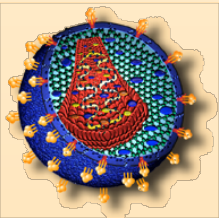


Retroviruses

TRACO

November 26, 2018

Frank Maldarelli



HIV Dynamics and Replication Program

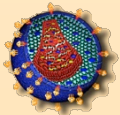
NCI-Frederick

NATIONAL
CANCER
INSTITUTE



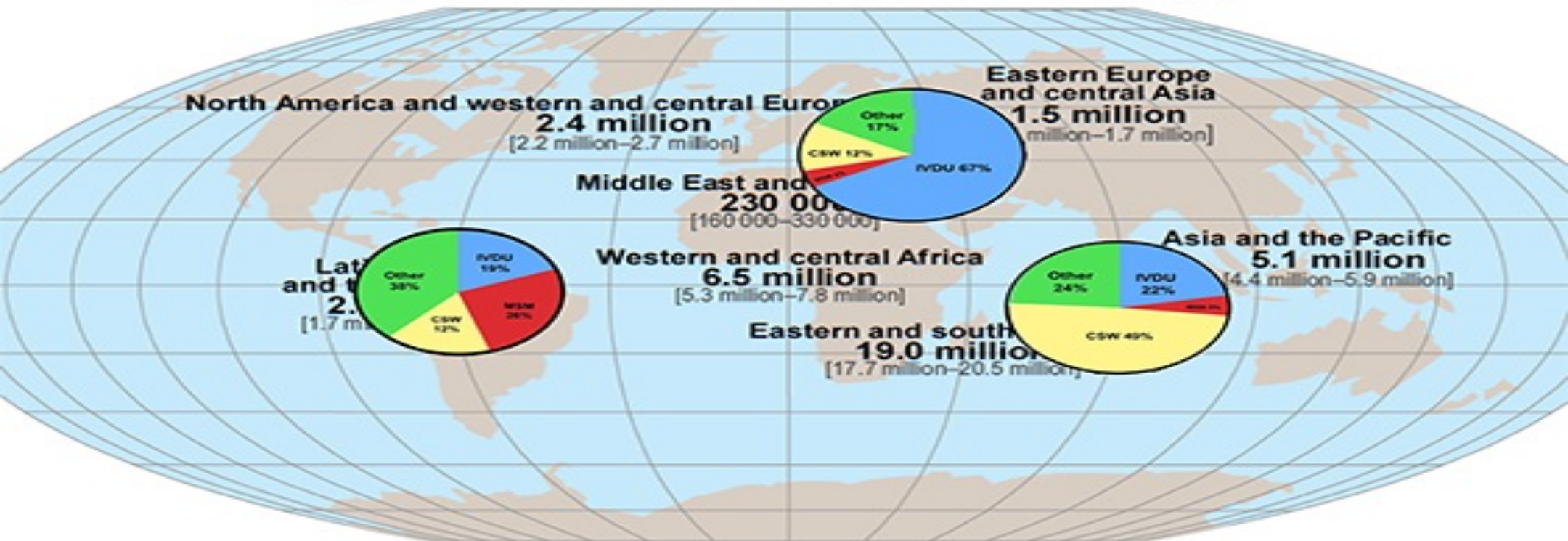
Retroviruses

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

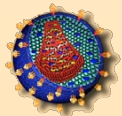


HIV-1 pandemic and risk

HIV-1 PANDEMIC AND RISK

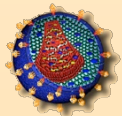


Total: 36.7 million [34.0 million–39.8 million] UNAIDS, 2015



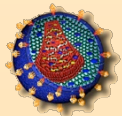
HIV Dynamics and Replication Program

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HIV Dynamics and Replication Program

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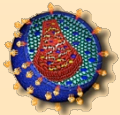


HIV Dynamics and Replication Program

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Retroviruses

- **Molecular Biology/Replication**



HIV Dynamics and Replication Program

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Retroviruses

Retroviruses

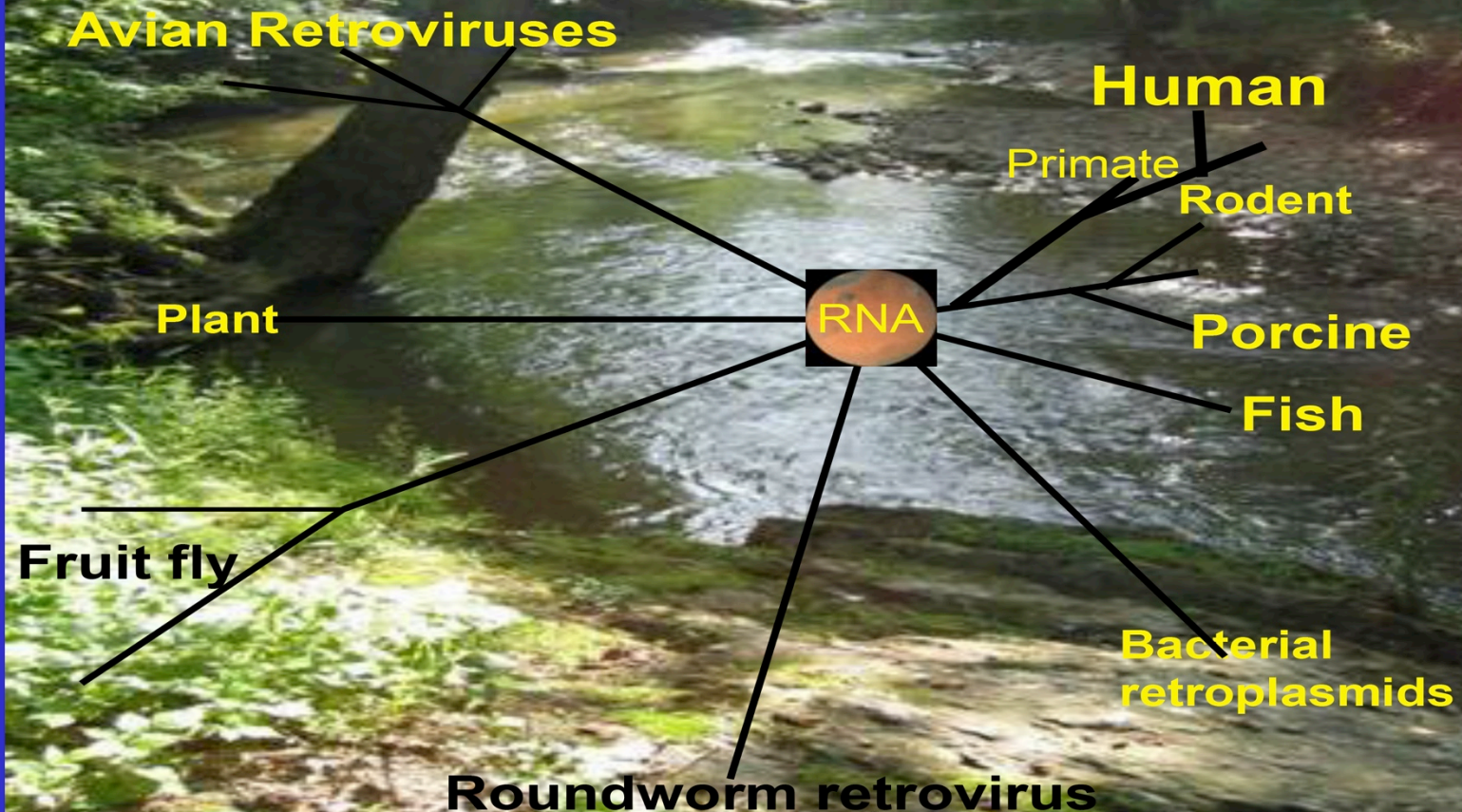
A group of RNA viruses that replicate via a DNA intermediate using Reverse Transcriptase.

A different paradigm for replication

Transition from RNA World?

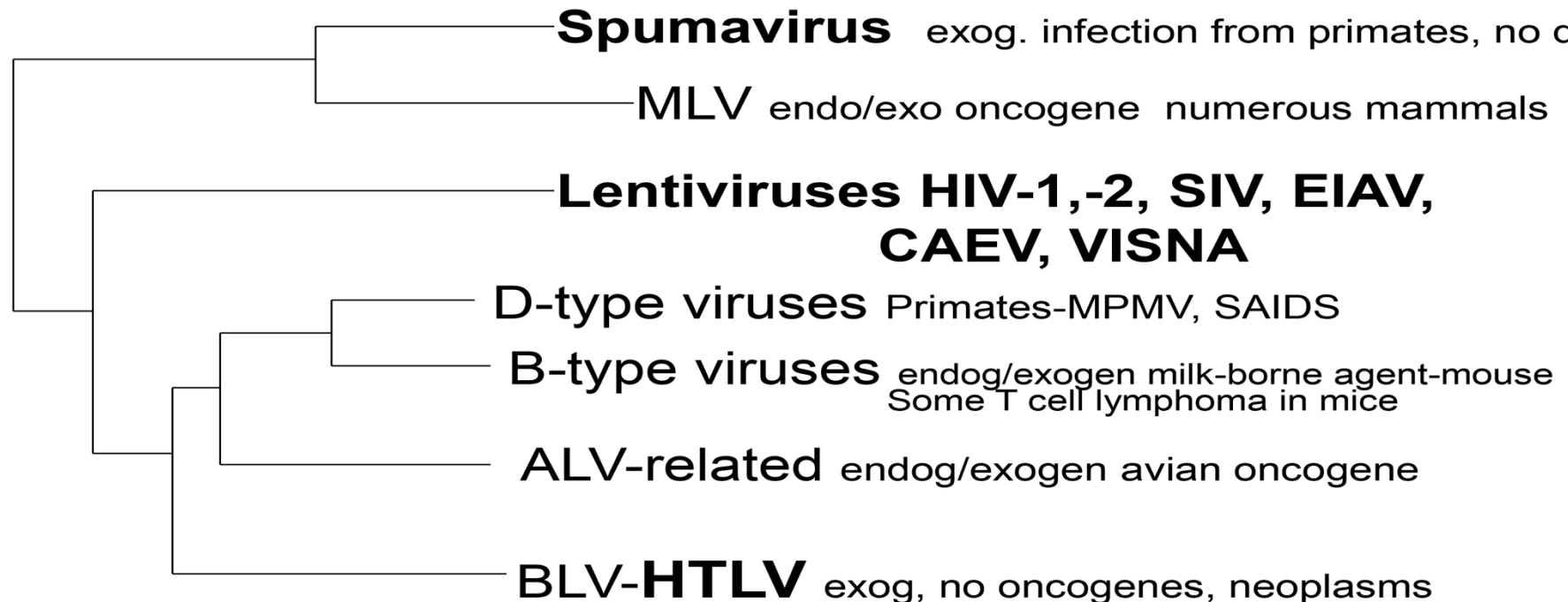
Retroelements

**Reverse Transcriptase and Retroelements
are all around you**



Retrovirus classification

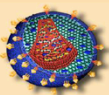
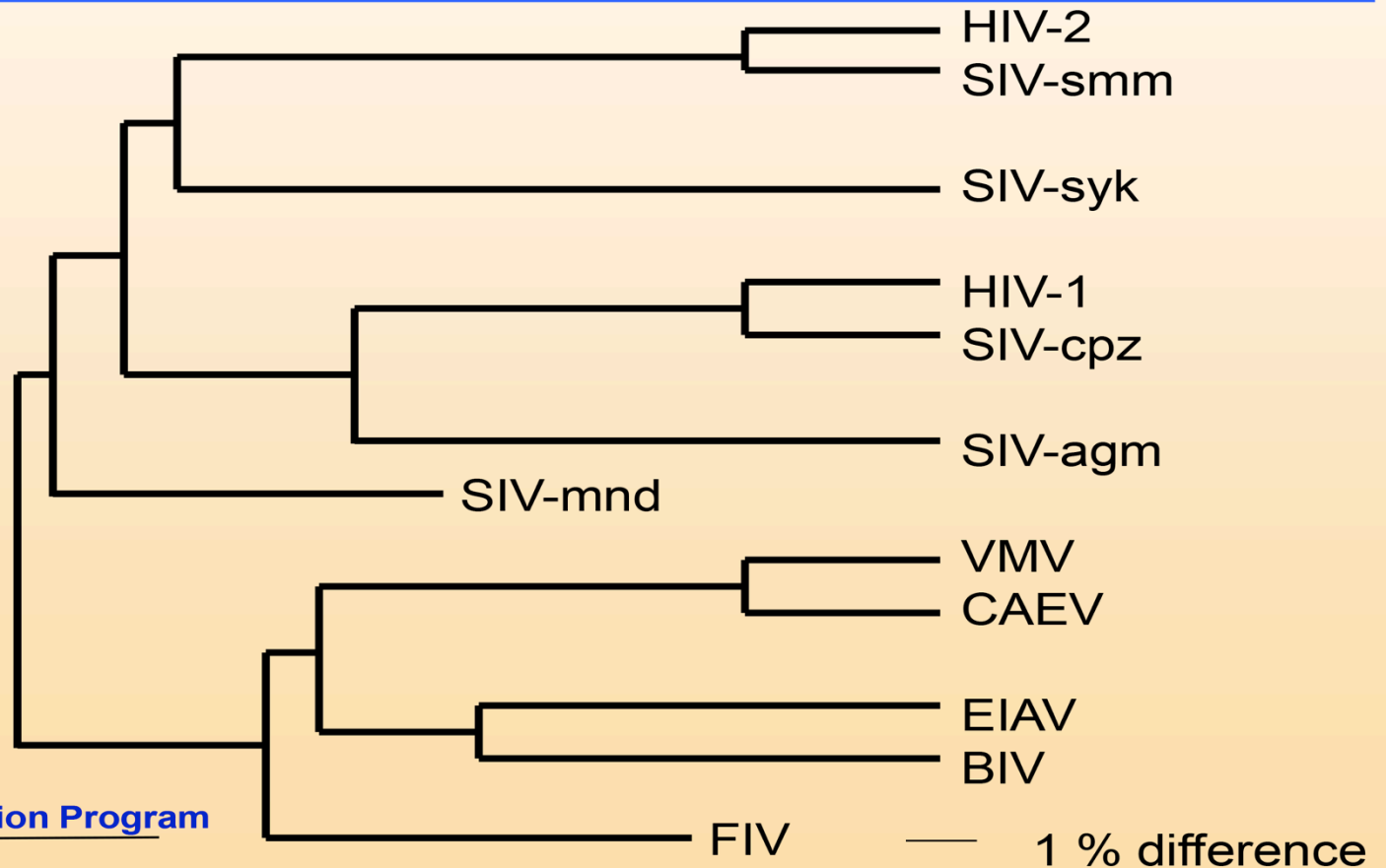
Retroviruses Classification by RT Sequence into Seven Families



Line length *not* to scale AND THERE IS NO UNIFORM TIME SCALE

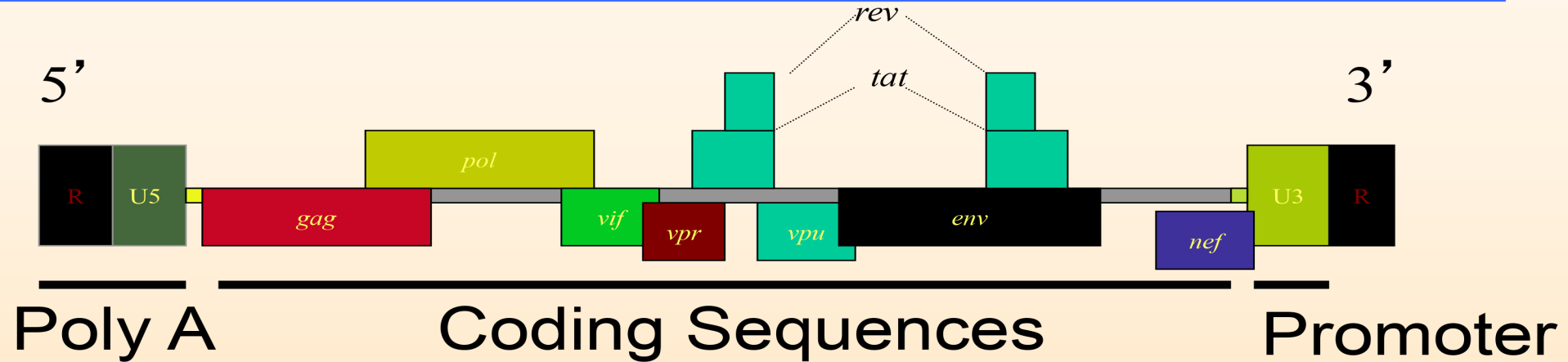
Lentivirus Relationships

Lentivirus Relationships



Retrovirus conventions

Retroviruses Conventions



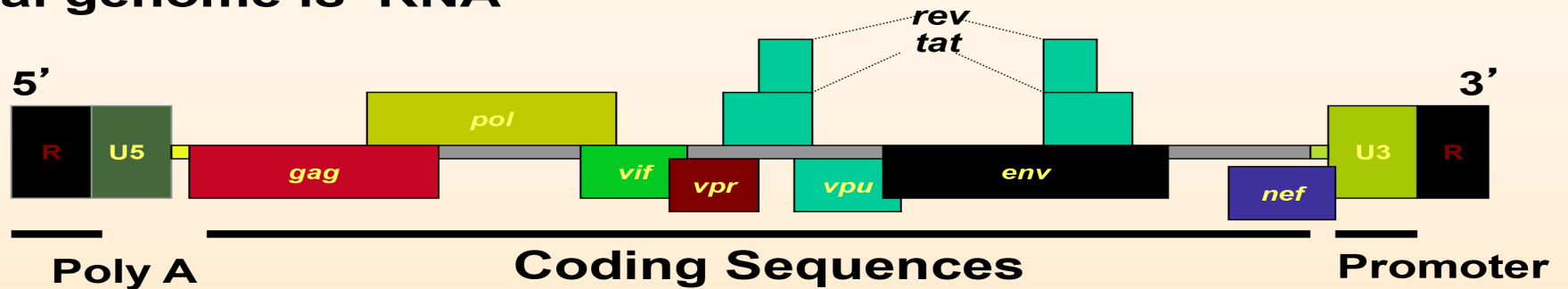
Names of genes in lower case *italics*, e.g., *pol*, *env*
Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120



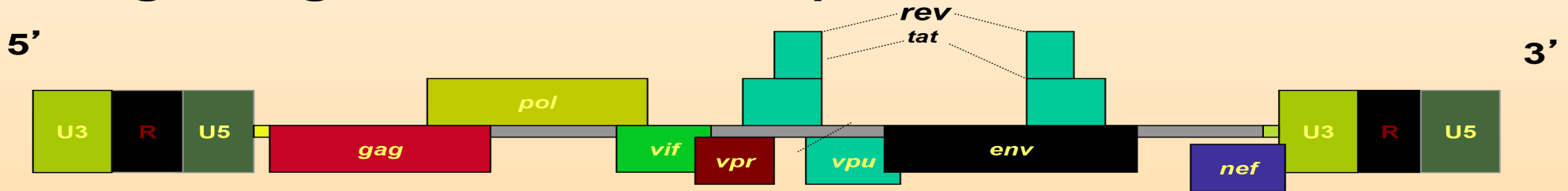
Retrovirus

Retroviruses Conventions

The viral genome is RNA

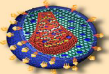


The integrated genome is called the provirus



Names of genes in lower case *italics*, e.g., *pol*, *env*

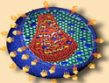
Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120



Retroviruses

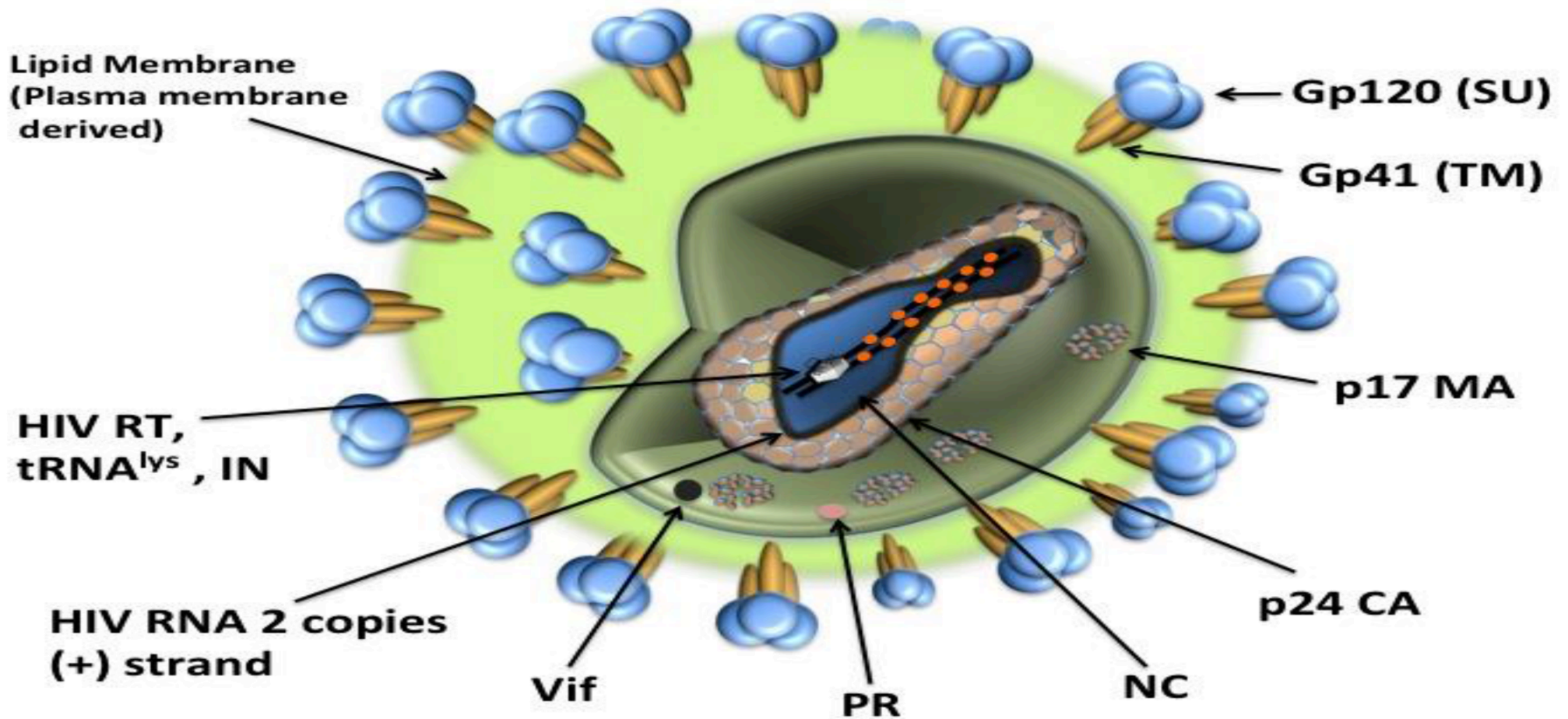
Retroviruses Glossary

- *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

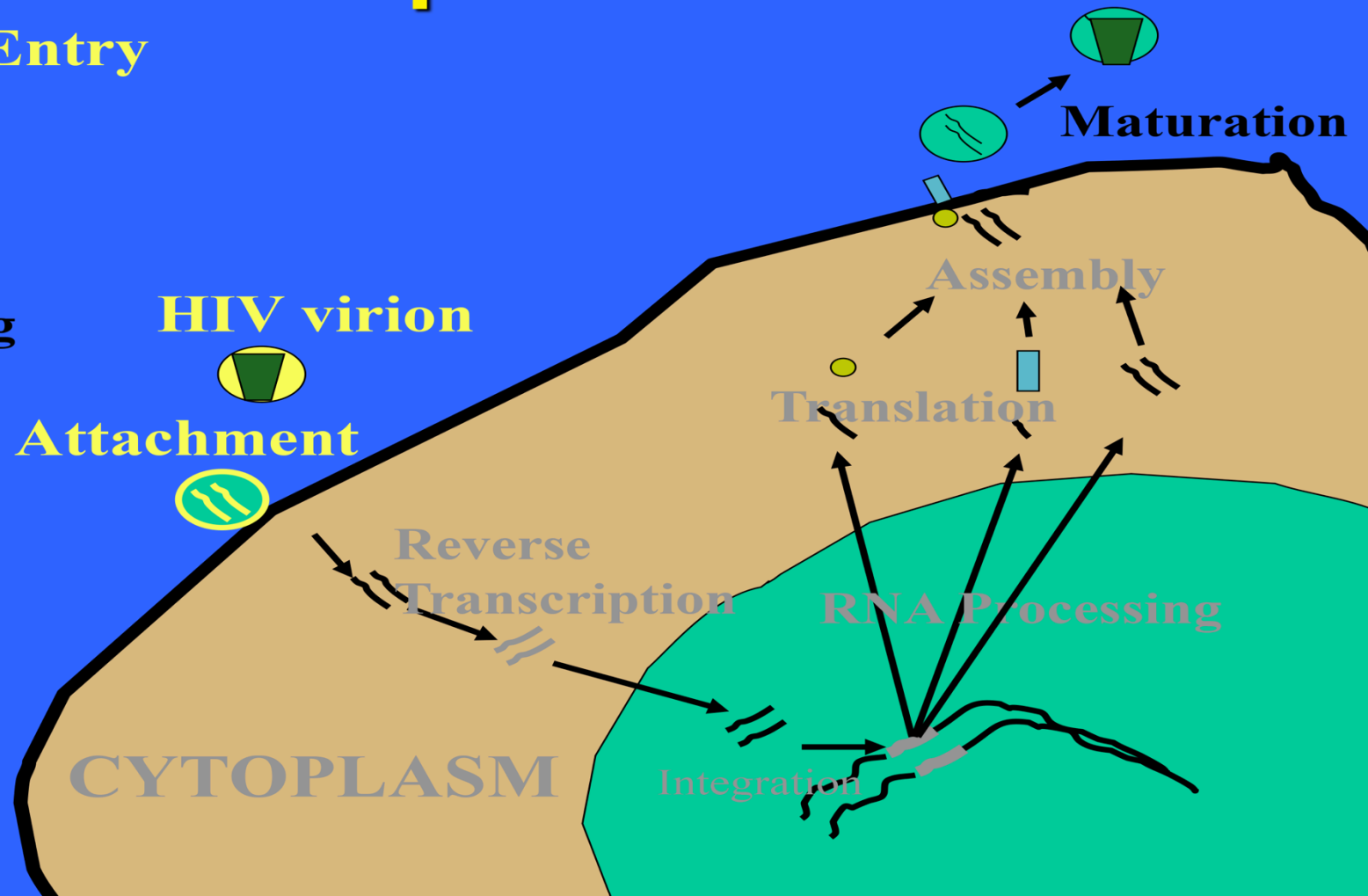
HIV Virion



HIV replication

HIV Replication

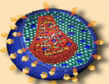
- **Attachment/Entry**
- **Reverse Transcription**
- **Integration**
- **Transcription**
- **RNA Processing**
- **Translation**
- **Assembly**
- **Maturation**

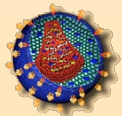


HIV attachment and Entry

HIV Attachment and Entry

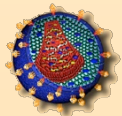
- **Virus Factors**
 - Attachment: Env glycoprotein gp120
 - Entry: Env glycoprotein gp41
- **Host Cell Factors**
 - Receptor
 - CD4
 - Co-receptor (major)
 - CXCR4
 - CCR5





HIV Dynamics and Replication Program

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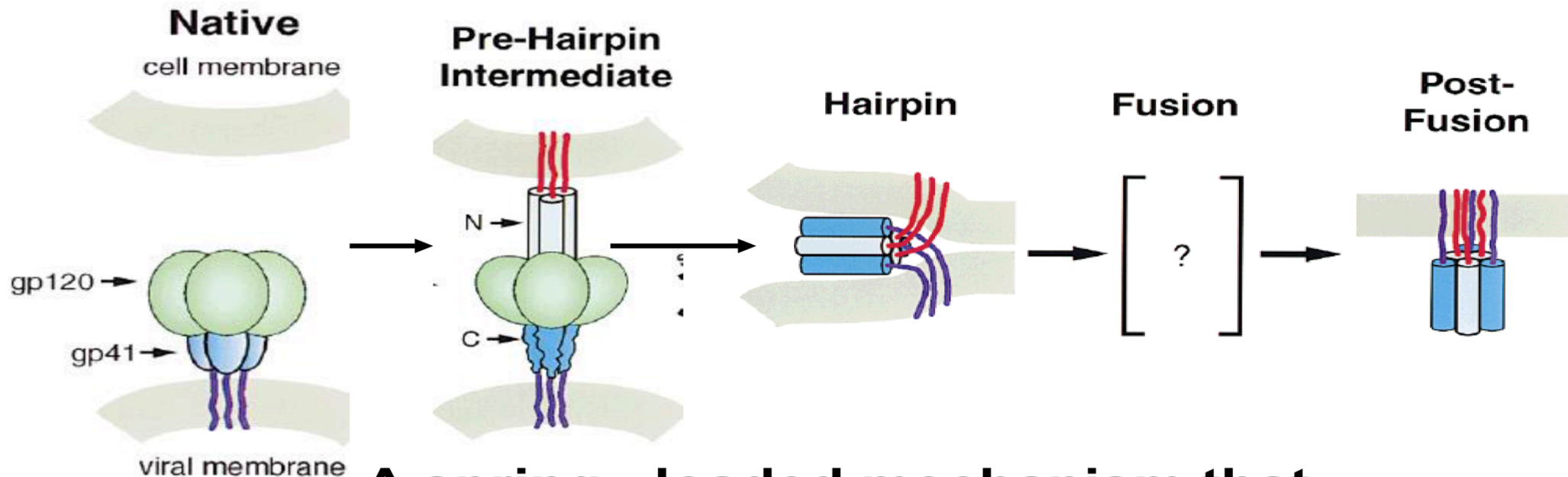


HIV Dynamics and Replication Program

NCI-Frederick

HIV Fusion-Gp41

HIV Fusion-Gp41



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

on Program

Uncoating

HIV Replication

- Attachment/Entry

- Reverse Transcription

- Integration

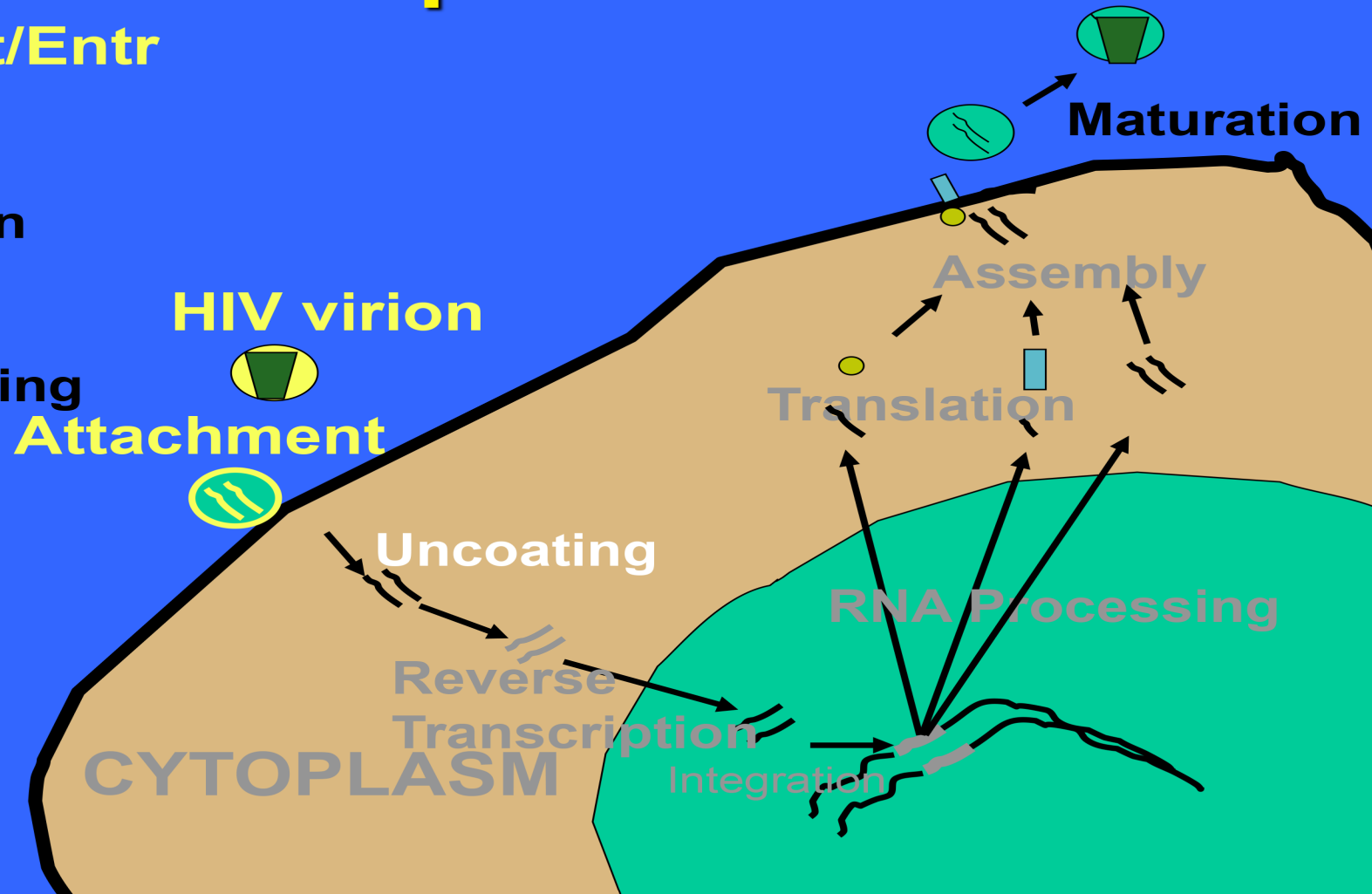
- Transcription

- RNA Processing

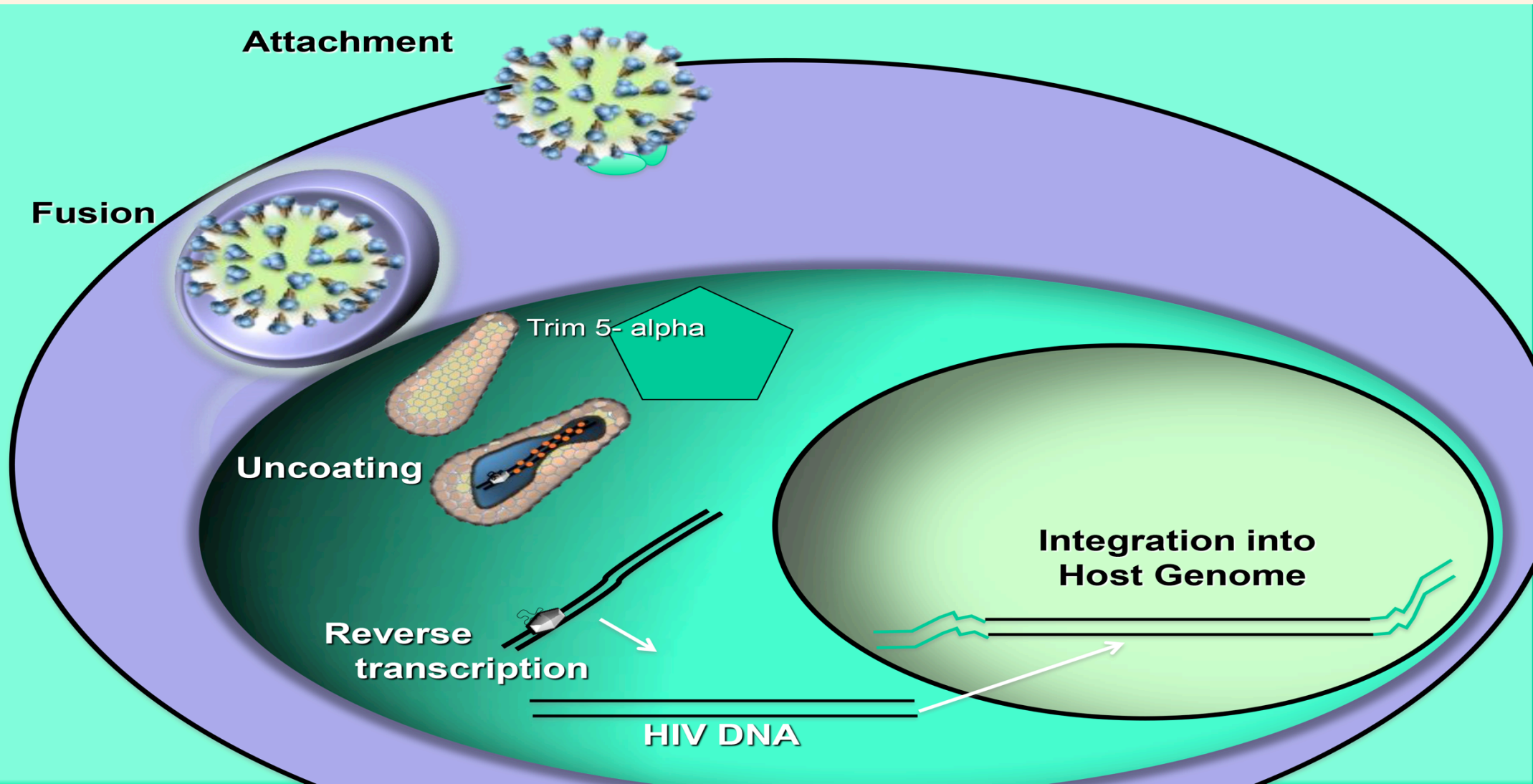
- Translation

- Assembly

- Maturation



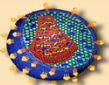
Uncoating



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



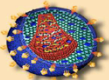
Post entry events

HIV Post – Entry Events

Host Trim5 Alpha

VIRUS

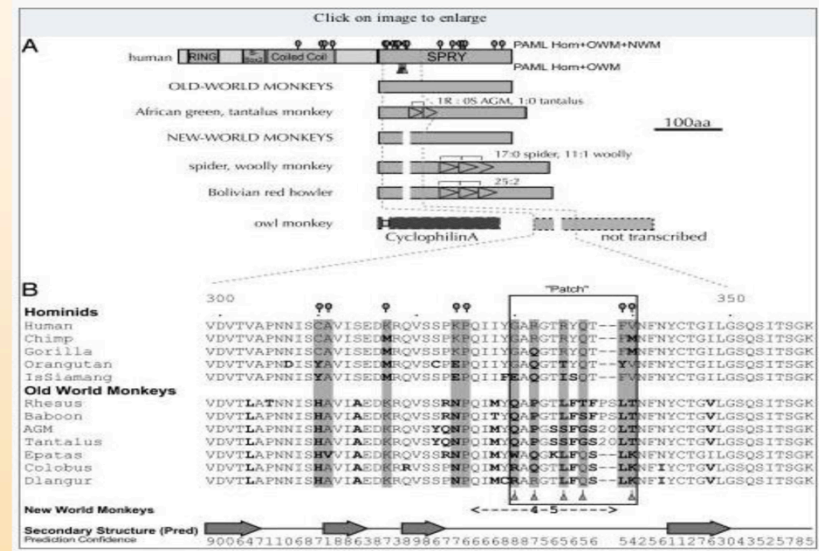
	Human	Chimp	Monkey
HIV	Infection	Infection	NO INFECTION
SIV Chimp	INFECTION	Infection	Poor infection
SIV Monkey	INFECTION	Poor infection	Infection



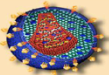
Trim 5-alpha

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

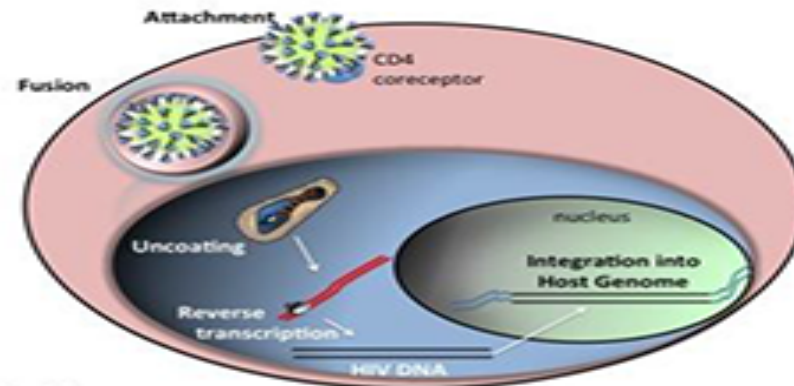


Generals are Always Fighting The Last War
Evolution can solve this problem but it will take time



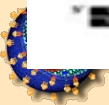
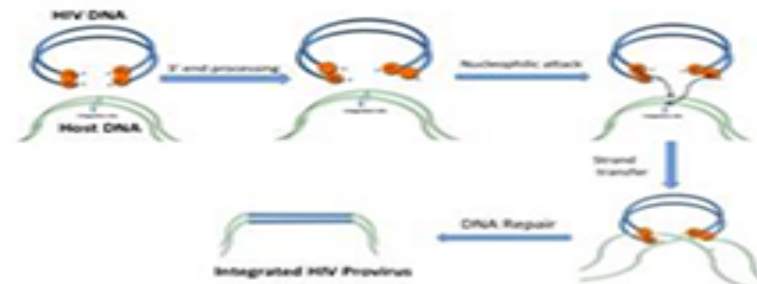
Reverse transcription

Figure 4



Reverse Transcription

Integration

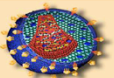


Enzymatic Activities

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**

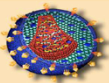
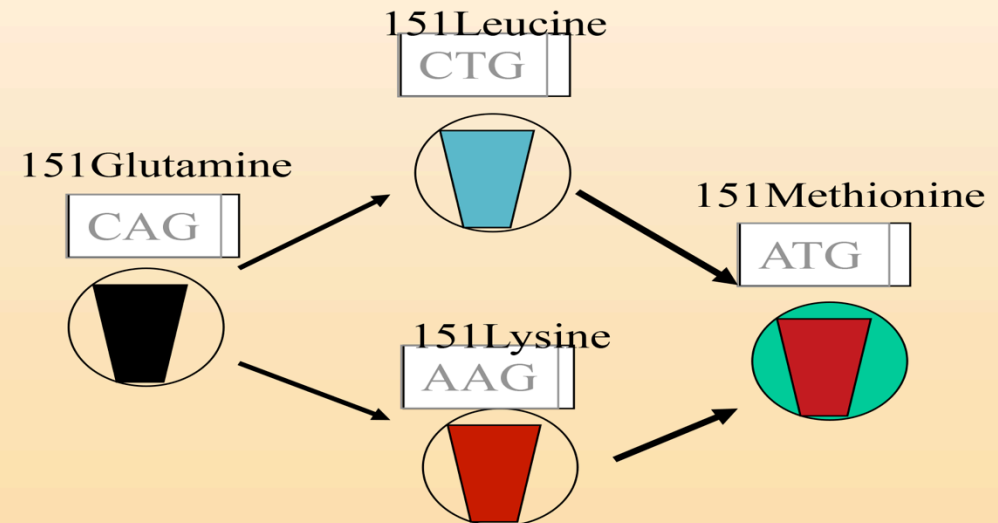
MUTANTS ARE LIKELY TO EXIST PRIOR TO THE THERAPY



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



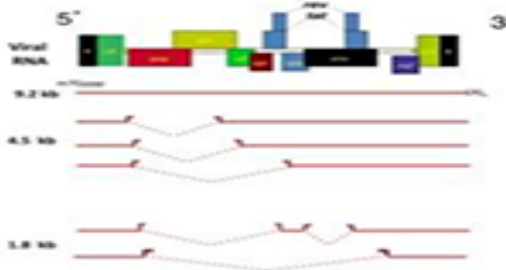
Transcription

Figure 5

Transcription



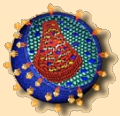
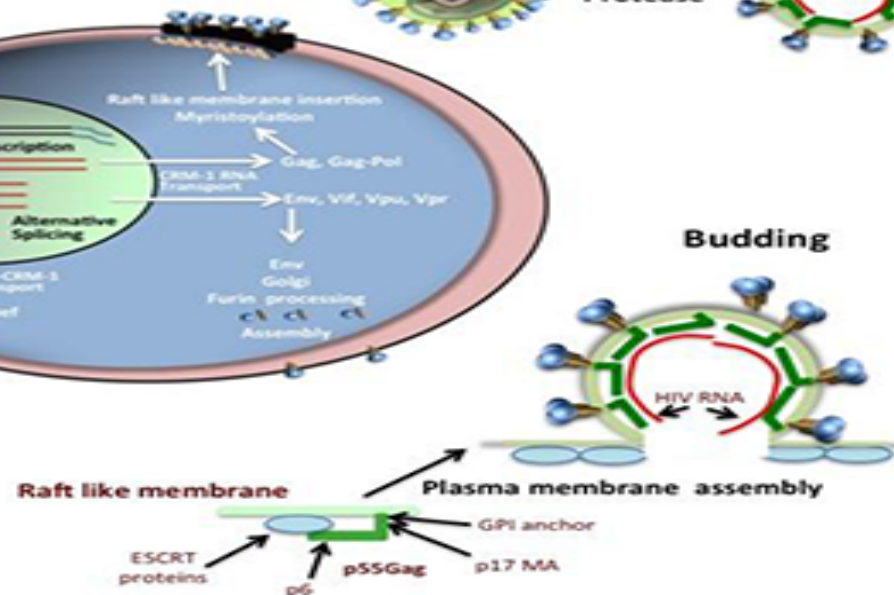
Post-Transcriptional Processing



Maturation



Budding

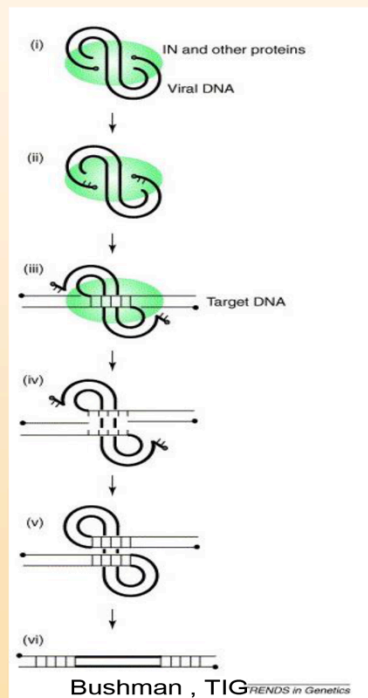


HIV Dynamics and Replication Program

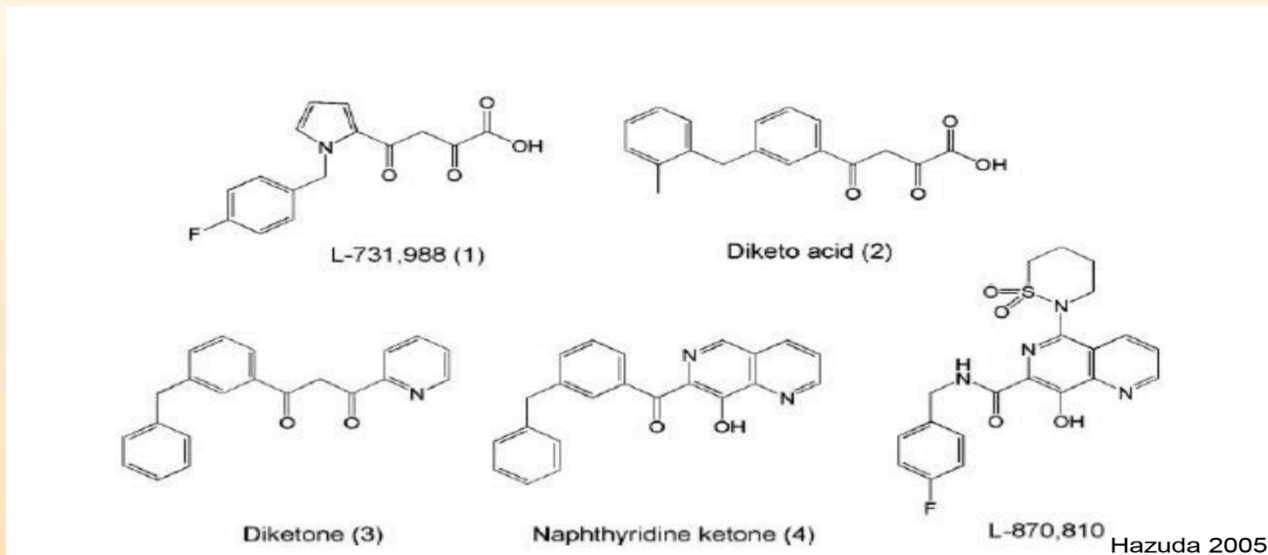
NCI-Frederick

Integration

Integration

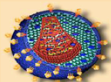


Multistep reaction

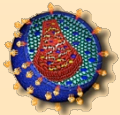
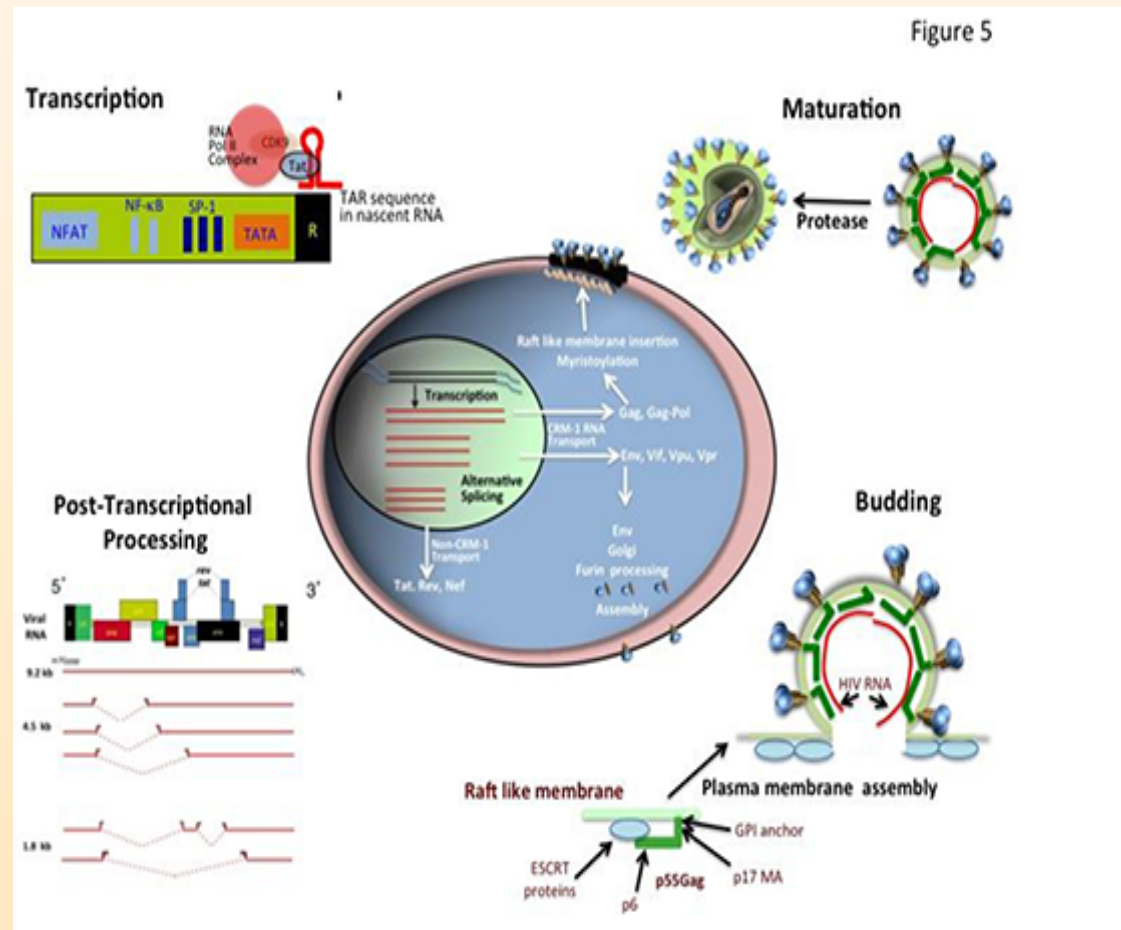


Hazuda 2005

Strong inhibitors

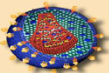
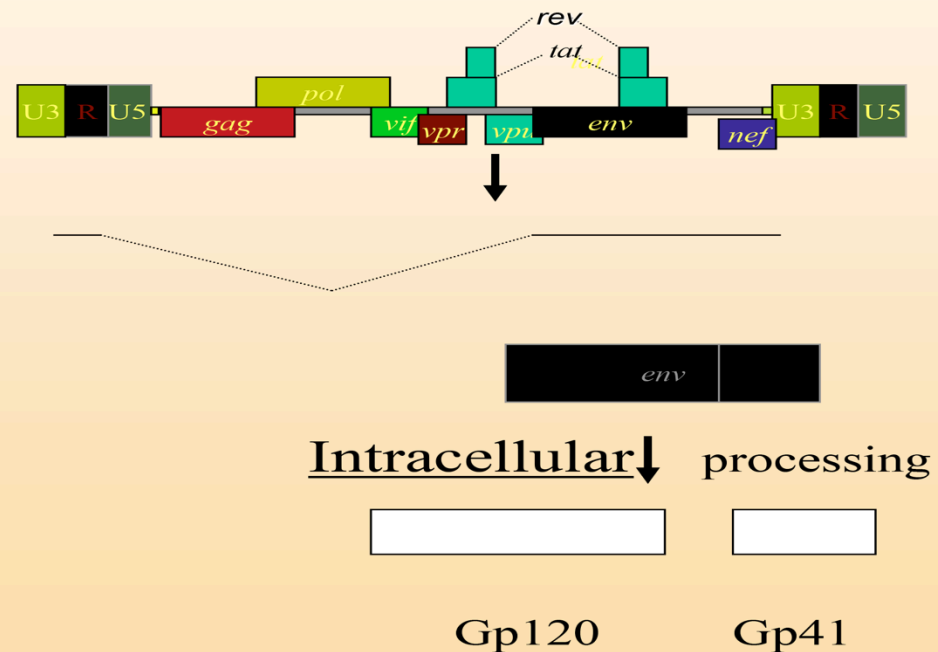
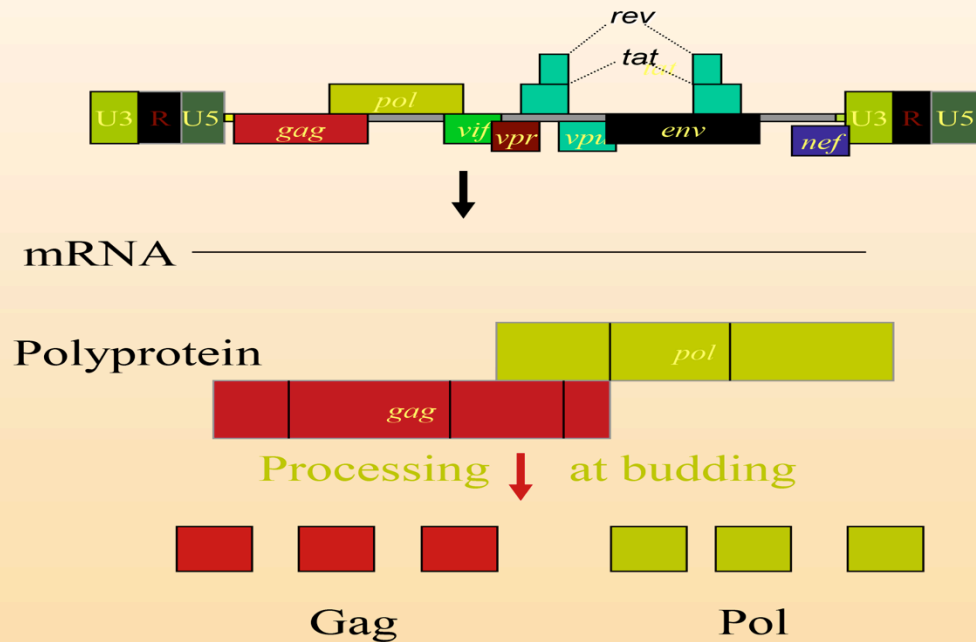


Maturation



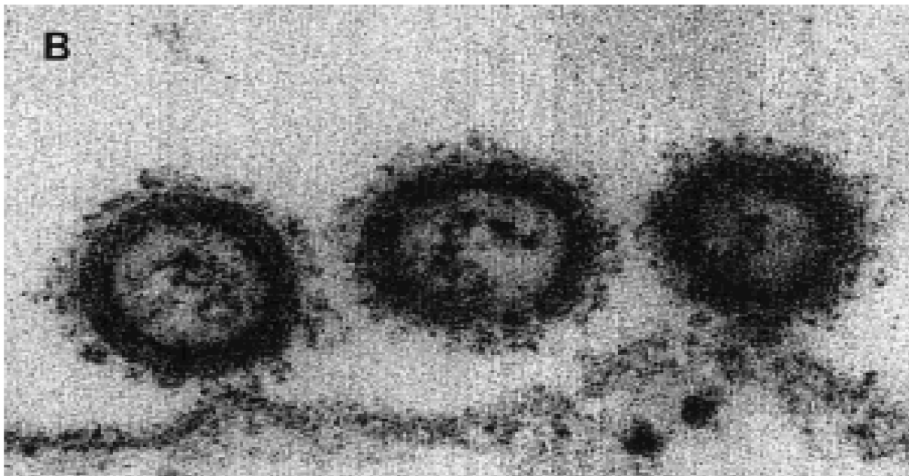
Translation

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



HIV Particle Maturation

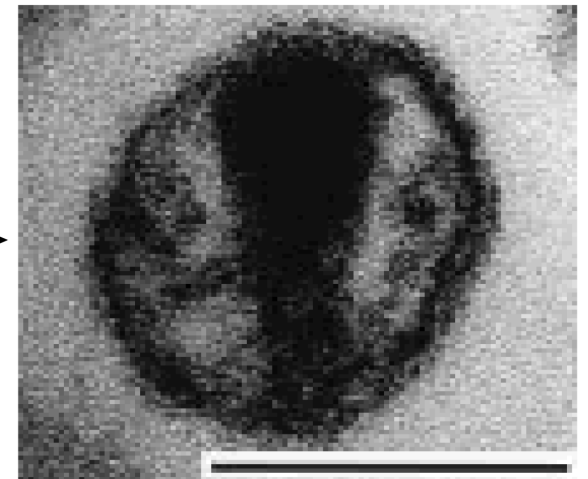
HIV Particle Maturation



Immature Particle
Noninfectious



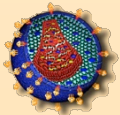
HIV
Protease



Mature Particle
Infectious

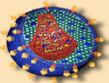
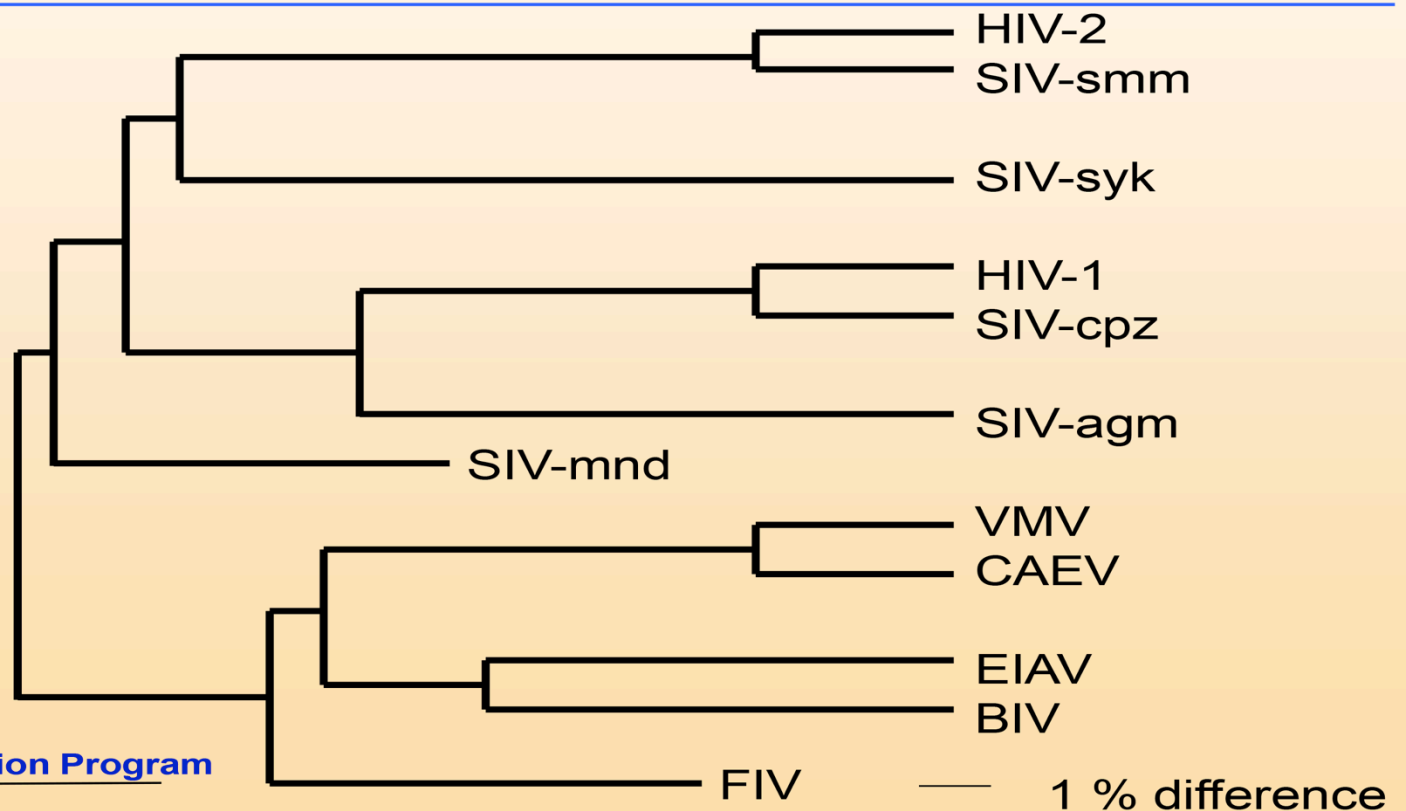
Retroviruses

- **Retroviruses in Human Populations**

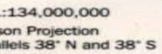


Lentivirus relationships

Lentivirus Relationships



HTLV DISTRIBUTION



HTLV-II Endemic (Amerindian and Pygmy tribes)

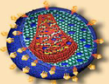
June 1998

Boundary representation is not necessarily authoritative

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**



Higher Primate Origins of HIV-1

Higher Primate Origins of HIV-1

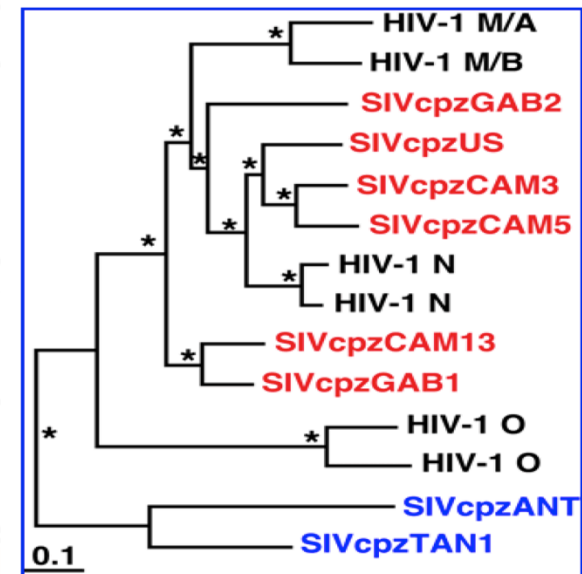
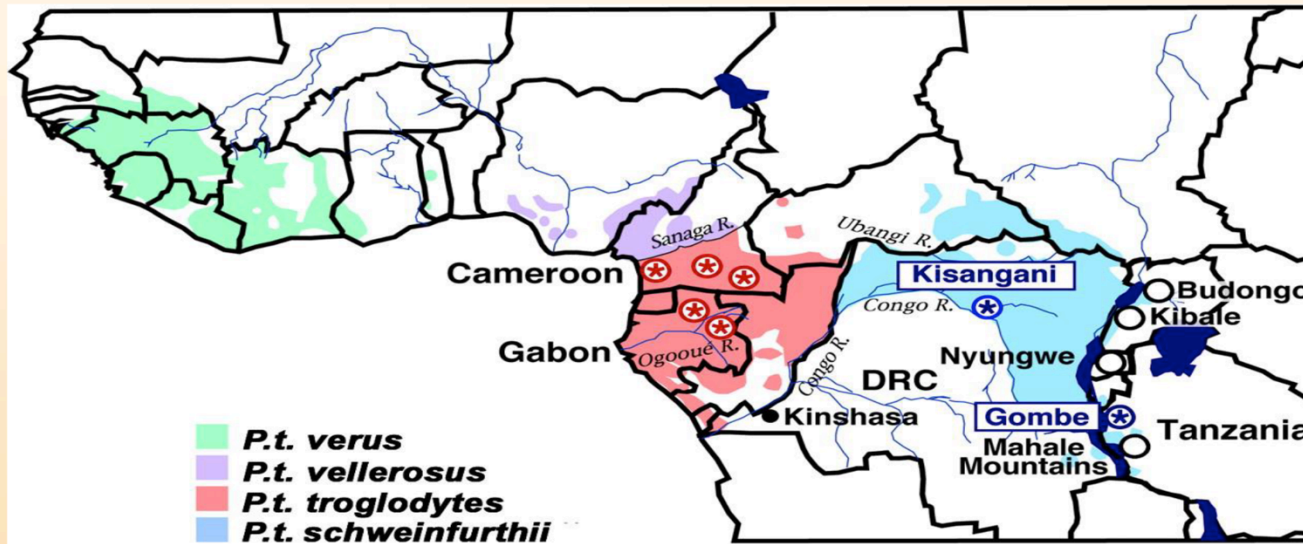
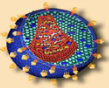
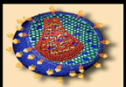


FIG. 2. Evolutionary relationships of SIVcpz and HIV-1 strains based on maximum-likelihood phylogenetic analyses of full-length envelope protein sequences (adapted from ref. 10). SIVcpz strains from *P. t. troglodytes* and *P. t. schweinfurthii* are highlighted in red and blue, respectively. Representative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



Bushmeat trade in Africa

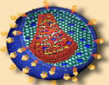
Bushmeat Trade in Central and West Africa



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**



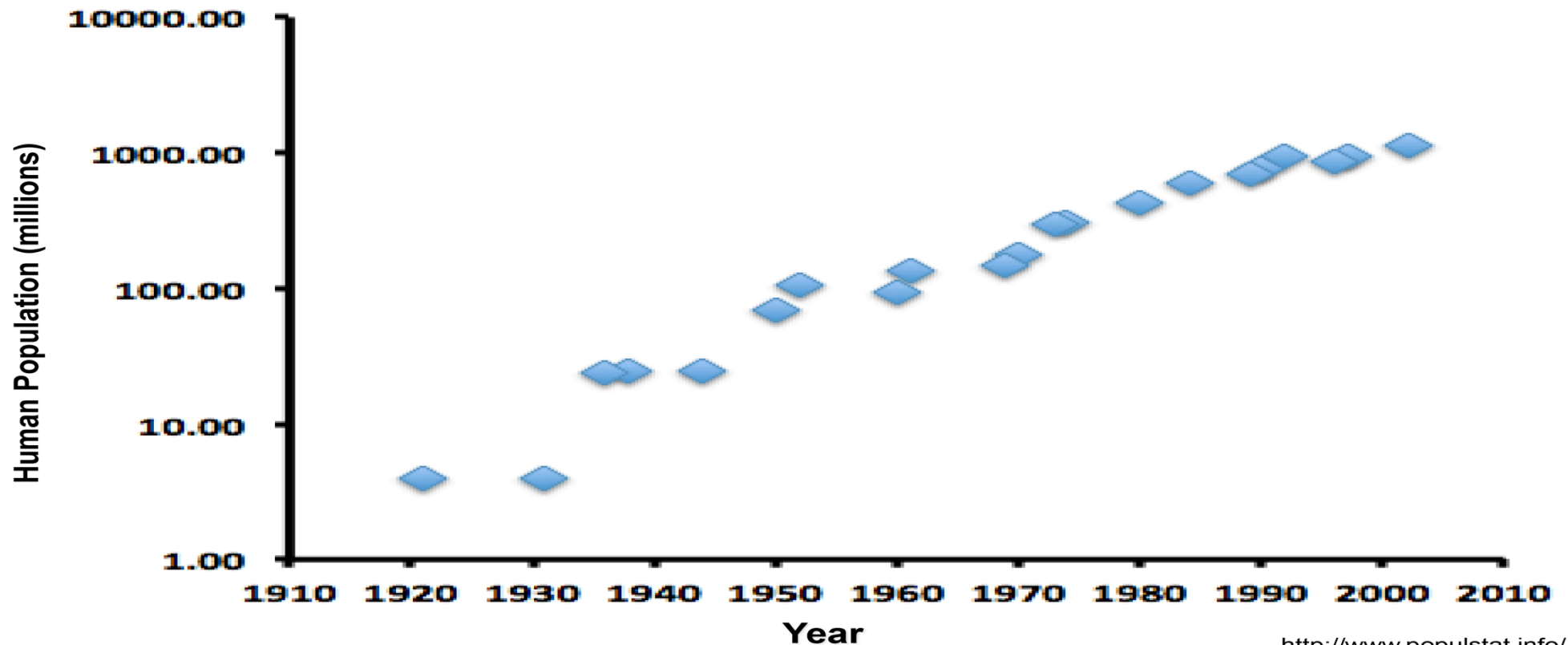
HIV Spread

A historical map of Africa, likely from a 19th-century travelogue. The map is oriented with North at the top. It features a grid of latitude and longitude lines. The continent of Africa is outlined in black, with internal borders highlighted in yellow, green, and red. A label 'AFRICA' is enclosed in an oval in the upper right corner. The map is surrounded by a decorative border.



HIV and population expansion

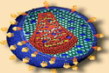
Zoonotic Transmission of HIV Coincides with Population Expansion in Africa



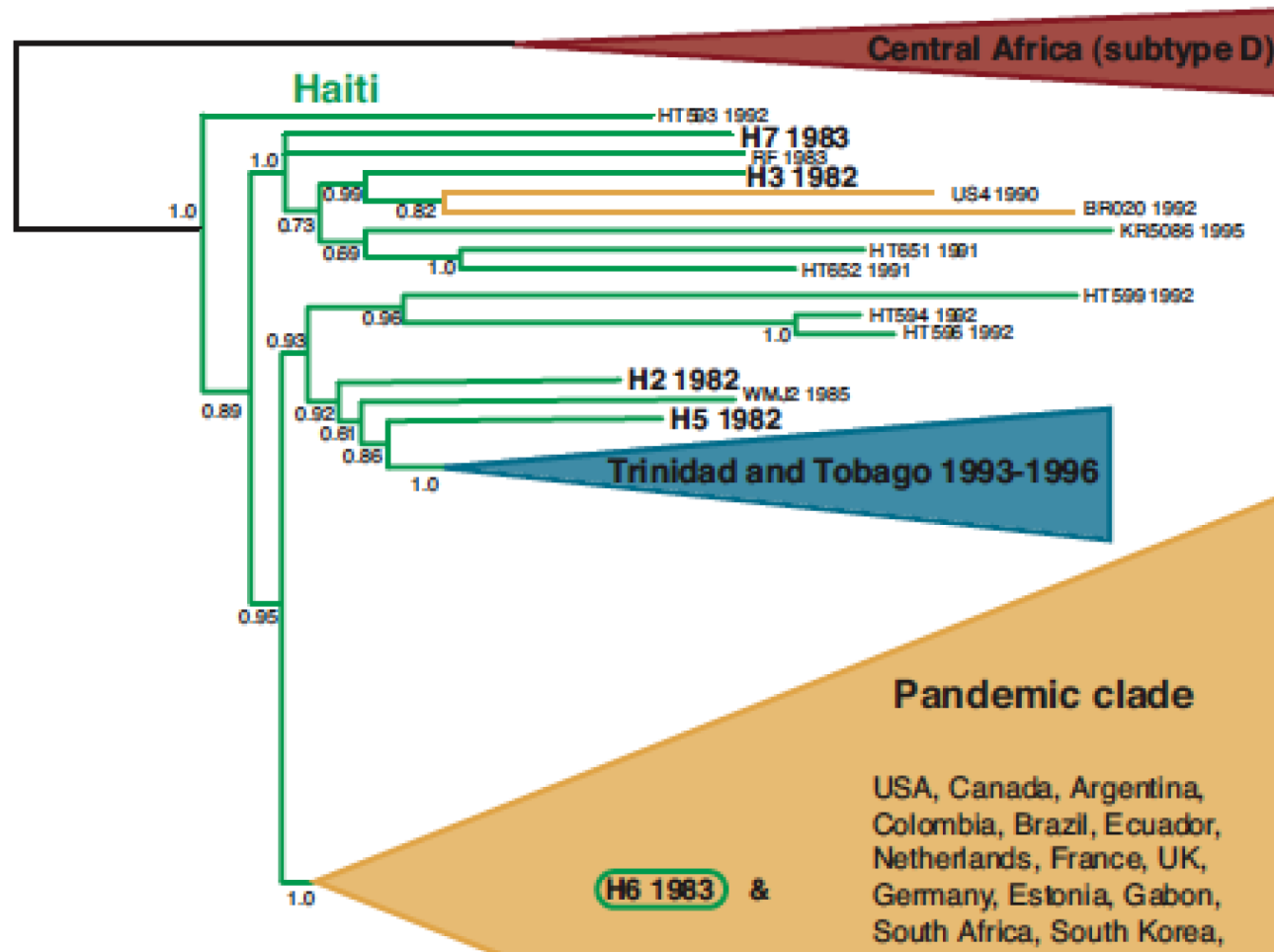
HIV spread

HIV Spread

- **Biologic**
 - **Blood and body fluid**
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 - **Mother to Child**
- **Non-Biologic**
 - **Political**
 - **Economic**
 - **Multiple Epidemics**



HIV evolution

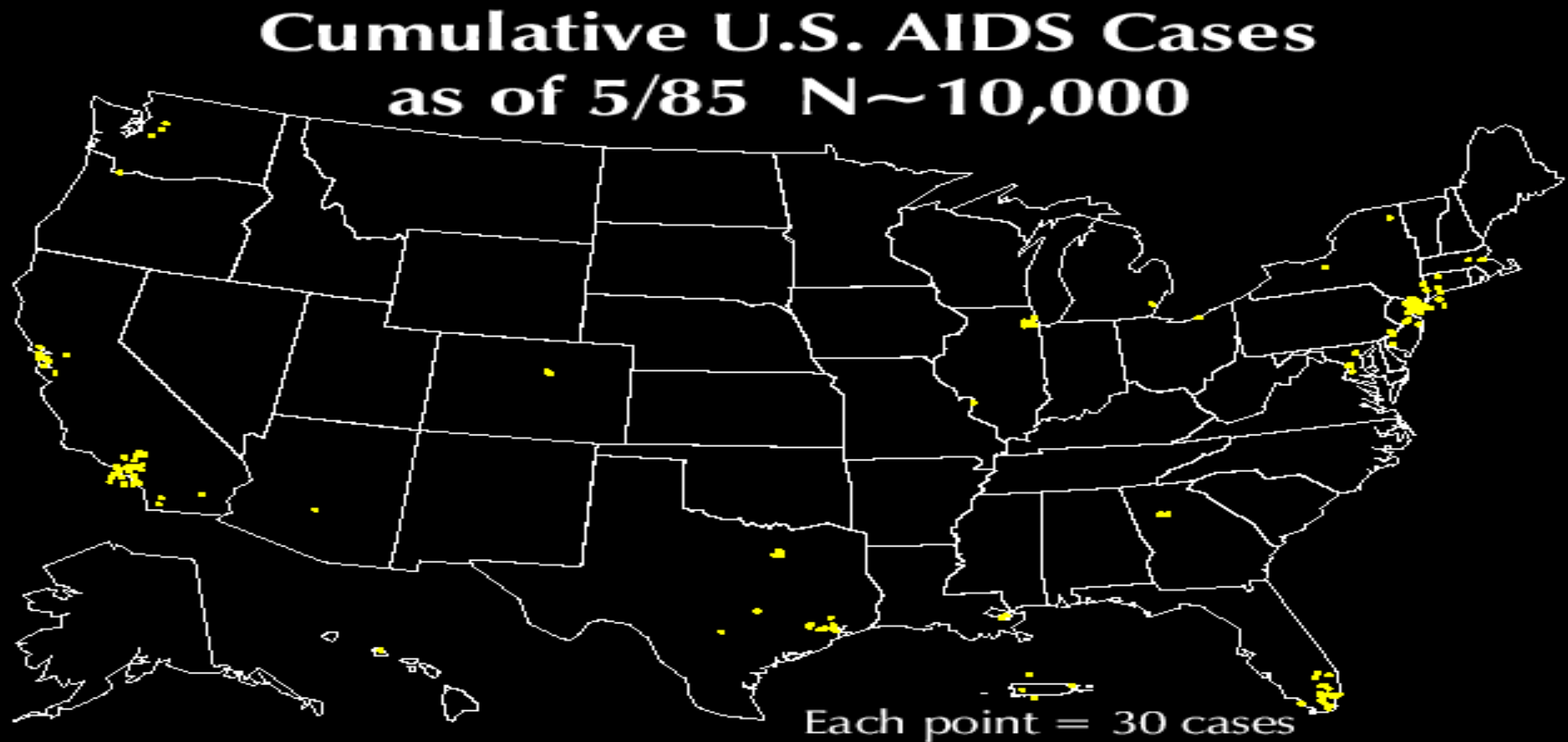


Cumulative U.S. AIDs cases as of 2/83 N = 1000

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

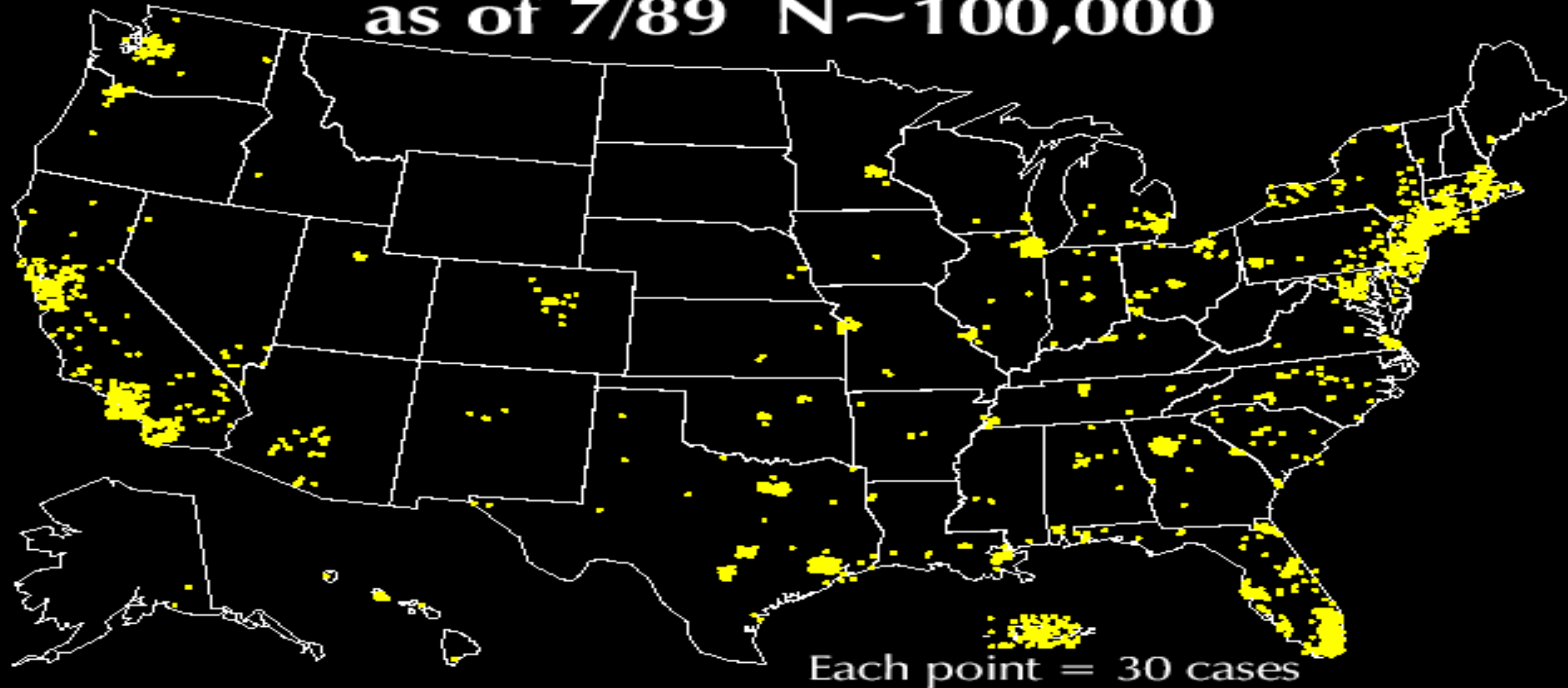


Cumulative U.S. AIDs cases as of 5/85 $N = 10000$

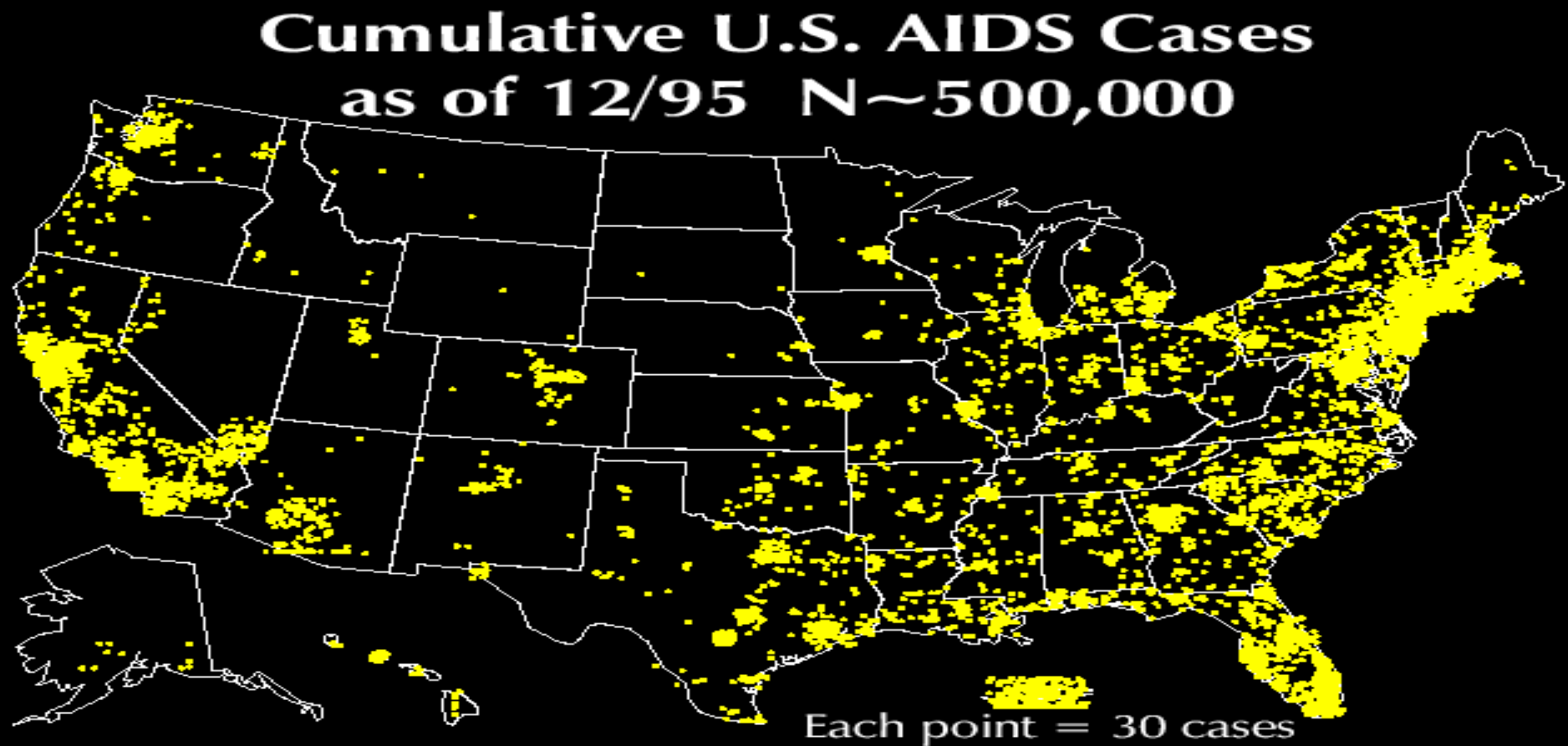


Cumulative AIDS cases as of 7/89 N = 100000

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



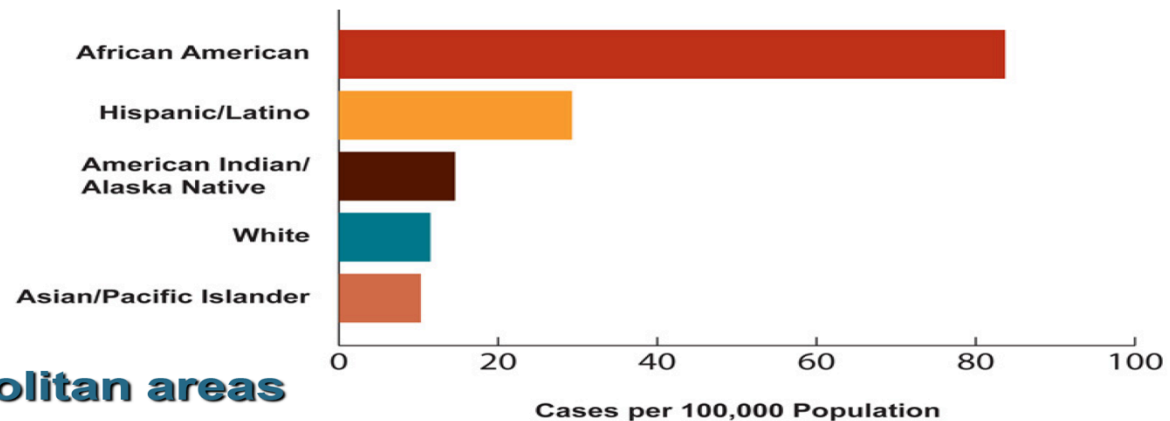
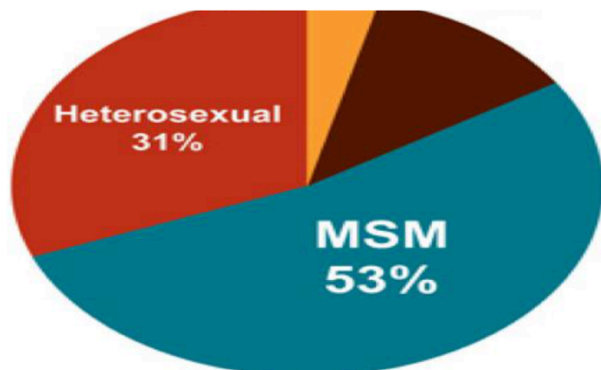
Cumulative AIDs cases as of 12/95 N = 500000



New cases of AIDS

New cases of HIV/AIDS—USA

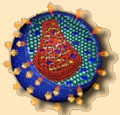
Estimates of New HIV Infections in the United States, 2006, By Transmission Category



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

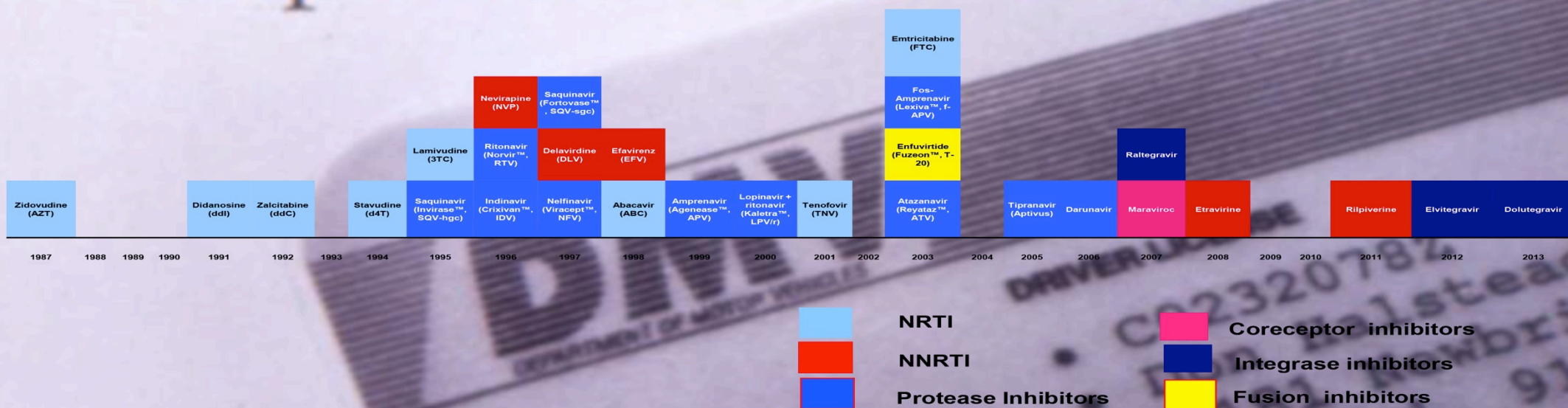


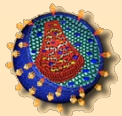
HIV Dynamics and Replication Program

NCI-Frederick

AIDS drugs

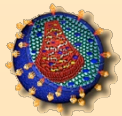
If you get the AIDS virus now,
you and your license could
expire at the same time.





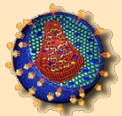
HIV Dynamics and Replication Program

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HIV Dynamics and Replication Program

NCI-Frederick

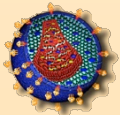


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Key Advances in HIV Therapy

- 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



Summary

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- **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**

