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, Sarcoidose)
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**
- **<u>Labordiagnostik:</u>**

  T- , B - , NK-Zell-Funktionen, Neutrophil-Funktionsteste, Komplement-Assays
- **Genetischer Hintergrund**

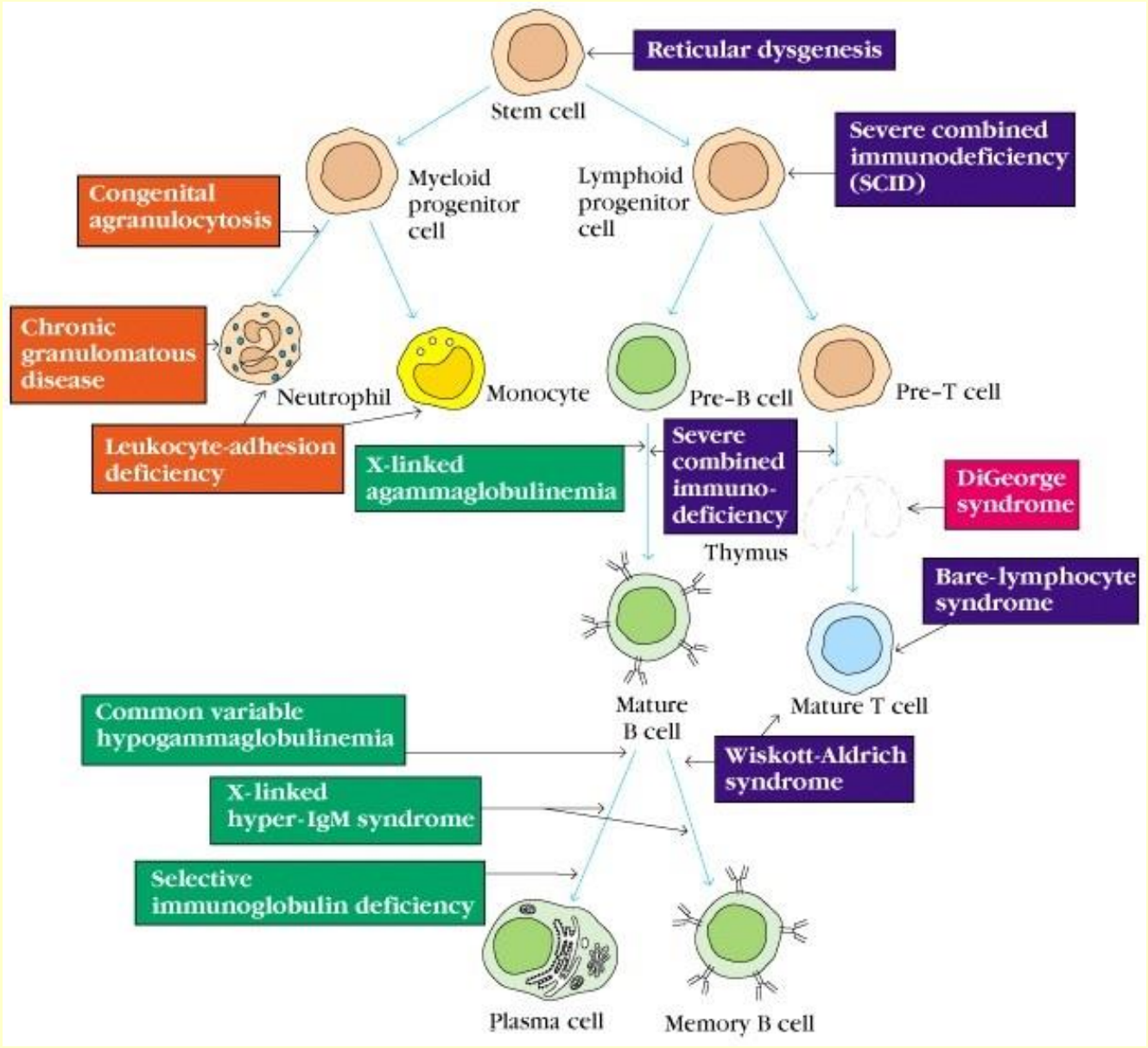
Hintergrund der Immundefekte

Defizienzen der angeborenen Immunität

B - Zell - Defizienzen

T- und B -Zell- Defizienzen

T - Zell - Defizienzen

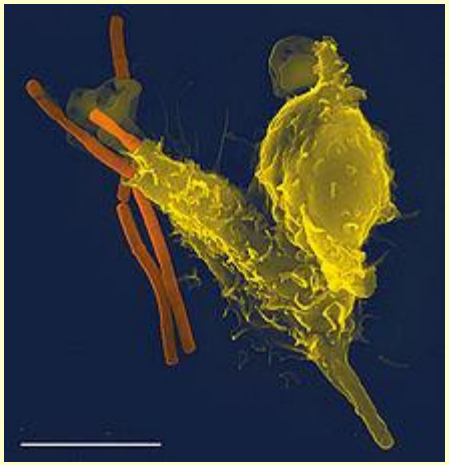


Erbliche Immundefekte

1. Angeborene Immunität

„Häufige ” zelluläre Immundefizienzen der angeborenen Immunität

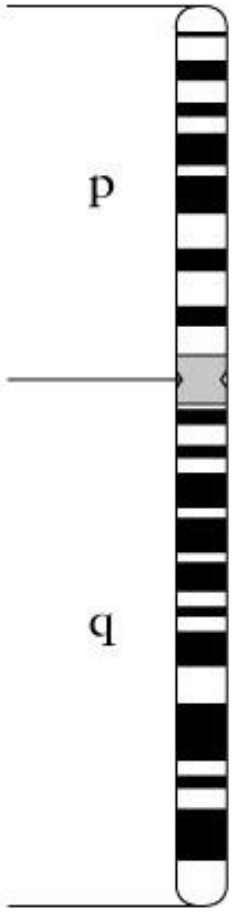
- **Granula– Defekte der Granulozyten/Monozyten**
- **Intrazelluläre Tötungsdefekte**
- **Störungen der Adhäsion und der Chemotaxis (LAD)**
- **Defekte der NK-Zellen**
- **Komplementsystem-Defekten**



Erbliche Immundefekte

2. Spezifische Immunität

- **meistens rezessive Krankheiten**
- **X -gekoppelt**



X - gekoppelte chronische Granulomatose (CGD)

Properdinmangel
Wiskott-Aldrich Syndrome (WAS)
CD43-gekoppelte Adhäsionsdefizienz

X-gekoppeltes Defekt SCID (severe combined immune deficiency)

X-gekoppelte Agammaglobulinämie (XLA)
Btk- Mangel, blockierte Ig-leichte-Kette-Rearrangierung

X-gekoppelte Hyper-IgM-Syndrome (XHM)

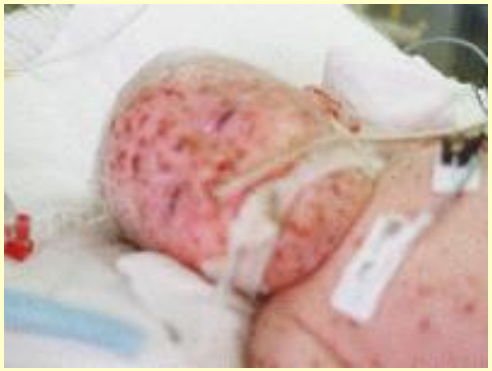
Schwere kombinierte Immundefekte (SCID)

- 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

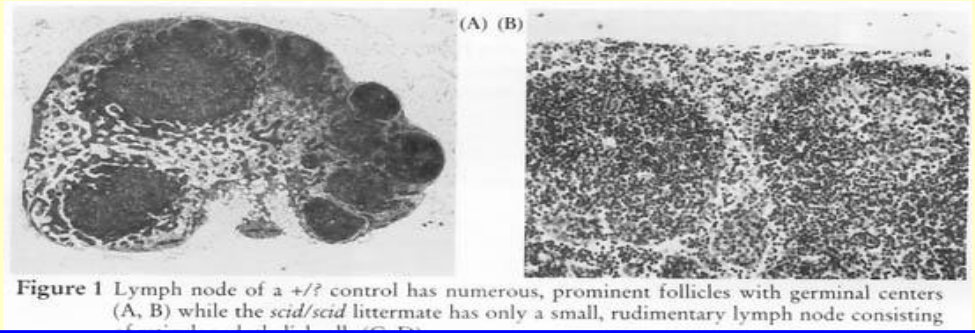
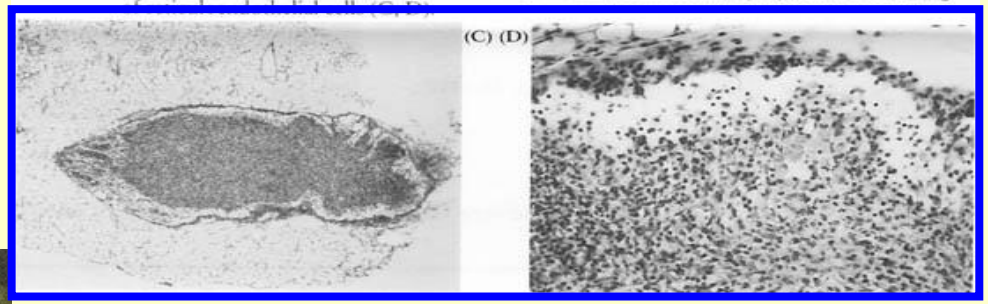
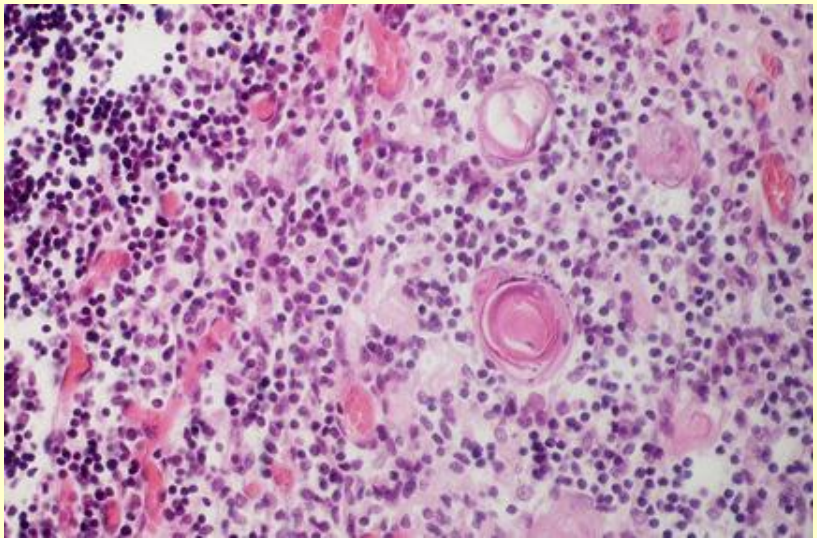


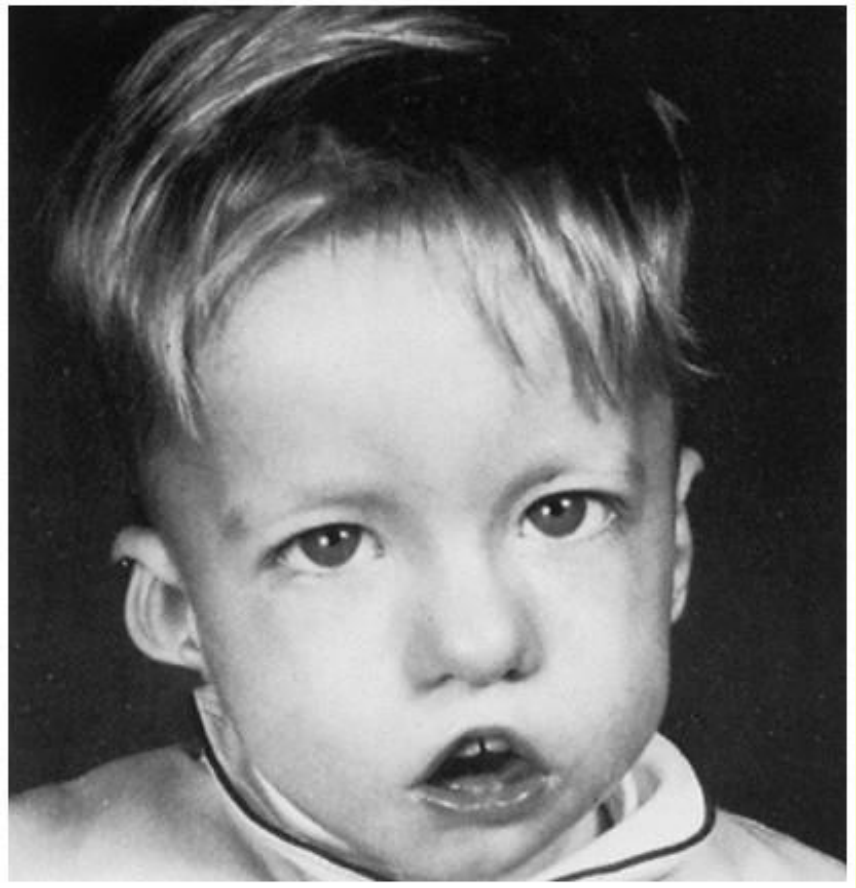
Figure 1 Lymph node of a +/? control has numerous, prominent follicles with germinal centers (A, B) while the *scid/scid* littermate has only a small, rudimentary lymph node consisting



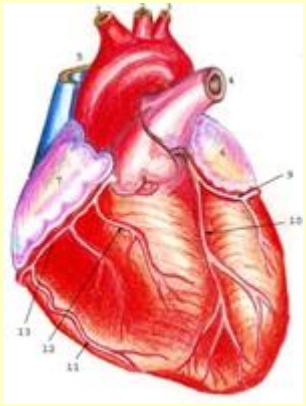
SCID

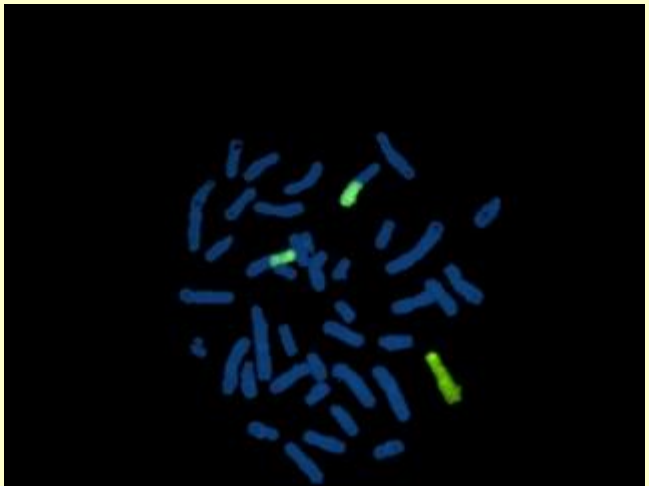


DiGeorge-Syndrom



KiDS-22q11 e.V.





B-Zell-Defizienzen

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

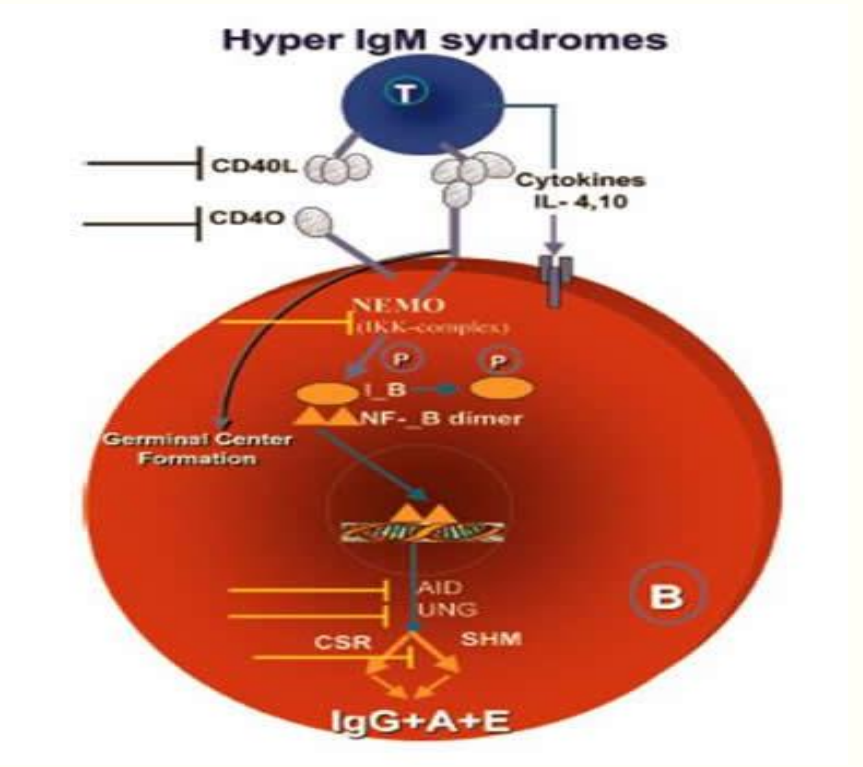
Beispiele:

- **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

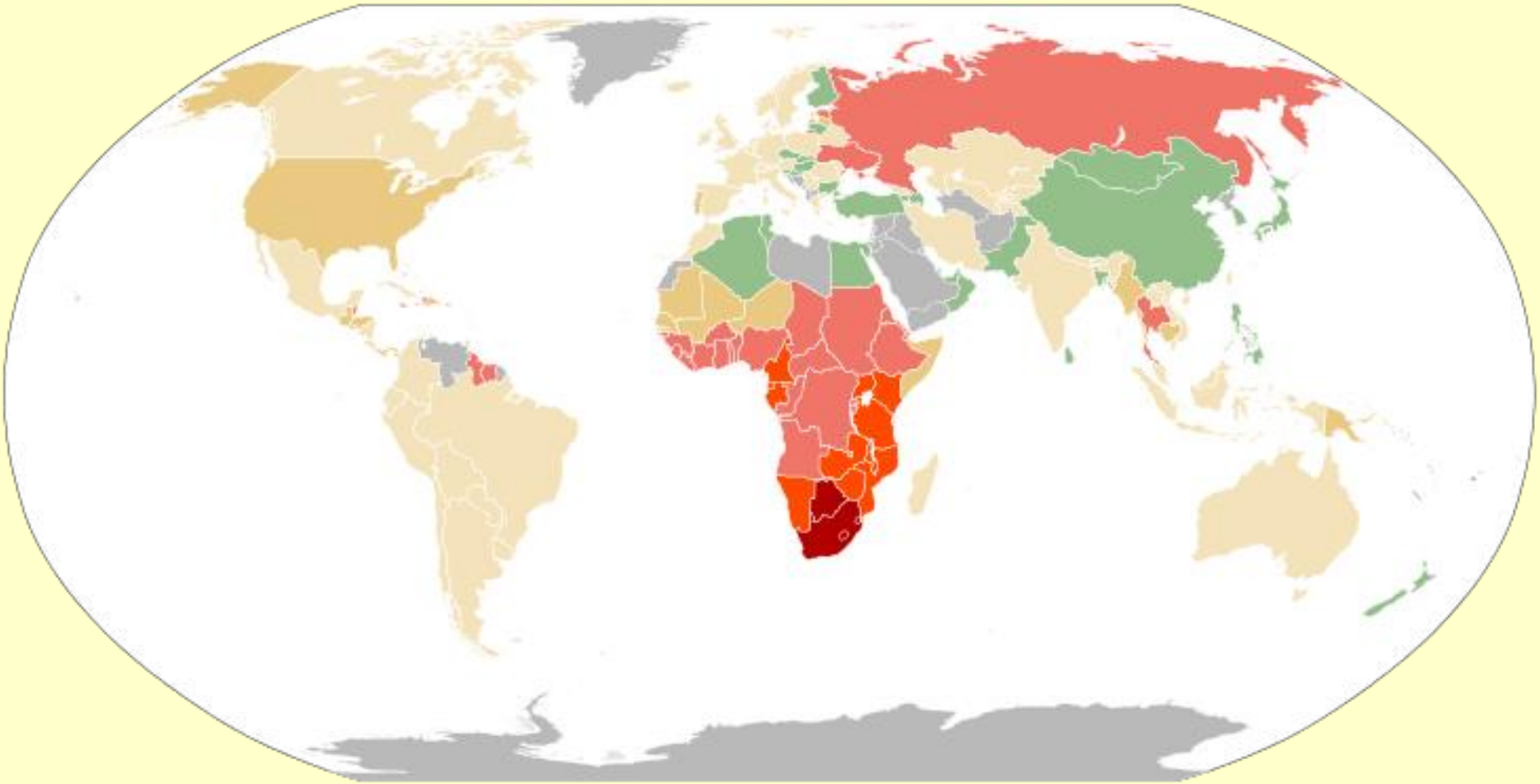
Epidemiologie (WHO)

	2000	2005	2010	2011	2012	2013	2014	2015/(2016*)
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]
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]
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]
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]
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]
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)
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**

Regionale Statistik (WHO - Dez 2015)

Region	People living with HIV (total)	New HIV infections			AIDS-related deaths (total)	Total number accessing antiretroviral therapy
		Total	Aged 15+	Aged 0–14		
Eastern and southern Africa	**19.0 million** [17.7 million–20.5 million]	**960 000** [830 000–1.1 million]	**910 000** [790 000–1.1 million]	**56 000** [40 000–76 000]	**470 000** [390 000–560 000]	**10 million**
Latin America and the Caribbean	**2.0 million** [1.7 million–2.3 million]	**100 000** [86 000–120 000]	**100 000** [84 000–120 000]	**2100** [1600–2900]	**50 000** [41 000–59 000]	**1.1 million**
Western and central Africa	**6.5 million** [5.3 million–7.8 million]	**410 000** [310 000–530 000]	**350 000** [270 000–450 000]	**66 000** [47 000–87 000]	**330 000** [250 000–430 000]	**1.8 million**
Asia and the Pacific	**5.1 million** [4.4 million–5.9 million]	**300 000** [240 000–380 000]	**280 000** [220 000–350 000]	**19 000** [16 000–21 000]	**180 000** [150 000–220 000]	**2.1 million**
Eastern Europe and central Asia	**1.5 million** [1.4 million–1.7 million]	**190 000** [170 000–200 000]	**190 000** [170 000–200 000]	---*	**47 000** [39 000–55 000]	**320 000**
Middle East and North Africa	**230 000** [160 000–330 000]	**21 000** [12 000–37 000]	**19 000** [11 000–34 000]	**2100** [1400–3200]	**12 000** [8700–16 000]	**38 000**
Western and central Europe and North America	**2.4 million** [2.2 million–2.7 million]	**91 000** [89 000–97 000]	**91 000** [88 000–96 000]	---*	**22 000** [20 000–24 000]	**1.4 million**

Epidemiologie



UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

World Health Organization

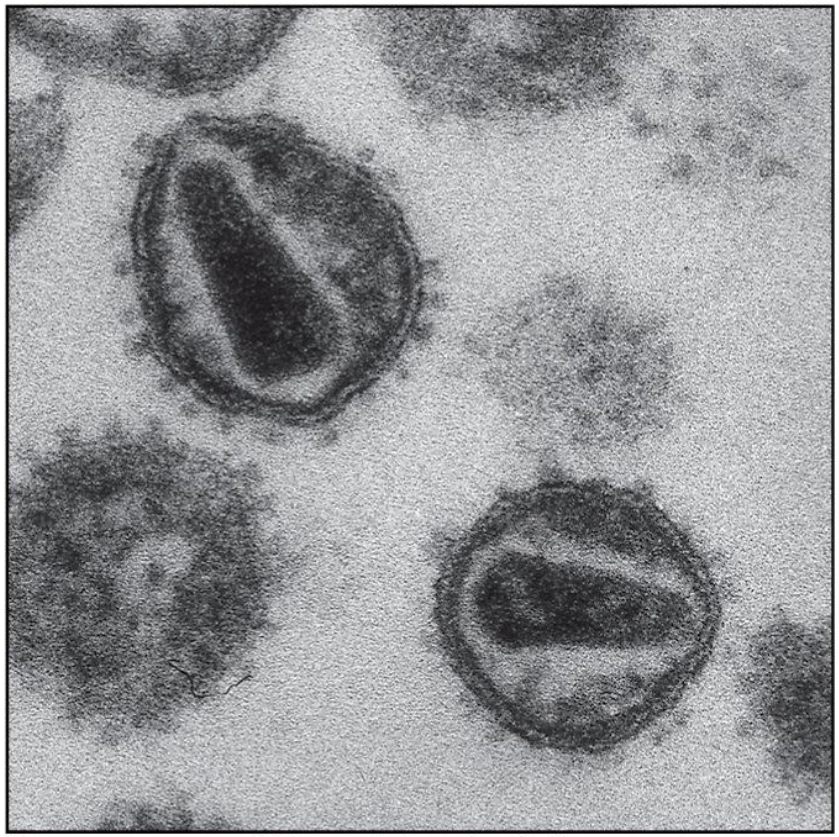
Übertragung

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**



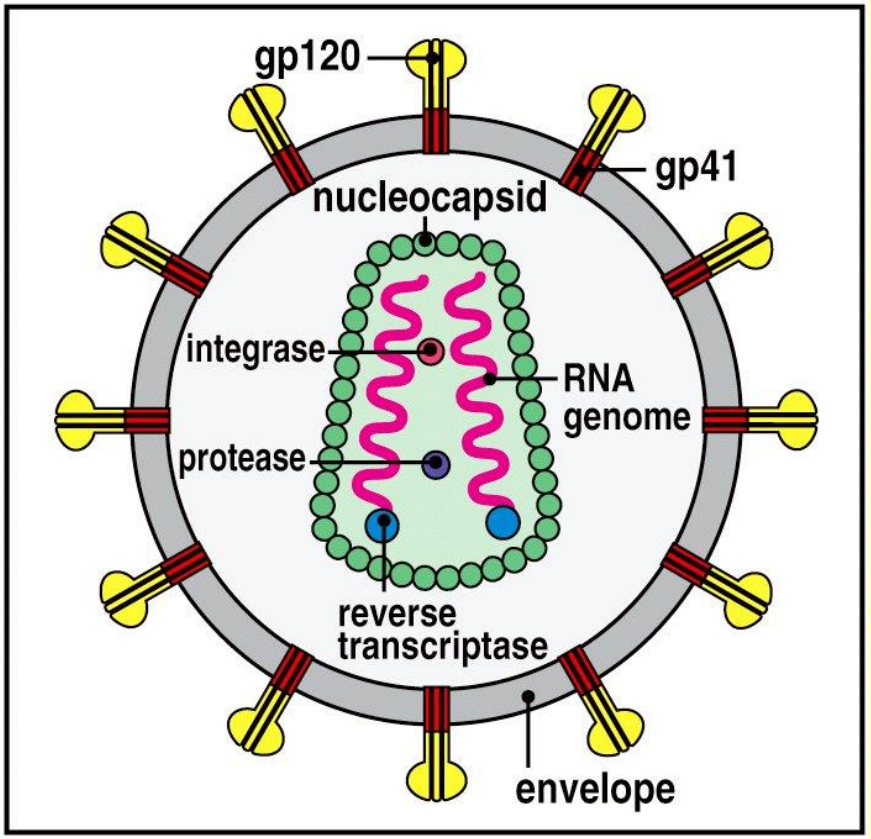
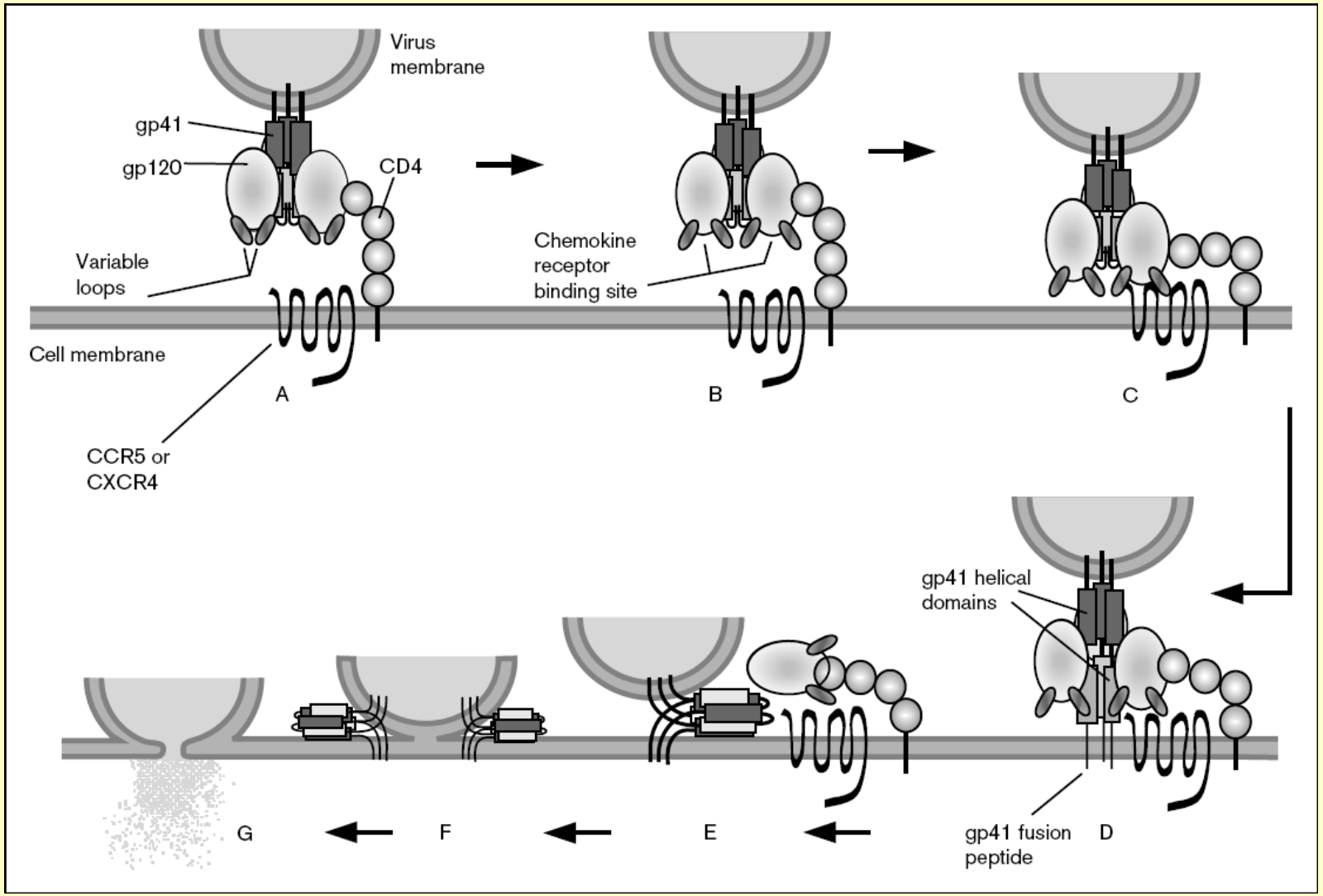


Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)

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”

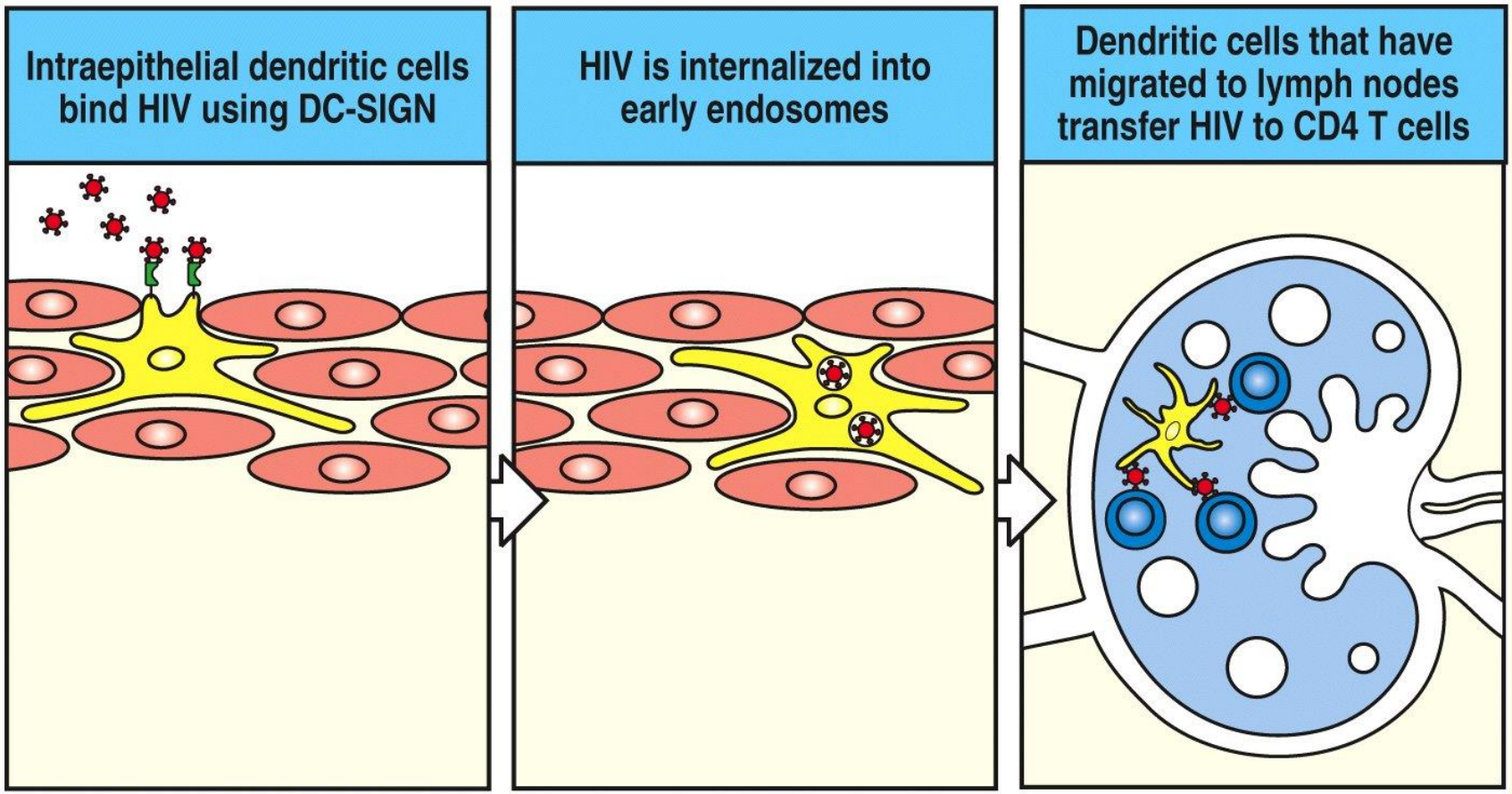
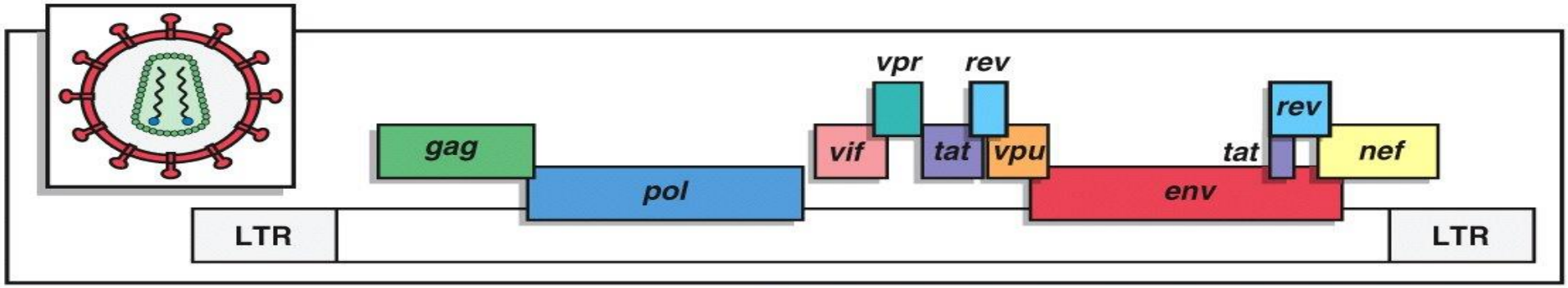


Figure 11-22 Immunobiology, 6/e. (© Garland Science 2005)

- geschichtetes squamöses Epithel (Vagina, Penis, Zervix, Anus) – die intraepithelische DC (DC-SIGN) –Virustransfer zu den Lymphknoten
- einschichtiges Epithel (Rektum, Endozervix) – CCR5 + galactosyl ceramide Exprimierung 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 *in vivo* und *in vitro* Abwärtsregulation von CD4 und MHC-II

HIV-Replikation 1.

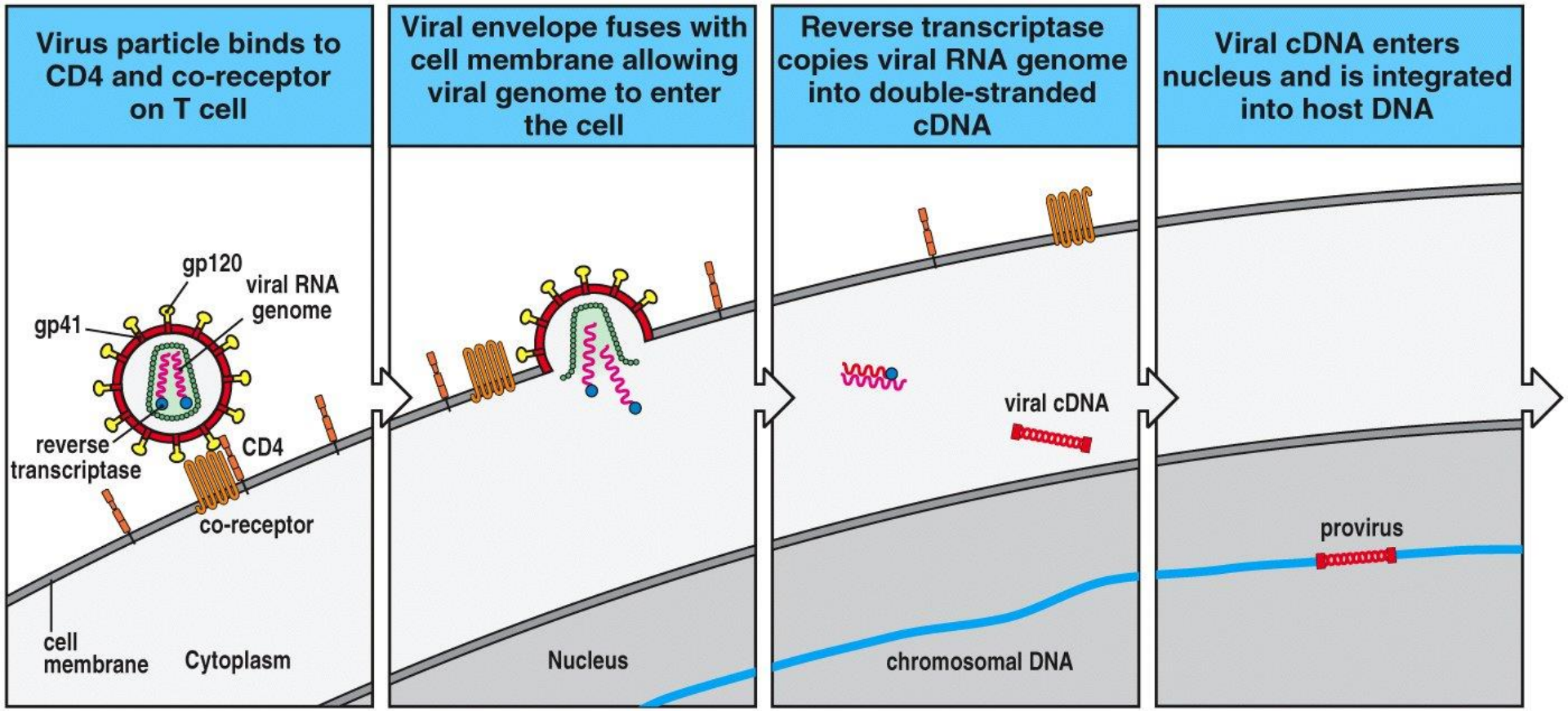
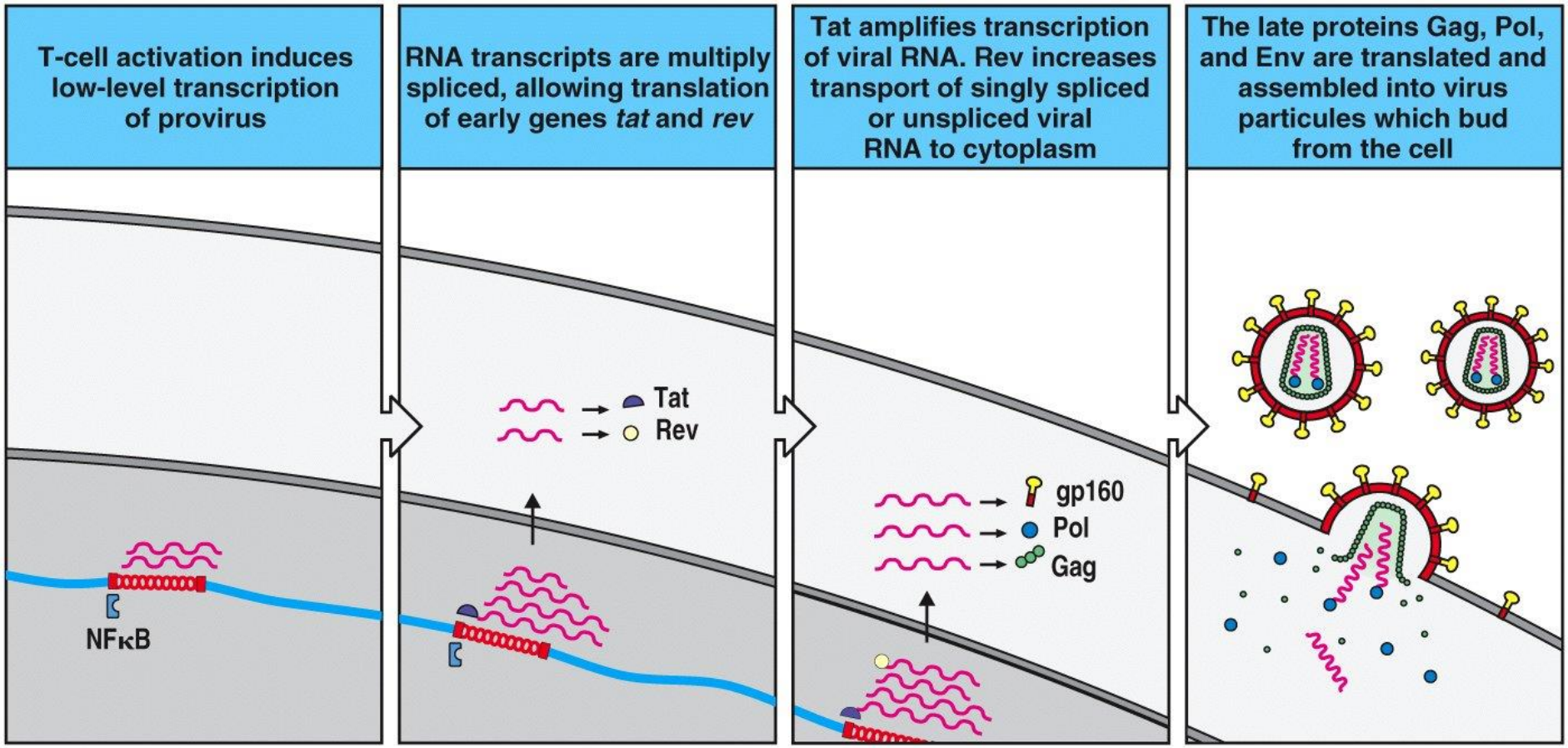


Figure 11-23 Immunobiology, 6/e. (© Garland Science 2005)

HIV-Replikation 2.



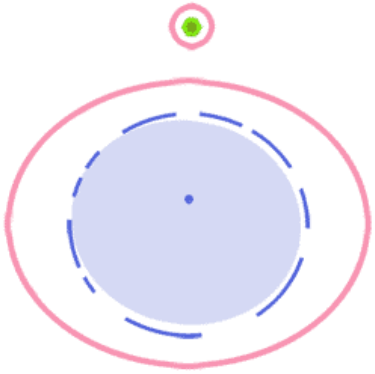
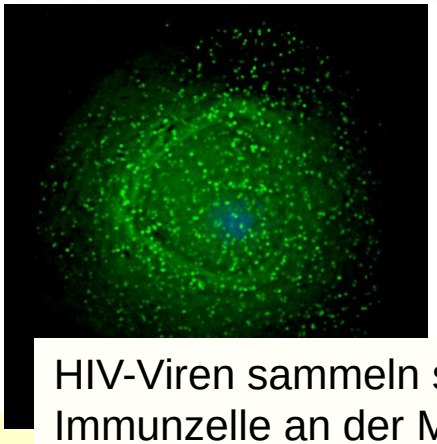
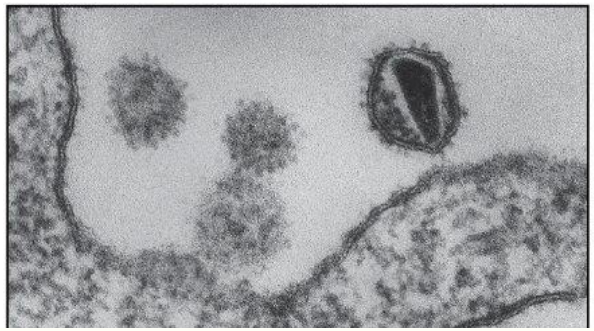


Figure 11-25 Imm 2005)





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

Immunantwort gegen HIV

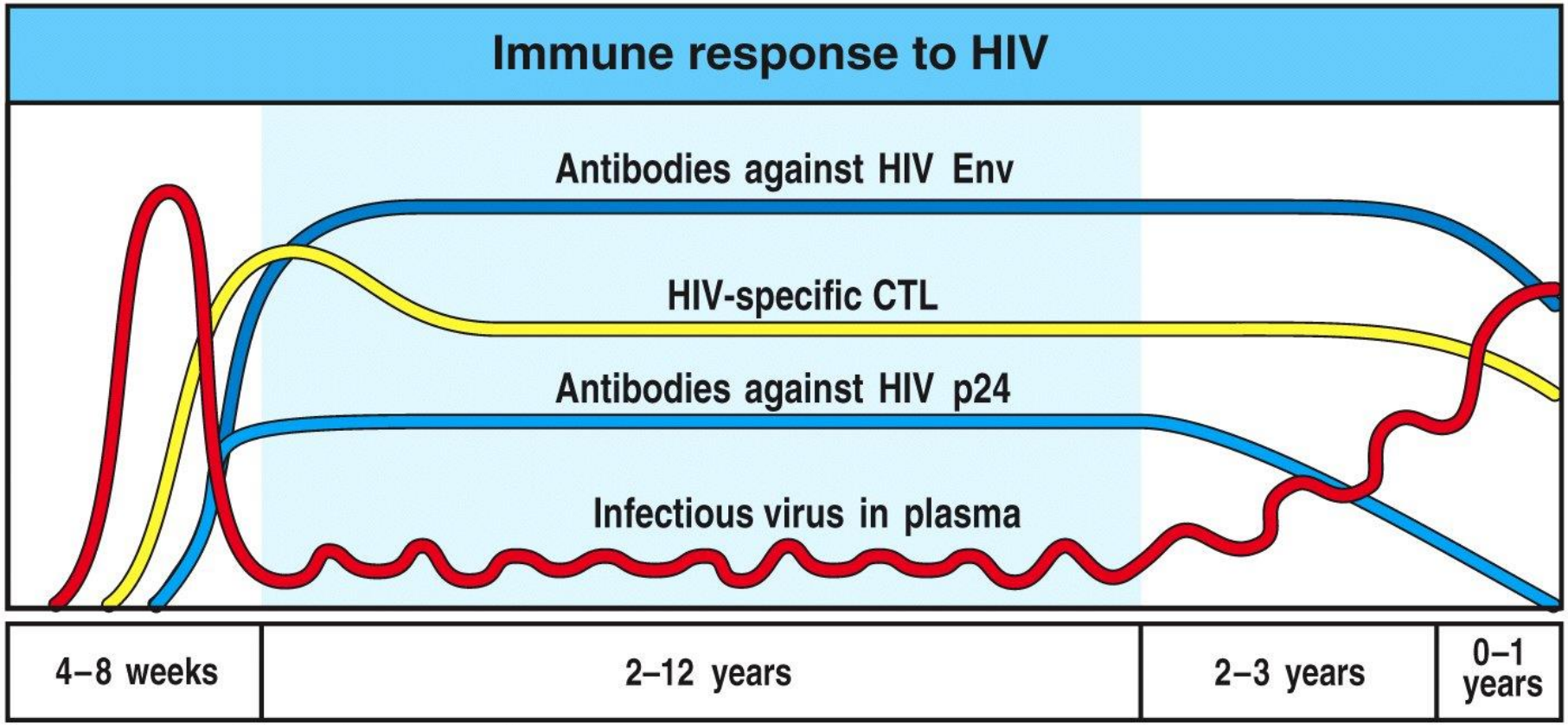
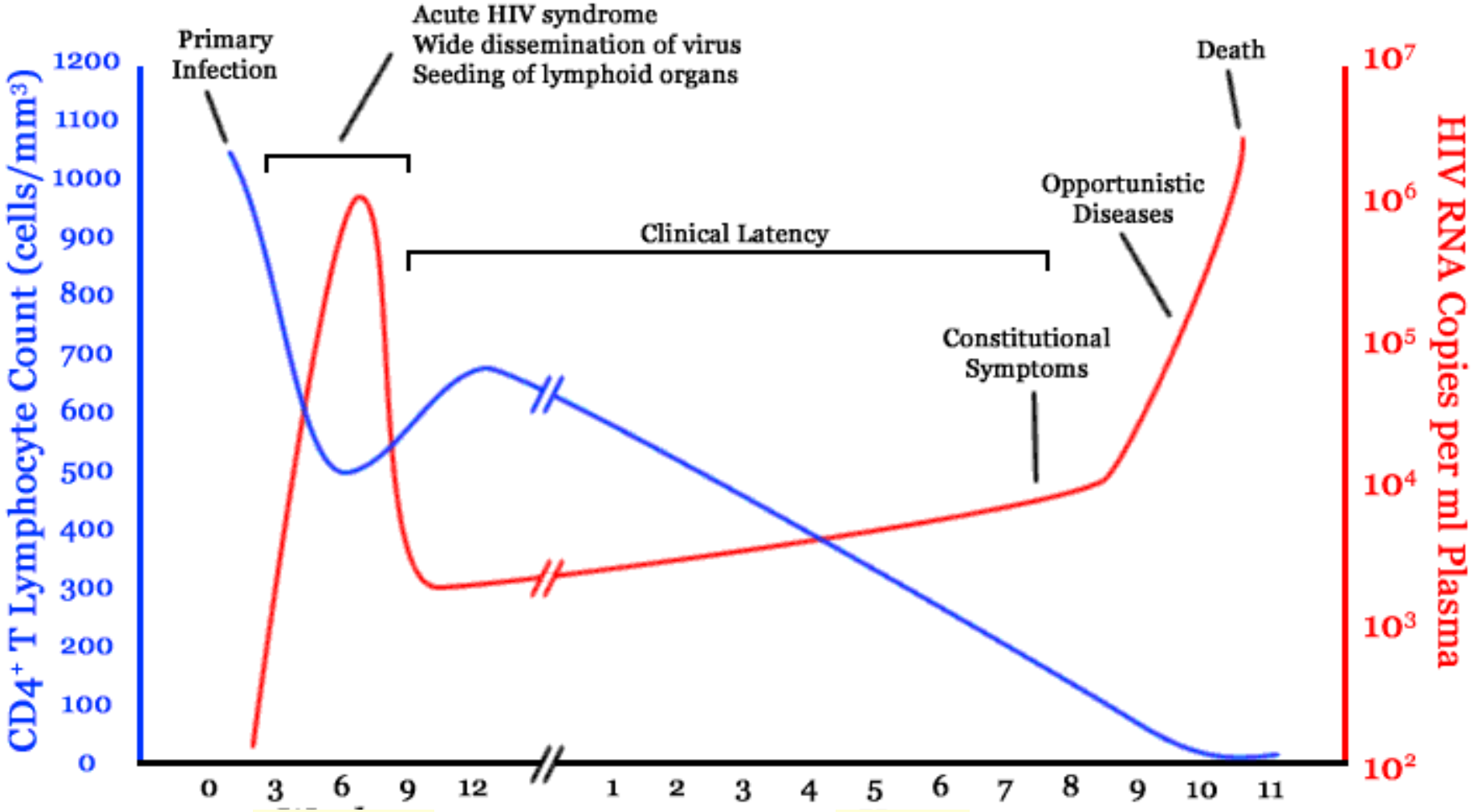


Figure 11-29 Immunobiology, 6/e. (© Garland Science 2005)

Problem: Th-Aktivierung löst Virusreplikation aus!

Klinischer Verlauf von AIDS



Stadieneinteilung der HIV-Infektion

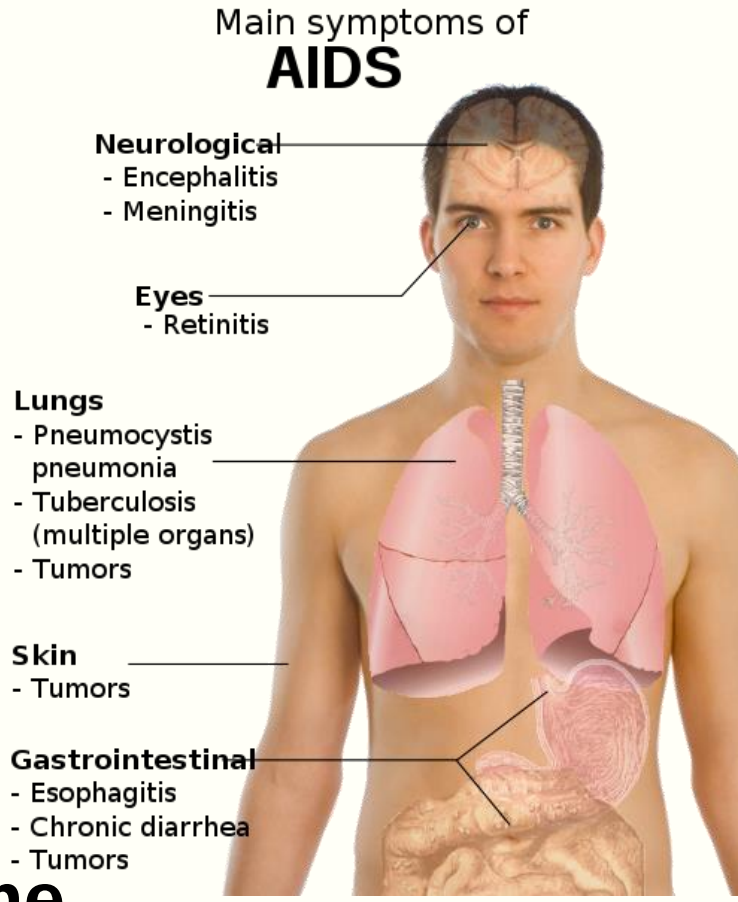
	klinische Kategorien		
CD4+ T-Zellzahl	A	B	C
> 500/µl	A1	B1	C1
200 - 499/µl	A2	B2	C2
< 200/µl	A3	B3	C3

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:

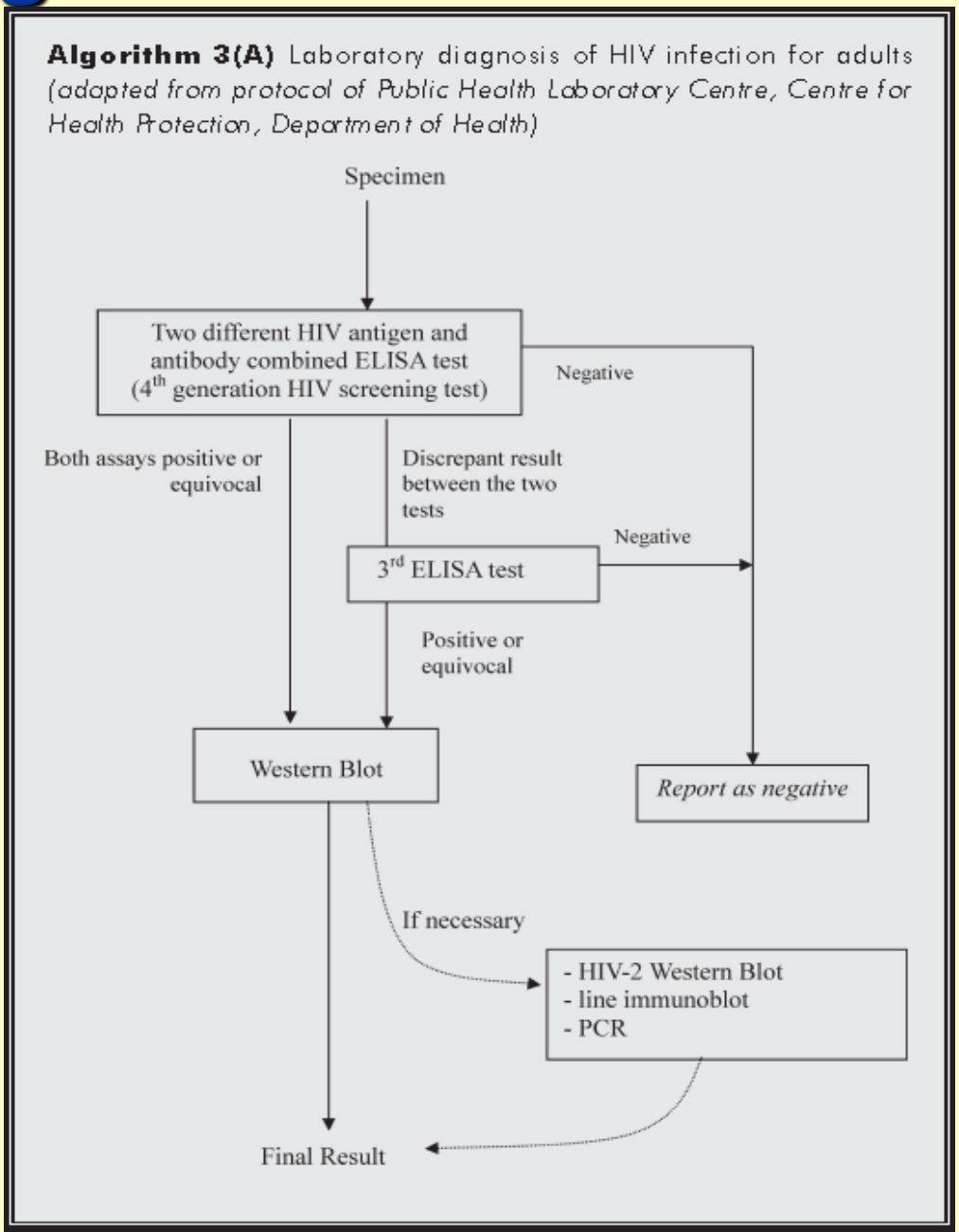
Kaposi-Sarkom

Non-Hodgkin-Lymphome

EBV-positive Burkitt-Lymphome

primäre Lymphome des Gehirns

Diagnostik der HIV-Infektion



Therapeutische Möglichkeiten (HAART)

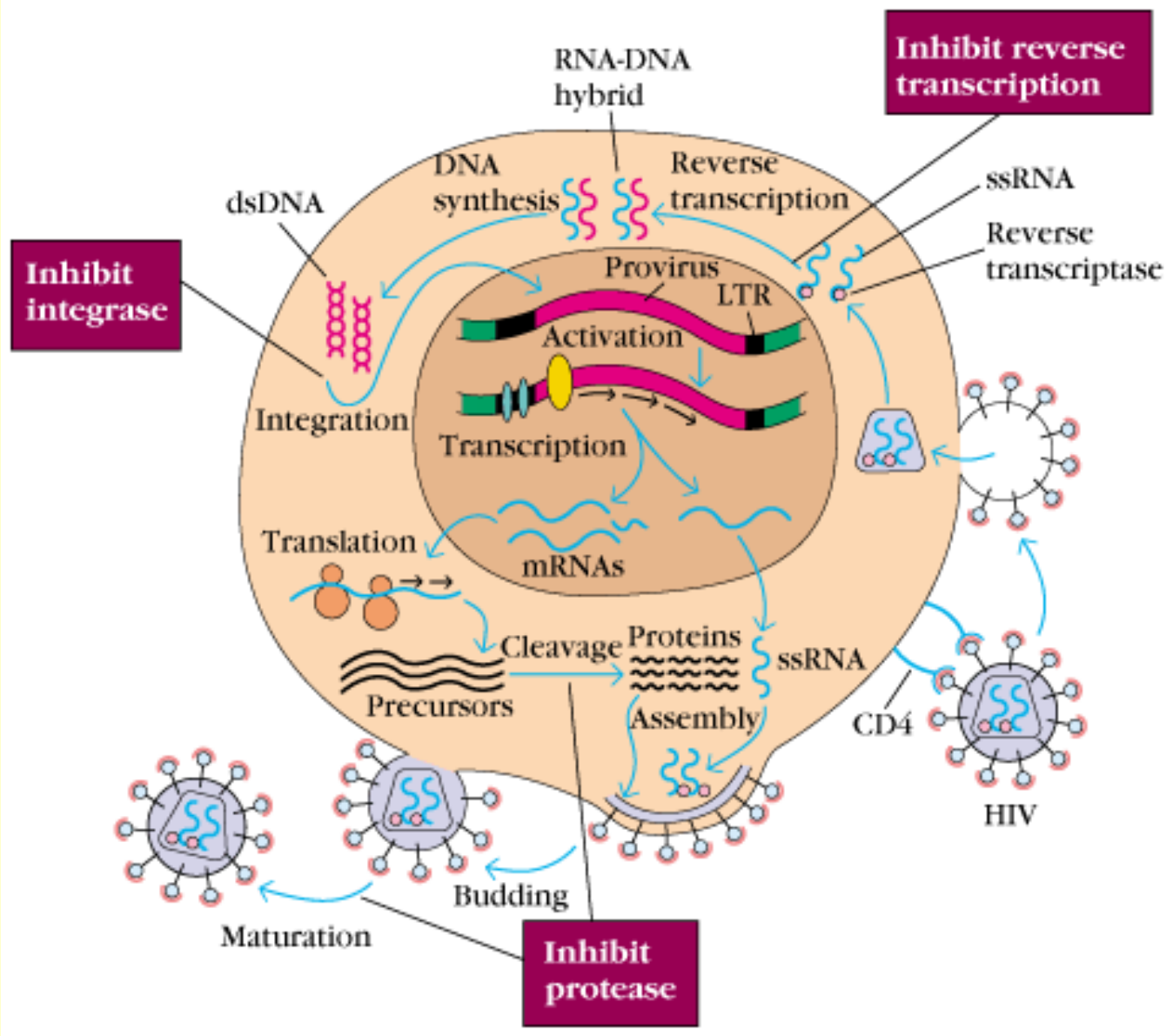
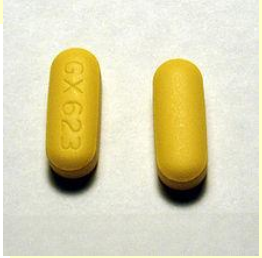
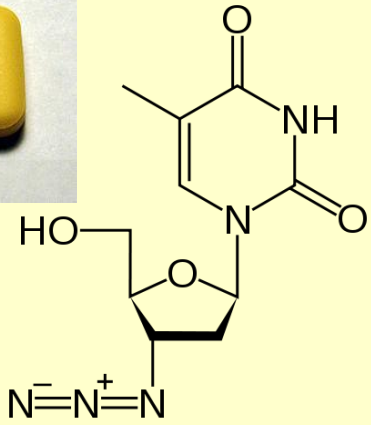


TABLE 19-5 SOME ANTI-HIV DRUGS IN CLINICAL USE

Generic name (other names)	Typical dosage	Some potential side effects
Reverse transcriptase inhibitors: Nucleoside analog		
Didanosine (Videx, ddI)	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

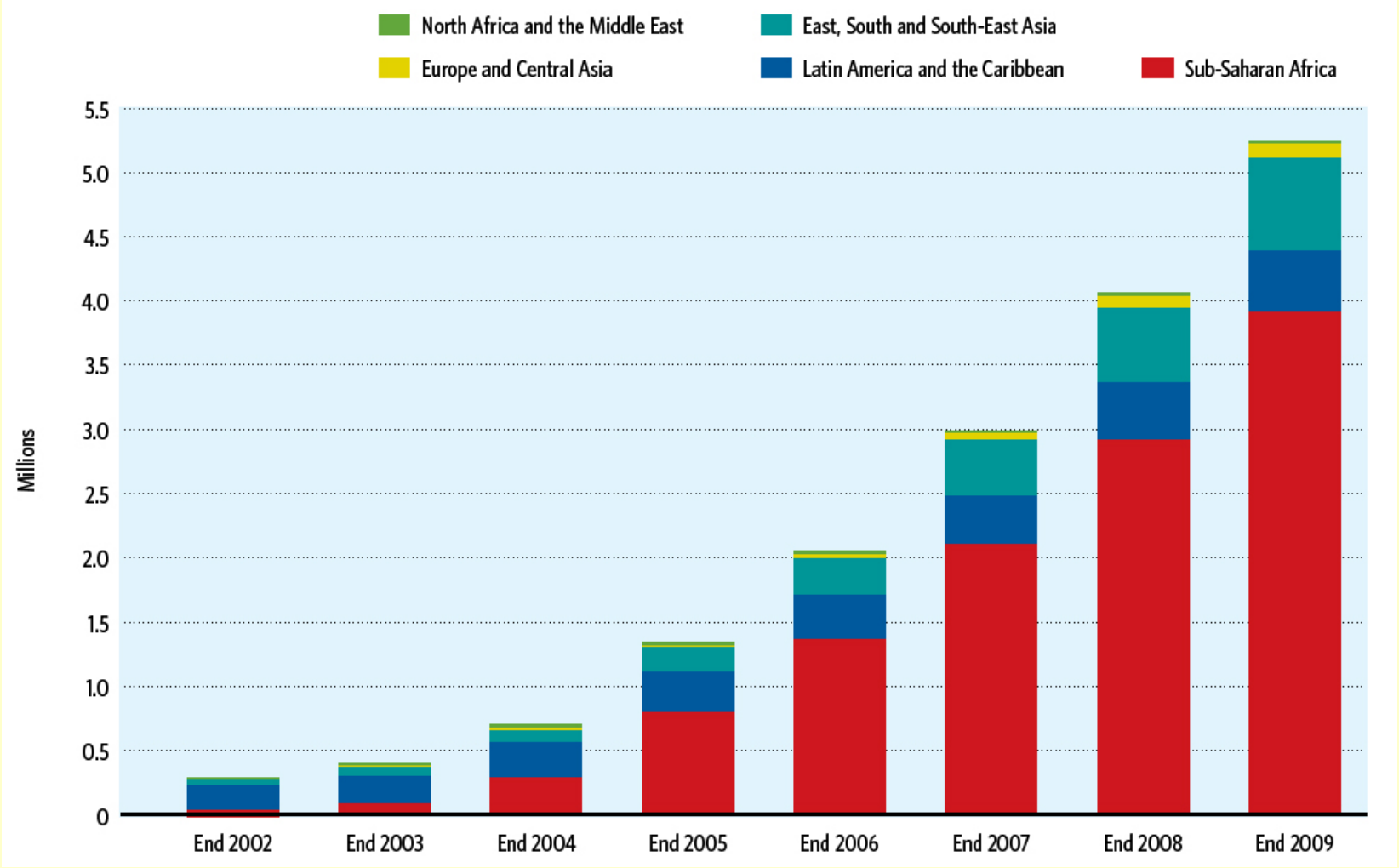
SOURCE: JG Bartlett and RD Moore, 1998, Improving HIV therapy, *Sci. Am.* **279**(1):87.





Azithothymidin (AZT)

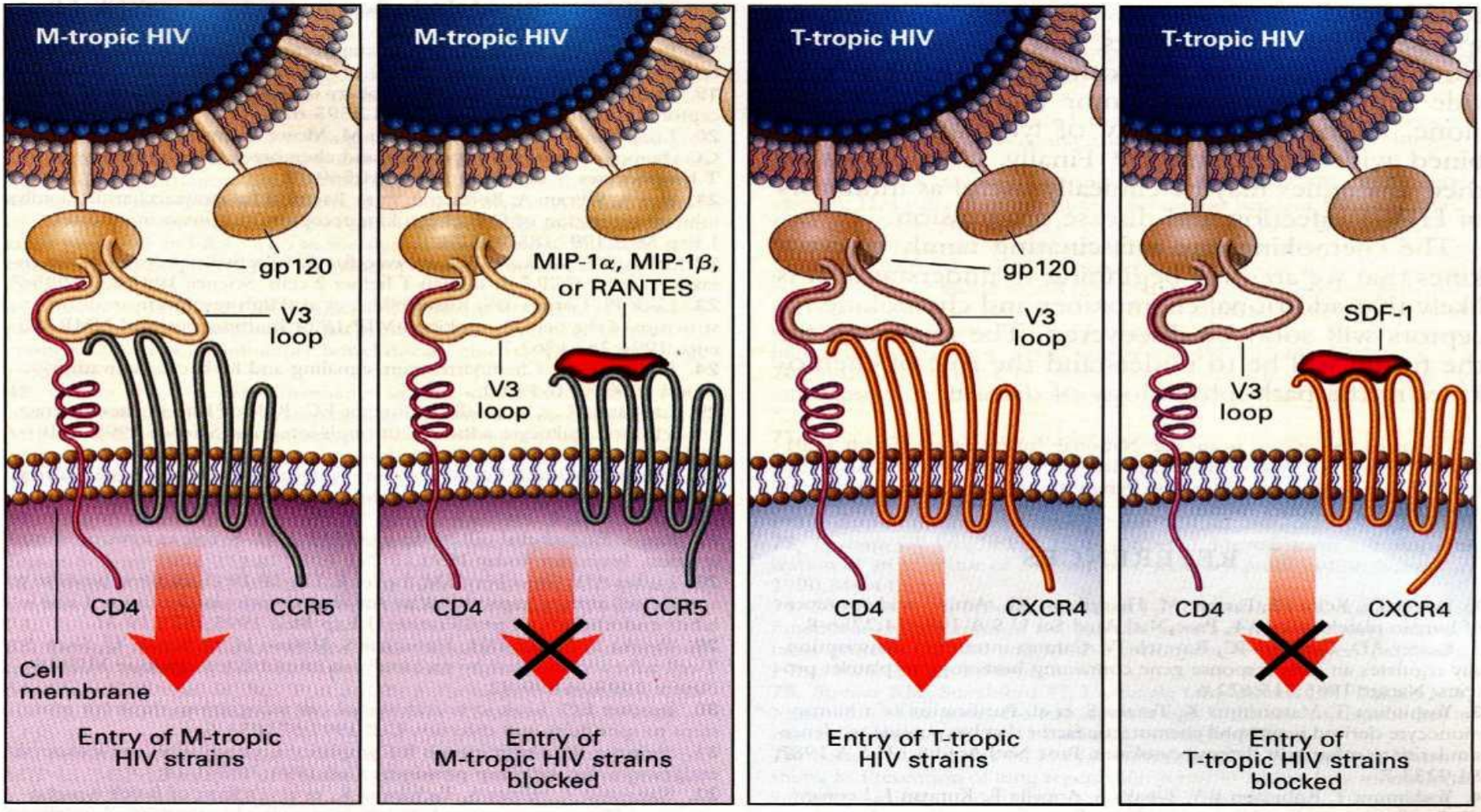
Antiretroviral therapy (2002-2009)



UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

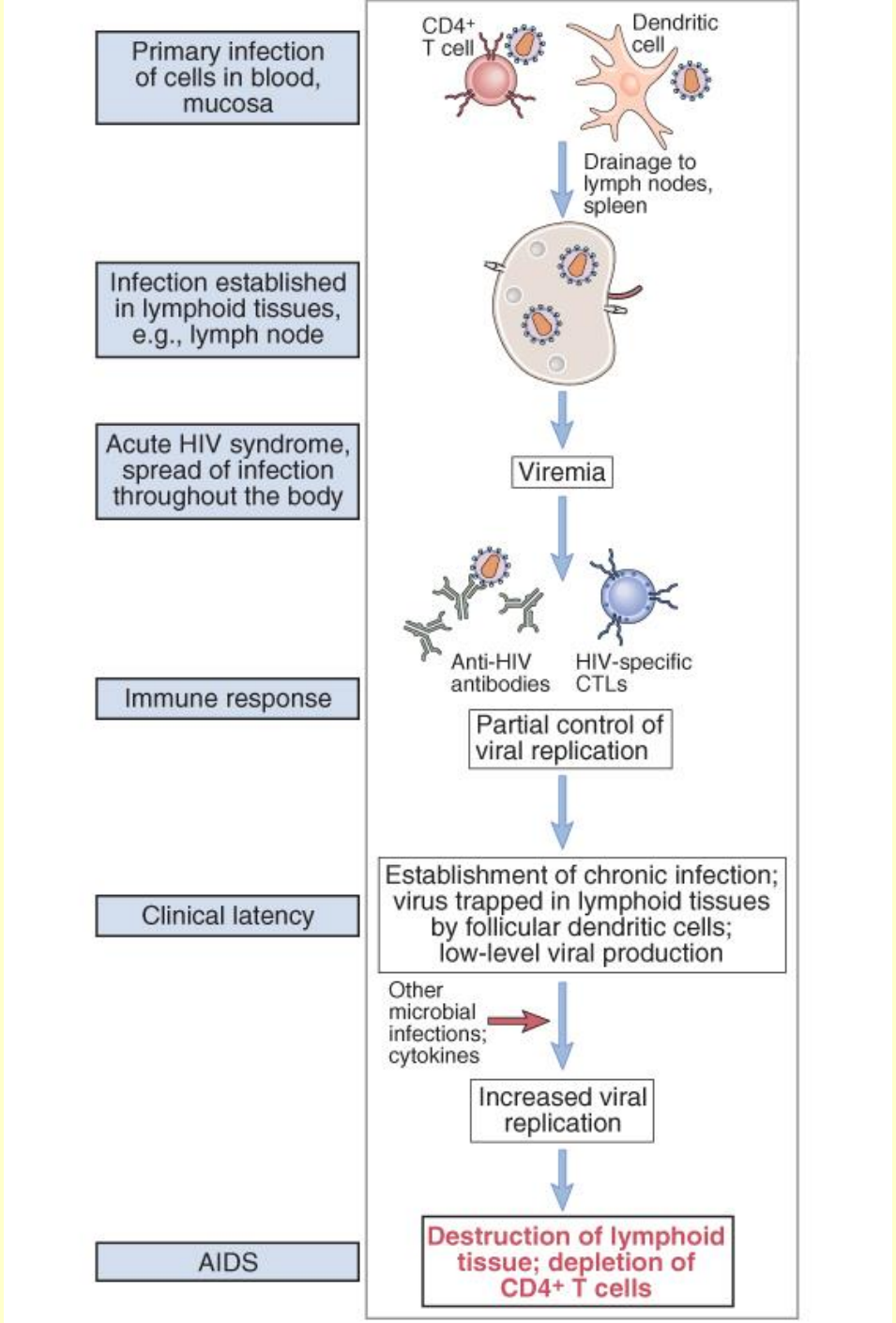
World Health Organization

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

Francoise Barré-Sinoussi

Frankreich

Luc Montaigner

Frankreich