

# **Retroviruses**

**TRACO Lecture Series**

**November 8, 2021**

**Frank Maldarelli**

**HIV Dynamics and Replication Program**

**NCI**

# **Retroviruses**

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

# Adults and Children Estimated to be Living with HIV 2020



**Total: 37.7 million [30.2 million – 45.1 million]**

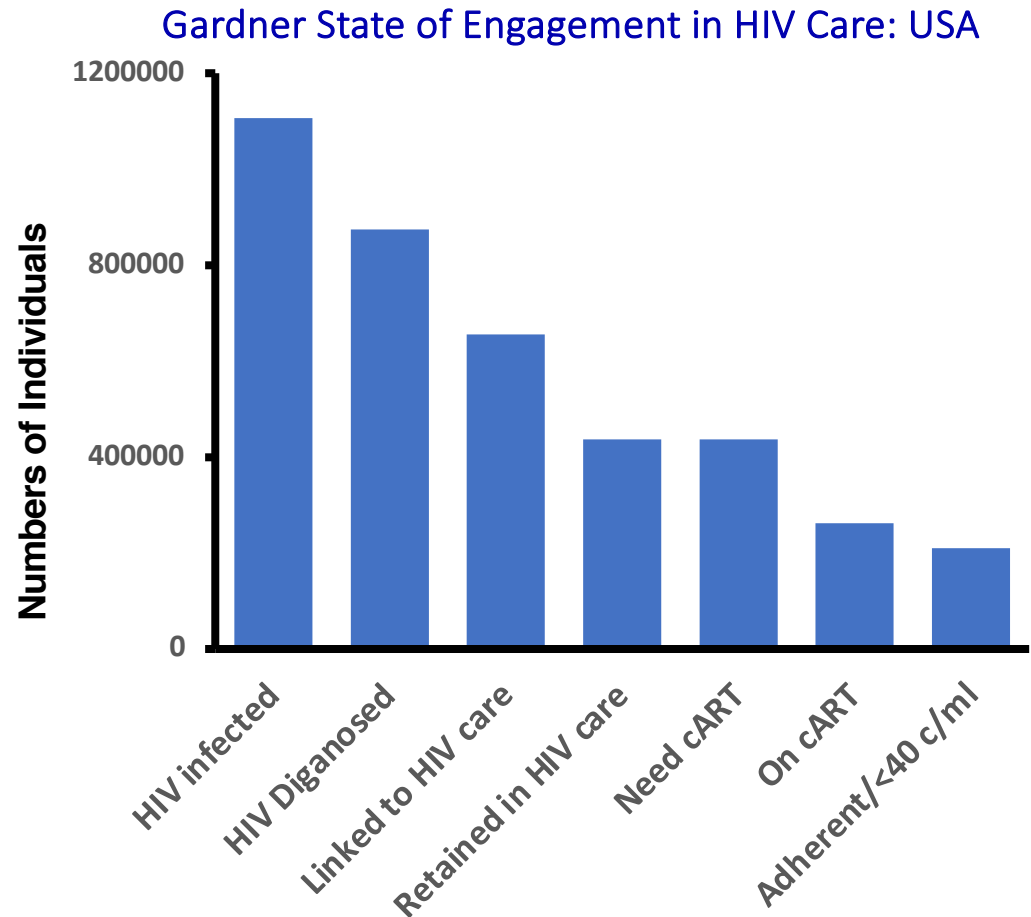
**27.7 million accessing antiretroviral therapy**

# 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



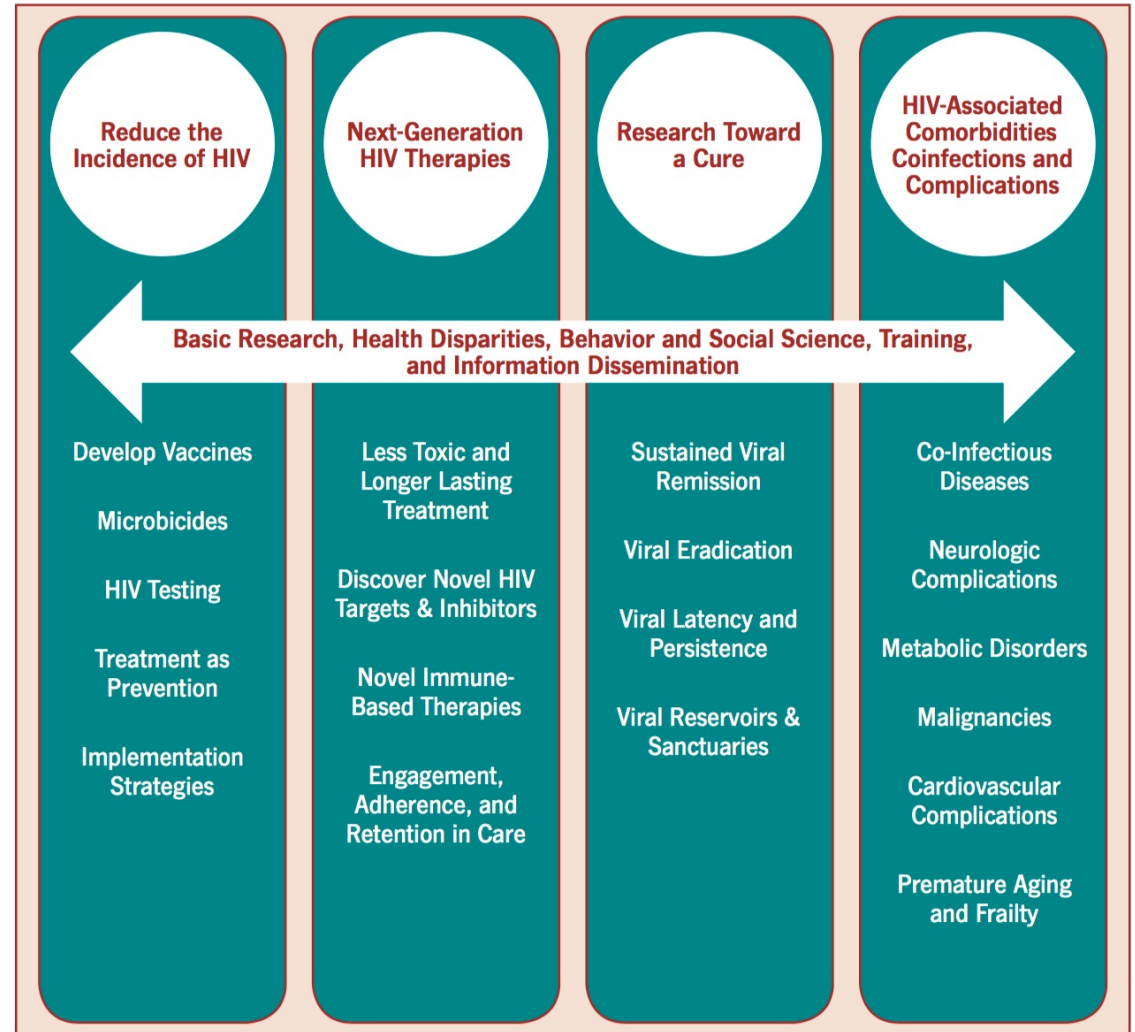


# The Need is Great: Research Priorities Office of AIDS Research 2018

## Distinct Areas

Cut across disciplines

## Specific Goals



# Retroviruses

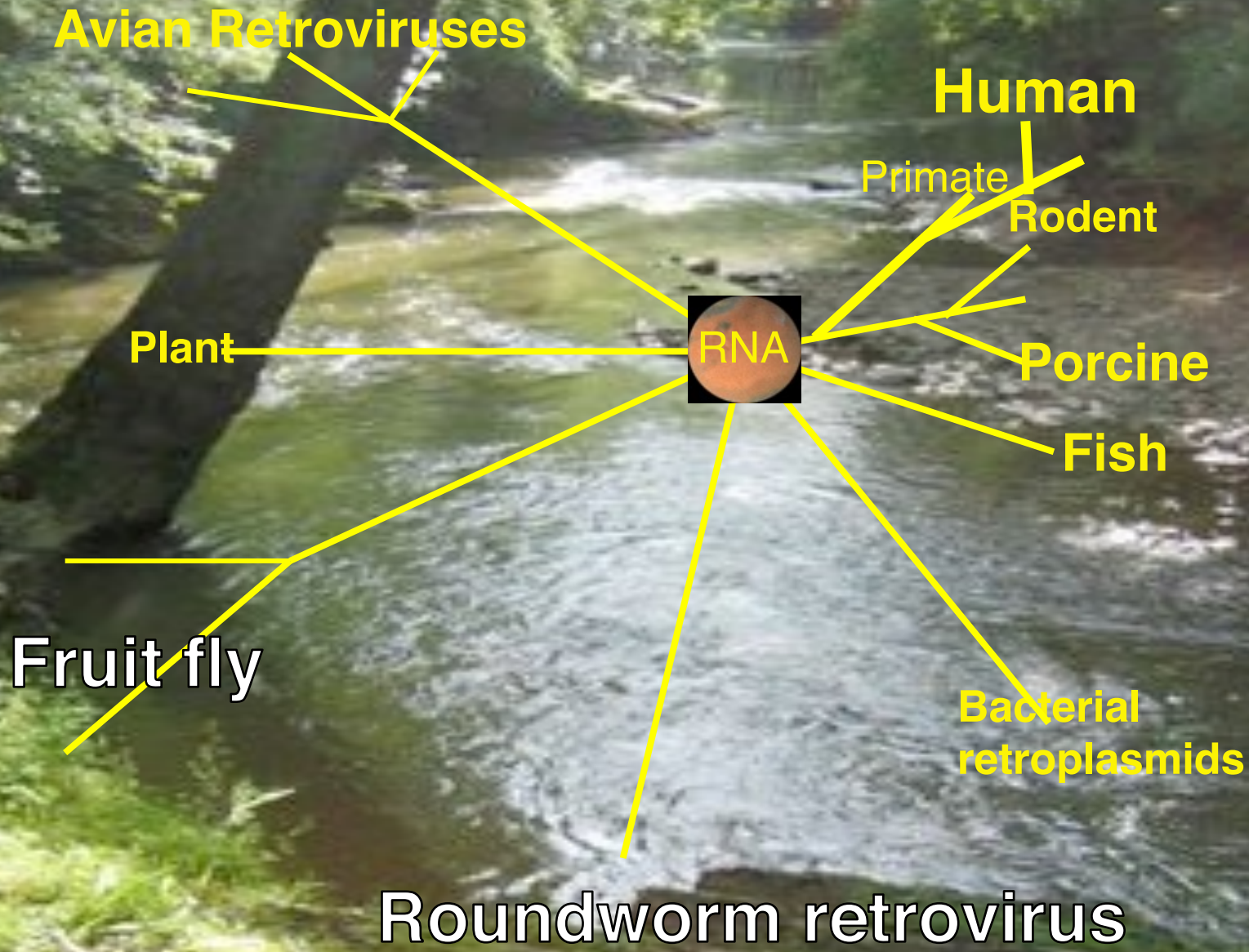
- Introduction
- **Molecular Biology/Replication**
- Retroviruses in Human Populations
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# Retroviruses

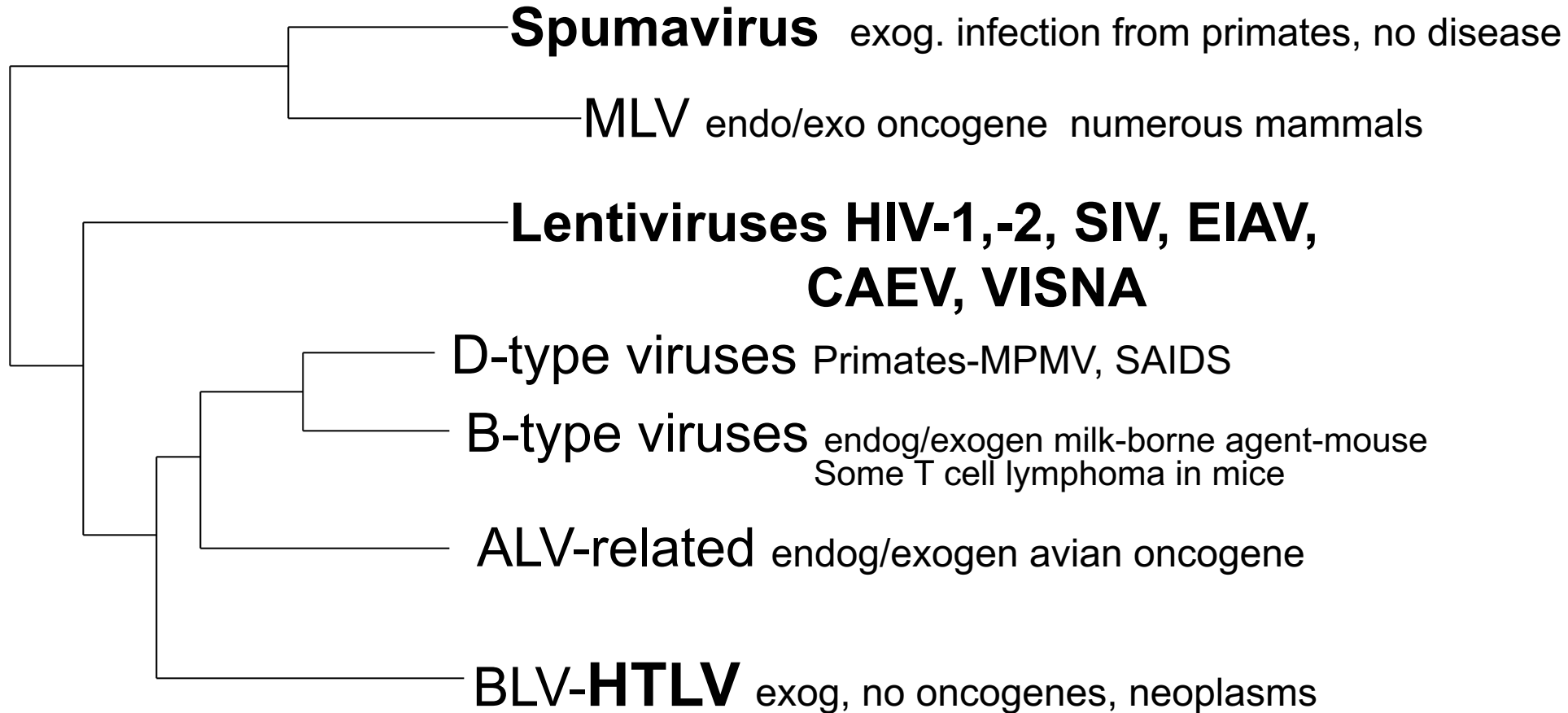
**A group of RNA viruses that replicate via a DNA intermediate using Reverse Transcriptase.**

An answer to an ancient challenge  
A different paradigm for replication  
Transition from RNA world?

# Reverse Transcriptase and Retroelements are all around you



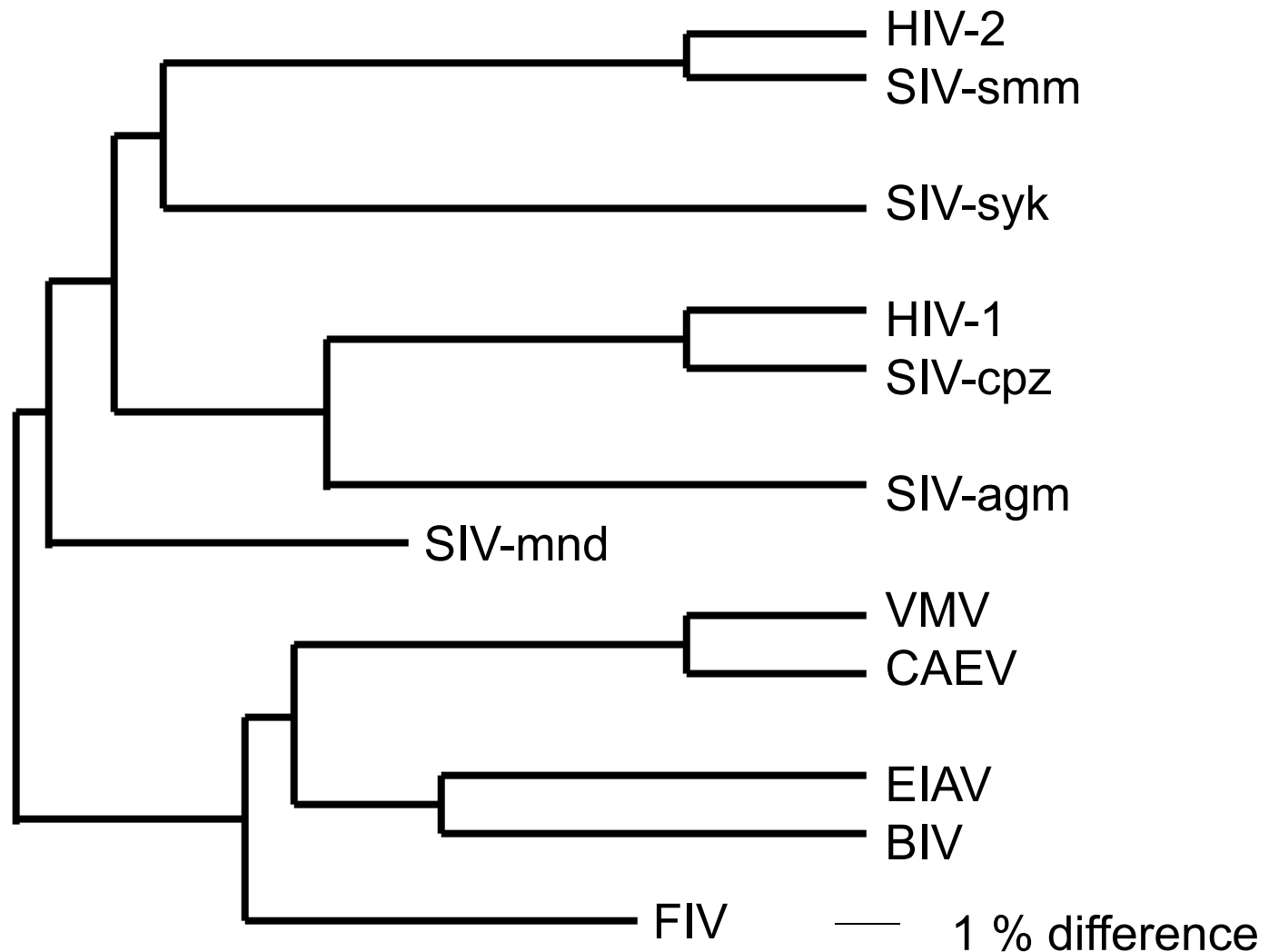
# Retroviruses Are Found in Virtually Every Vertebra



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

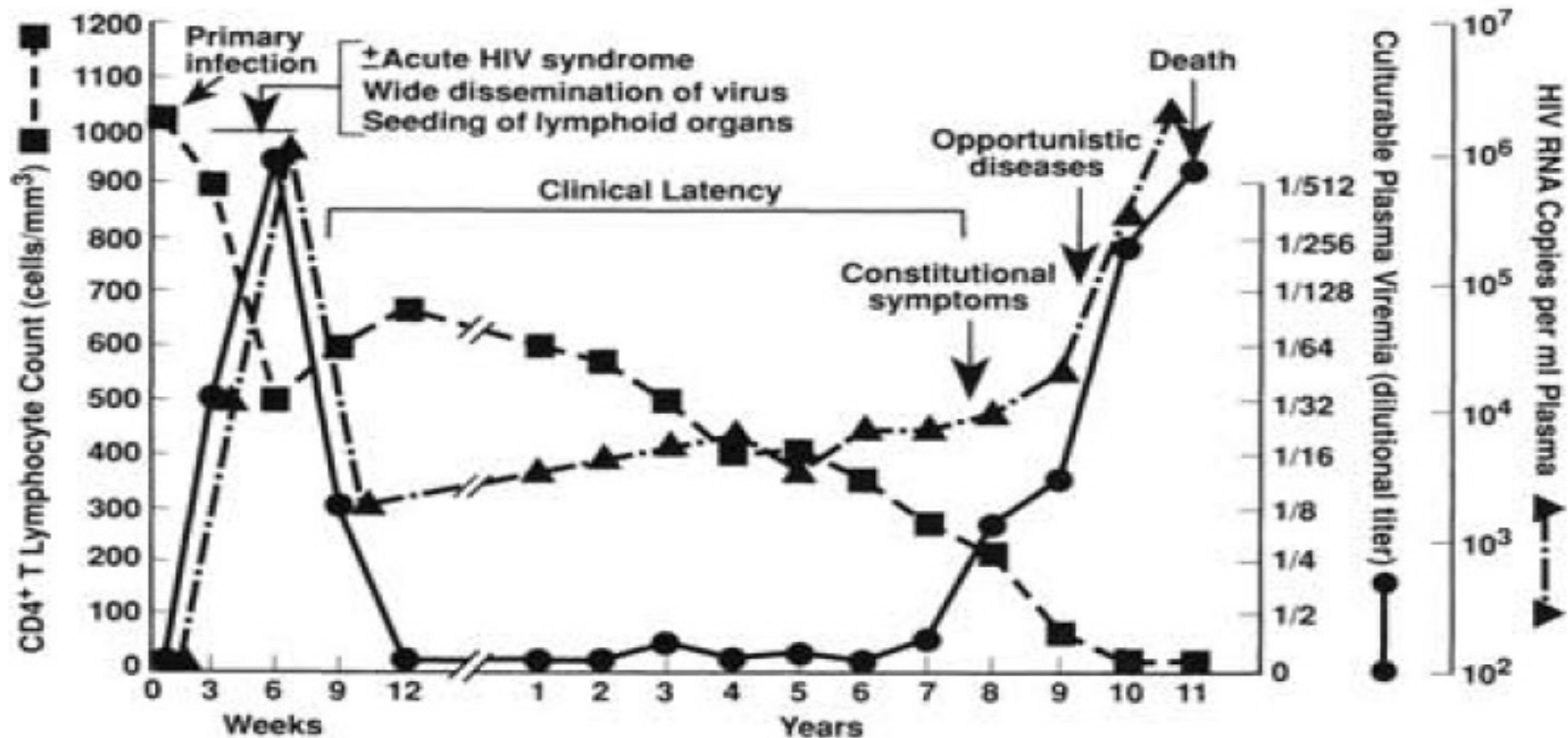
# Lentivirus Relationships

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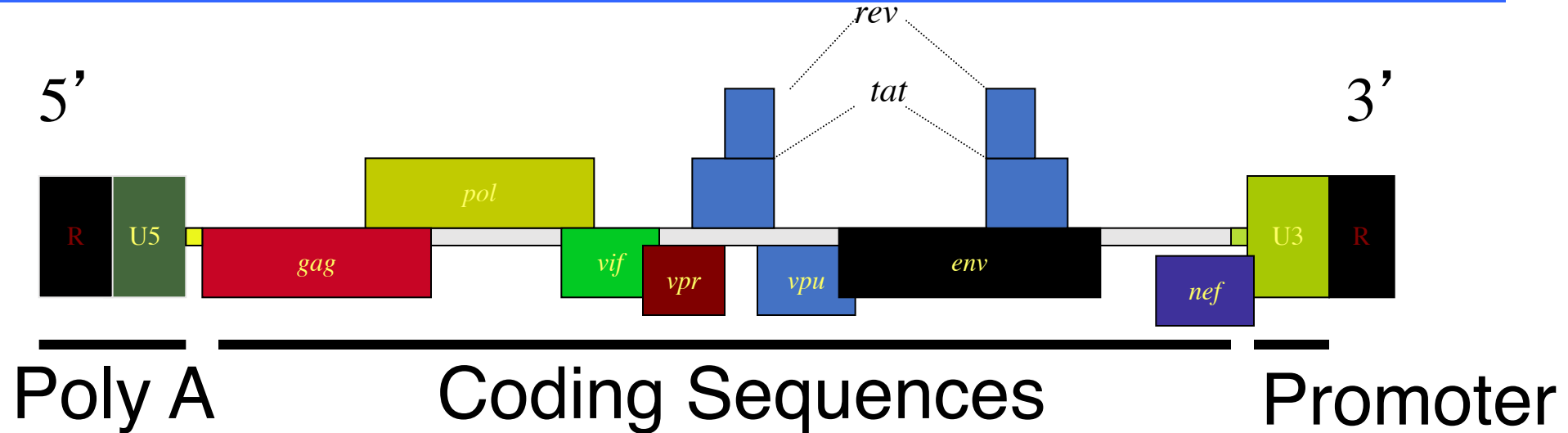




# HIV Infection Course



# Retroviruses Conventions

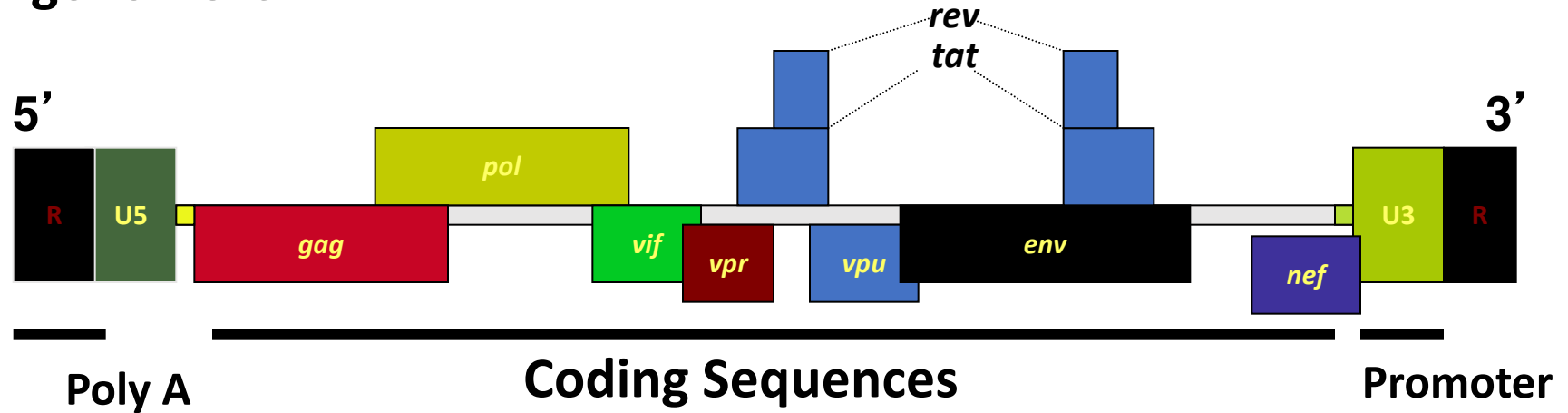


**Names of genes in lower case *italics*, e.g., *pol*, *env***  
**Protein gene products are capitalized, e.g., Reverse Transcriptase, Gp120**

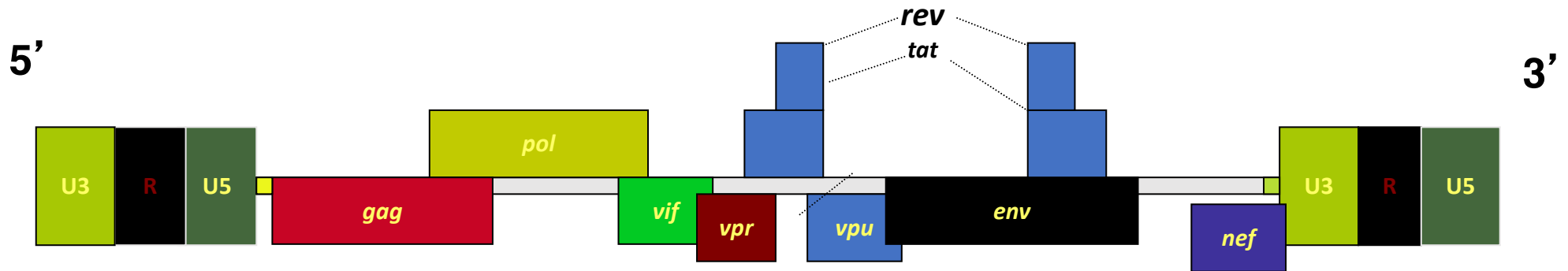


# Retroviruses Conventions

The viral genome is RNA



The integrated genome is called the provirus



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

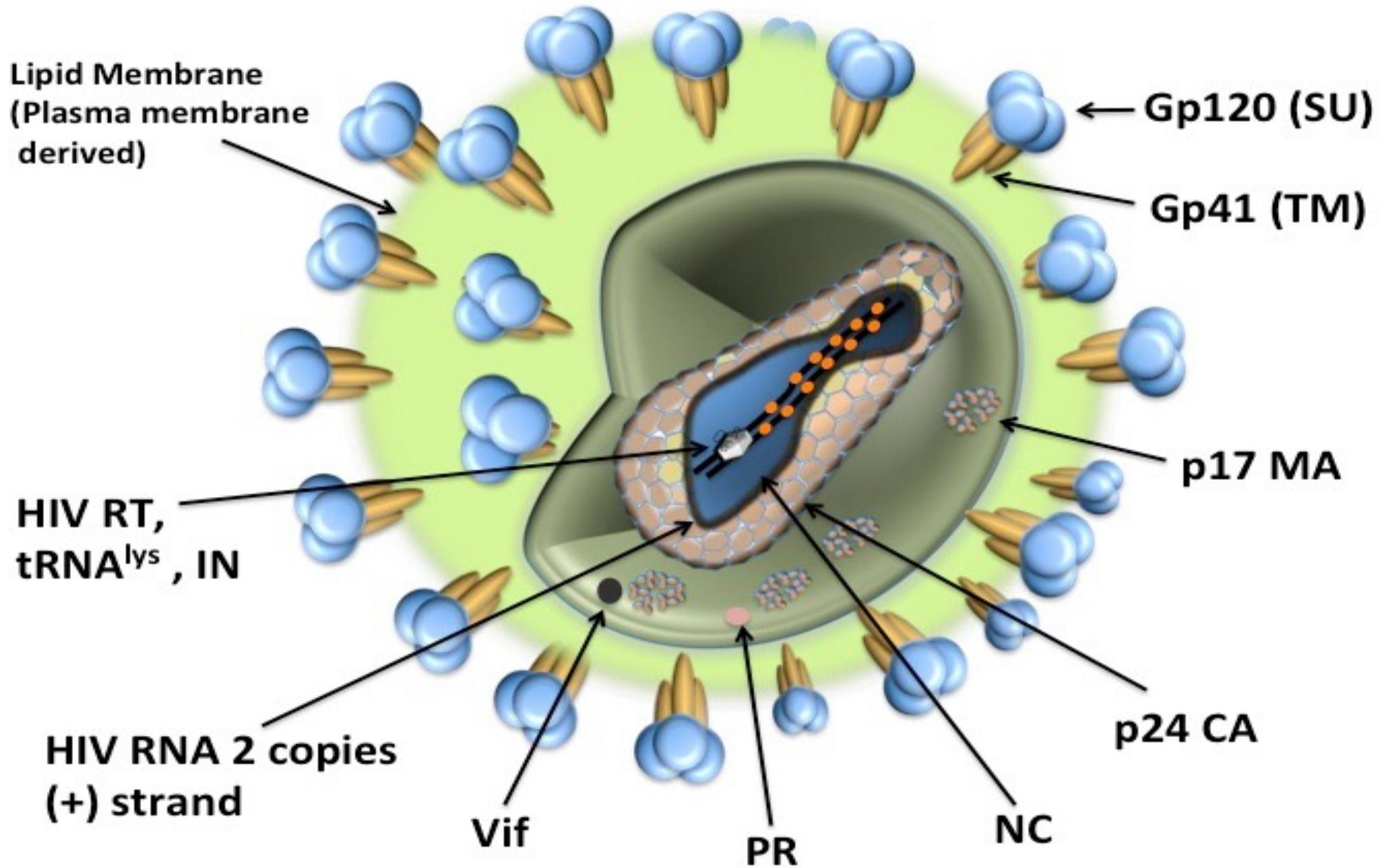
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# Retroviruses Glossary

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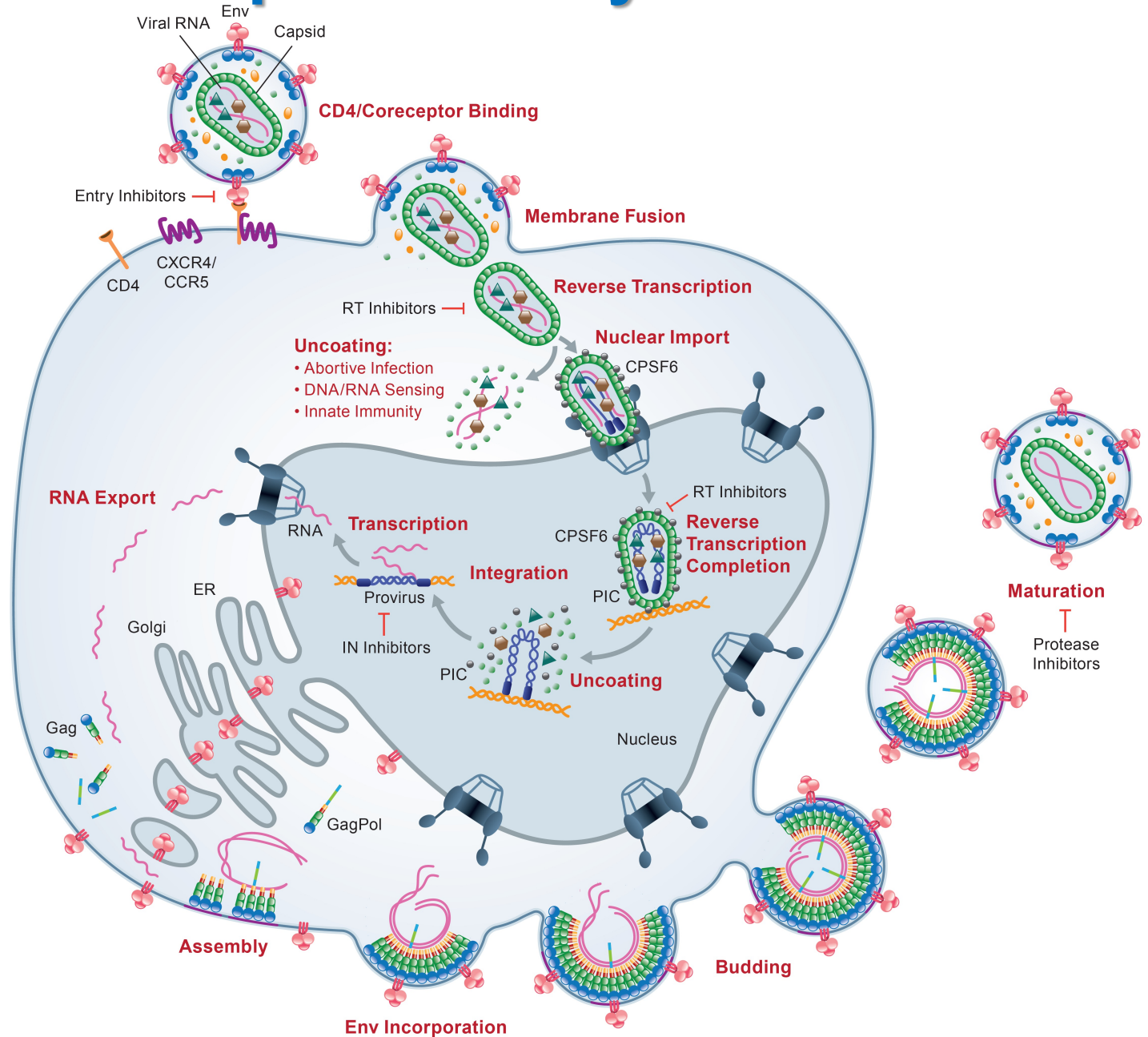
- *gag: group antigen*
- *pol: polymerase*
- *env: envelope*
- *tat: Transactivator*
- *rev: Regulator of Expression of Virion proteins*
- U3: unique sequence in 3' region
- U5: Unique sequence in 5' region
- R: Repeat sequence
- PBS Primer binding site for initiation of RT
- Ppt: polypurine tract primer for RT
- TAR: Tat activating sequence
- RRE: Rev responsive element
- Provirus: copy of retrovirus that is integrated into host genome

# HIV Virion



# HIV-1 Replication Cycle

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



# HIV Attachment and Entry

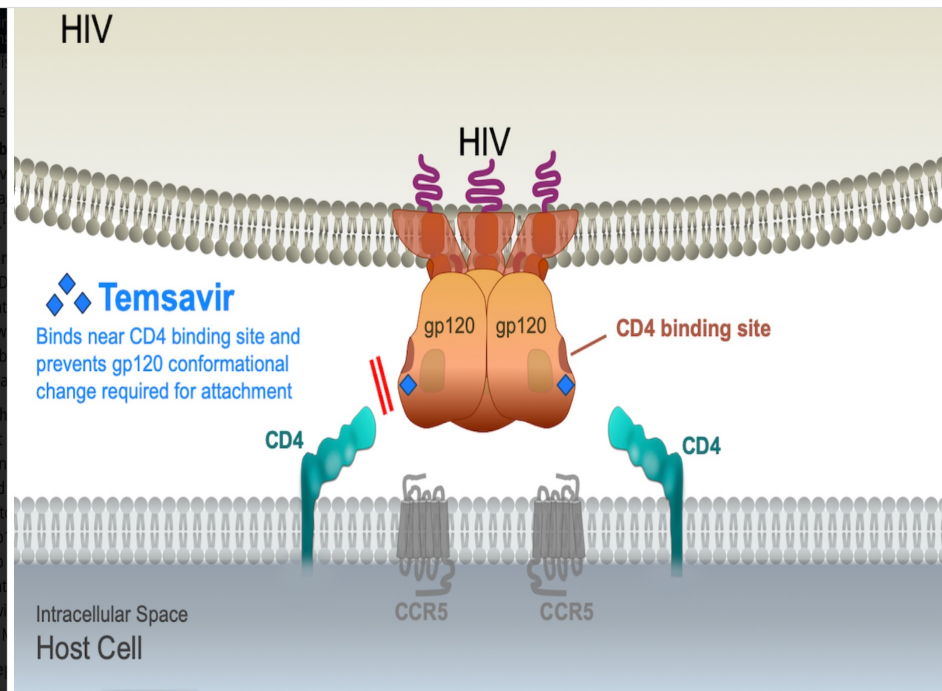
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- **Virus Factors**
  - Attachment: Env glycoprotein gp120
  - Entry: Env glycoprotein gp41
- **Host Cell Factors**
  - Receptor
    - CD4
  - Co-receptor (major)
    - CXCR4
    - CCR5

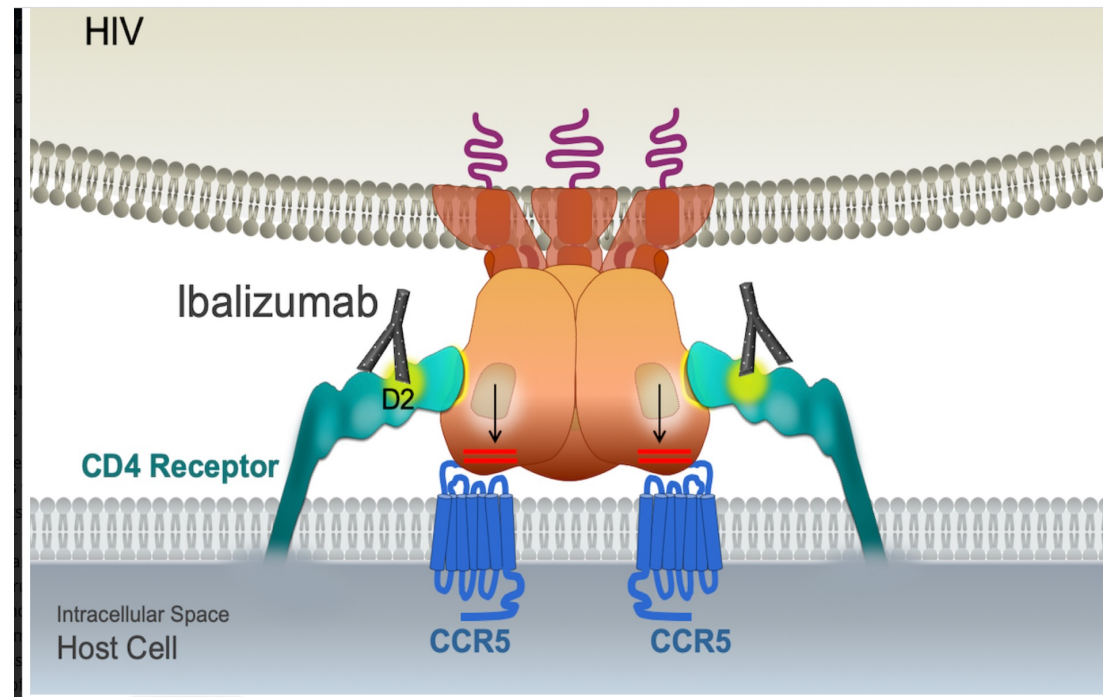


# Blocking the HIV Receptor: Ibalizumab and Fostemsavir

## Fostemsavir

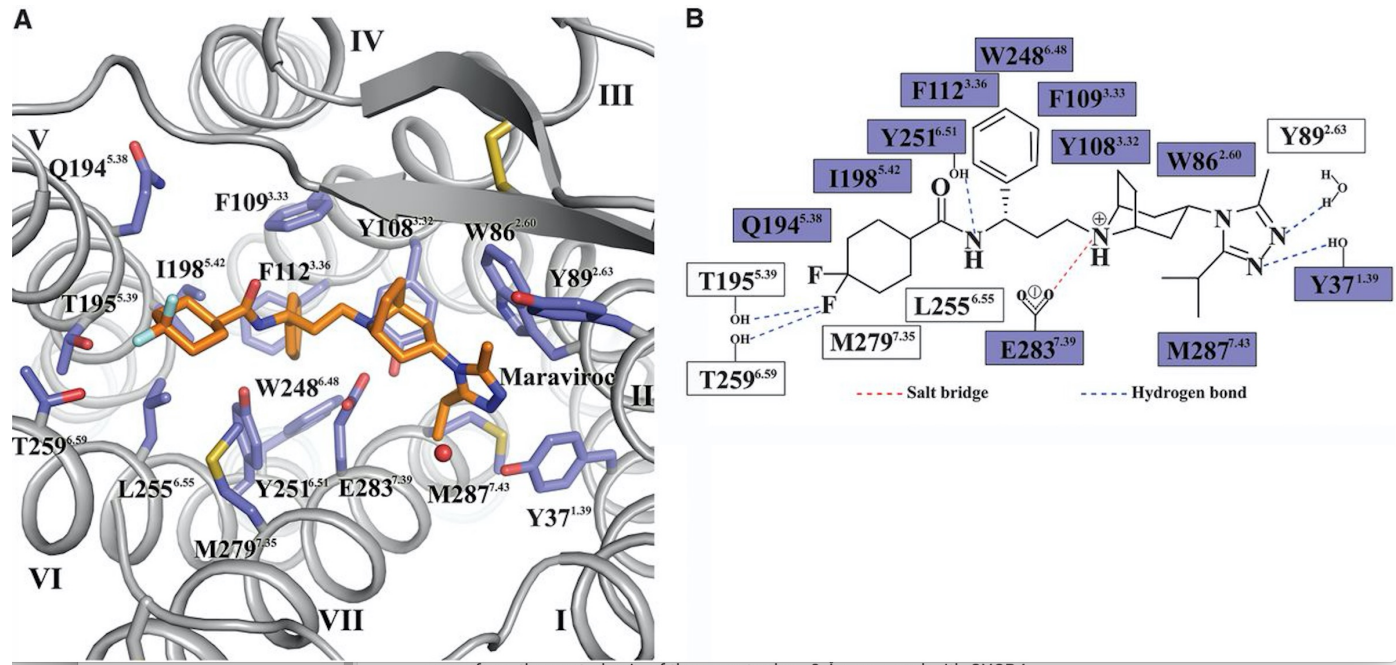
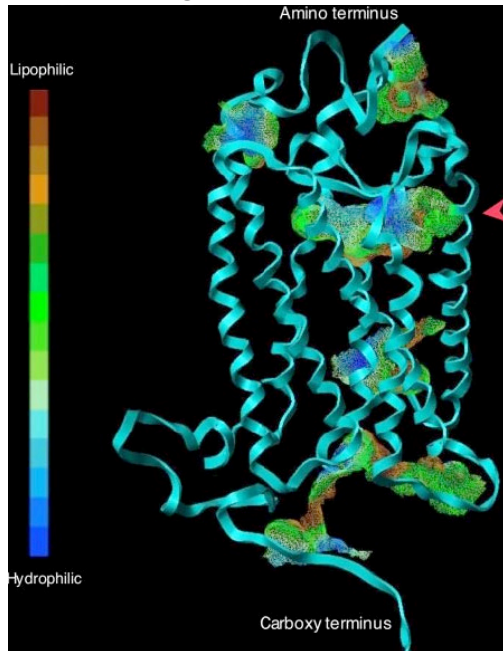


## Ibalizumab



# Blocking the HIV Coreceptor: Maraviroc

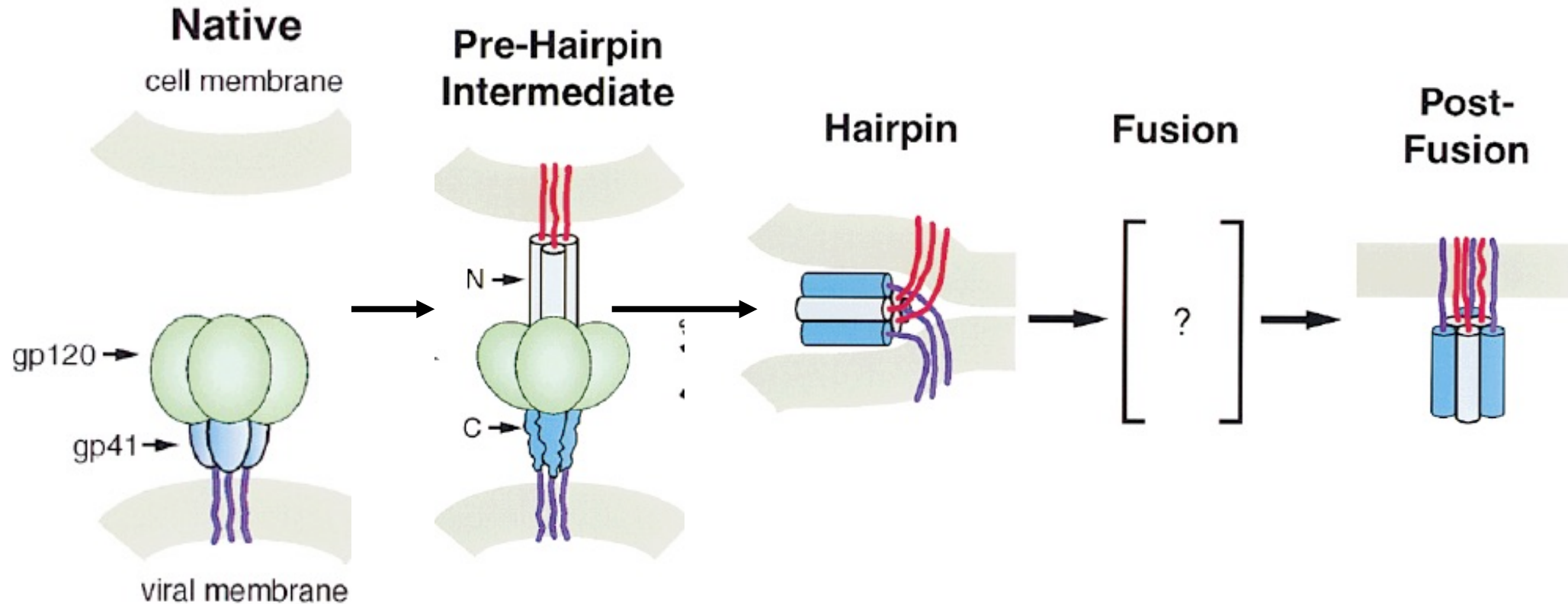
## Crystallographic Structure



- 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: Enfuvirtide

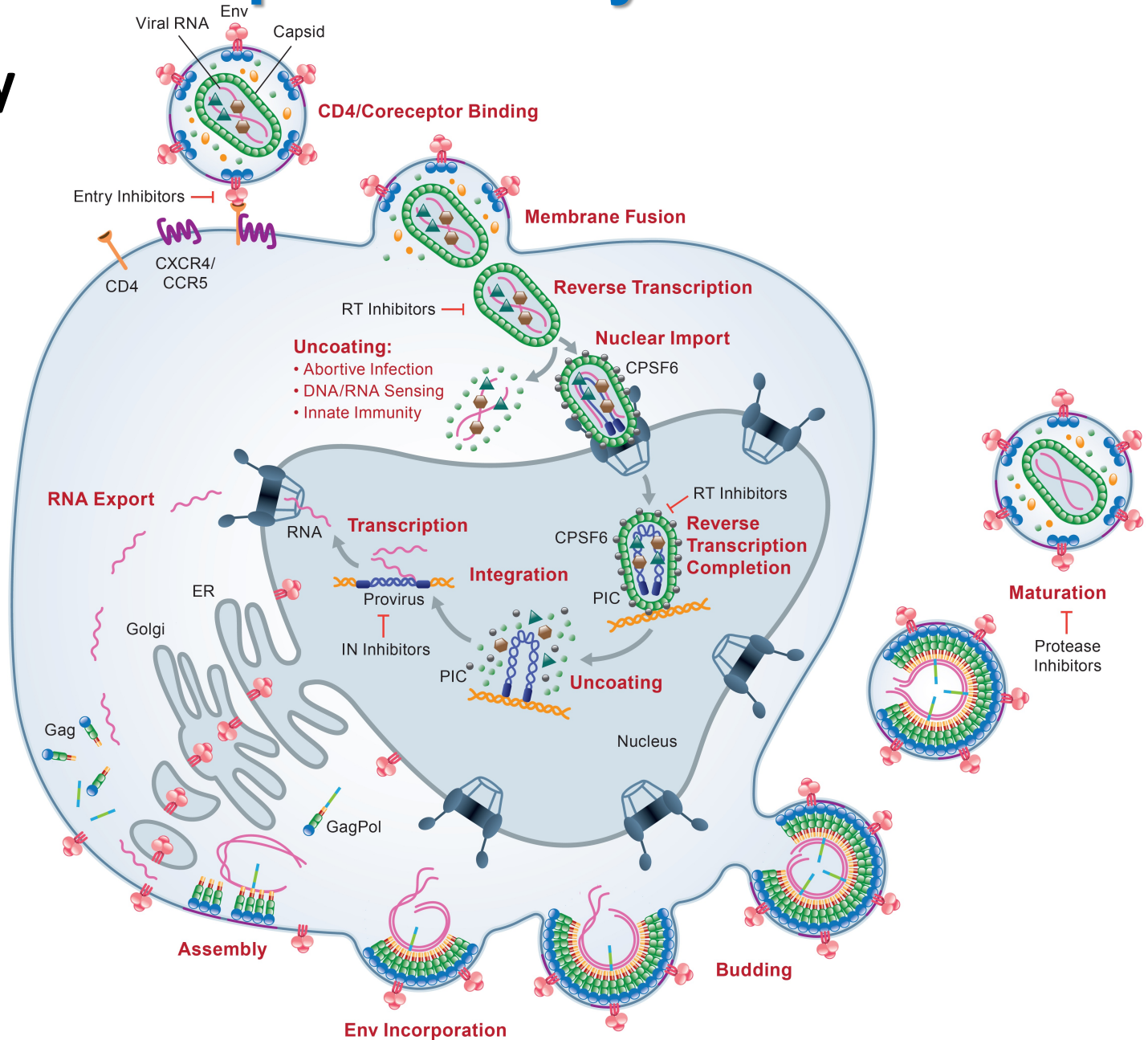
## Blocking a Spring-Loaded Mechanism





# HIV-1 Replication Cycle

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



# **HIV Post – Entry Events**

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- **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

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## Host Trim5 Alpha

**VIRUS**

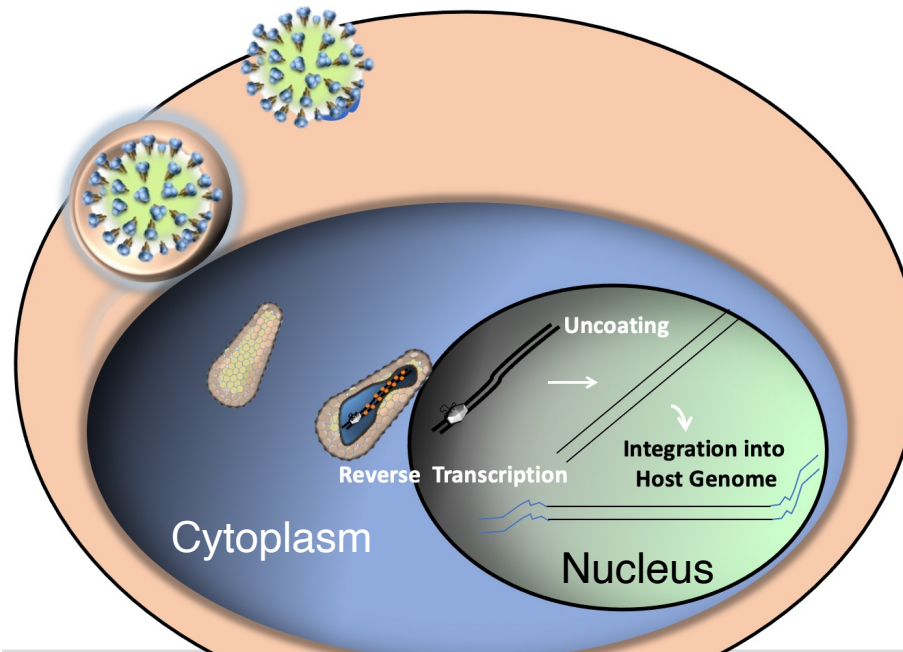
	Human	Chimp	Monkey
HIV	Infection	Infection	<b>NO INFECTION</b>
SIV Chimp	<b>INFECTION</b>	Infection	Poor infection
SIV Monkey	<b>INFECTION</b>	Poor infection	Infection

# **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

**Generals are Always Fighting The Last War**  
**Evolution can solve HIV Infection but it will take time**

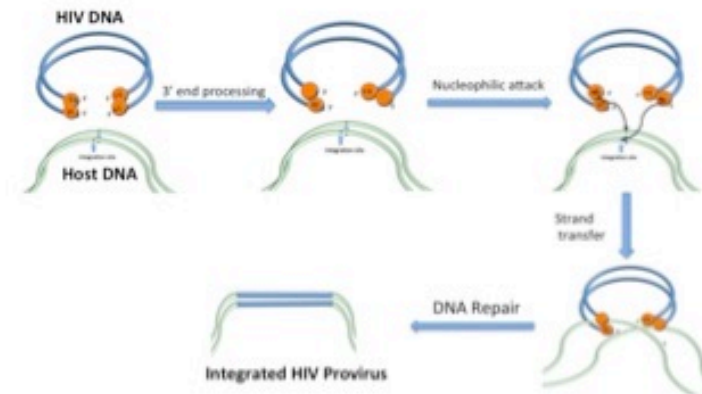
# HIV Reverse Transcription, Uncoating, and Integration



## Reverse Transcription



## Integration



# Reverse Transcriptase Enzymatic Activities

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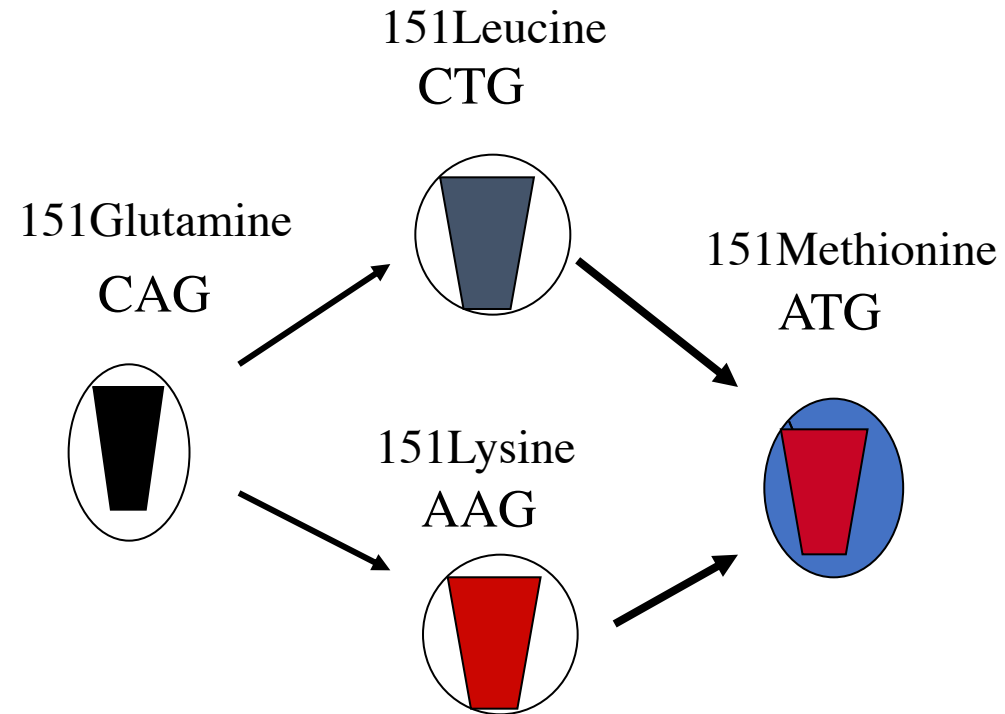
- RNA-dependent DNA Polymerase
- RNase H
- DNA-dependent DNA Polymerase
- Error rate on order of 1-4 / 100,000 bases synthesized
- Recombination occurs during reverse transcription permitting reassortment of sequences
- Replication rapid and error prone

**MUTANTS ARE LIKELY TO EXIST PRIOR TO THE THERAPY**

# Error-Prone HIV Replication is a Pathogenic Determinant

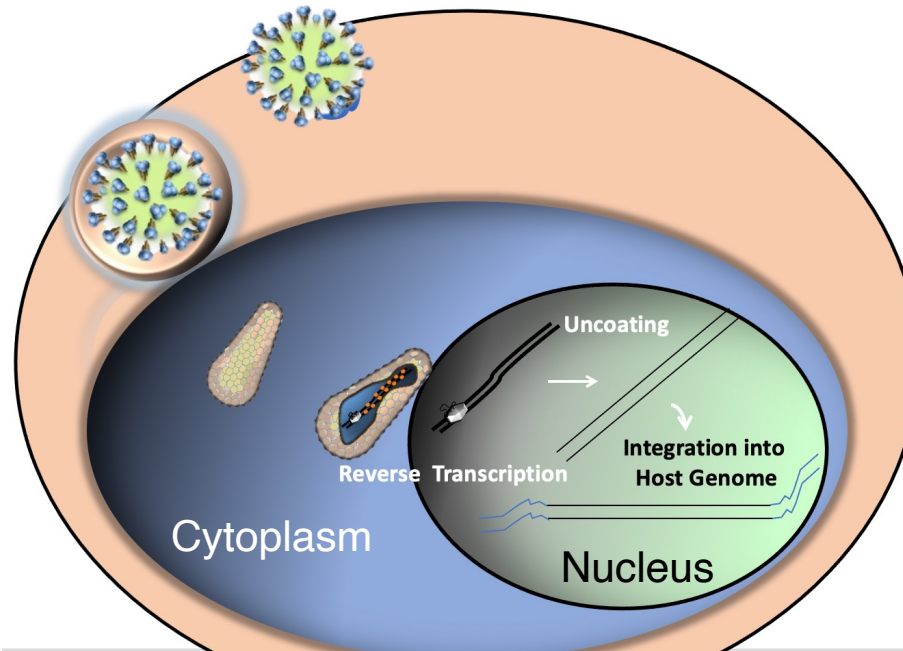
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- Each round of HIV replication generates numerous mutants.
- The ability of the mutants to replicate (viral “fitness”) may vary greatly.
- The virus population can respond rapidly to a selective pressure





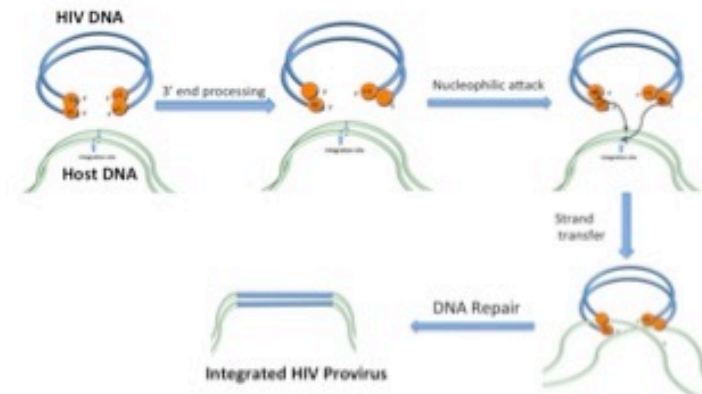
# HIV Reverse Transcription, Uncoating, and Integration



## Reverse Transcription

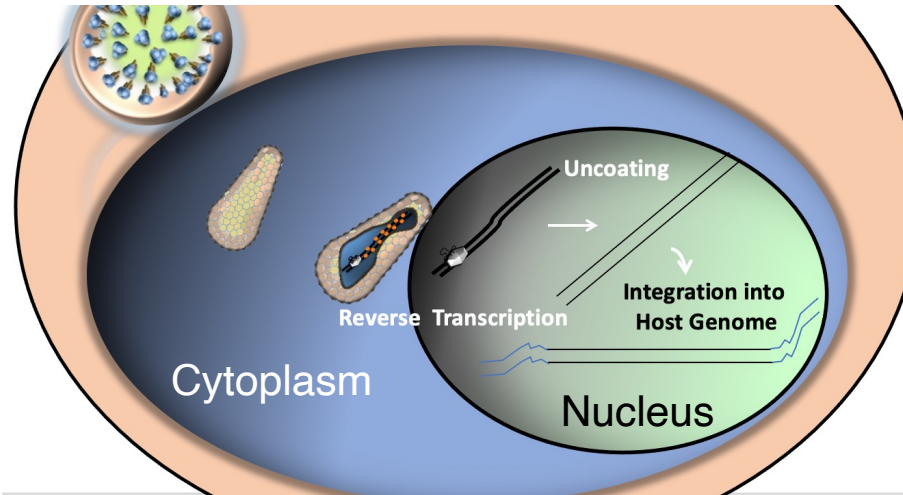


## Integration





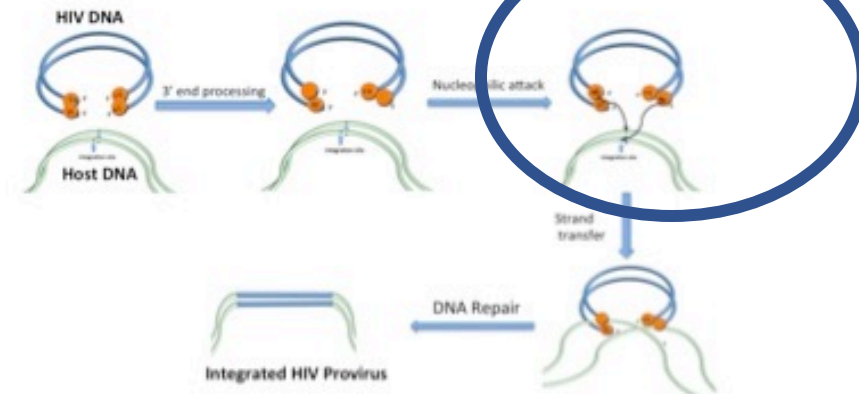
# HIV Reverse Transcription, Uncoating, and Integration



## Reverse Transcription



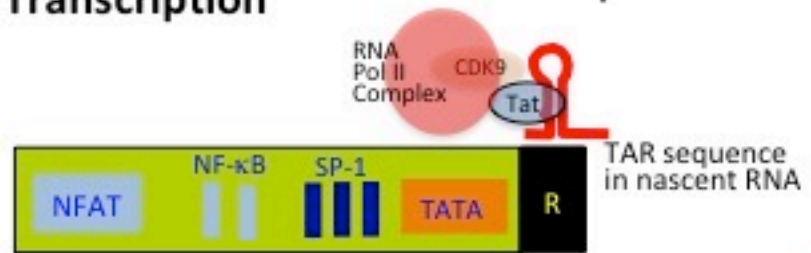
## Integration



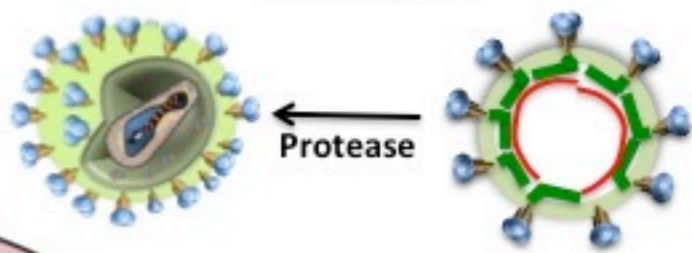
Integrase Inhibitors

# Late Events in Replication

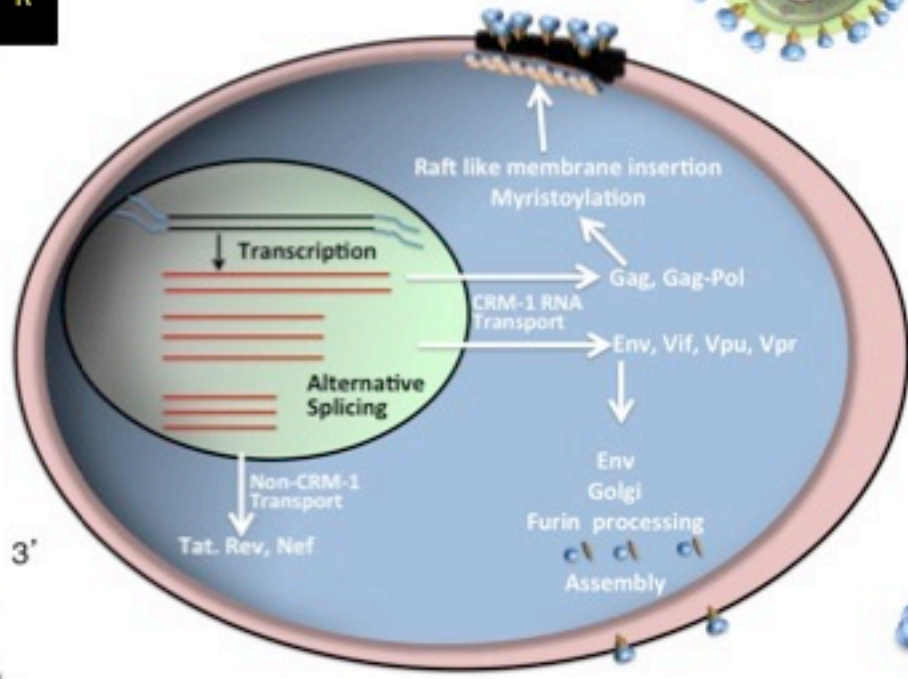
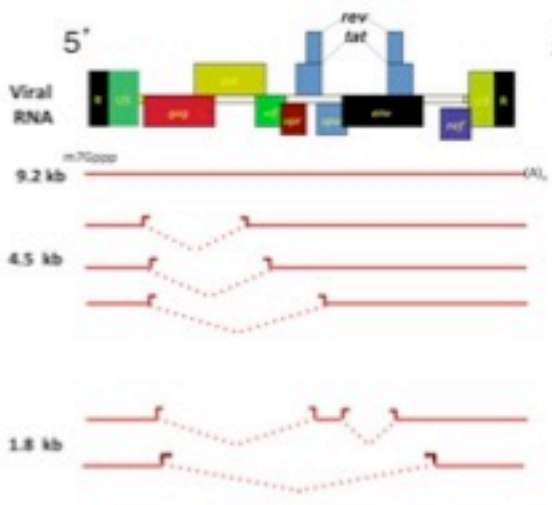
## Transcription



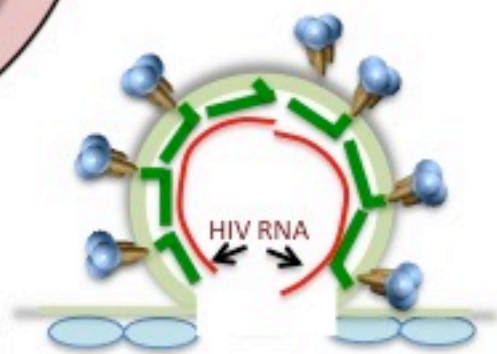
## Maturation



## Post-Transcriptional Processing

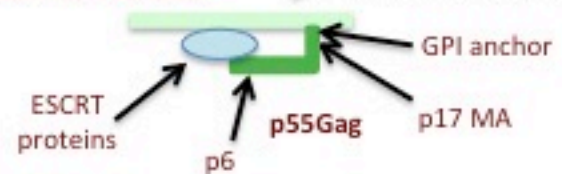


## Budding



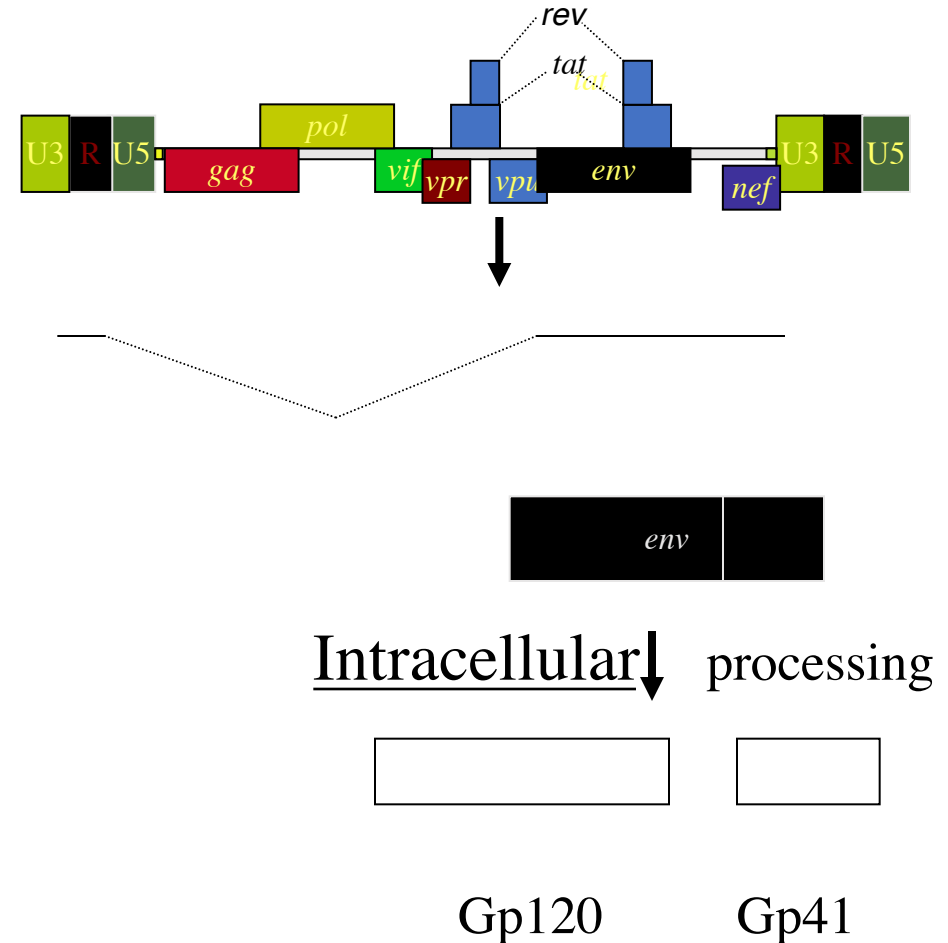
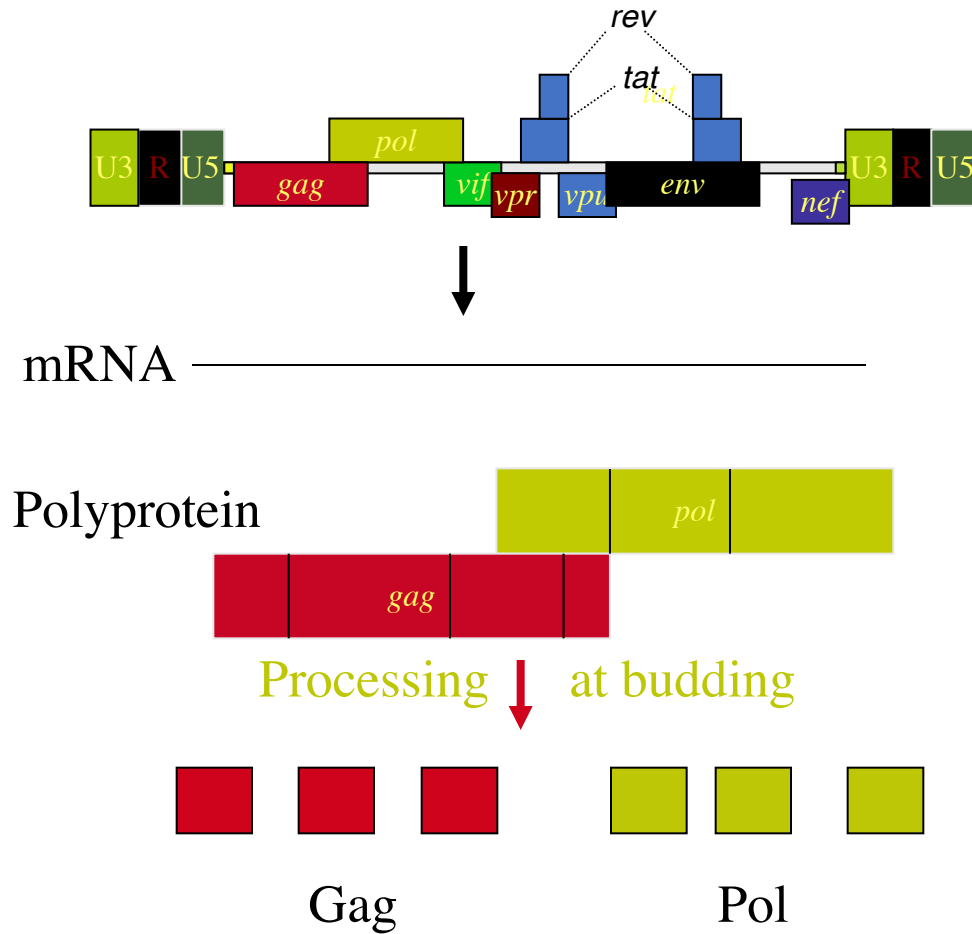
## Raft like membrane

## Plasma membrane assembly

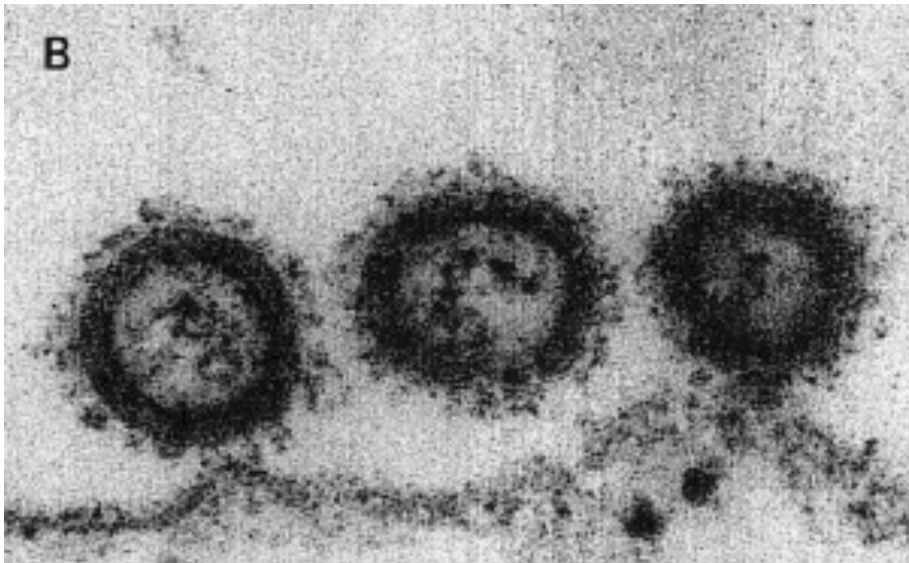


# Translation of HIV *gag/pol* and *env* Paradigm: Process

## Polyprotein Precursors



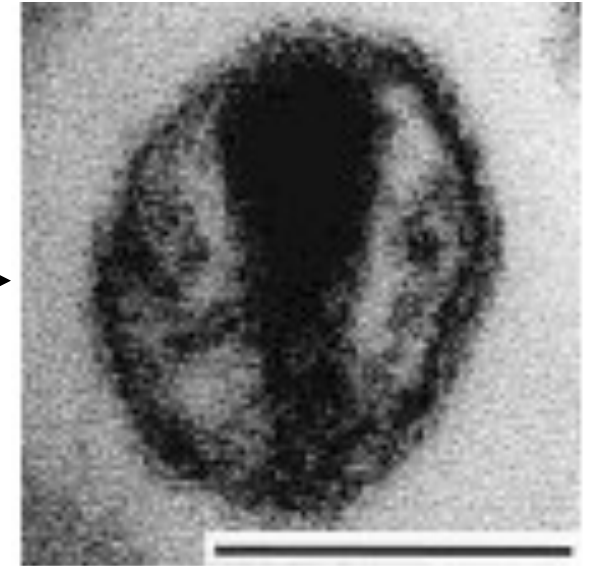
# HIV Particle Maturation



**Immature Particle**  
**Noninfectious**



**HIV**  
**Protease**

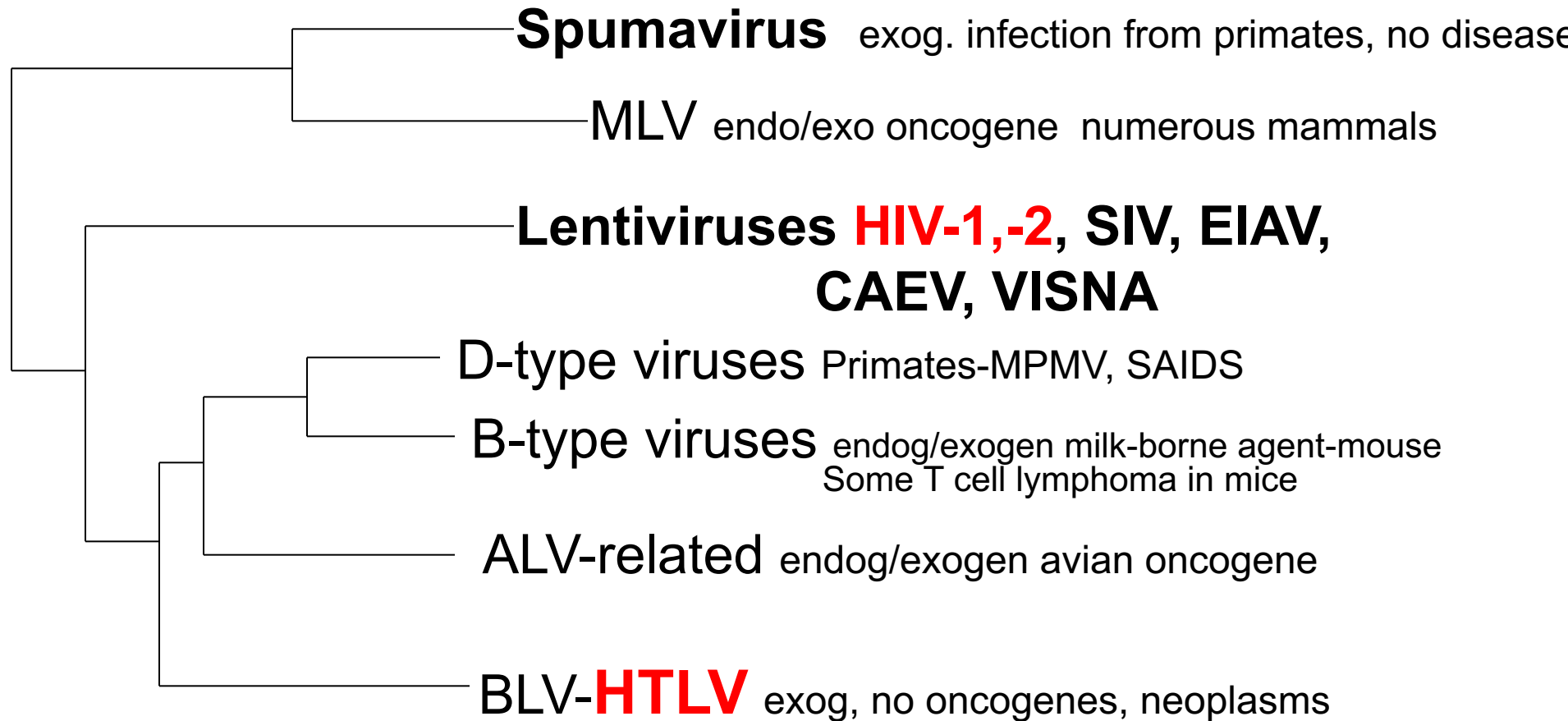


**Mature Particle**  
**Infectious**

# Retroviruses

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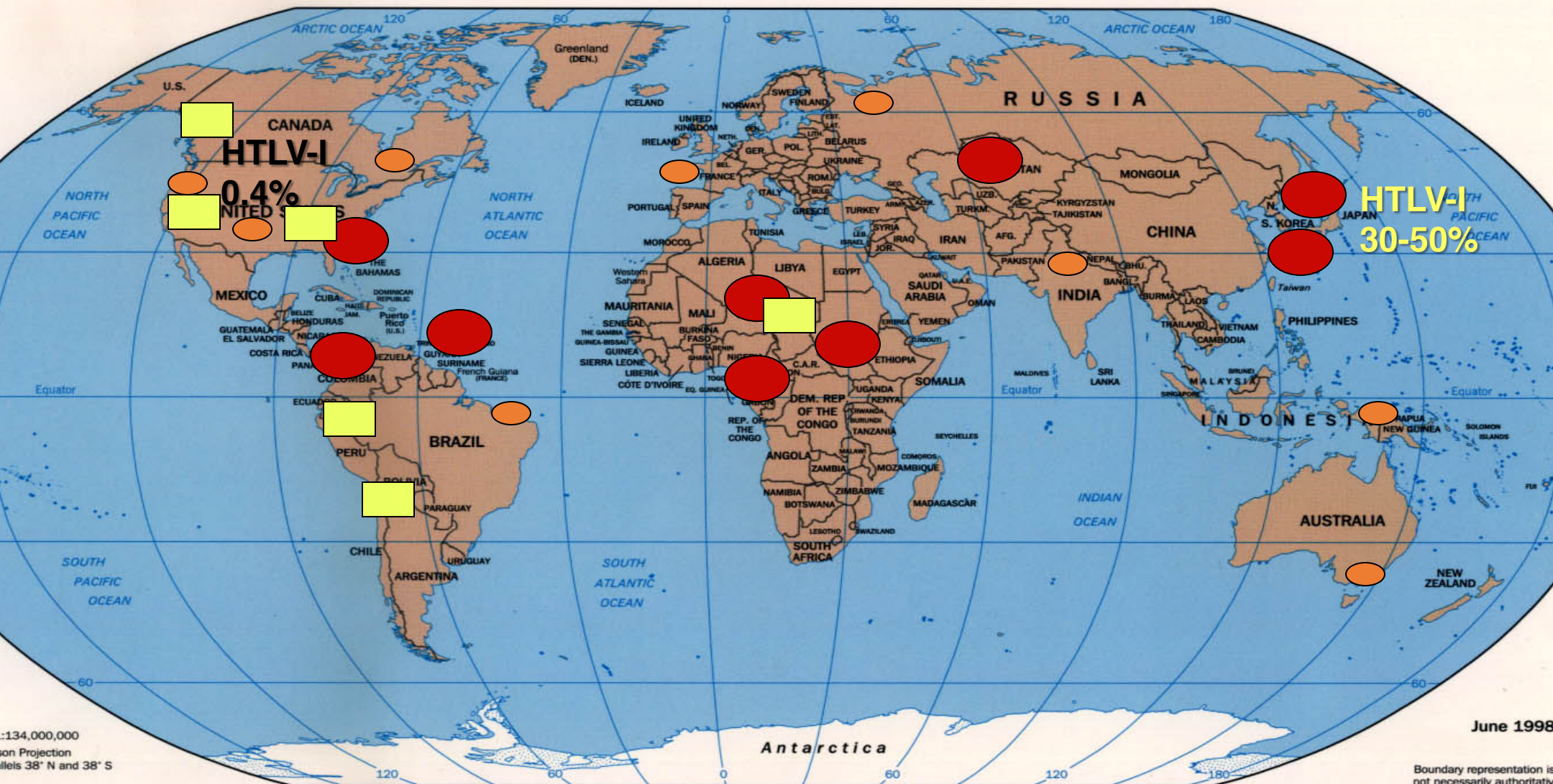
# Human Retroviruses




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



# HTLV DISTRIBUTION 10-15 Million Individuals



**HTLV-I Sporadic**   
**HTLV-I High endemicity**

### HTLV-II Endemic (Amerindian and Pygmy tribes)

June 1998

Boundary representation is not necessarily authoritative

(ROO

# HTLV-I ATL

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- **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**

**HTLV can also cause Neurologic Syndromes**

**How Do We Get These Viruses in the First Place?**



# Higher Primate Origins of HIV-1

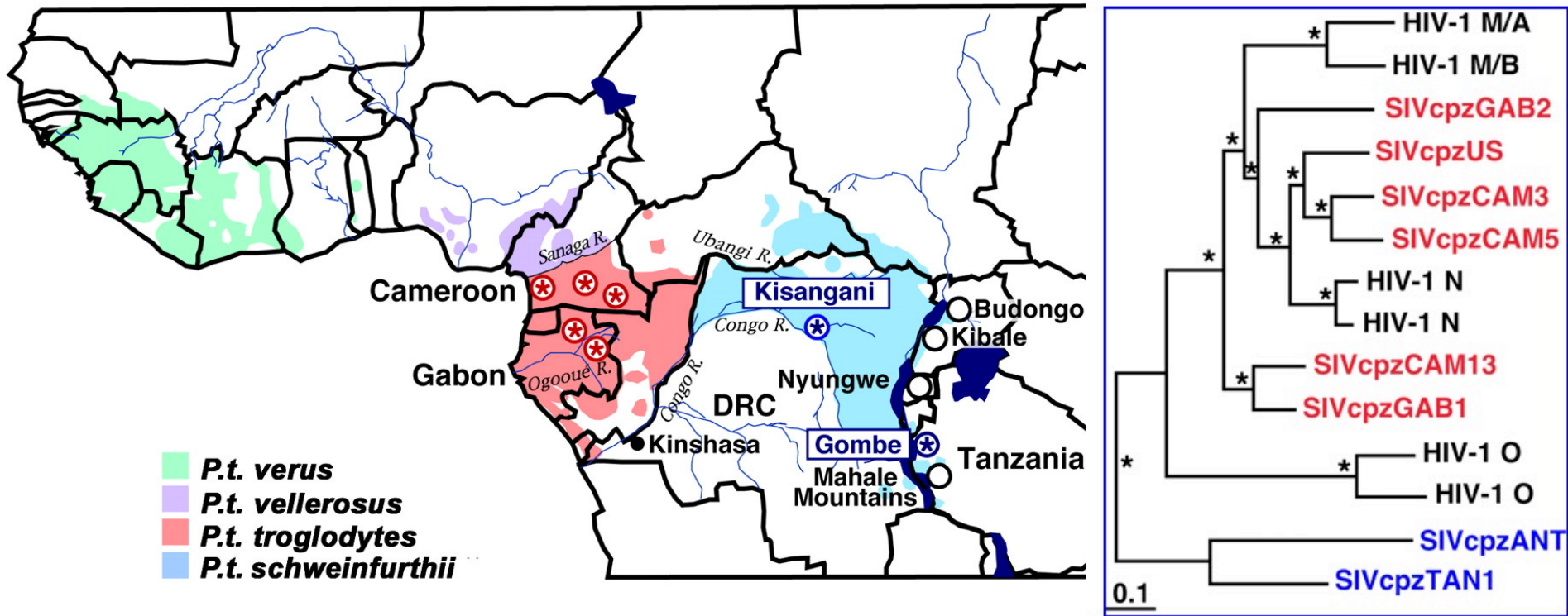


FIG. 2. Evolutionary relationships of SIVcpz and HIV-1 strains based on maximum-likelihood phylogenetic analyses of full-length envelope protein sequences (adapted from ref. 10). SIVcpz strains from *P. t. troglodytes* and *P. t. schweinfurthii* are highlighted in red and blue, respectively. Representative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

## Potential opportunities for Zoonotic Events



Poacher



Chophouse



Bushmeat market

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

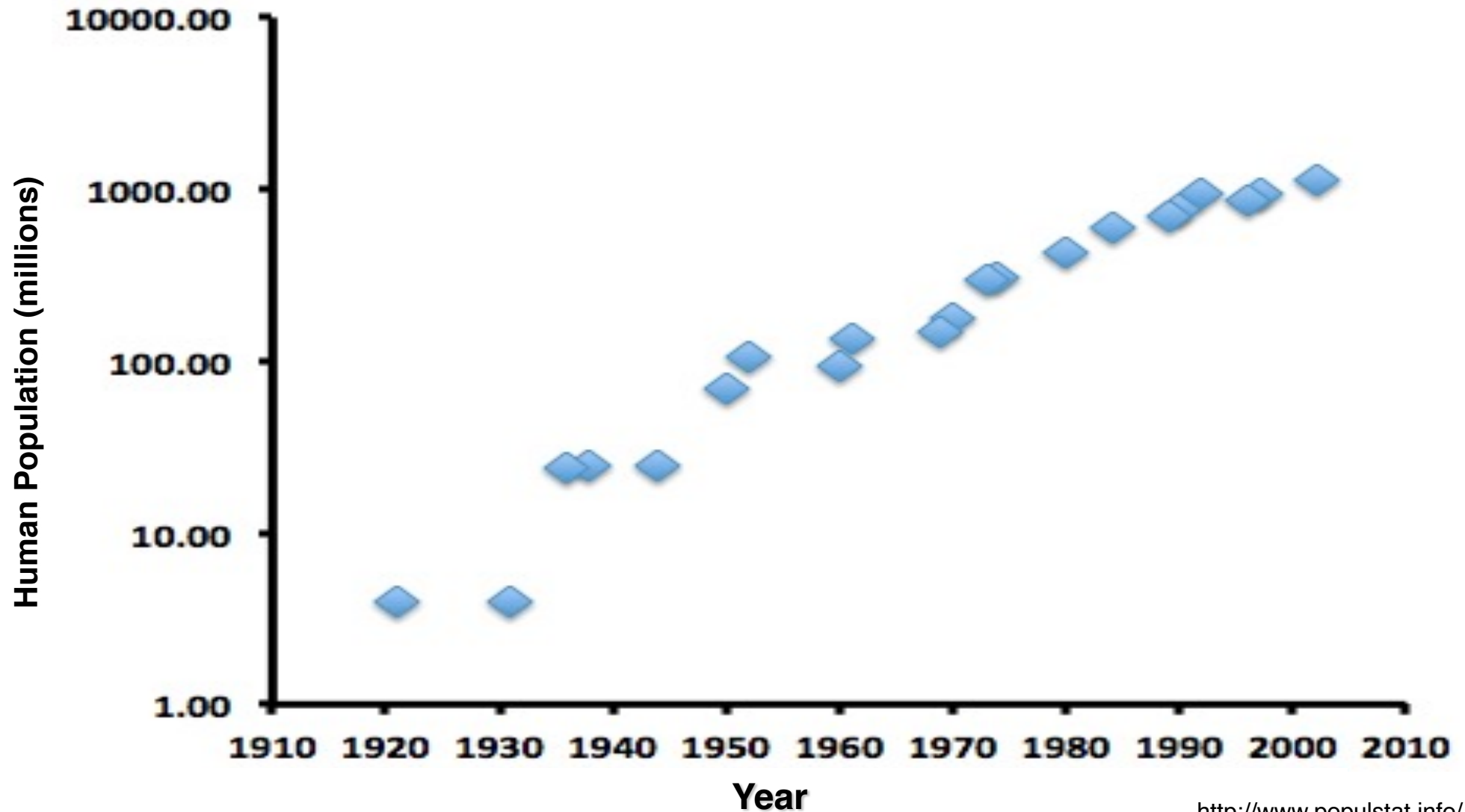
BUT WHY THEN?

# HIV Spread

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

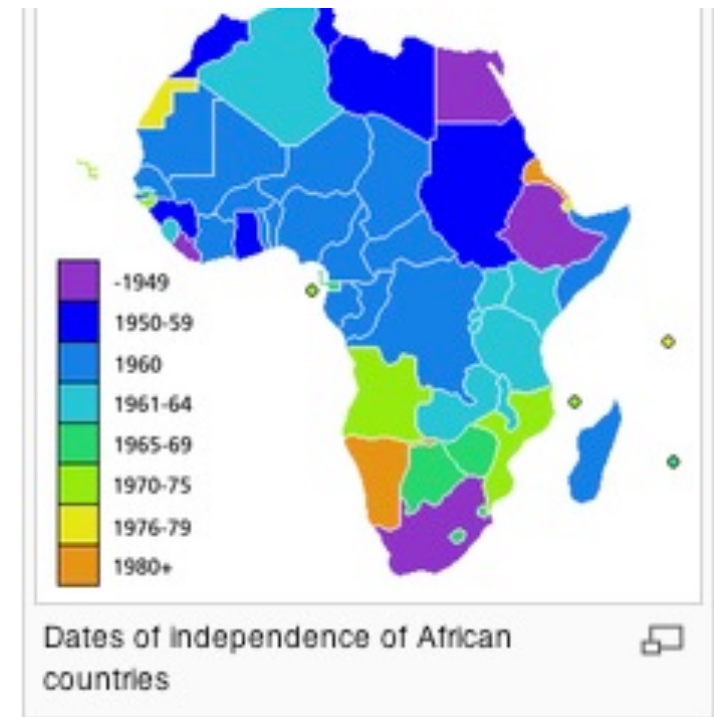
# Zoonotic Transmission of HIV Coincides with Population Expansion in Africa





# HIV Spread

- Modes of Transmission  
Political



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



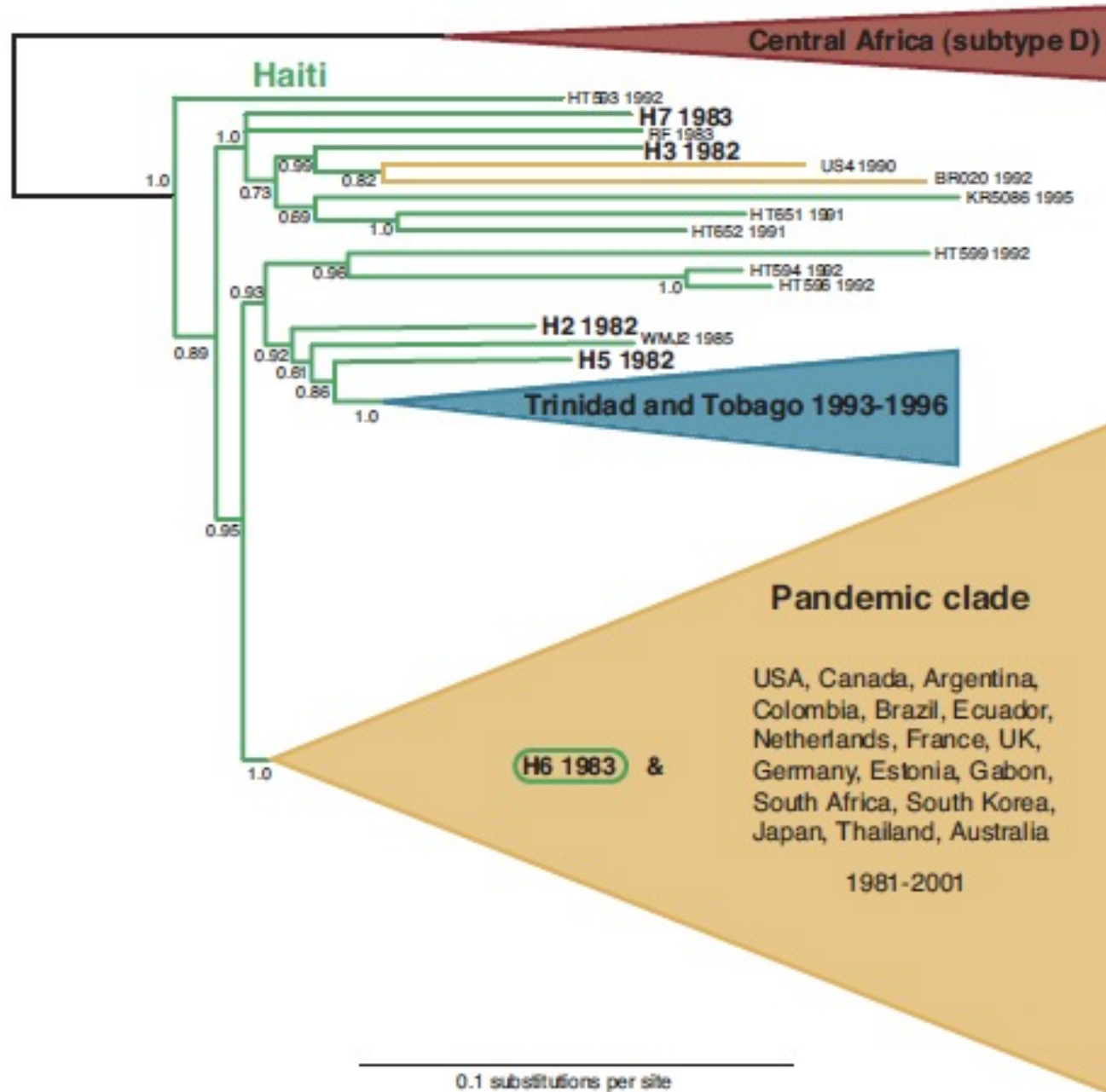
# HIV Spread

- Modes of Transmission  
Trans Africa Highway





# HIV Spread

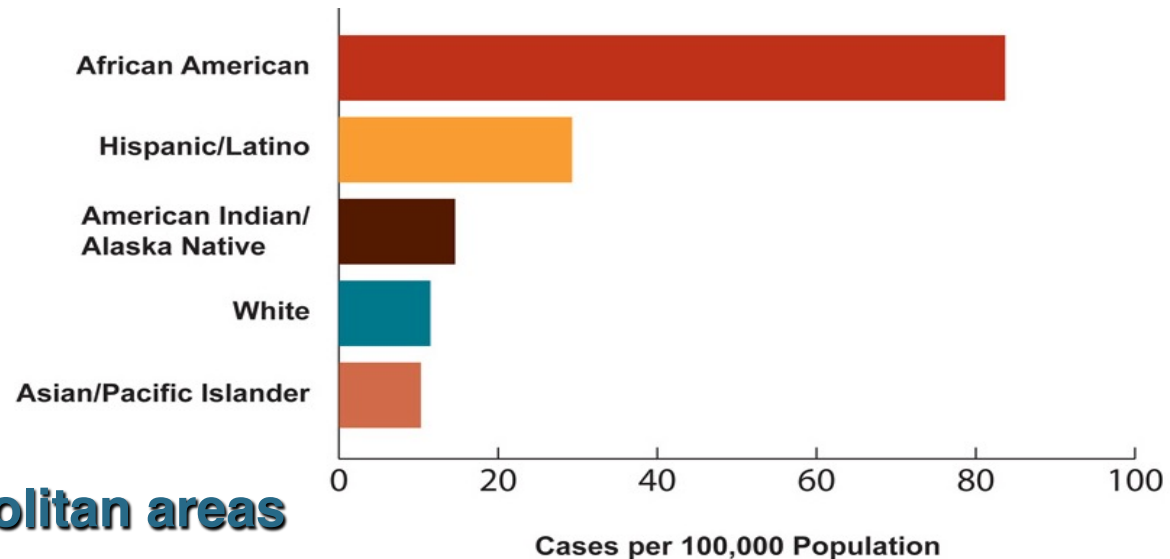
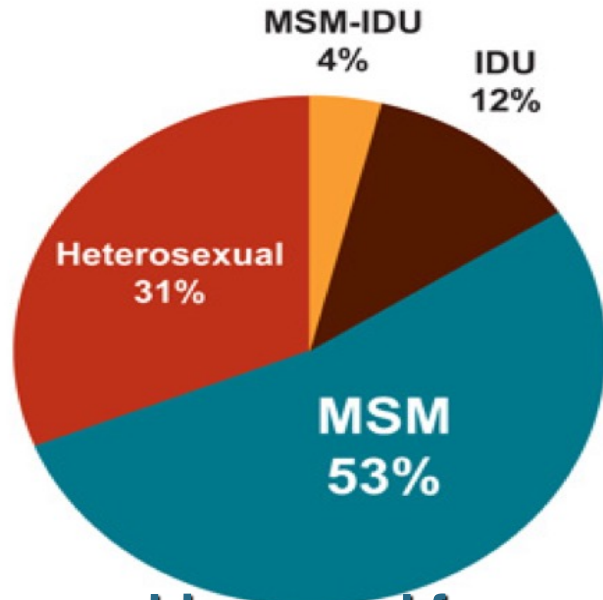


Worobey et al.

Fig. 1. The abridged majority-rule consensus tree summarizing the results from the MrBayes analysis of complete *env* genes. The branch lengths represent the

# HIV: A Maturing Epidemic

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



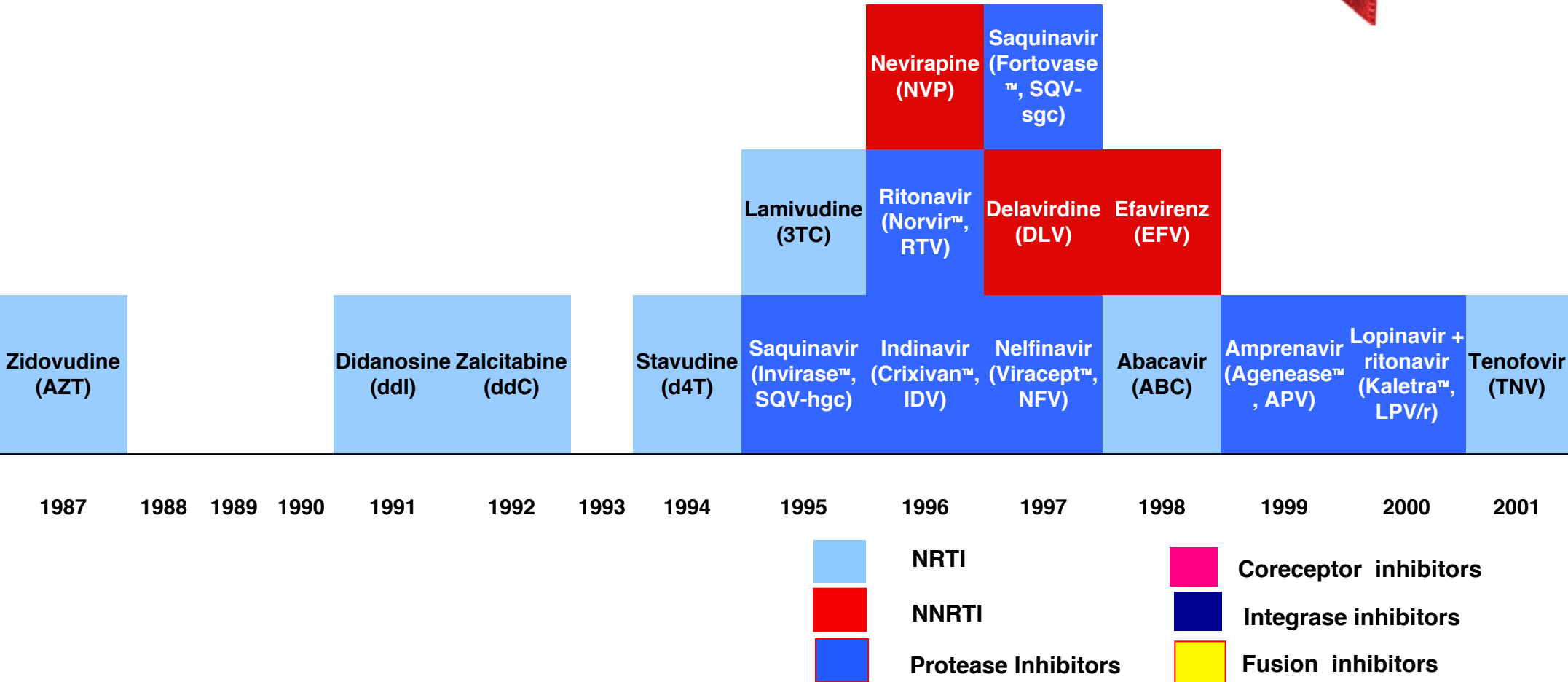
*JAMA 2008*

- **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**

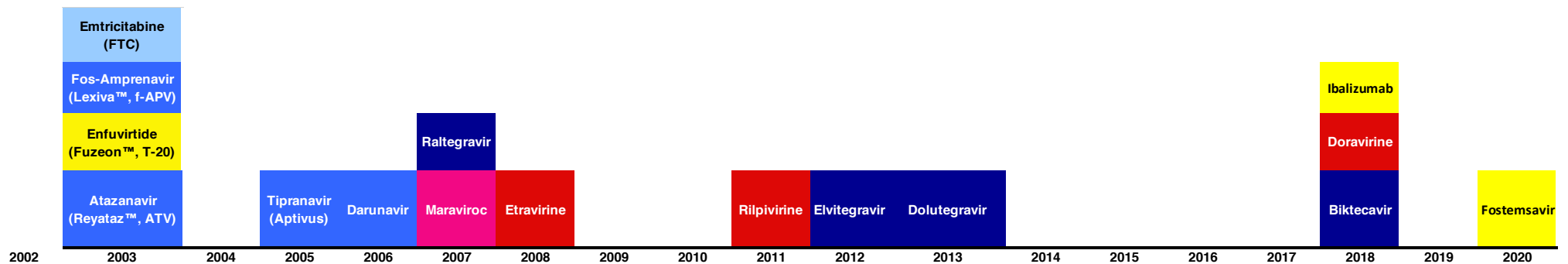
# 90-90-90: TREATMENT FOR ALL

GETTING TO  
**ZERO**





1 DECEMBER  
WORLD  
AIDS  
DAY



# Key Advances And Challenges in HIV Therapy

- **Advances**

- Pre-exposure Prophylaxis (PrEP)
  - Adherent prophylaxis is effective
- Adherence is essential: SMART Study
  - Continuous therapy essential to avoid AIDS and other complications
- Early Therapy Preferred: START Study
  - Earlier therapy is initiated, greater preservation of immunity
  - Initiation within days of identification

- **Challenges**

- Vaccines
- Cure



# Lessons

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