**



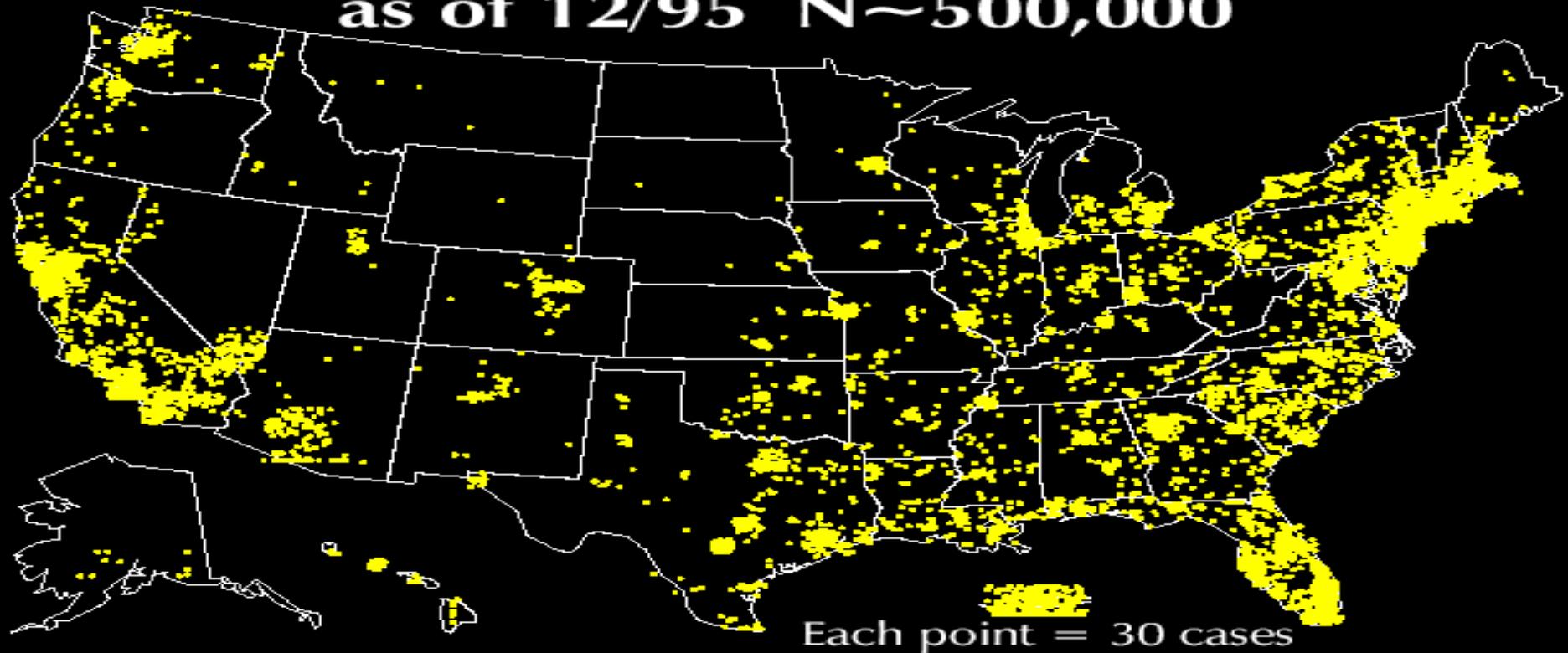
# Cumulative AIDS cases as of 7/89 N = 100000

Cumulative U.S. AIDS Cases  
as of 7/89 N ~ 100,000

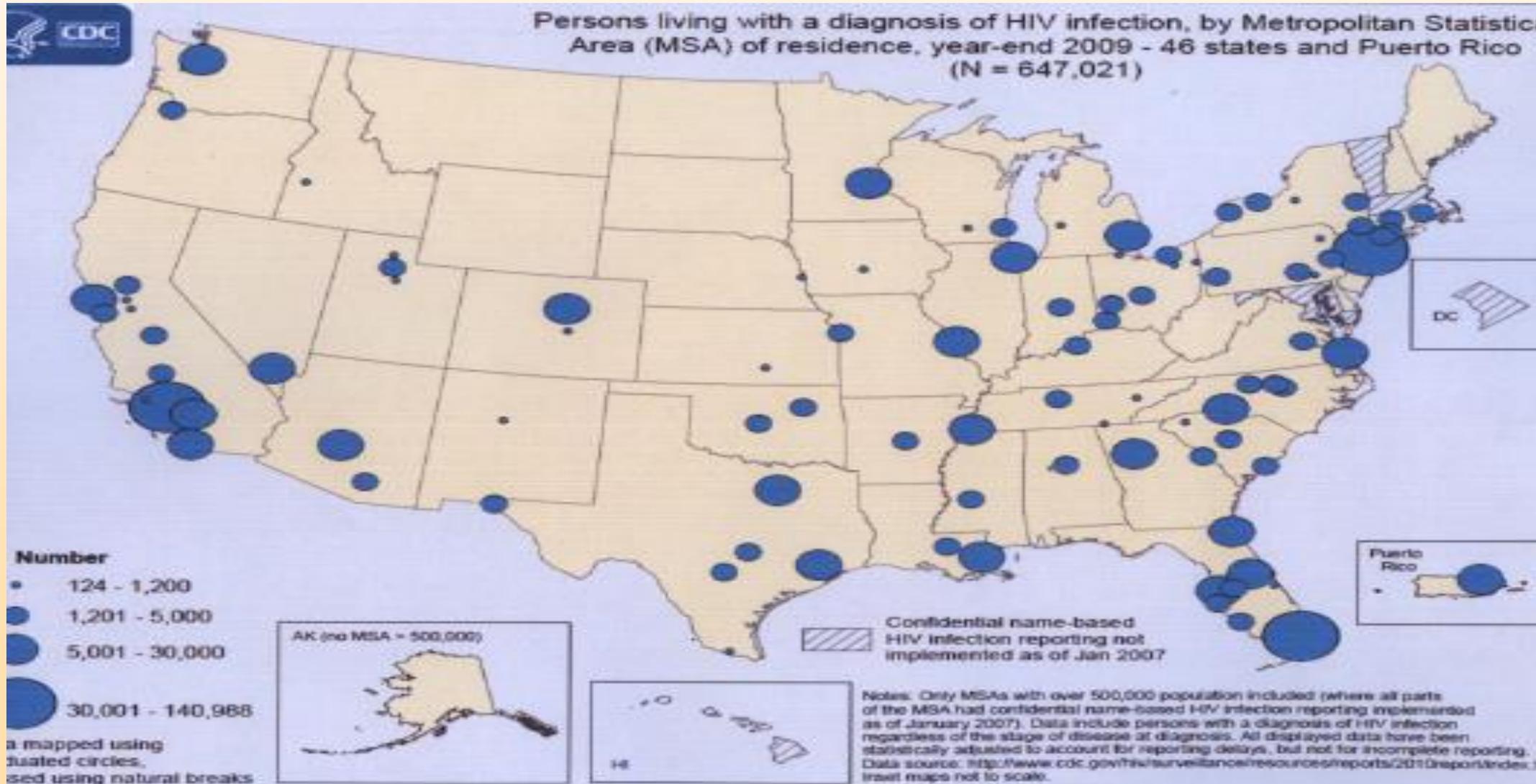


# Cumulative AIDS cases as of 12/95 $N = 500000$

Cumulative U.S. AIDS Cases  
as of 12/95  $N \sim 500,000$

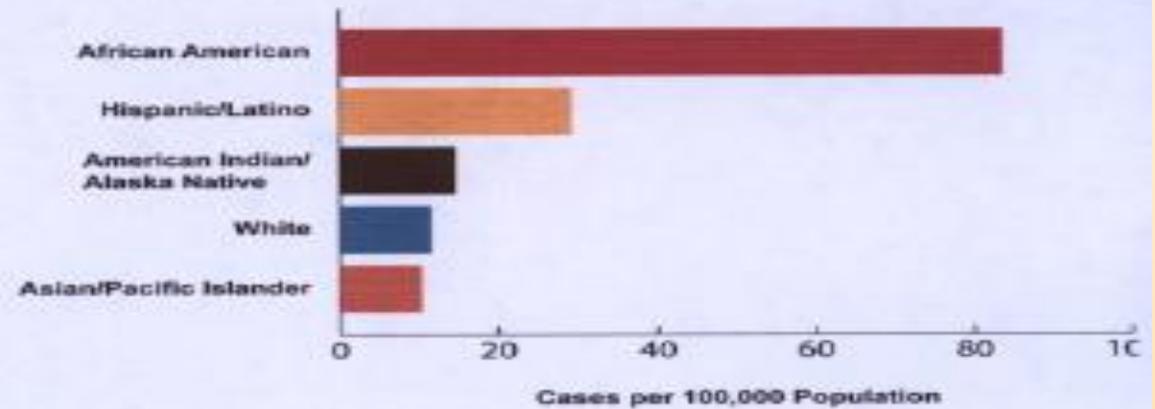
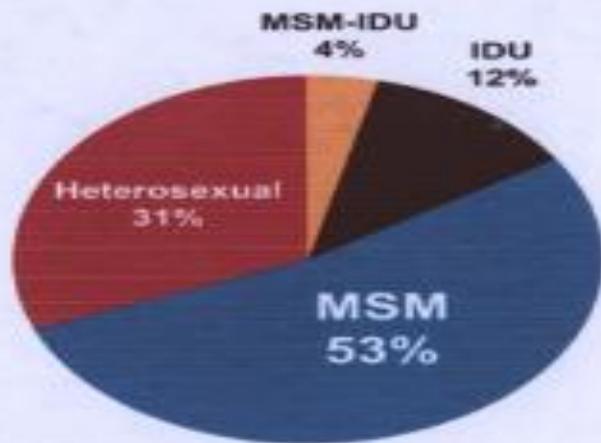


# HIV infection map



# New cases of HIV/AIDS-USA

## New cases of HIV/AIDS—USA



JAMA 2008



# Trends in US HIV Epidemic (CDC)

- **Race/ethnicity**
  - African Americans exceed white/not hispanic as most common patients living with AIDS
- **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
  - By 2015, 50% of Persons living with HIV will be >50 yo



## AIDS warning

If you get the AIDS virus now  
you and your license could  
expire at the same time.

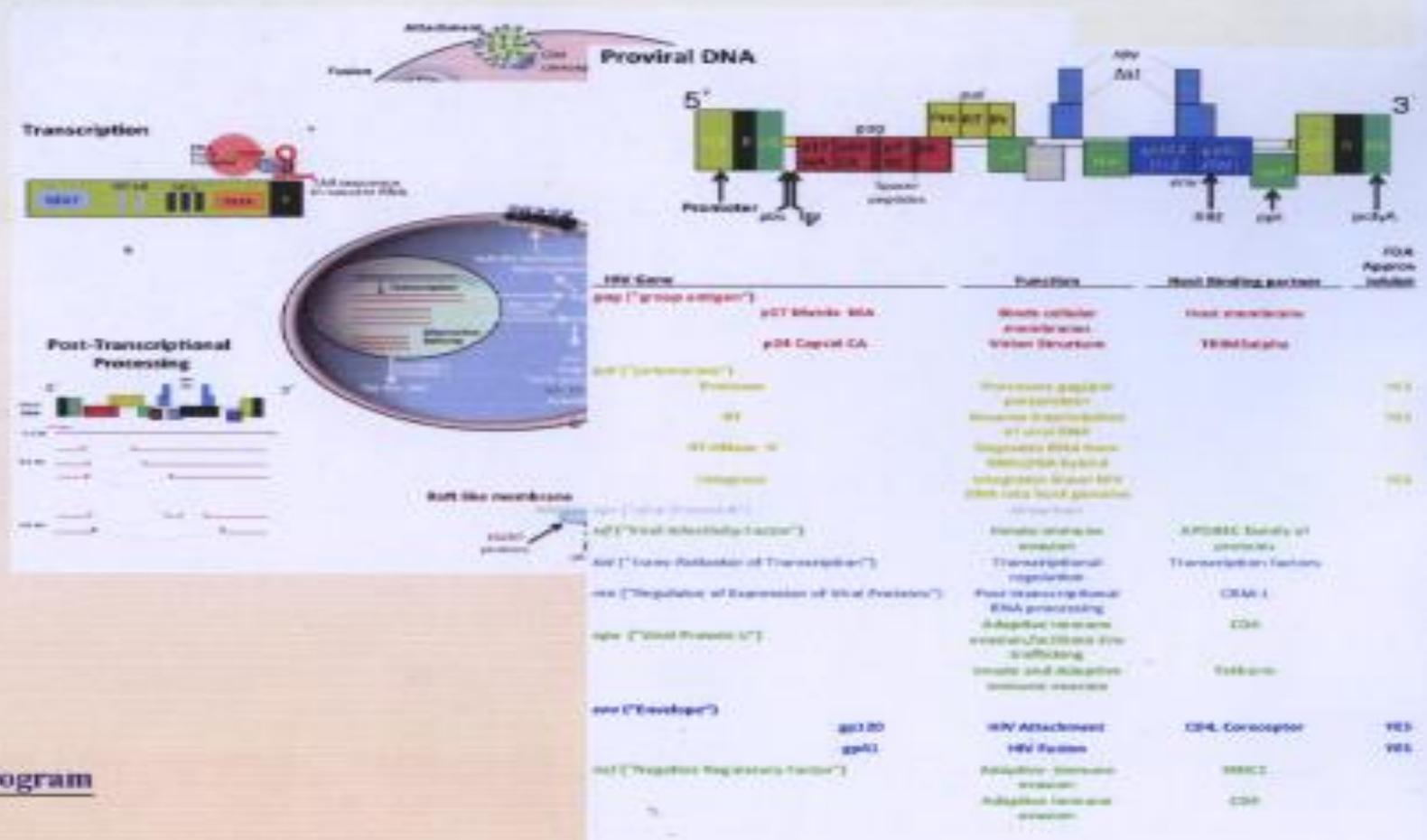
**DMV**  
DEPARTMENT OF MOTOR VEHICLES

DRIVER LICENSE

• C02320782  
Don Halste  
01 Newb

# HIV Replication Steps Serve as Antiviral Targets

## HIV Replication Steps Serve as Antiviral Targets



# AIDS warning

If you get the AIDS virus now  
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# Retroviruses: Lessons



**HIV Drug Resistance Program**

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# Summary:

- Viruses are bad and should be avoided



# Summary

- **Viruses are bad and should be avoided**
- **except when they save the planet**



# Summary

- Viruses are bad and should be avoided
- except when they save the planet
- and maybe it saves you from the next virus



# Summary

- Viruses are bad and should be avoided
- except when they save the planet
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- Epidemics are not single events



# Summary

- Viruses are bad and should be avoided
- except when they save the planet
- and maybe it saves you from the next virus
- Epidemics are not single events
- Epidemics evolve

