

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

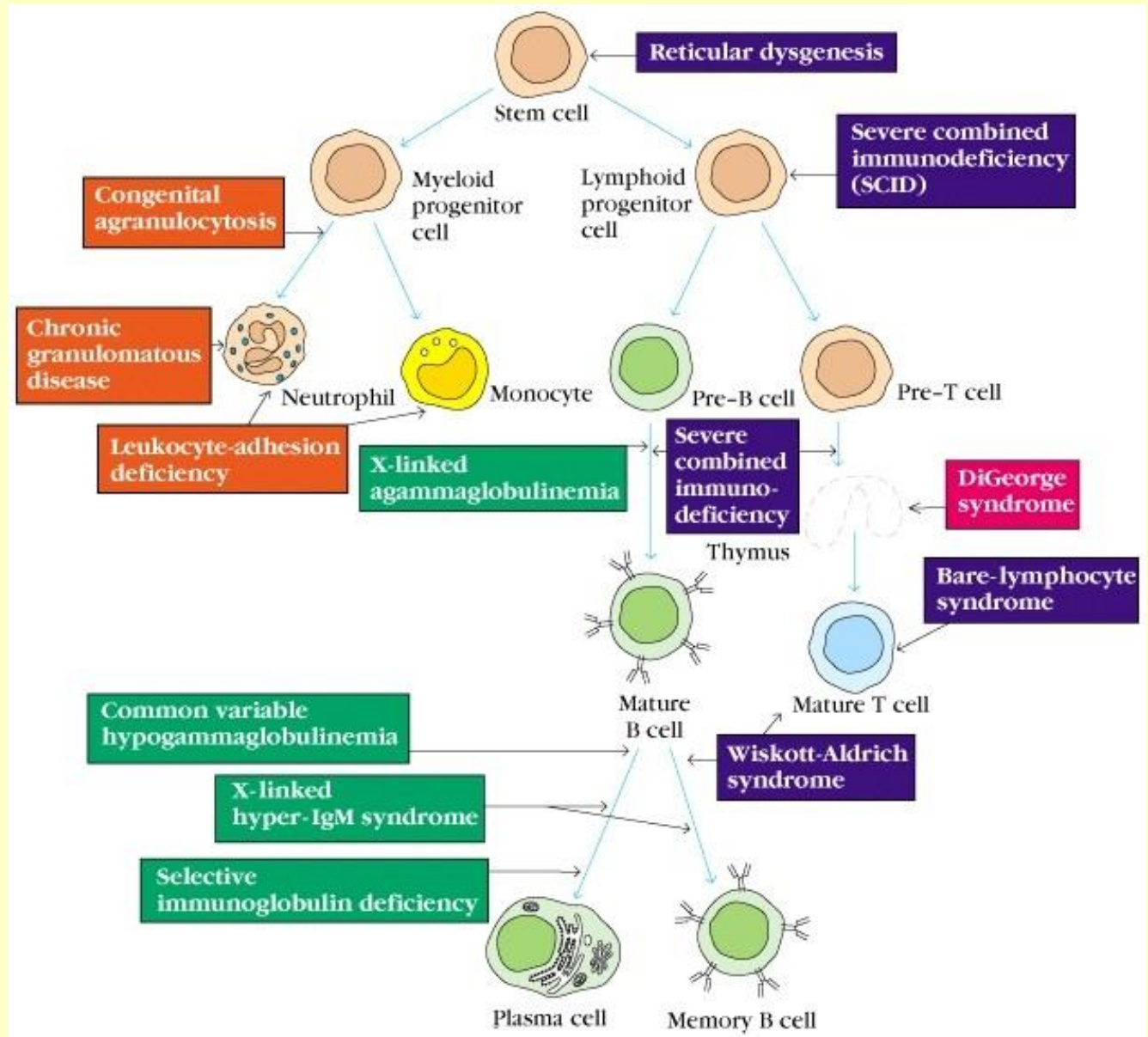
Allgemeine klinische Symptome

- **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

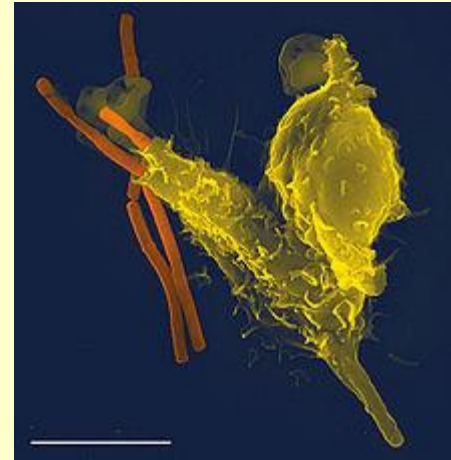
T - Zell - Defizienzen

Erbliche Immundefekte

1. Angeborene Immunität

„Häufige ” zelluläre Immundefizienzen der angeborenen Immunität

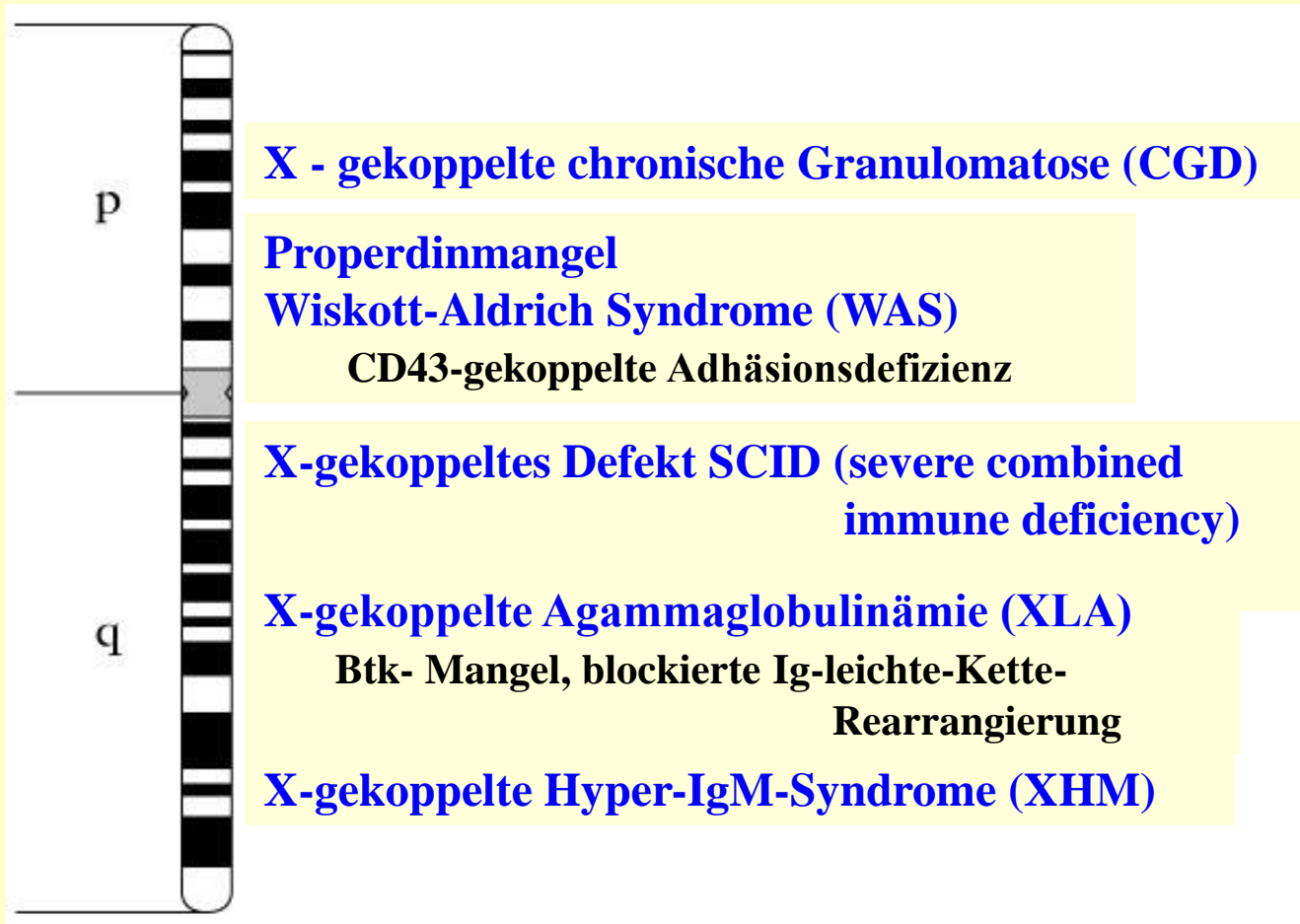
- Granula– Defekte der Granulozyten/Monozyten
- Intrazelluläre Tötungsdefekte
- Störungen der Adhäsion und der Chemotaxis (LAD)
- Defekte der NK-Zellen
- Komplementsystem-Defekten



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 γ -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

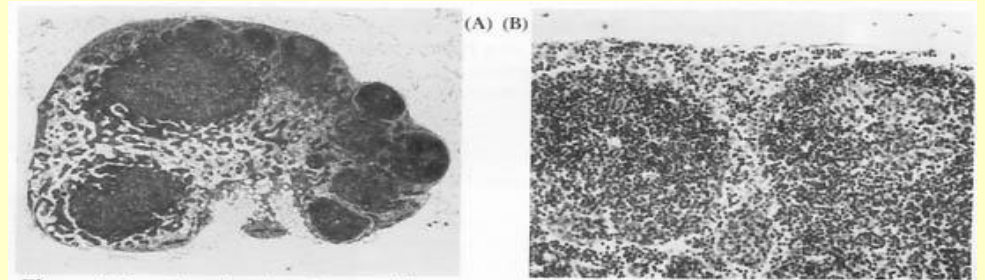
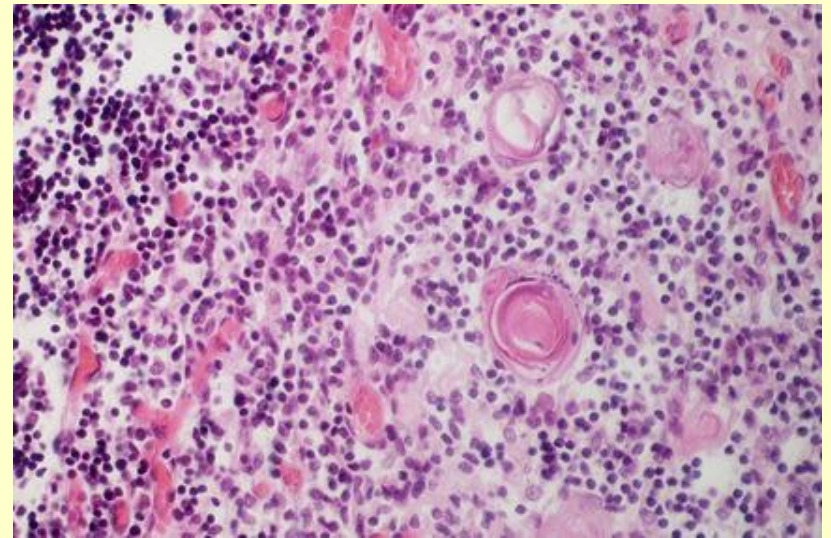
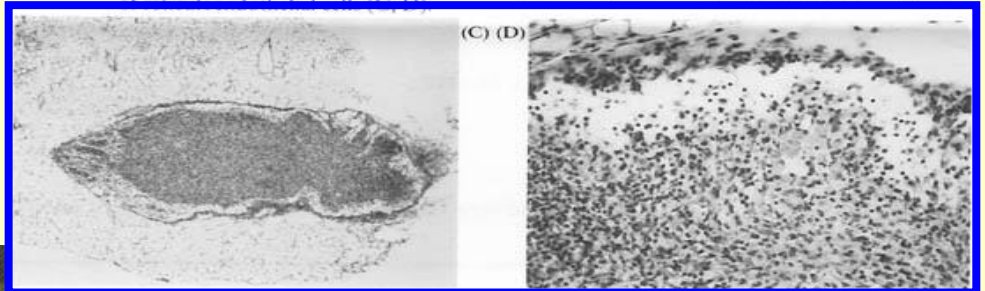
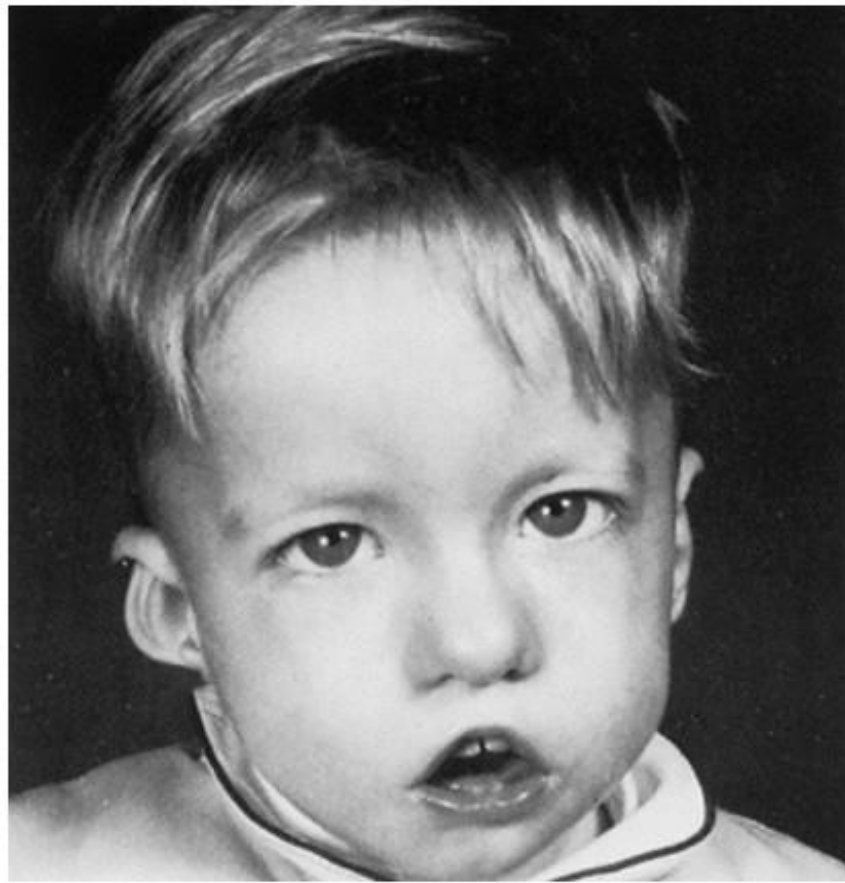


Figure 1 Lymph node of a $+/\pm$ control has numerous, prominent follicles with germinal centers (A, B) while the $scid/scid$ littermate has only a small, rudimentary lymph node consisting

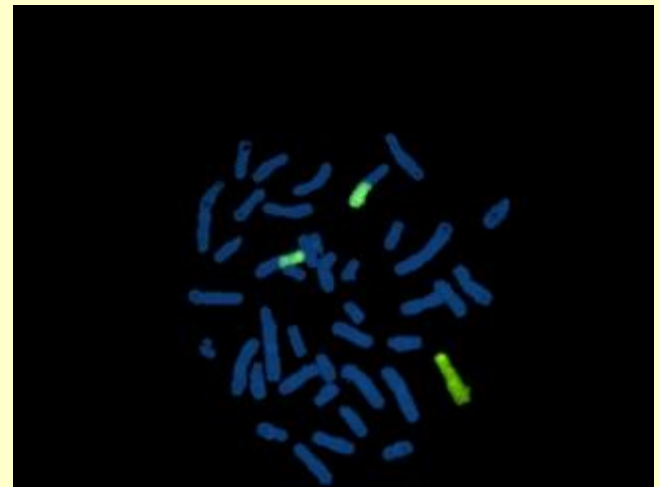
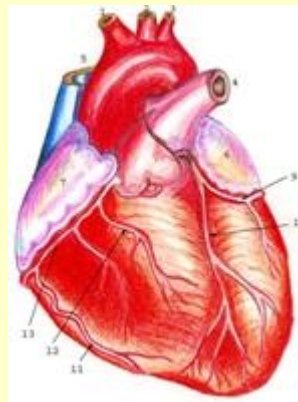
SCID



DiGeorge-Syndrom



KiDS-22q11 e.V.



B-Zell-Defizienzen

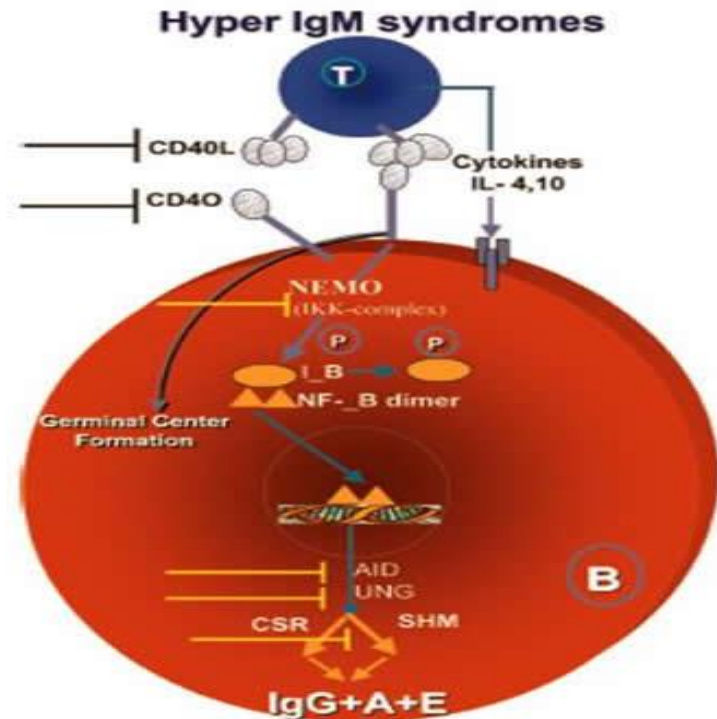
Erhöhte Infektionsanfälligkeit (Atemwege) für extrazelluläre Bakterien (pyrogene=eitererregende) Bakterien mit Polysacharidhülle (*H. influenzae*, *S. pneumoniae*)

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-Syndrom** –
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

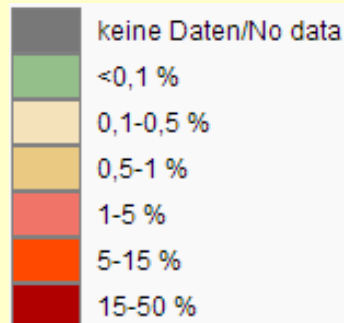
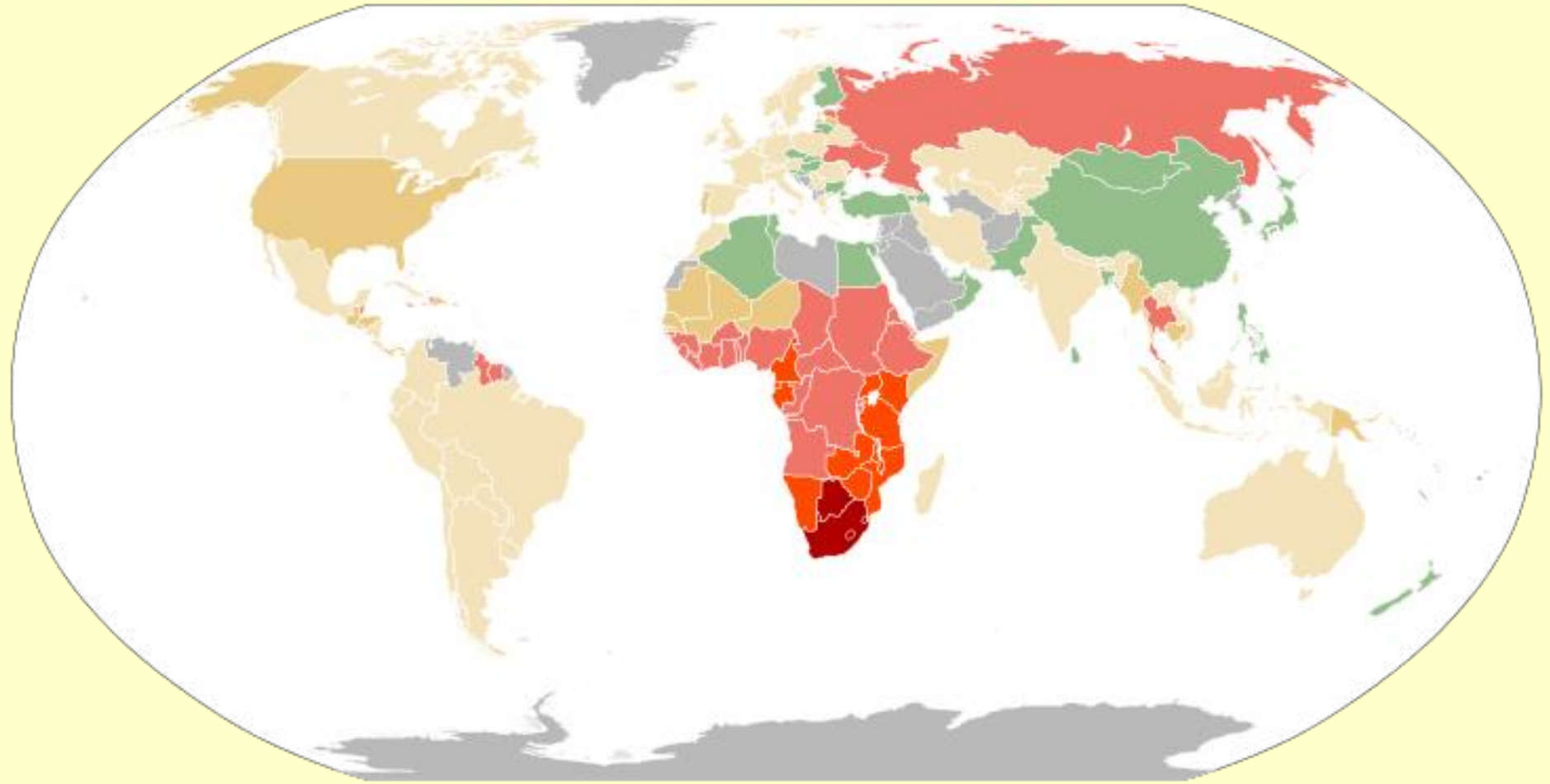
Epidemiologie (WHO)

	2000	2005	2010	2011	2012	2013	2014	2015/(2016*)	2022
People living with HIV	28.9 million [26.5 million–31.7 million]	31.8 million [29.4 million–34.5 million]	33.3 million [30.8 million–36.1 million]	33.9 million [31.4 million–36.7 million]	34.5 million [31.9 million–37.4 million]	35.2 million [32.6 million–38.1 million]	35.9 million [33.3 million–38.9 million]	36.7 million [34.0 million–39.8 million]	39 million
New HIV Infections (total)	3.2 million [2.9 million–3.5 million]	2.5 million [2.3 million–2.8 million]	2.2 million [2.0 million–2.5 million]	2.2 million [1.9 million–2.5 million]	2.2 million [1.9 million–2.4 million]	2.1 million [1.9 million–2.4 million]	2.1 million [1.9 million–2.4 million]	2.1 million [1.8 million–2.4 million]	1.3 million
New HIV infections (aged 15+)	2.7 million [2.5 million–3.0 million]	2.1 million [1.9 million–2.3 million]	1.9 million [1.7 million–2.1 million]	1.9 million [1.7 million–2.2 million]	1.9 million [1.7 million–2.2 million]	1.9 million [1.7 million–2.2 million]	1.9 million [1.7 million–2.2 million]	1.9 million [1.7 million–2.2 million]	1.2 million
New infections (aged 0–14)	490 000 [430 000–560 000]	450 000 [390 000–510 000]	290 000 [250 000–350 000]	270 000 [220 000–330 000]	230 000 [190 000–290 000]	200 000 [160 000–250 000]	160 000 [130 000–220 000]	150 000 [110 000–190 000]	130.000
AIDS-related deaths	1.5 million [1.3 million–1.8 million]	2.0 million [1.7 million–2.3 million]	1.5 million [1.3 million–1.7 million]	1.4 million [1.2 million–1.7 million]	1.4 million [1.2 million–1.6 million]	1.3 million [1.1 million–1.5 million]	1.2 million [990 000–1.4 million]	1.1 million [940 000–1.3 million]	630.000
People accessing treatment	770 000 [680 000–800 000]	2.2 million [1.9 million–2.2 million]	7.5 million [6.6 million–7.8 million]	9.1 million [8.0 million–9.5 million]	11 million [9.6 million–11.4 million]	13 million [11.4 million–13.5 million]	15 million [13.2 million–15.6 million]	18.2 million [16.1 million–19.0 million] (*June 2016) 17 million [15.0 million–17.7 million] (end 2015)	29.8 million
Resources available for HIV (low- and middle-income countries)	4.8 billion	9.4 billion	15.9 billion	18.3 billion	19.5 billion	19.6 billion	19.2 billion	19 billion	20.8 billion

Regionale Statistik (WHO - Dez 2022)

	People living with HIV	New HIV Infections	Infections (Adults, aged 15+)	Infections (Children, aged 0-14)	AIDS-related deaths
Global	39.0 million [33.1 million - 45.7 million]	1.3 million [1.0 million - 1.7 million]	1.2 million [900 000 - 1.6 million]	130 000 [90 000 - 210 000]	630 000 [480 000 - 880 000]
Asia and the Pacific	6.5 million [5.3 million - 7.8 million]	300 000 [220 000 - 400 000]	290 000 [210 000 - 380 000]	12 000 [8600 - 18 000]	150 000 [110 000 - 220 000]
Caribbean	330 000 [290 000 - 380 000]	16 000 [11 000 - 21 000]	14 000 [10 000 - 19 000]	1 500 [1 100 - 2 100]	5 600 [4100 - 7500]
Eastern and southern Africa	20.8 million [17.4 million - 24.5 million]	500 000 [370 000 - 670 000]	440 000 [330 000 - 590 000]	58 000 [38 000 - 100 000]	260 000 [200 000 - 370 000]
Eastern Europe and central Asia	2.0 million [1.8 million - 2.1 million]	160 000 [140 000 - 180 000]	160 000 [130 000 - 180 000]	... [... - ...]	48 000 [38 000 - 58 000]
Latin America	2.2 million [2.0 million - 2.5 million]	110 000 [94 000 - 130 000]	110 000 [90 000 - 130 000]	3800 [2900 - 4700]	27 000 [21 000 - 35 000]
Middle East and North Africa	190 000 [160 000 - 220 000]	17 000 [13 000 - 23 000]	16 000 [12 000 - 21 000]	1700 [1300 - 2100]	5300 [4000 - 7100]
Western and central Africa	4.8 million [4.2 million - 5.5 million]	160 000 [110 000 - 250 000]	110 000 [66 000 - 190 000]	51 000 [34 000 - 69 000]	120 000 [96 000 - 160 000]
Western and central Europe and North America	2.3 million [1.9 million - 2.6 million]	58 000 [46 000 - 69 000]	57 000 [46 000 - 69 000]	... [... - ...]	13 000 [9300 - 17 000]

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

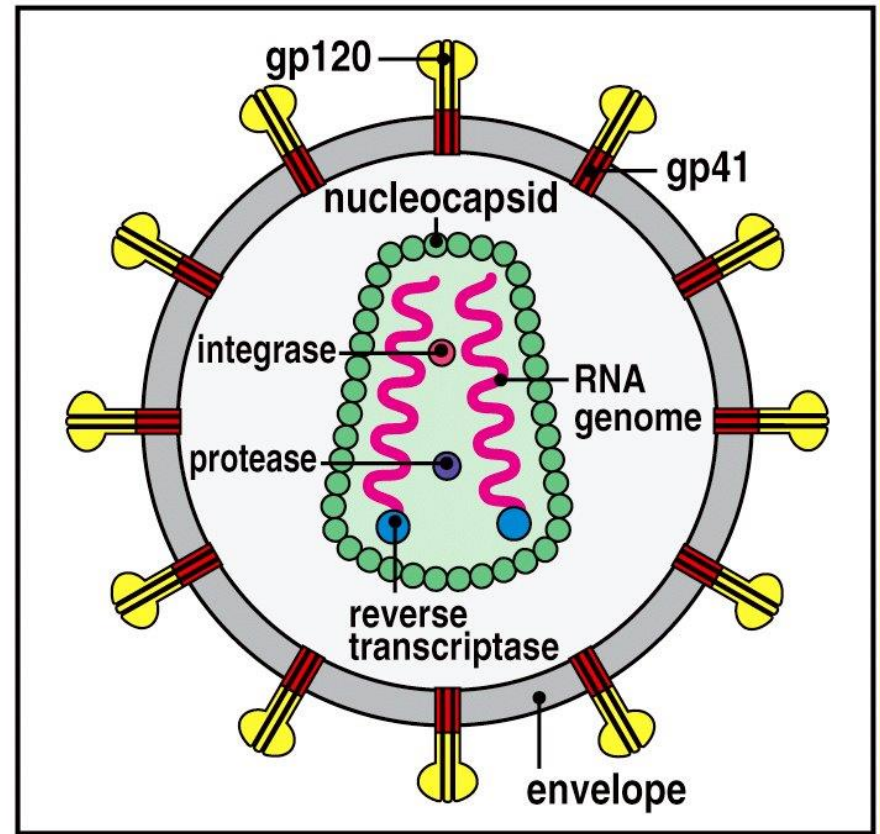
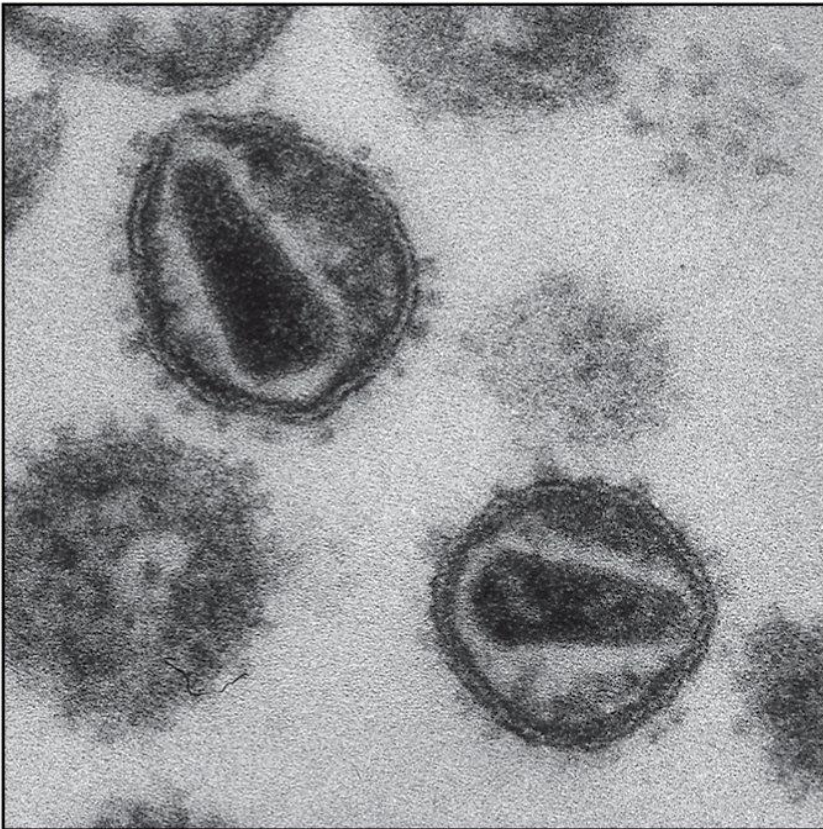
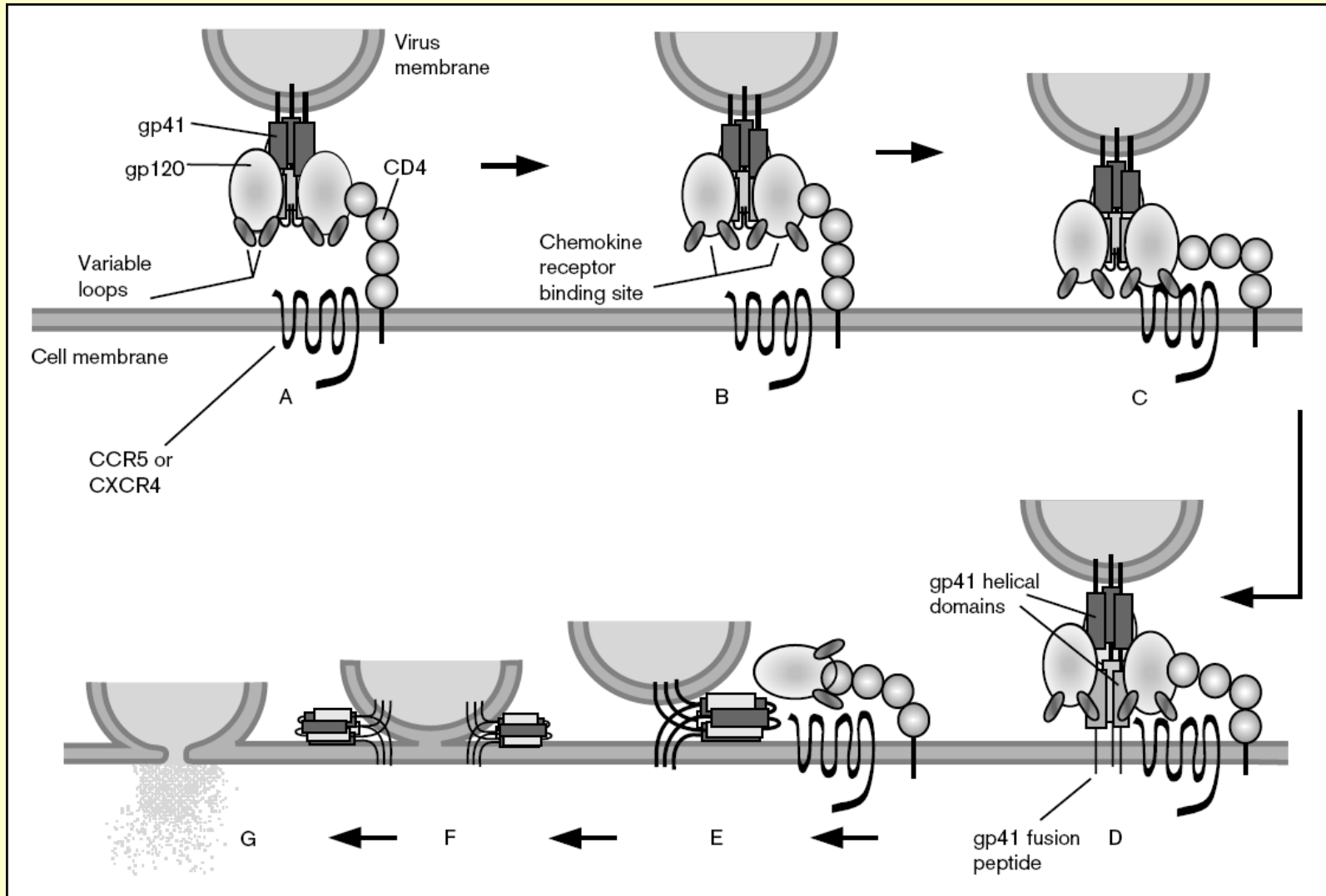


Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)

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“

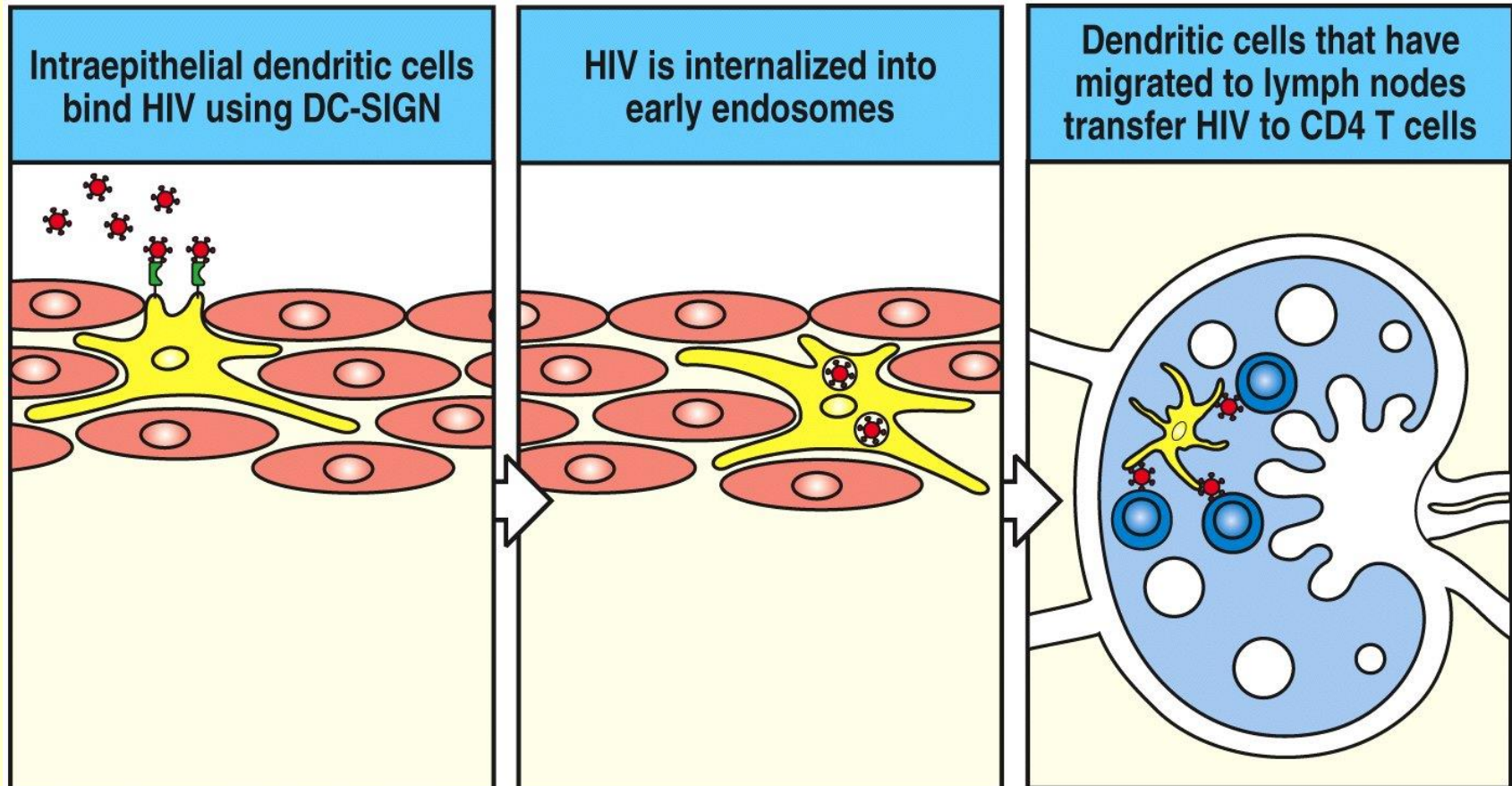
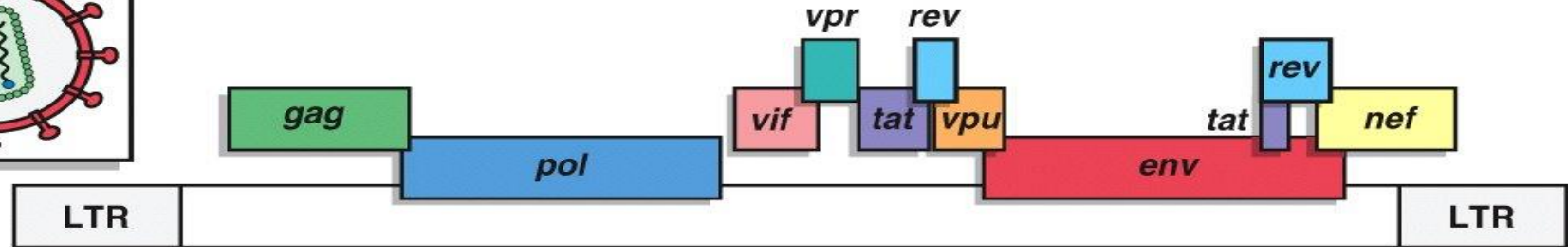
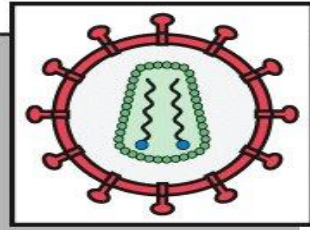


Figure 11-22 Immunobiology, 6/e. (© Garland Science 2005)

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

HIV-Replikation 1.

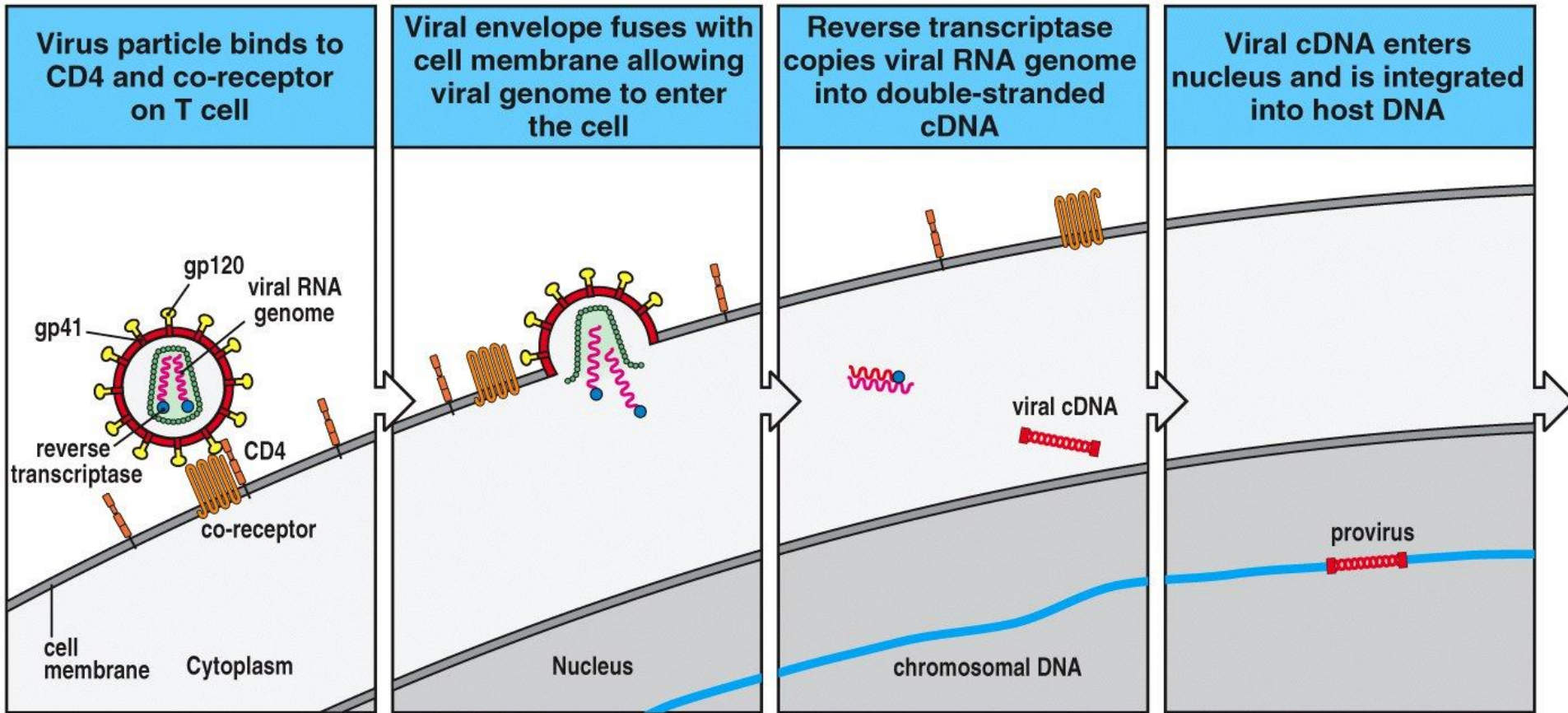
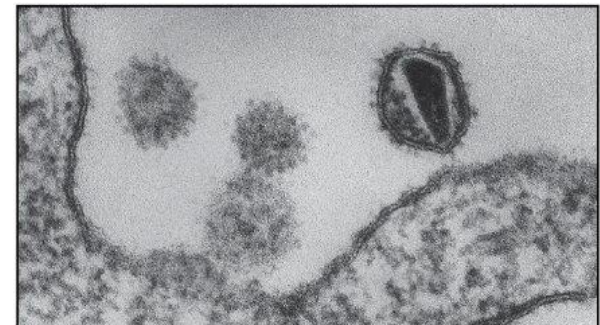
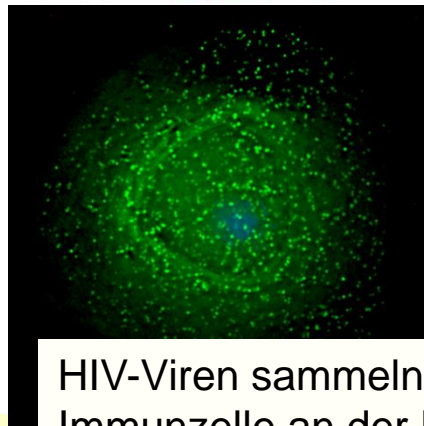
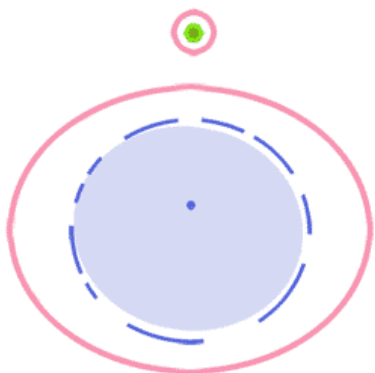
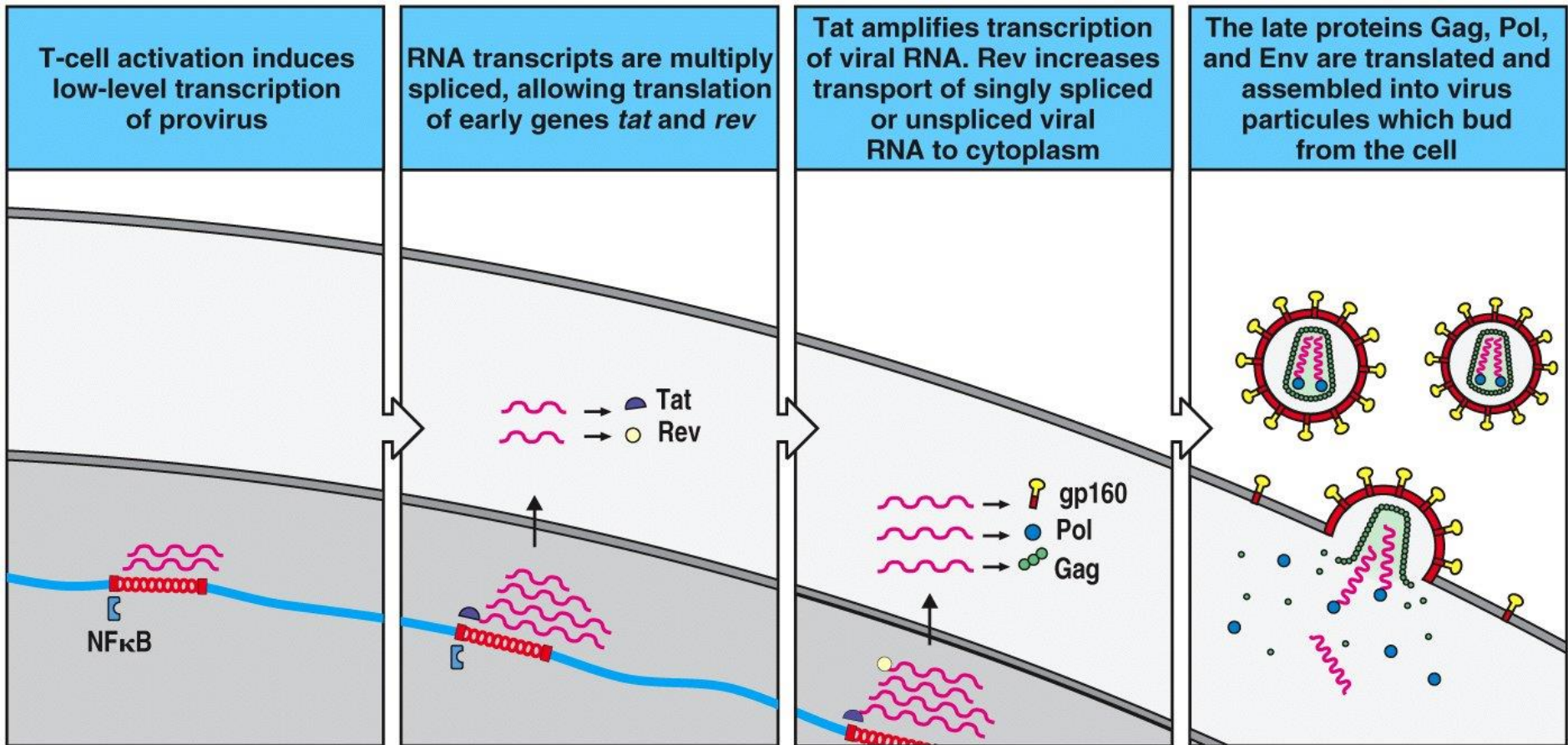


Figure 11-23 Immunobiology, 6/e. (© Garland Science 2005)

HIV-Replikation 2.



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

Immunantwort gegen HIV

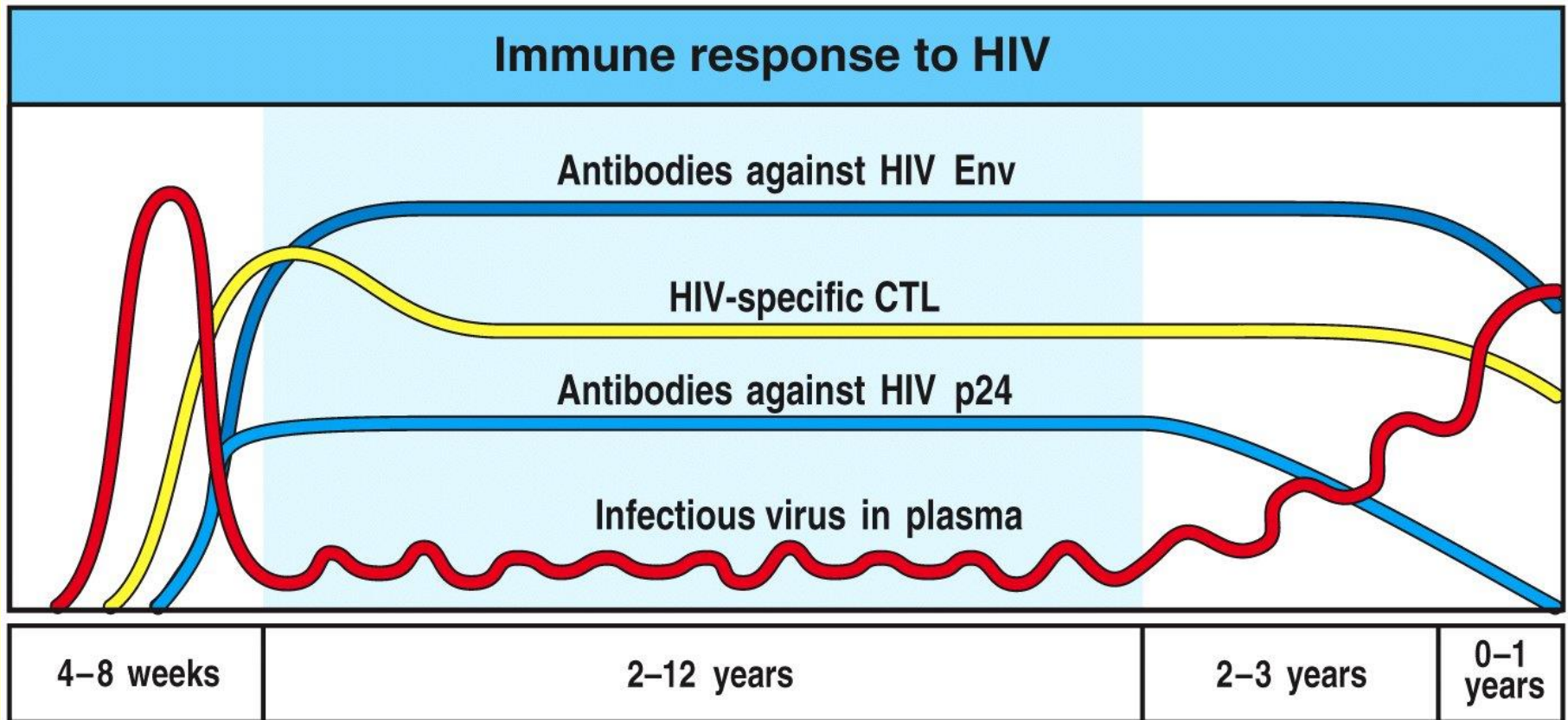
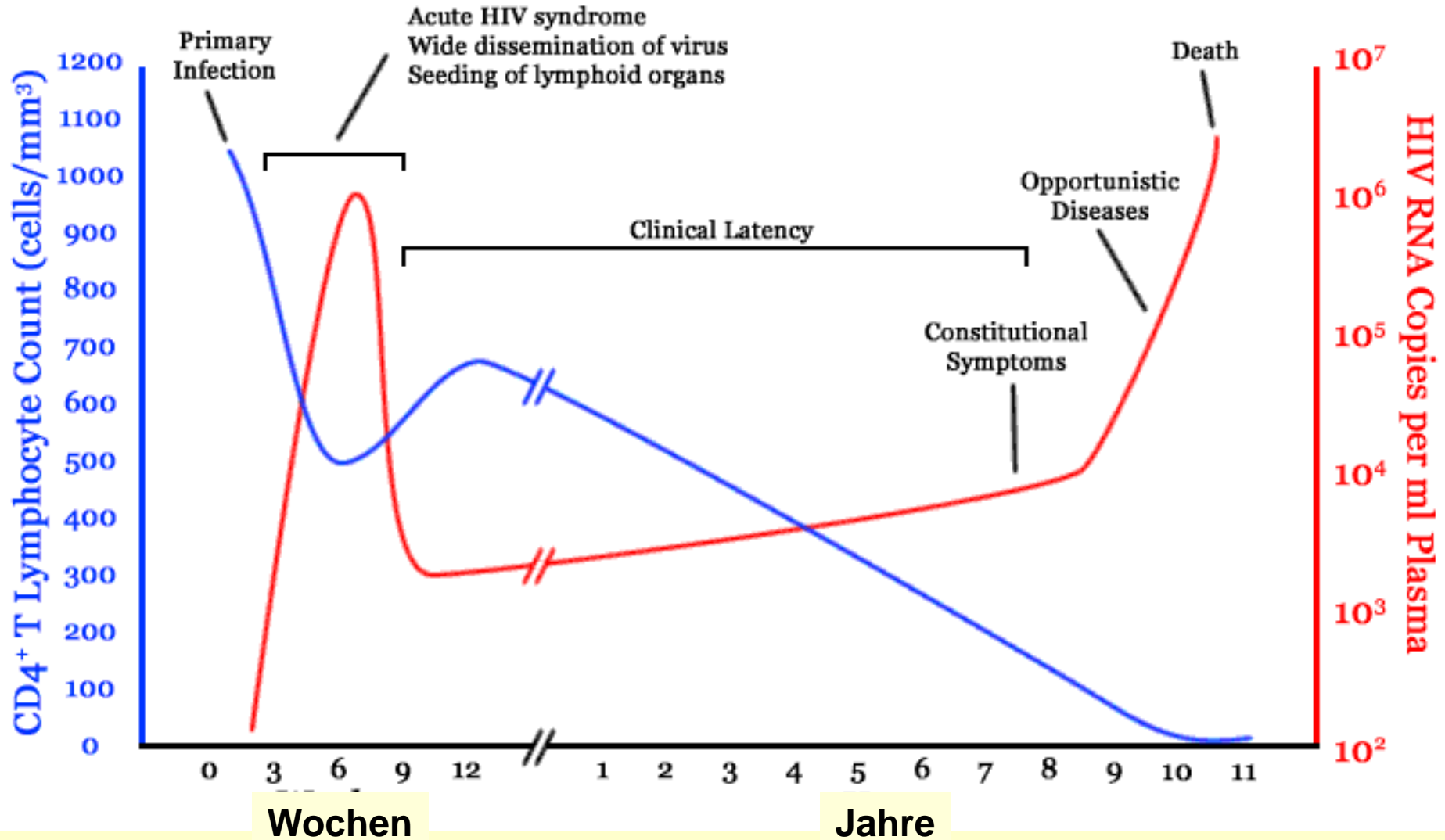


Figure 11-29 Immunobiology, 6/e. (© Garland Science 2005)

Problem: Th-Aktivierung löst Virusreplikation aus!

Klinischer Verlauf von AIDS



Stadieneinteilung der HIV-Infektion

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

Die grüne Buchstaben entsprechen des AIDS Krankheitsbildes

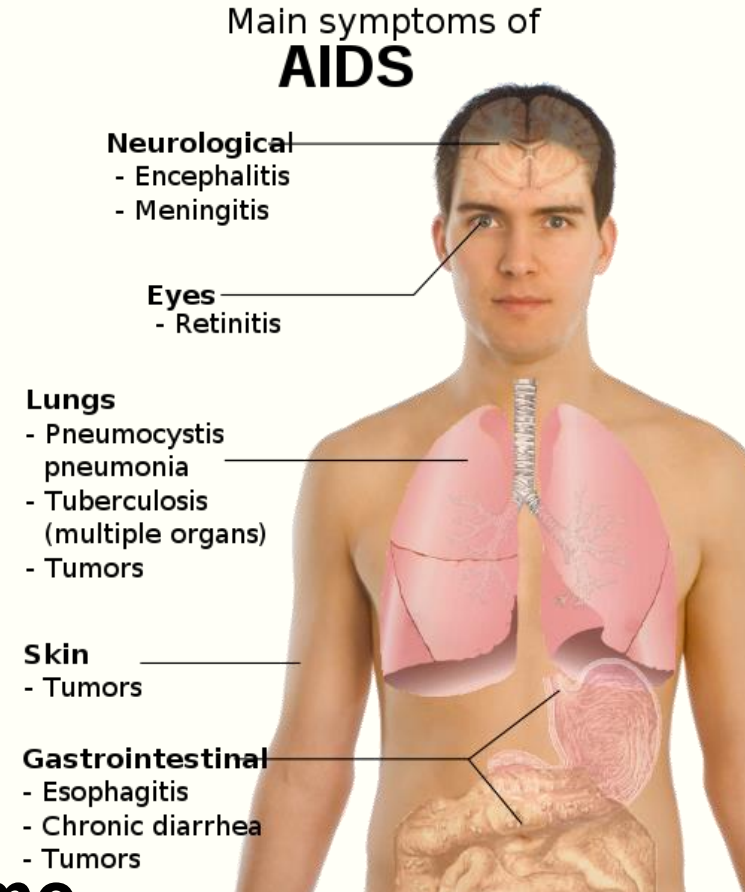
Todesursachen bei AIDS-Kranken

Opportunistische Infektionen:

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

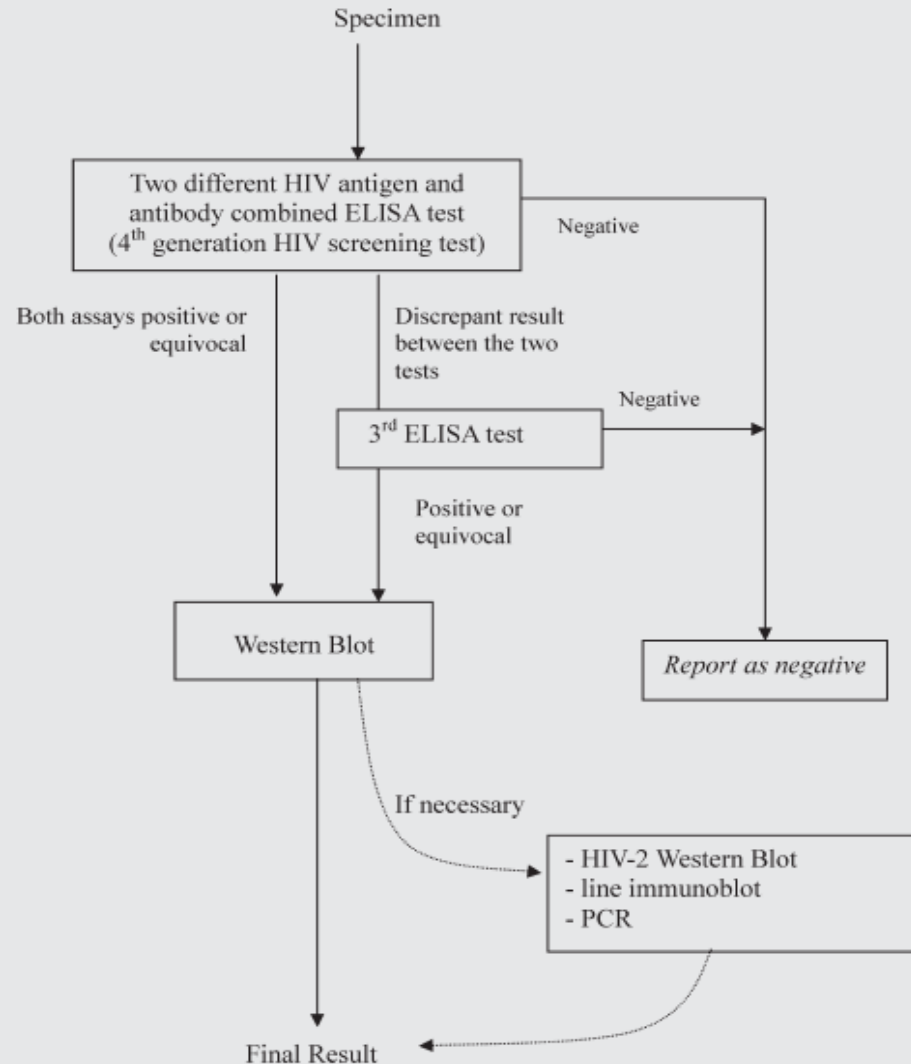
Krebserkrankungen:

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)

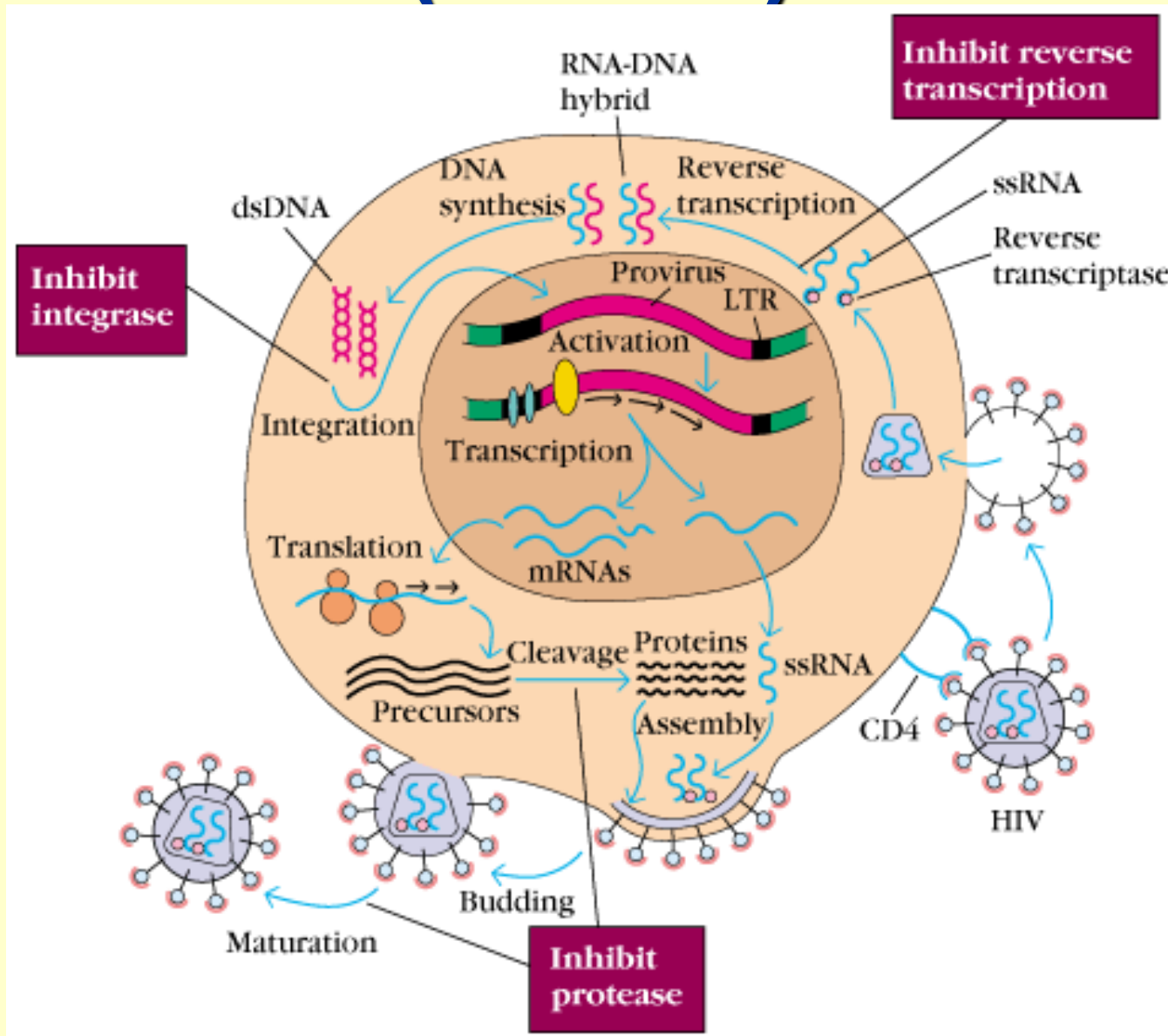
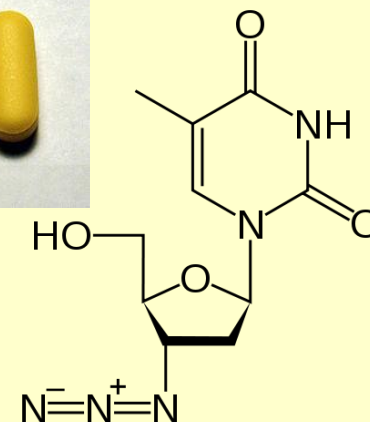
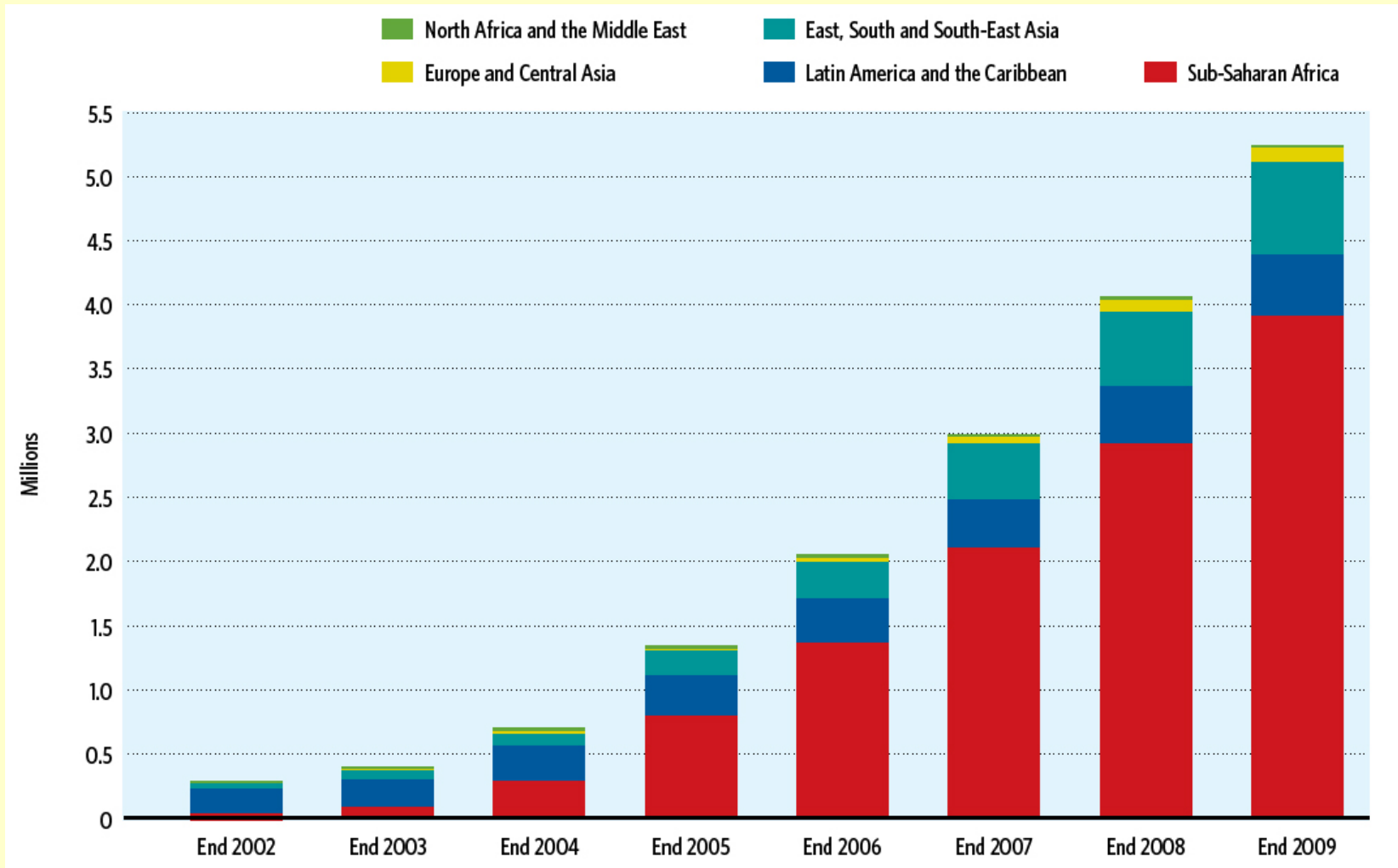


TABLE 19-5 SOME ANTI-HIV DRUGS IN CLINICAL USE

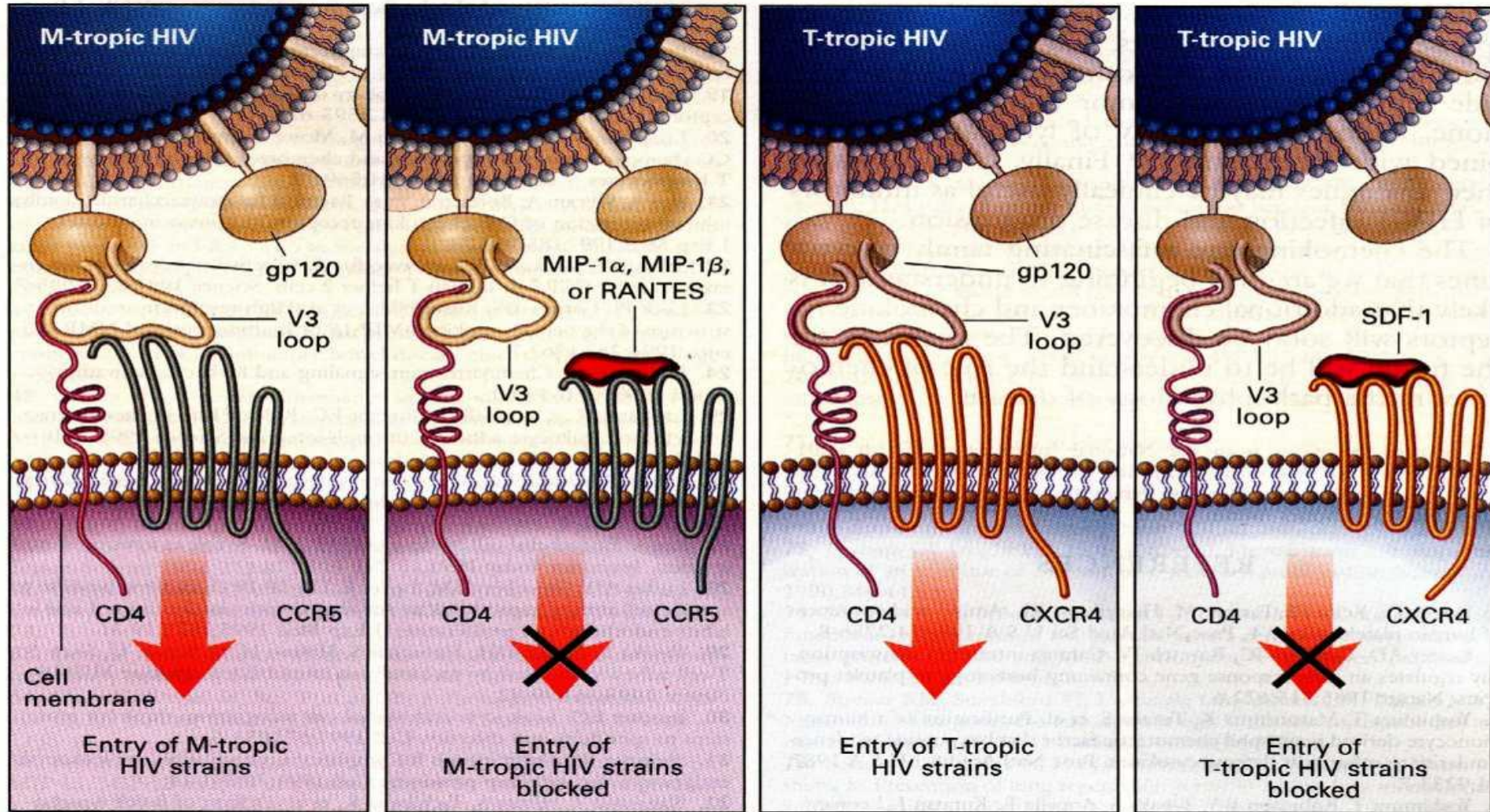
Generic name (other names)	Typical dosage	Some potential side effects
Reverse transcriptase inhibitors: Nucleoside analog		
Didanosine (Videx, ddl)	2 pills, 2 times a day on empty stomach	Nausea, diarrhea, pancreatic inflammation, peripheral neuropathy
Lamivudine (EpiVir, 3TC)	1 pill, 2 times a day	Usually 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
Reverse transcriptase inhibitors: Nonnucleoside analogues		
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
Protease inhibitors		
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)



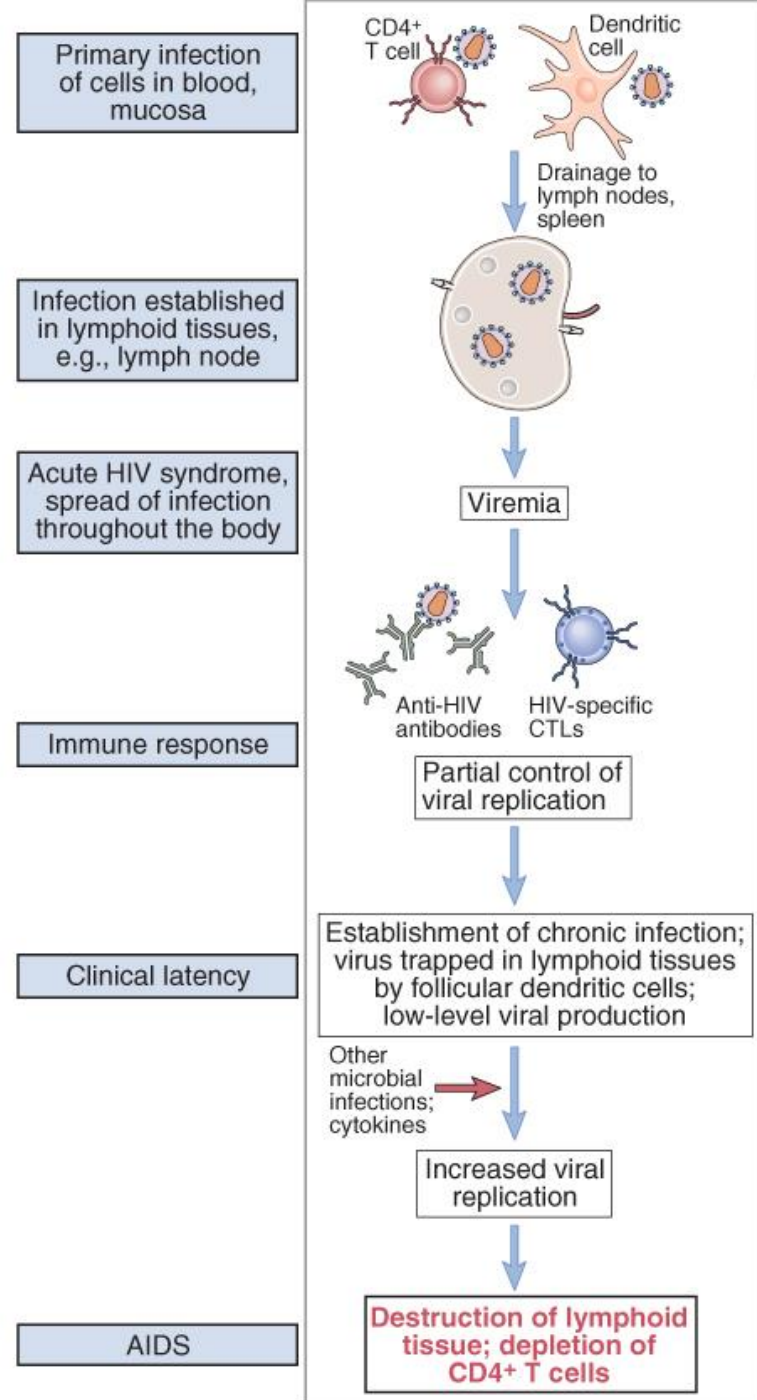
Liganden von Kemokinrezeptoren hemmen HIV- Aufnahme in die Zielzellen



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