

# Grundlagen der Immunologie

**Erbliche und erworbene  
Immundefekte**

# Gruppen der Immundefizienzen

## I. Erbliche

- 1) Defizienz von Phagozyten
- 2) Defizienz von Komplementen
- 3) Kombinierte Defizienzen (SCID)
- 4) T-Zell-Defizienzen
- 5) B-Zell-Defizienzen

## II. Erworbene

- 1) Maligne Erkrankungen (Tumoren, besonders Erkrankungen der Blutbildung)
- 2) Systemerkrankungen (autoimmune Krankheiten, Sarkoidose)
- 3) Infektionskrankheiten/AIDS
- 4) medikamentöse Immunsuppression (z.B.: autoimmune Krankheiten, Transplantation)
- 5) Strahlensyndrom
- 6) Mangelernährung
- 7) Verbrennungen

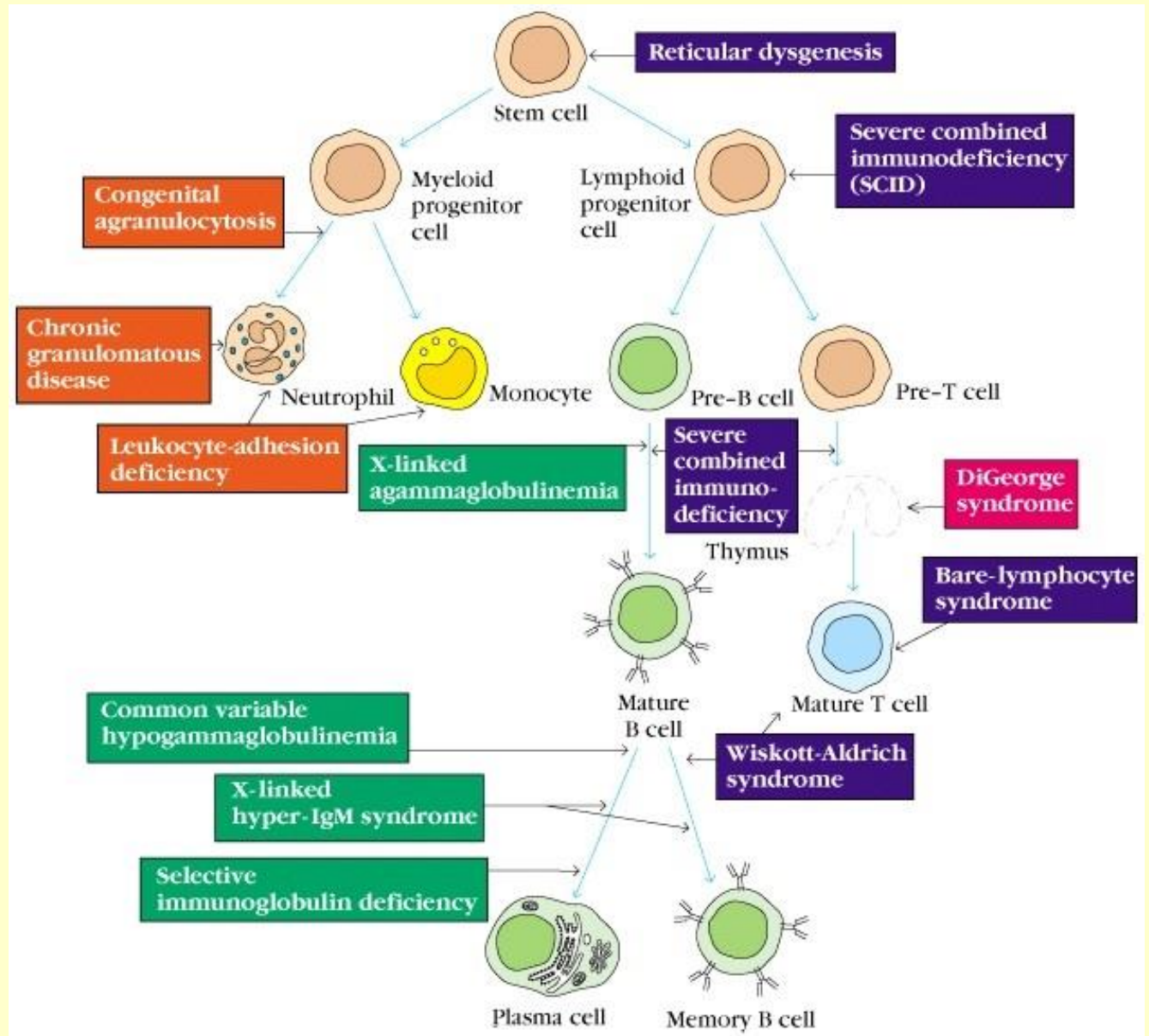
# Allgemeine klinische Symptome

- **sich ständig wiederholende Infektionen**
- **Haut-, Schleimhautrötungen**
- **chronischer Durchfall**
- **Ermüdbarkeit**
- **Hepato-Splenomegalie**
- **Autoimmunität**
- **Chronische Osteomyelitis**

# Diagnostik

- Anamnese, vor allem die Infektionen
- Familiengeschichte wegen erblicher Defekte
- Höhe, Gewicht und Entwicklung des Kindes
- Reaktion auf Impfungen
- Labordiagnostik:
  - T- , B - , NK-Zell-Funktionen, Neutrophil-Funktionsteste, Komplement-Assays
- Genetischer Hintergrund

# Hintergrund der Immundefekte



Defizienzen der angeborenen Immunität

B - Zell - Defizienzen

T- und B -Zell-Defizienzen

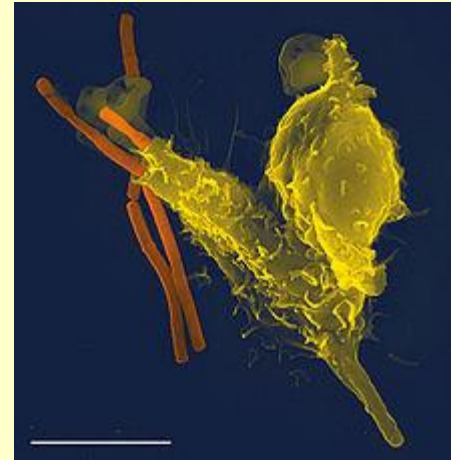
T - Zell - Defizienzen

# **Erbliche Immundefekte**

## **1. Angeborene Immunität**

# „Häufige ” zelluläre Immundefizienzen der angeborenen Immunität

- Granula– Defekte der Granulozyten/Monozyten
- Intrazelluläre Tötungsdefekte
- Störungen der Adhäsion und der Chemotaxis (LAD)
- Defekte der NK-Zellen
- Komplementsystem-Defekten

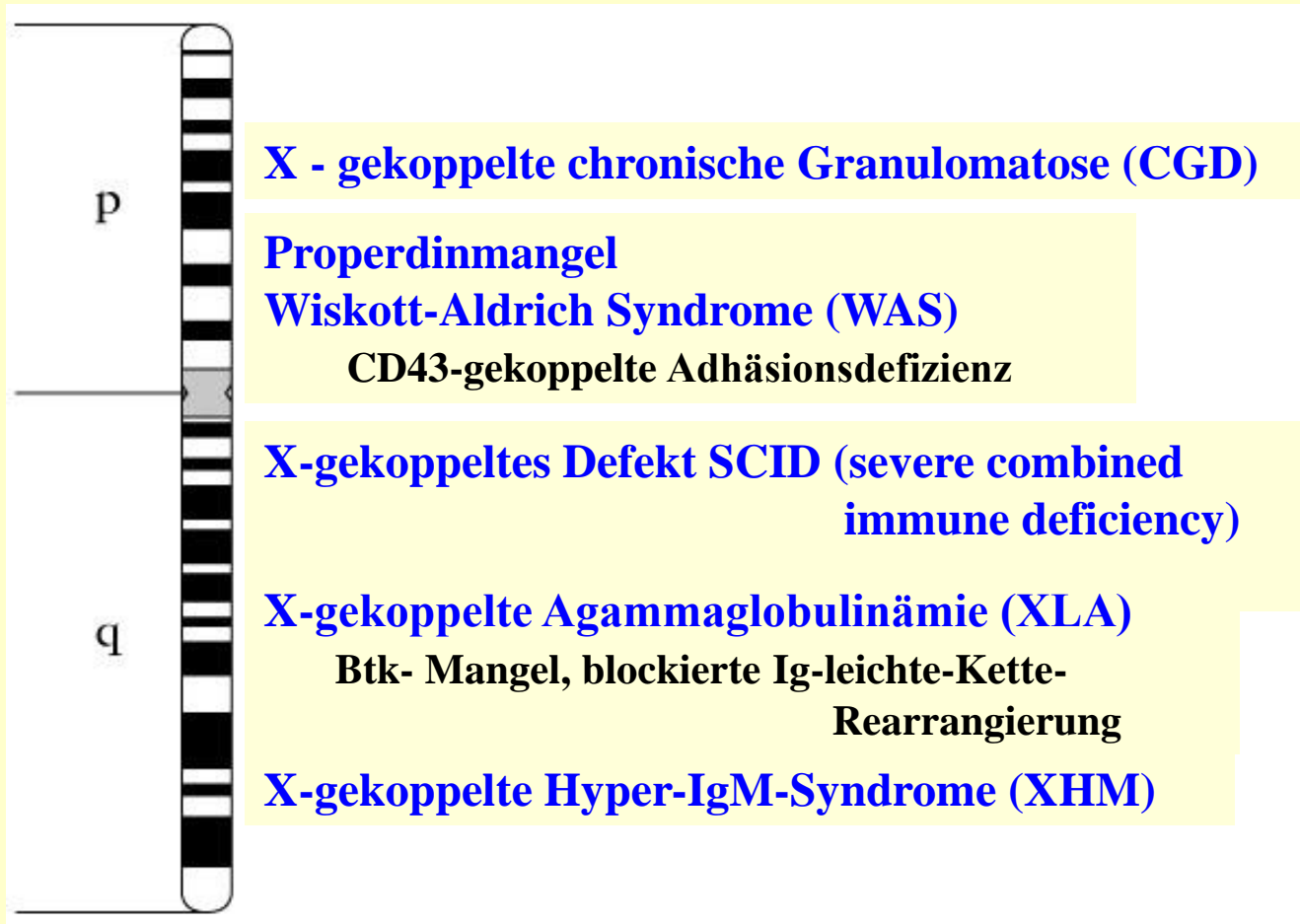


# **Erbliche Immundefekte**

## **2. Spezifische Immunität**



- meistens rezessive Krankheiten
- X -gekoppelt



# **Schwere kombinierte Immundefekte (SCID)**

- **T- und B-Zell-Defekte**
- **Allgemeine erhöhte Anfälligkeit für Infektionen im 3-6 Monat**
- **Atemwege, Gastrointestinaltrakt, Haut**
- **weder Thymus noch Lymphknoten noch Tonsillen sind nachweisbar**

# Hintergrund von SCID

- **ADA - Mangel (Adenosindesaminase)**
- **PNP - Mangel (Purinnucleotidphosphorylase)**
- **X-gekoppeltes Defekt – Defekt der gemeinsamen  $\gamma$ -Kette mehrerer Zytokinrezeptoren (IL-2, IL-4, IL-7, IL-9, IL-15)**
- **Autosomale SCID – fehlerhafte DNA- Reparatur**
- **RAG-1-, RAG-2-Defizienz (Omenn's Syndrom)**
- **ZAP-70-Defizienz**

# SCID

Normal

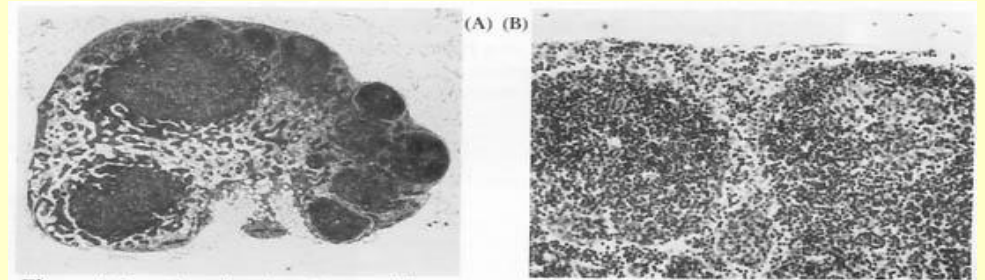
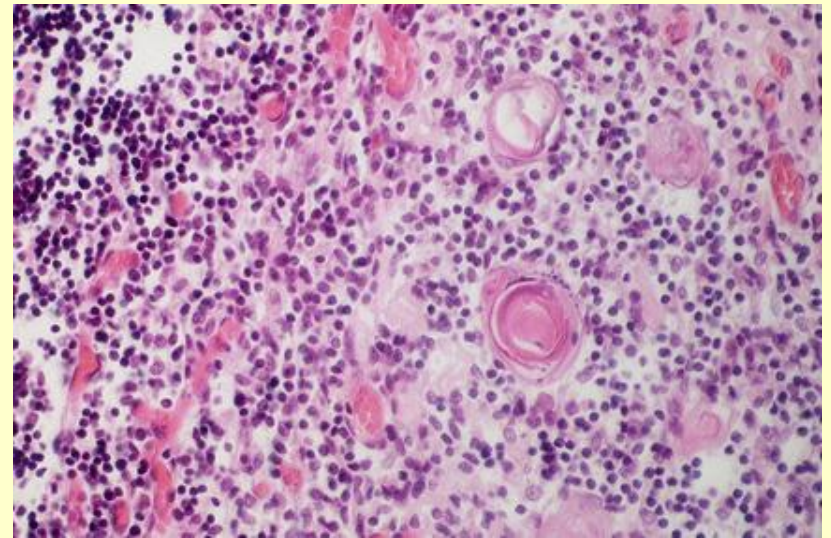
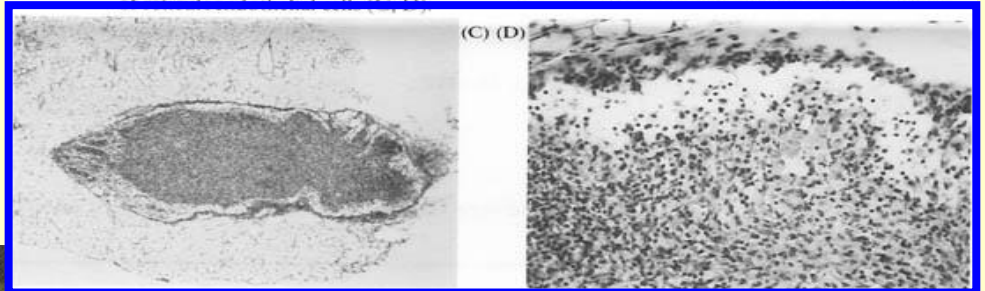
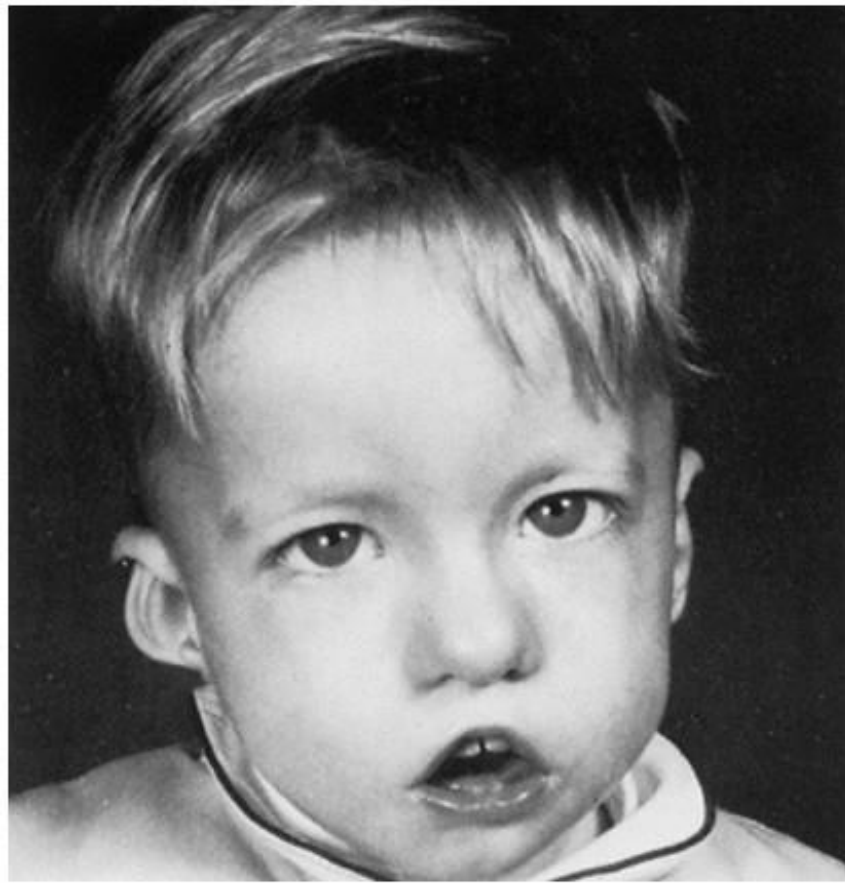


Figure 1 Lymph node of a +/+ control has numerous, prominent follicles with germinal centers (A, B) while the *scid/scid* littermate has only a small, rudimentary lymph node consisting

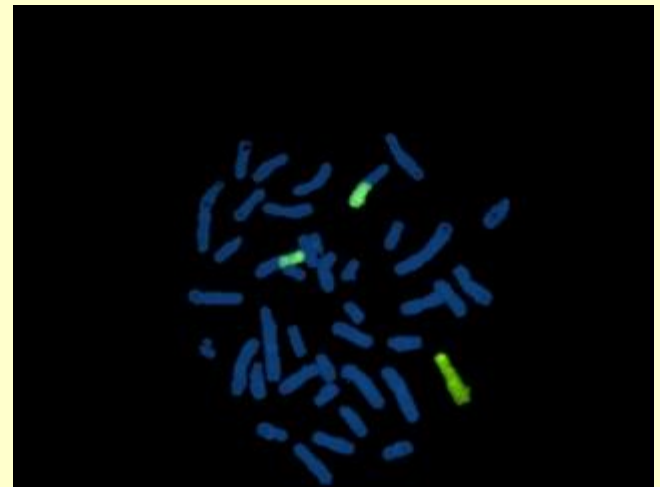
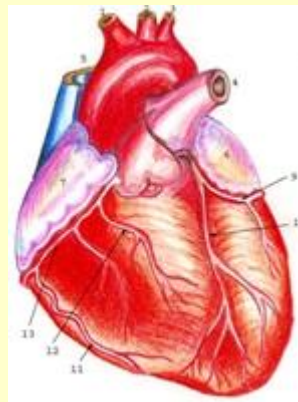
SCID



# DiGeorge-Syndrom



KiDS-22q11 e.V.





# B-Zell-Defizienzen

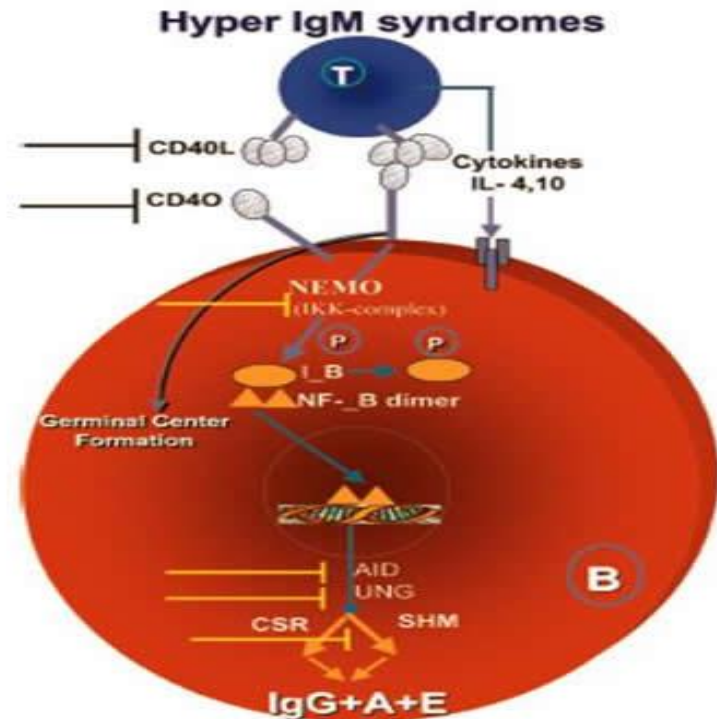
Erhöhte Infektionsanfälligkeit (Atemwege) für extrazelluläre Bakterien (pyrogene=eitererregende) Bakterien mit Polysacharidhülle (*H. influenzae*, *S. pneumoniae*)

Beispiele:

- **Variables Immundefekt** – MHC-gekoppelt, gestörte IgA- und IgG-Produktion
- **X-gekoppelte Agammaglobulinämie** (Bruton) – Verlust der Btk-Tyrosinkinase, keine B-Zellen (Reifungsblock im Prä-B-Zell-Stadium)

# B-Zell-Defizienzen

**X-gekoppelte  
Hyper-IgM-Syndrome** –  
fehlerhaftes CD40-  
Ligand,  
kein Isotypenwechsel



**Selektiver IgA-Mangel** – MHC-gekoppelt, keine IgA-  
Synthese, Infektionen der Atemwege,  
Frequenz: 1/400!

# **Erworbene Immundefekten**

## **HIV-Infektion**

**und der Pathomechanismus von AIDS**



# Epidemiologie (WHO)

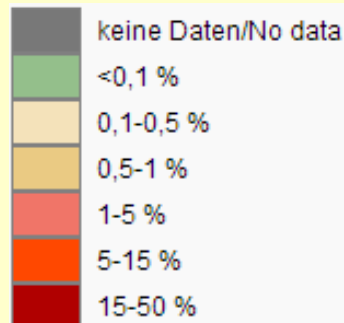
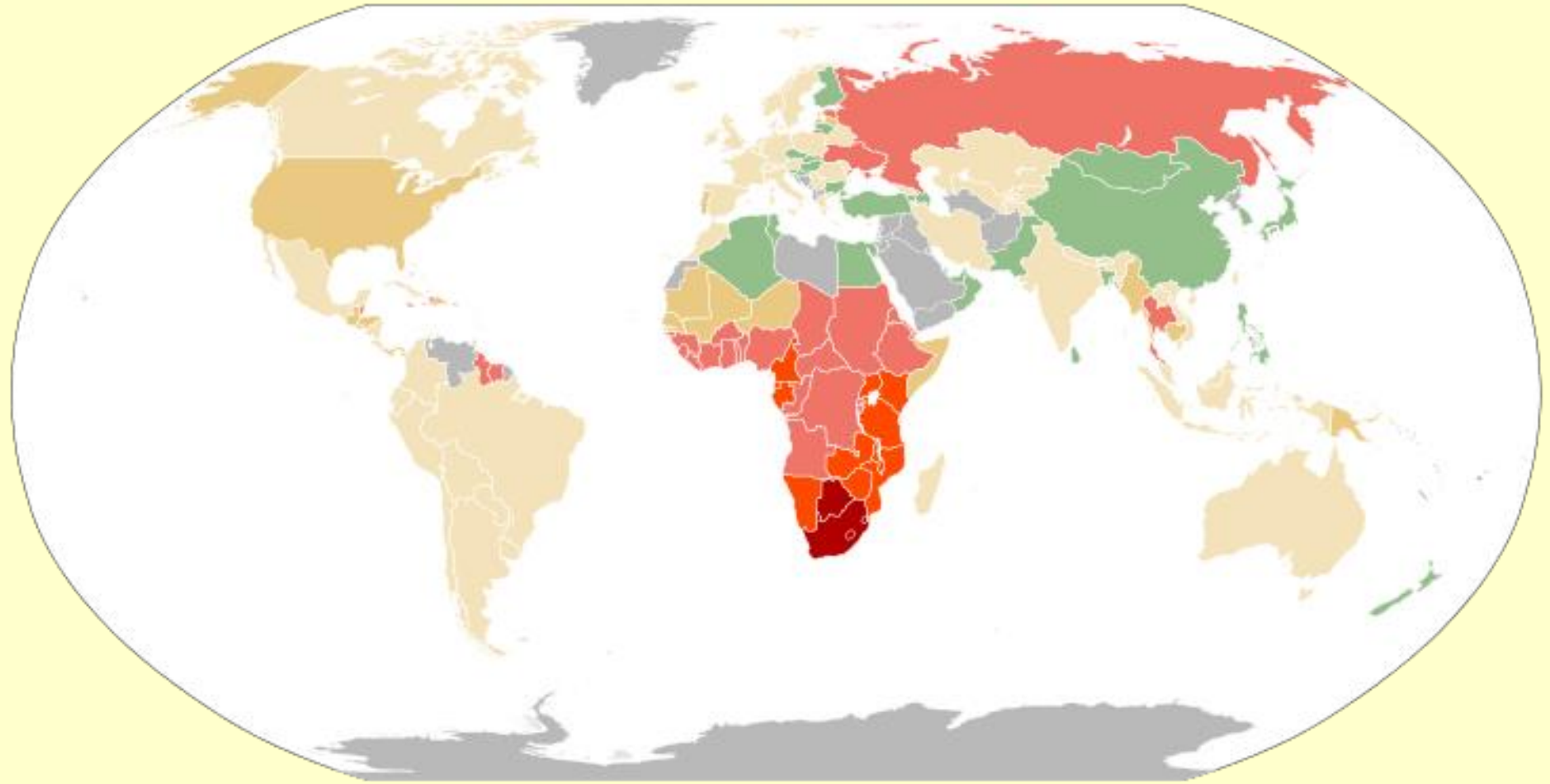
	2000	2005	2010	2015	2016	2017	2018	2019	2020/ *june2021	2023
<b>People living with HIV</b>	25.5 million [20.5 million–30.7 million]	28.6 million [23.0 million–34.3 million]	31.1 million [25.0 million–37.3 million]	34.6 million [27.7 million–41.4 million]	35.3 million [28.3 million–42.2 million]	35.9 million [28.8 million–43.0 million]	36.6 million [29.3 million–43.8 million]	37.2 million [29.8 million–44.5 million]	37.7 million [30.2 million–45.1 million]	39 Million (33.1-45.7 M)
<b>New HIV infections (total)</b>	2.9 million [2.0 million–3.9 million]	2.4 million [1.7million–3.4 million]	2.1 million [1.5 million–2.9 million]	1.8 million [1.3 million–2.4 million]	1.7 million [1.2 million–2.4 million]	1.7 million [1.2 million–2.3 million]	1.6 million [1.1 million–2.2 million]	1.5 million [1.1 million–2.1 million]	1.5 million [1.0 million–2.0 million]	1.3 Millionen (1.0-1.7)
<b>New HIV infections (aged 15+ years)</b>	2.3 million [1.6 million–3.2 million]	2.0 million [1.4 million–2.7 million]	1.8 million [1.3 million–2.5 million]	1.6 million [1.1 million–2.2 million]	1.5 million [1.1 million–2.1 million]	1.5 million [1.0 million–2.1 million]	1.4 million [1.0 million–2.0 million]	1.4 million [960 000–1.9 million]	1.3 million [910 000–1.8 million]	1.2 Millionen
<b>New HIV infections (aged 0–14 years)</b>	520 000 [340 000–820 000]	480 000 [310 000–750 000]	320 000 [210 000–510 000]	190 000 [130 000–300 000]	190 000 [120 000–290 000]	180 000 [120 000–280 000]	170 000 [110 000–260 000]	160 000 [100 000–250 000]	150 000 [100 000–240 000]	130 000
<b>AIDS-related deaths</b>	1.5 million [1.1 million–2.2 million]	1.9 million [1.3 million–2.7 million]	1.3 million [910 000–1.9 million]	900 000 [640 000–1.3 million]	850 000 [600 000–1.2 million]	800 000 [570 000–1.2 million]	750 000 [530 000–1.1 million]	720 000 [510 000–1.1 million]	680 000 [480 000–1.0 million]	630 000
<b>People accessing antiretroviral therapy</b>	560 000 [560 000–560 000]	2.0 million [2.0 million–2.0 million]	7.8 million [6.9 million–7.9 million]	17.1 million [14.6 million–17.3 million]	19.3 million [16.6 million–19.5 million]	21.5 million [19.6 million–21.7 million]	23.1 million [21.9 million–23.4 million]	25.5 million [24.5 million–25.7 million]	27.5 million [26.5 million–27.7 million] / *28.2 million	29.8 Millionen
<b>HIV resources available**</b>	US\$ 5.1 billion	US\$ 9.3 billion	US\$ 16.6 billion	US\$ 20.3 billion	US\$ 20.7 billion	US\$ 22.3 billion	US\$ 22.0 billion	US\$ 21.6 billion	US\$ 21.5 billion	20.8 Billionen

# Regionale Statistik (WHO - Dez 2018)

## Regional HIV and AIDS statistics and features | 2018

	Adults and children living with HIV	Adults and children newly infected with HIV	Adult and child deaths due to AIDS
<b>Eastern and southern Africa</b>	20.6 million [18.2 million–23.2 million]	800 000 [620 000–1.0 million]	310 000 [230 000–400 000]
<b>Western and central Africa</b>	5.0 million [4.0 million–6.3 million]	280 000 [180 000–420 000]	160 000 [110 000–230 000]
<b>Middle East and North Africa</b>	240 000 [160 000–390 000]	20 000 [8500–40 000]	8400 [4800–14 000]
<b>Asia and the Pacific</b>	5.9 million [5.1 million–7.1 million]	310 000 [270 000–380 000]	200 000 [160 000–290 000]
<b>Latin America</b>	1.9 million [1.6 million–2.4 million]	100 000 [79 000–130 000]	35 000 [25 000–46 000]
<b>Caribbean</b>	340 000 [290 000–390 000]	16 000 [11 000–24 000]	6700 [5100–9100]
<b>Eastern Europe and central Asia</b>	1.7 million [1.5 million–1.9 million]	150 000 [140 000–160 000]	38 000 [28 000–48 000]
<b>Western and central Europe and North America</b>	2.2 million [1.9 million–2.4 million]	68 000 [58 000–77 000]	13 000 [9400–16 000]
<b>TOTAL</b>	37.9 million [32.7 million–44.0 million]	1.7 million [1.4 million–2.3 million]	770 000 [570 000–1.1 million]

# Epidemiologie



# Übertragung

## Übertragung durch Körperflüssigkeiten:

- **Blut**
- **Samenflüssigkeit**
- **Vaginalsekret**
- **Muttermilch**
- **durch Plazenta**

# HIV

- HIV-1 (weltweit - mehr virulent) / HIV-2 (Westafrika, Indien – geringer virulent)
- Retrovirus, Lentivirus
- infiziert CD4 T-Zellen, dendritische Zellen und Makrophagen

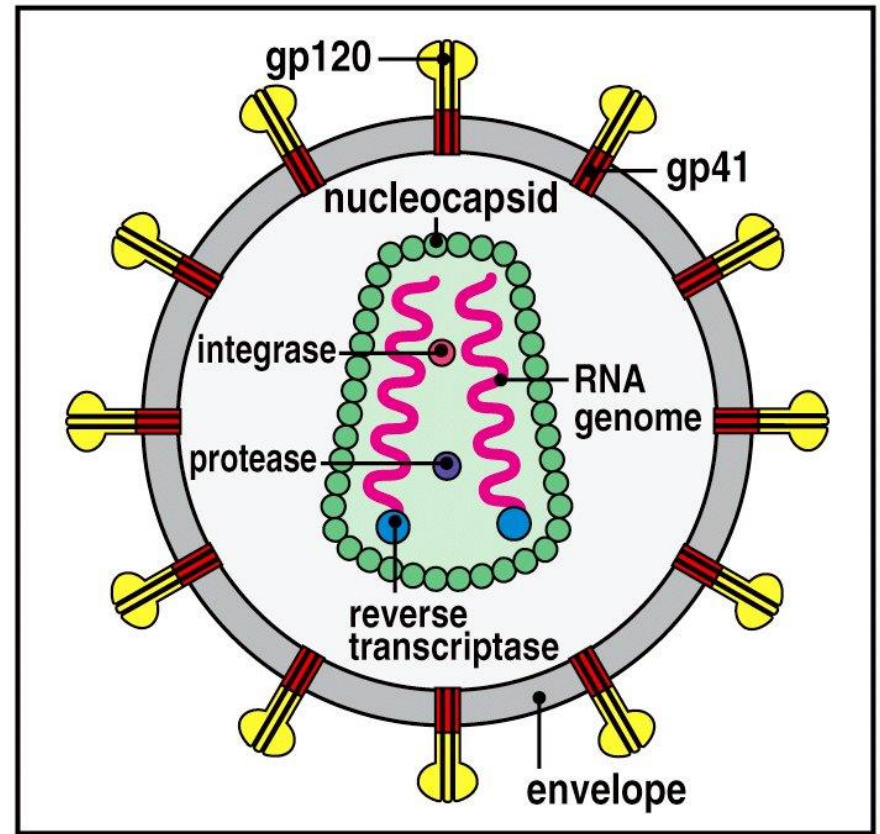
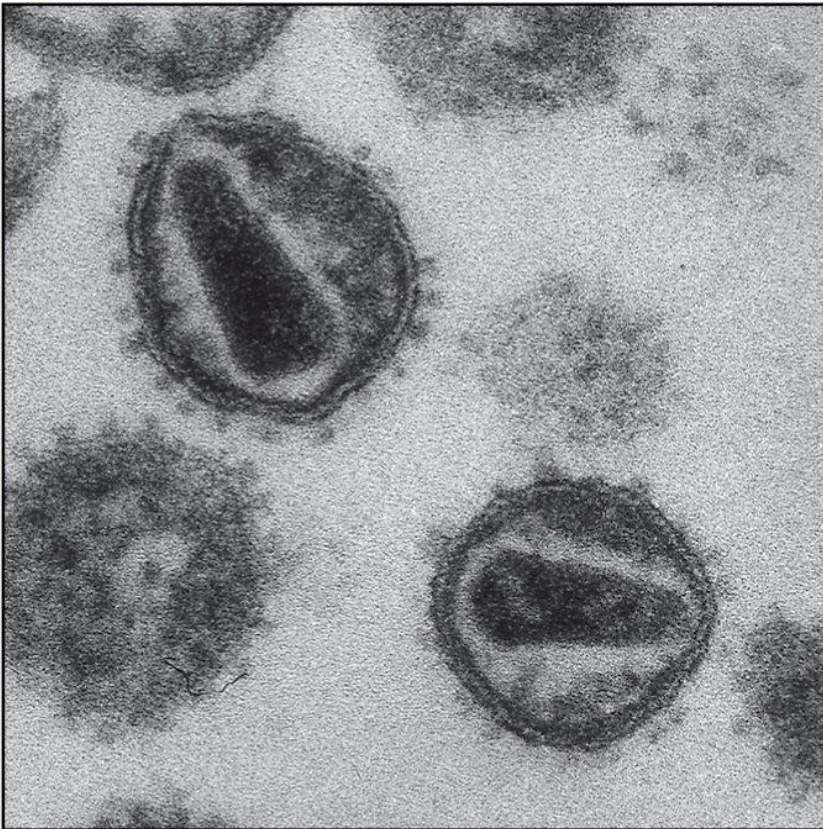


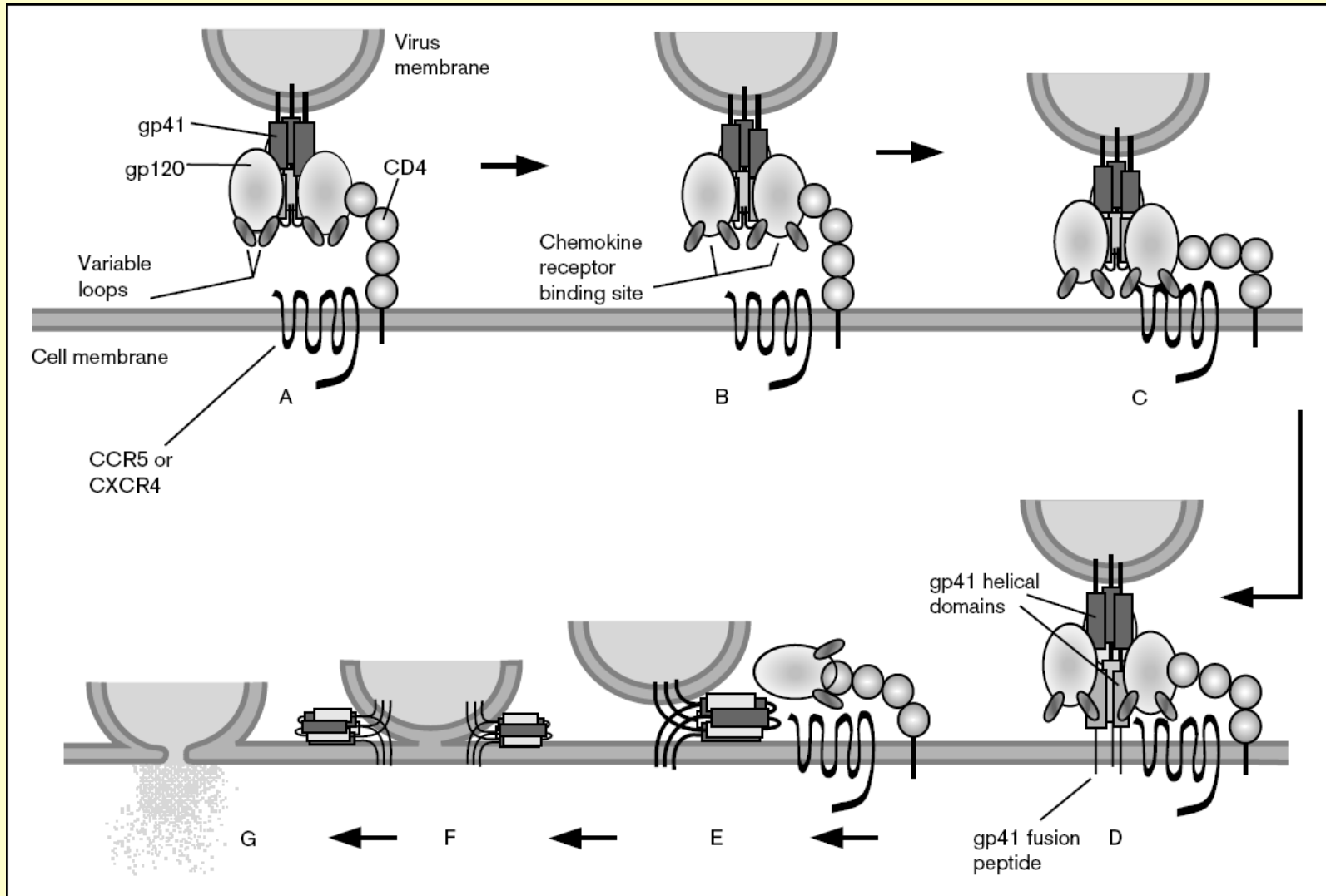
Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)



# HIV-Rezeptoren

- Gp120-Rezeptor = **CD4**
- **DC-SIGN**: „dendritic cell specific intercellular adhesion molecule 3 (ICAM-3) grabbing non-integrin“ (Bindung von HIV an diesen Rezeptor erfolgt keinen Viraleintritt)
- Ko-Rezeptoren = **Kemokinrezeptoren**
  - **CCR5** – dendritische Zellen, Makrophagen, CD4 T-Zellen - „**macrophage-tropic**“ „**R5**“ – vorzugsweise durch Geschlechtsverkehr übertragen
  - **CXCR4** – aktivierte T-Zellen – „**lymphocyte-tropic**“ „**X4**“

# Rolle der Kemokinrezeptoren in HIV-Infektion



In: Farida Shaheen and Ronald G. Collman: Co-receptor antagonists as HIV-1 entry inhibitors (Current Opinion in Infectious Diseases 2004, 17:7–16)

# Transport von HIV zu lymphatischen Geweben – Das „Trojanische Pferd“

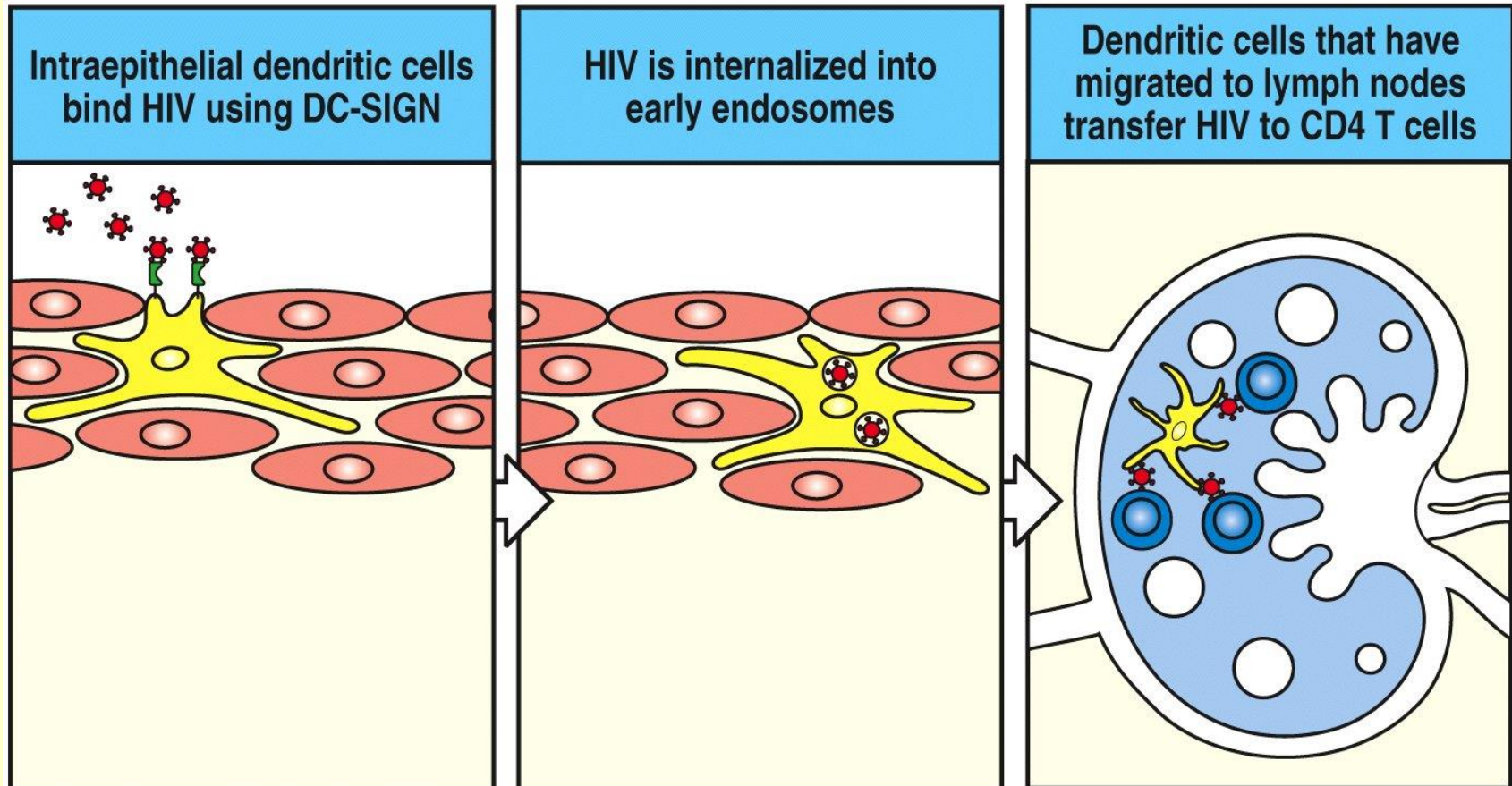
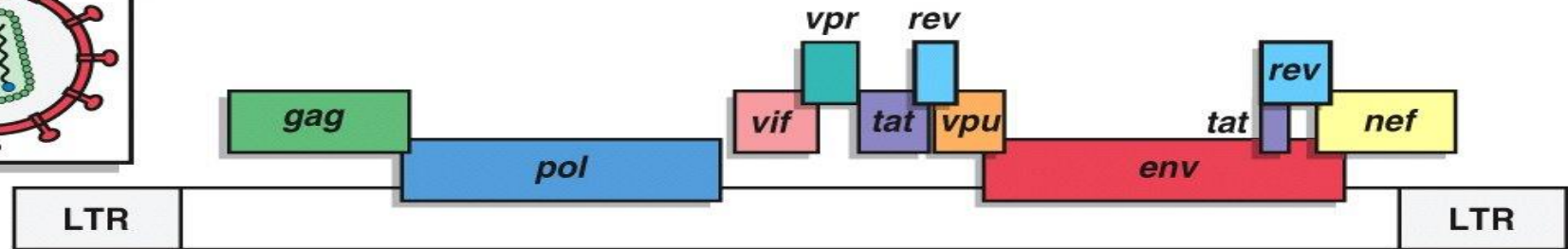
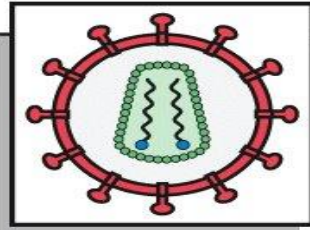


Figure 11-22 Immunobiology, 6/e. (© Garland Science 2005)

- geschichtetes squamöses Epithel (Vagina, Penis, Zervix, Anus) – die intraepithelische DC (**DC-SIGN**) – Virustransfer zu den Lymphknoten
- einschichtiges Epithel (Rektum, Endozervix) – **CCR5 + galactosyl ceramide** Expressierung an Epithel – Virustransfer zu submukosalen DC + T-Zellen



# HIV-Genom



Gen	Genprodukt / Funktion
<b>gag</b> (gruppenspezifisches Antigen)	Proteine für Viruskern und – matrix
<b>pol</b> (Polymerase)	Reverse Transkriptase, Protease und Integrase
<b>env</b> (Virushülle)	Transmembranglykoproteine gp 120 und gp 41
<b>tat</b> (Transaktivator)	Transkriptionsverstärker
<b>rev</b> (Regulator der viralen Expression)	Ermöglicht Export von teilgespleißter und ungespleißter Transkripte aus dem Zellkern
<b>vif</b> (Infektiosität des Virus)	Beeinflusst Infektiosität der Viruspartikel
<b>vpr</b> (virales R-Protein)	DNA-Transport in den Zellkern; erhöht Virusproduktion; hält Zellzyklus an
<b>vpu</b> (virales U-Protein)	Stimuliert intrazellulären Abbau von CD4 Verstärkt Virusfreisetzung durch die Membran
<b>nef</b> (negativer Kontrollfaktor)	Verstärkt Virusreplikation <i>in vivo</i> und <i>in vitro</i> Abwärtsregulation von CD4 und MHC-II

# HIV-Replikation 1.

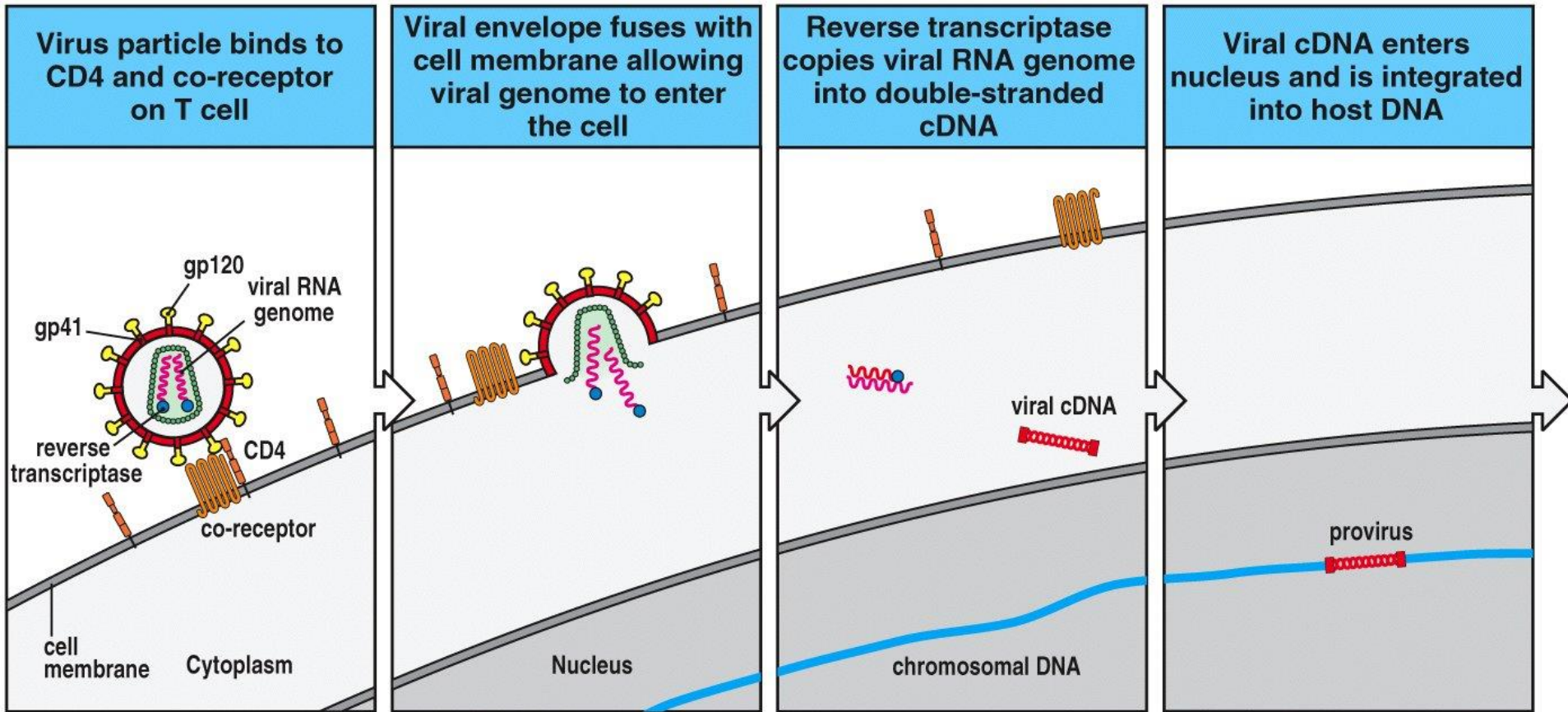
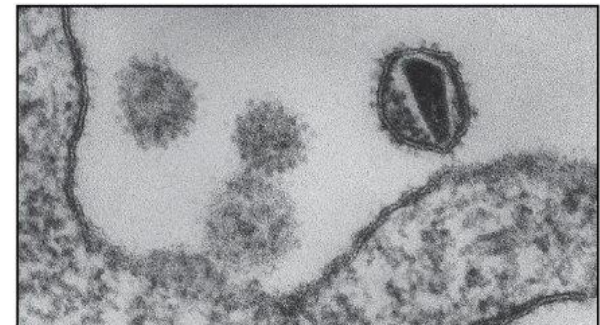
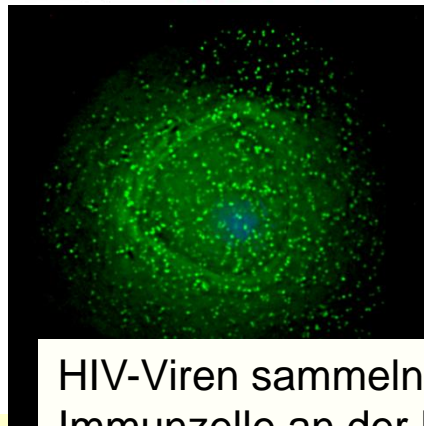
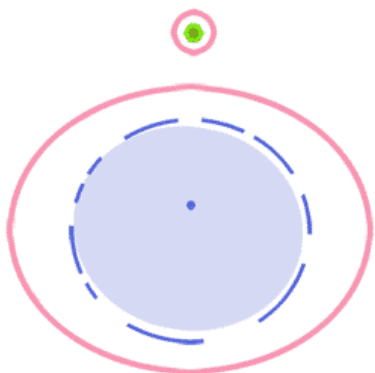
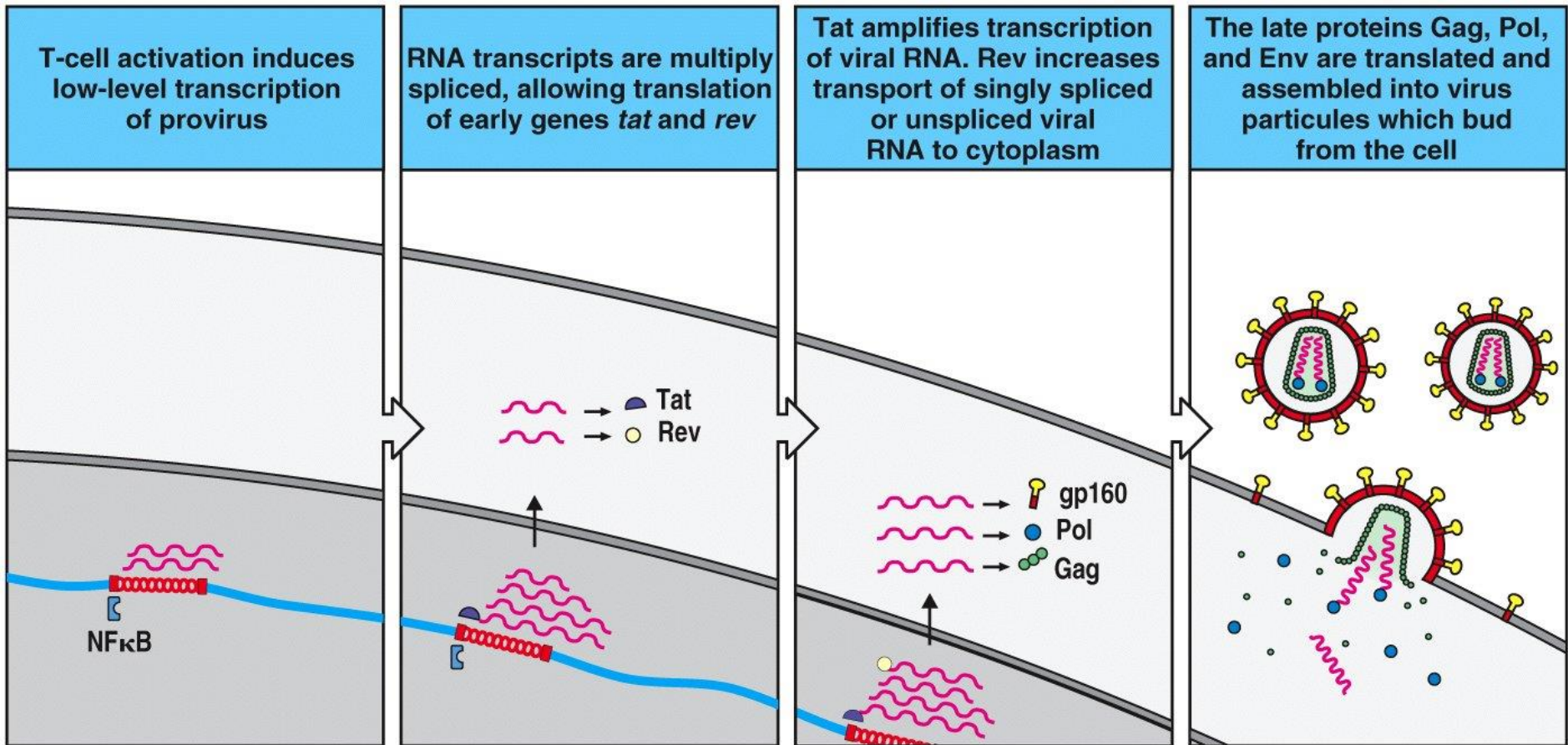


Figure 11-23 Immunobiology, 6/e. (© Garland Science 2005)

# HIV-Replikation 2.



HIV-Viren sammeln sich vor dem Verlassen der Immunzelle an der Membran



# Immunantwort gegen HIV

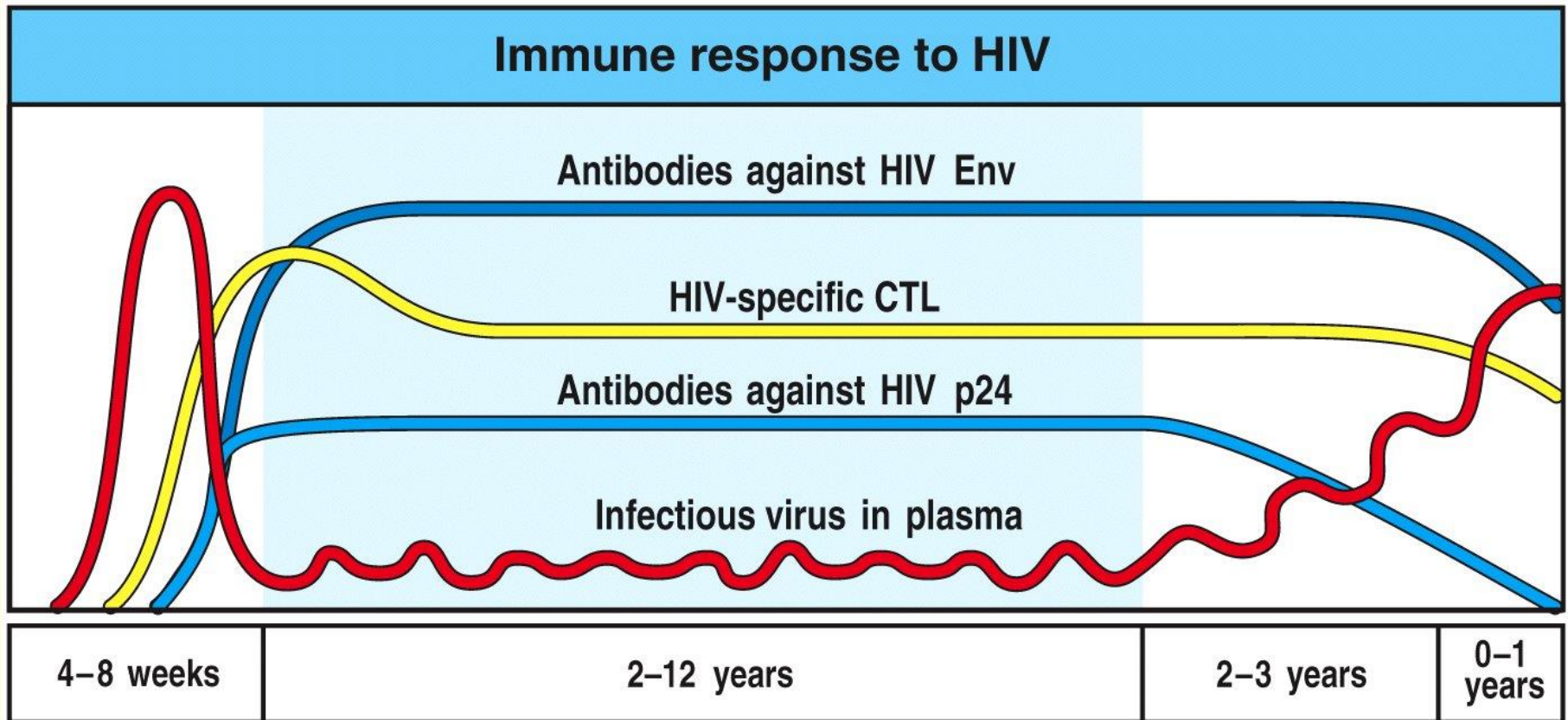
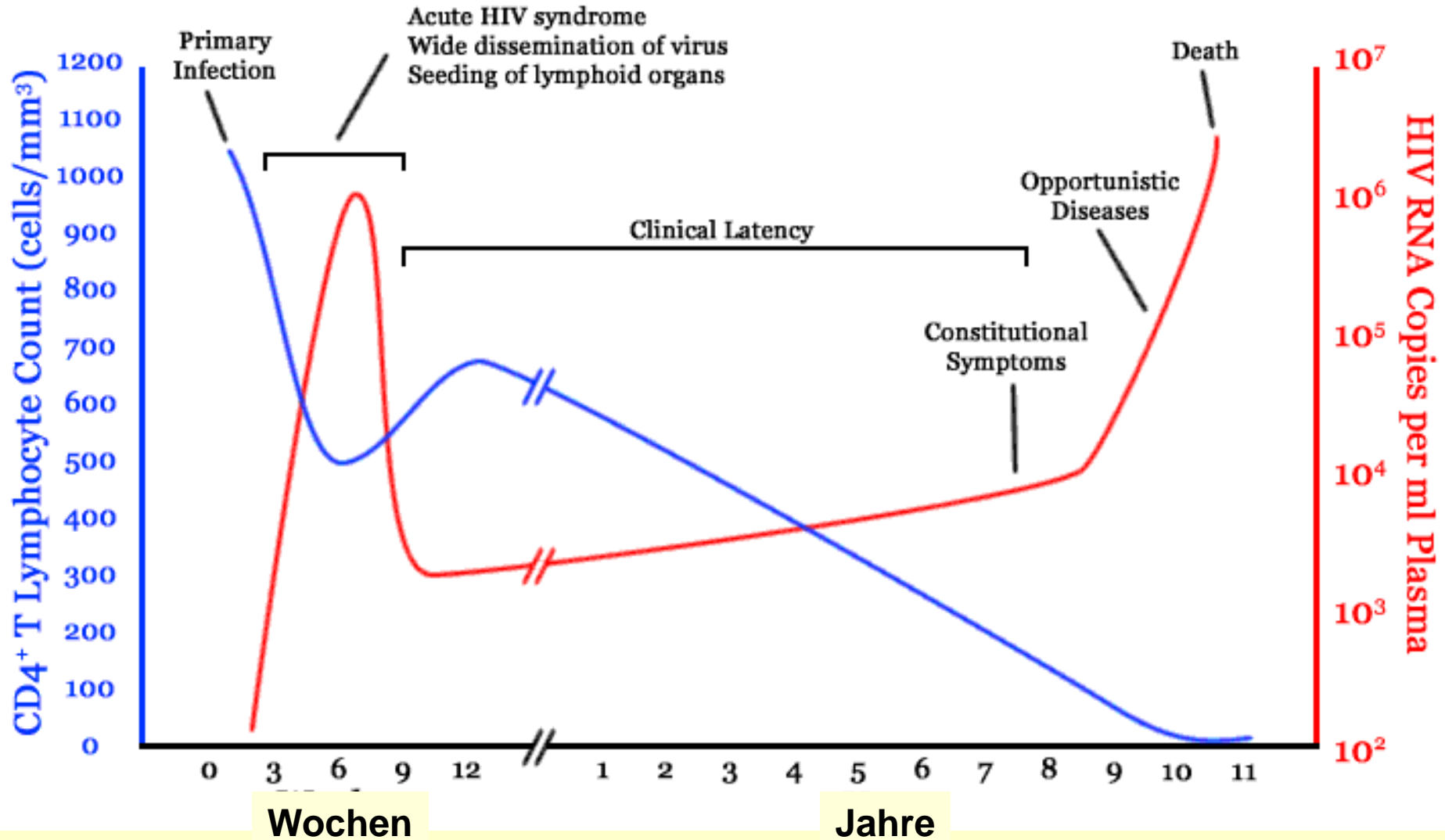


Figure 11-29 Immunobiology, 6/e. (© Garland Science 2005)

**Problem: Th-Aktivierung löst Virusreplikation aus!**

# Klinischer Verlauf von AIDS



# Stadieneinteilung der HIV-Infektion

	klinische Kategorien		
CD4+ T-Zellzahl	A	B	C
> 500/ $\mu$ l	A1	B1	C1
200 - 499/ $\mu$ l	A2	B2	C2
< 200/ $\mu$ l	A3	B3	C3

Die grüne Buchstaben entsprechen des AIDS Krankheitsbildes

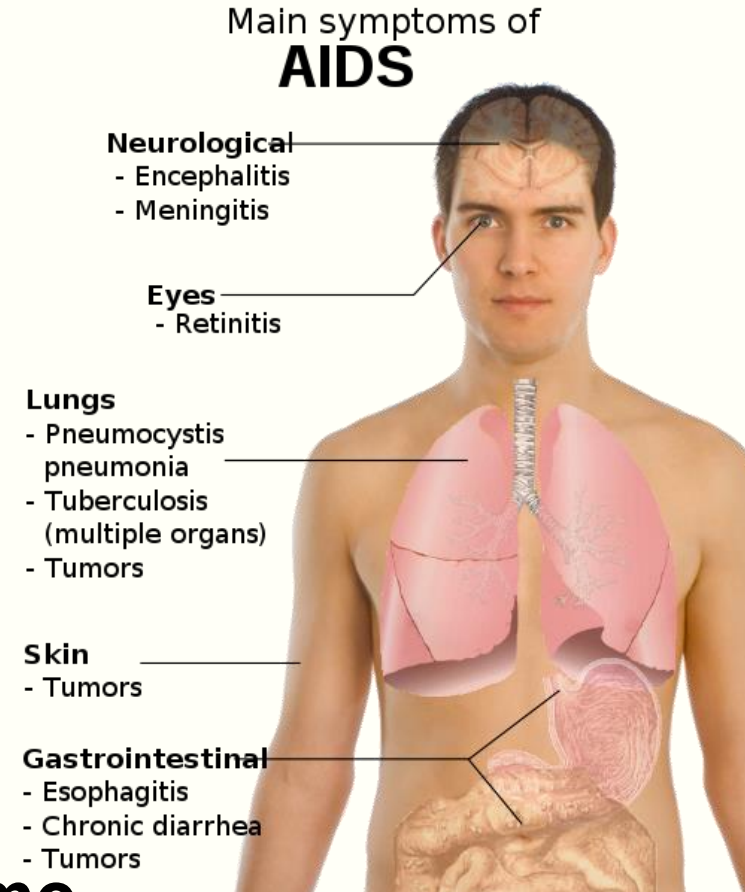
# Todesursachen bei AIDS-Kranken

## Opportunistische Infektionen:

- **Parasiten:** Toxoplasma, Cryptosporidium, Leishmania, Microsporidium
- **Bakterien:** Mycobacterium-Stämme, Salmonella-Stämme
- **Viren:** HSV, CMV, VZV

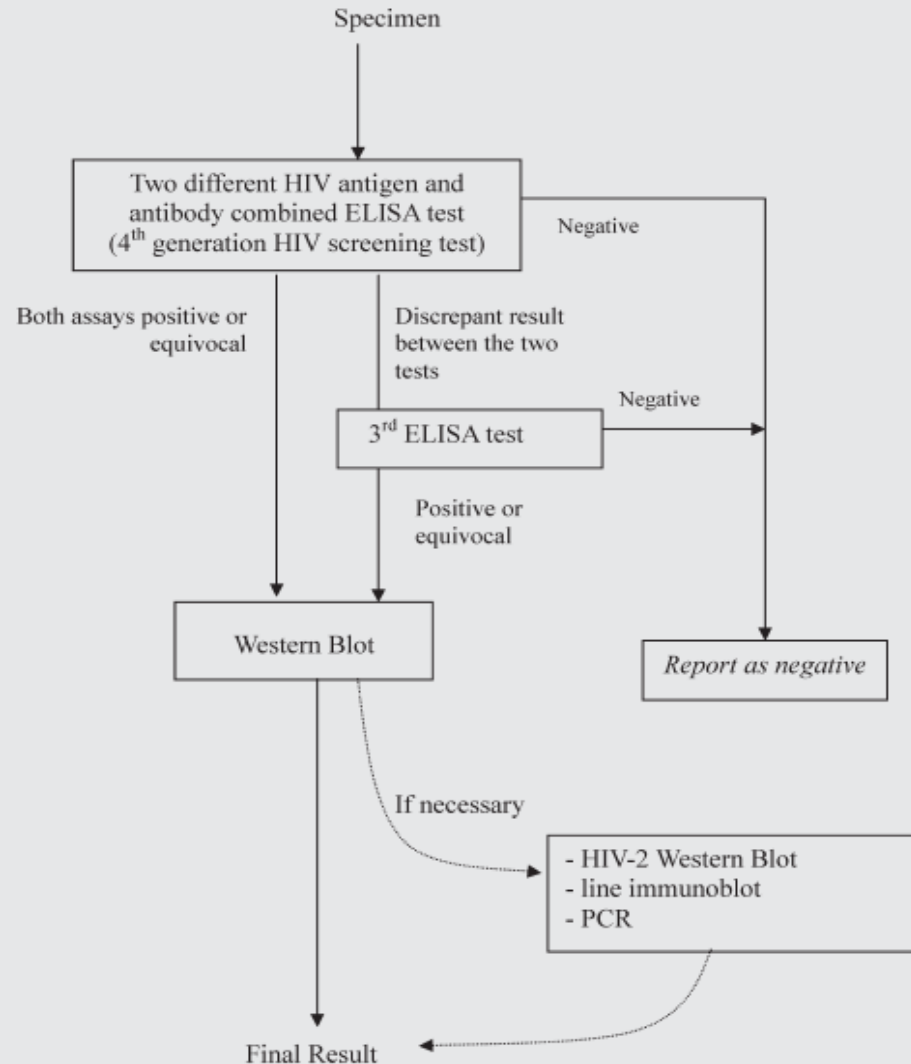
## Krebserkrankungen:

**Kaposi-Sarkom**  
**Non-Hodgkin-Lymphome**  
**EBV-positive Burkitt-Lymphome**  
**primäre Lymphome des Gehirns**



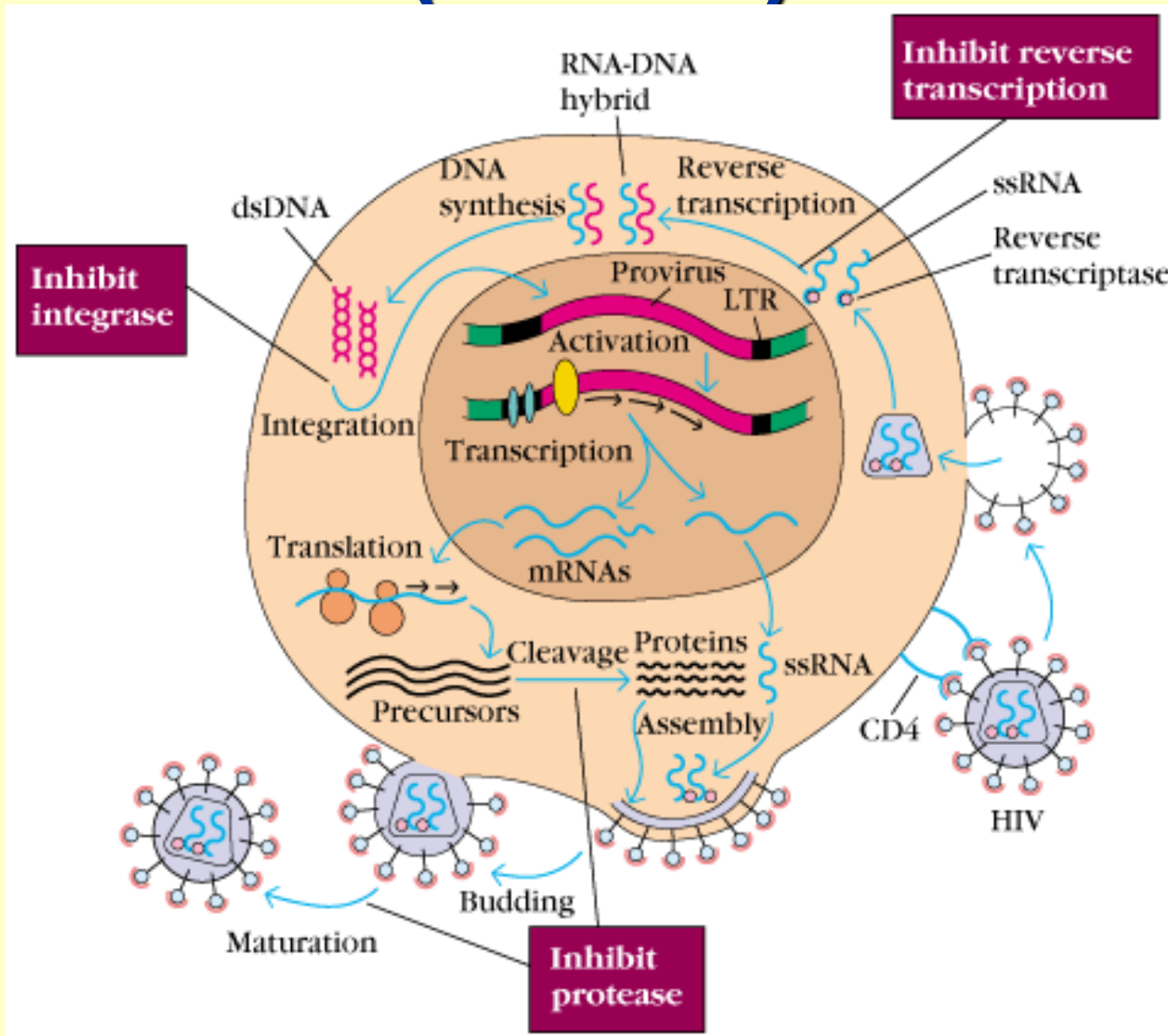
# Diagnostik der HIV-Infektion

**Algorithm 3(A)** Laboratory diagnosis of HIV infection for adults  
(adapted from protocol of Public Health Laboratory Centre, Centre for Health Protection, Department of Health)



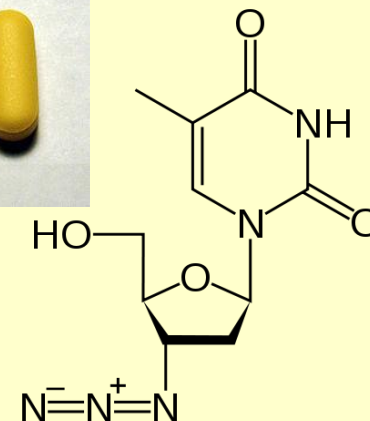


# Therapeutische Möglichkeiten (HAART)

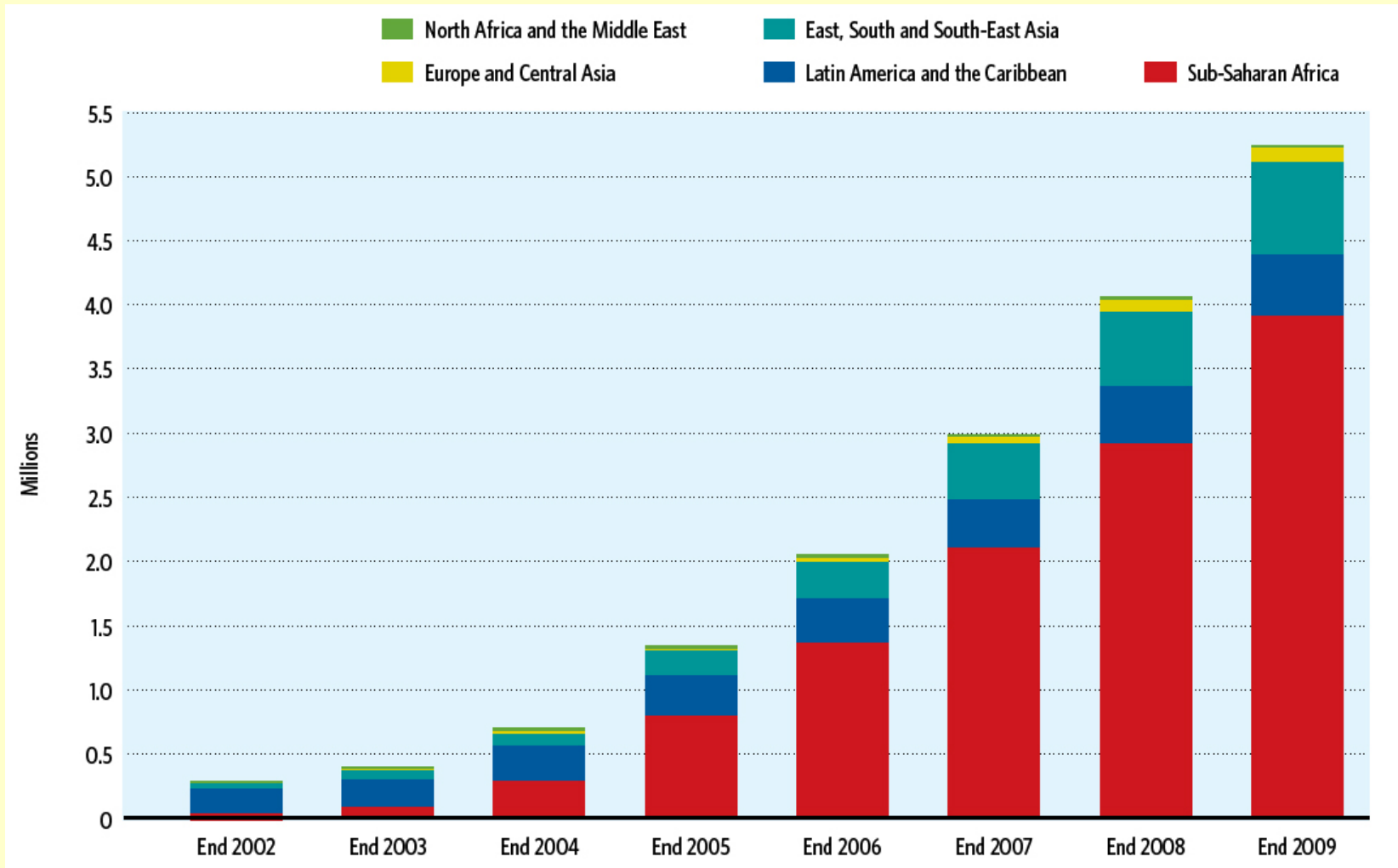


**TABLE 19-5 SOME ANTI-HIV DRUGS IN CLINICAL USE**

Generic name (other names)	Typical dosage	Some potential side effects
<b>Reverse transcriptase inhibitors: Nucleoside analog</b>		
Didanosine (Videx, ddl)	2 pills, 2 times a day on empty stomach	Nausea, diarrhea, pancreatic inflammation, peripheral neuropathy
Lamivudine (EpiVir, 3TC)	1 pill, 2 times a day	Usually none
Stavudine (Zerit, d4T)	1 pill, 2 times a day	Peripheral neuropathy
Zalcitabine (HIVID, ddC)	1 pill, 3 times a day	Peripheral neuropathy, mouth inflammation, pancreatic inflammation
Zidovudine (Retrovir, AZT)	1 pill, 2 times a day	Nausea, headache, anemia, neutropenia (reduced levels of neutrophil white blood cells), weakness, insomnia
Pill containing lamivudine and zidovudine (Combivir)	1 pill, 2 times a day	Same as for zidovudine
<b>Reverse transcriptase inhibitors: Nonnucleoside analogues</b>		
Delavirdine (Rescriptor)	4 pills, 3 times a day (mixed into water); not within an hour of antacids or didanosine	Rash, headache, hepatitis
Nevirapine (Viramune)	1 pill, 2 times a day	Rash, hepatitis
<b>Protease inhibitors</b>		
Indinavir (Crixivan)	2 pills, 3 times a day on empty stomach or with a low-fat snack and not within 2 hours of didanosine	Kidney stones, nausea, headache, blurred vision, dizziness, rash, metallic taste in mouth, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Nelfinavir (Viracept)	3 pills, 3 times a day with some food	Diarrhea, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Ritonavir (Norvir)	6 pills, 2 times a day (or 4 pills, 2 times a day if taken with saquinavir) with food and not within 2 hours of didanosine	Nausea, vomiting, diarrhea, abdominal pain, headache, prickling sensation in skin, hepatitis, weakness, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Saquinavir (Invirase, a hard-gel capsule; Fortovase, a soft-gel capsule)	6 pills, 3 times a day (or 2 pills, 2 times a day if taken with ritonavir) with a large meal	Nausea, diarrhea, headache, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance

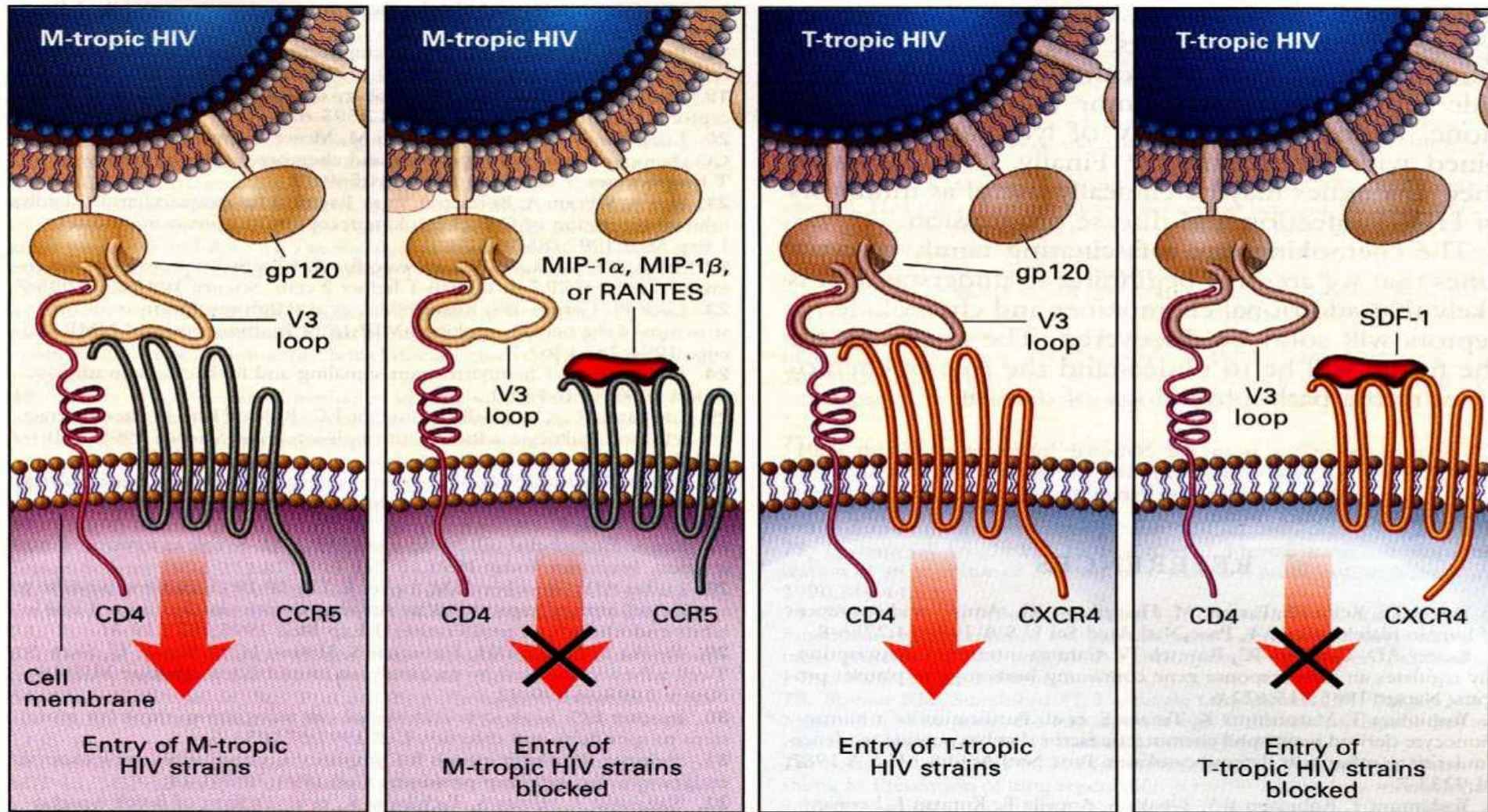
**Azithothymidin (AZT)**

# Antiretroviral therapy (2002-2009)





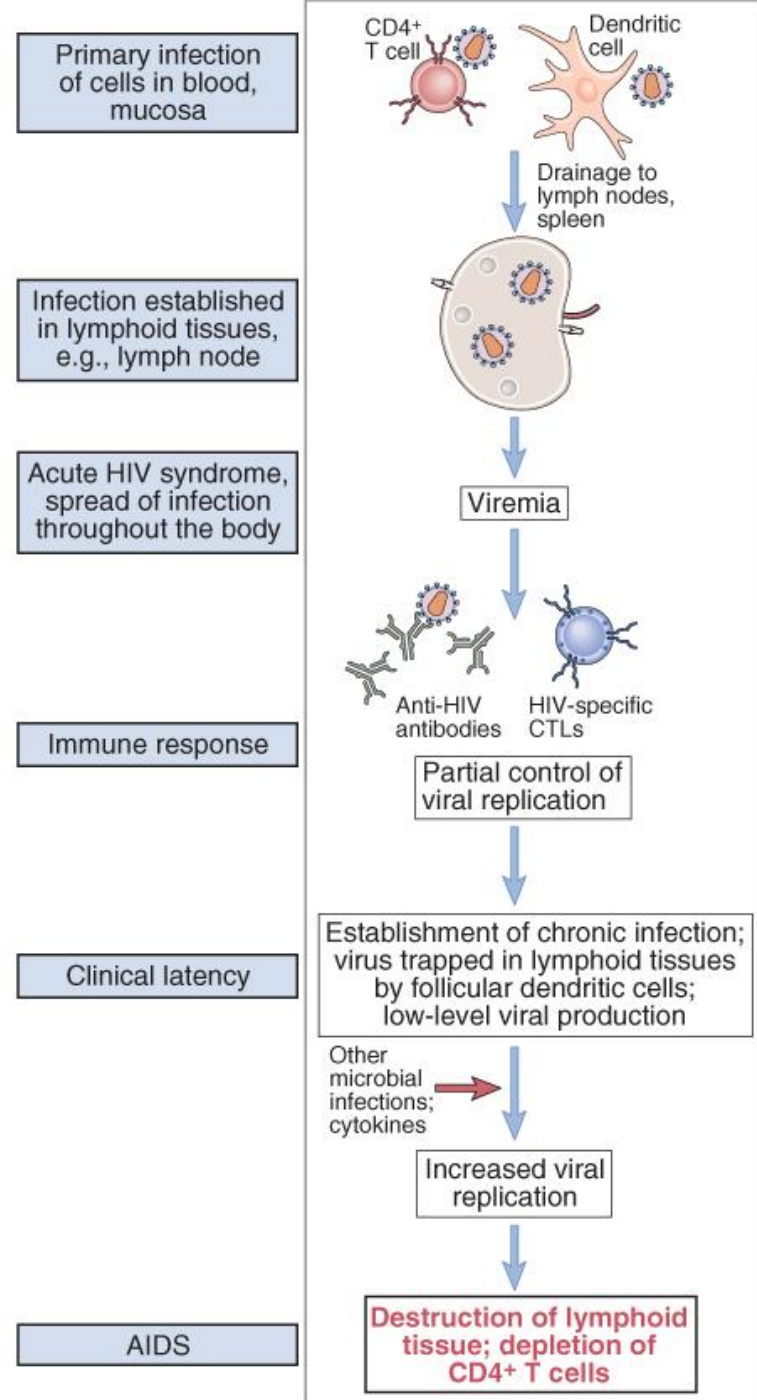
# Liganden von Kemokinrezeptoren hemmen HIV- Aufnahme in die Zielzellen



# Der Verlauf der HIV-Infektion



Dez. 1





# Die Nobelpreisträger in Physiologie / Medizin 2008

**HPV**



Harald zur Hausen  
*Deutschland*

**HIV**



Françoise  
Barré-Sinoussi  
*Frankreich*



Luc Montagnier  
*Frankreich*