Human Immunodeficiency Viruses

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content

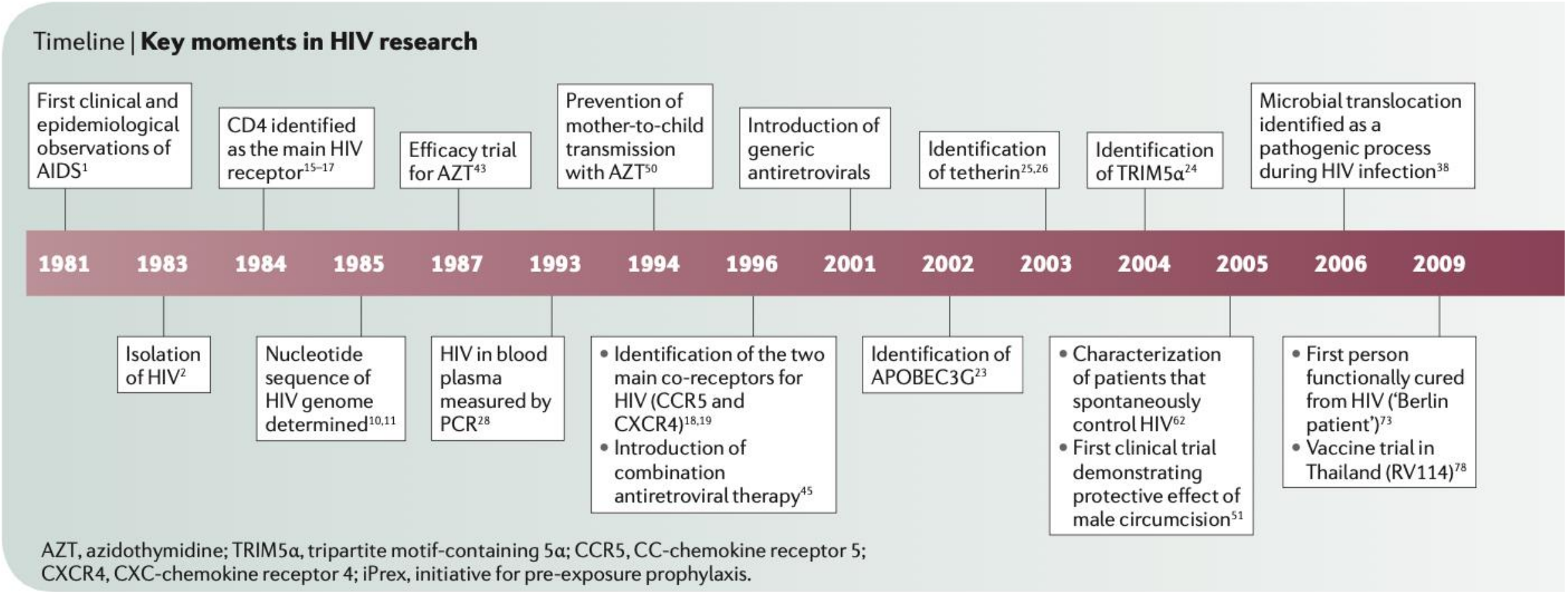
- Discovery & origin
- Epidemic

- Classification
- Replication & transmission

- Course of infection & pathogenesis

- Therapy & resistance & cure

HIV research timeline



Barré-Sinoussi et al. 2023

First cases and discovery

A20 L

RARE CANCER SEEN IN 41 HOMOSEXUALS

Outbreak Occurs Among Men in New York and California —8 Died Inside 2 Years

By LAWRENCE K. ALTMAN

Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. Eight of the victims died less than 24 months after the diagnosis was made.

The cause of the outbreak is unknown, and there is as yet no evidence of contagion. But the doctors who have made the diagnoses, mostly in New York City and the San Francisco Bay area, are alerting other physicians who treat large numbers of homosexual men to the problem in an effort to help identify more cases and to reduce the delay in offering chemotherapy treatment.

The sudden appearance of the cancer, called Kaposi's Sarcoma, has prompted a medical investigation that experts say could have as much scientific as public health importance because of what it may teach about determining the causes of more common types of cancer.

First Appears in Spots

Doctors have been taught in the past

CENTERS FOR DISEASE CONTROL

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

June 5, 1981 / Vol. 30 / No. 21

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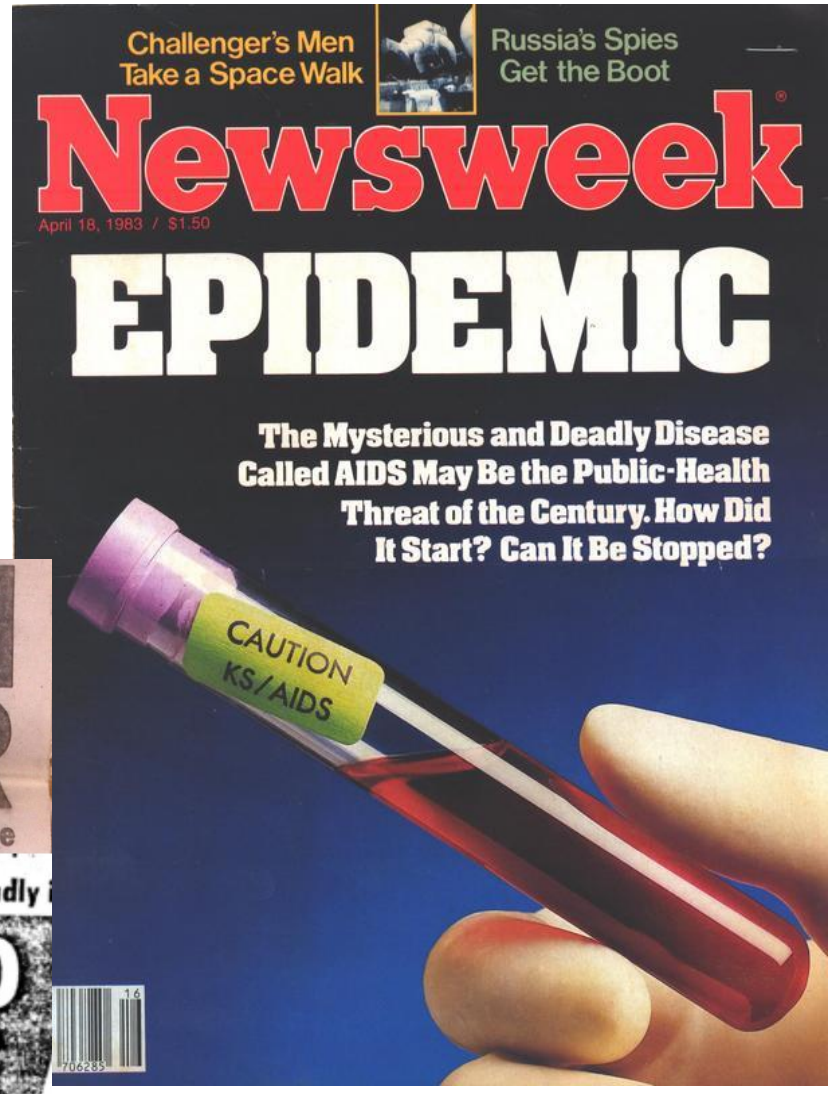
Epidemiologic Notes and Reports

Pneumocystis Pneumonia — Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.



First cases and discovery

1981 Increased number of reports of patients with rare diseases (Karposis sarconama, Pneumocystis pneumonia)

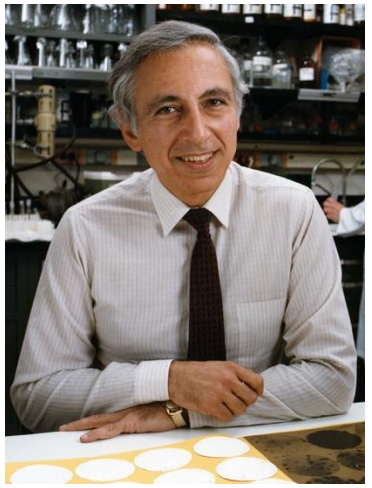
1982 Disease described as AIDS

1983 Barré-Sinoussi/Montagnier & Gallo, independently, published the identification of a novel retrovirus -> later HIV

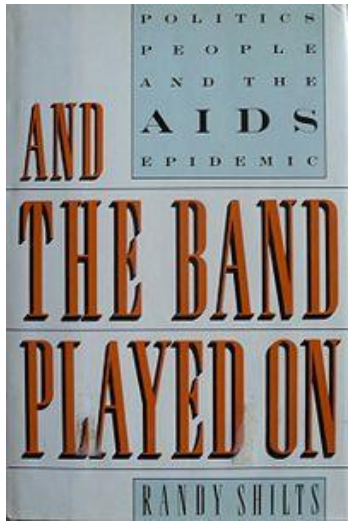
1987 Dispute over diagnostics ownership settled by US and French government

Françoise Barré-Sinoussi

Luc Montagnier

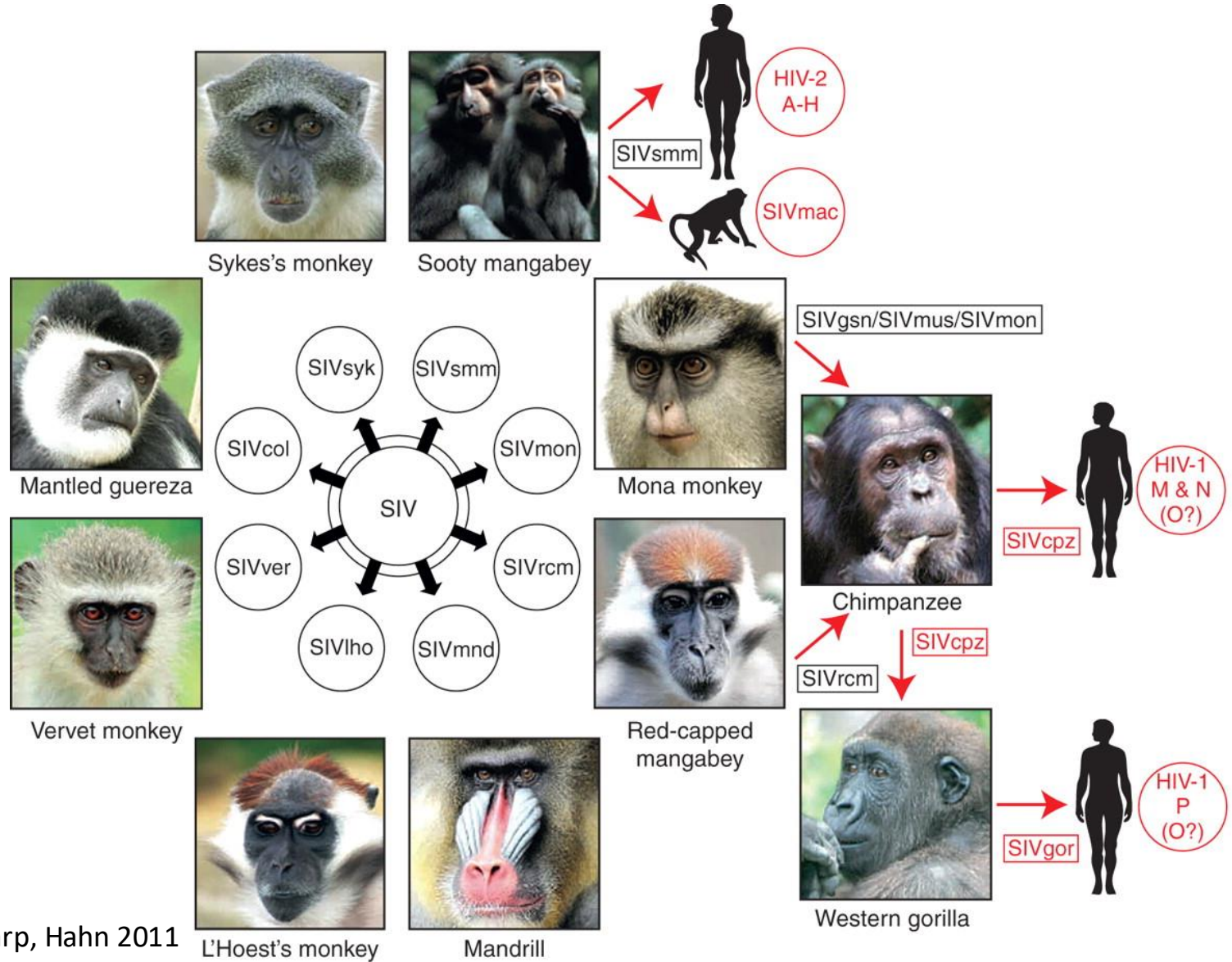


Robert Gallo

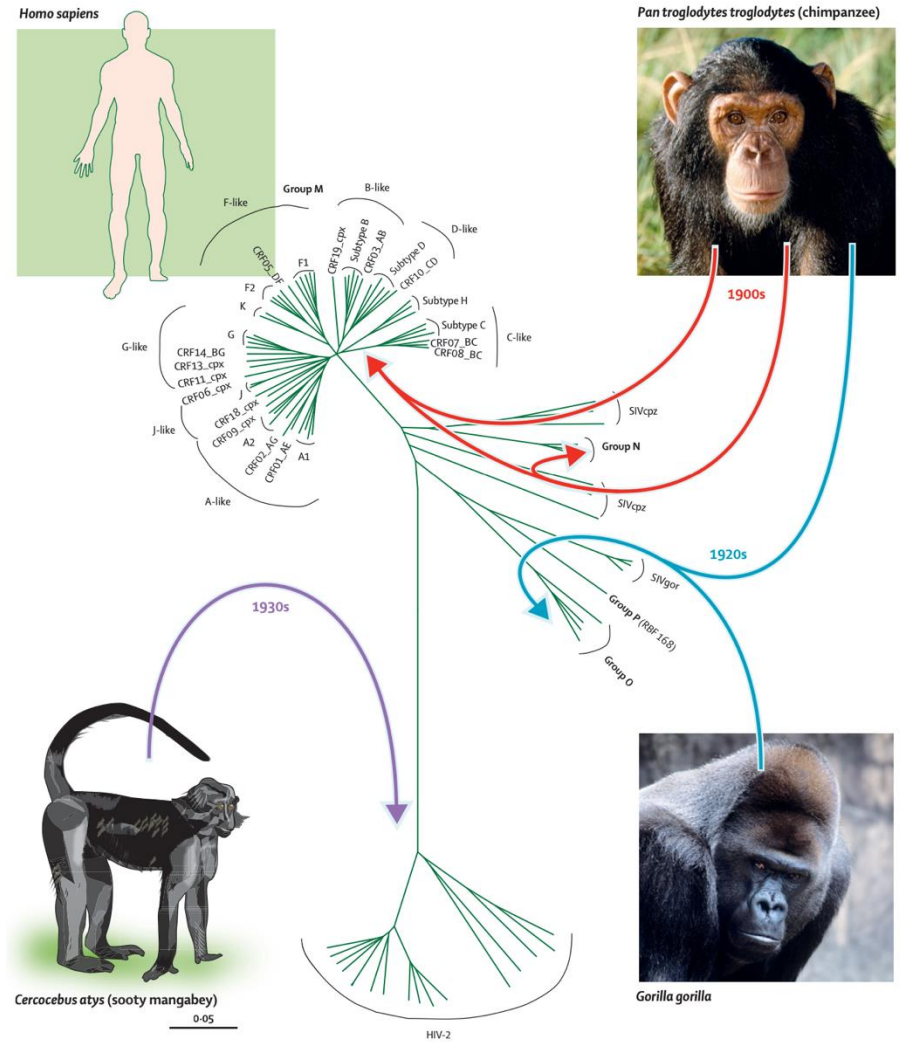


Book and movie about the drama how HIV has been discovered

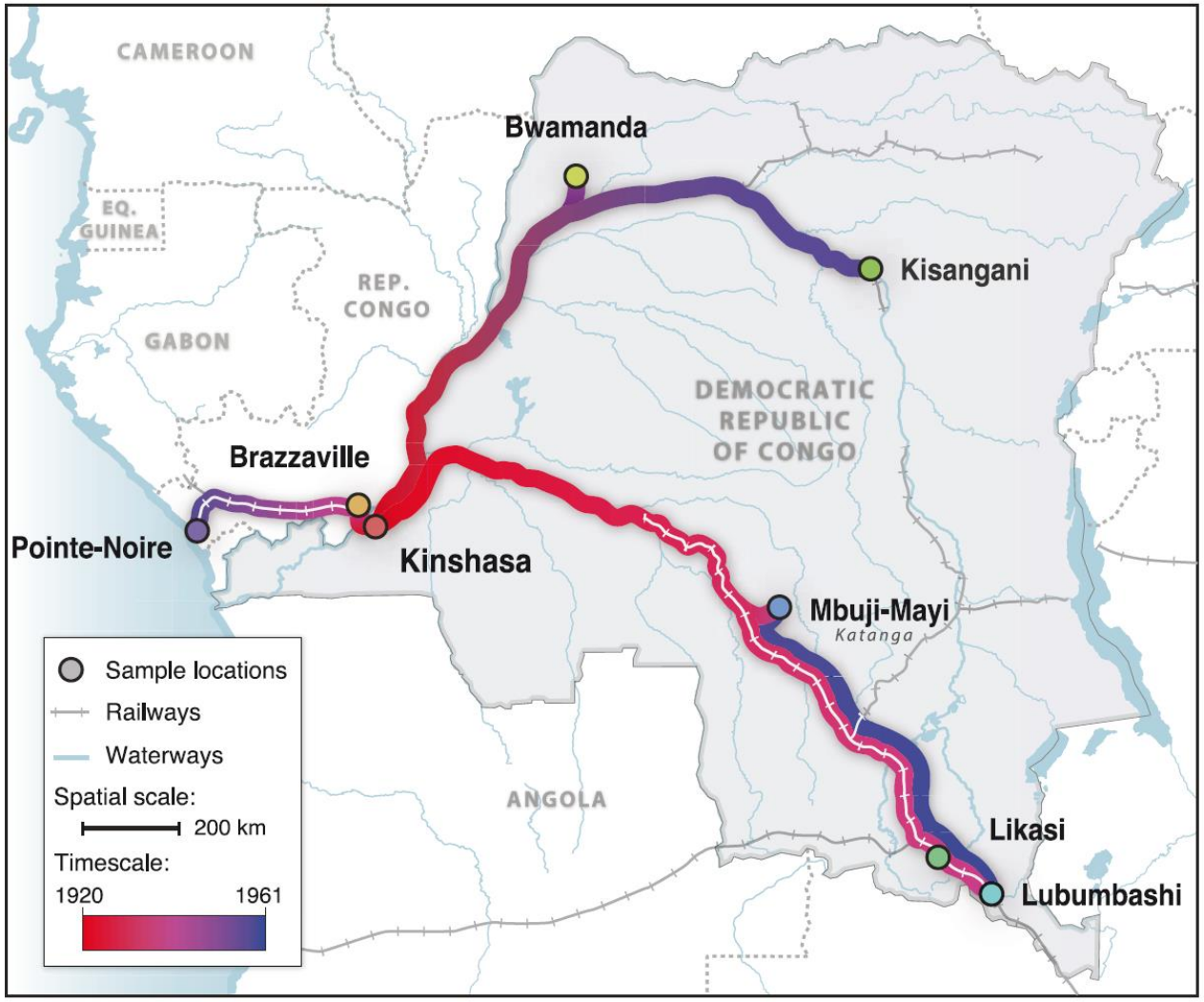
Origin of HIV



Sharp, Hahn 2011

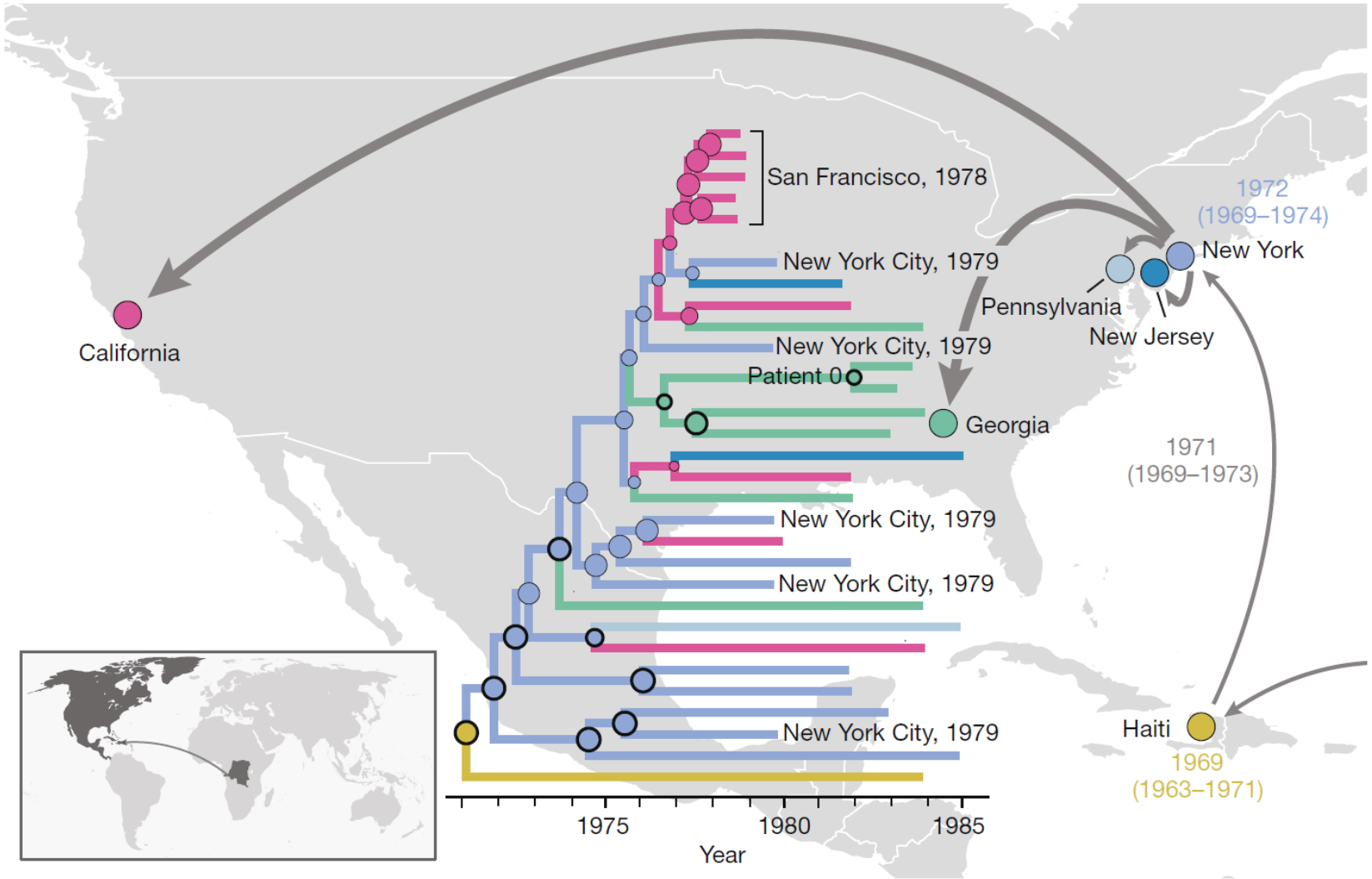


The early events in the HIV epidemic



Science 2014 DOI: 10.1126/science.1256739

The early events in the HIV epidemic



LETTER

doi:10.1038/nature19827

1970s and 'Patient 0' HIV-1 genomes illuminate early HIV/AIDS history in North America

Michael Worobey[1], Thomas D. Watts[1], Richard A. McKay[2], Marc A. Suchard[3], Timothy Granade[4], Dirk E. Teuwen[5], Beryl A. Koblin[6], Walid Heneine[4], Philippe Lemey[7] & Harold W. Jaffe[4]

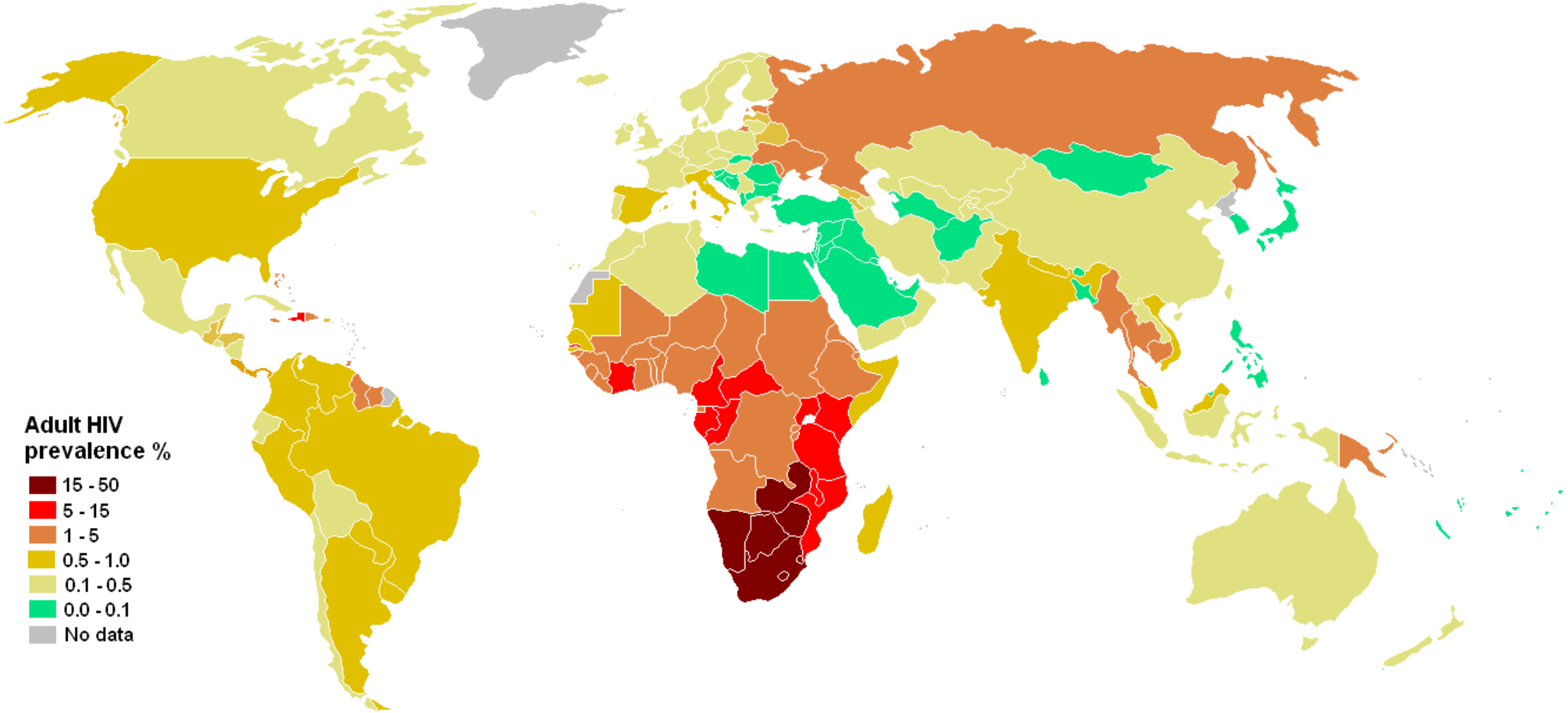
HIV epidemic

Global HIV statistics

- 38.4 million people globally with HIV in 2021.
- 1.5 million people newly infected in 2021.
- 650 000 people died from AIDS-related illnesses in 2021.
- 28.7 million people were accessing antiretroviral therapy in 2021.
- 84.2 million people have become infected with HIV since the start of the epidemic.
- 40.1 million died from AIDS-related illnesses since the start of the epidemic.

https://www.unaids.org/en/resources/fact-sheet

HIV epidemic



https://commons.wikimedia.org/wiki/File:AIDS_and_HIV_prevalence_2008.svg

HIV break #1

What have we learned?

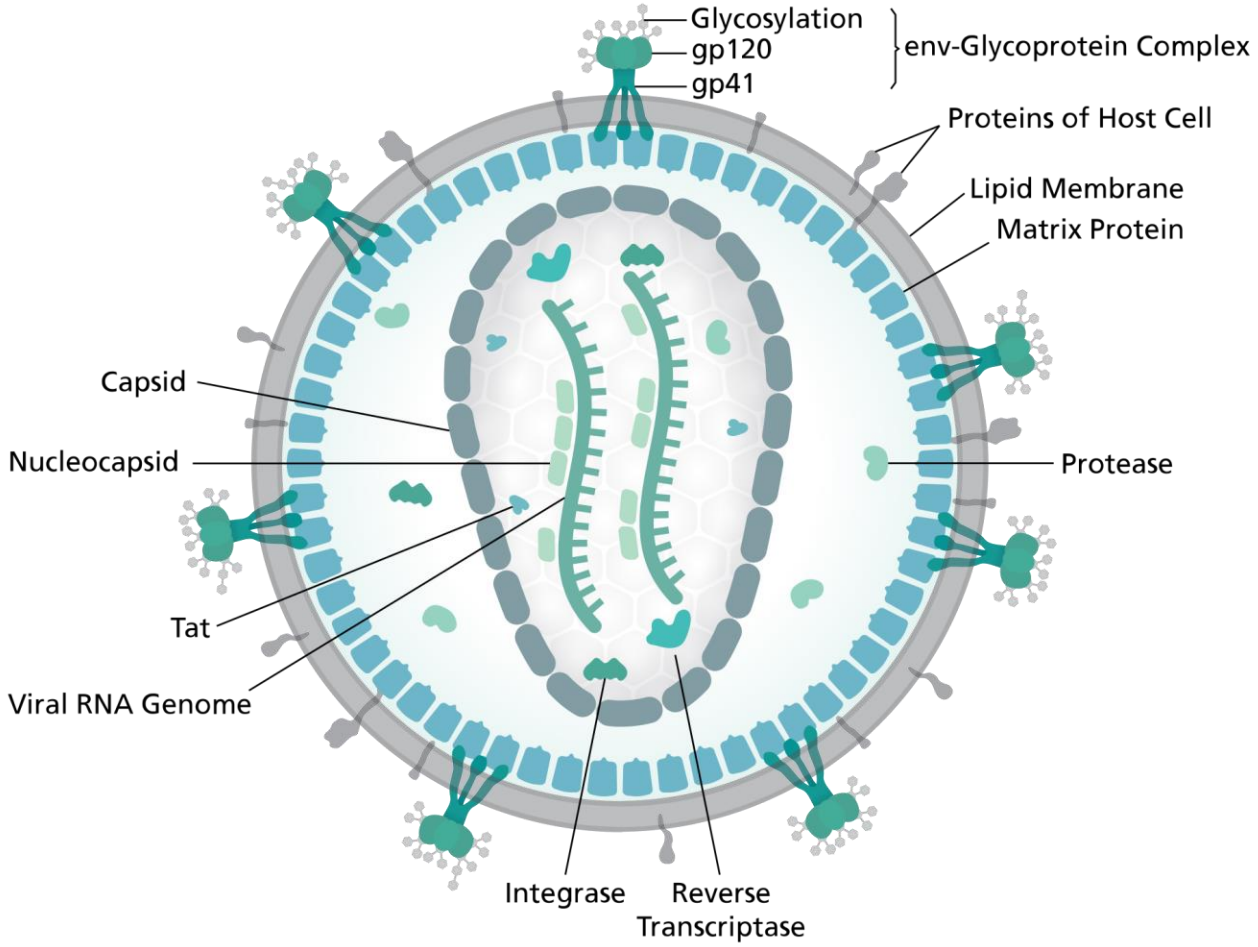
1. HIV has been detected in the early 1980s
2. However, it has been around for quite a while…
3. Subtypes took a different route through primates and spilled over into the human population
4. Still a lot of people are infected, die and/or do not have access to treatment

What is HIV?

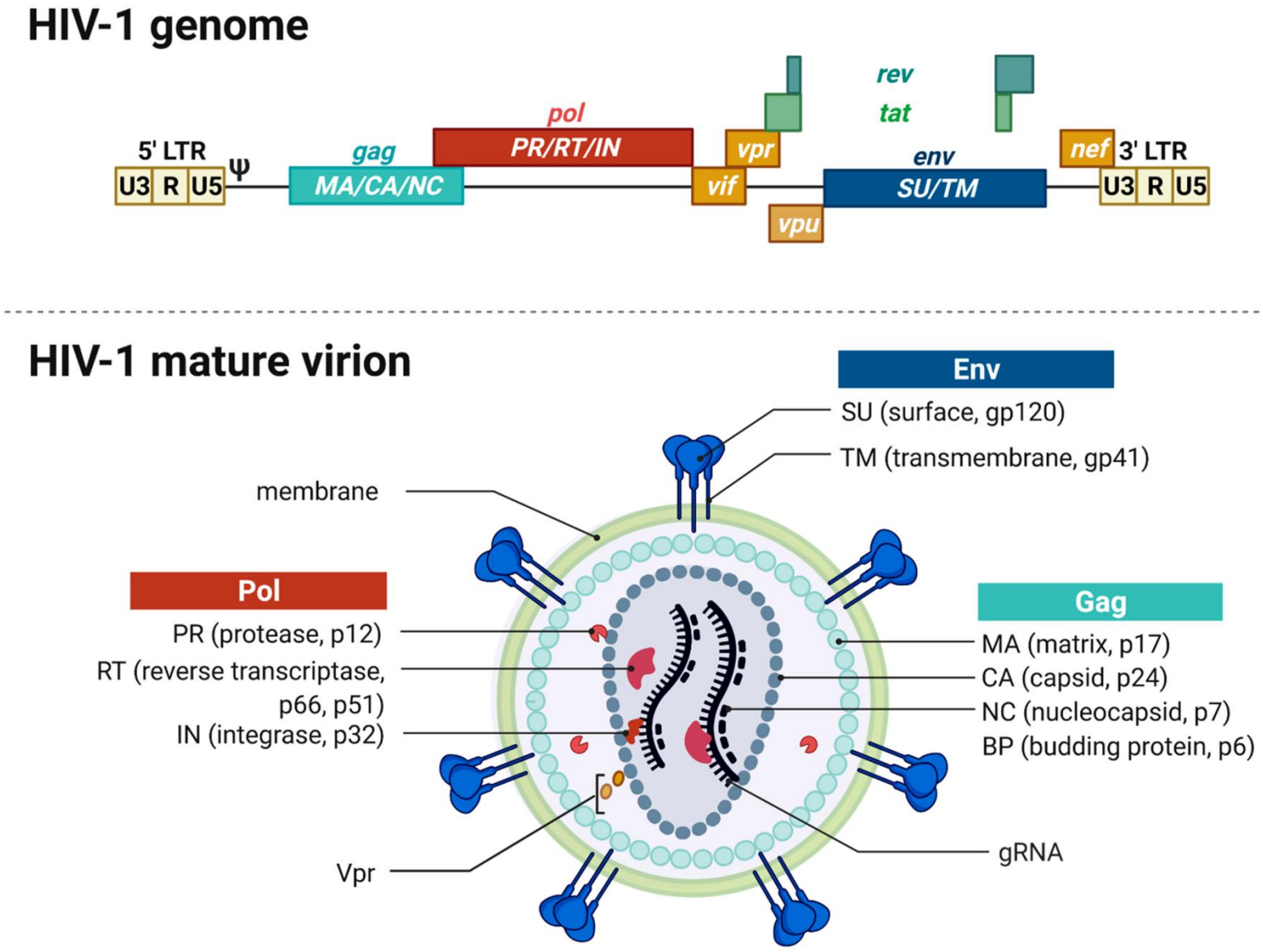
- Family: Retroviridae
- Genus: Lentiviruses

- Positive-sense ssRNA genome (~9.8 kb)
- 2 copies packaged

Potential targets for diagnostics and antiviral therapy



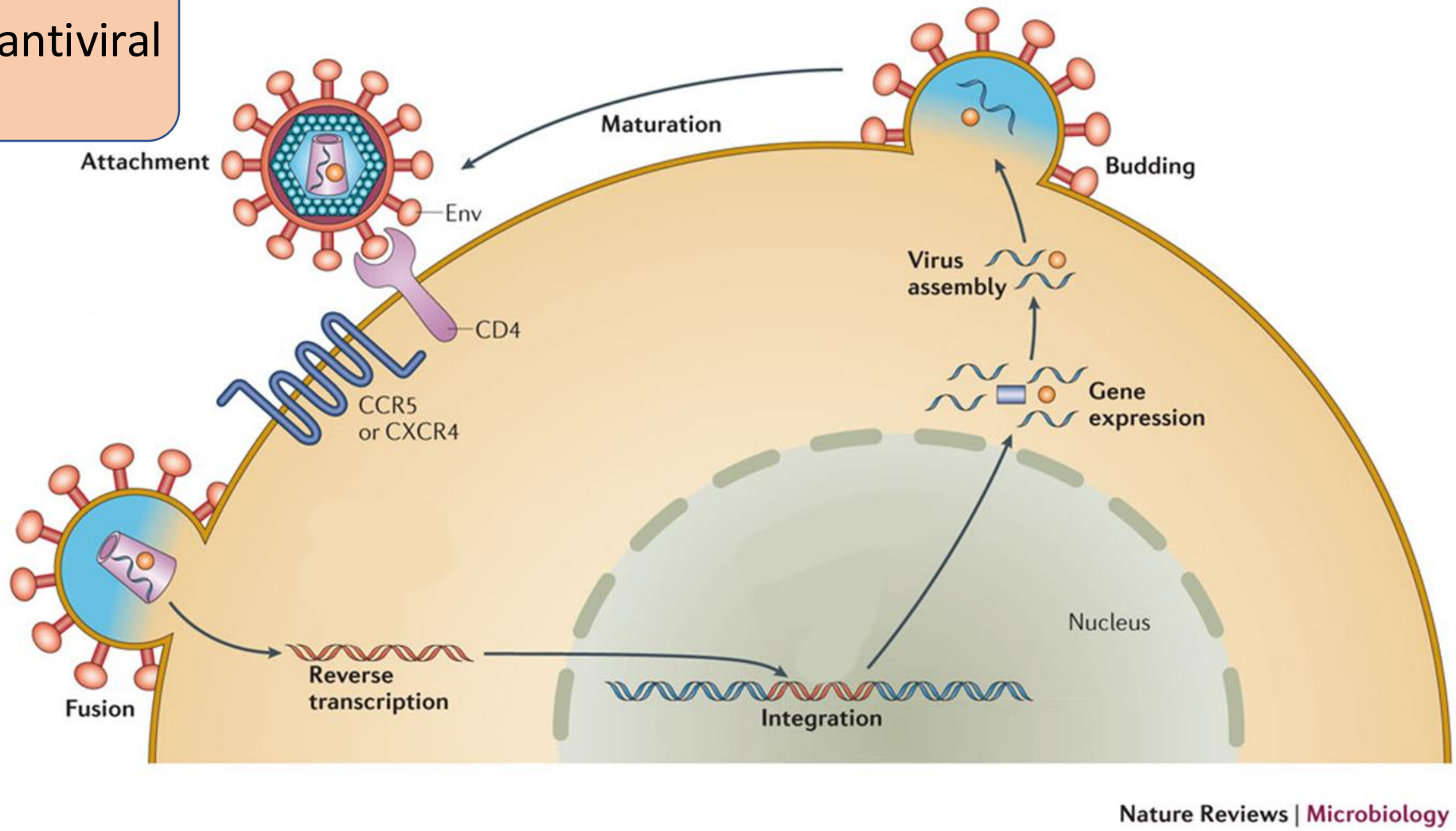
HIV genome



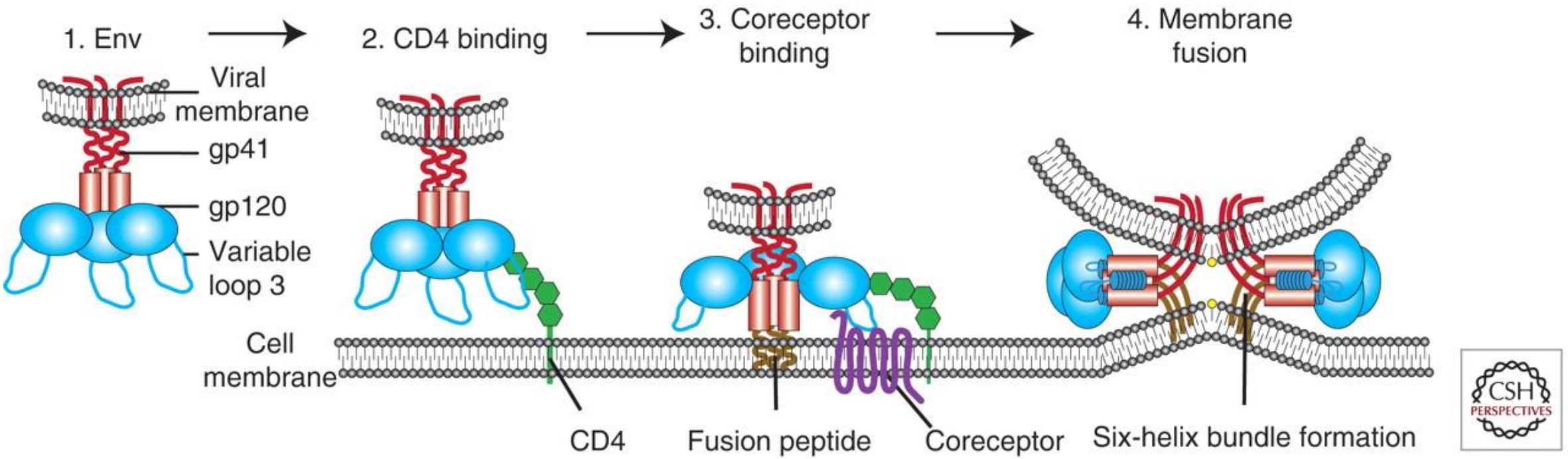
Heuvel et al. 2022

How HIV propagates

Potential targets for diagnostics and antiviral therapy



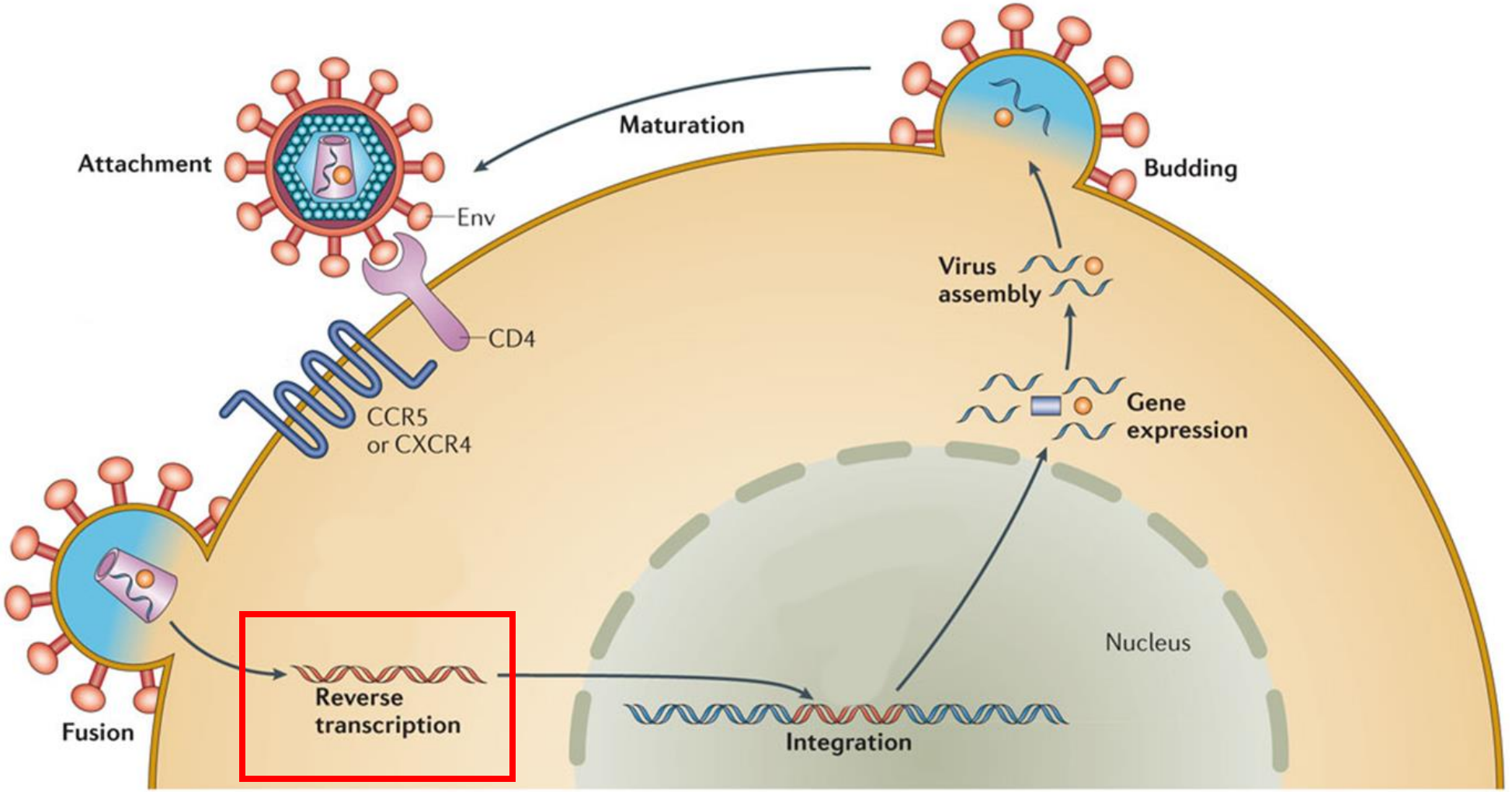
HIV entry



Receptor can determine cell tropism:

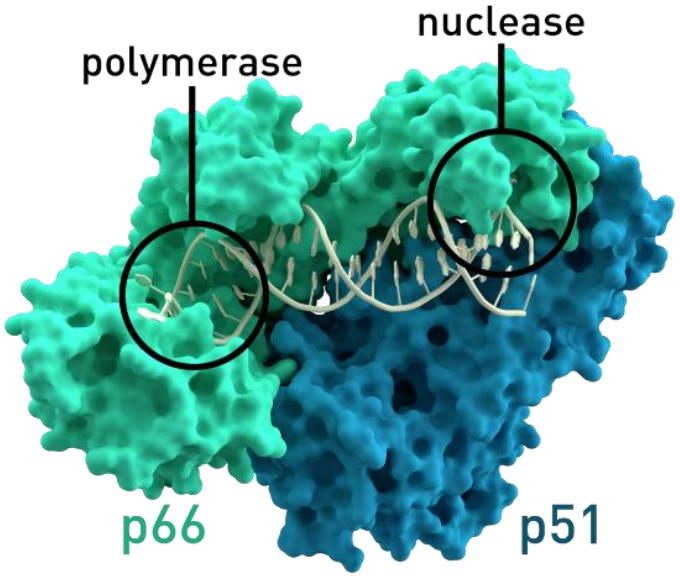
Receptor	CD4
Co-receptor	CCR5
Co-receptor	CXCR4

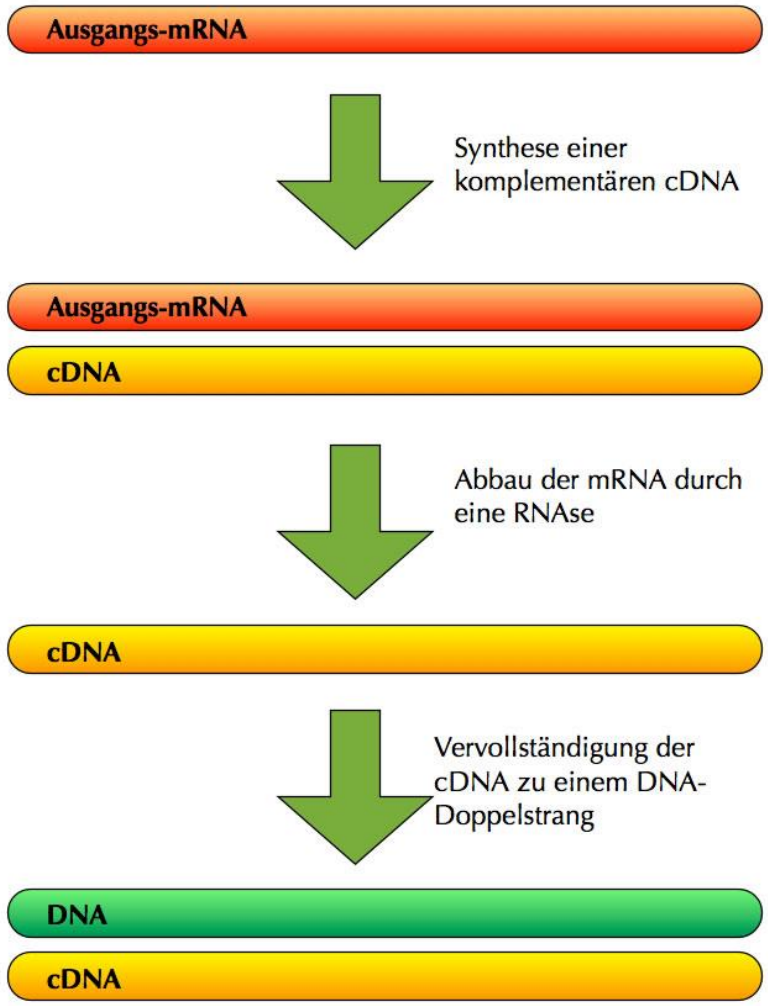
HIV reverse transcription



Nature Reviews | Microbiology

Reverse transcription





RT enzyme: RNA-dependent DNA-polymerase
Synthesis of DNA from RNA template

RNase H-activity: degrades RNA from RNA:DNA hybrids

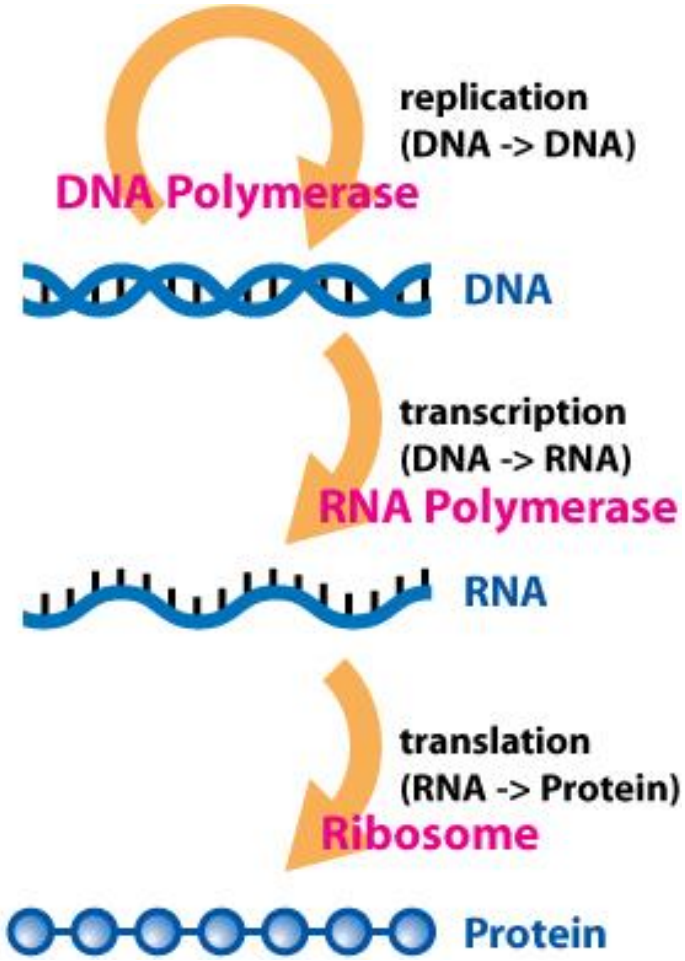
no proof-reading function (no 3‘-5‘-Exonuklease activity)
high mutation rate

Reverse transcription & the central dogma of biology

Discovered by David Baltimore (Nobel prize)

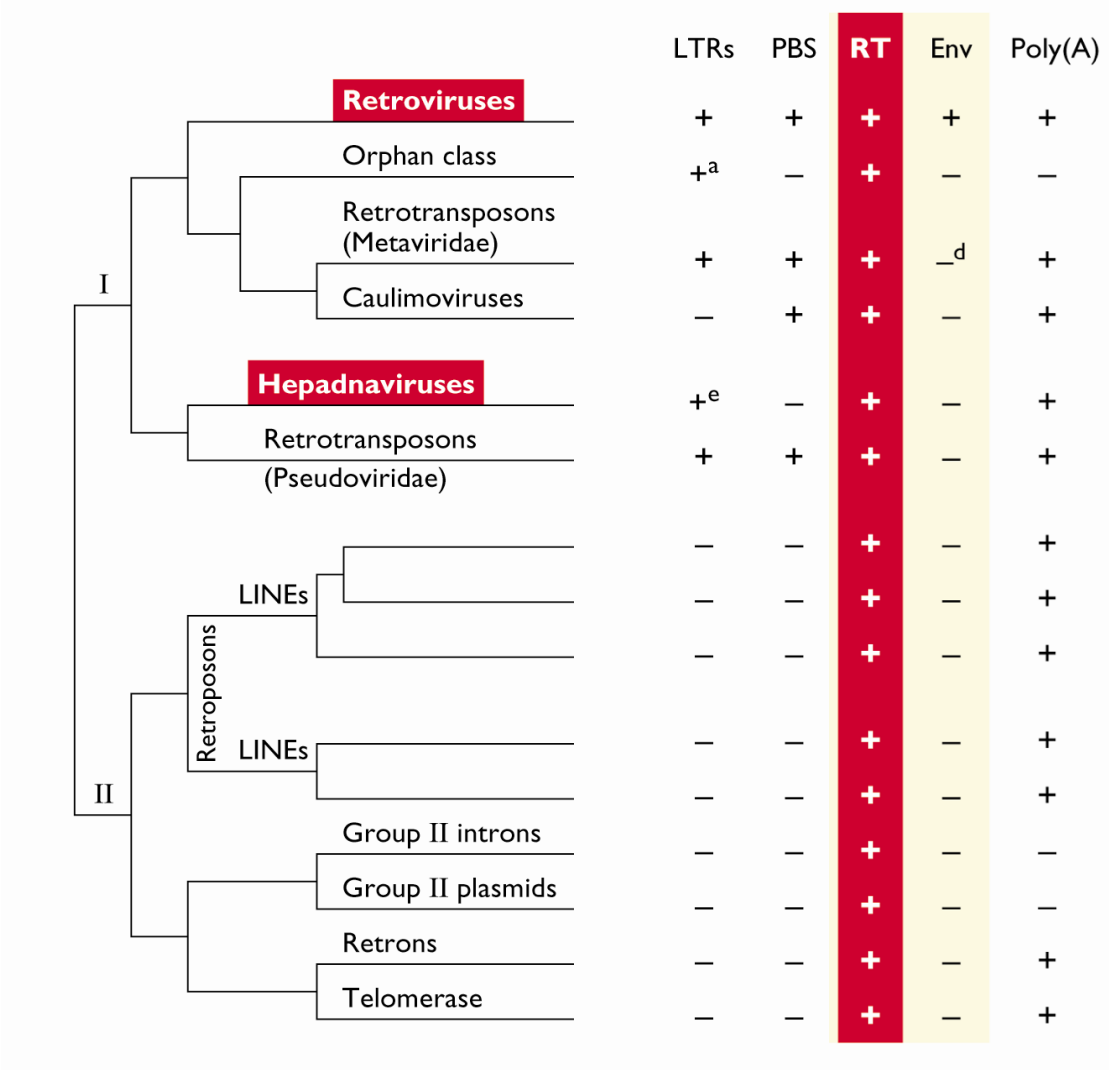
Information flows from:
DNA –> RNA and can go back to DNA

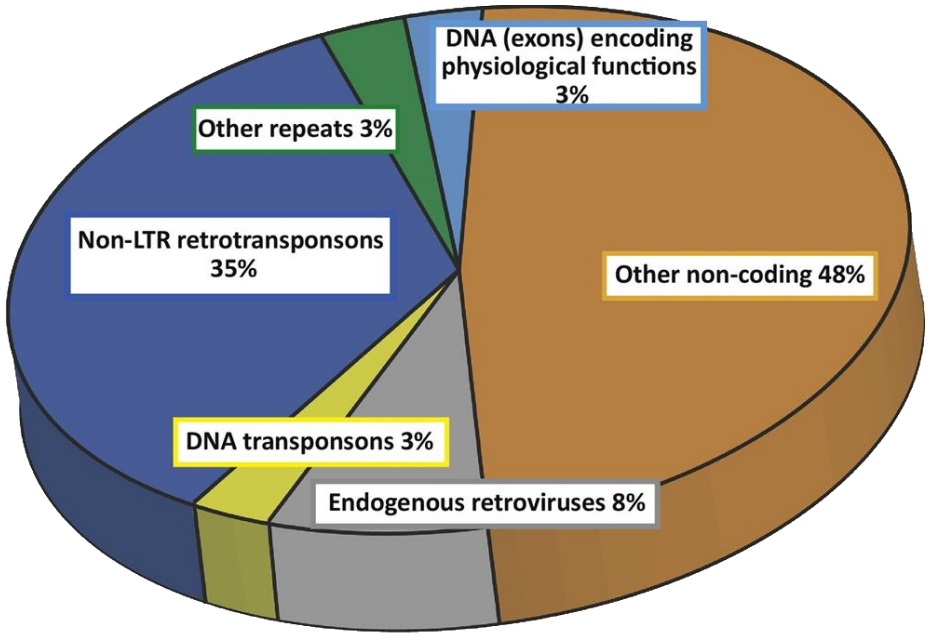
Applied in molecular biology (RT-PCR)



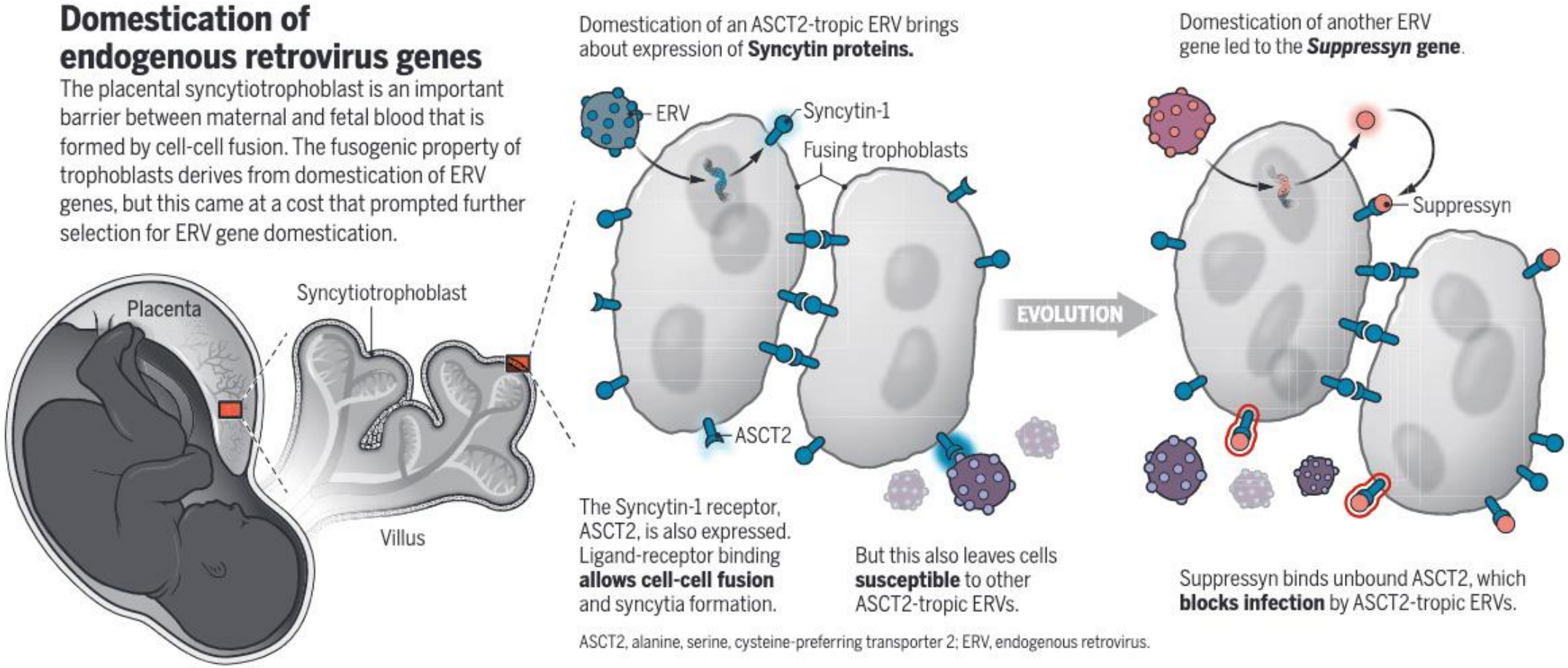
https://en.wikipedia.org/wiki/Central_dogma_of_molecular_biology

Who can reverse transcribe?



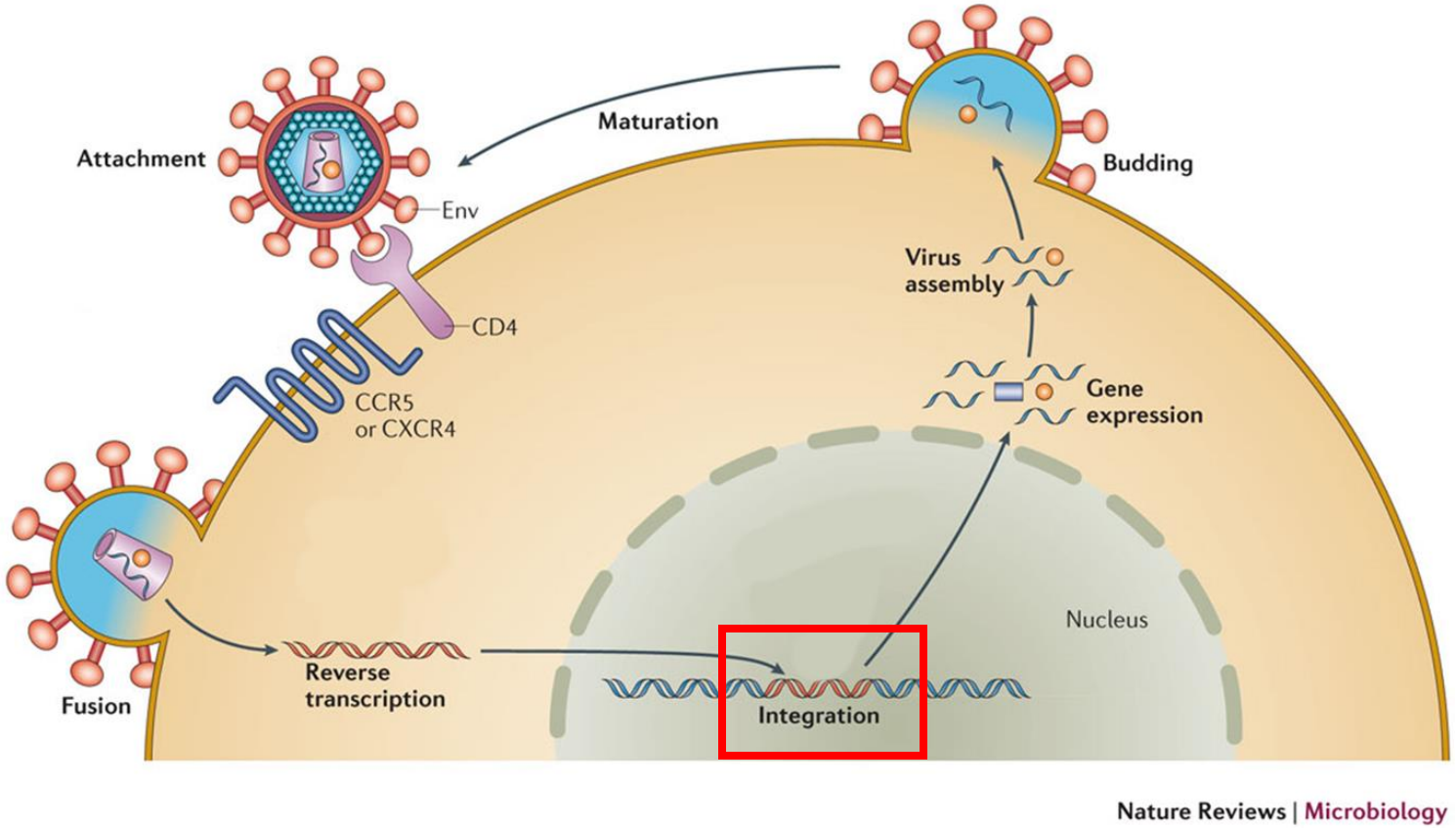


Domestication of retroviruses – an evolutionary boost

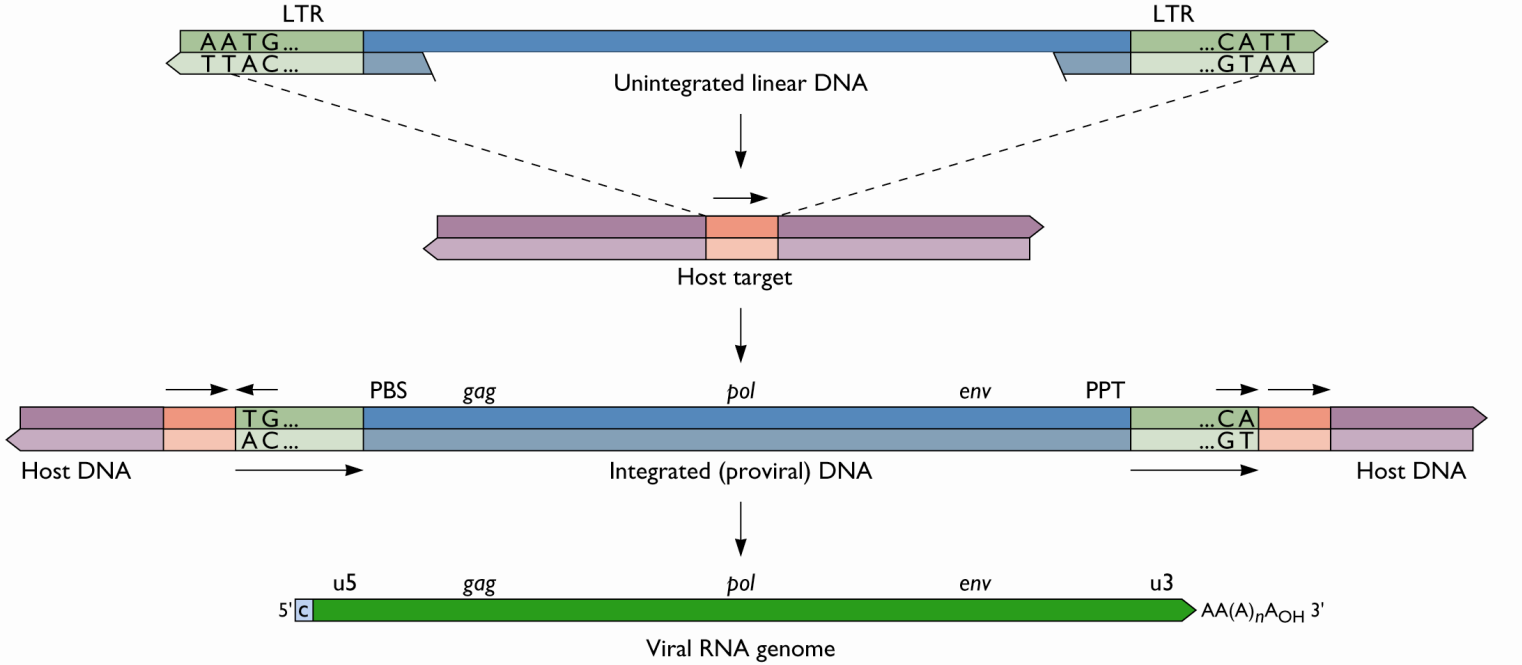


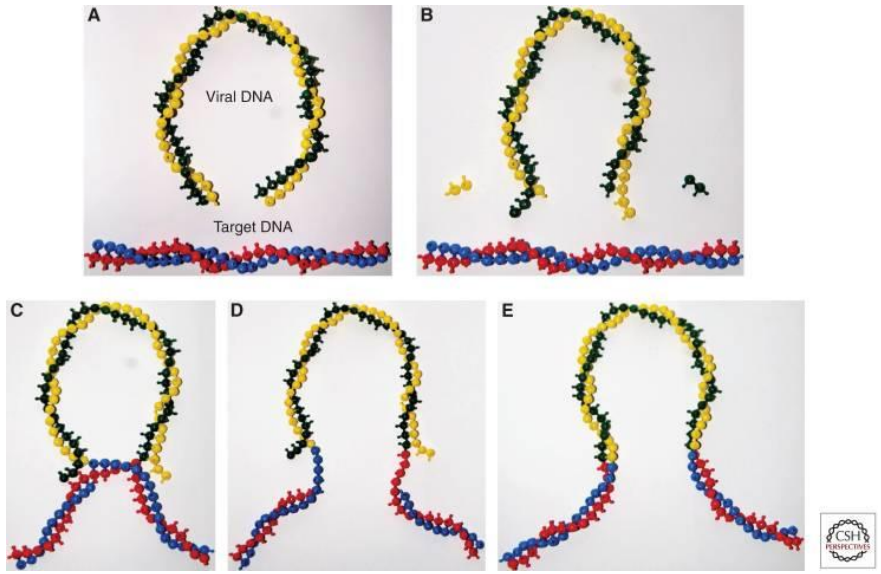
https://www.science.org/doi/10.1126/science.ade4942

Integration



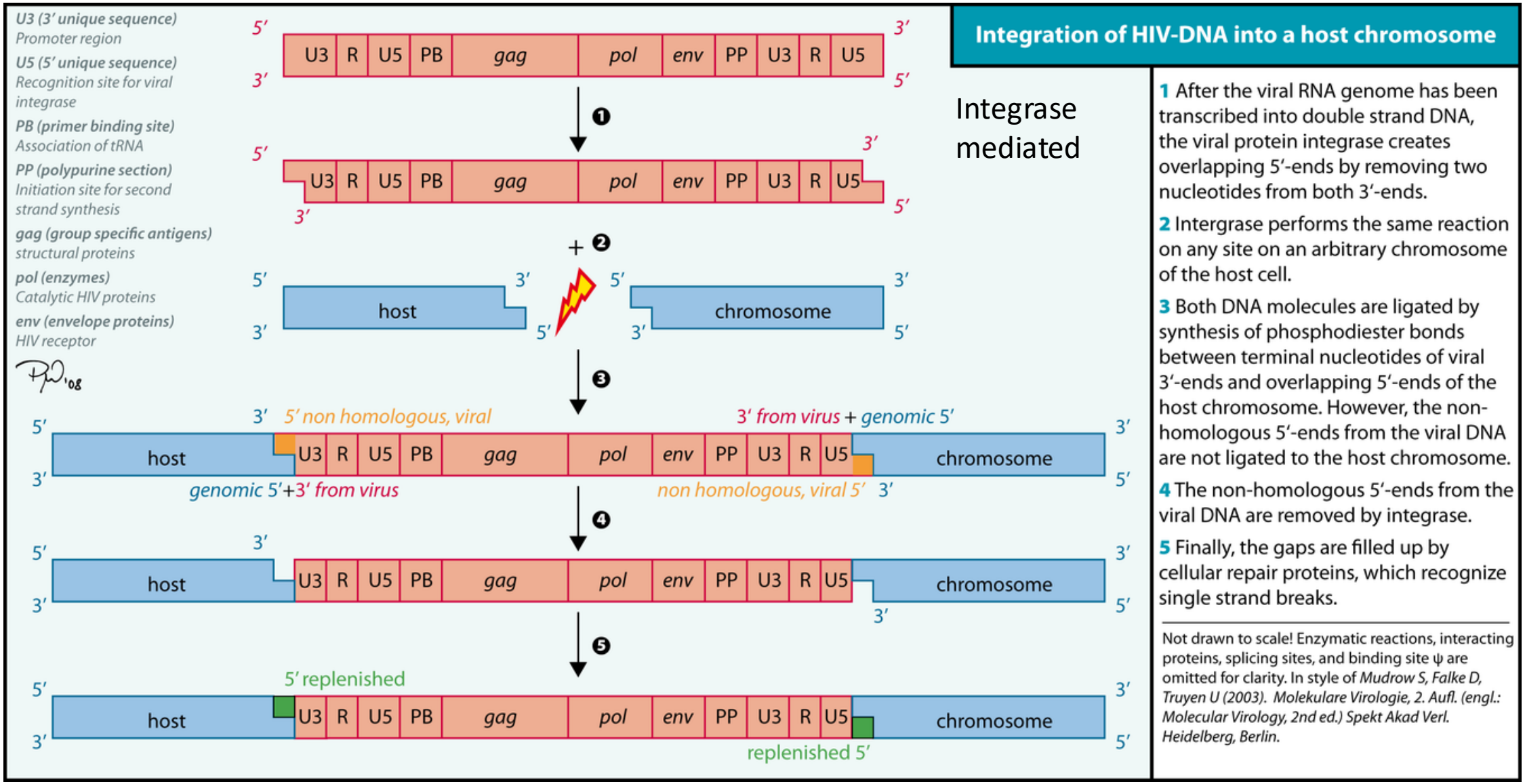
Integration



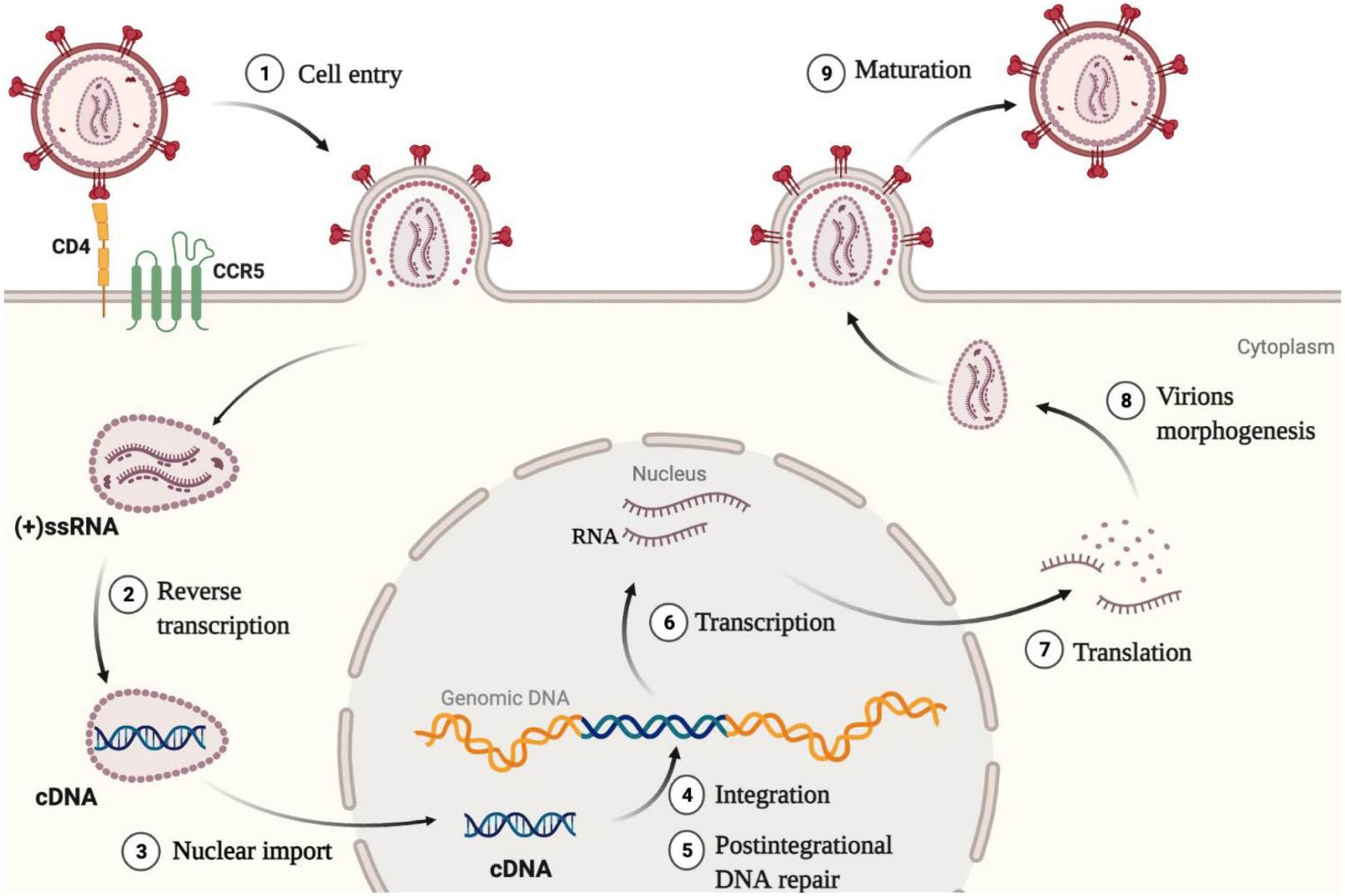


- processing of *provirus* by integrase
  - release of two nucleotides
- integration in target region of cellular genome
  - duplication of flanking host sequences

Integration

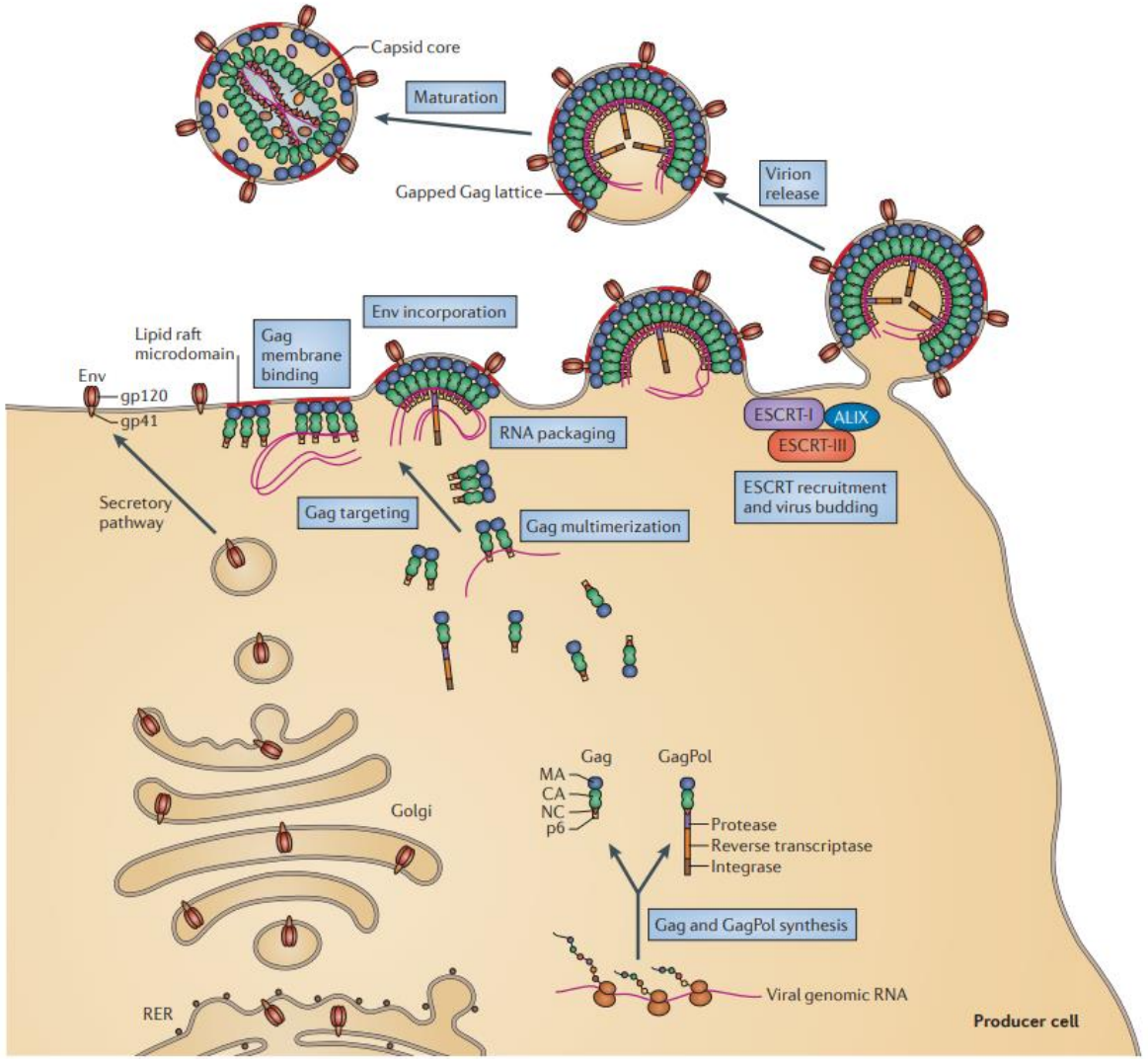


Requirements for virion formation: transcription and translation



Rozina et al. 2022

HIV budding and maturation



Viral glycoproteins

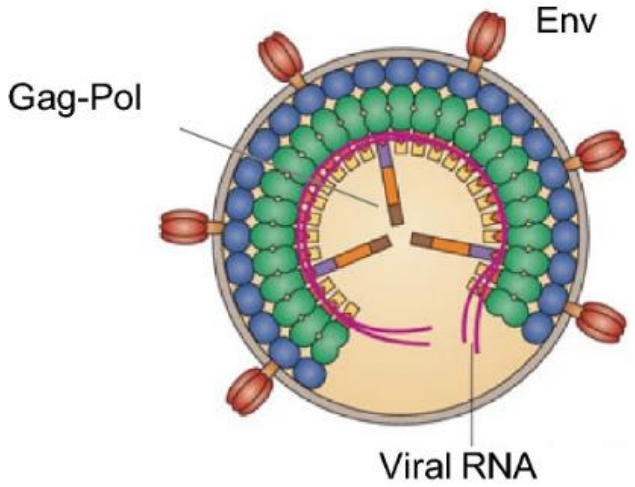
- processing through TGN
- transport via secretory pathway to cell membrane

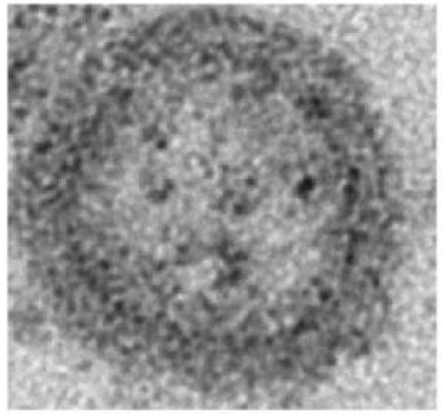
Gag, Gag/Pol

- synthesis of viral RNA in cytosol
- Gag multimerisation and binding to *lipid rafts*
- binding of viral genomic RNA to Gag
- transport of Gag/Pol to membrane
- budding initiation via ESCRT-complex
- maturation of new particles by proteolytic cleavage

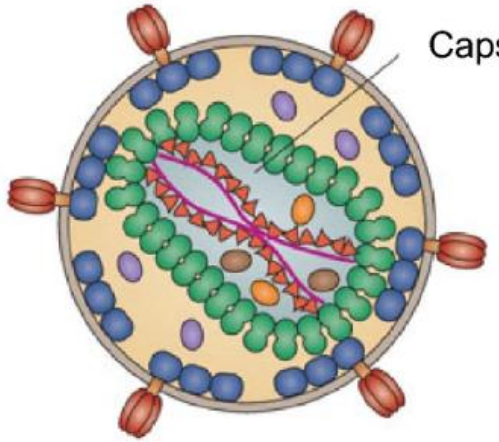
HIV budding and maturation

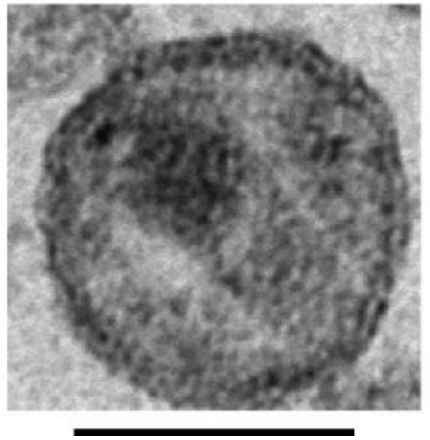
Immature HIV-1 virion



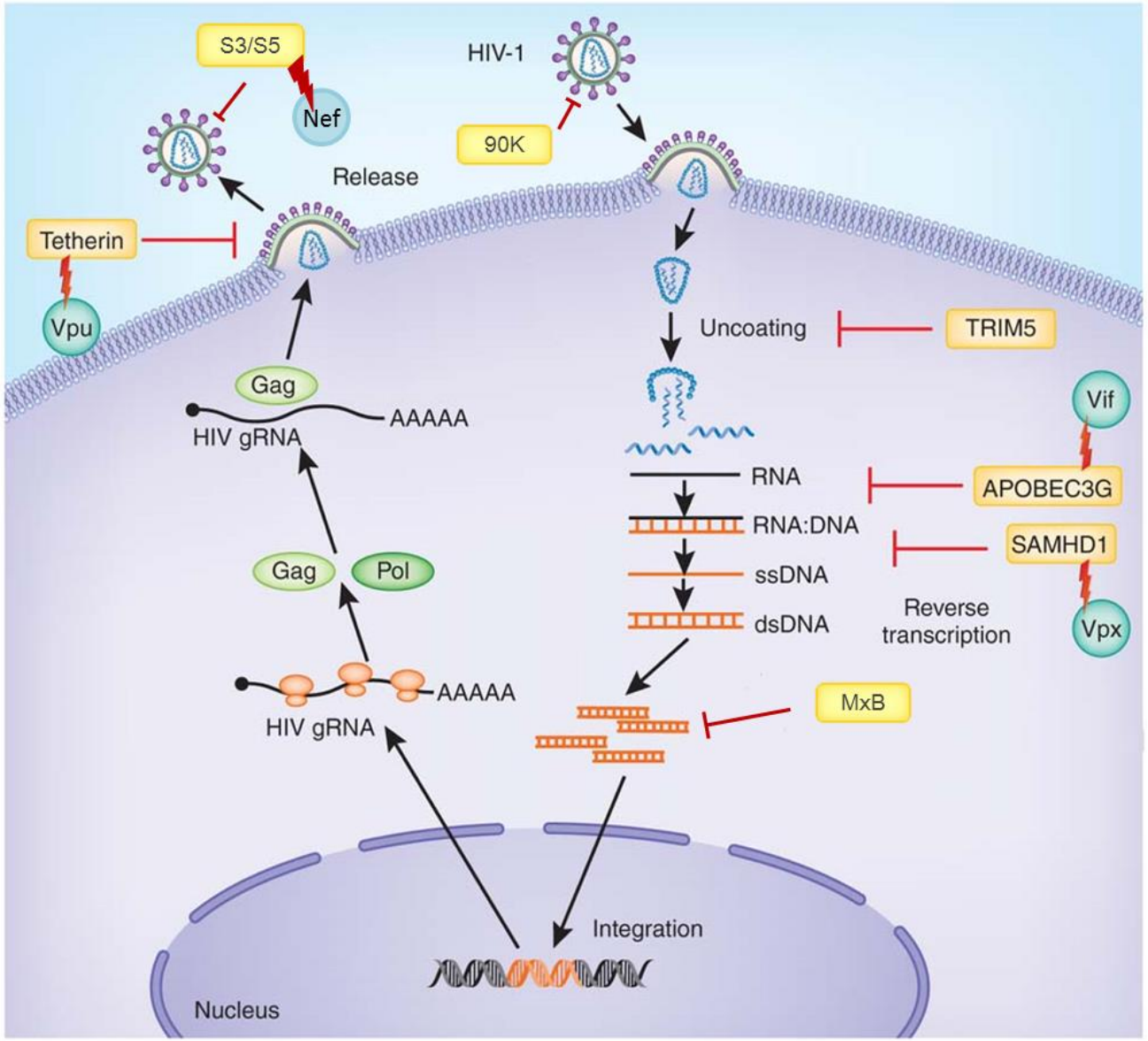


Mature HIV-1 virion

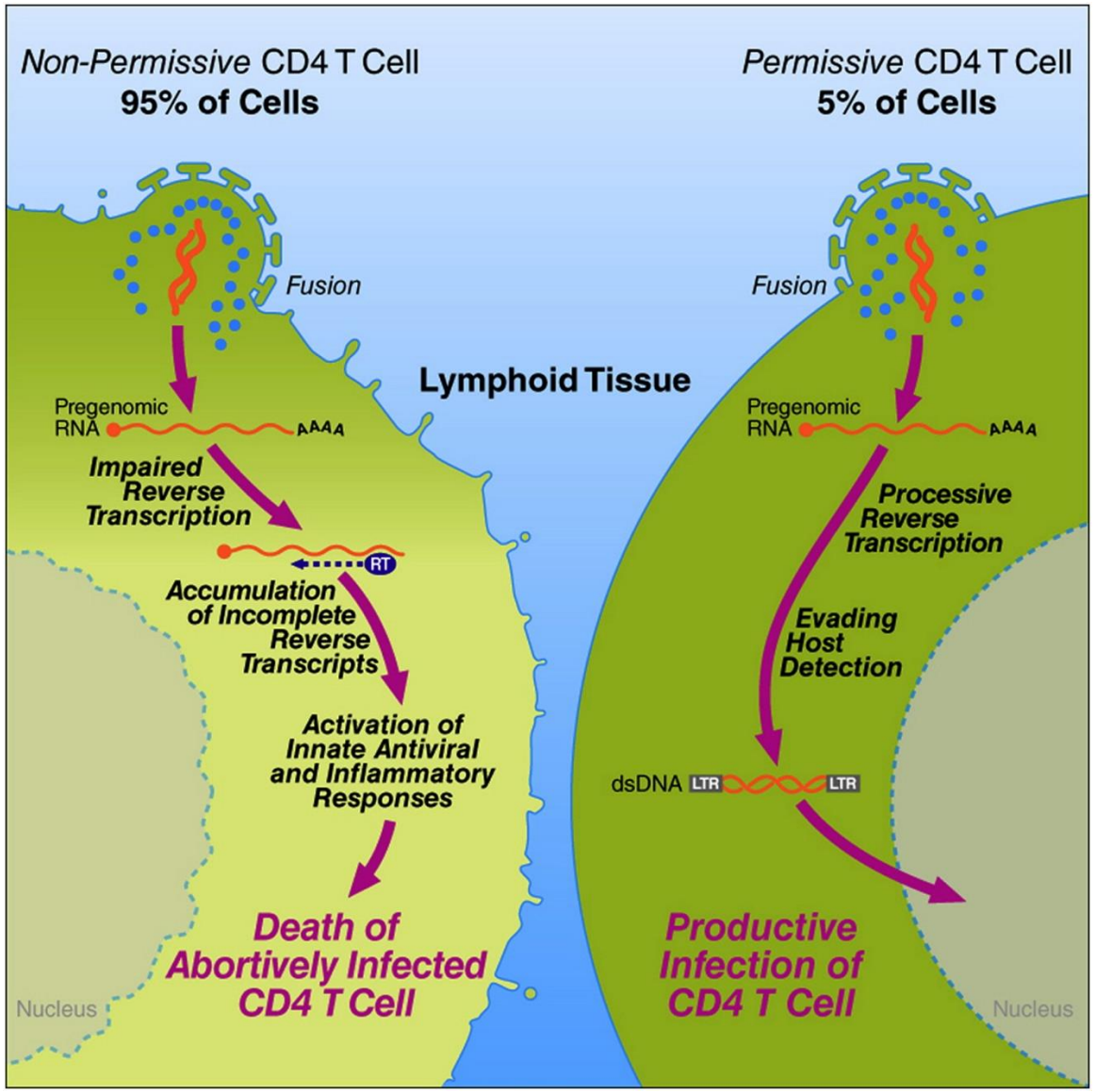




Innate immune response – how to restrict HIV replication



Infected != infected



- >95% of CD4 T cells dying after infection with HIV are not productively infected
- Cell death involves abortive infection of nonpermissive CD4 T cells
- The nonpermissive state leads to accumulation of abortive HIV reverse transcripts
- These transcripts elicit suicidal innate antiviral and inflammatory responses

HIV break #2

What have we learned?

1. HIV is a retrovirus – what makes a retrovirus a retrovirus?
2. How does HIV infect, replicate and releases virions?

   Which receptors or enzymes are involved?
3. How can the body use these steps to intervene?
4. Are all viruses bad?

HIV transmission

Ungeschützter Geschlechtsverkehr

Benutzen gebrauchter Nadeln
(Drogenkonsum)

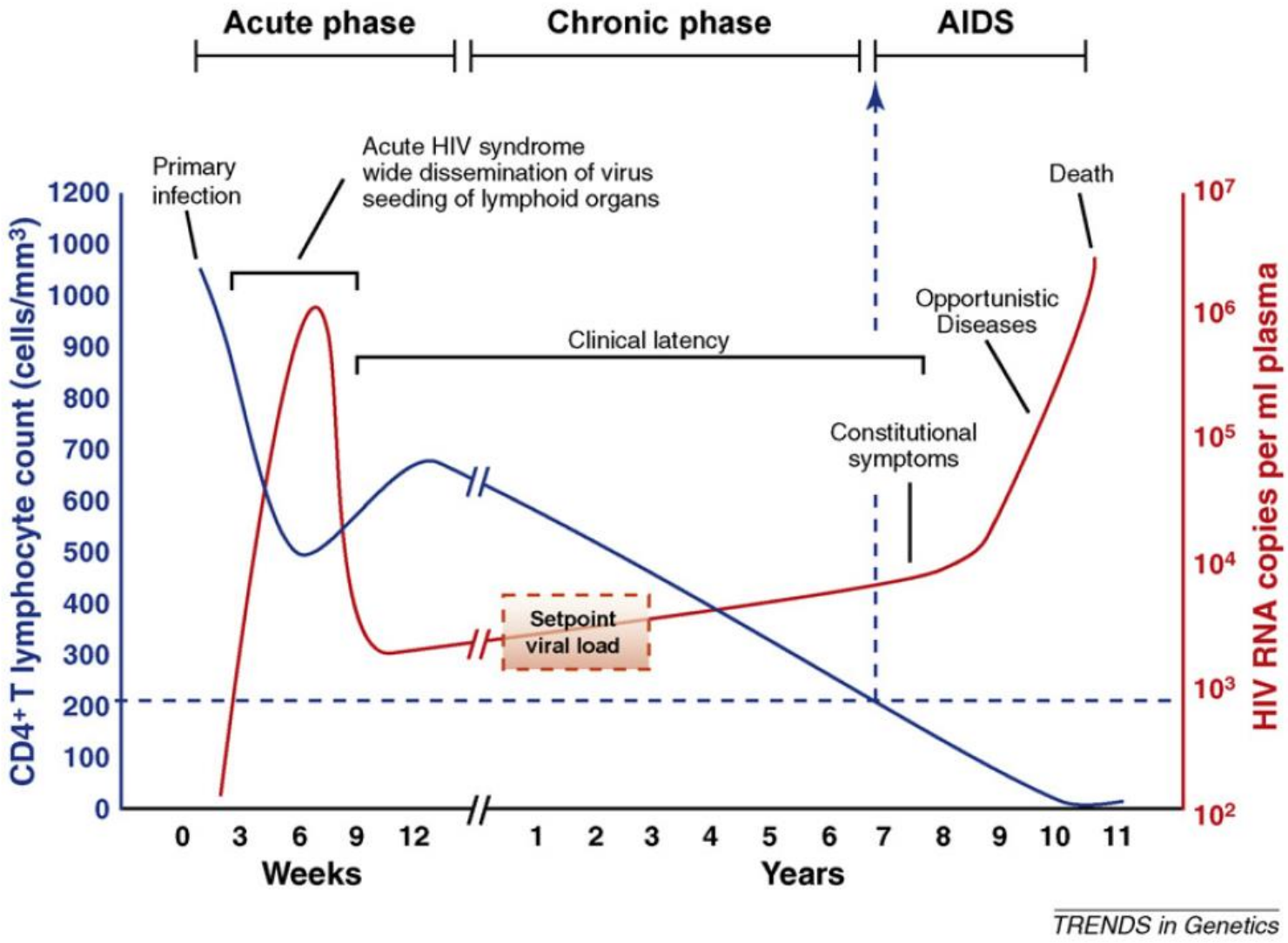
Blut Bluttransfusion

Geburt (von Mutter auf Kind)

Nicht-sterile Instrumente

Course of infection

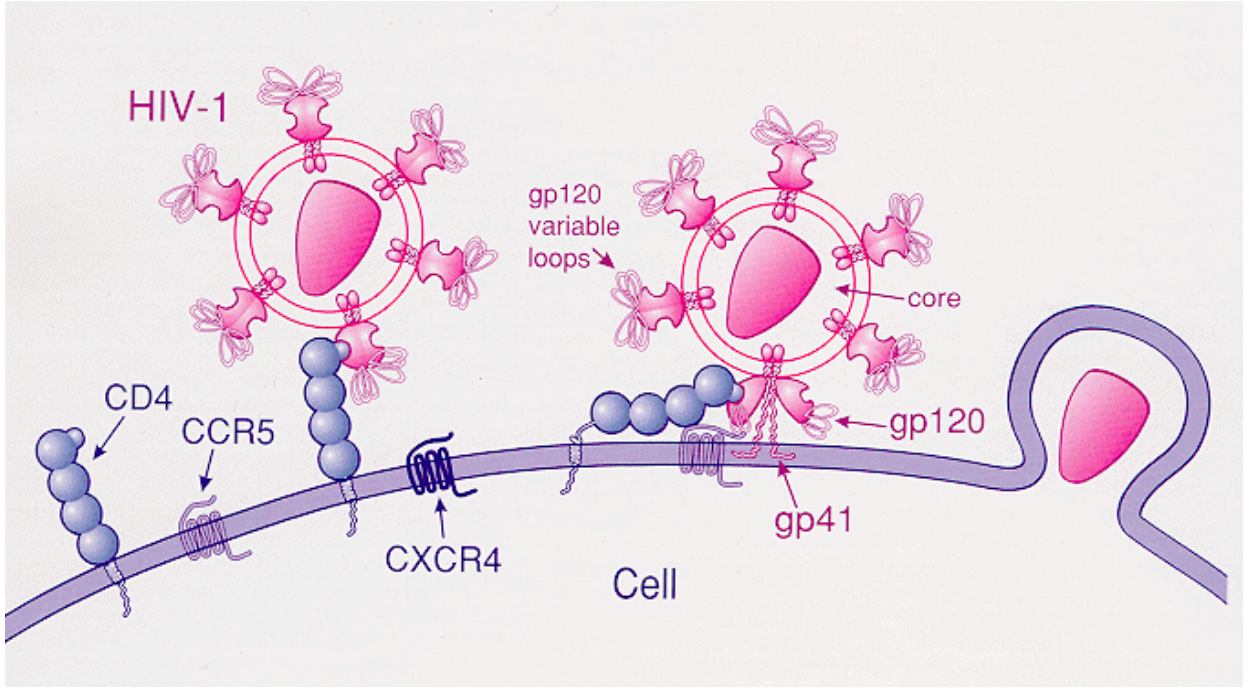
1. Acute HIV infection
   - 2 to 4 weeks after infection
   - Flu-like symptoms
   - HIV blood level very high
   - High risk of transmission
2. Chronic HIV infection
   - Asymptomatic or clinical latency
   - No HIV-related symptoms
   - HIV transmission still possible
   - Chronic infection progresses to AIDS in about 10 years
3. AIDS
   - CD4 cell count < 200 cells/mm^3
   - Accumulation of opportunistic infections
   - Without treatment survival ~ 3 years



HIV pathogenesis

Primärer Rezeptor: CD4

Korezeptoren: CCR5 und/oder CXCR4
- bestimmen Tropismus



- **T-Helferzellen**
- Makrophagen
- Monozyten
- dendritische Zellen

Zerstörung von CD4-Helferzellen

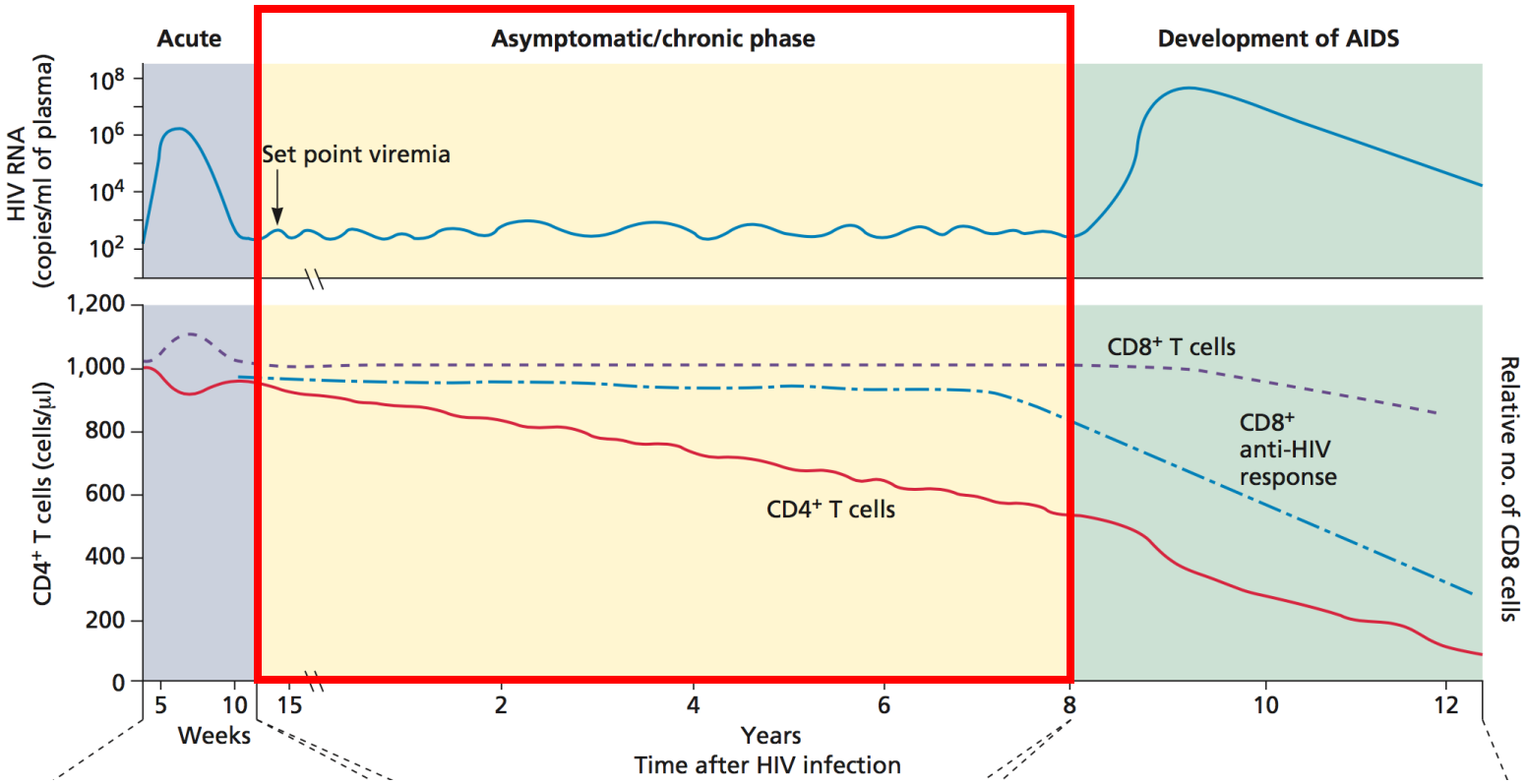
- direkte virale Abtötung infizierter Zellen (Apoptose, Zellschäden)
- indirekte Zerstörung infizierter Zellen durch gesunde Zellen des Immunsystems

Akute HIV Infektion (Stadium A)

- Bis ca. 4 Wochen nach der Infektion
- Symptome (unspezifisch und variabel):
  - Fieber
  - Hautausschlag
  - Müdigkeit
  - Lymphadenopathie
  - Hals- und Kopfschmerzen
  - Muskel- und Gelenkschmerzen
  - Orale und genitale Ulzerationen
- Klingt in der Regel innerhalb von 2 Wochen ab

- Oft nicht erkannt→ Grippe oder Pfeiffersche Drüsenfieber als Diagnose
- Hohe Viruslast in dieser Phase → hohe Infektiosität
- Darmassoziiertes lymphatisches Gewebe ist zentrales HIV-Ziel
  - 30-60% der T Gedächtniszellen werden innerhalb von 10 Tagen zerstört

Asymptomatische Phase (Stadium B)



- Gleichgewicht zwischen Virusvermehrung und Virusabwehr
- Dauer: Monate bis Jahrzehnte
- ggf. nicht-AIDS-definierende Erkrankungen u.a.
  - Mäßiges Fieber > 38,5 °C, Chronischer Durchfall, Gürtelrose (Herpes zoster), Pilzinfektionen der Mundhöhle

AIDS (Stadium C)

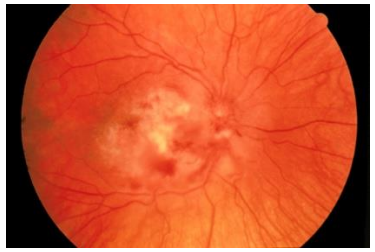
Opportunistische Infektionen:

- u.a. Lungenentzündungen durch *Pneumocystis carinii*, Pilzerkrankungen von Speiseröhre und Atemwegen, CMV Retinitis

Tumorerkrankungen

- Kaposi-Sarkom (Humane Herpesvirus 8 (HHV-8))
- Maligne Lymphome (u.a. durch EBV)

CMV Retinitis



Kaposi-Sarkom

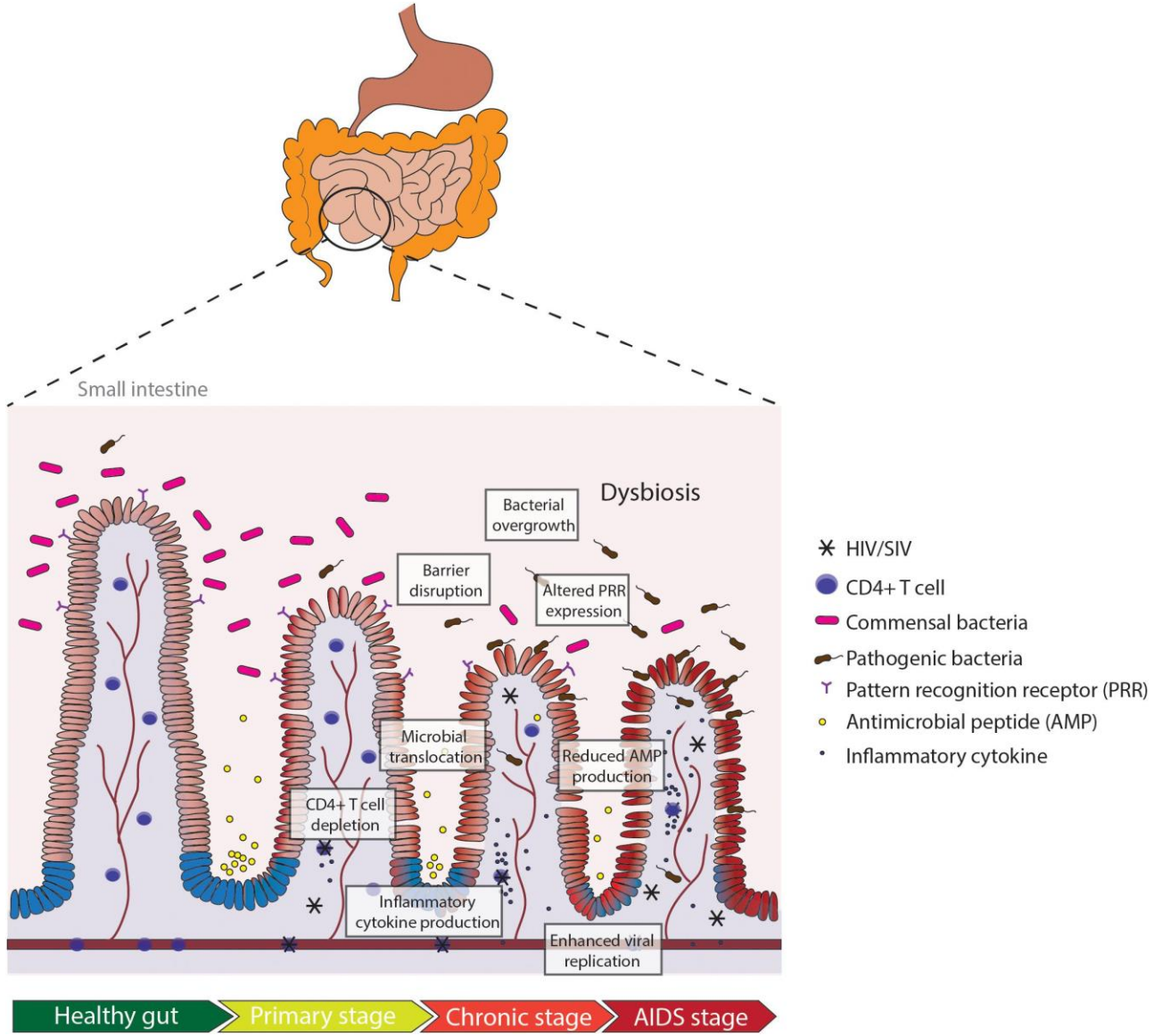
Burkittt-Lymphome

Wasting-Syndrom:

- starker Gewichtsverlust, anhaltender Durchfall, Fieber/Abgeschlagenheit

HIV-assoziierte Enzephalopathie

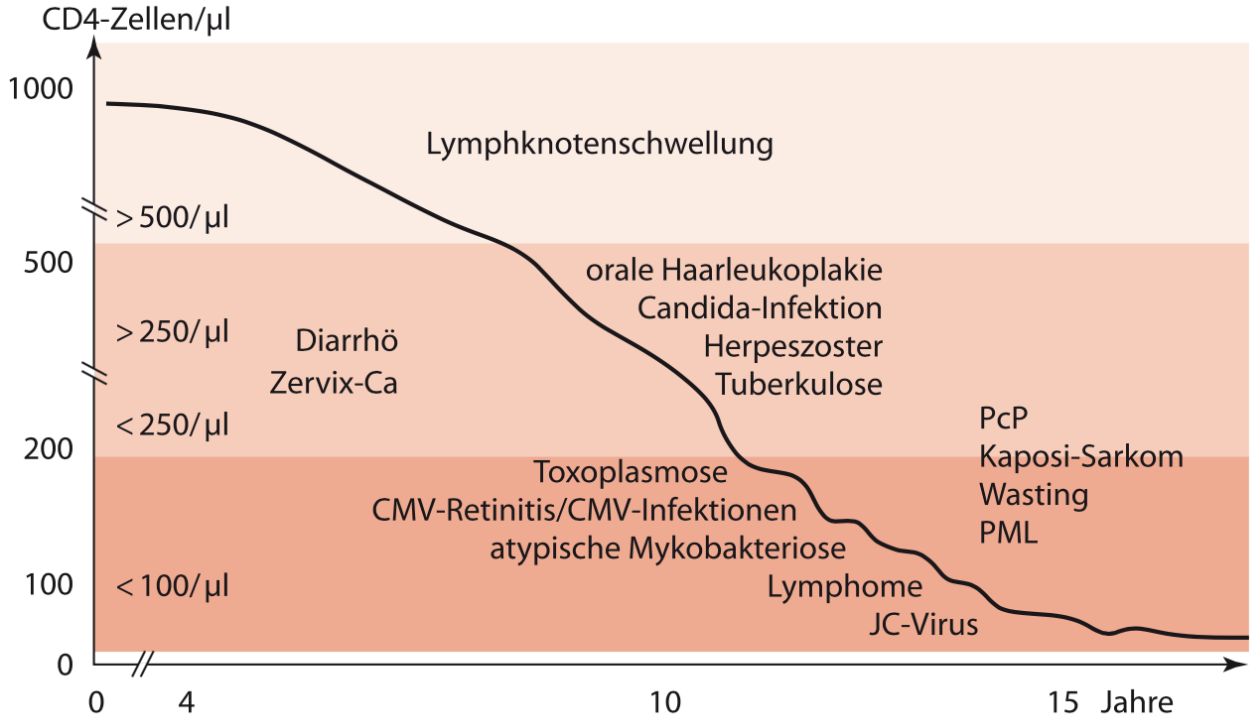
HIV tropism and pathogenesis in the gut



Crakes and Jiang 2019

What is AIDS?

Opportunistische Infektionen durch Erreger die bei immunkompetenten Personen keine oder nur milde Krankheitssymptome hervorrufen.



z.B. Kaposi-Sarkom durch Humanes Herpesvirus

Bei Erkrankten kommt es zu lebensbedrohlichen opp. Infektionen und Tumoren.

HIV break #3

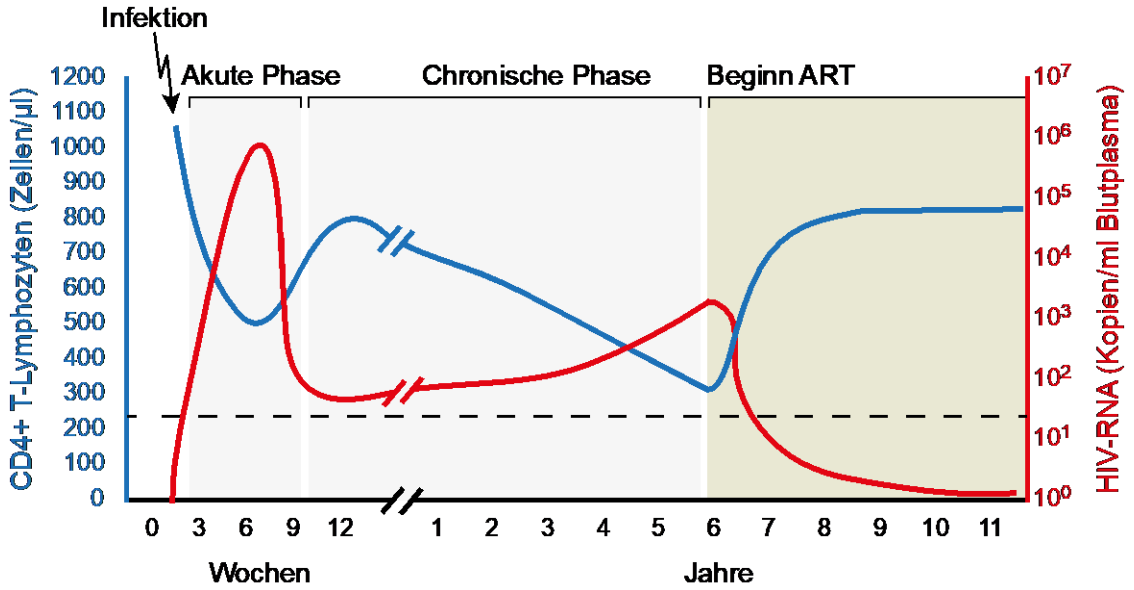
What have we learned?

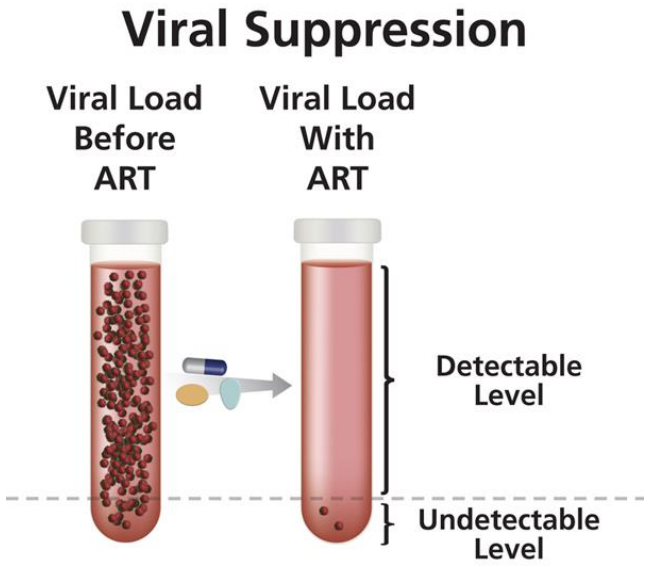
1. How is HIV transmitted?
2. Which phases of infection are typically observed during HIV infection?

   Are there markers for disease severity?

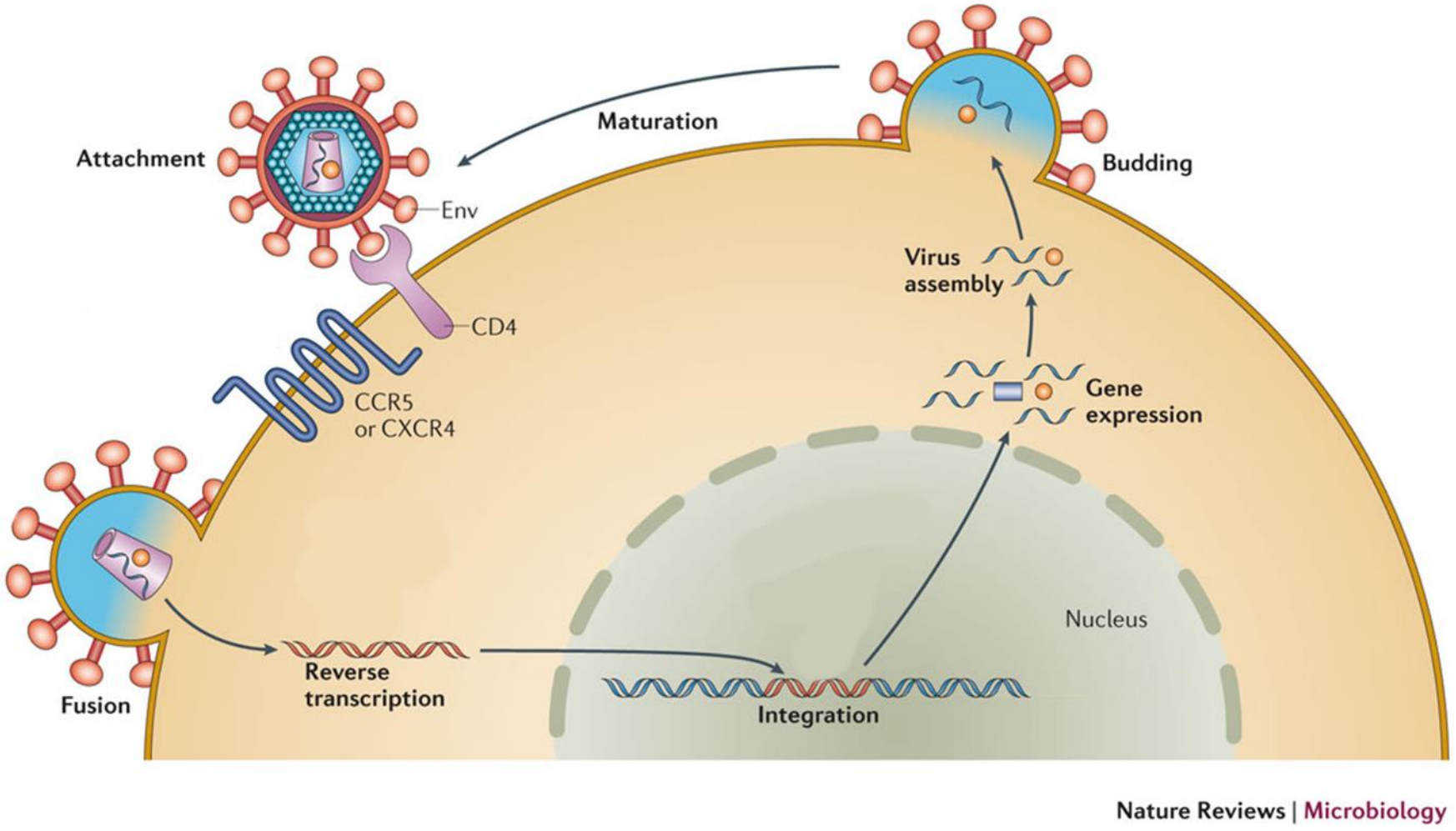
Therapeutics

- Reduction of plasma viral load under level of detection of RT-qPCR (50 copies/mL)
- Combination therapies and very good medical adherence of patients important
- Development of drug resistance slows down
- Otherwise: fast development of resistance up to virological failure

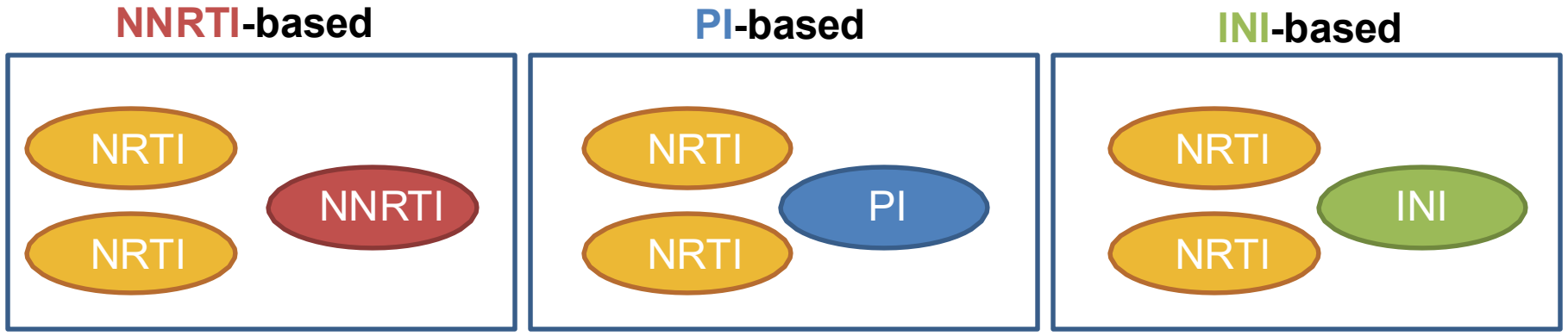




Where to hit


Attachment
Env
CD4
CCR5
or CXCR4
Fusion
Reverse
transcription
Integration
Nucleus
Gene
expression
Virus
assembly
Budding
Maturation
Nature Reviews | Microbiology

Therapeutics – antiretroviral therapy (ART)



substance:

NRTI- nucleoside reverse transcriptase inhibitor

NNRTI- non-nucleoside reverse transcriptase inhibitor

PI- protease inhibitor

INI- integrase inhibitor

EI- entry inhibitor

FI- fusion inhibitor

target:

Reverse Transcriptase (Blockierung katalytisches Zentrum)

Reverse Transcriptase (conformational changes)

Protease (wrong substrate)

Integrase (blocks catalytic activity)

gp120-V3/CCR5-Co-receptor (selective binding to CCR5 Co-receptor)

gp41 (direct binding to HR-2 domain of gp41)

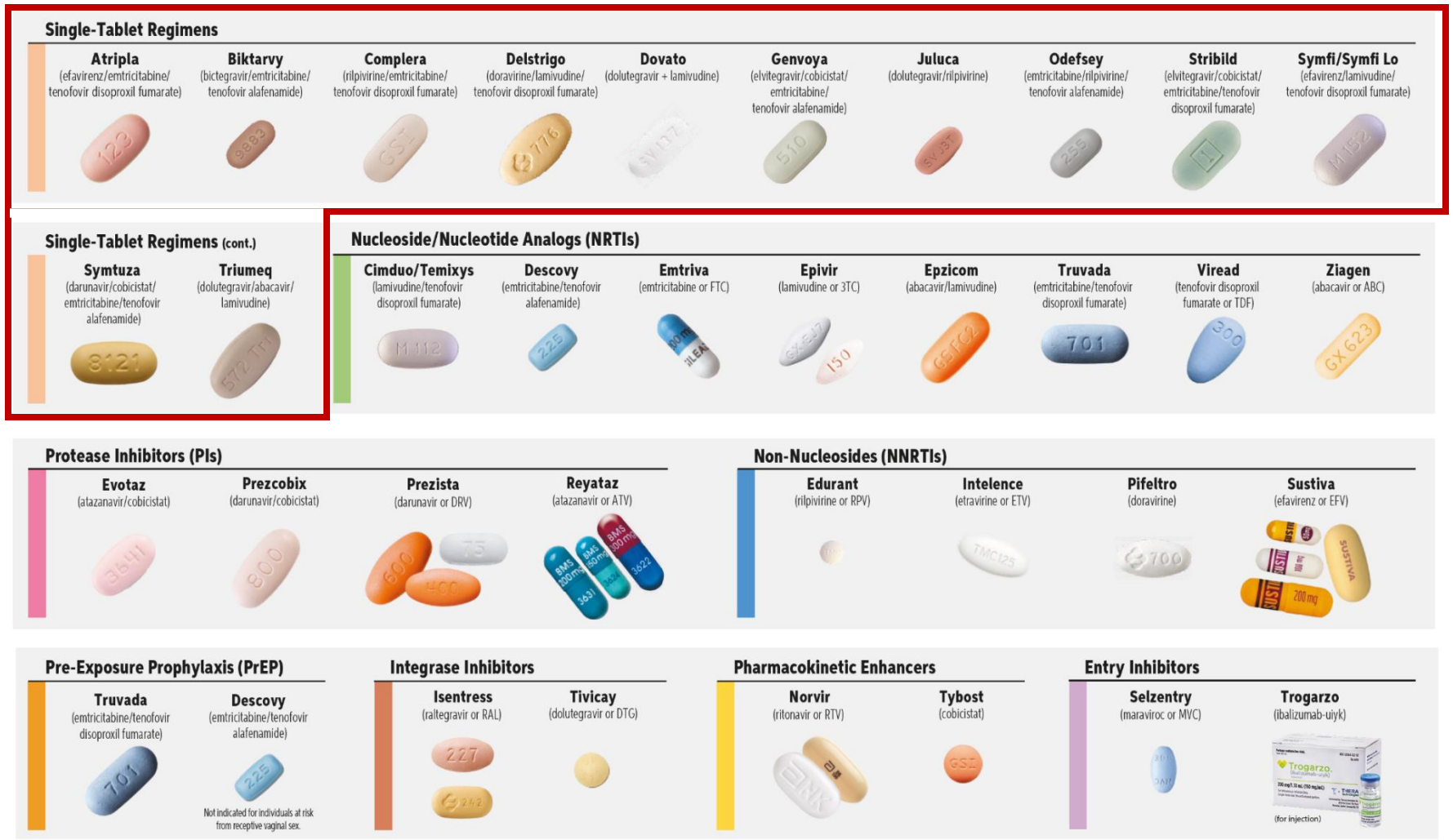
Therapeutics: Combination therapy NRTIs and PIs

	Combivir® + Crixivan® + Norvir®	Videx® + Zerit® + Viracept®	Combivir® + Norvir® + Agenerase®
morning			
evening			

complicated treatment regiments with
patients experiencing low levels of suffering

→ bad adherence

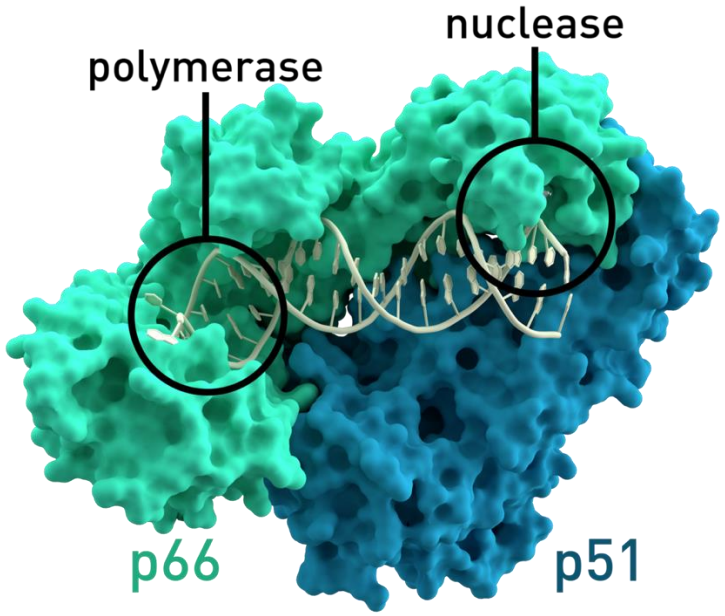
Therapeutics



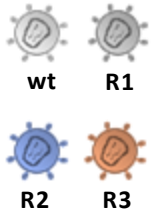
90’s: up to 20 pills daily in different intervals – today: 1 pill a day

Therapeutics

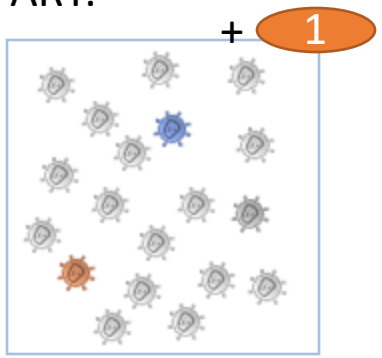
- extremely high production rates
  - 10^{10} new virions every day
- error prone RT
  - no *proof-reading* function
- “diploid” ssRNA genome
  - recombination through RT
- high prevalence rates
  - double infections



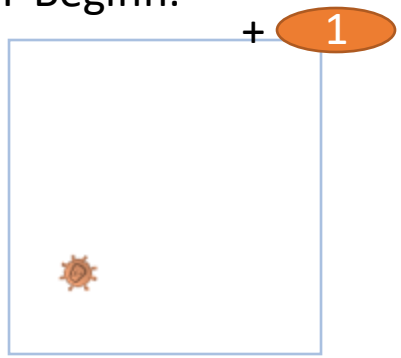
Therapeutics and resistance



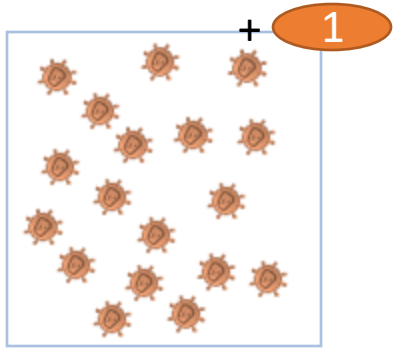
Vor ART:



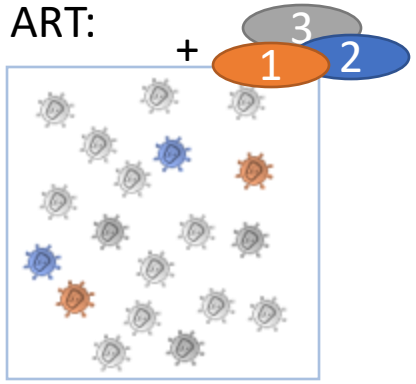
ART-Beginn:



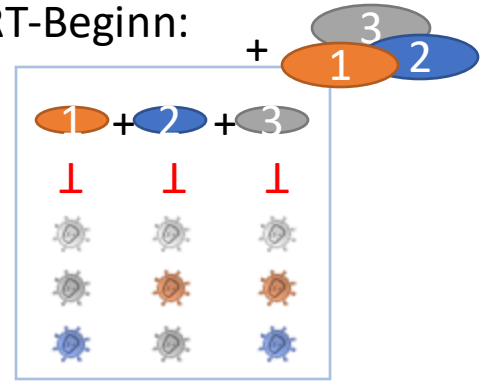
Im ART-Verlauf:



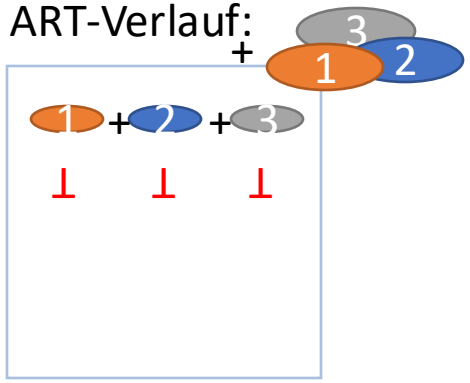
Vor ART:



ART-Beginn:



Im ART-Verlauf:



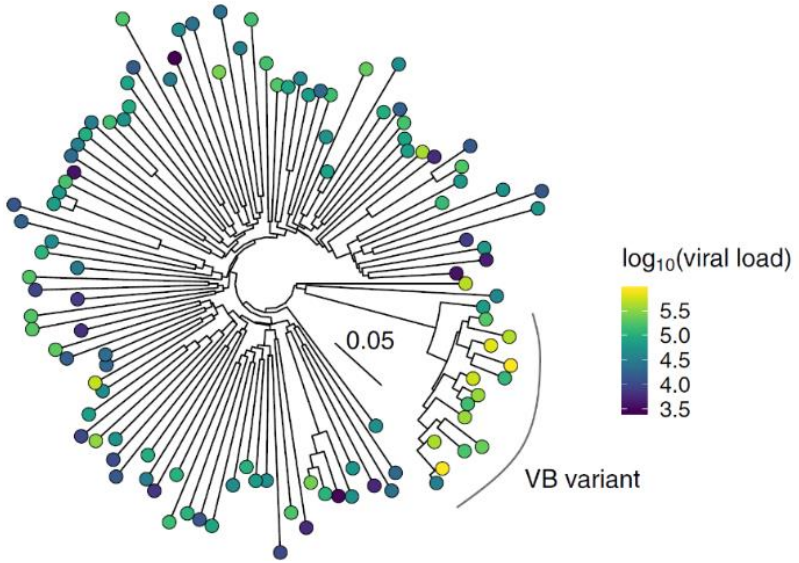
New highly virulent subtype B variant

RESEARCH ARTICLE | HIV

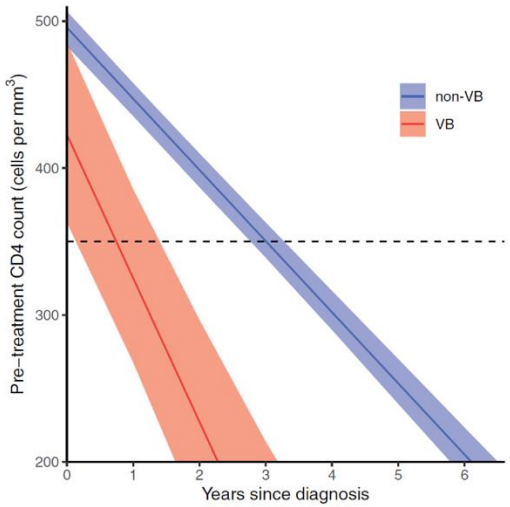
A highly virulent variant of HIV-1 circulating in the Netherlands

CHRIS WYMANT, DANIELA BEZEMER, FRANÇOIS BLANQUART, LUCA FERRETTI, ASTRID GALL, MATTHEW HALL, TANYA GOLUBCHIK, MARGREET BAKKER, SWEE HOE ONG, [...] THE BEEHIVE COLLABORATION† +25 authors Authors Info & Affiliations

SCIENCE • 3 Feb 2022 • Vol 375, Issue 6580 • pp. 540-545 • DOI: 10.1126/science.abk1688

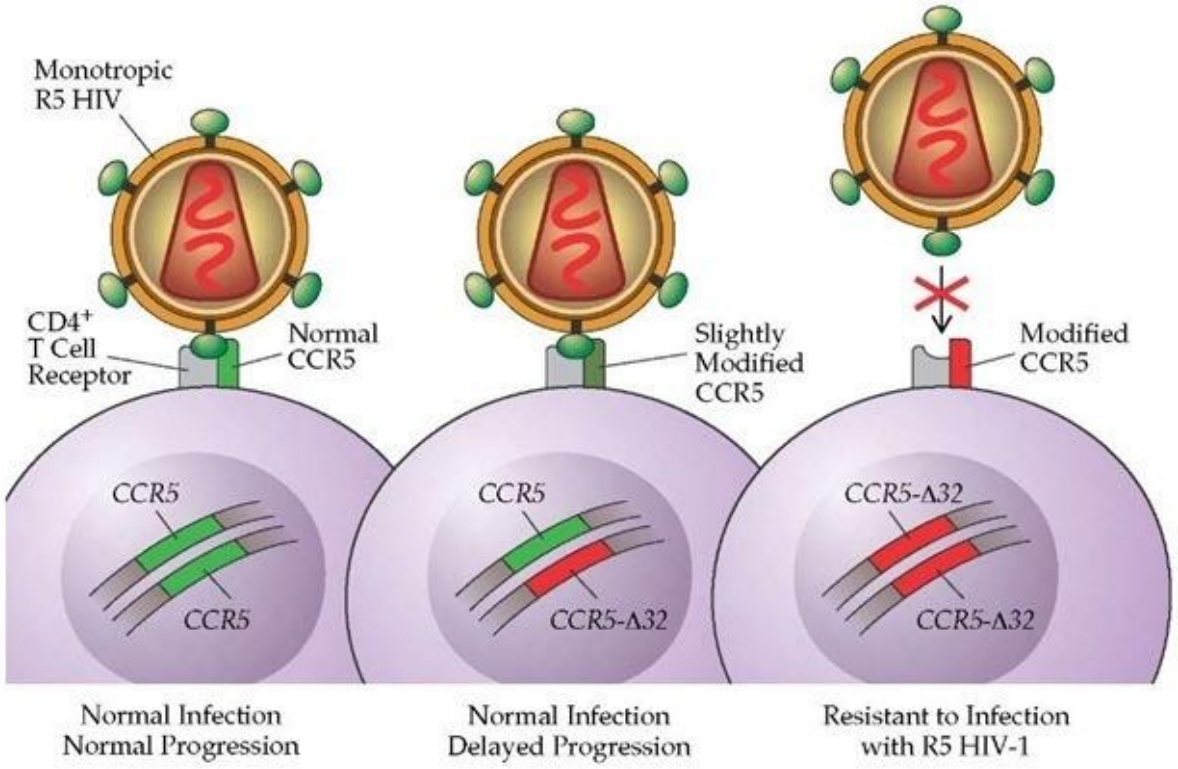


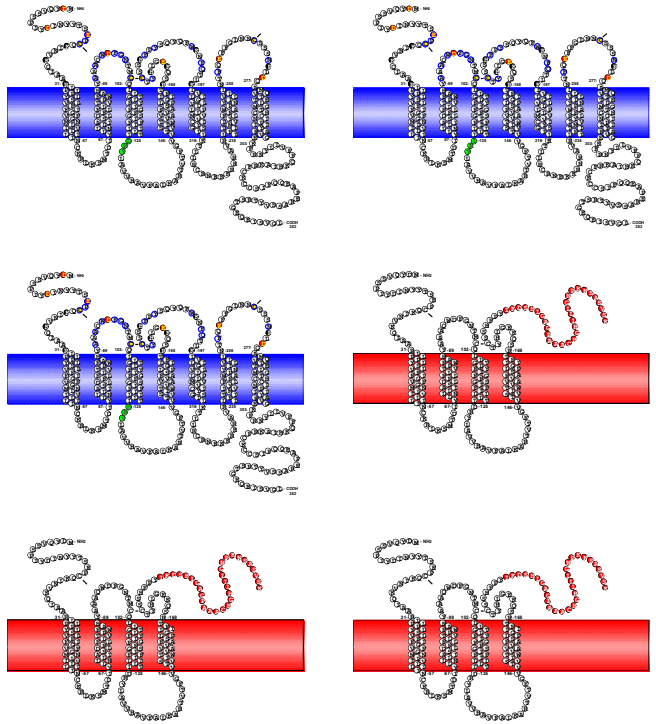
- HIV-1 VB - *virulent subtype B*
- evolved ca. 1998 in the Netherlands
- viral load ca. 3,5-5,5 times higher
- progression to AIDS without therapy twice as fast



- **But:**
  - **ART is potent**
  - **number of new infections seems to decline**

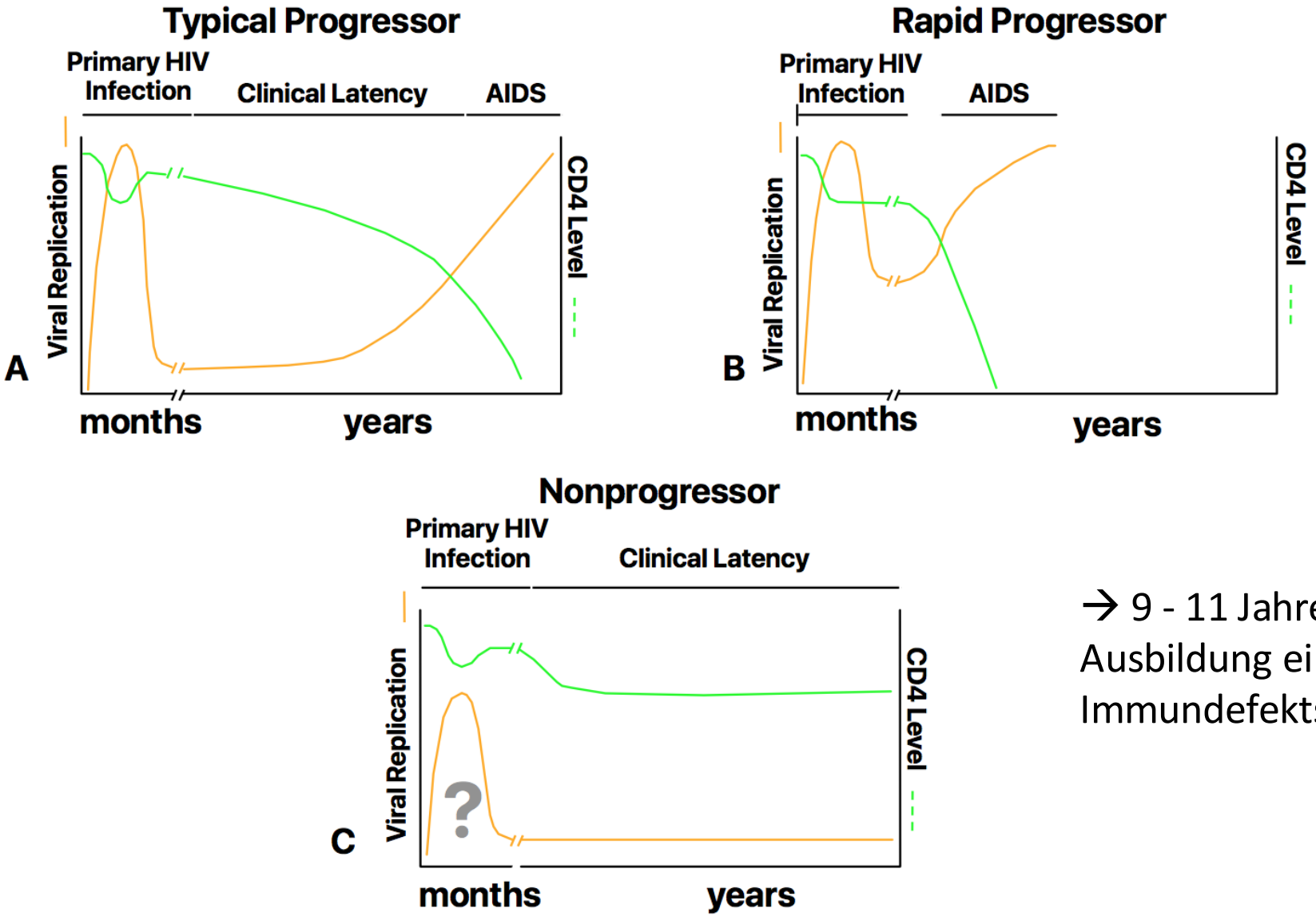
Natural protection CCR5Δ32





- wild type
  - not protected
- heterozygous
  - not protected
  - delayed progression
- homozygous for CCR5Δ32
  - protected
  - immunocompetent
  - 1% of Caucasian population

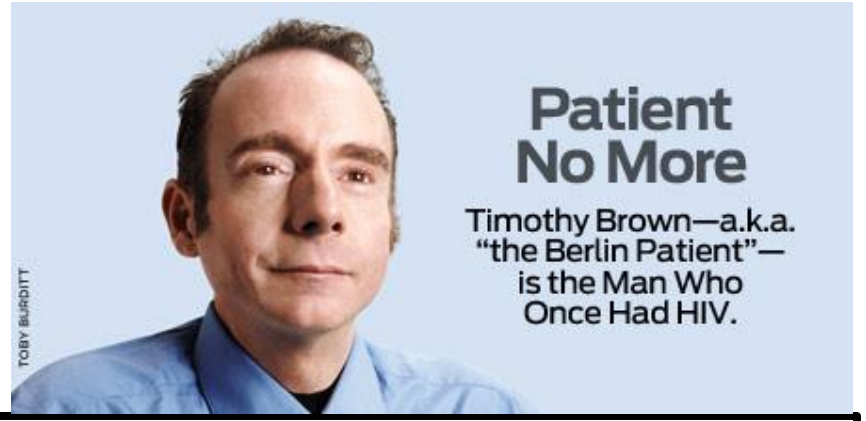
Variabler Verlauf der HIV-1-Infektion



→ 9 - 11 Jahre nach Erstinfektion bis zur Ausbildung eines schweren Immundefekts

The cure

- The „Berlin“ patient
  - acute myoloide leucaemia
  - allogenic stem cell transplantation
  - CCR5Δ32 homozygous donor
- no ART necessary
- no HIV-1 detectable



LETTER

https://doi.org/10.1038/s41586-019-1027-4

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

Ravindra K. Gupta[1,2,3,4,5]*, Sultan Abdul-Jawad[1], Laura E. McCoy[1], Hoi Ping Mok[4], Dimitra Peppa[3,6], Maria Salgado[7], Javier Martinez-Picado[7,8,9], Monique Nijhuis[10], Annemarie M. J. Wensing[10], Helen Lee[11], Paul Grant[12], Eleni Nastouli[12], Jonathan Lambert[13], Matthew Pace[6], Fanny Salasc[4], Christopher Monit[1], Andrew J. Innes[14,15], Luke Muir[1], Laura Waters[3], John Frater[6,16], Andrew M. L. Lever[4,17], Simon G. Edwards[3], Ian H. Gabriel[14,15,18,19] & Eduardo Olavarria[14,15,19]

February 12, 2009
N Engl J Med 2009; 360:692-698
DOI: 10.1056/NEJMoa0802905

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

Lenacapavir

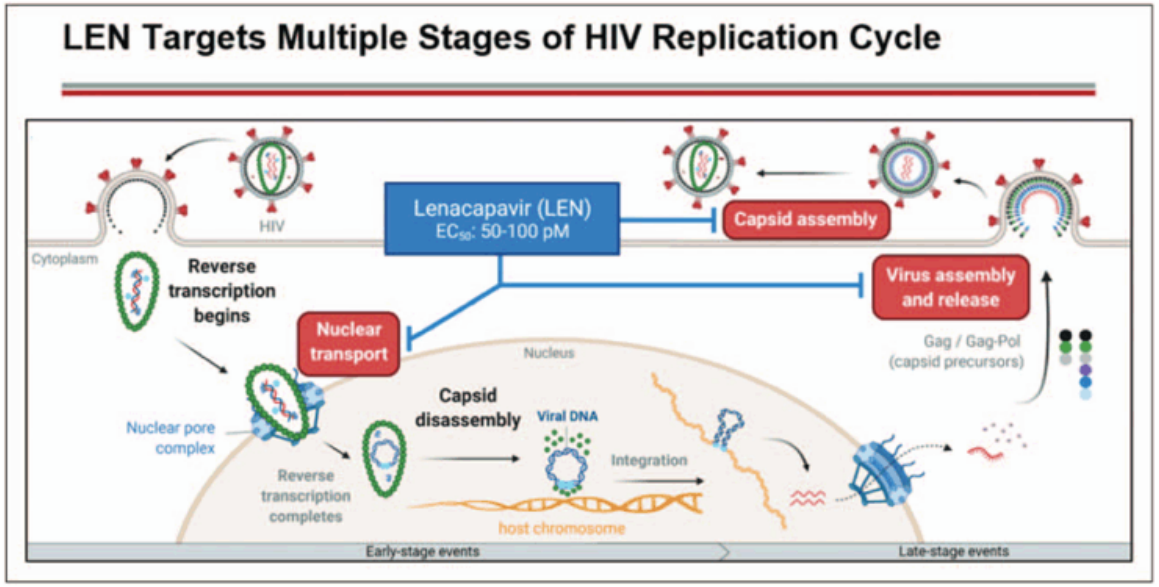
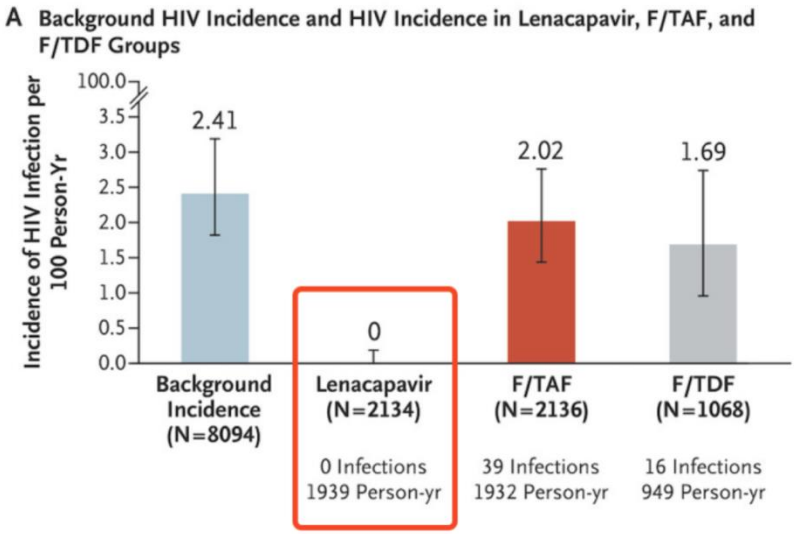
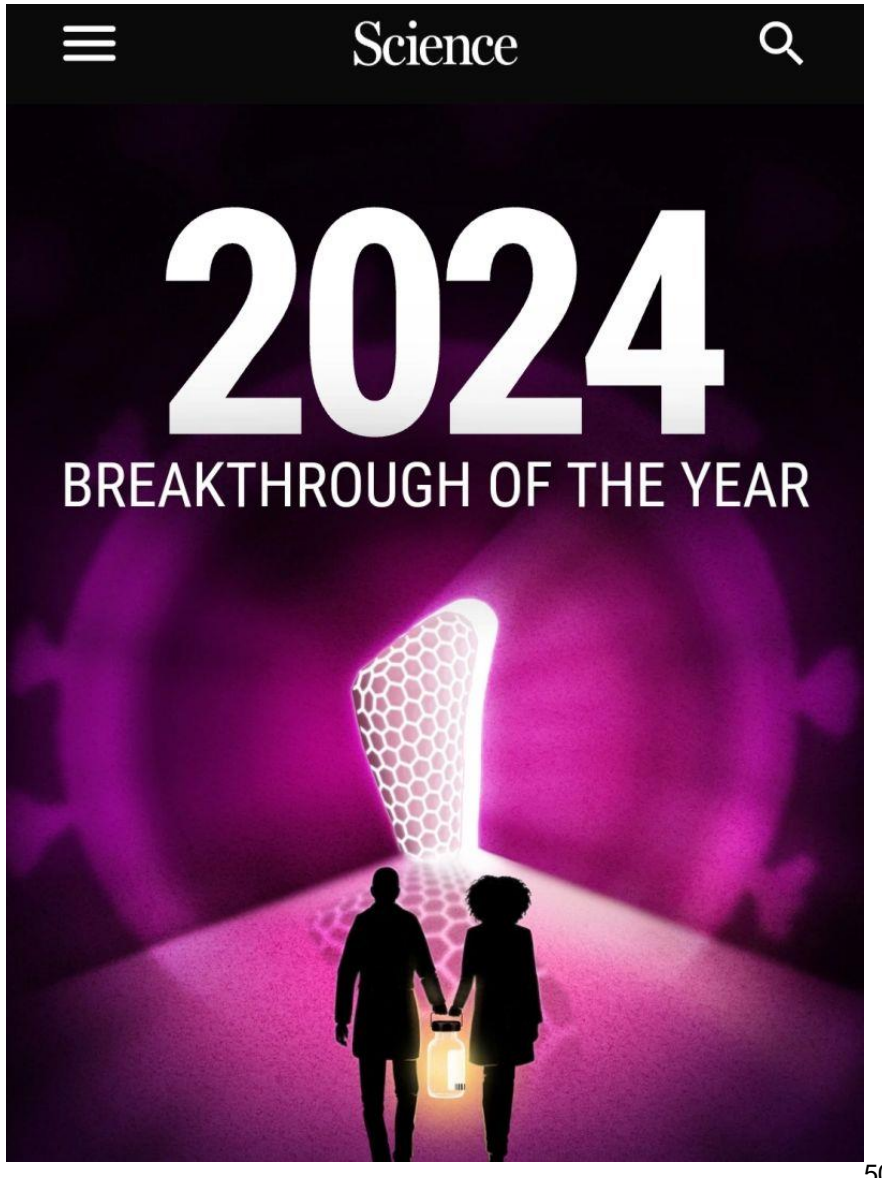


FIGURE 1. Lenacapavir targets multiple stages of the HIV replication cycle. Adapted from [4**,5].





HIV break #4

What have we learned?

1. What is required for efficient therapy?

   How did therapy change with the years?
2. How do drug resistant mutations evolve?
3. What does a patient need to clear HIV infection?

Summary

1. Discovery & origin of HIV
2. High clinical relevance
3. Classification & structure
4. Replication cycle
5. Other retroviruses
6. Transmission & pathogenesis
7. Therapy & resistance
8. Functional clearance