

Human Immunodeficiency Viruses

André Gömer

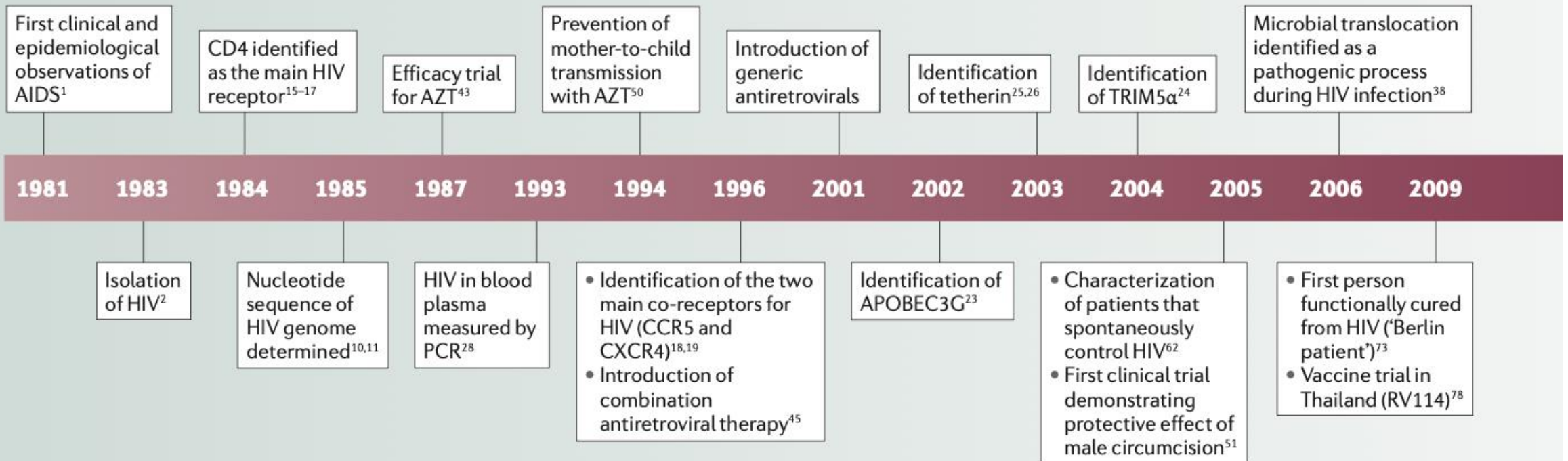
Department of Molecular & Medical Virology

content

- Discovery & origin
- Epidemic
- Classification
- Replication & transmission
- Course of infection & pathogenesis
- Therapy & resistance & cure

HIV research timeline

Timeline | Key moments in HIV research



AZT, azidothymidine; TRIM5α, tripartite motif-containing 5α; CCR5, CC-chemokine receptor 5; CXCR4, CXC-chemokine receptor 4; iPrex, initiative for pre-exposure prophylaxis.

First cases and discovery

CENTERS FOR DISEASE CONTROL

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

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

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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.

20,000 ARE INFECTED... AND IT'S GETTING WORSE

Britain threatened by gay virus plague

By BARBARA JONES, Medical Correspondent

THE killer AIDS virus is now spreading at the rate of about 100 cases a day in London alone.

Doctors estimate that as many as 20,000 people are already infected and will be carriers for life.

New curb on AIDS peril

Killer blood tests ordered at donor centres

Worried about funeral expenses?

REAGAN'S FURY AS PLO BOSS SLIPS NET

I'D SHOOT MY SON IF HE HAD AIDS, SAYS VICAR!

TV Star fails for polo as worth a mint!

MY DOOMED GAY PLAGUE

News of the World investigates the deadly

Challenger's Men Take a Space Walk

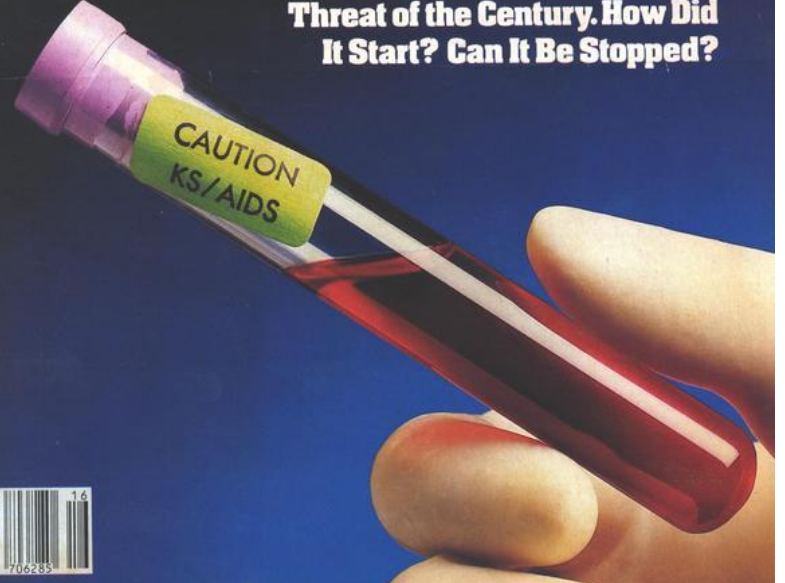
Russia's Spies Get the Boot

Newsweek

April 18, 1983 / \$1.50

EPIDEMIC

The Mysterious and Deadly Disease Called AIDS May Be the Public-Health Threat of the Century. How Did It Start? Can It Be Stopped?



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

First cases and discovery

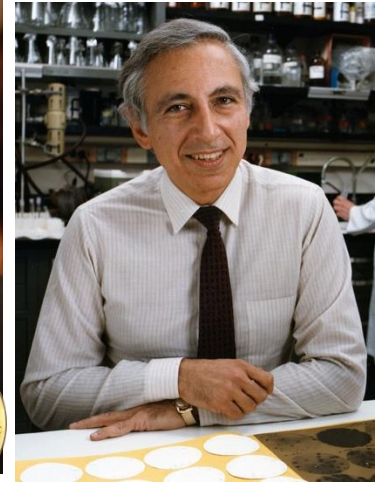
- 1981 Increased number of reports of patients with rare diseases (Kaposi sarcoma, Pneumocystis pneumonia)
- 1982 Disease described as AIDS
- 1983 Barré-Sinoussi/Montagnier & Gallo, independently, published the identification of a novel retrovirus
-> later HIV
- 1987 Dispute over diagnostics ownership settled by US and French government



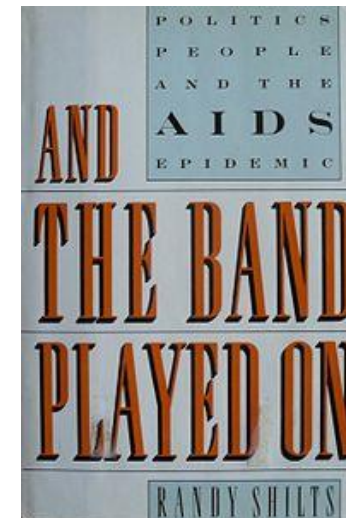
Françoise
Barré-Sinoussi



Luc
Montagnier

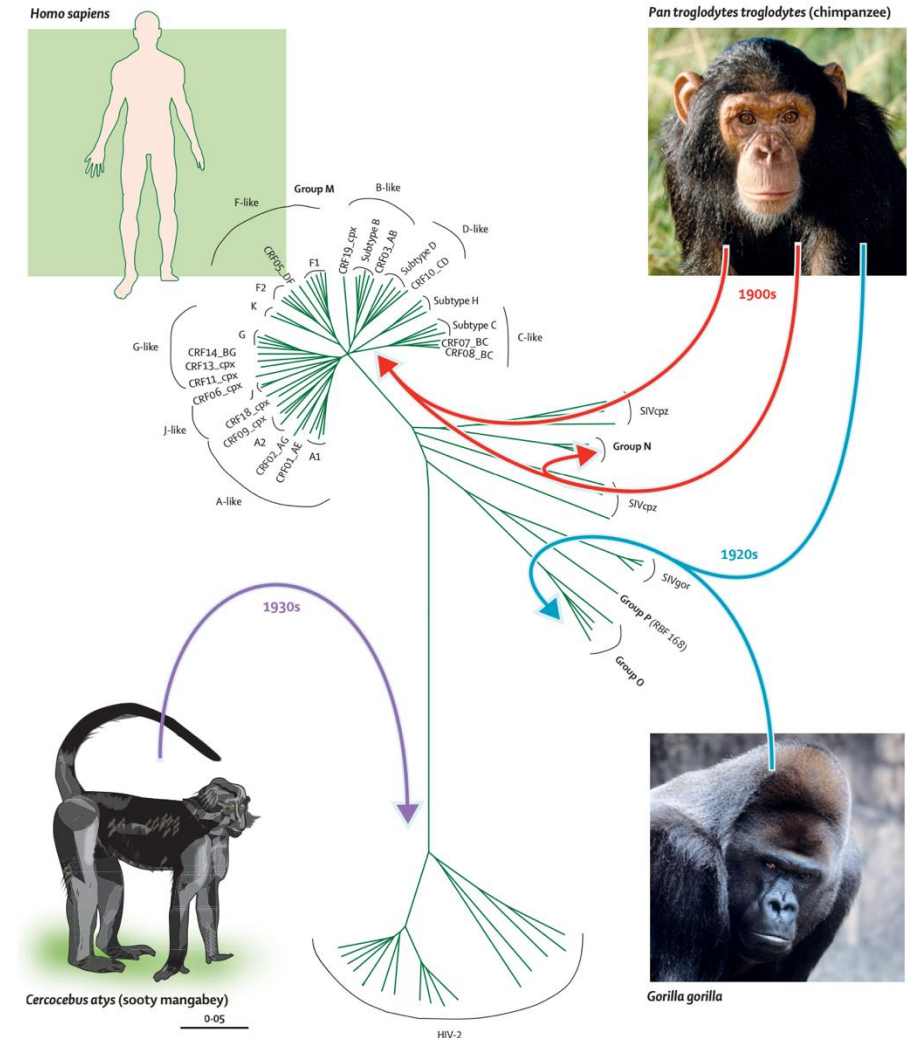
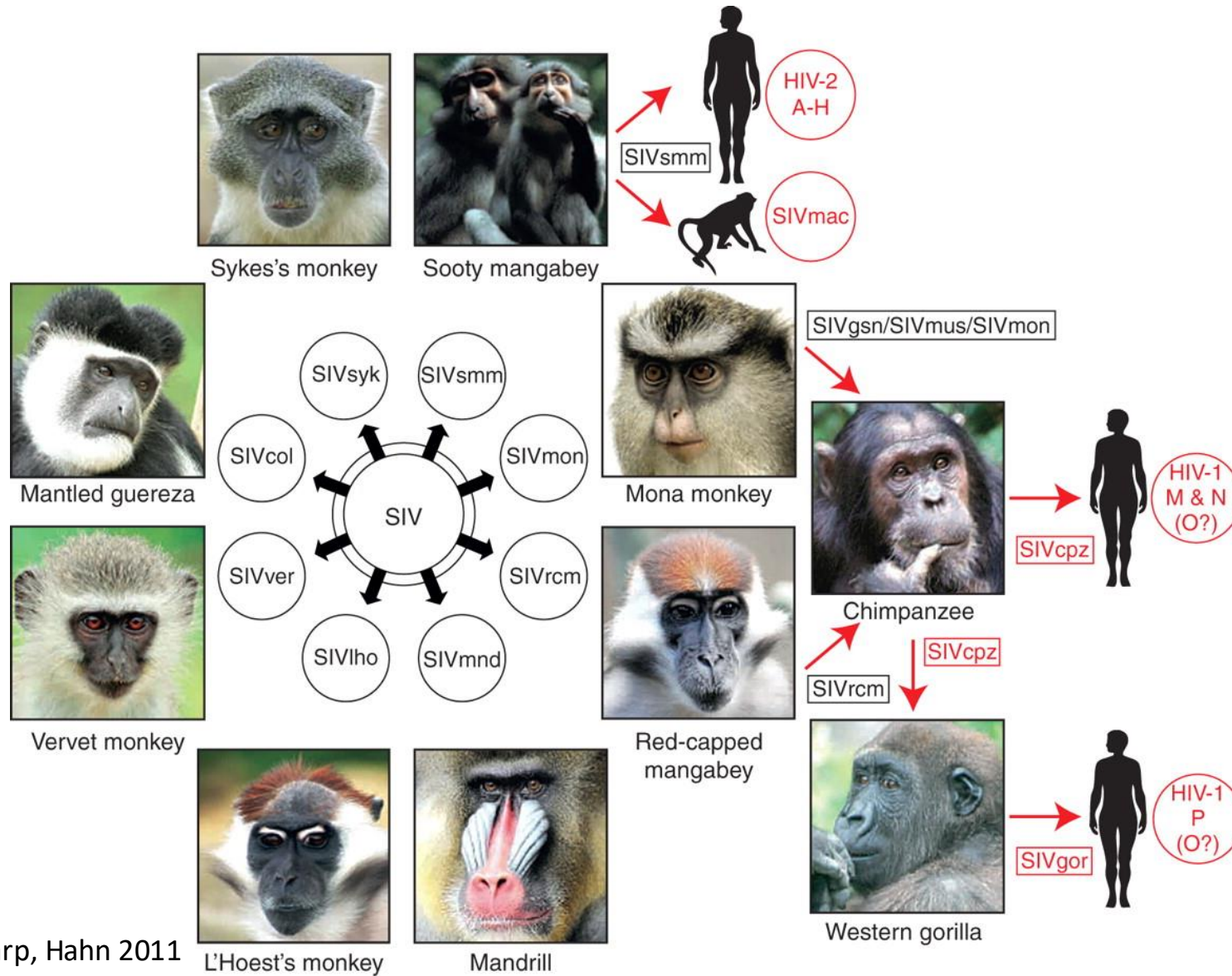


Robert
Gallo

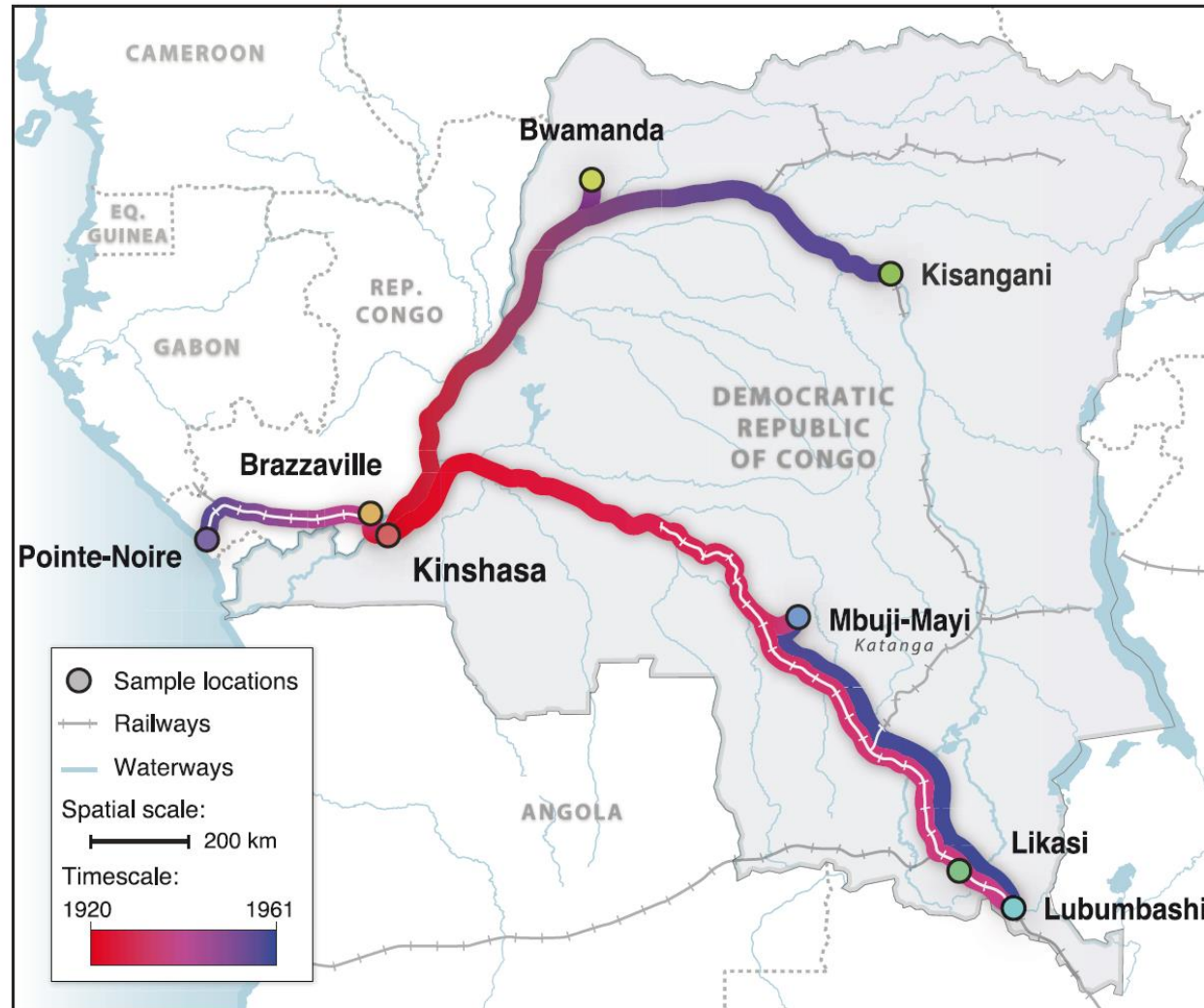


Book and movie about the drama how HIV has been discovered

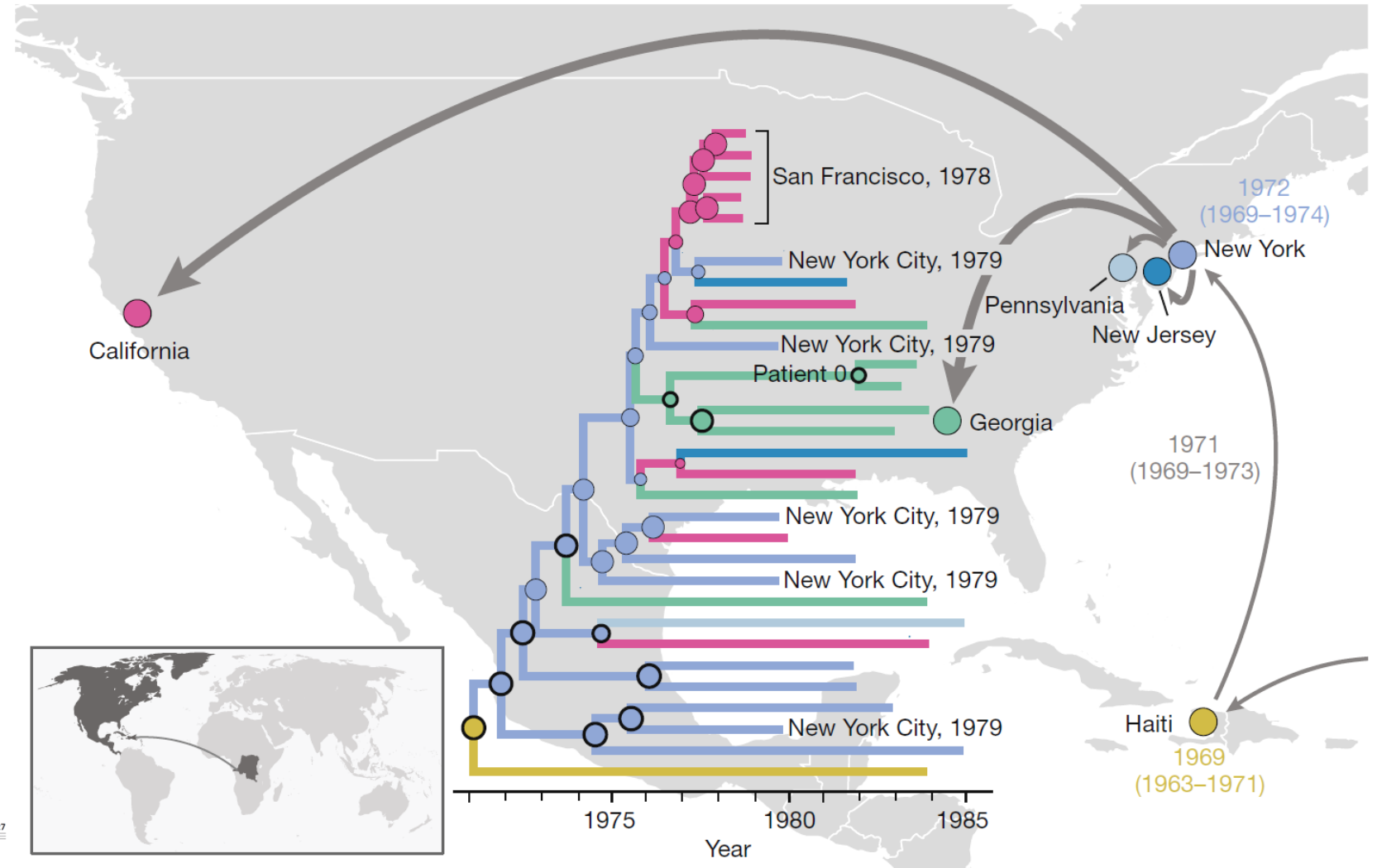
Origin of HIV



The early events in the HIV epidemic



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

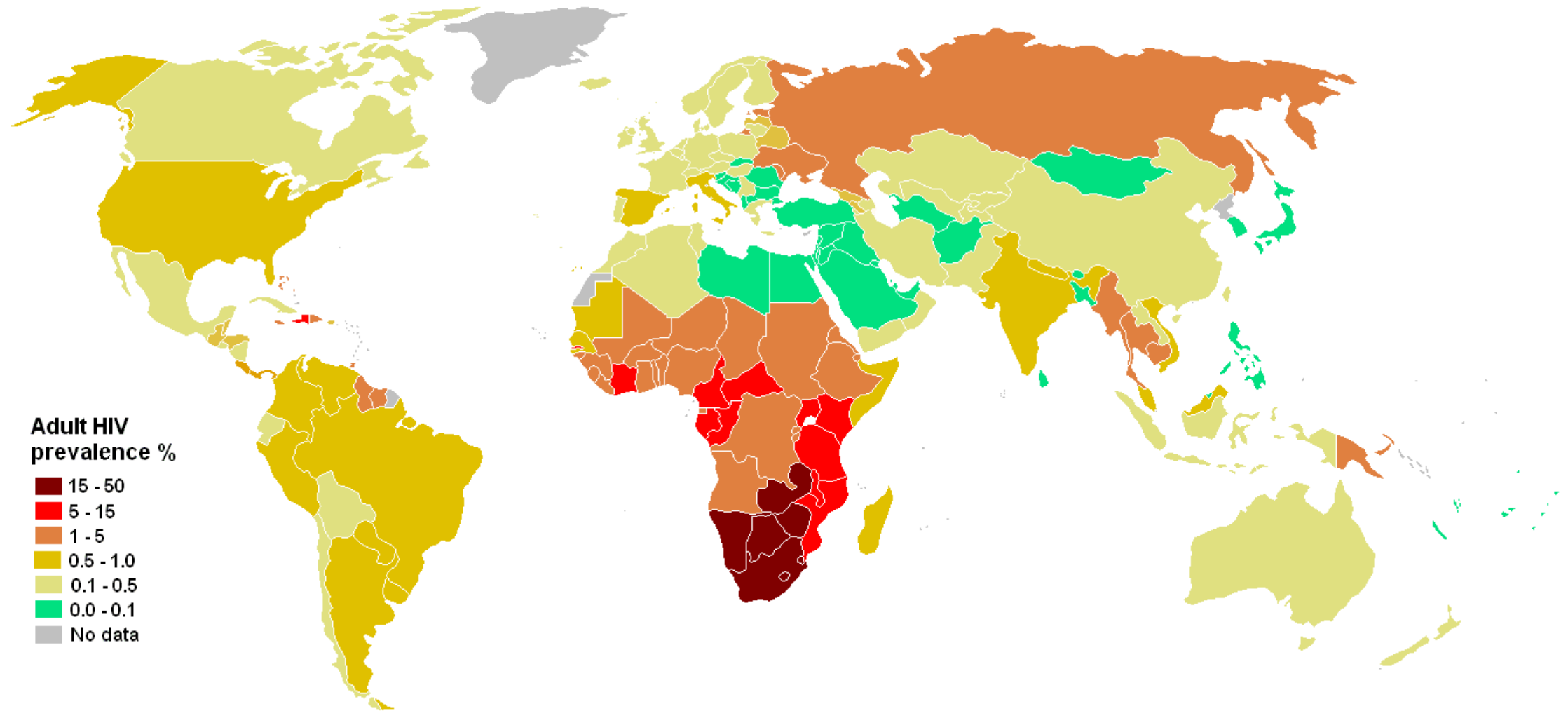
Michael Worobey¹, Thomas D. Watts¹, Richard A. McKay², Marc A. Suchard³, Timothy Granade⁴, Dirk E. Teuwen⁵, Beryl A. Koblin⁶, Walid Heneine⁴, Philippe Lemey⁷ & Harold W. Jaffe⁴

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.

HIV epidemic



HIV break #1

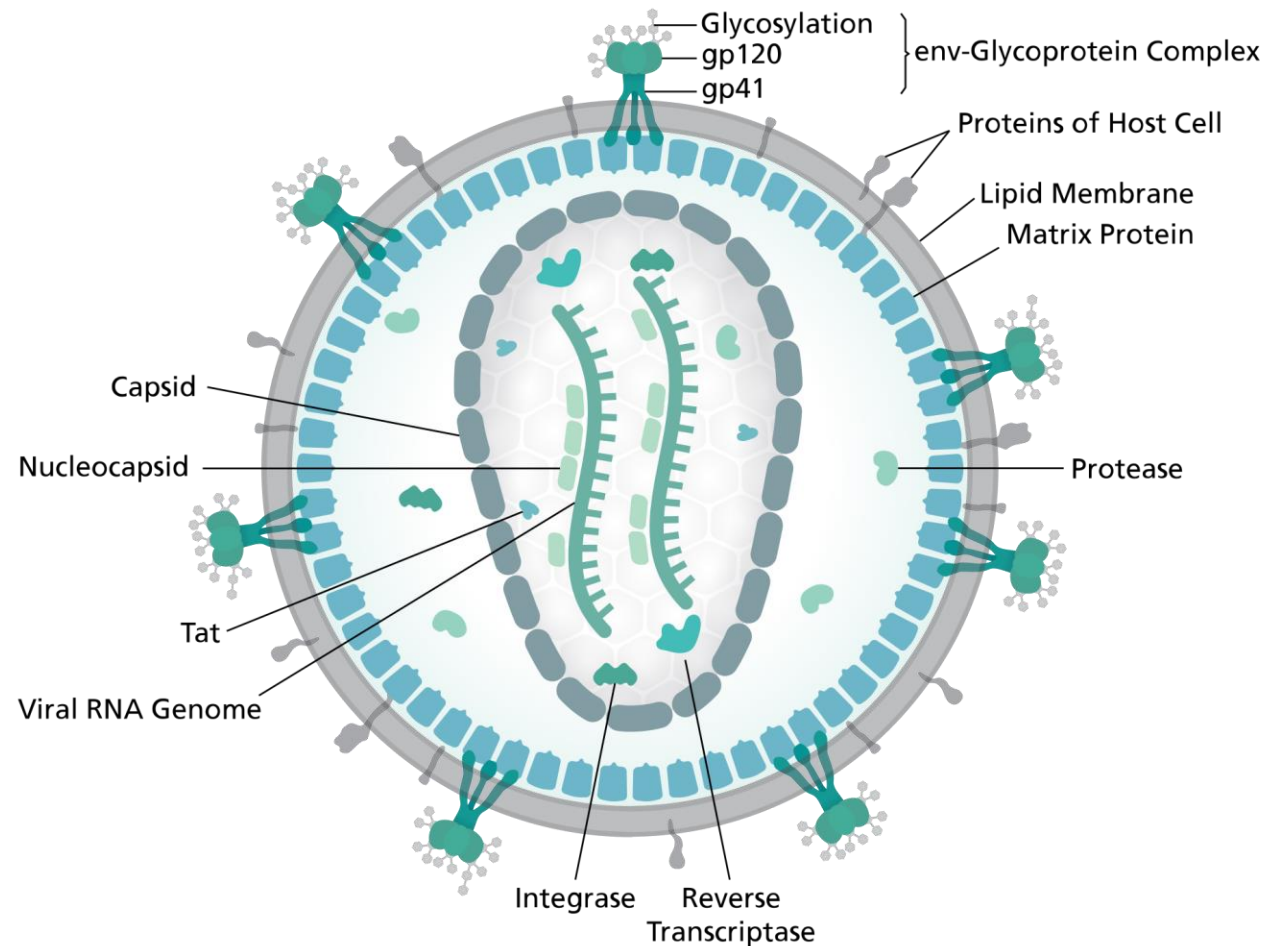
What have we learned?

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?

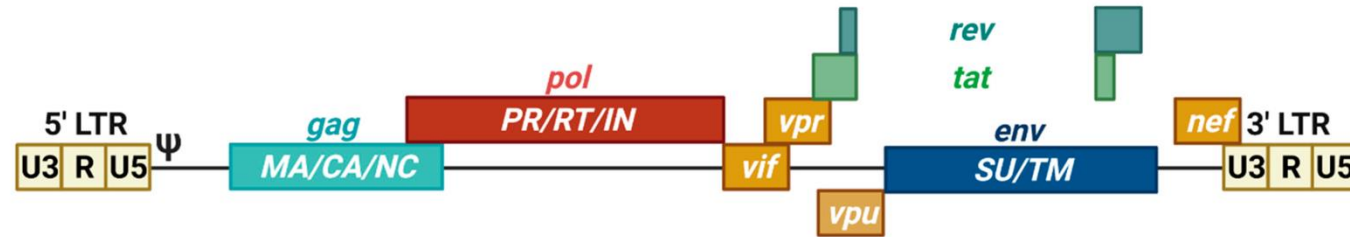
- Family: Retroviridae
- Genus: Lentiviruses
- Positive-sense ssRNA genome (~9.8 kb)
- 2 copies packaged

Potential targets for
diagnostics and antiviral
therapy

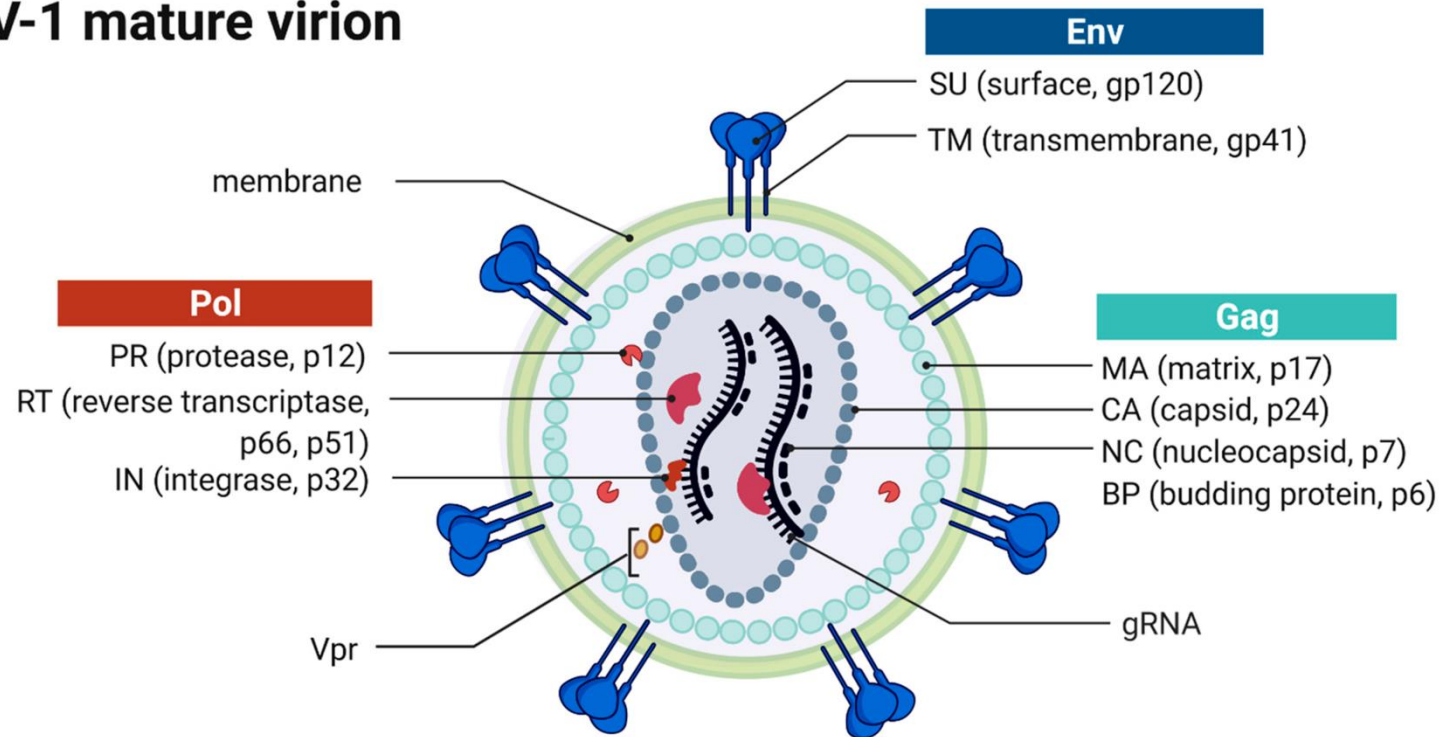


HIV genome

HIV-1 genome

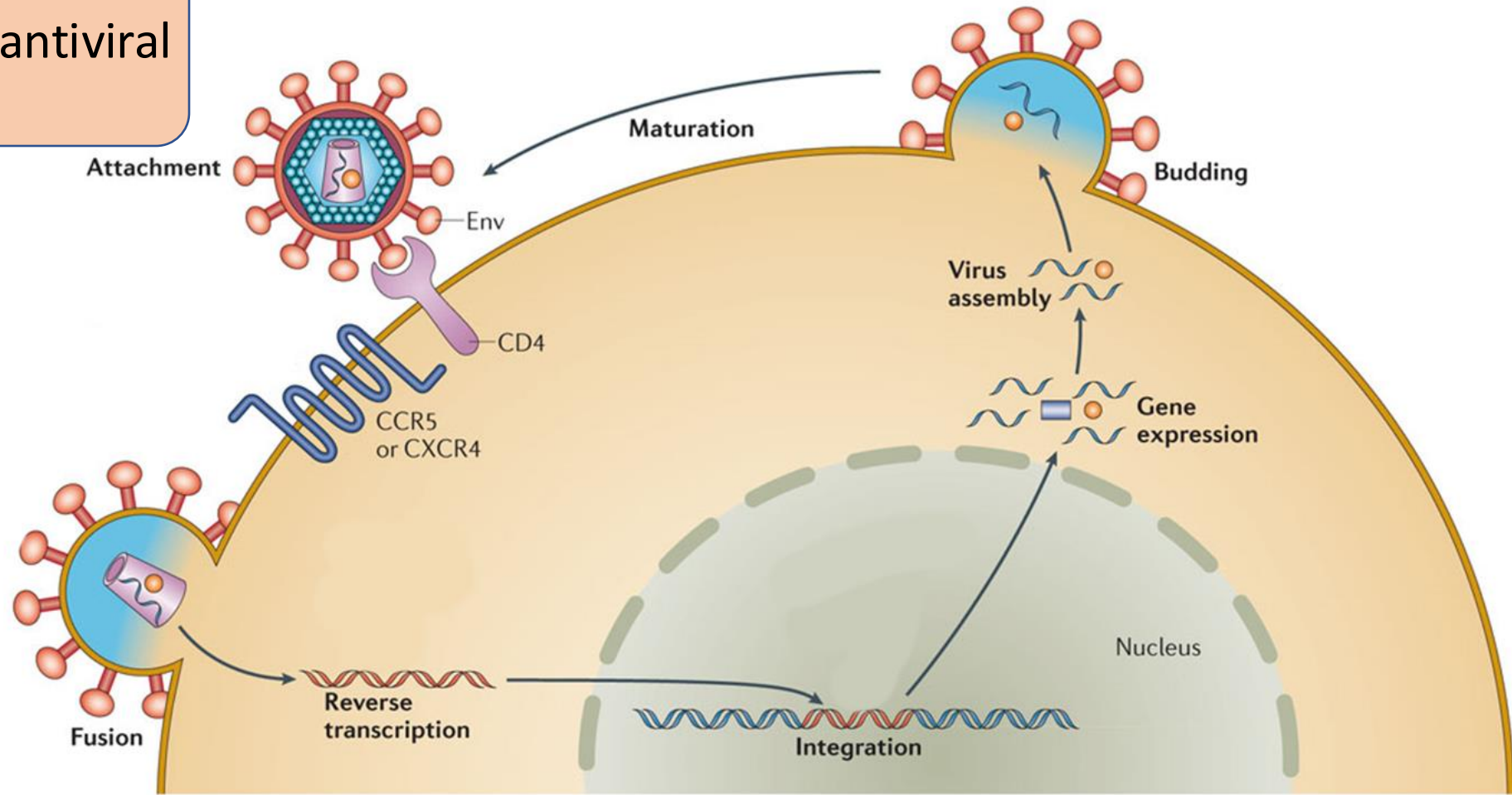


HIV-1 mature virion

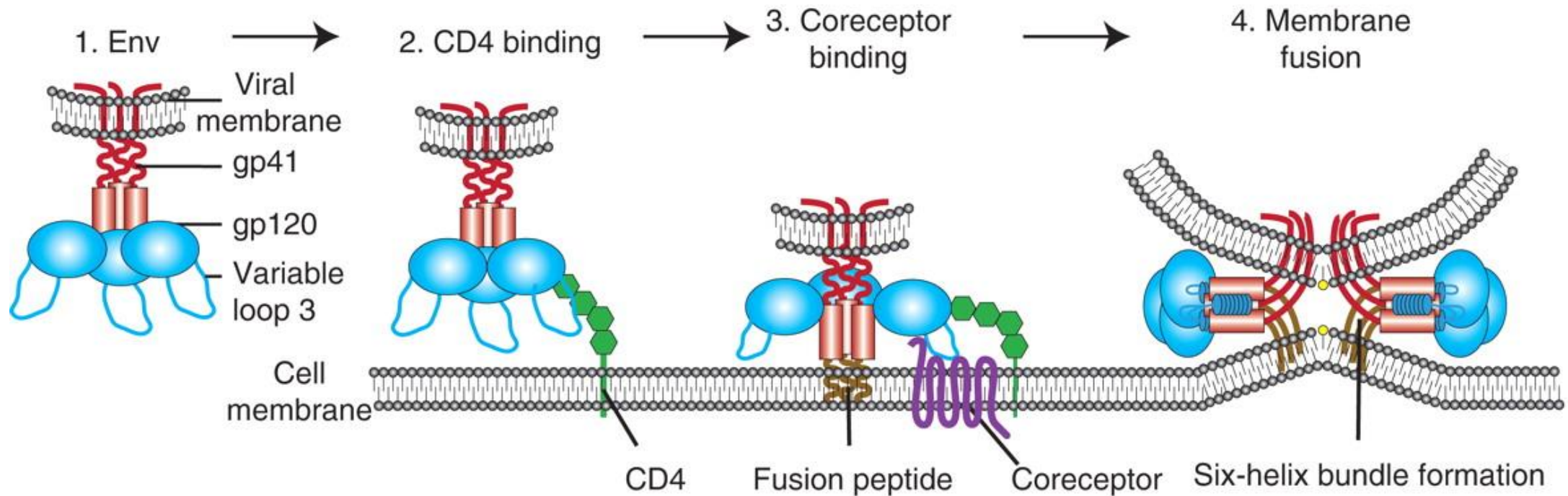


How HIV propagates

Potential targets for
diagnostics and antiviral
therapy



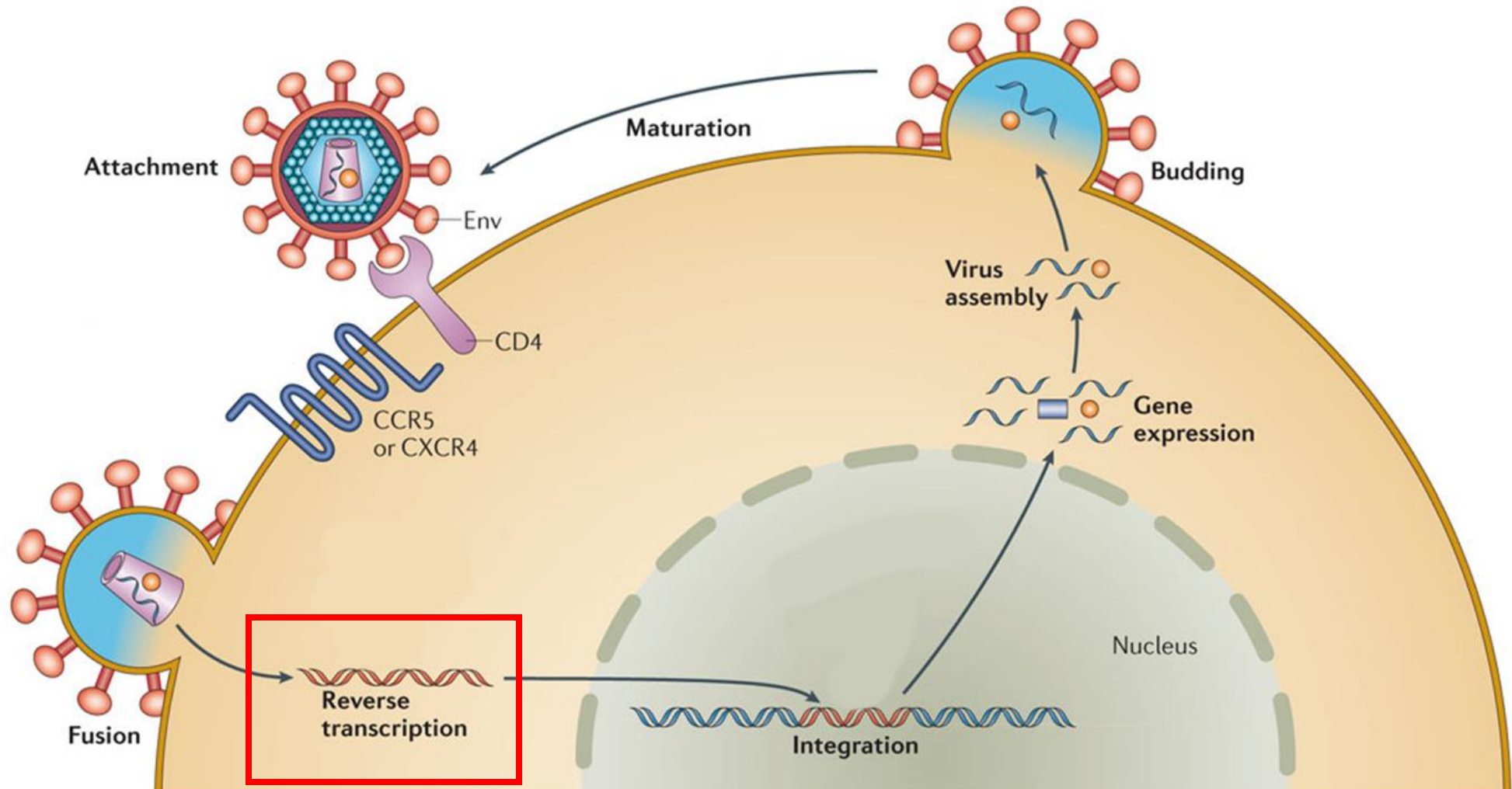
HIV entry



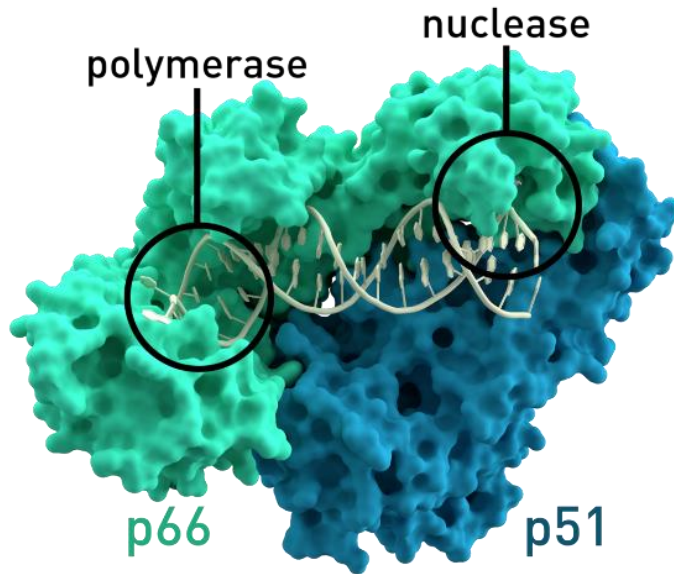
Receptor can determine cell tropism:

Receptor	CD4
Co-receptor	CCR5
Co-receptor	CXCR4

HIV reverse transcription



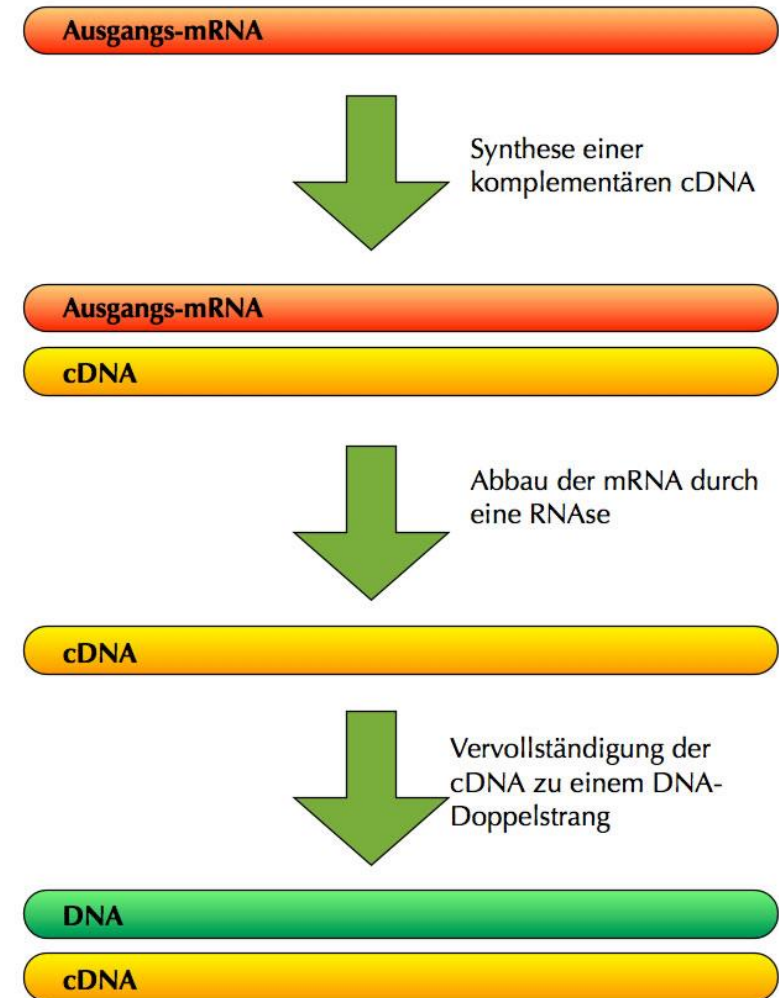
Reverse transcription



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



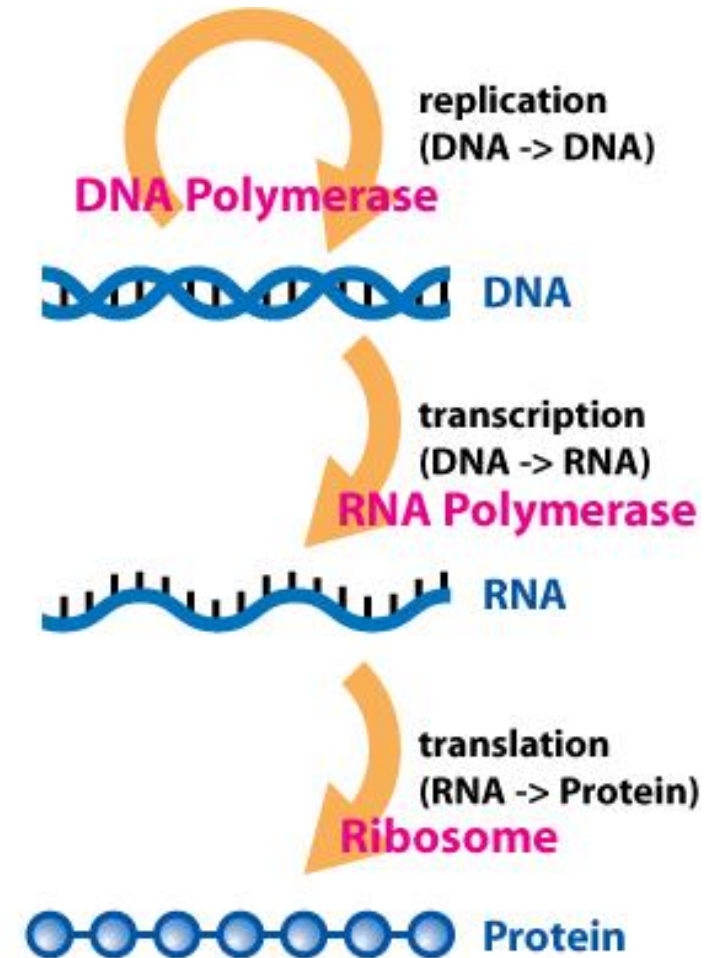
Reverse transcription & the central dogma of biology

Discovered by David Baltimore (Nobel prize)

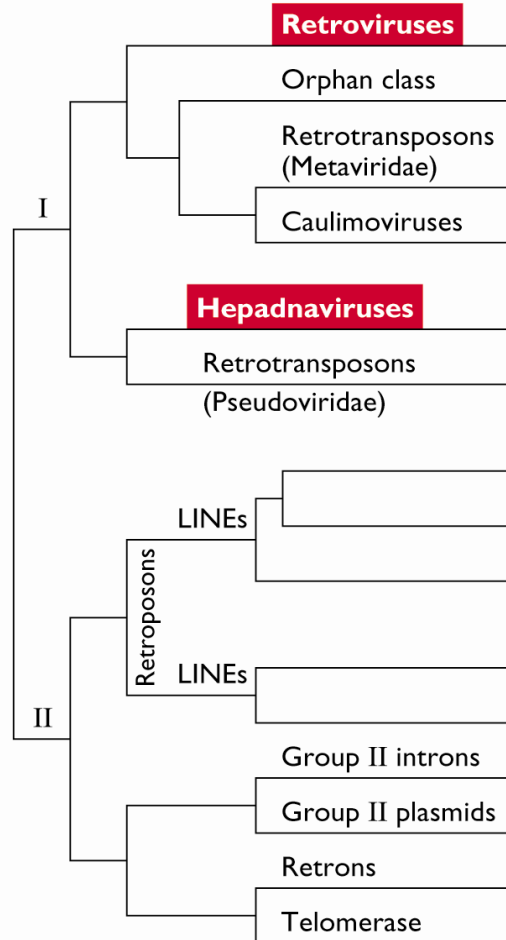
Information flows from:

DNA → RNA and can go back to DNA

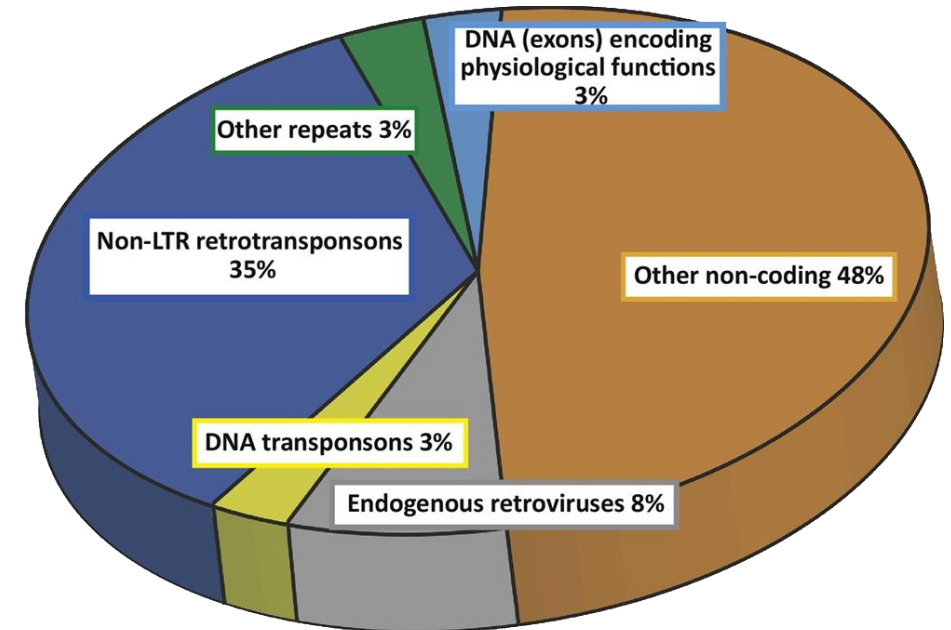
Applied in molecular biology (RT-PCR)



Who can reverse transcribe?



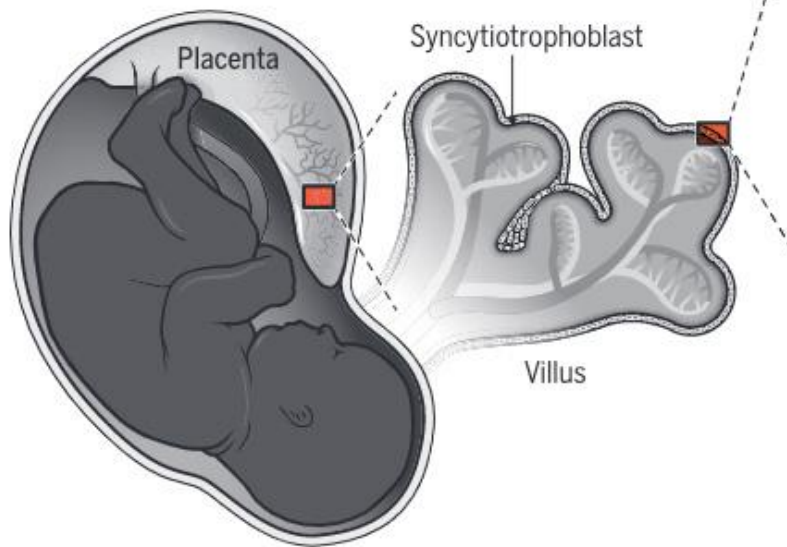
LTRs	PBS	RT	Env	Poly(A)
+	+	+	+	+
+ ^a	-	+	-	-
+	+	+	- ^d	+
-	+	+	-	+
+ ^e	-	+	-	+
+	+	+	-	+
-	-	+	-	+
-	-	+	-	+
-	-	+	-	+
-	-	+	-	+
-	-	+	-	-
-	-	+	-	-
-	-	+	-	+
-	-	+	-	+



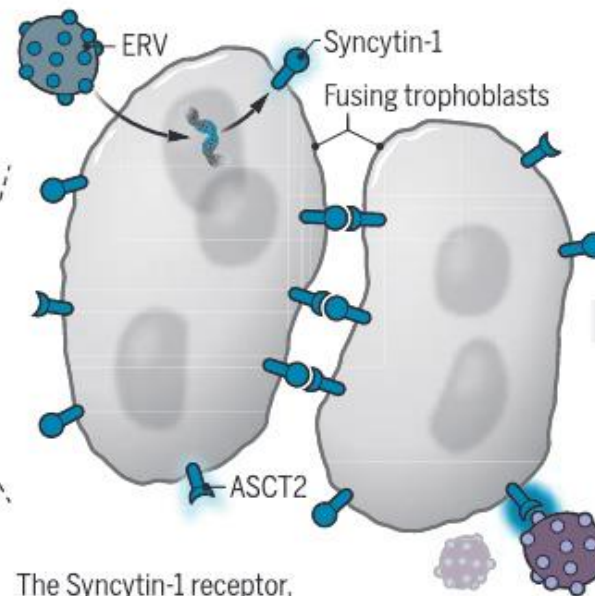
Domestication of retroviruses – an evolutionary boost

Domestication of endogenous retrovirus genes

The placental syncytiotrophoblast is an important barrier between maternal and fetal blood that is formed by cell-cell fusion. The fusogenic property of trophoblasts derives from domestication of ERV genes, but this came at a cost that prompted further selection for ERV gene domestication.



Domestication of an ASCT2-tropic ERV brings about expression of **Syncytin** proteins.

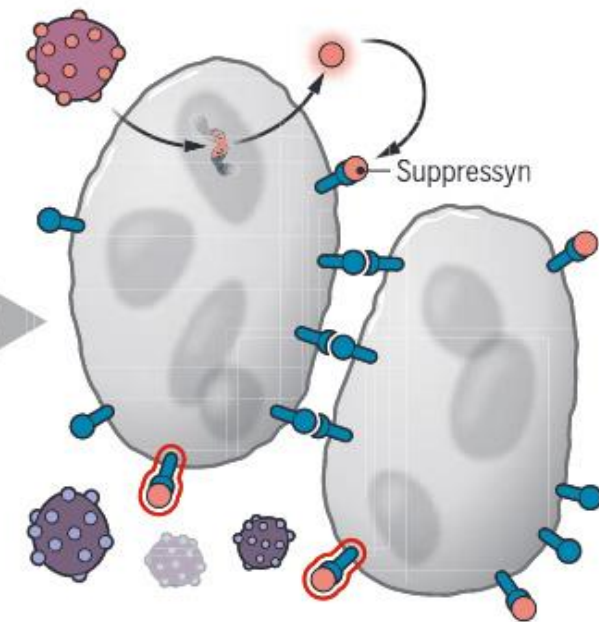


The Syncytin-1 receptor, ASCT2, is also expressed. Ligand-receptor binding **allows cell-cell fusion** and syncytia formation.

But this also leaves cells **susceptible** to other ASCT2-tropic ERVs.

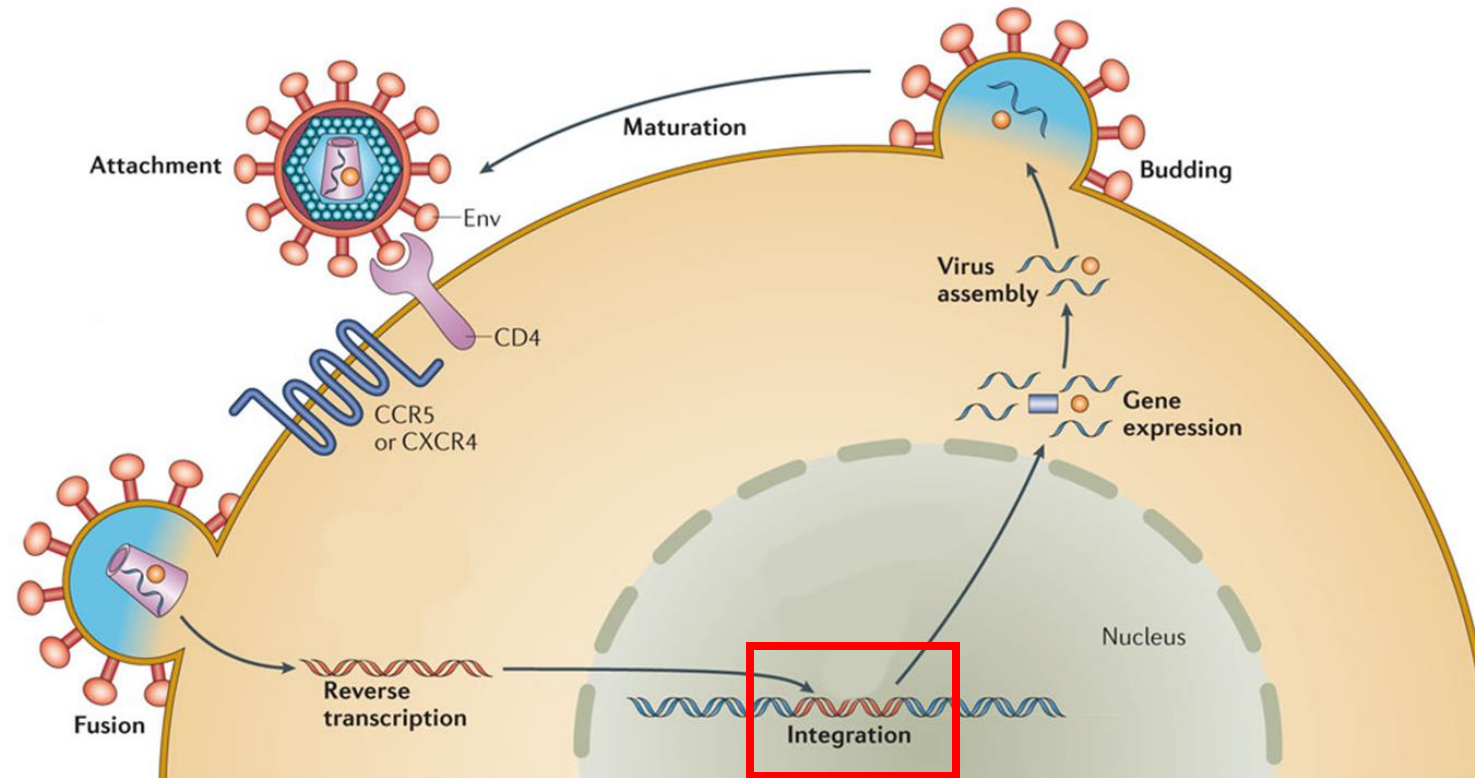
ASCT2, alanine, serine, cysteine-preferring transporter 2; ERV, endogenous retrovirus.

Domestication of another ERV gene led to the **Suppressyn** gene.



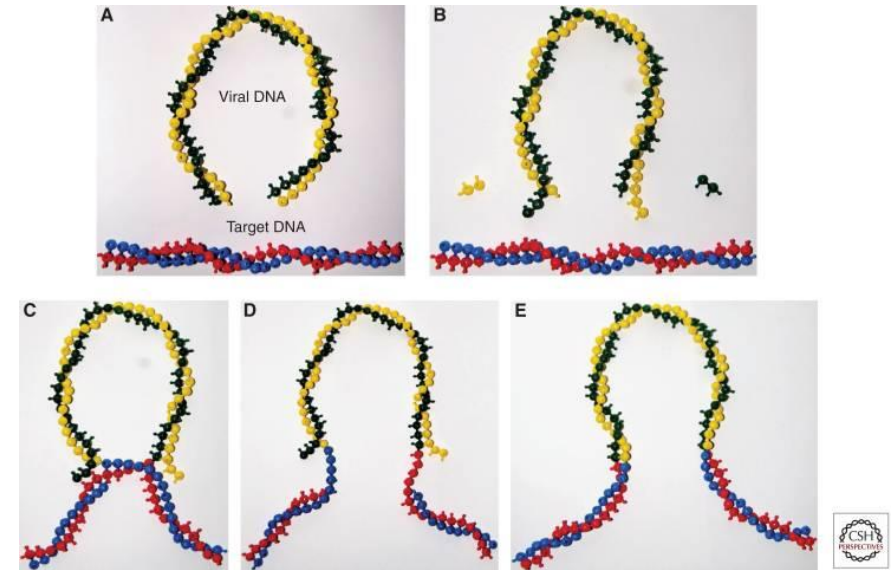
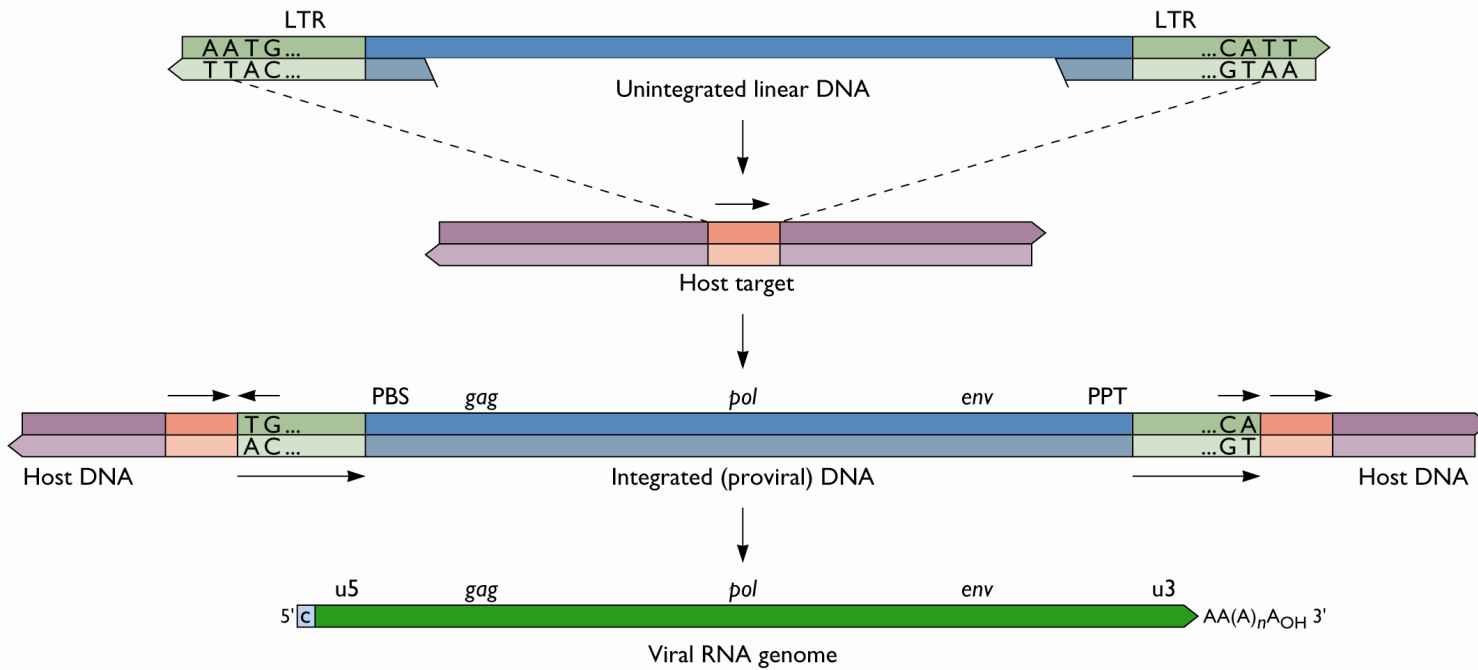
Suppressyn binds unbound ASCT2, which **blocks infection** by ASCT2-tropic ERVs.

Integration



Nature Reviews | Microbiology

Integration



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

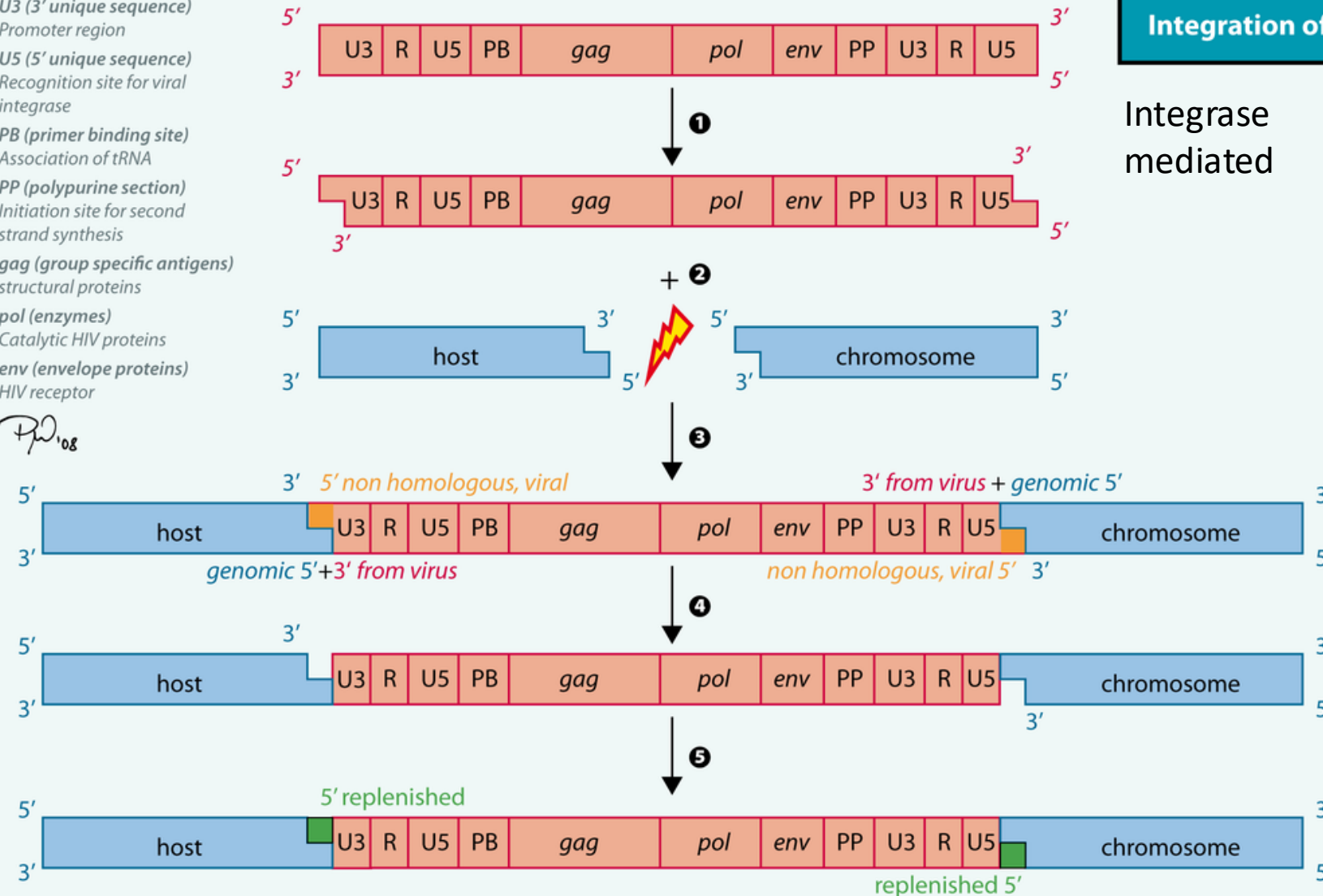
Integration

U3 (3' unique sequence)
 Promoter region
U5 (5' unique sequence)
 Recognition site for viral integrase
PB (primer binding site)
 Association of tRNA
PP (polypurine section)
 Initiation site for second strand synthesis
gag (group specific antigens)
 structural proteins
pol (enzymes)
 Catalytic HIV proteins
env (envelope proteins)
 HIV receptor

PD'08

Integration of HIV-DNA into a host chromosome

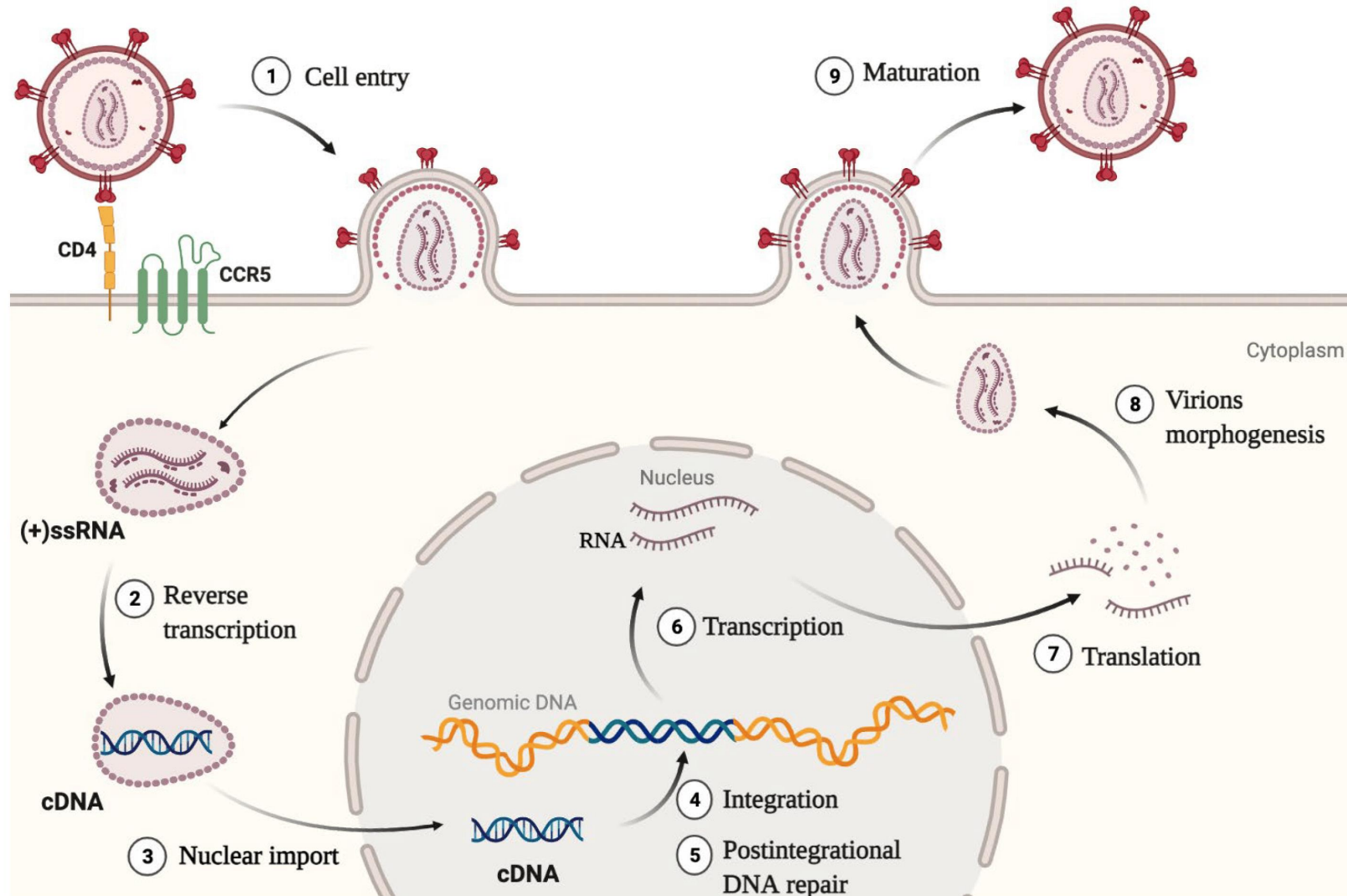
Integrase mediated



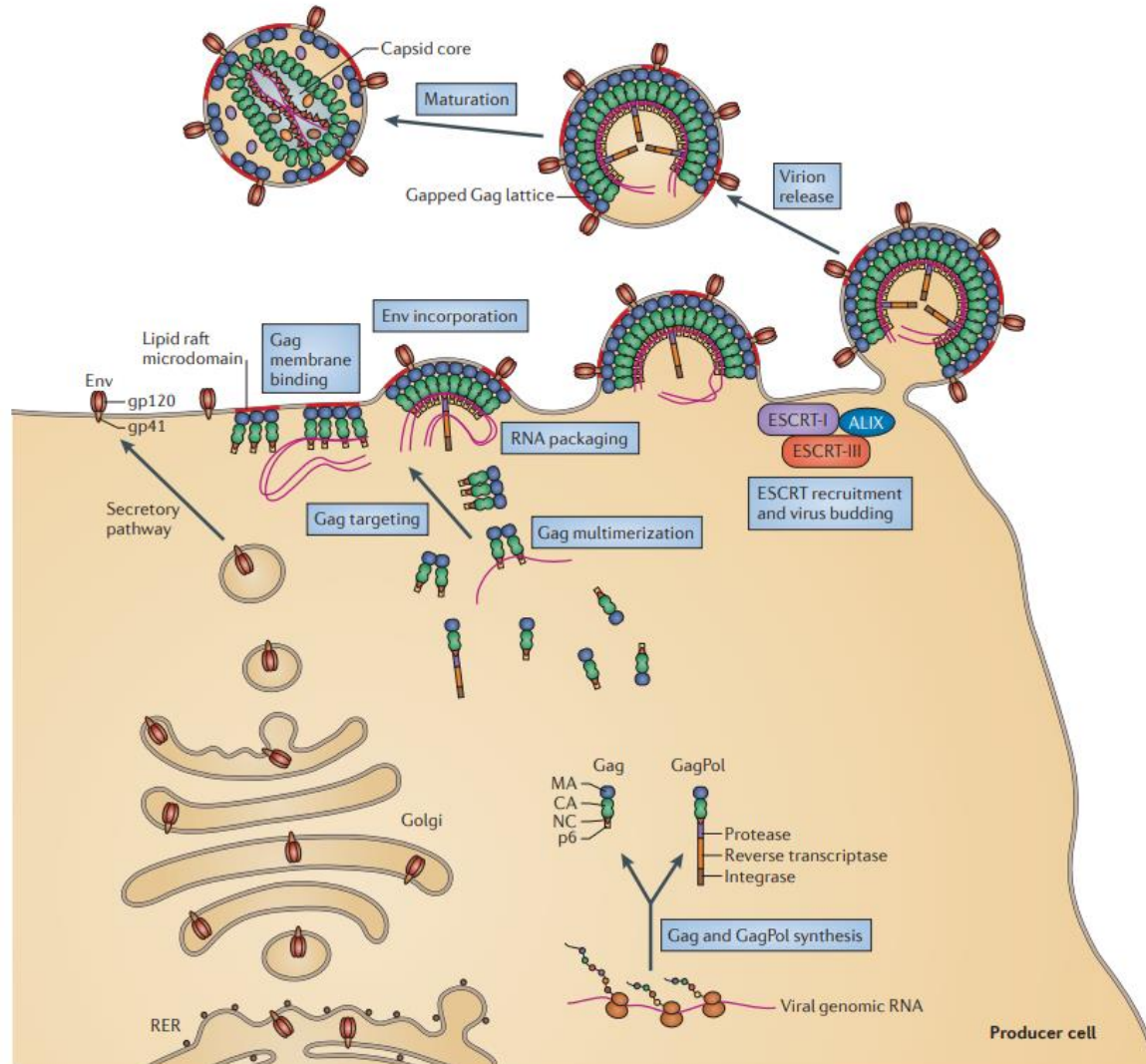
- 1 After the viral RNA genome has been transcribed into double strand DNA, the viral protein integrase creates overlapping 5'-ends by removing two nucleotides from both 3'-ends.
- 2 Integrase performs the same reaction on any site on an arbitrary chromosome of the host cell.
- 3 Both DNA molecules are ligated by synthesis of phosphodiester bonds between terminal nucleotides of viral 3'-ends and overlapping 5'-ends of the host chromosome. However, the non-homologous 5'-ends from the viral DNA are not ligated to the host chromosome.
- 4 The non-homologous 5'-ends from the viral DNA are removed by integrase.
- 5 Finally, the gaps are filled up by cellular repair proteins, which recognize single strand breaks.

Not drawn to scale! Enzymatic reactions, interacting proteins, splicing sites, and binding site ψ are omitted for clarity. In style of Mudrow S, Falke D, Truyen U (2003). *Molekulare Virologie*, 2. Aufl. (engl.: *Molecular Virology*, 2nd ed.) Spektr Akad Verl. Heidelberg, Berlin.

Requirements for virion formation: transcription and translation



HIV budding and maturation



Viral glycoproteins

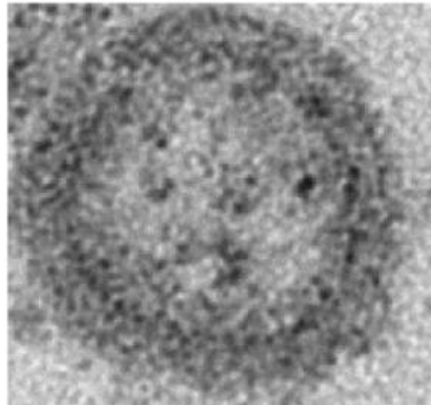
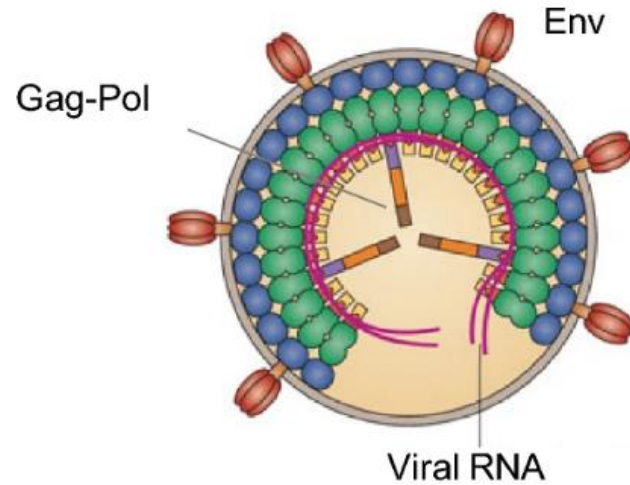
- processing through TGN
- transport via secretory pathway to cell membrane

Gag, Gag/Pol

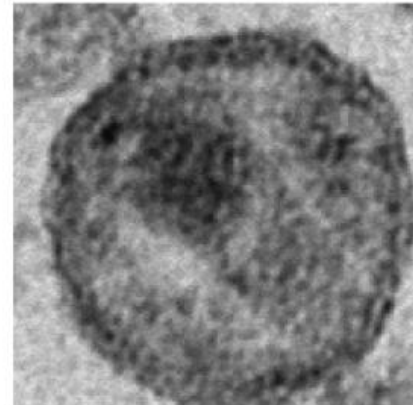
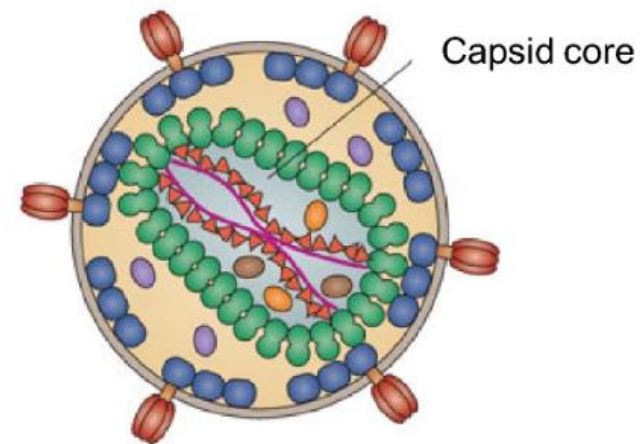
- synthesis of viral RNA in cytosol
- Gag multimerisation and binding to *lipid rafts*
- binding of viral genomic RNA to Gag
- transport of Gag/Pol to membrane
- budding initiation via ESCRT-complex
- maturation of new particles by proteolytic cleavage

HIV budding and maturation

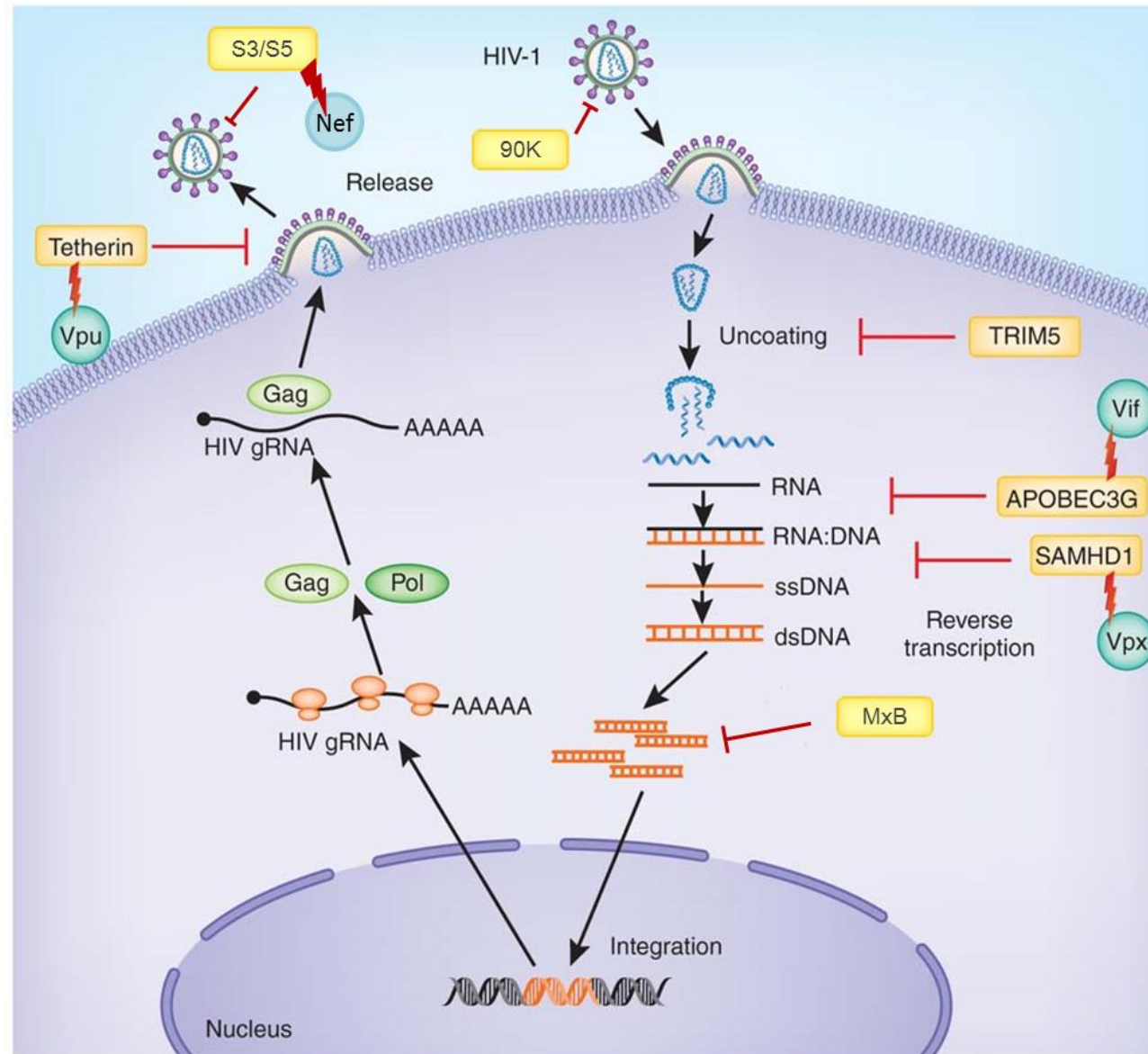
Immature HIV-1 virion



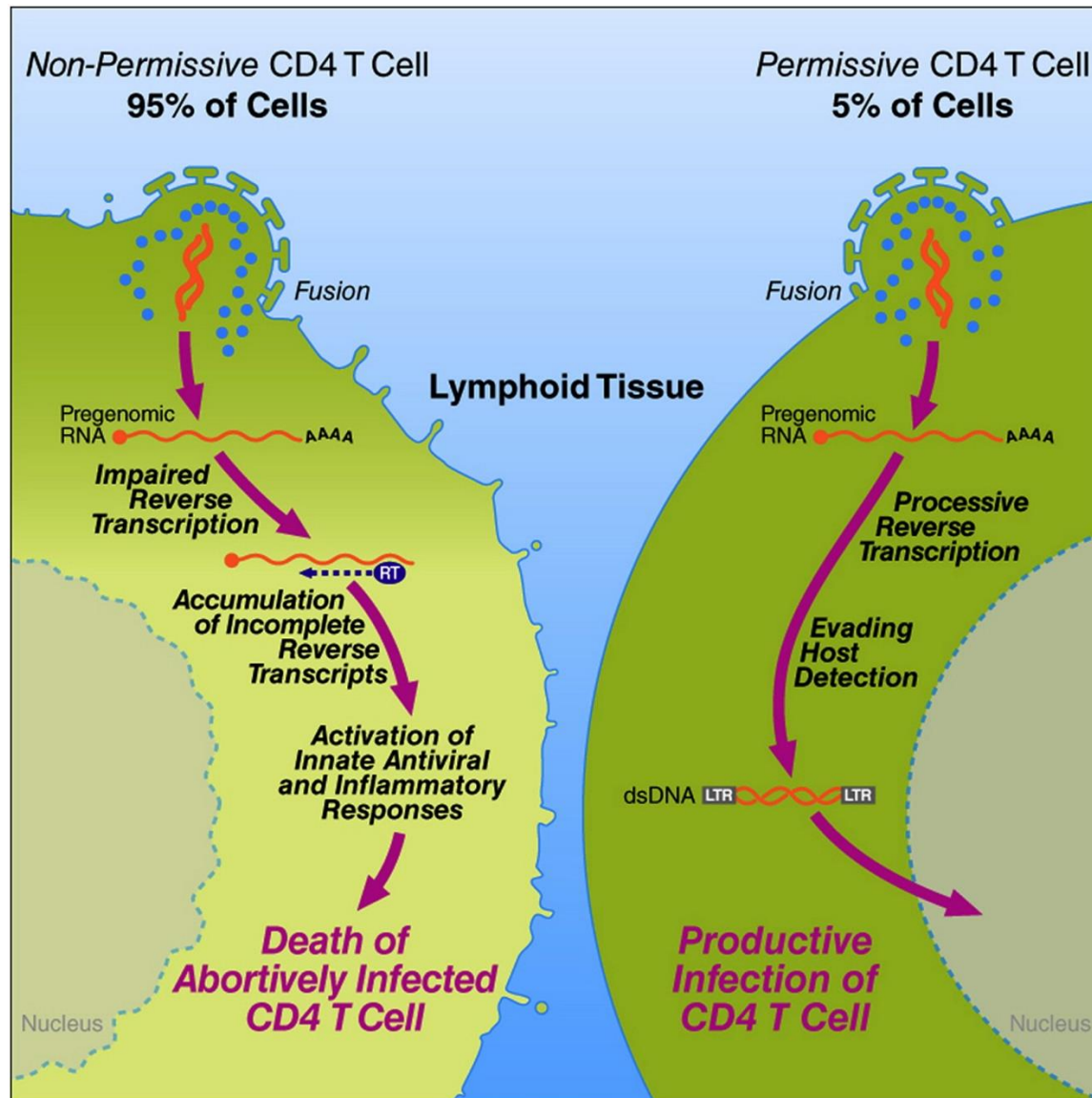
Mature HIV-1 virion



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

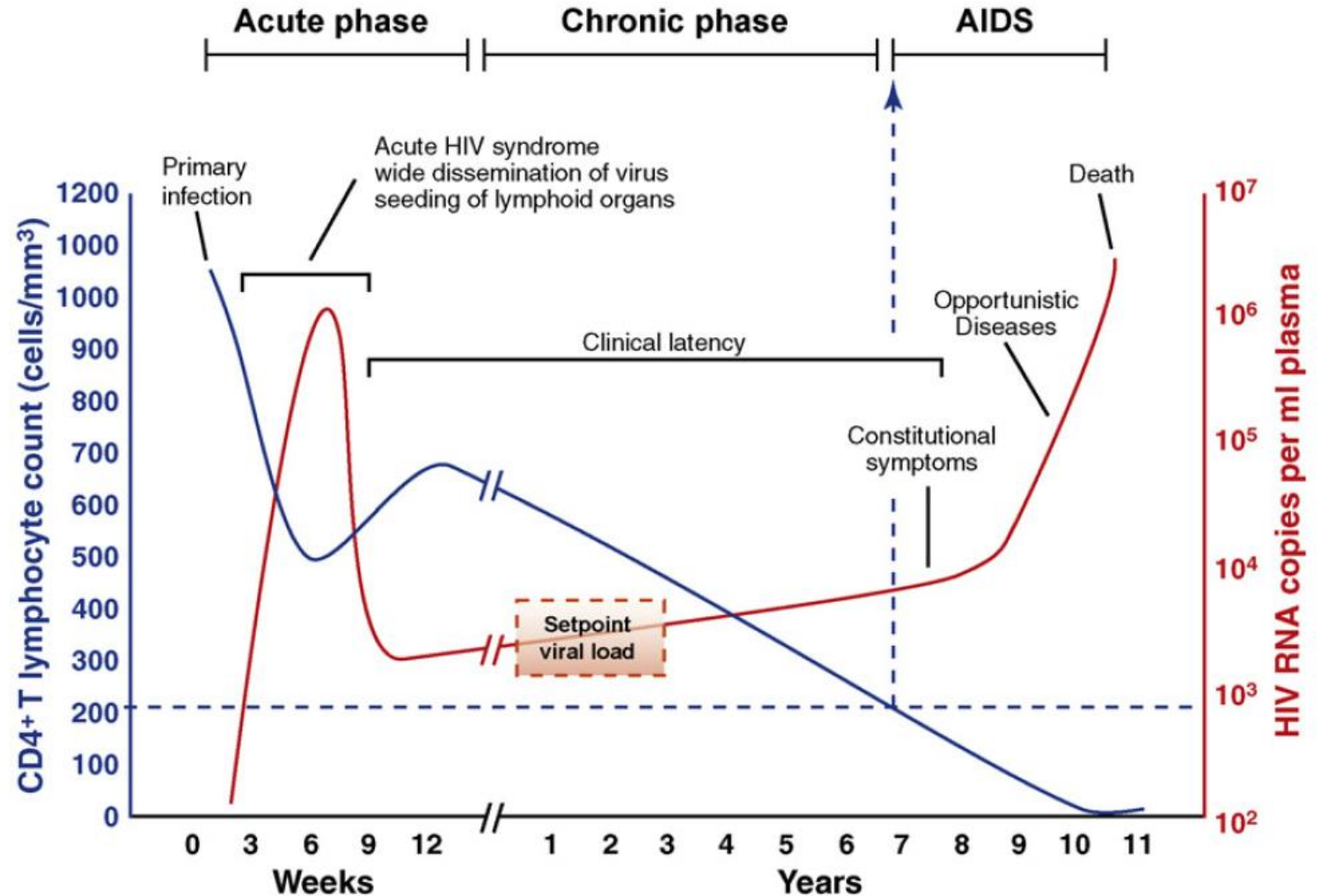
- 2 to 4 weeks after infection
- Flu-like symptoms
- HIV blood level very high
- High risk of transmission

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/mm³
- Accumulation of opportunistic infections
- Without treatment survival ~ 3 years



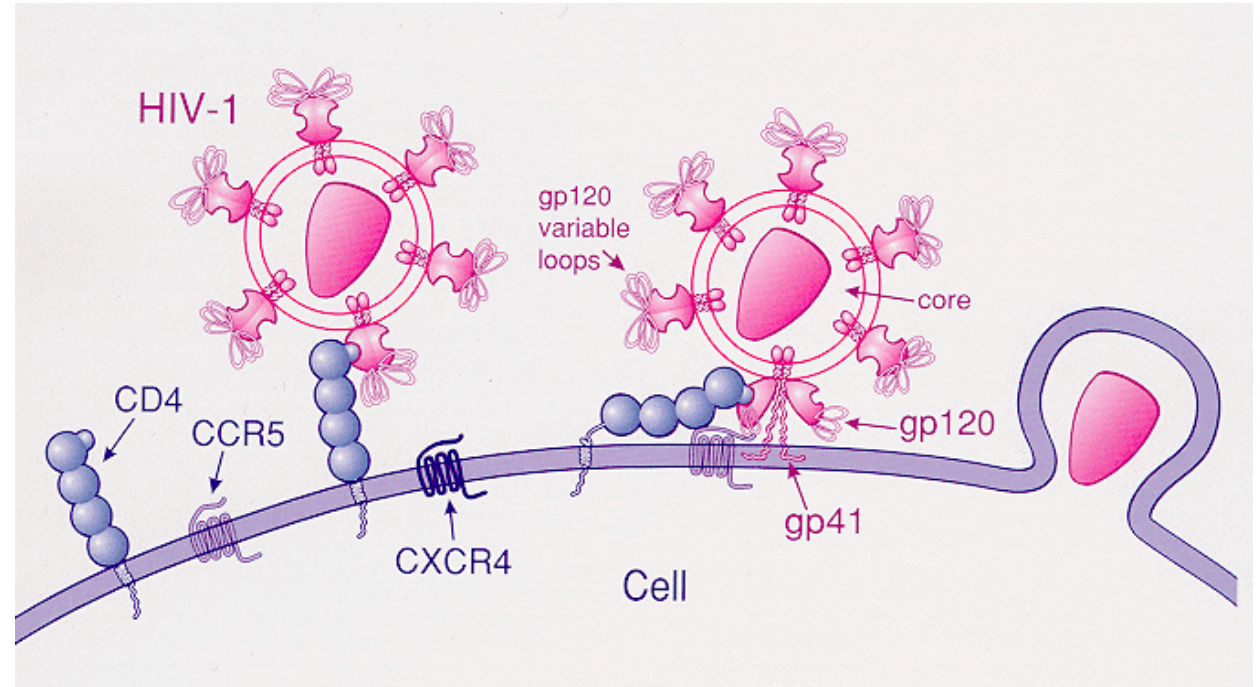
TRENDS in Genetics

HIV pathogenesis

Primärer Rezeptor: CD4

Korezeptoren: CCR5 und/oder CXCR4

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



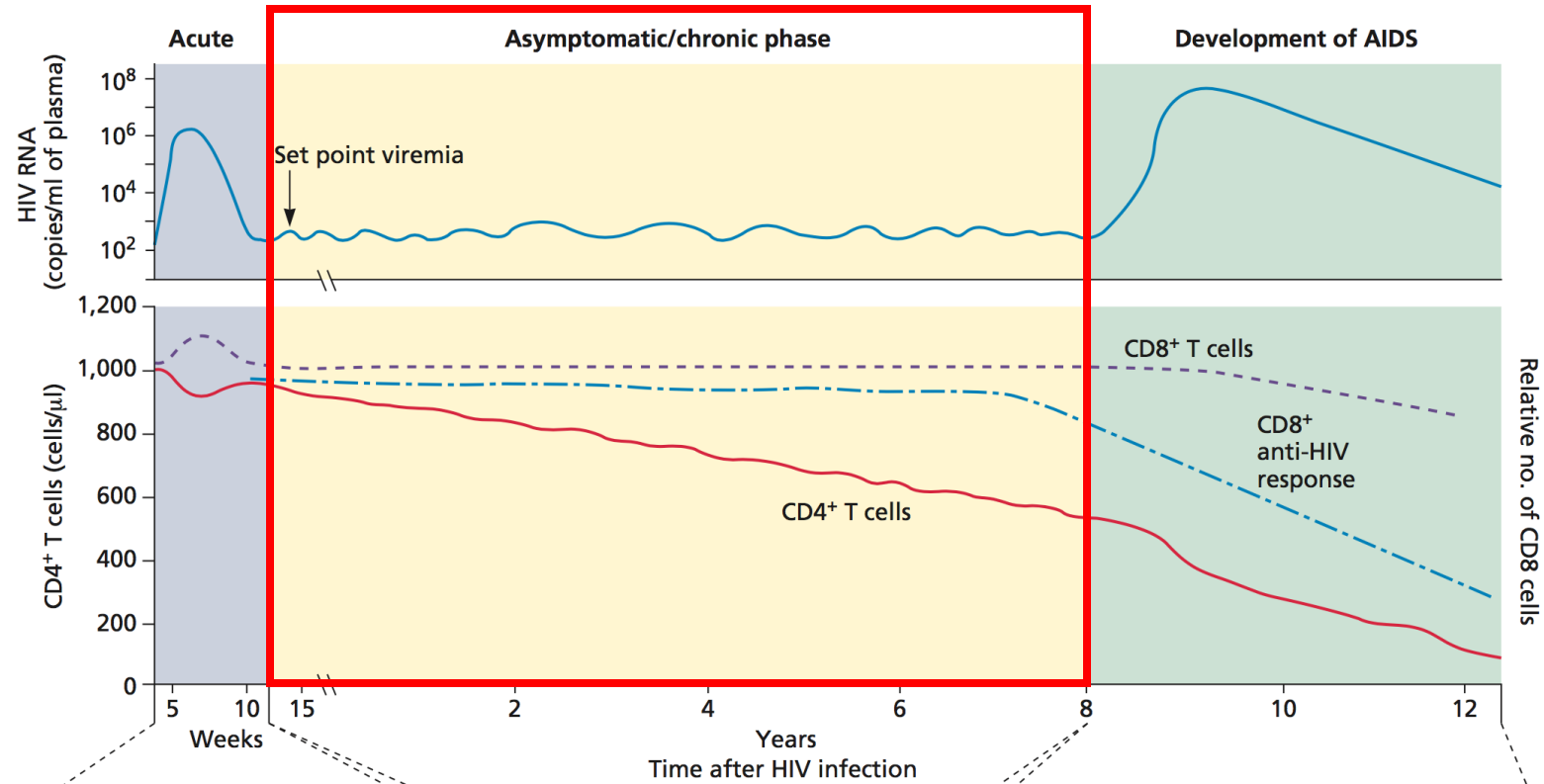
Zerstörung von CD4-Helferzellen

- 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 $> 38,5^\circ\text{C}$, Chronischer Durchfall, Gürtelrose (Herpes zoster), Pilzinfektionen der Mundhöhle

AIDS (Stadium C)

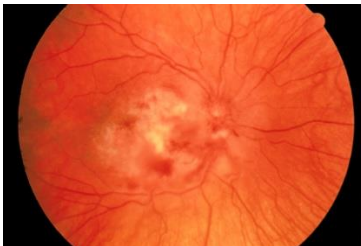
Opportunistische Infektionen:

- 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)

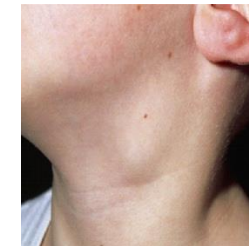
CMV Retinitis



Kaposi-Sarkom



Burkitt-Lymphome

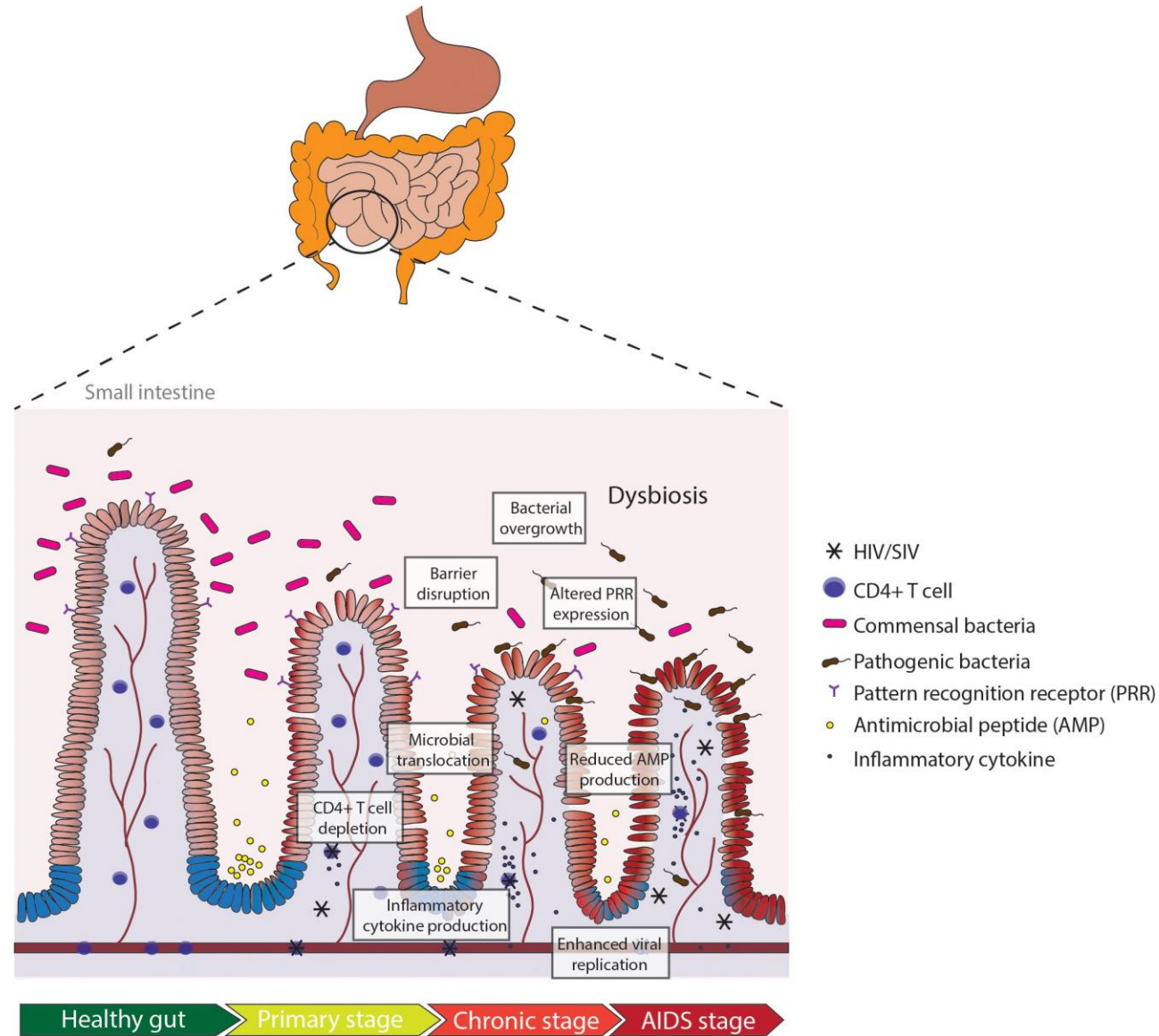


Wasting-Syndrom:

- starker Gewichtsverlust, anhaltender Durchfall, Fieber/Abgeschlagenheit

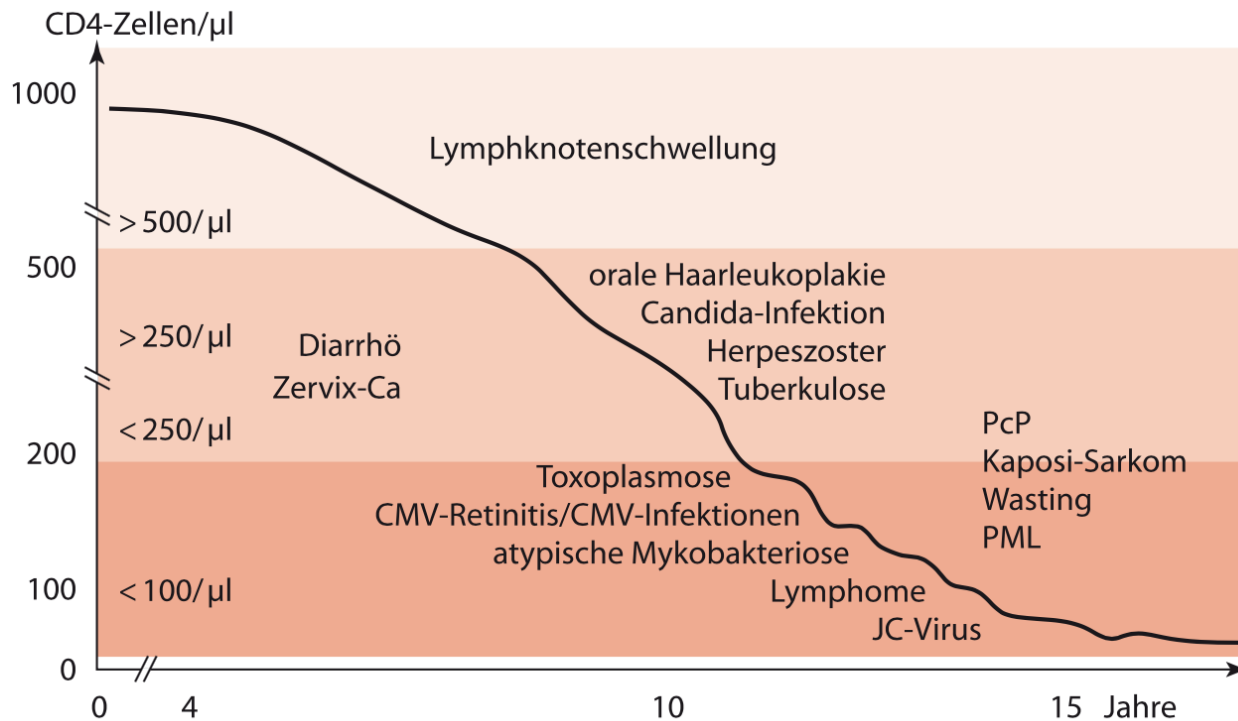
HIV-assoziierte Enzephalopathie

HIV tropism and pathogenesis in the gut



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

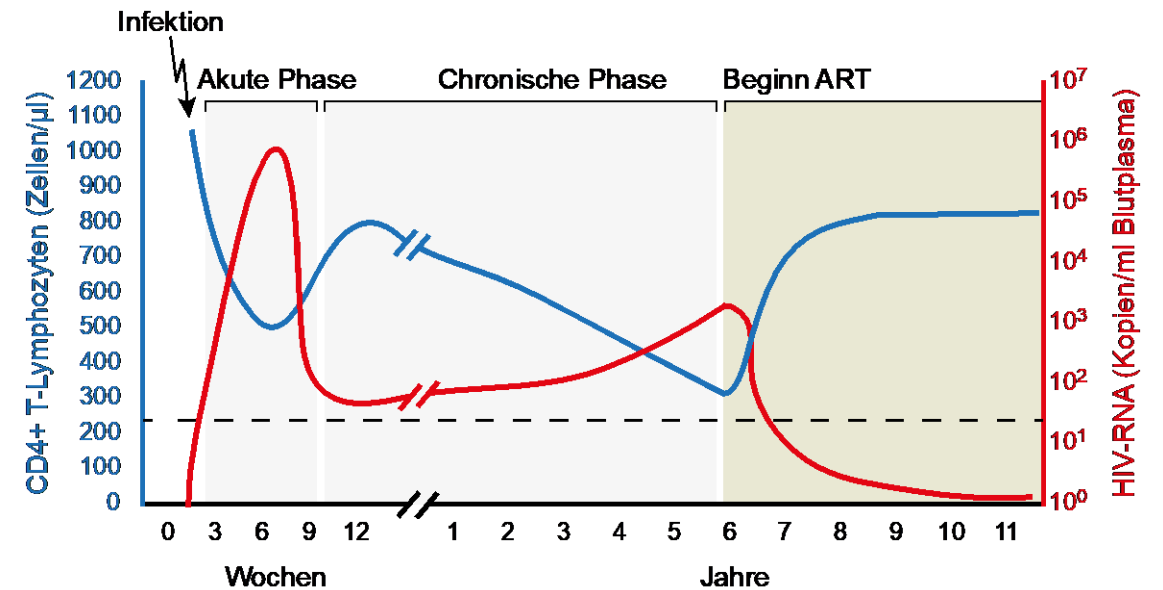
What have we learned?

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

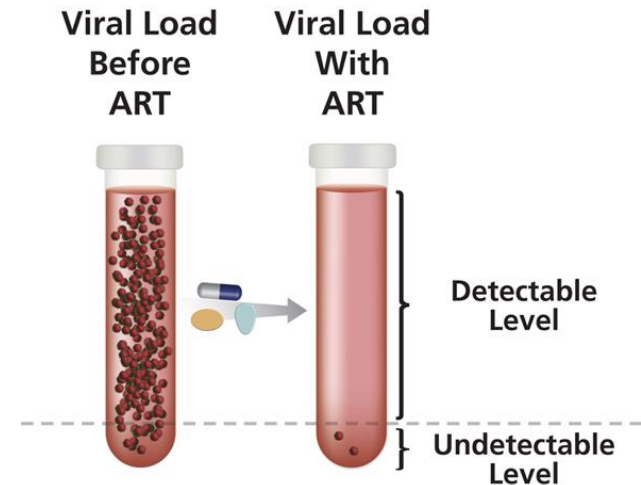
Are there markers for disease severity?

Therapeutics

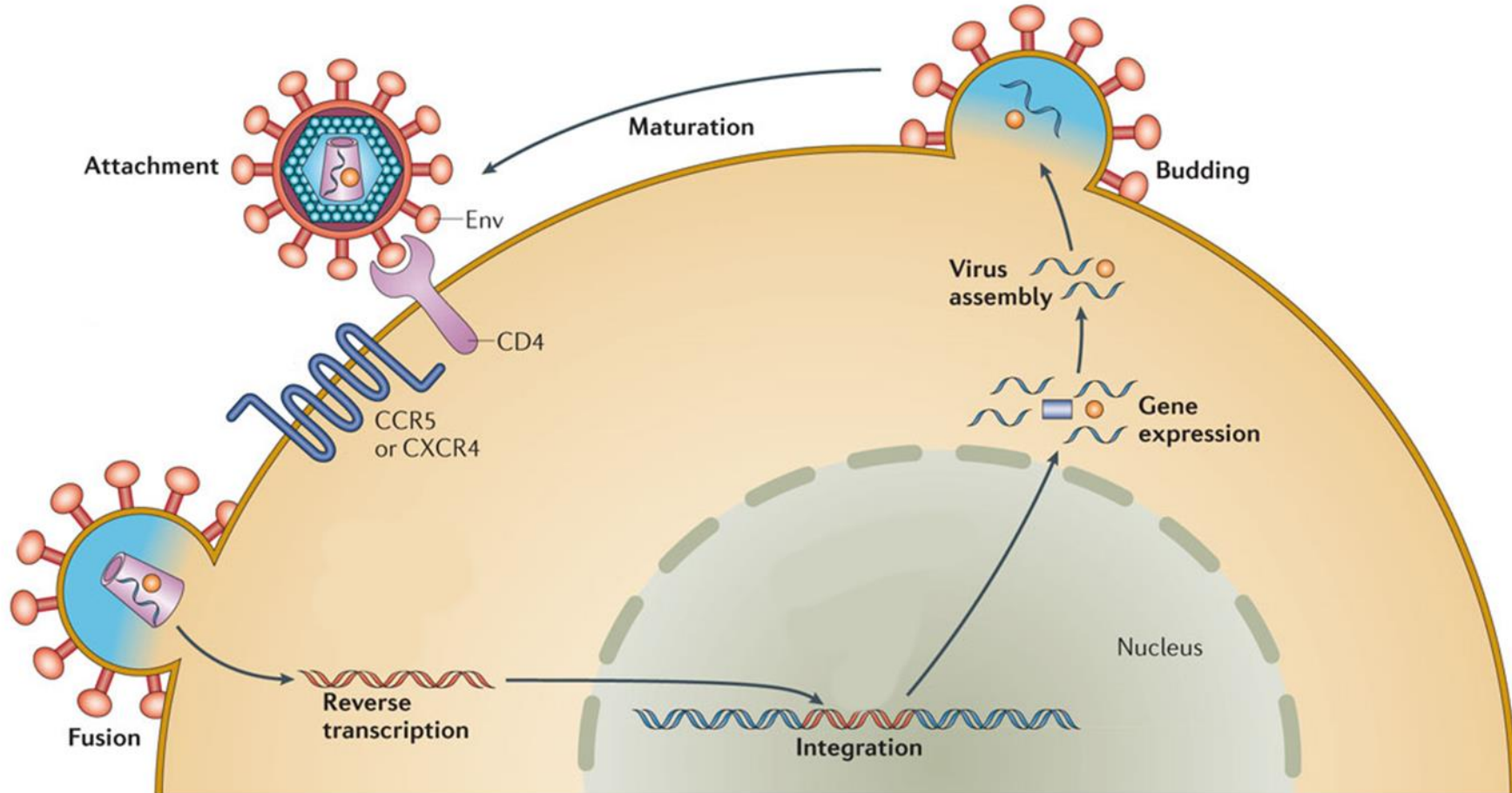
- Reduction of plasma viral load under level of detection of RT-qPCR (50 copies/mL)
- Combination therapies and very good medical adherence of patients important
- Development of drug resistance slows down
- Otherwise: fast development of resistance up to virological failure



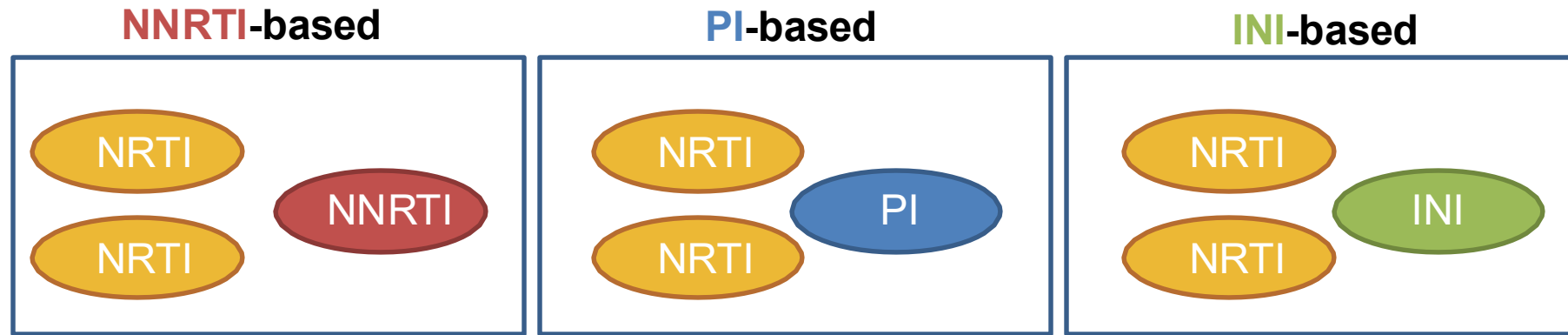
Viral Suppression



Where to hit



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

morning

Combivir[®] +
Crixivan[®] + Norvir[®]



evening



Videx[®] + Zerit[®] +
Viracept[®]



Combivir[®] +
Norvir[®] +
Agenerase[®]



complicated treatment regimens with
patients experiencing low levels of suffering

→ **bad adherence**

Therapeutics

Single-Tablet Regimens									
Atripla (efavirenz/emtricitabine/ tenofovir disoproxil fumarate)	Biktarvy (bictegravir/emtricitabine/ tenofovir alafenamide)	Complera (rilpivirine/emtricitabine/ tenofovir disoproxil fumarate)	Delstrigo (doravirine/lamivudine/ tenofovir disoproxil fumarate)	Dovato (dolutegravir + lamivudine)	Genvoya (elvitegravir/cobicistat/ emtricitabine/ tenofovir alafenamide)	Juluca (dolutegravir/rilpivirine)	Odefsey (emtricitabine/rilpivirine/ tenofovir alafenamide)	Stribild (elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate)	Symfi/Symfi Lo (efavirenz/lamivudine/ tenofovir disoproxil fumarate)
									

Single-Tablet Regimens (cont.)		Nucleoside/Nucleotide Analogs (NRTIs)							
Symtuza (darunavir/cobicistat/ emtricitabine/tenofovir alafenamide)	Triumeq (dolutegravir/abacavir/ lamivudine)	Cimduo/Temixys (lamivudine/tenofovir disoproxil fumarate)	Descovy (emtricitabine/tenofovir alafenamide)	Emtriva (emtricitabine or FTC)	Epivir (lamivudine or 3TC)	Epzicom (abacavir/lamivudine)	Truvada (emtricitabine/tenofovir disoproxil fumarate)	Viread (tenofovir disoproxil fumarate or TDF)	Ziagen (abacavir or ABC)
									

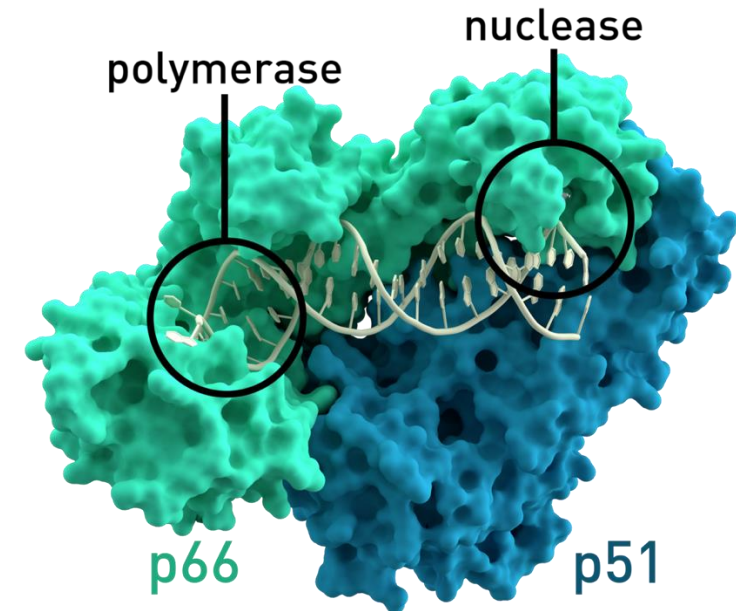
Protease Inhibitors (PIs)				Non-Nucleosides (NNRTIs)			
Evotaz (atazanavir/cobicistat)	Prezcobix (darunavir/cobicistat)	Prezista (darunavir or DRV)	Reyataz (atazanavir or ATV)	Edurant (rilpivirine or RPV)	Intence (etravirine or ETV)	Pifeltro (doravirine)	Sustiva (efavirenz or EFV)
							

Pre-Exposure Prophylaxis (PrEP)		Integrase Inhibitors		Pharmacokinetic Enhancers		Entry Inhibitors	
Truvada (emtricitabine/tenofovir disoproxil fumarate)	Descovy (emtricitabine/tenofovir alafenamide)	Isentress (raltegravir or RAL)	Tivicay (dolutegravir or DTG)	Norvir (ritonavir or RTV)	Tybost (cobicistat)	Selzentry (maraviroc or MVC)	Trogarzo (ibalizumab-uiyk)
	 Not indicated for individuals at risk from receptive vaginal sex.						 (for injection)

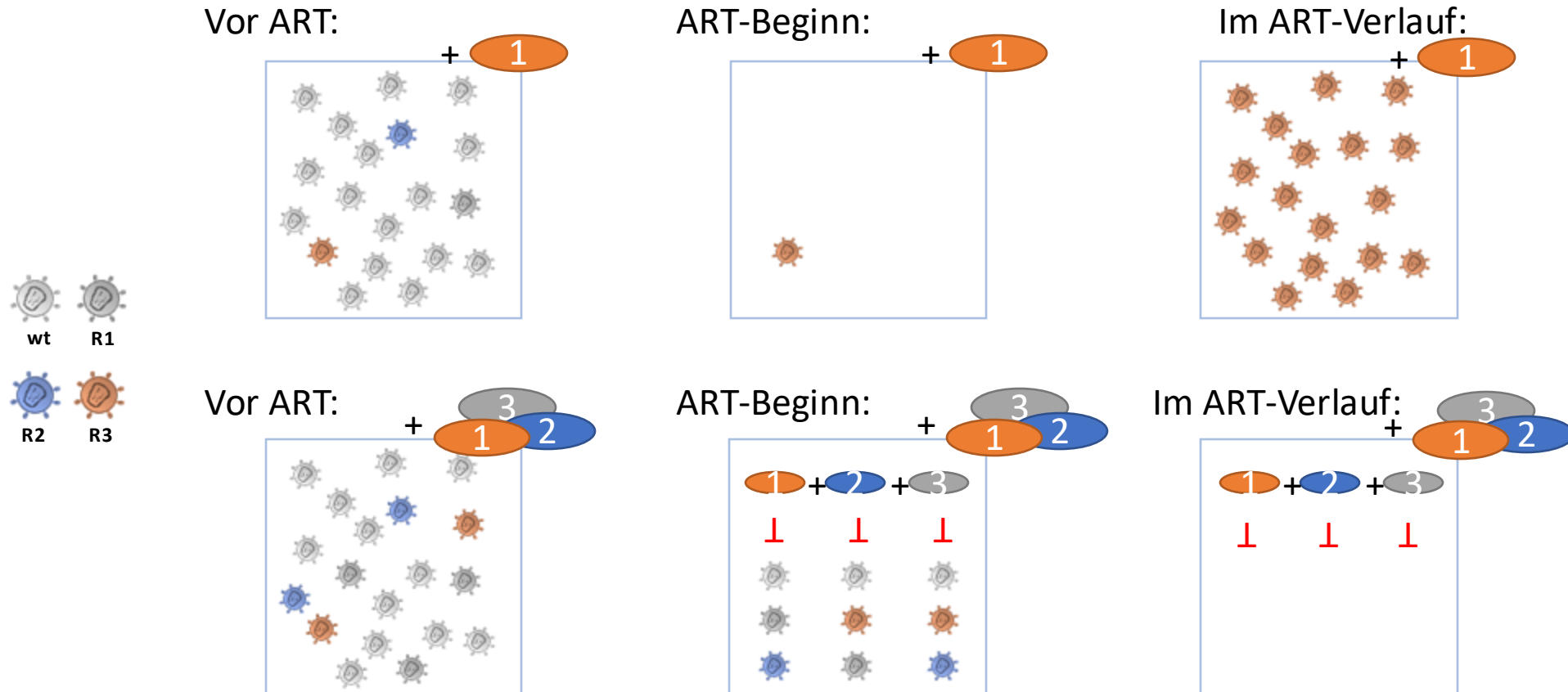
90's: up to 20 pills daily in different intervals – today: 1 pill a day

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



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 .

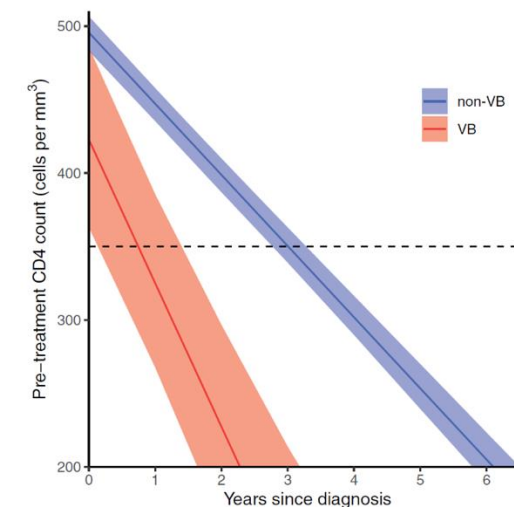
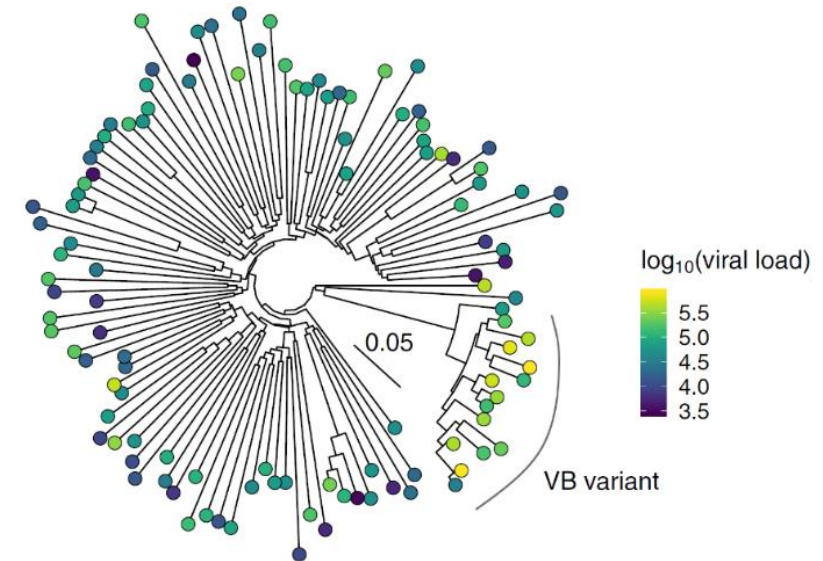
MARGREET BAKKER, SWEE HOE ONG , [] THE BEEHIVE COLLABORATION† +25 authors [Authors Info & Affiliations](#)

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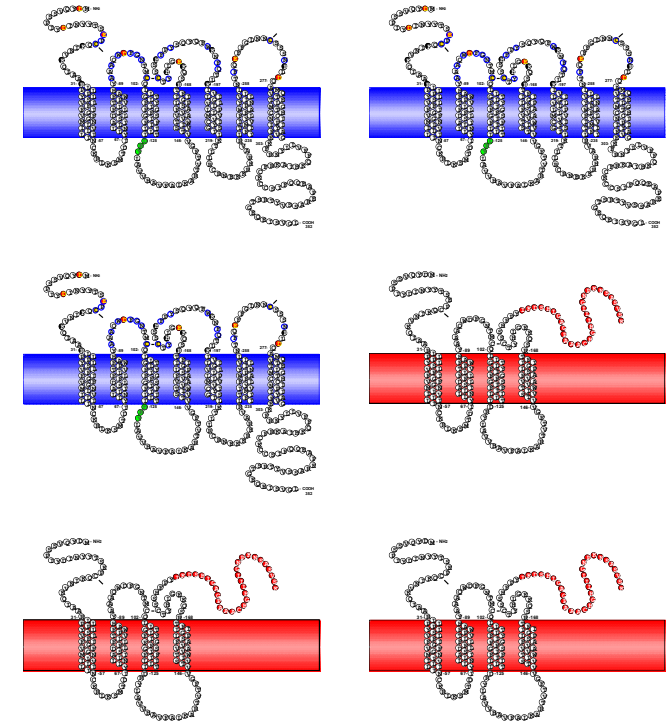
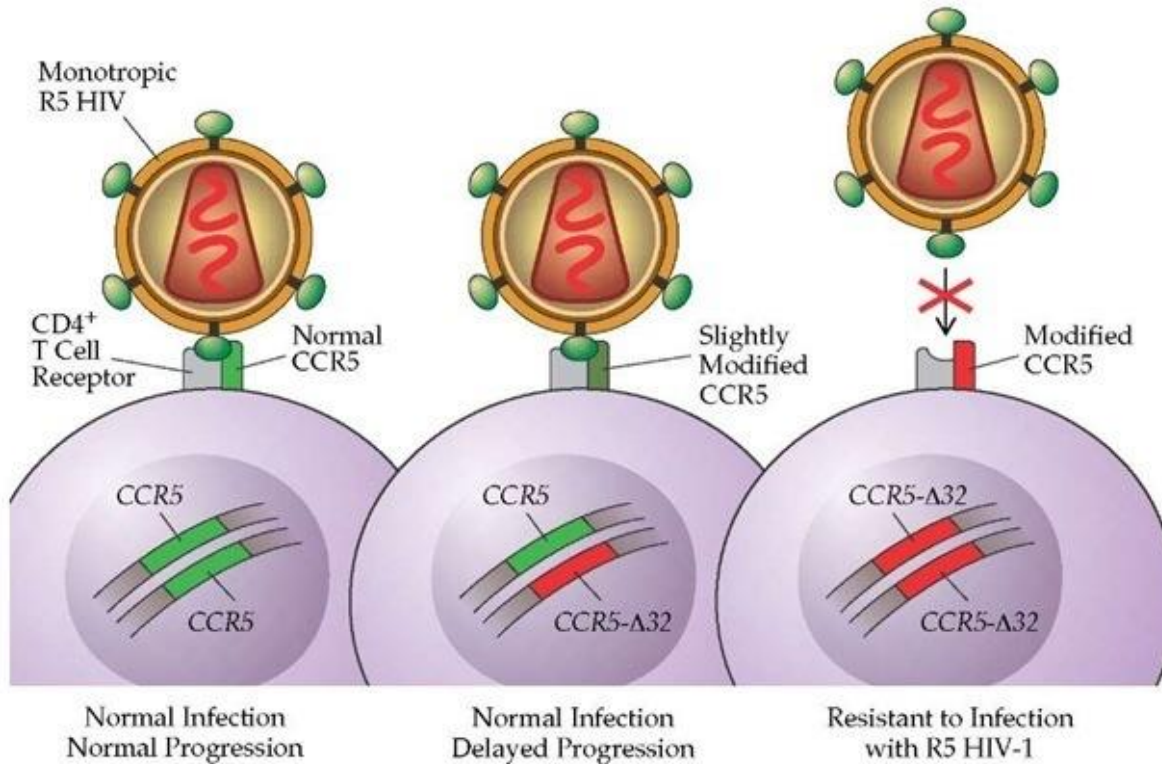
- HIV-1 VB - *virulent subtype B*
- evolved ca. 1998 in the Netherlands
- viral load ca. 3,5-5,5 times higher
- progression to AIDS without therapy twice as fast

➤ But:

- ART is potent
- number of new infections seems to decline

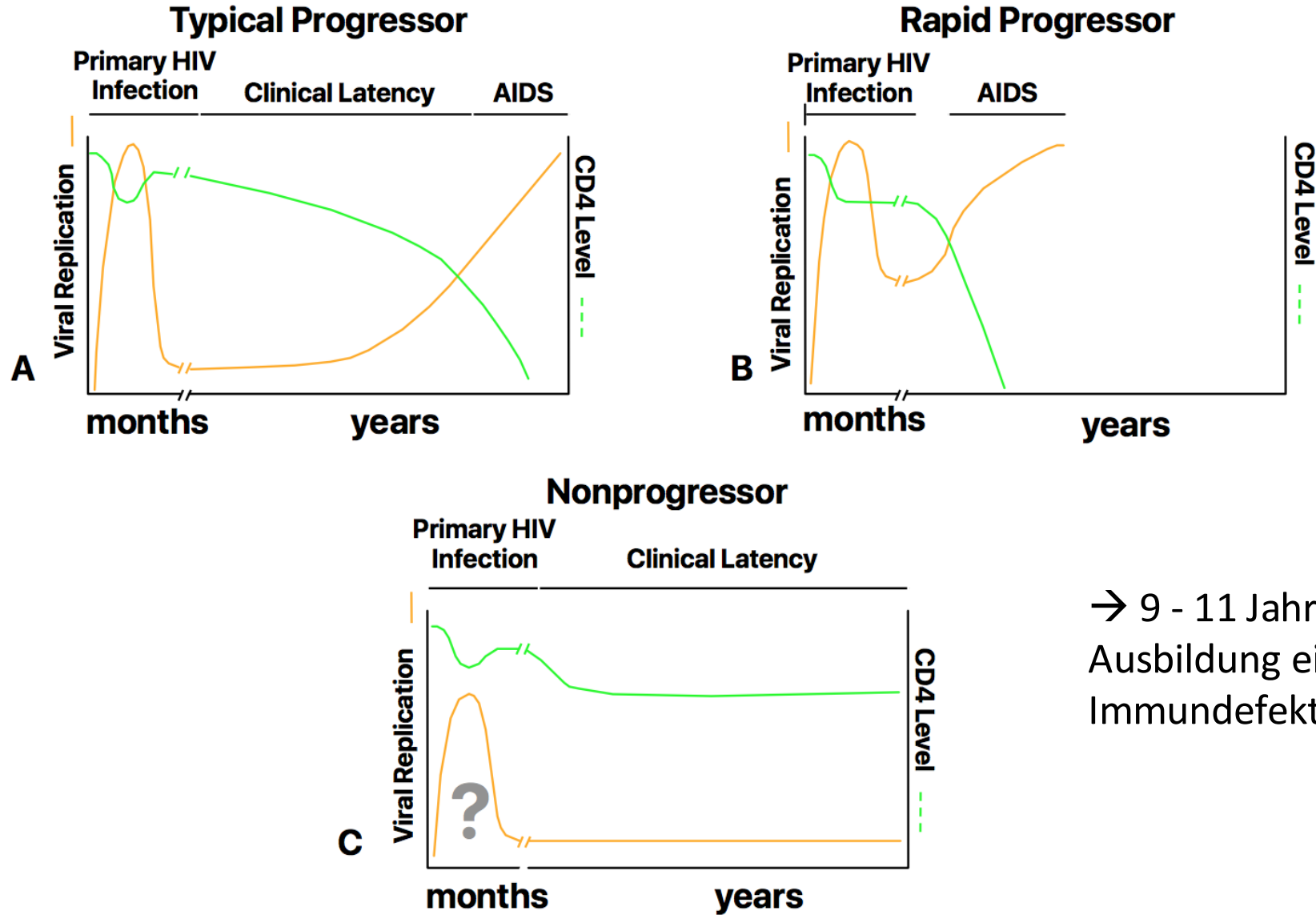


Natural protection CCR5 Δ 32



- wild type
 - not protected
- heterozygous
 - not protected
 - delayed progression
- homozygous for CCR5 Δ 32
 - protected
 - immunocompetent
 - 1% of Caucasian population

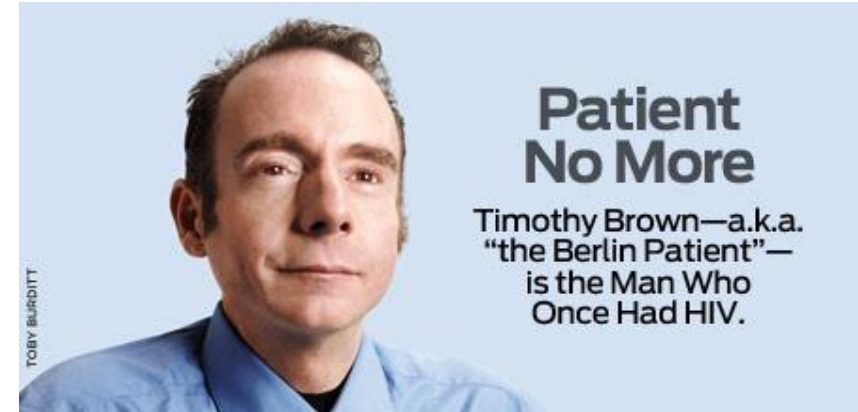
Variabler Verlauf der HIV-1-Infektion



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

The cure

- The „Berlin“ patient
 - acute myeloide leucaemia
 - allogenic stem cell transplantation
 - CCR5 Δ 32 homozygous donor
- no ART necessary
- no HIV-1 detectable



LETTER

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

HIV-1 remission following CCR5 Δ 32/ Δ 32 haematopoietic stem-cell transplantation

Ravindra K. Gupta^{1,2,3,4,5*}, Sultan Abdul-Jawad¹, Laura E. McCoy¹, Hoi Ping Mok⁴, Dimitra Peppas^{3,6}, Maria Salgado⁷, Javier Martinez-Picado^{7,8,9}, Monique Nijhuis¹⁰, Annemarie M. J. Wensing¹⁰, Helen Lee¹¹, Paul Grant¹², Eleni Nastouli¹², Jonathan Lambert¹³, Matthew Pace⁶, Fanny Salas⁴, Christopher Monit¹, Andrew J. Innes^{14,15}, Luke Muir¹, Laura Waters³, John Frater^{6,16}, Andrew M. L. Lever^{4,17}, Simon G. Edwards³, Ian H. Gabriel^{14,15,18,19} & Eduardo Olavarria^{14,15,19}

February 12, 2019
N Engl J Med 2019; 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

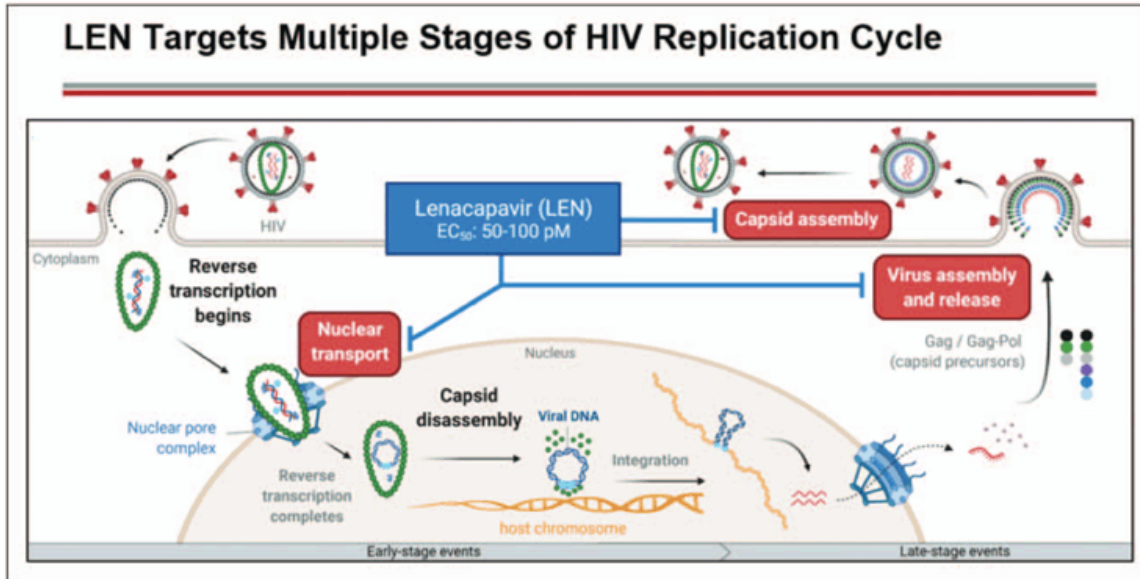
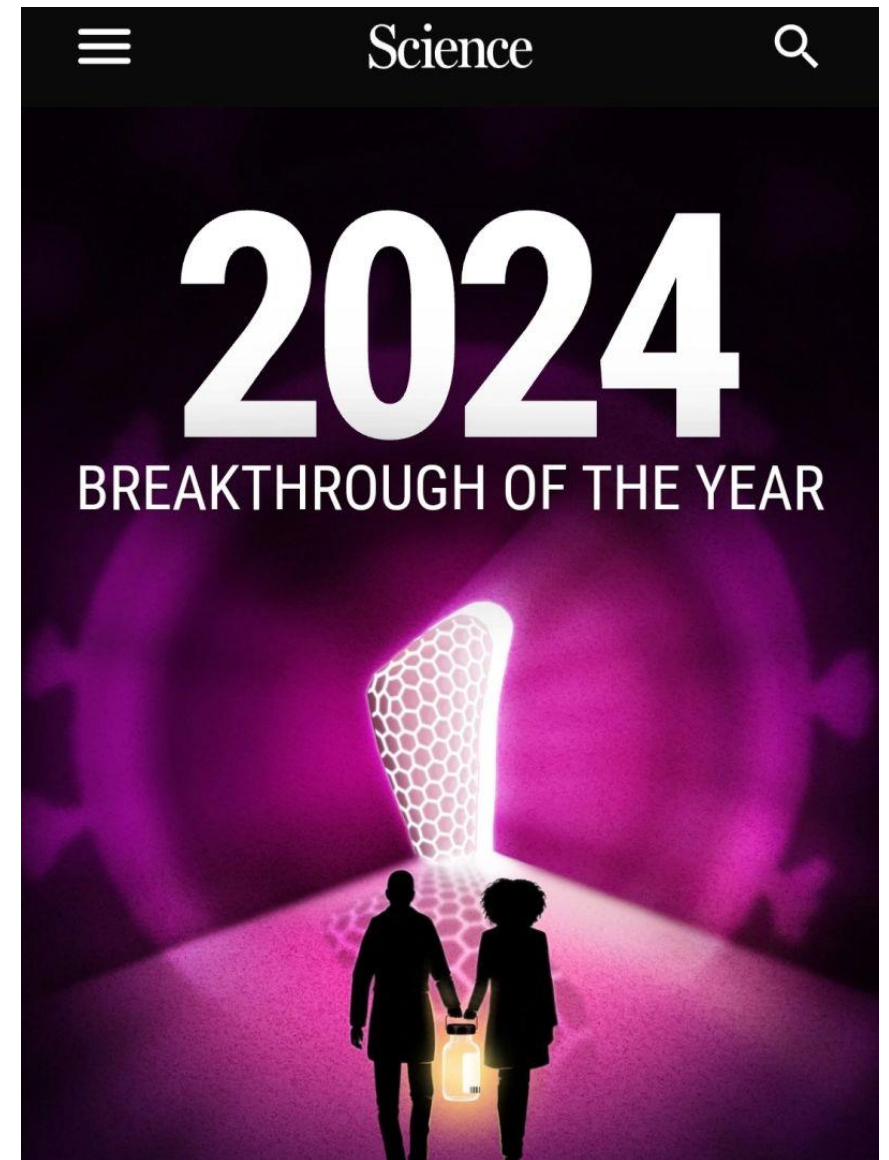
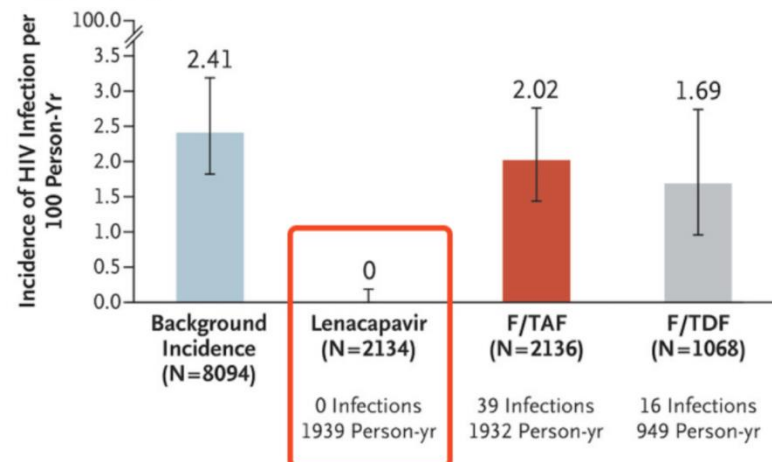


FIGURE 1. Lenacapavir targets multiple stages of the HIV replication cycle. Adapted from [4**,5].

A Background HIV Incidence and HIV Incidence in Lenacapavir, F/TAF, and F/TDF Groups



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