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**

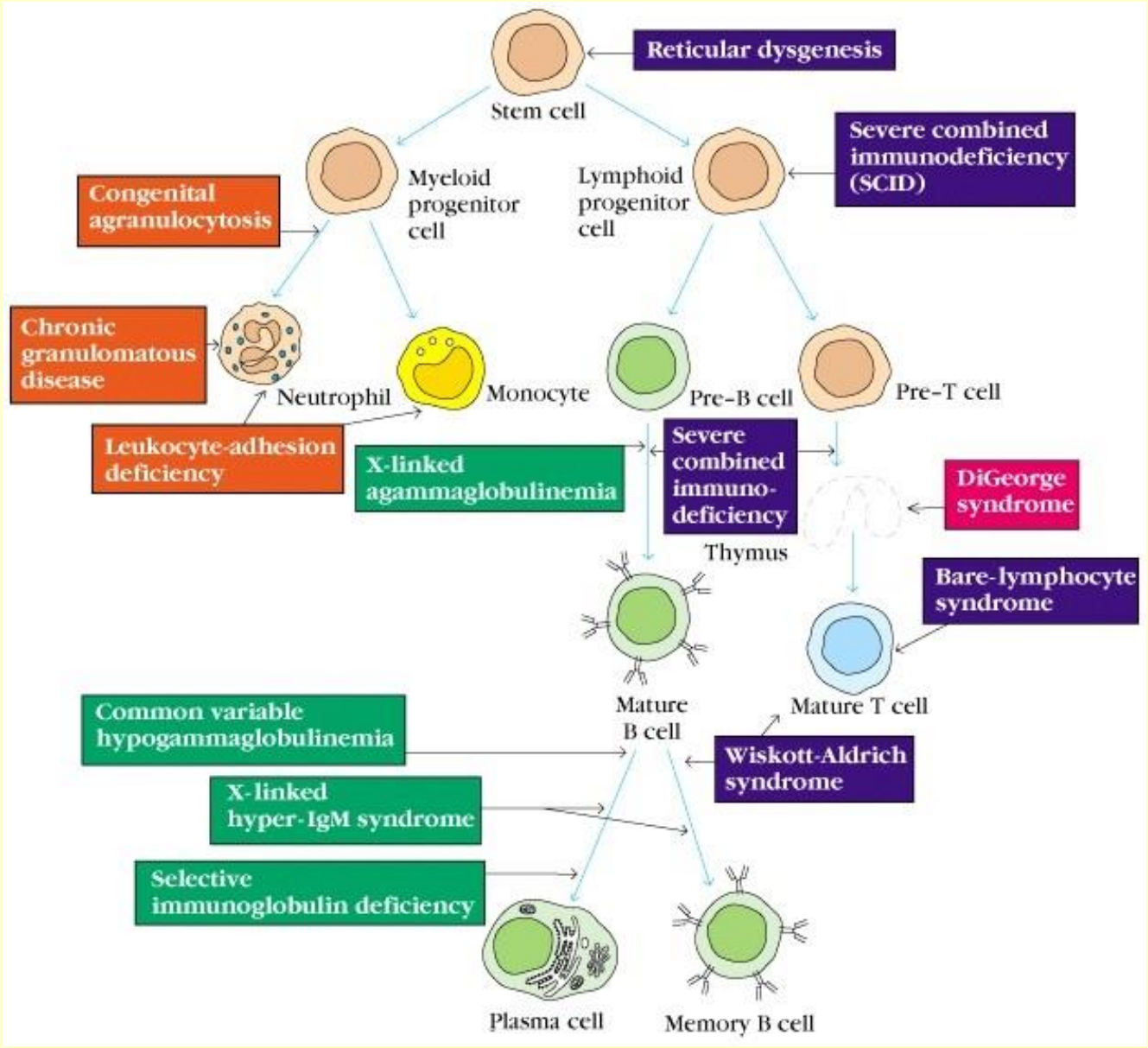
Hintergrund der Immundefekte

Defizienzen der angeborenen Immunität

B - Zell - Defizienzen

T- und B -Zell- Defizienzen

T - Zell - Defizienzen

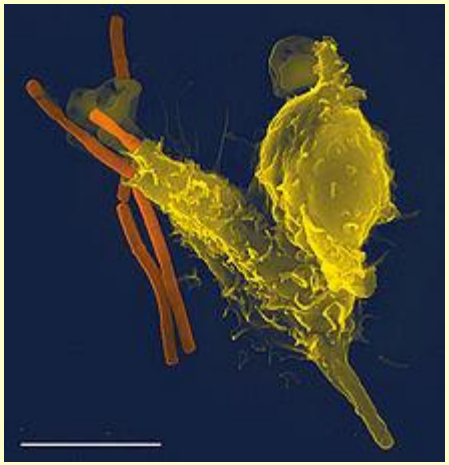


Erbliche Immundefekte

1. Angeborene Immunität

„Häufige ” zelluläre Immundefizienzen der angeborenen Immunität

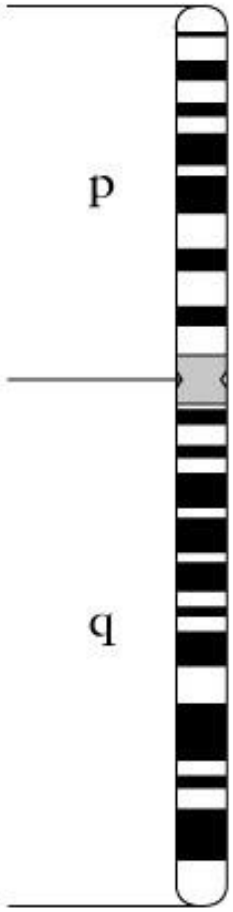
- **Granula– Defekte der Granulozyten/Monozyten**
- **Intrazelluläre Tötungsdefekte**
- **Störungen der Adhäsion und der Chemotaxis (LAD)**
- **Defekte der NK-Zellen**
- **Komplementsystem-Defekten**



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)

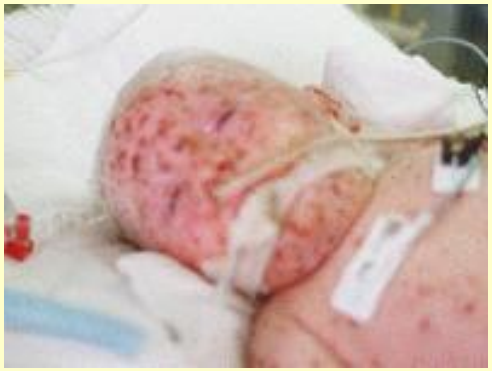
Schwere kombinierte Immundefekte (SCID)

- 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

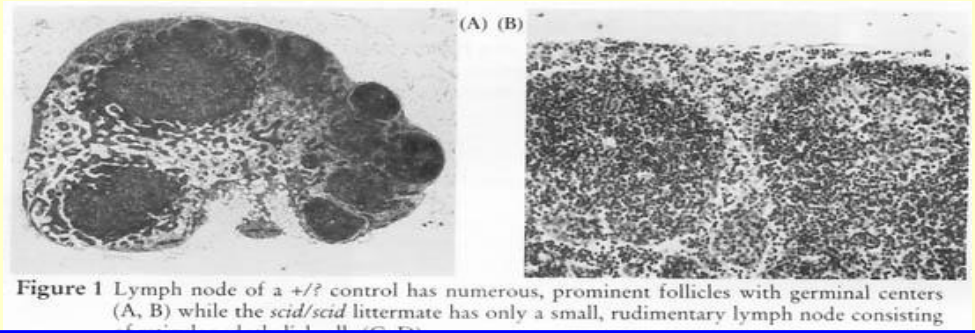
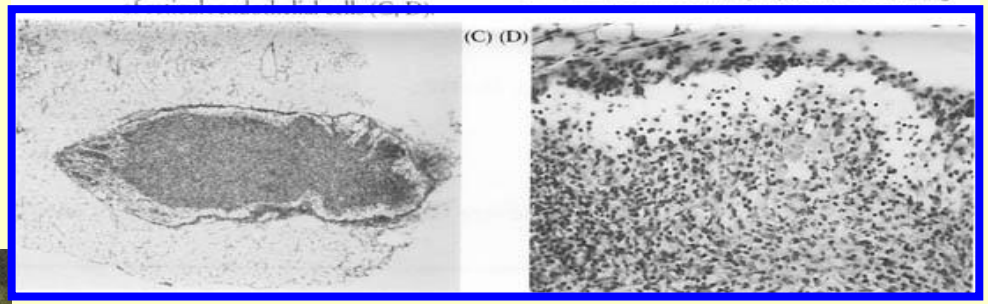
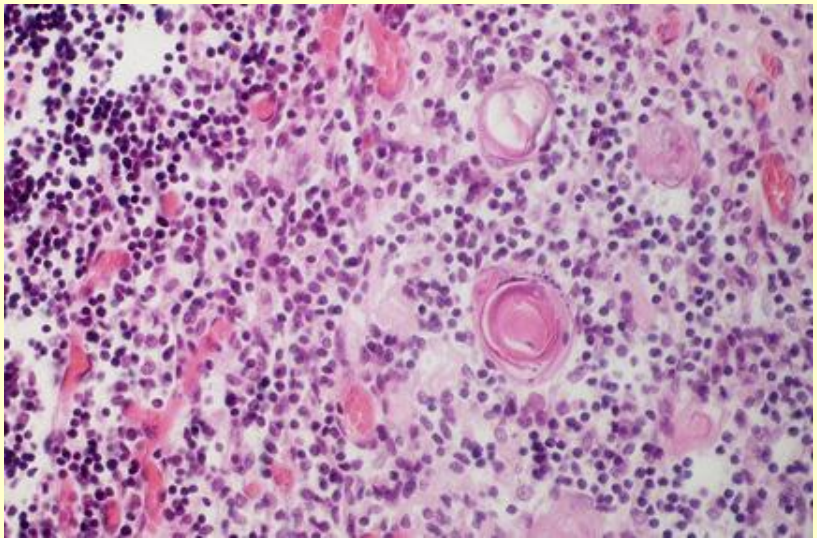


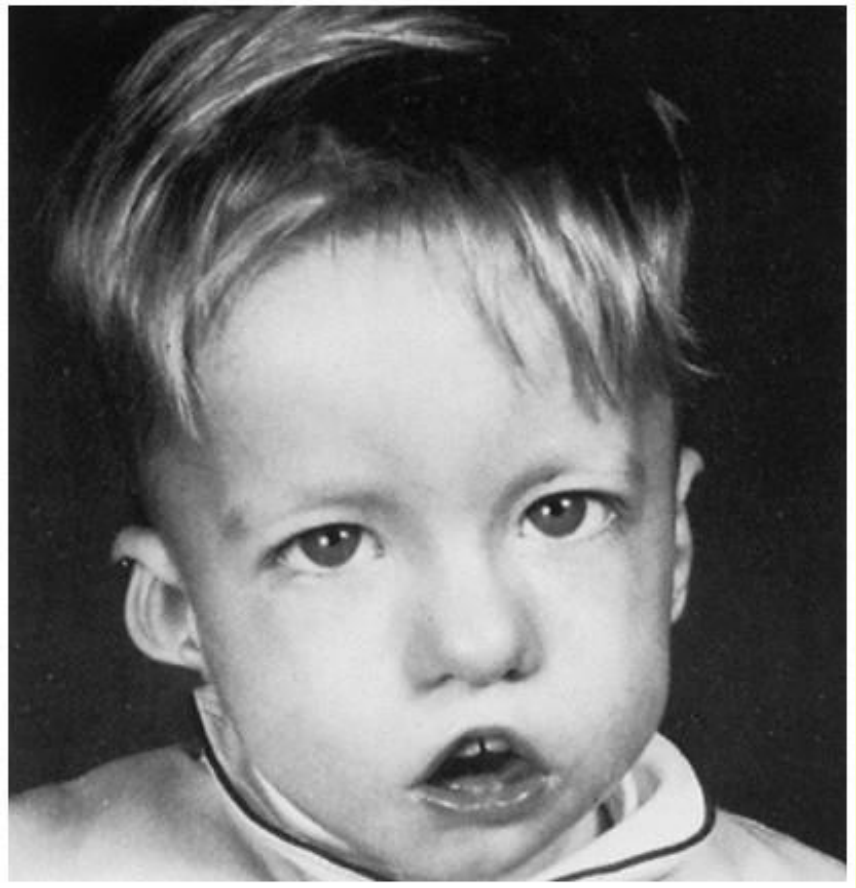
Figure 1 Lymph node of a +/? control has numerous, prominent follicles with germinal centers (A, B) while the *scid/scid* littermate has only a small, rudimentary lymph node consisting



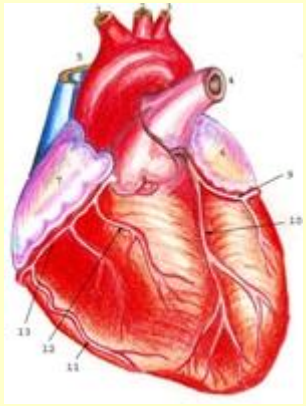
SCID

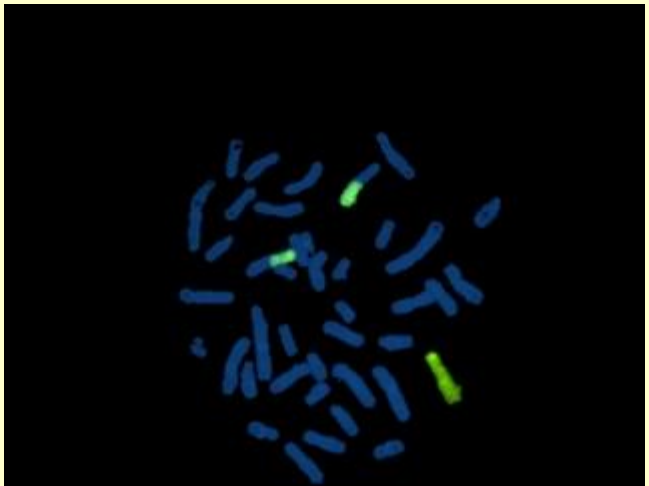


DiGeorge-Syndrom



KiDS-22q11 e.V.





B-Zell-Defizienzen

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

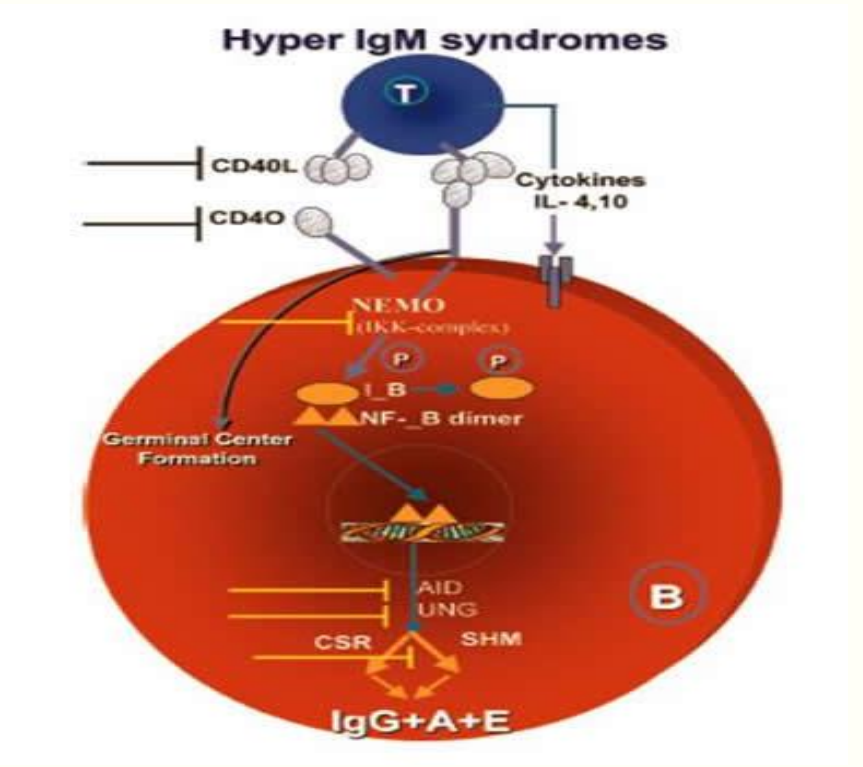
Beispiele:

- **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)

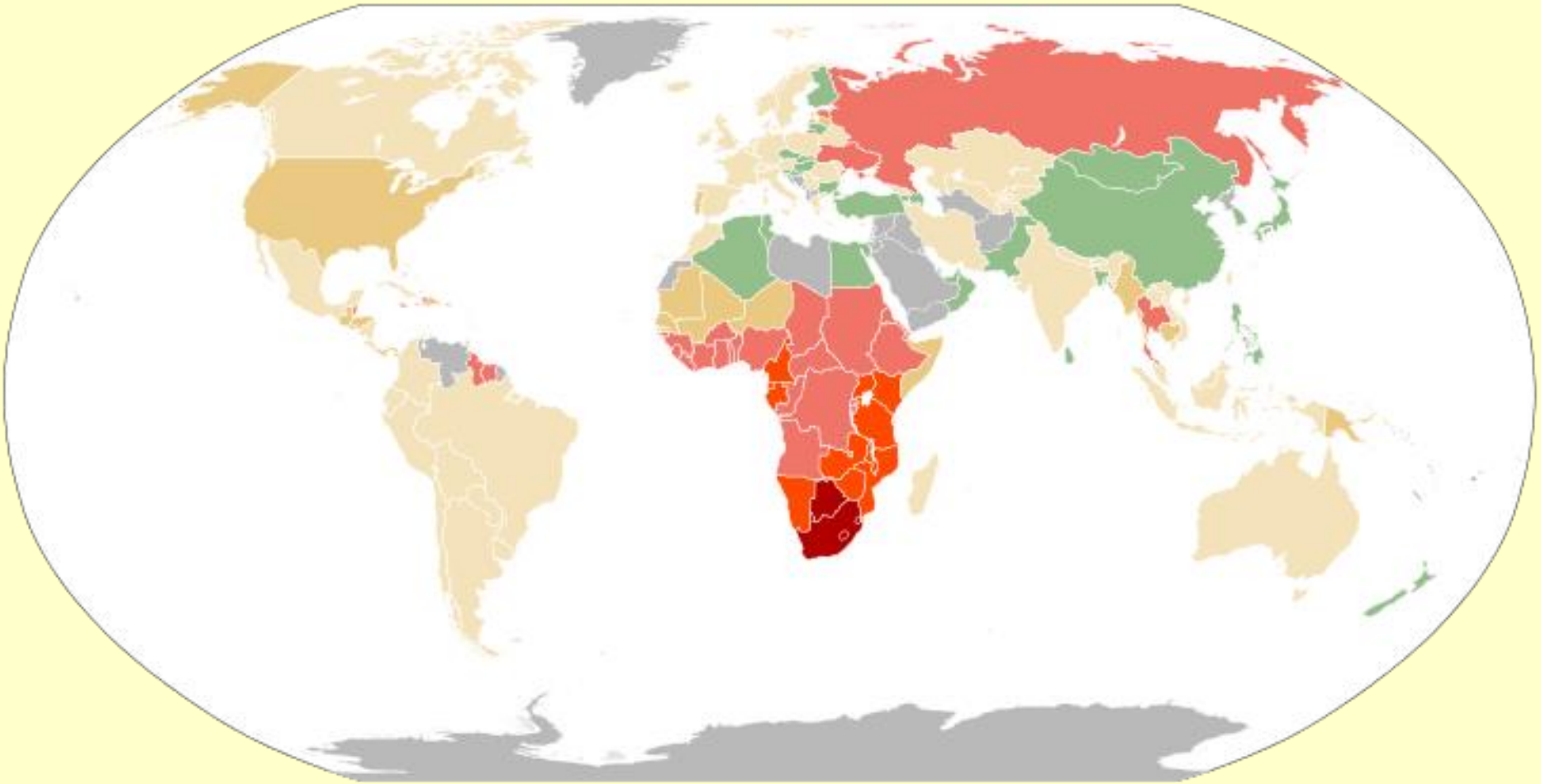
	2000	2005	2010	2015	2016	2017	2018	2019	2020/ *june2021	2023
People living with HIV	25.5 million [20.5 million–30.7 million]	28.6 million [23.0 million–34.3 million]	31.1 million [25.0 million–37.3 million]	34.6 million [27.7 million–41.4 million]	35.3 million [28.3 million–42.2 million]	35.9 million [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)
New HIV infections (total)	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)
New HIV infections (aged 15+ years)	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
New HIV infections (aged 0–14 years)	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
AIDS-related deaths	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
People accessing antiretroviral therapy	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
HIV resources available**	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
Eastern and southern Africa	20.6 million [18.2 million–23.2 million]	800 000 [620 000–1.0 million]	310 000 [230 000–400 000]
Western and central Africa	5.0 million [4.0 million–6.3 million]	280 000 [180 000–420 000]	160 000 [110 00–230 000]
Middle East and North Africa	240 000 [160 000–390 000]	20 000 [8500–40 000]	8400 [4800–14 000]
Asia and the Pacific	5.9 million [5.1 million–7.1 million]	310 000 [270 000–380 000]	200 000 [160 000–290 000]
Latin America	1.9 million [1.6 million–2.4 million]	100 000 [79 000–130 000]	35 000 [25 000–46 000]
Caribbean	340 000 [290 000–390 000]	16 000 [11 000–24 000]	6700 [5100–9100]
Eastern Europe and central Asia	1.7 million [1.5 million–1.9 million]	150 000 [140 000–160 000]	38 000 [28 000–48 000]
Western and central Europe and North America	2.2 million [1.9 million–2.4 million]	68 000 [58 000–77 000]	13 000 [9400–16 000]
TOTAL	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



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

World Health Organization

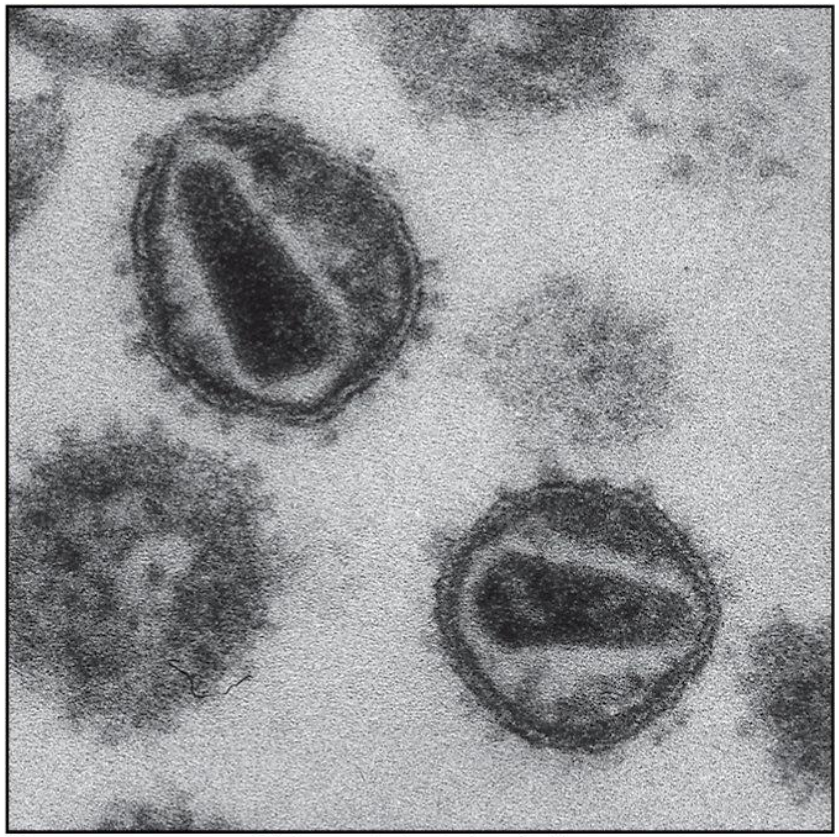
Übertragung

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**



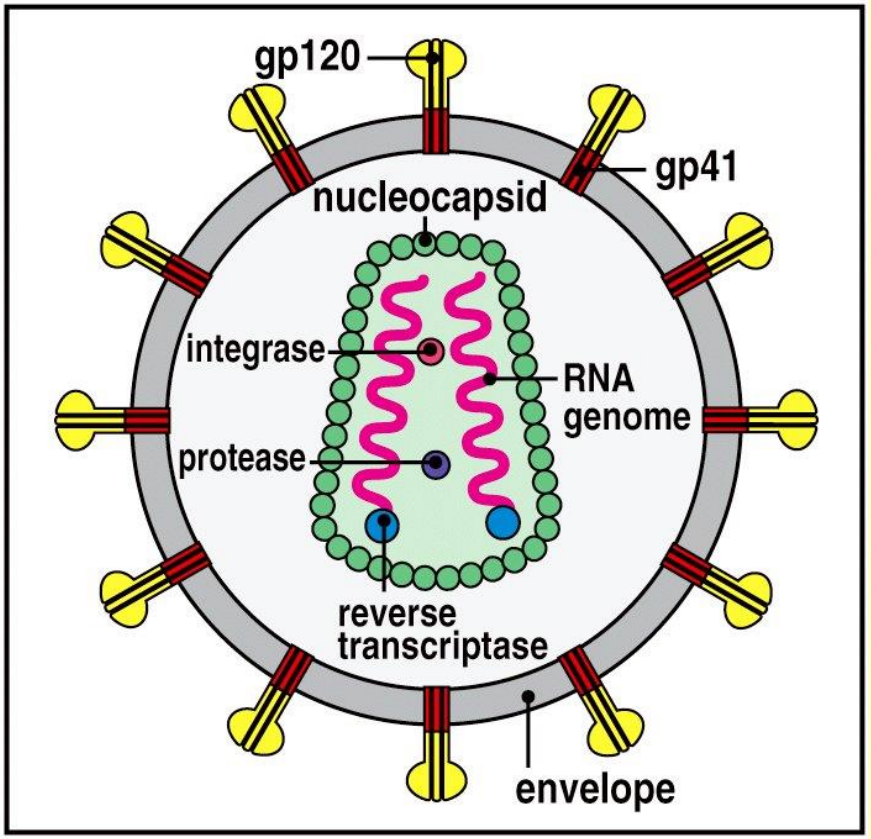
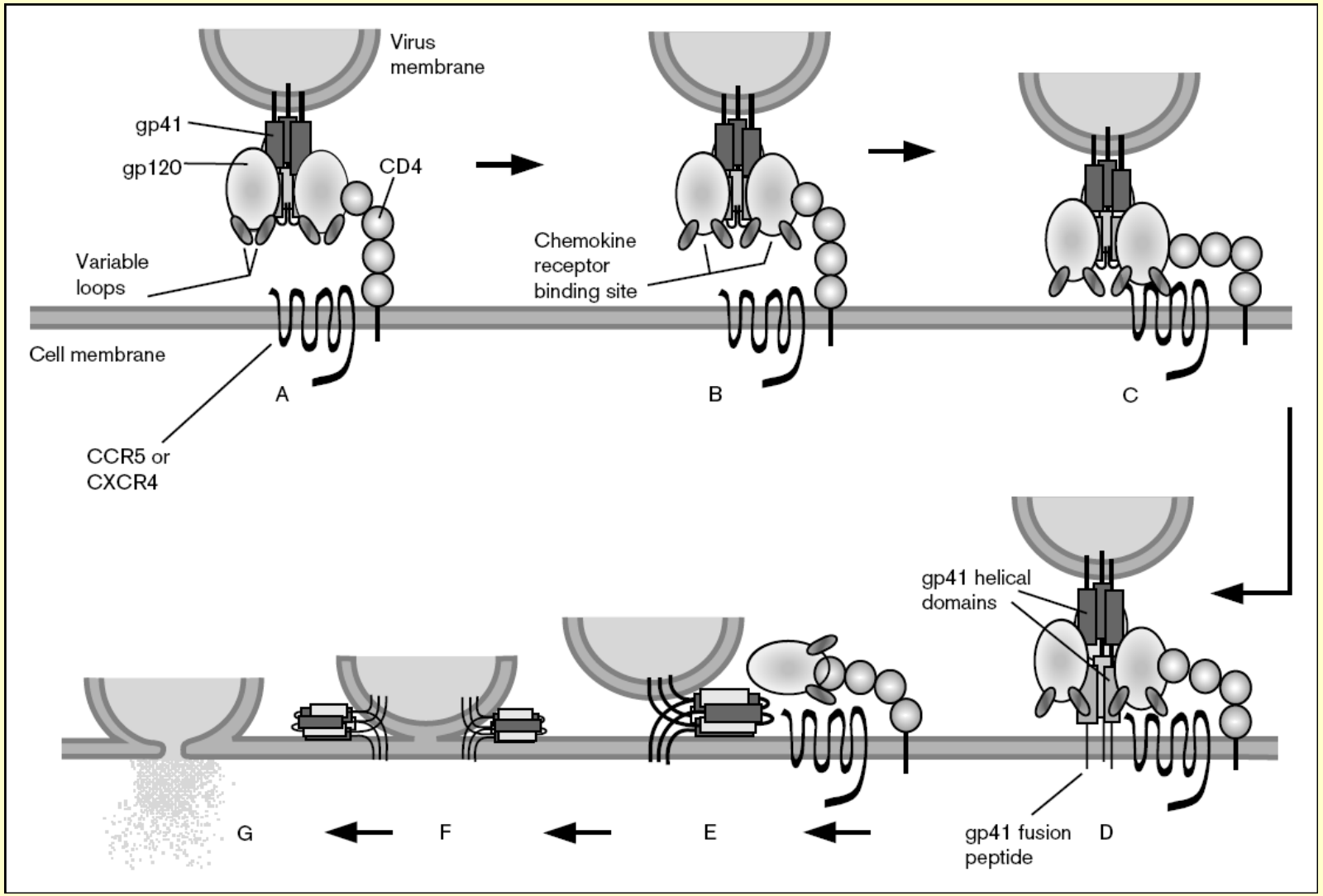


Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)

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”

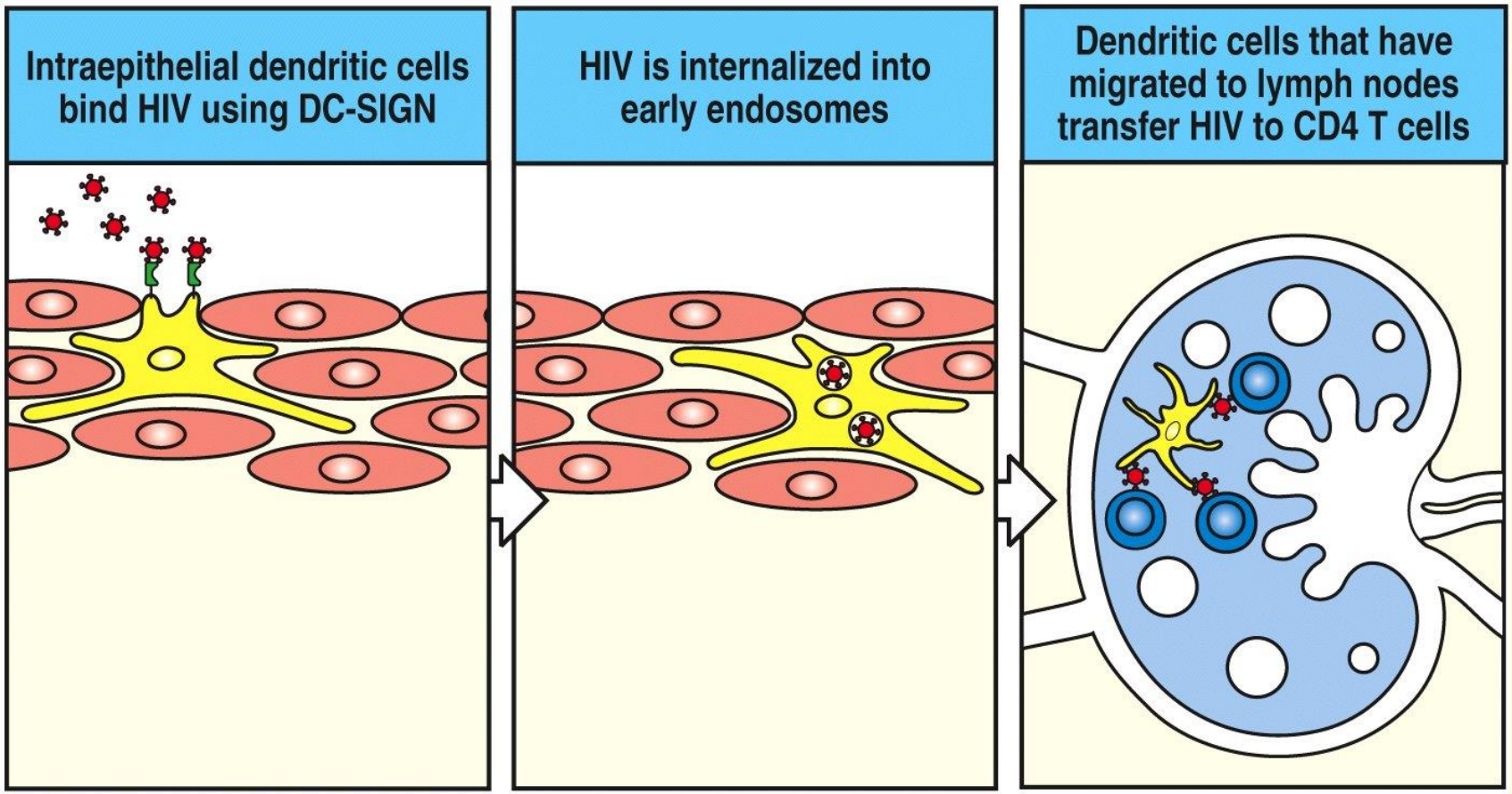
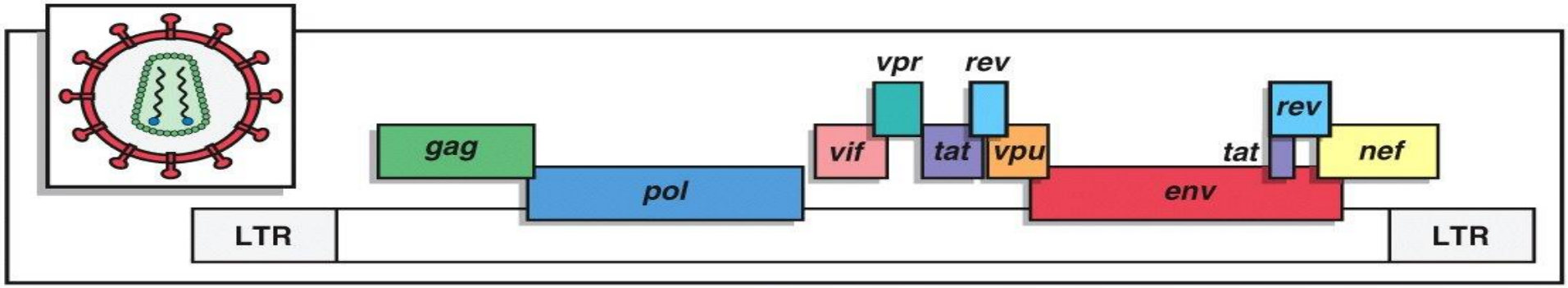


Figure 11-22 Immunobiology, 6/e. (© Garland Science 2005)

- 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.

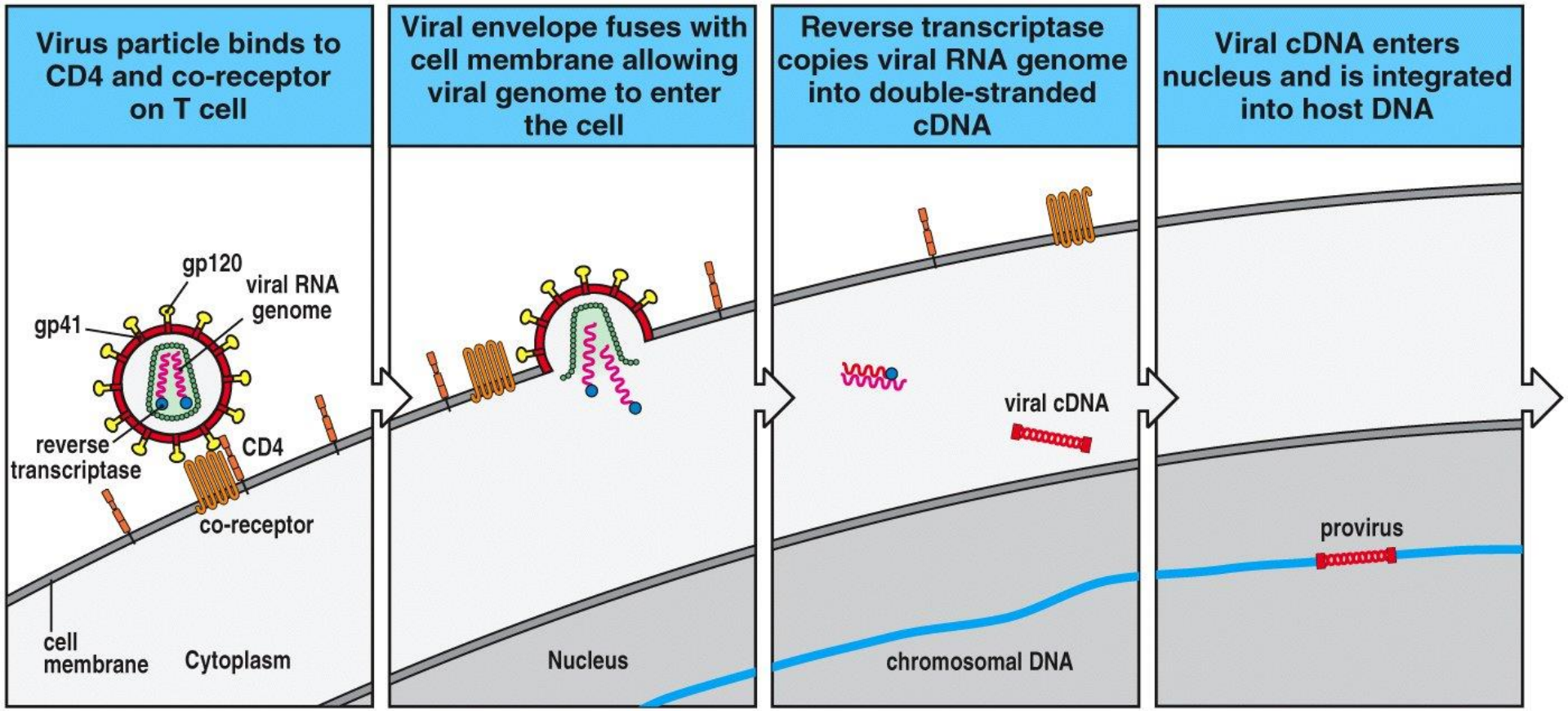
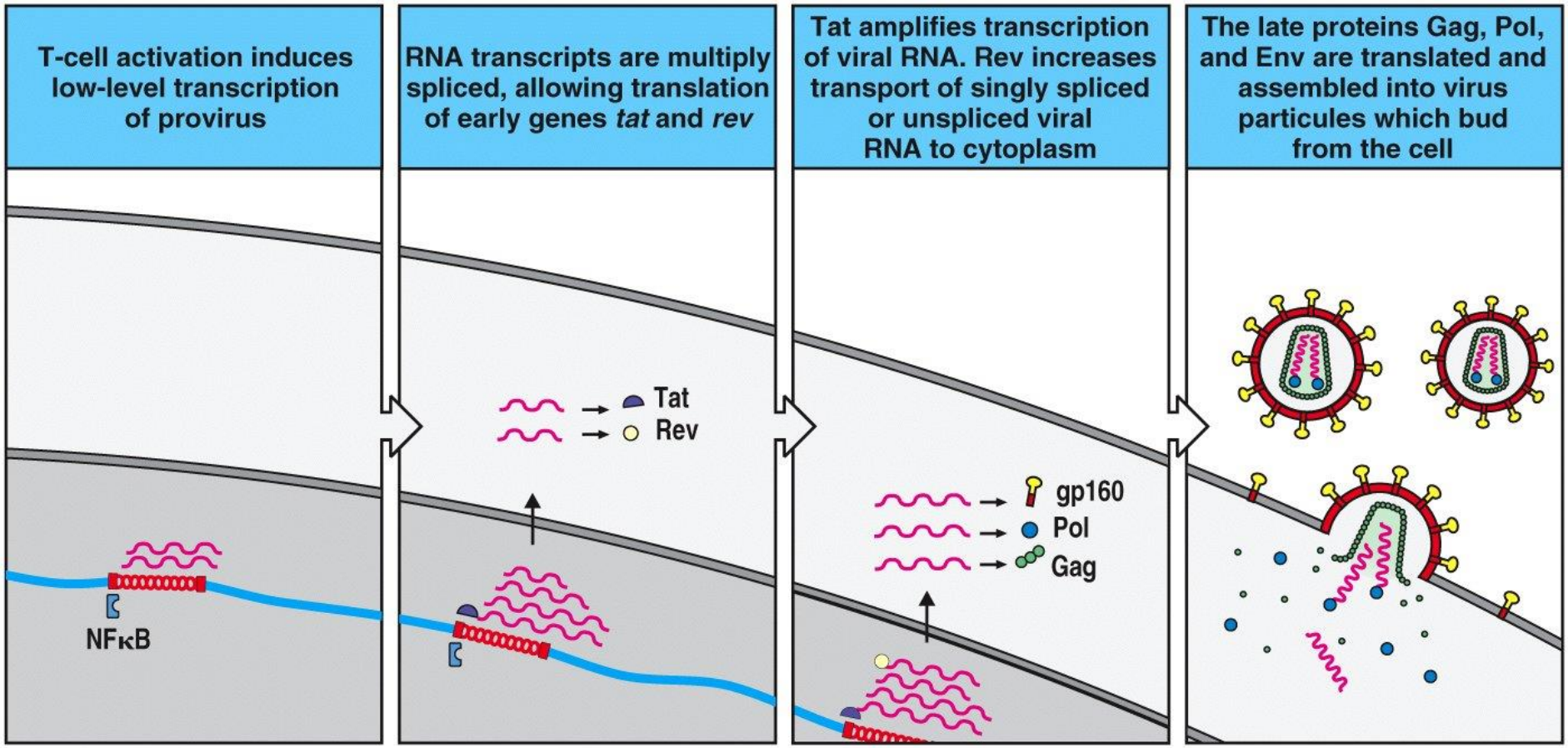


Figure 11-23 Immunobiology, 6/e. (© Garland Science 2005)

HIV-Replikation 2.



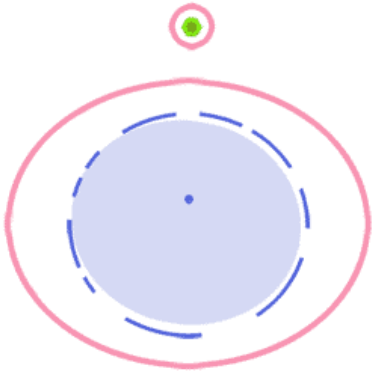
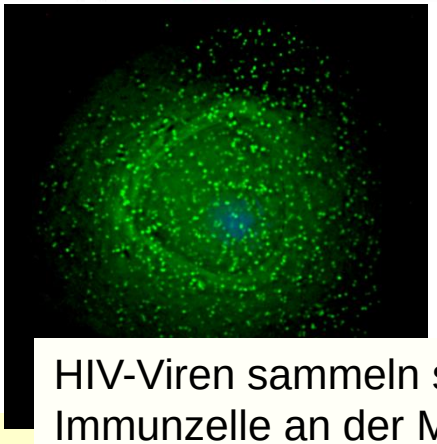
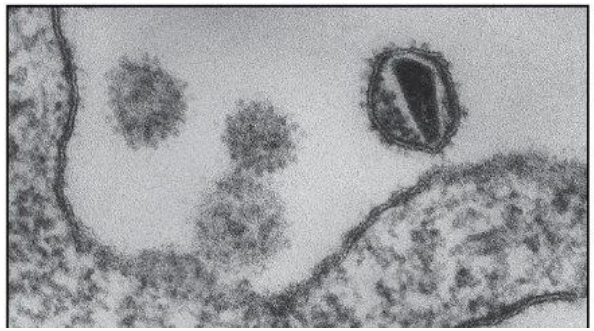


Figure 11-25 Imm 2005)





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

Immunantwort gegen HIV

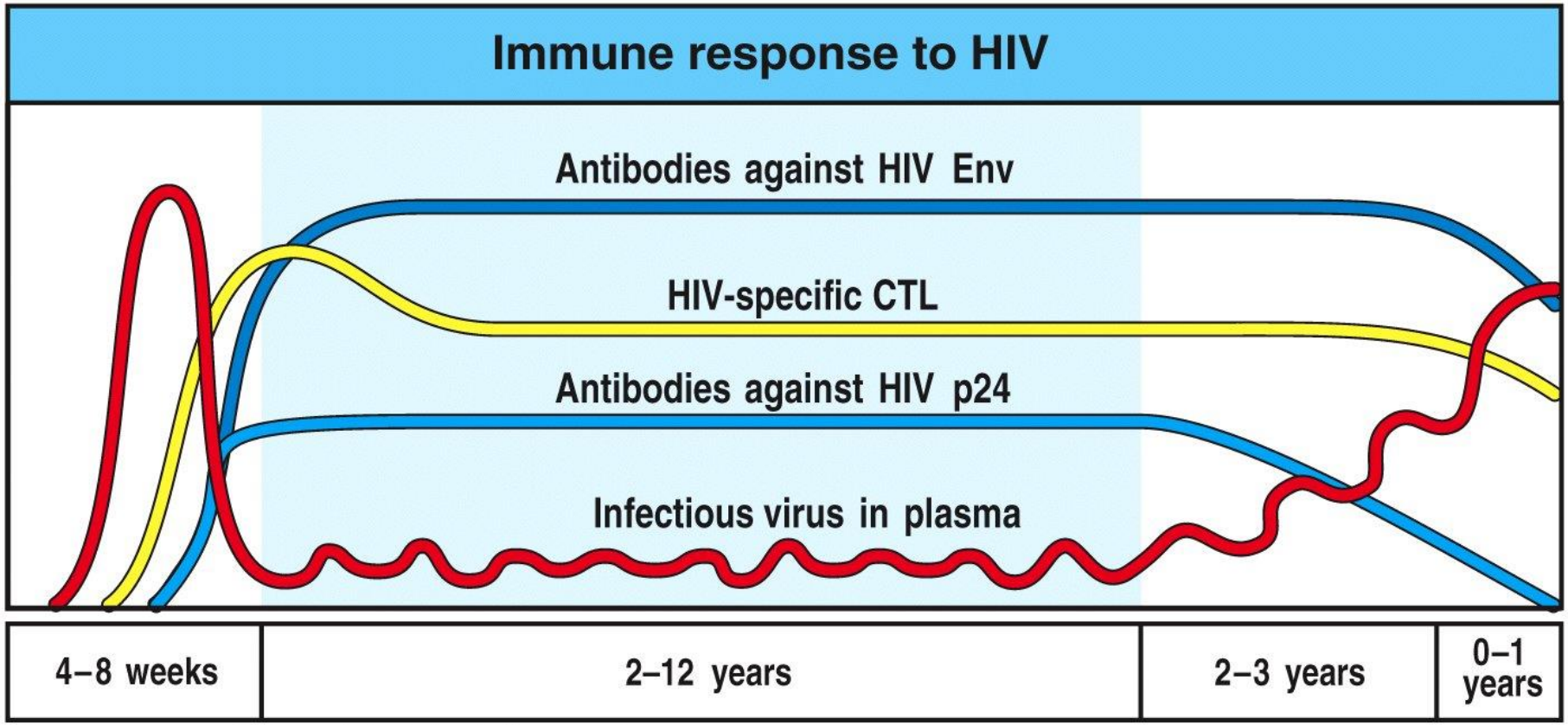
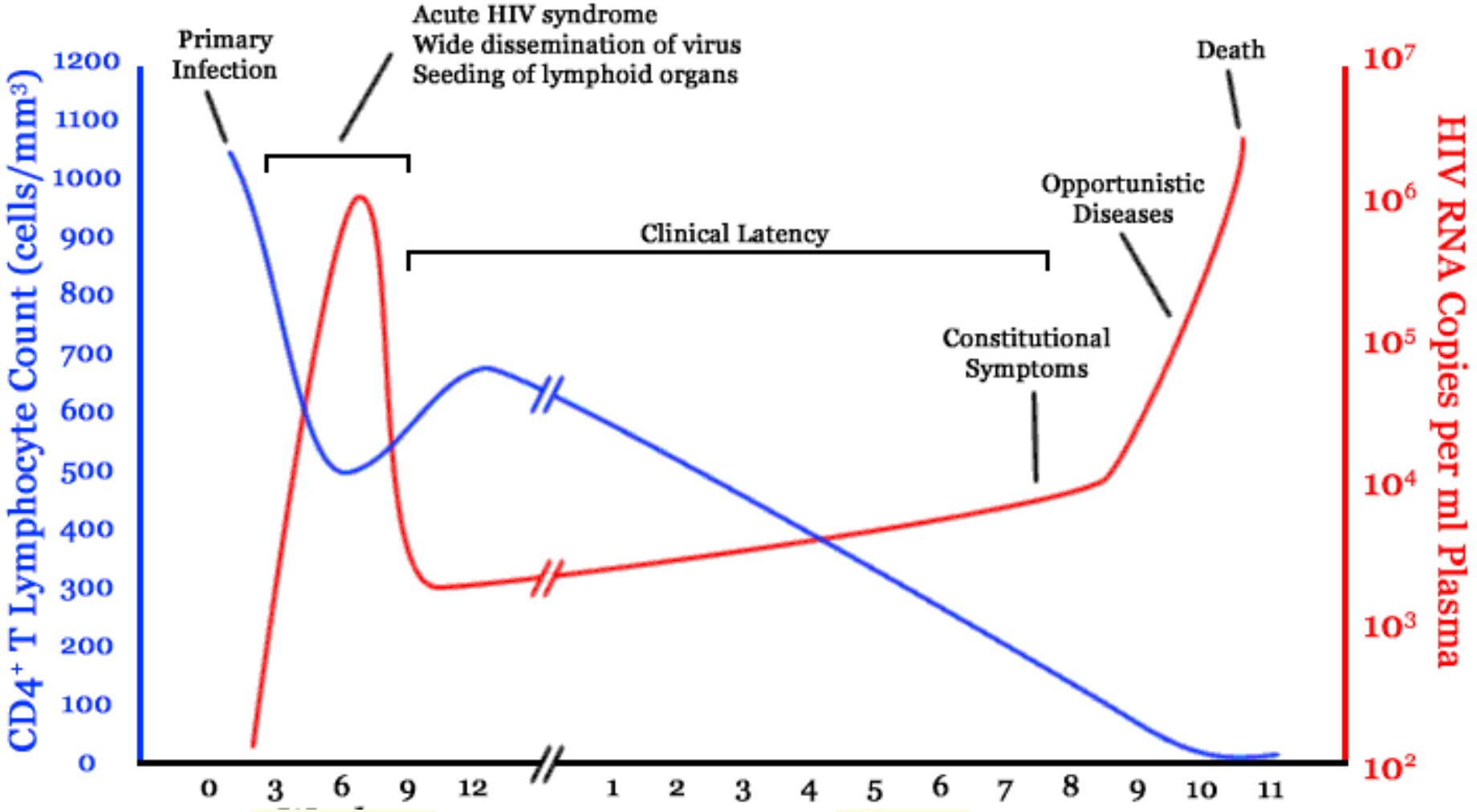


Figure 11-29 Immunobiology, 6/e. (© Garland Science 2005)

Problem: Th-Aktivierung löst Virusreplikation aus!

Klinischer Verlauf von AIDS



Stadieneinteilung der HIV-Infektion

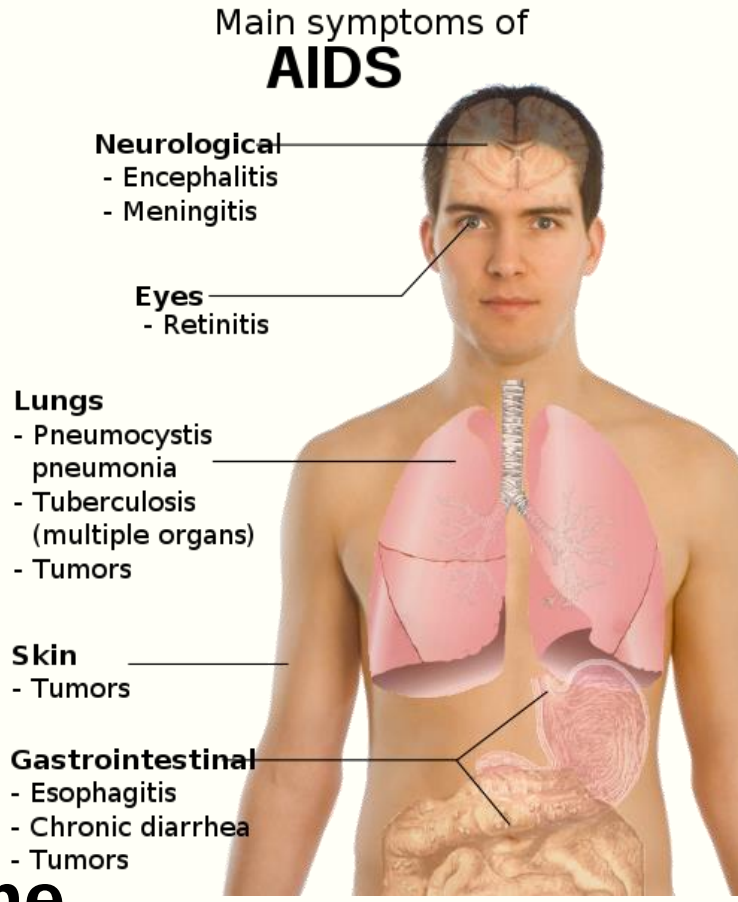
	klinische Kategorien		
CD4+ T-Zellzahl	A	B	C
> 500/µl	A1	B1	C1
200 - 499/µl	A2	B2	C2
< 200/µl	A3	B3	C3

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:

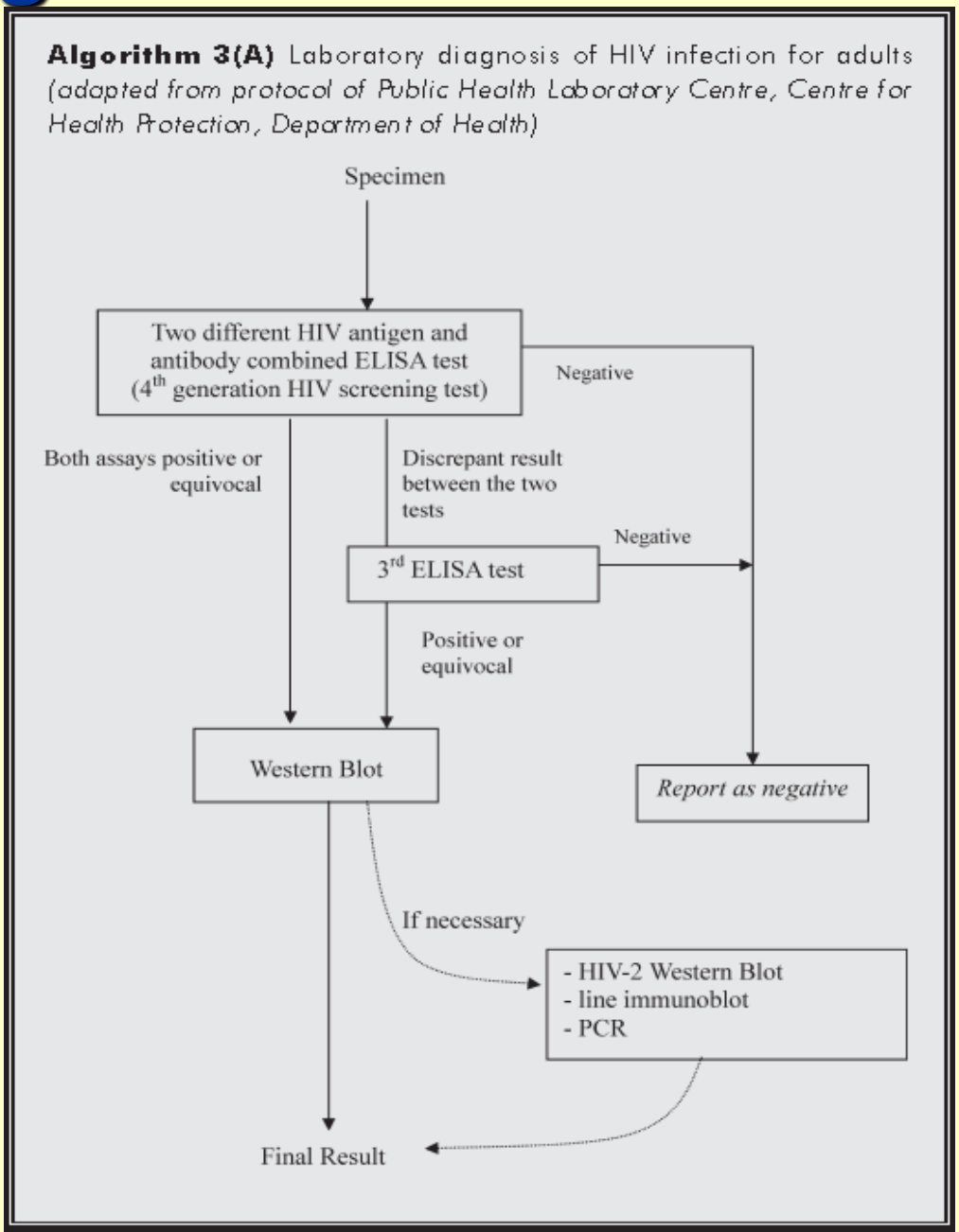
Kaposi-Sarkom

Non-Hodgkin-Lymphome

EBV-positive Burkitt-Lymphome

primäre Lymphome des Gehirns

Diagnostik der HIV-Infektion



Therapeutische Möglichkeiten (HAART)

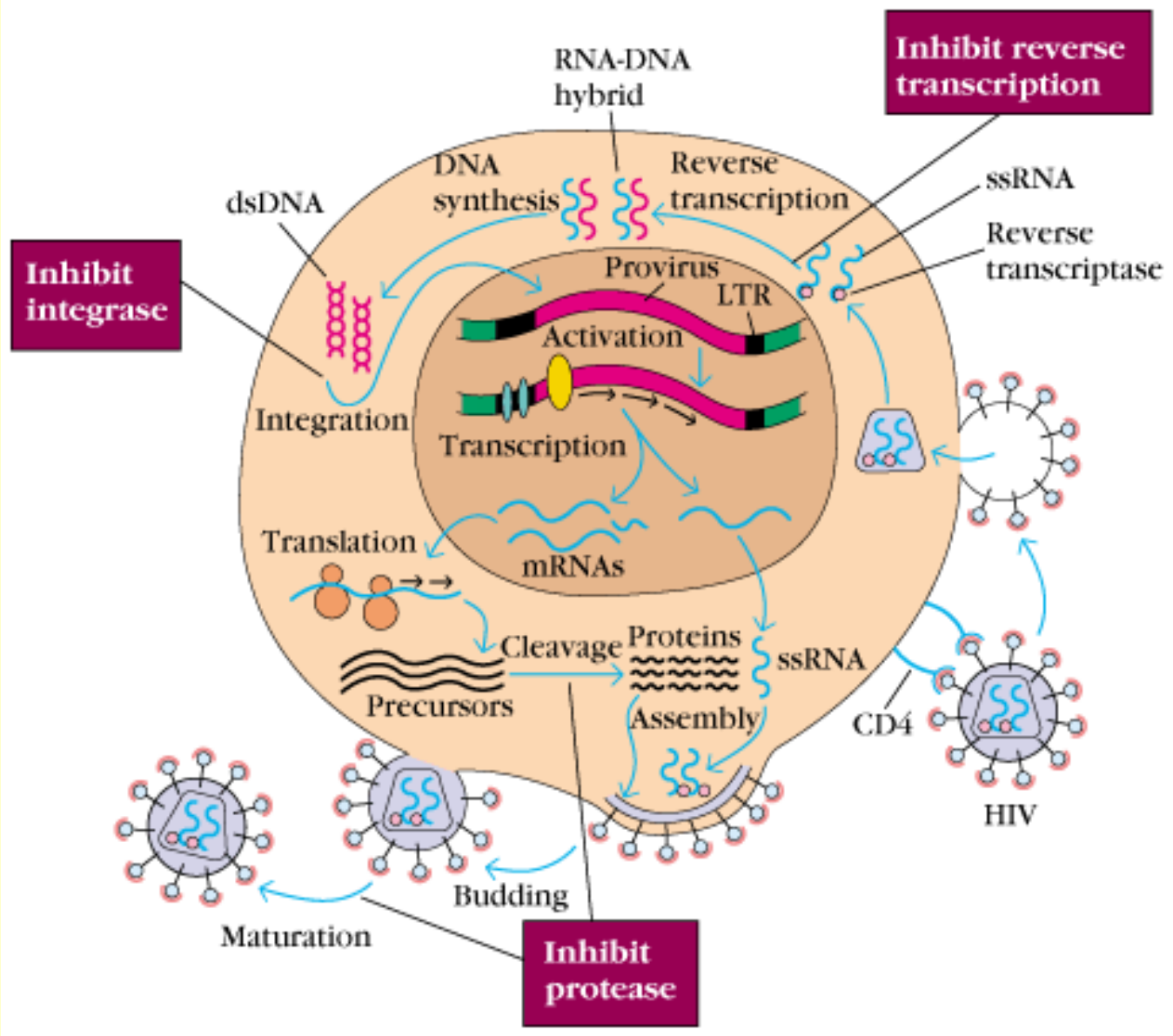
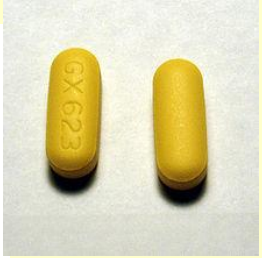
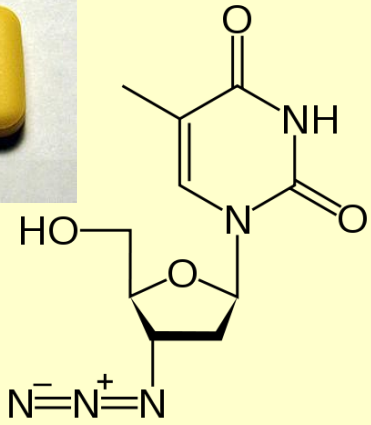


TABLE 19-5 SOME ANTI-HIV DRUGS IN CLINICAL USE

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

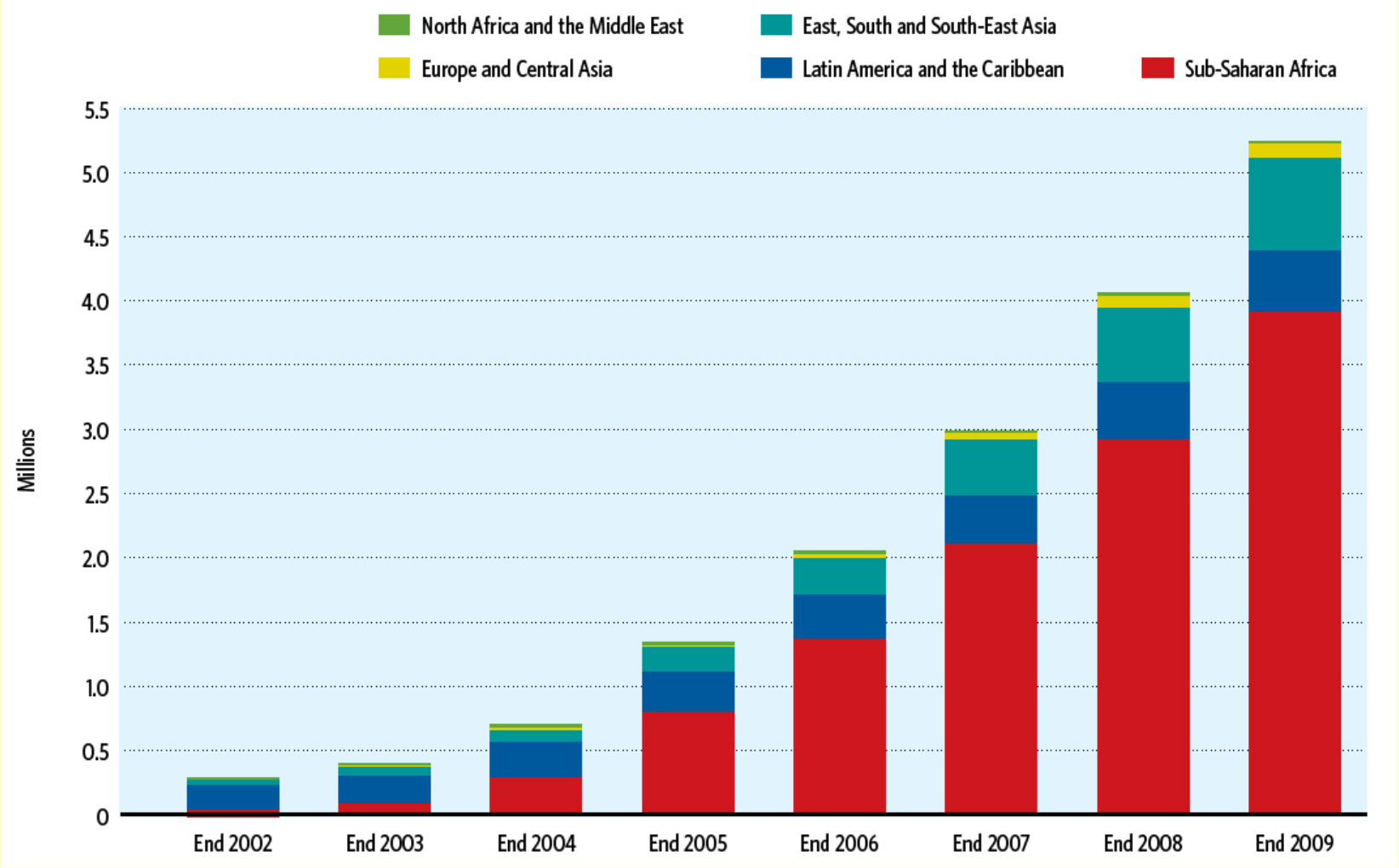
SOURCE: JG Bartlett and RD Moore, 1998, Improving HIV therapy, *Sci. Am.* **279**(1):87.





Azithothymidin (AZT)

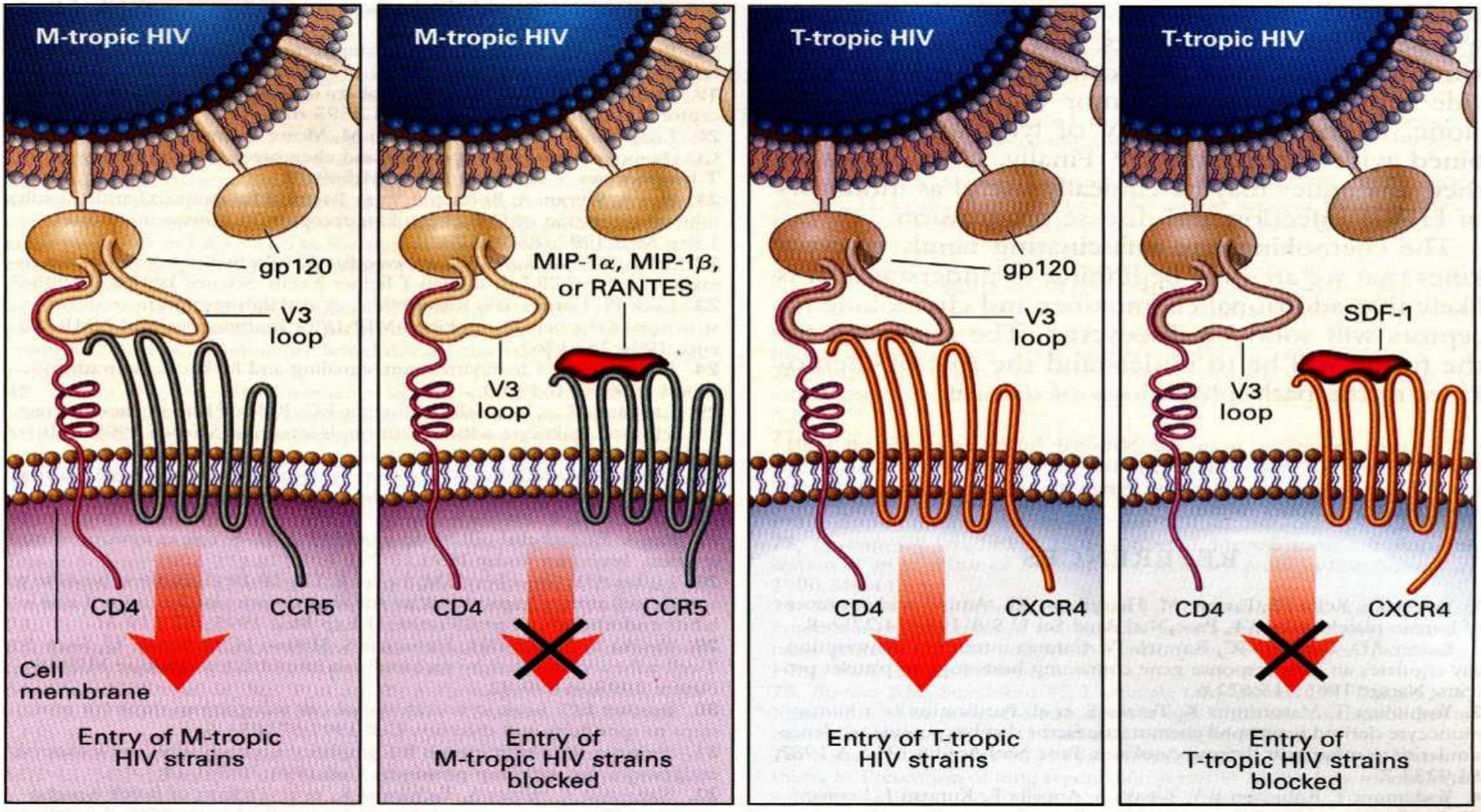
Antiretroviral therapy (2002-2009)



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

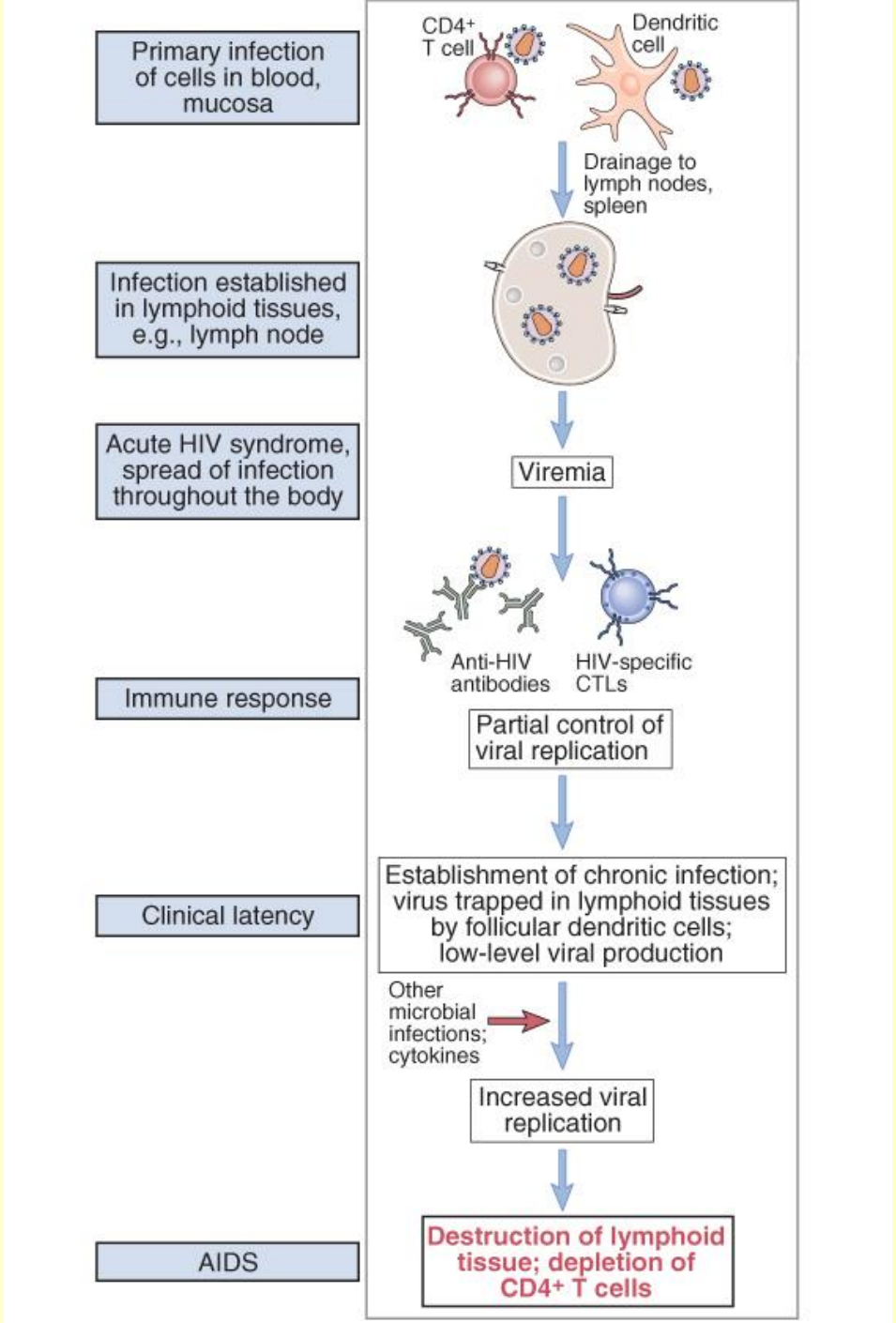
World Health Organization

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