Immunodeficiencies

Christine Schütt

cs

Ten warning signs of immunodeficiency

Two or more of the warning signs listed here suggest that an immune evaluation may be warranted

1. **Eight or more ear infections in 1 yr**
2. **Two or more sinus infections in 1 yr**
3. **Oral antibiotics produce little help; need for i.v. antibiotics to clear infections**
4. **Two or more episodes of pneumonia in 1 yr**
5. **Failure to thrive, with or without diarrhea**
6. **Recurring deep skin or organ abscess**
7. **Oral or cutaneous candidiasis after age 1**
8. **One or more episodes of meningitis, osteomyelitis, cellulitis, or sepsis**
9. **History of autoimmune disease, lymphadenopathy, or splenomegaly**
10. **Family history of immunodeficiency**

Hamilton R, Cunningham-Rundles, C. in
Manual of Clinical Immunology (Rose, Hamilton, Detrick, ed.) 2002

Algorithm for evaluation of frequent infections

INITIAL EVALUATION
History, Physical examination
Height and Weight
Family history
Complete blood count, Platelet count
Culture and X Ray results

If two or more from Table “Ten warning signs“ and HIV negative

IMMUNOGLOBULINS / ANTIBODIES COMPLEMENT
Quantitative Immunoglobulins
Antibody to Tetanus, Diphtheria, Pneumococci
Isohemagglutinins
CH50

If above normal and / or failure to thrive, fungal and / or viral infections

T LYMPHOCYTE FUNCTIONS:
Skin testing, Tetanus, Mumps, Candida etc.
T cell counts
T cell subsets, CD4/CD8
Lymphocyte stimulation to mitogens or antigens

If above normal and / or if recurrent deep abscesses

PHAGOCYTIC EVALUATION:
Absolute Neutrophil counts
IgE level
NBT reduction, Dihydrorhodamine oxidation
Chemiluminescence

Hamilton R, Cunningham-Rundles, C. in
Manual of Clinical Immunology (Rose, Hamilton, Detrick, ed.) 2002

Inborn immune deficiencies can affect all functions of the immune system

- B cell maturation or function
- T cell maturation or function
- T and B cells simultaneously
- cooperation of T and B cells
- Ag presentation
- phagocytosis
- complement
- trafficking / adhesion

www.esid.org

92 diseases
4000 patients
1 to1000 patients/disease

Congenital defects of phagocytic number and/or function part I

Disease	Affected cells	Functional defects	Inheritance	Features
Severe congenital neutropenia	N	-	AR	Subgroup with G-CSF-R mutation and MDS / AML
Cyclic neutropenia	Mainly N	-	AR	Oscillations of reticulocytes, platelets and other leukocytes
Leukocyte adhesion defect 1 [deficiency of beta chain (CD18) of LFA-1,Mac 1,p150,95]	N+M+L+NK	Chemotaxis, adherence, endocytosis	AR	Delayed cord separation, chronic skin ulcers, periodontitis, leukocytosis, defective T+ NK cell cytotoxicity
Leukocyte adhesion defect 2 (failure to convert GDP mannose to fucose)	Mainly N+M	Chemotaxis, rolling	AR	Delayed wound healing, chronic skin ulcers, periodontitis, mental retardation,leukocytosis Bombay blood group
Chediak-Higashi syndrome	Mainly N+M+NK	Chemotaxis	AR	Oculo-cutaneous albinism, giant granules of all nucleated cells, terminal, haemophagocytic syndrome
Specific granule deficiency	N	Chemotaxis	AR	N with bi-lobed nuclei

Report of a WHO Scientific Group, Clin.Exp.Immunol. 1997, 109, Suppl.1

Congenital defects of phagocytic number and/or function part II

Disease	Affected cells	Functional defects	Inheritance	Features
Schwachmann syndrome	N	Chemotaxis	AR	Anaemia, thrombocytopenia, pancreatic insufficiency, condrodysplasia, hypo-gammaglobulinaemia
Chronic granulomatous disease (a) X-linked CGD (deficiency of 91kD chain of cytochrome b)	N+M	Killing (faulty production of superoxide metabolites)	XL	McLeod phenotype*
(b) Autosomal recessive (deficiencies of 22kD chain of cytochrome b or P47 or P67 cytosol factors)	N+M	Killing-as above	AR	-
Neutrophil G6PD deficiency	N+M	Killing	XL	Anaemia
Myeloperoxidase deficiency	N	Killing	AR	-
IFNγ receptor deficiency	N+M+L+NK	Killing	AR	Extreme susceptibility to mycobacteria

* Some patients have deletions in the short arm of the X chromosome; in these patients additional features including McLeod retinitis pigmentosa and Duchenne muscular dystrophy may be found.

Report of a WHO Scientific Group, Clin.Exp.Immunol. 1997, 109, Suppl.1

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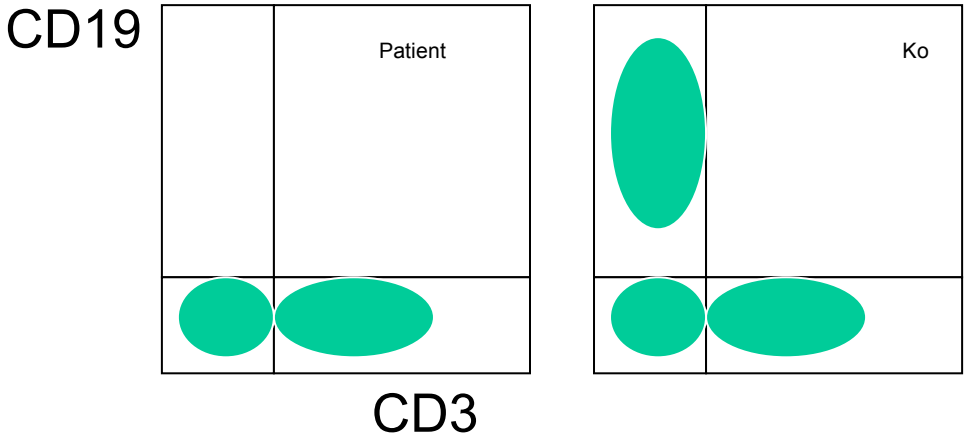
Ein 2-jähriger Junge kommt mit schwerer Pneumonie nachts in in Ihre Aufnahme. Ihnen fällt auf, dass er keine Tonsillen hat. Anamnestisch imponieren wiederholte Erysipele (Streptokokken-infektionen der Haut) und Otitiden. Das Kind ist regulär entwickelt. Die Eltern sind ob der häufigen Infektionen nicht beunruhigt, berichten aber, dass zwei Onkel mütterlicherseits in jungen Jahren (offenbar an Infektionen) verstarben. Der Junge hat vier gesunde Schwestern. Die Familie ernährt sich streng vegetarisch.

Was fällt Ihnen im Gegensatz zu den anderen Kollegen sofort ein?

Was veranlassen Sie sofort?
Was veranlassen Sie am nächsten Tag?
Was bei der Entlassung?

PRAXIS

Immunstatus: Immunglobuline fehlen
Komplementfaktoren normal



T Zellzahlen normal,
komplettes Fehlen der B Zellen.
normaler LTT

XLA

X-linked agammaglobulinemia

Predominantly antibody deficiencies part I

Associated designation	Serum Ig	Circulating B cells	Presumed pathogenesis	Inheritance	Associated features
1. X-linked agammaglobulinaemia	All isotypes decreased	Profoundly decreased	Mutations in *btk* gene	XL	-
2. X-linked hyper IgM syndrome	IgM and IgD increased or normal other isotopes decreased	IgM and IgD bearing cells present others absent	Unknown	XL	Neutropenia Thrombocytopenia Haemolytic anaemia gastrointestinal and liver involvement
3. Ig heavy-chain gene deletions	IgG1 or IgG2,IgG4 absent and in some cases IgE and IgA2 absent	Normal or decreased	Chromosomal deletion at 14q32	AR	-
4. κ Chain deficiency mutations at AR	Ig(K) decreased: antibody response normal or decreased	Normal or decreased κ-bearing cells	Point mutations at chromosome 2p11 in some patients	AR	-
5. Selective deficiency of IgG subclasses with or without IgA deficiency	Decrease in one or more IgG isotypes	Normal or immature	defects of isotype differentiation	Unknown	-

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Report of a WHO Scientific Group, Clin.Exp.Immunol. 1997, 109, Suppl.1

Predominantly antibody deficiencies part II

Associated designation	Serum Ig	Circulating B cells	Presumed pathogenesis	Inheritance	Associated features
6. Antibody deficiency with normal Igs	Normal	Normal	Unknown	Unknown	-
7. Common variable immunodeficiency	Various decreases of multiple isotypes	Normal or decreased	Variable; undetermined	Variable	
8. IgA deficiency	IgA1 and IgA2 decreased	Normal or decreased sIgA+	Failure of terminal differentiation in IgA+B cells	Variable	Autoimmune and allergic disorders
9.Transient hypo-gammaglobulinaemia of infancy	IgG and IgA decreased	Normal	Differentiation defect: delayed maturation of helper function	Unknown	Frequent in families with other IDs
10. Autosomal recessive agammaglobulinaemia	All isotopes decreased	Profoundly decreased	Intrinsic defect pre-B to B-cell differentiation	AR	-

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Report of a WHO Scientific Group, Clin.Exp.Immunol. 1997, 109, Suppl.1

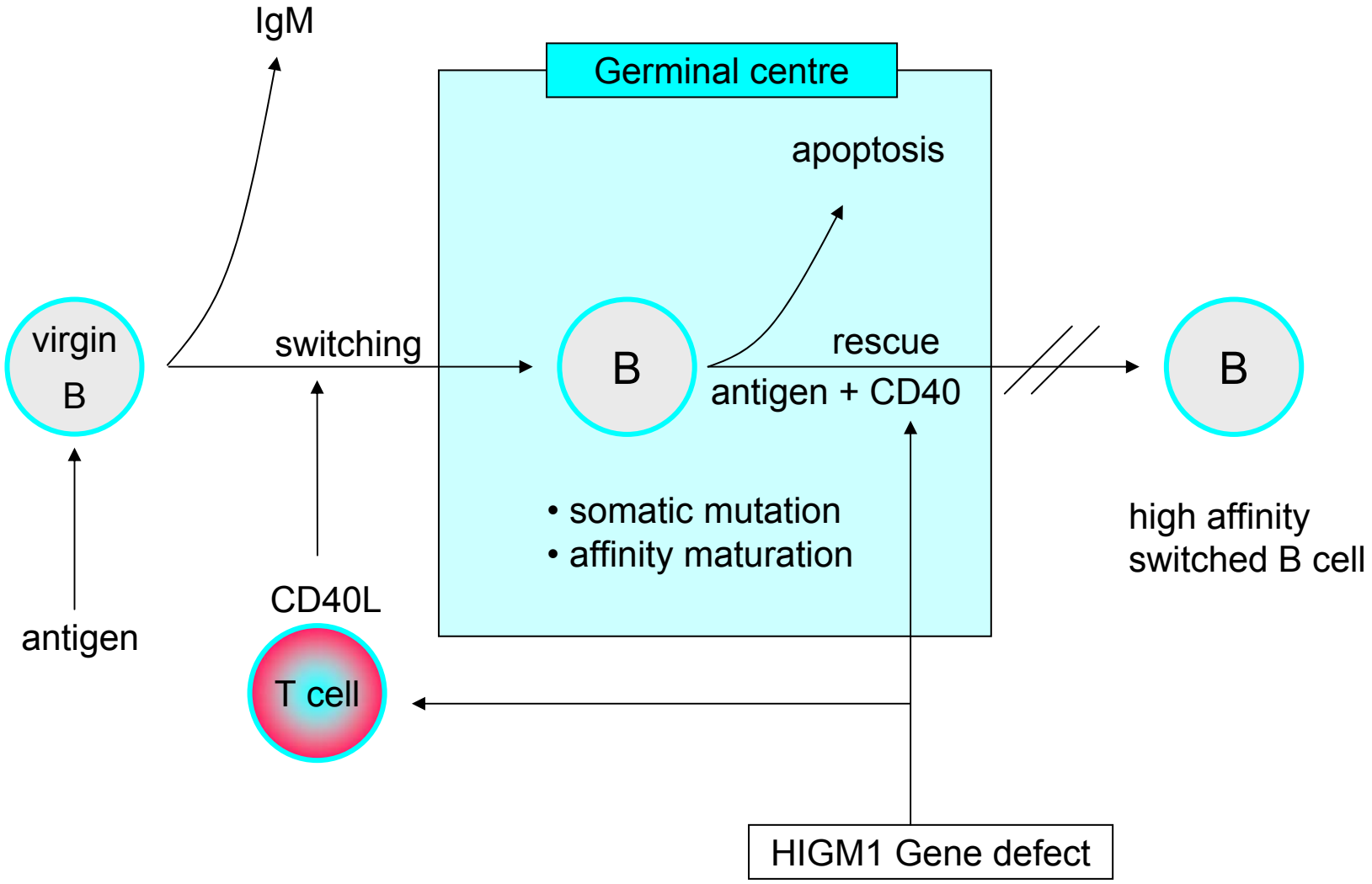
PRAXIS

Ein 5-jähriger Junge fiel bei der Vorschuluntersuchung durch starken Soorbefall und Bläschen auf der Mundschleimhaut auf. Sie bekommen das Kind überwiesen. Er ist weinerlich und ängstlich. Seit dem 1.Lebensjahr hatte er ständig wiederkehrende Sinusitiden, mit 3 Jahren eine Pneumocystis carinii - Pneumonie. Die Familienanamnese bietet keinen Hinweis auf Infektneigungen. Die Eltern erscheinen gestresst durch das permanent kränkelnde Kind.

Laborbefunde:
β-hämolysierende Streptokokken im Rachenabstrich,
keine spezifischen Antikörpertiter gegen Streptokokken,
normale B-,T-,NK-Zell- und Monozytenzahlen,
Neutropenie,
Blutgruppe 0, antiA 1:3200, antiB 1:800 (stark erhöht),
IgA und IgG nicht nachweisbar, stark erhöhtes IgM

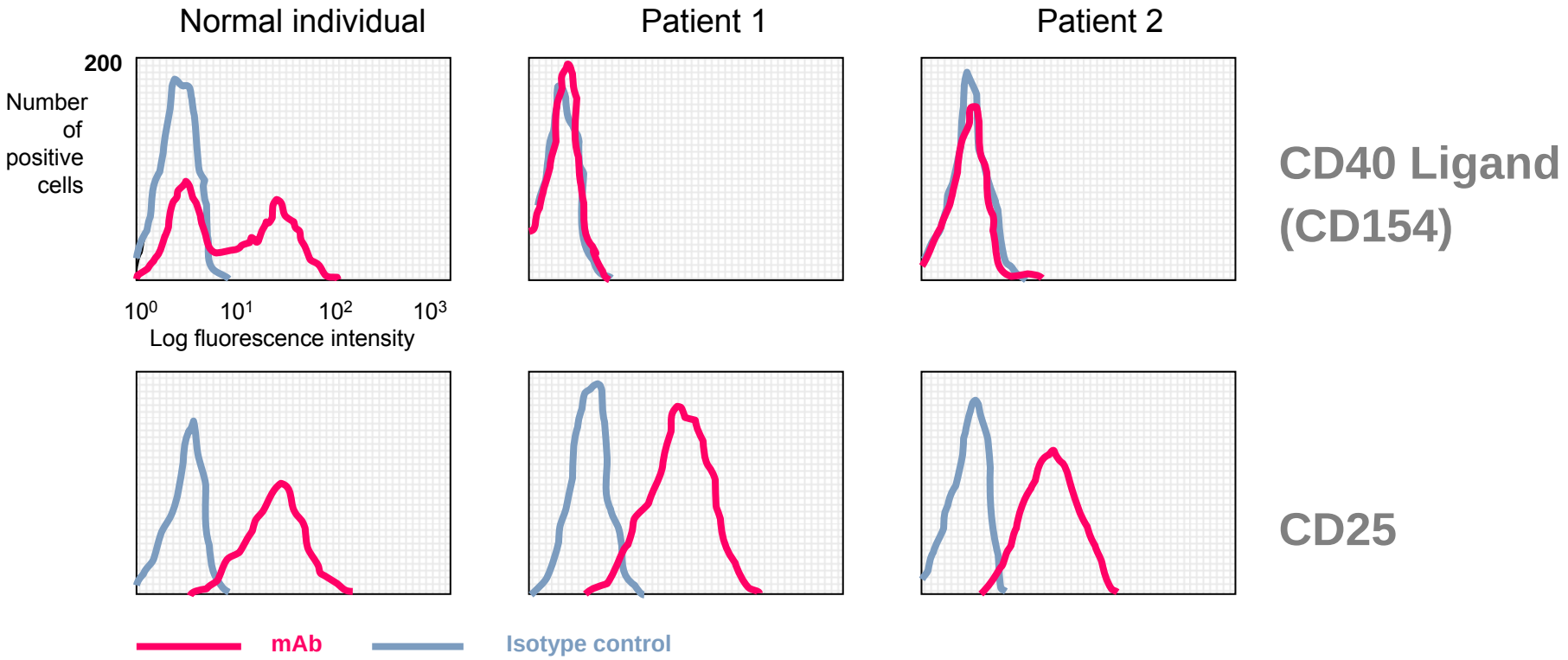
Welche Verdachtsdiagnose wollen Sie abklären lassen?

CD40 ligand function



Defective CD40L expression in HIGM1 would interfere with cytokine-induced heavy-chain switching and rescue of high-affinity switched cells in the germinal centre. The defect in non-X-linked forms of HIGM has not been identified.

X-linked hyper-IgM syndrome



T cells from a healthy individual and from two patients with X-linked hyper-IgM syndrome were stimulated in vitro and analysed for the expression of CD40-Ligand and of CD25 (as a control). The T cells from the hyper-IgM patients do not express CD40-Ligand

CD 154 expression

whole blood cell cultures
5h stimulation with PMA / Ionomycin

	$CD154^+$ $CD4^+$	
	% positive cells	fluorescence intensivity
patient K., M.	0	0
healthy volunteer A	71	284
healthy volunteer B	60	192

CD40L Defect

no class switching → IgM , but no IgG, IgA

no costimulatory function in T cell activation → no lymphocytosis during infection

no restimulation of APC → altered cytokine release
no GM-CSF production by macrophages
→ neutropenia

no regular TH1 response to bacteria or fungi:
→ sore
→ bacterial infection

therapy : **Ig substitution**
G-CSF, GM-CSF

Combined immunodeficiencies part I

Designation	Serum Ig	Circulating B cells	Circulating T cells	Presumed pathogenesis	Inheri-tance	Associated features
1. T-B+ SCID						
(a) X-linked (γ c deficiency)	Decreased	Normal or increased	Markedly decreased	Mutations in γ chain of IL2,4,7,9,15 receptors	XL	
(b) Autosomal recessive (Jak3 deficiency)	Decreased	Normal or increased	Markedly decreased	Mutation in Jak3	AR	
2. T-B- SCID						
(a) RAG 1/2 deficiency	Decreased	Markedly increased	Markedly decreased	Mutations in RAG 1/2 genes	AR	
(b) Adenosine deaminase (ADA) deficiency	Decreased	Progressive decrease	Progressive decrease	T-cell and B-cell defects from toxic metabolites (e.g. dATP,S-adenosyl homo-cysteine) due to enzyme deficiency	AR	
(c) Reticular dysgenesis	Decreased	Markedly decreased	Markedly decreased	Defective maturation of T and B cells and myeloid cells (stem cell defect)	AR	Granulocytopenia Thrombocytopenia
3. X-linked hyper IgM syndrome	IgM & IgD increased or normal;other isotypes decreased	IgM & IgD bearing cells present other absent	Normal	Mutations in CD40 ligand gene	XL	Neutropenia Thrombocytopenia Haemolytic anaemia gastrointestinal & liver involvement

Report of a WHO Scientific Group, Clin.Exp.Immunol. 1997, 109, Suppl.1

Combined immunodeficiencies part II

Designation	Serum Ig	Circulating B cells	Circulating T cells	Presumed pathogenesis	Inheri-tance	Associated features
4. Purine nucleoside phosphorylase (PNP) deficiency	Normal or decreased	Normal	Progressive decrease	T-cell defect from toxic metabolites (e.g. dGTP) due to enzyme deficiency	AR	Autoimmune haemolytic anaemia: neurological symptoms
5. MHC class II deficiency	Normal or decreased	Normal	Normal, decrease CD4 numbers	Mutation in transcription factors (CIITA or RFX-5 genes) for MHC class II molecules	AR	
6. CD3 γ or CD3 ε deficiency	Normal	Normal	Normal	Defective transcription of CD3 γ or CD3 ε chain	AR	
7. ZAP-70 deficiency	Normal	Normal	Decreased CD8, normal CD4	Mutations in ZAP-70 kinase gene	AR	
8. TAP-2 deficiency	Normal	Normal	Decreased CD8, normal CD4	Mutations in TAP-2 gene	AR	MHC class I deficiency

Report of a WHO Scientific Group, Clin.Exp.Immunol. 1997, 109, Suppl.1

Other well-defined immunodeficiency syndromes

Designation	Serum Ig and antibodies	Circulating B cells	Circulating T cells	Genetic effect	Inheritance	Associated features
1. Wiskott-Aldrich syndrome	Decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA and IgE	Normal	Progressive decrease	Mutations in WASp gene; cytoskeletal defect affecting haematopoietic stem cell derivatives	XL	Thrombocytopenia; small defective platelets; eczema; lymphomas; autoimmune disease
2. Ataxia-telangiectasia	Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased	Normal	Decreased	Mutations in A-T gene (ATM); disorder of cell cycle check-point pathway leading to chromosomal instability	XL	Ataxia; telangiectasia; increased alpha fetoprotein; lympho-reticular and other malignancies; increased X-ray sensitivity
3. DiGeorge anomaly	Normal or decreased	Normal	Decreased or normal	Contiguous gene defect in 90 % affecting thymic development	De novo defect or AD	Hypoparathyroidism: conotruncal mal-formation; abnormal facies; partial mono-somy of 22q11-pter or 10p in some patients

Report of a WHO Scientific Group, Clin.Exp.Immunol. 1997, 109, Suppl.1

Incidence of the primary immunodeficiency diseases

Immune defect	Estimated frequency
Selective IgA deficiency	1:400 to 1:1,000
C2 deficiency	1:10,000 to 1:28,000
DiGeorge anomaly	1:66,000
Common variable immunodeficiency	1:83,000
Mucocutaneous candidiasis	1:103,000
Chronic granulomatous disease	1:181,000
X-linked agammaglobulinemia	1:103,000

Das Wichtige ist, dass Sie daran denken, einen Immunologen zu konsultieren

Hamilton R, Cunningham-Rundles, C. in
Manual of Clinical Immunology (Rose, Hamilton, Detrick, ed.) 2002

PRAXIS

Ein männlicher retardierter Säugling wird aus einem peripheren Krankenhaus mit Verdacht auf einen Immundefekt überwiesen. Er ist 8 Monate alt und muss permanent wegen akuten Infekten stationär aufgenommen und antibiotisch behandelt werden.

Welche immunologische Stufendiagnostik ist jetzt durchzuführen?

PRAXIS

Befund

Nr: 4727

FACS - Analyse

	Gpt/l	%
Leukozyten:	2,10	
Lyphozyten:	0,85	40,33
Monozyten:	0,37	17,52
Granulozyten:	0,89	42,15
T-Zellen:	0,51	24,19
T4 (helper)	0,0045!!	0,21!!
T8 (z.tox/supp.)	0,48	22,91
B-Zellen:	0,18	8,57
NK-Zellen:	0,19	9,24

T4/T8 = 0,01 !!!

3.

Phagozytosetest

	pos. Granu.	Flour.-intens.
0°C	1,90 %	16
37°C	98,90 %	872

1.

2.

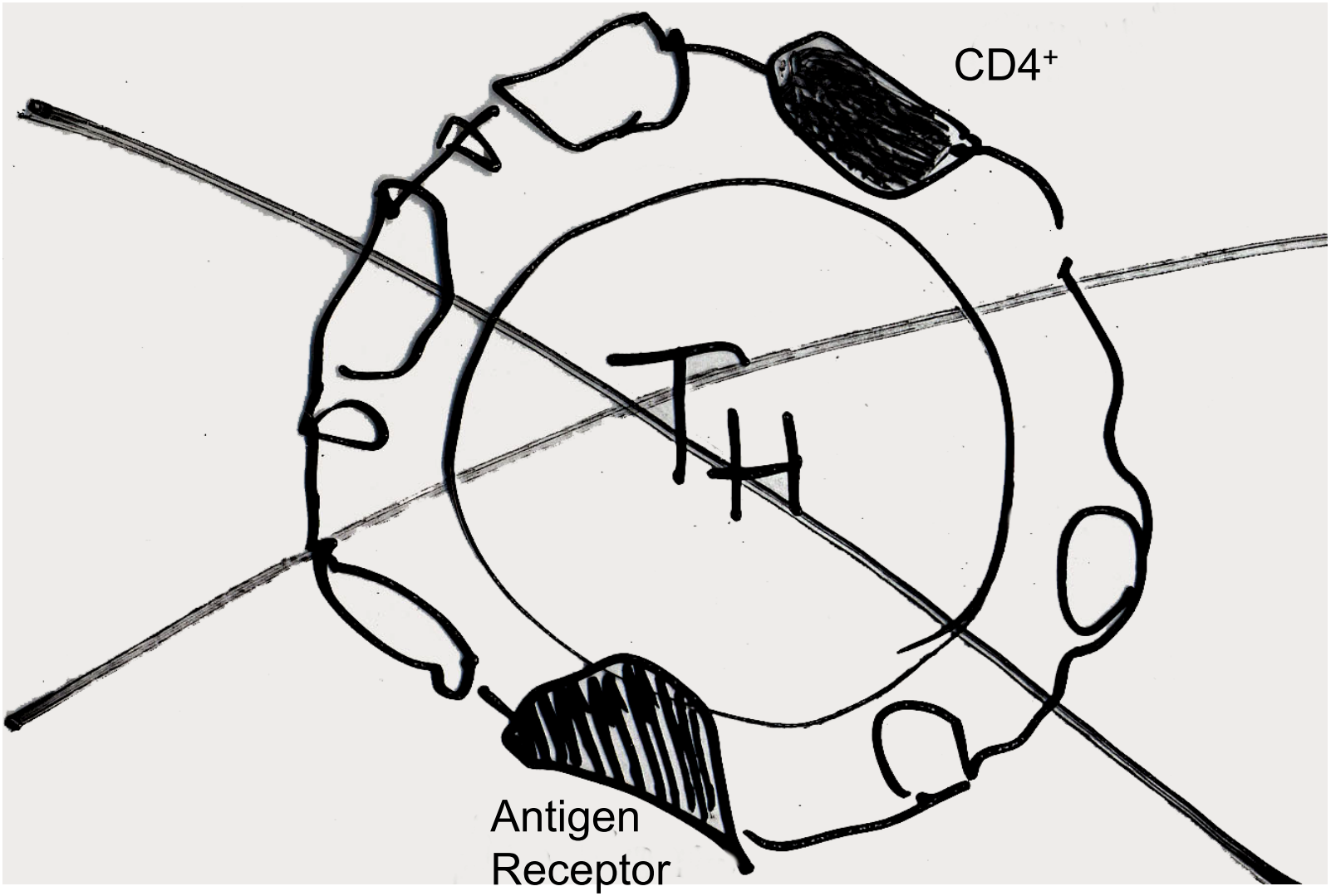
Antikörper gegen		Lymphozyten-Gate (%)
CD14	Monozyten , (Gr.z.)	0,47
CD19	B-Zellen	21,11
CD19+CD5+		13,46
CD5	T-Ly , B-Subset	54,53
CD4	T-Helfer , (Monozyten)	0,83
CD4+CD8+	unreife T-Zellen	0,00
CD8	zy.tox./Supp.T-Z , NK	61,07
CD16 , 56	NK-Z. , T-Sub. , gr., Mo.	25,17
CD16 , 56+CD3+		2,25
CD3	T-Lymphozyten	59,42
CD3+HLA-DR+	akt. T-Zellen	9,38
HLA-DR	B-Ly , Mo , akt.T-Ly , NK	32,19
CD10	CALLA , B-Vorl. , Gr.z.	0,00
CD10+HLA-DR+	CALLA , B-Vorl.	0,00
HLA-DR	B-Ly , Mo , akt.T-Ly , NK	52,72
CD45RA		75,90
CD45RA+CD4+	naive T-Helferzellen	0,05!!
CD45RO		23,99
CD45RO+CD4+	Memory-T-Helferzellen	0,52
CD57	NK-Zellen , T.-Sub.	20,27
CD8+CD57+		18,61!!
CD13	gran./monoz. Reihe	1,09
CD34	Progenitorzellen	0,00
CD13+CD34+		0,02
IgM	Oberfl.-IgM	16,40
IgA	Oberfl.-IgA	0,05
IgD	Oberfl.-IgD	9,75
IgG	Oberfl.-IgG	0,68
kappa	Ig auf B , Mo , Gr , (NK)	10,89
kappa+CD19+		9,91
lambda	Ig auf B , Mo , Gr , (NK)	11,15
lambda+CD19+		9,22
CD3+CD4+	T-Helfer-Z.	0,53!!
CD3+CD8+	zytotx./Suppr.-T-Z.	56,80

4.

csFall 12a

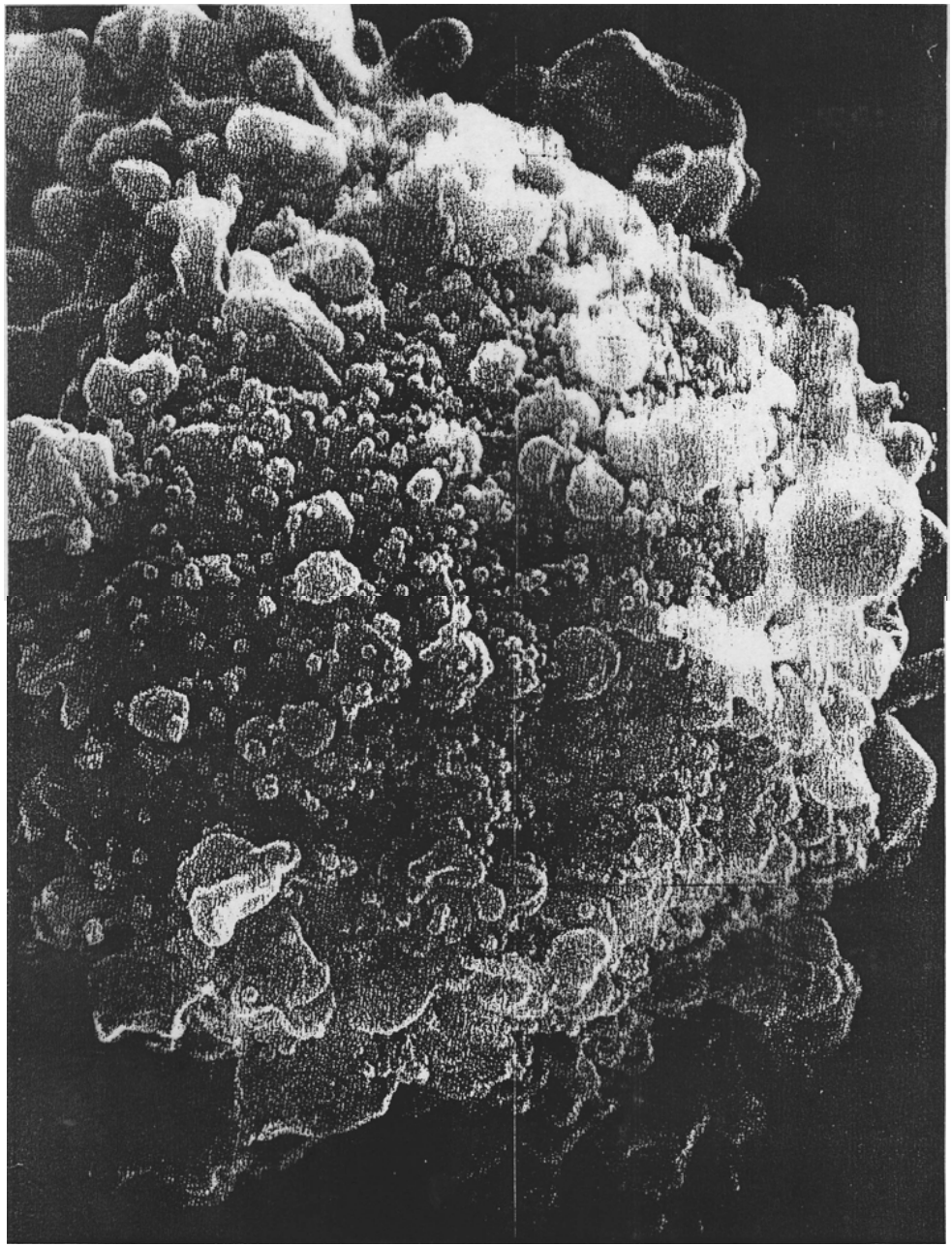
Aquired Immunodeficiency Syndrome

Elimination of T-Helper Cells



Breakdown of Immune Competence

HIV-infected T cell



Scientific American 1988

Absolute T cell number

1ml whole blood	2 Mio lymphocytes
	2 Gpt/l

~ 70 % CD3+

among them 45 % CD4+ (TH)
25 % CD8+ (CTL)

~ 10 % NK
~ 10 % B
~ 10 % monocytes

1,2 Gpt/l	T
0,8 Gpt/l	TH
<0,2 Gpt/l (200/µl)	TH increased infection risk !

0,0045

cs163

A new theory on the origin of Aids

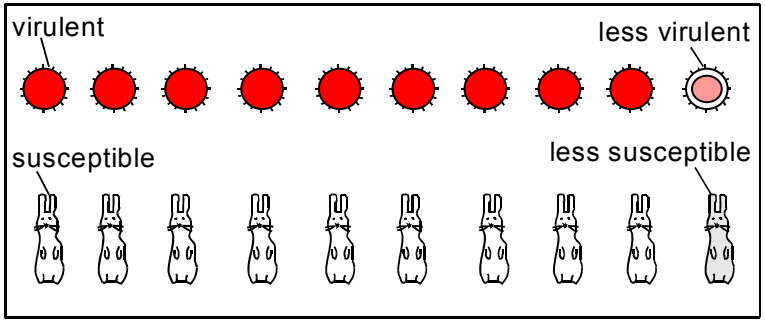
Edward Hooper „The River“ (Little, Brown):

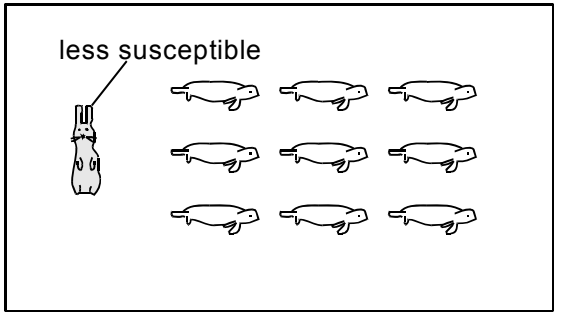
virus contaminated Polio-Vaccine
produced in chimpanzees (with endogenous SIV-1):

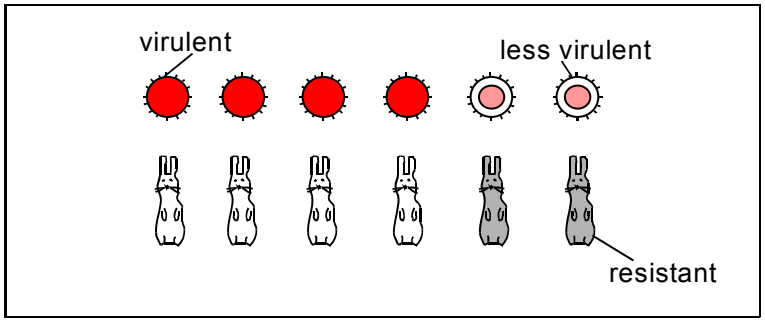
1957 – 1960	Poliomyelitis vaccination of 1 million people of Ruanda, Burundi and Kongo
1959*	first (now documented) HIV infection in Kinshasa
1960 – 80	28 new cases in Central Africa
1976	Zaire → Haiti → USA (1978/79) → Europe → etc.

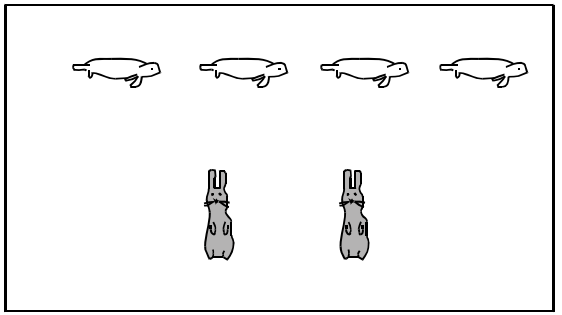
*in the time before 1959 no HIV- positive sera in Central Africa

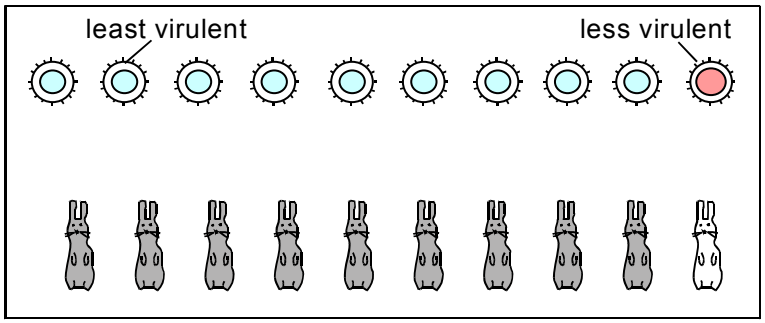
What we learned from Myxomatosis in Australia

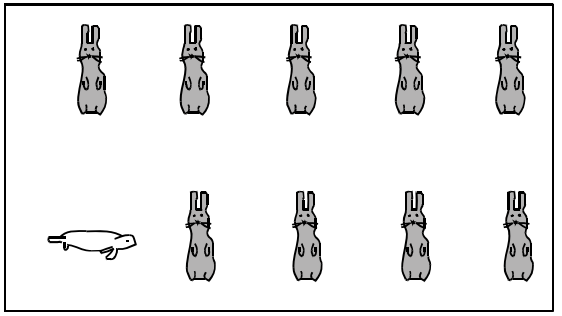












CASE OF THE RESISTANT RABBITS illustrates the mutual evolution of a virus and its host. Myxoma virus was introduced into Australia in an effort to get rid of wild rabbits. Virulent viruses killed most of the rabbits, but a few animals happend to be less susceptible; they survived (right) and multiplied. The virulent viruses eventually killed them, but a few truly resistant rabbits were spared. Meanwhile natural selection favored the evolution of avirulent virus strains (because a virus does best of its host survives). Eventually a resistant rabbit population was established, coexisting with a largely avirulent virus.

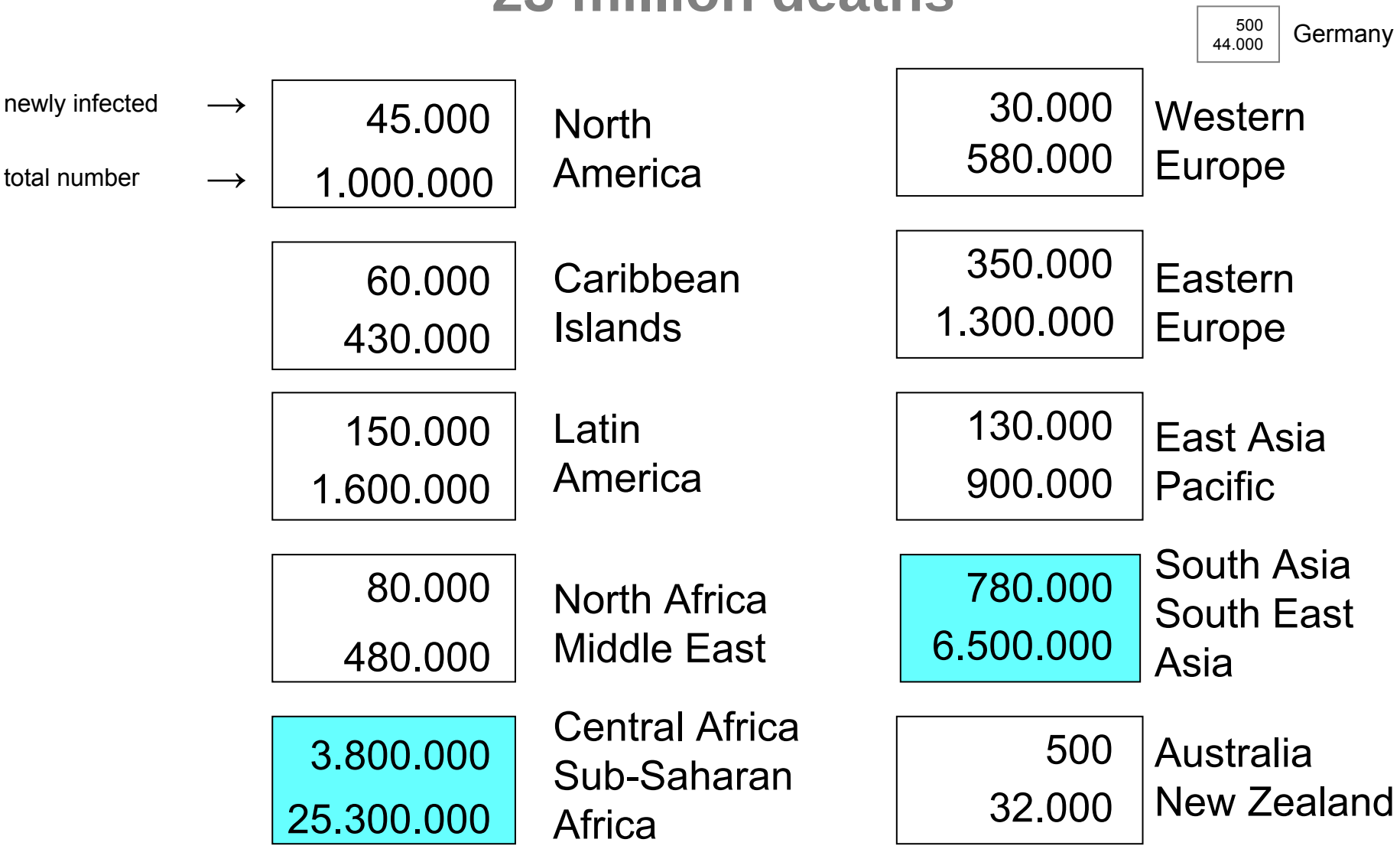
Grundlagen der Immunologie für Mediziner

mittwochs / HS Innere Medizin
5. Semester

Datum	Themenkatalog
05.11.08, 15.00-17.00 Uhr	Einführung. Das Immunsystem
12.11.08, 15.00-17.00 Uhr	Antikörper
19.11.08, 15.00-17.00 Uhr	Antikörperfunktionen
26.11.08, 15.00-17.00 Uhr	Zelluläre Immunität
03.12.08, 15.00-17.00 Uhr	Zytokine, Immunregulation
10.12.08, 15.00-17.00 Uhr	Labormethoden
17.12.08, 15.00-17.00 Uhr	Pathogene Immunreaktionen
07.01.09, 15.00-17.00 Uhr	Allergien
14.01.09, 15.00-17.00 Uhr	Tumor / Transplantationsimmunologie
21.01.09, 10.00-11.00 Uhr	Autoimmunität
28.01.09, 10.00-11.00 Uhr	Immundefekte
04.02.09 10.00-12.00 Uhr	Immuntherapien
11.02.08 verlegt auf 04.02.	Immuntherapien
18.02.08 10.00-12.00 Uhr	Repetition
Klausur :	20.2.09 15.30-16.15 Uhr HS Makarenkostr.

erscheint am 6.2.2009,
bei amazon vorbestellbar

Aids worldwide : 38 million infected people and 23 million deaths



UNAIDS 2004

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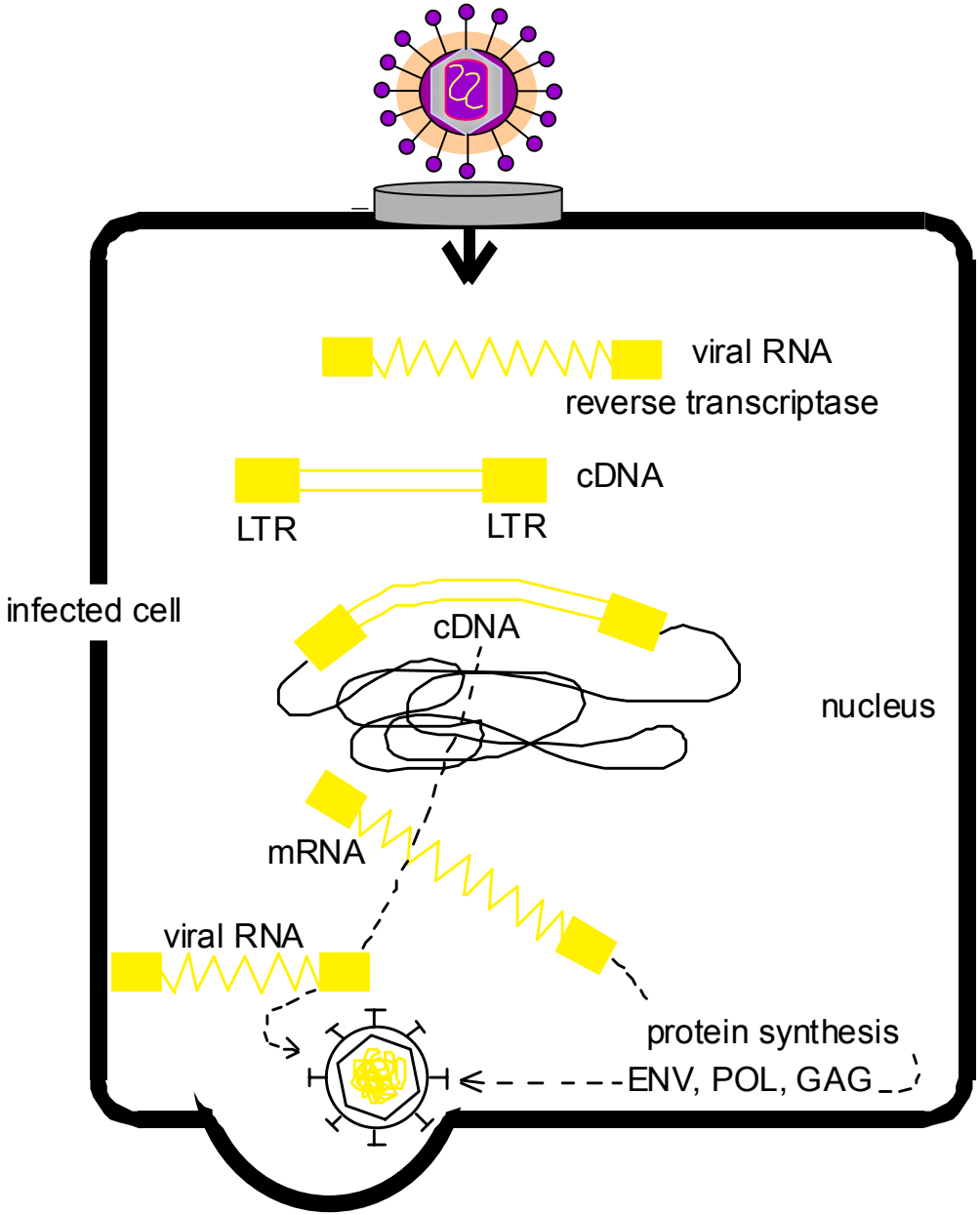
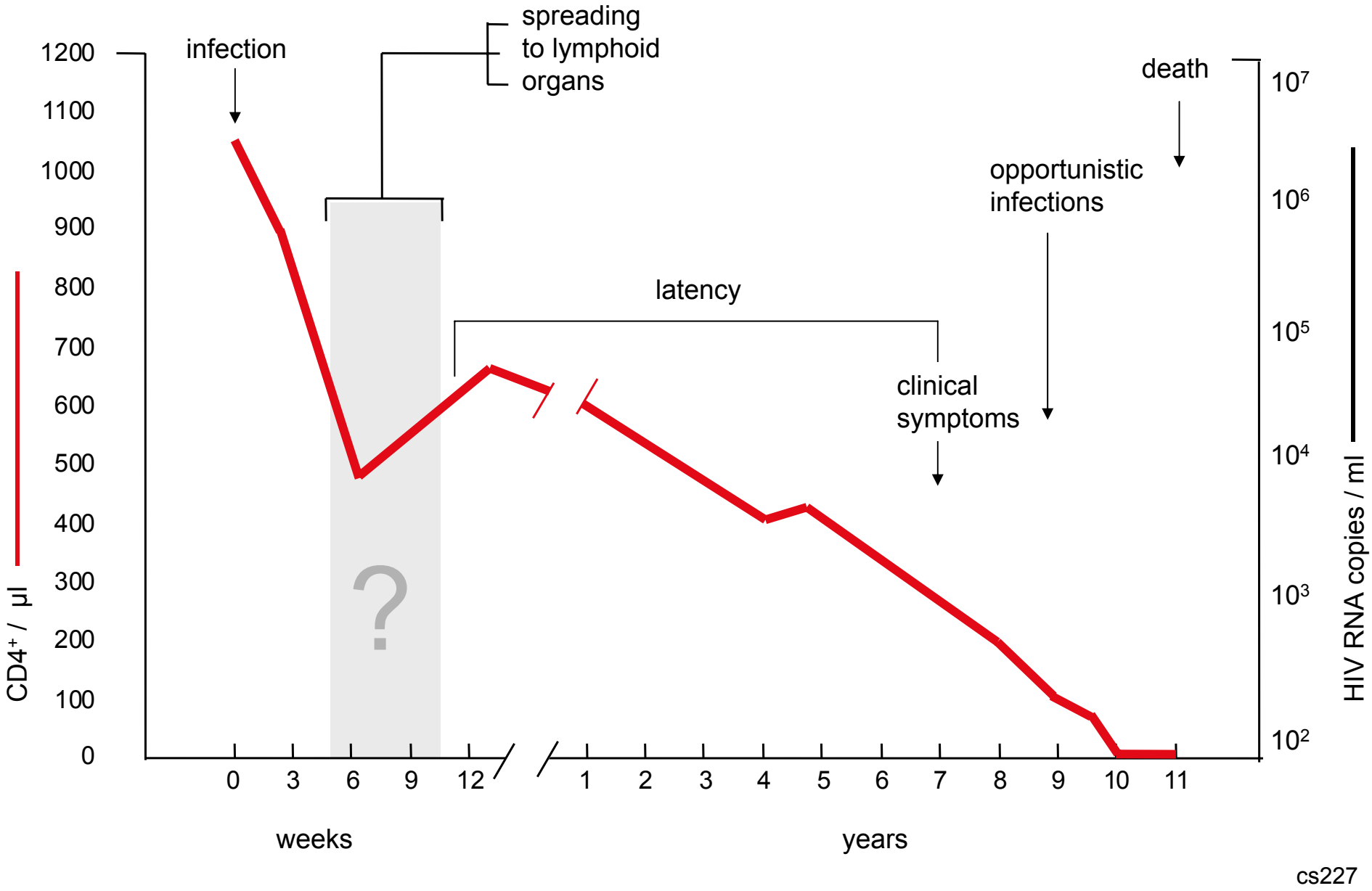
Viral Replication



Time course of HIV infection



cs227

Virus load

RNA in plasma;
$7 \cdot 10^{10}$ particle/d
half life time 2-3 days

< 10.000 virus equivalents
→ long term survivors

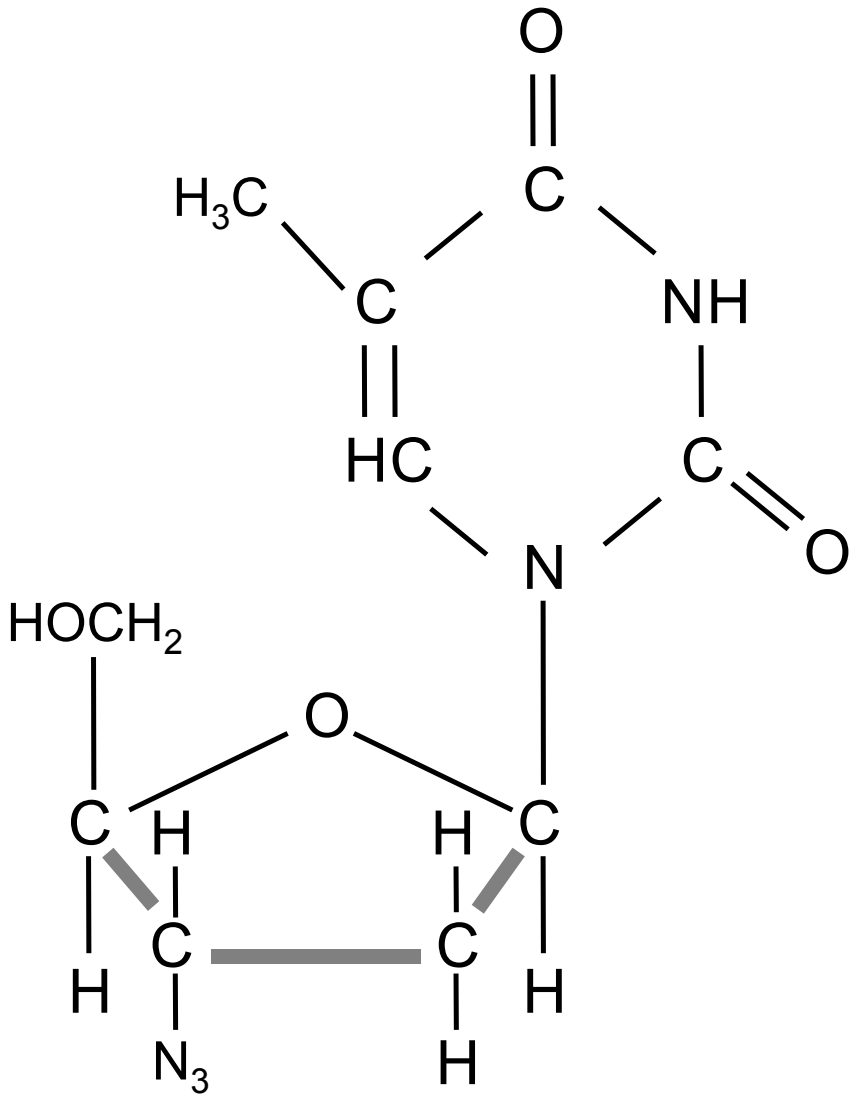
< 100.000 in pregnant woman
→ no transmission

HIV therapy as early as possible

A free of symptoms , 5.000 RNA copies / ml
<500 $CD4^+$ / µl

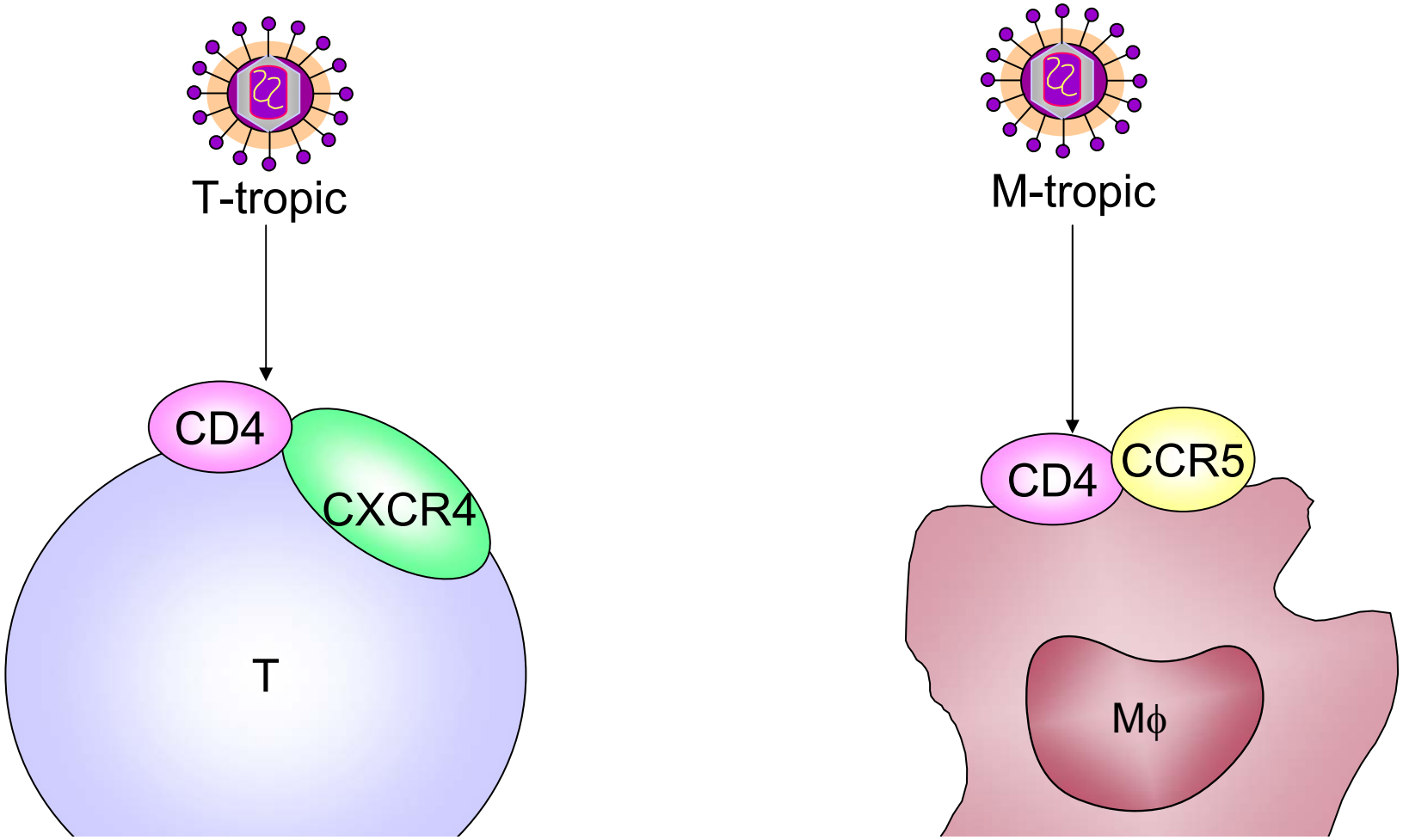
B free of symptoms , 30.000 RNA copies / ml
>500 $CD4^+$ / µl

AZT



3´Azido-2´,3´-dideoxythymidine (AZT, zidovudine)

HIV entry



CCR5, the receptor for MIP-1α, MIP-1β and RANTES, was identified as the major co-receptor for macrophage-tropic strains of HIV-1. The chemokine receptor CXCR4 (fusin), was identified as the co-receptor for T-cell-tropic strains of HIV…

HIV progression

progressive ⟷ non-progressive HIV infection

increased apoptosis
of $CD4^+$ and $CD8^+$

rapid deletion of $CD8^+$

$CD8^+$ produce C-C chemokines *

resistance to HIV : mutation of CCR5
(homocygous defect in
1% of Caucasians!)

* African Green Monkey (SIV^+):
lymphokine suppressor activity

HIV infection

1. → in latence phase active virus production : $7 \cdot 10^{10}$ particle / d

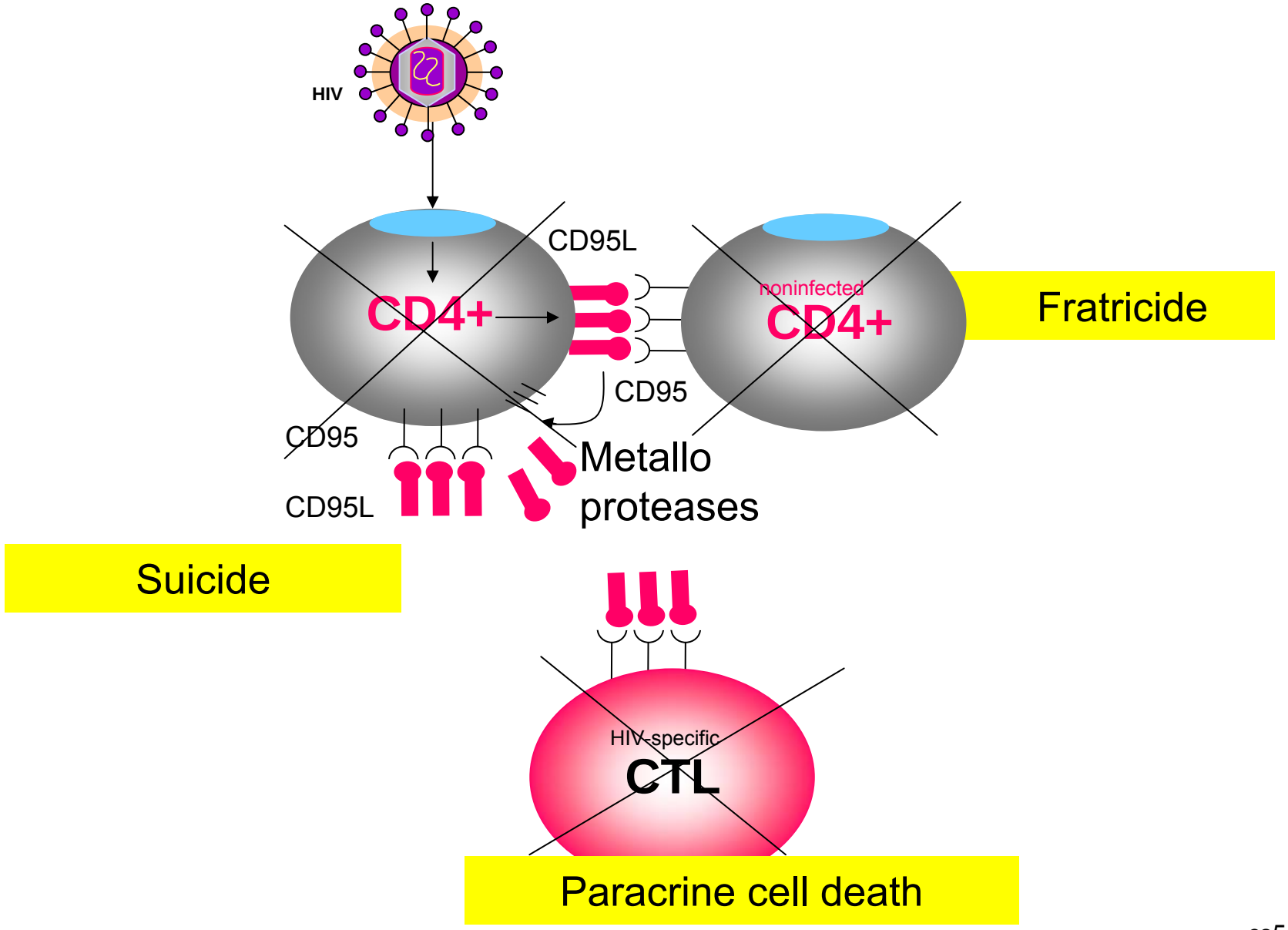
2. → host´s cytokine production:

proinflammatory	→	viral replication ↑
antiinflammatory	→	viral replication ↓
β – chemokines (C-C) RANTES, MIP - 1α MIP - 1β	→	viral replication ↓

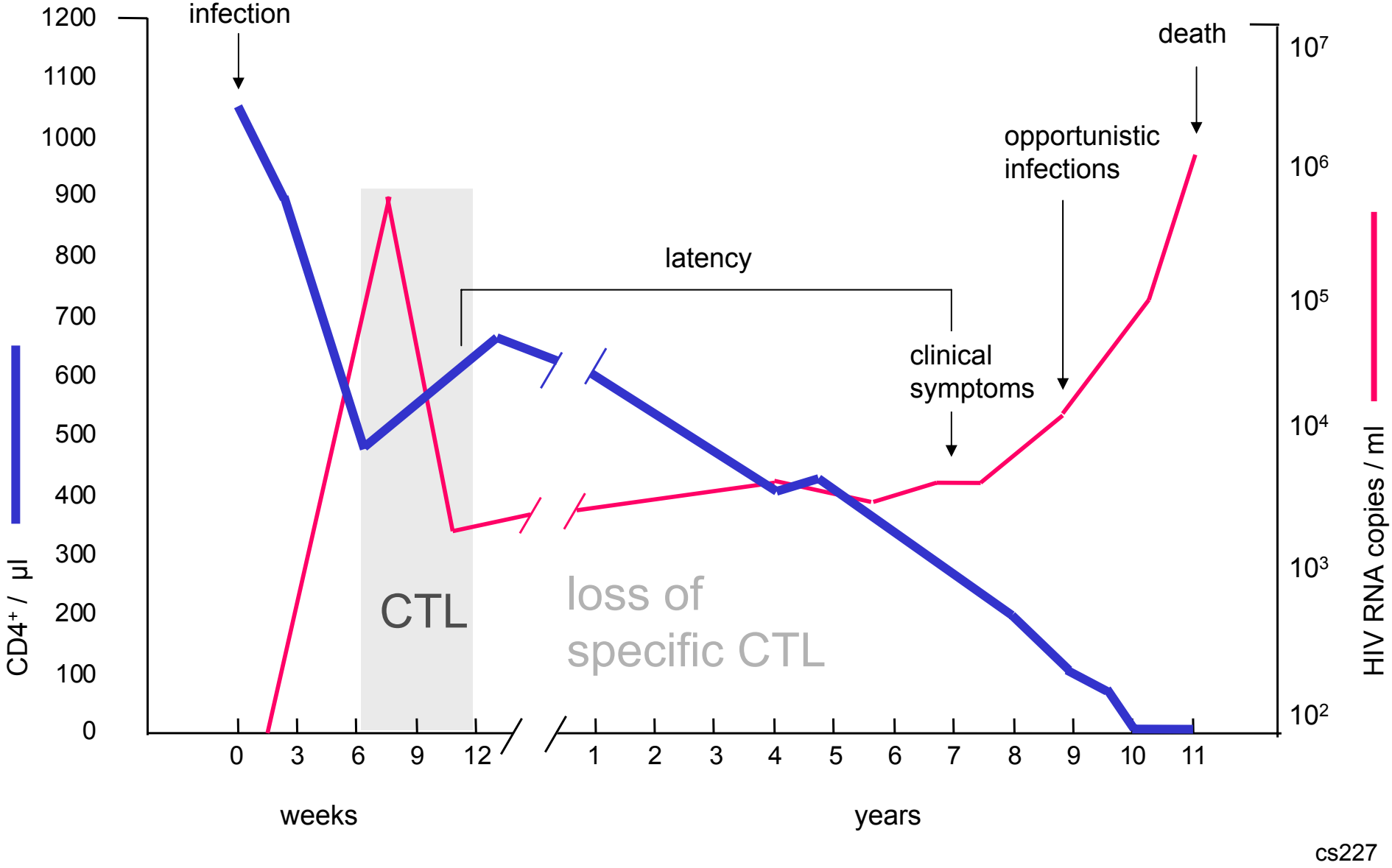
3. → host´s $CD8^+$ T cells ⟶ soluble suppressor factors (e.g. IL16) ⟶ long term survivors

4. → host´s CD8+ T cells ⟶ CTL response

Apoptotic loss of infected and noninfected cells



Time course of HIV infection



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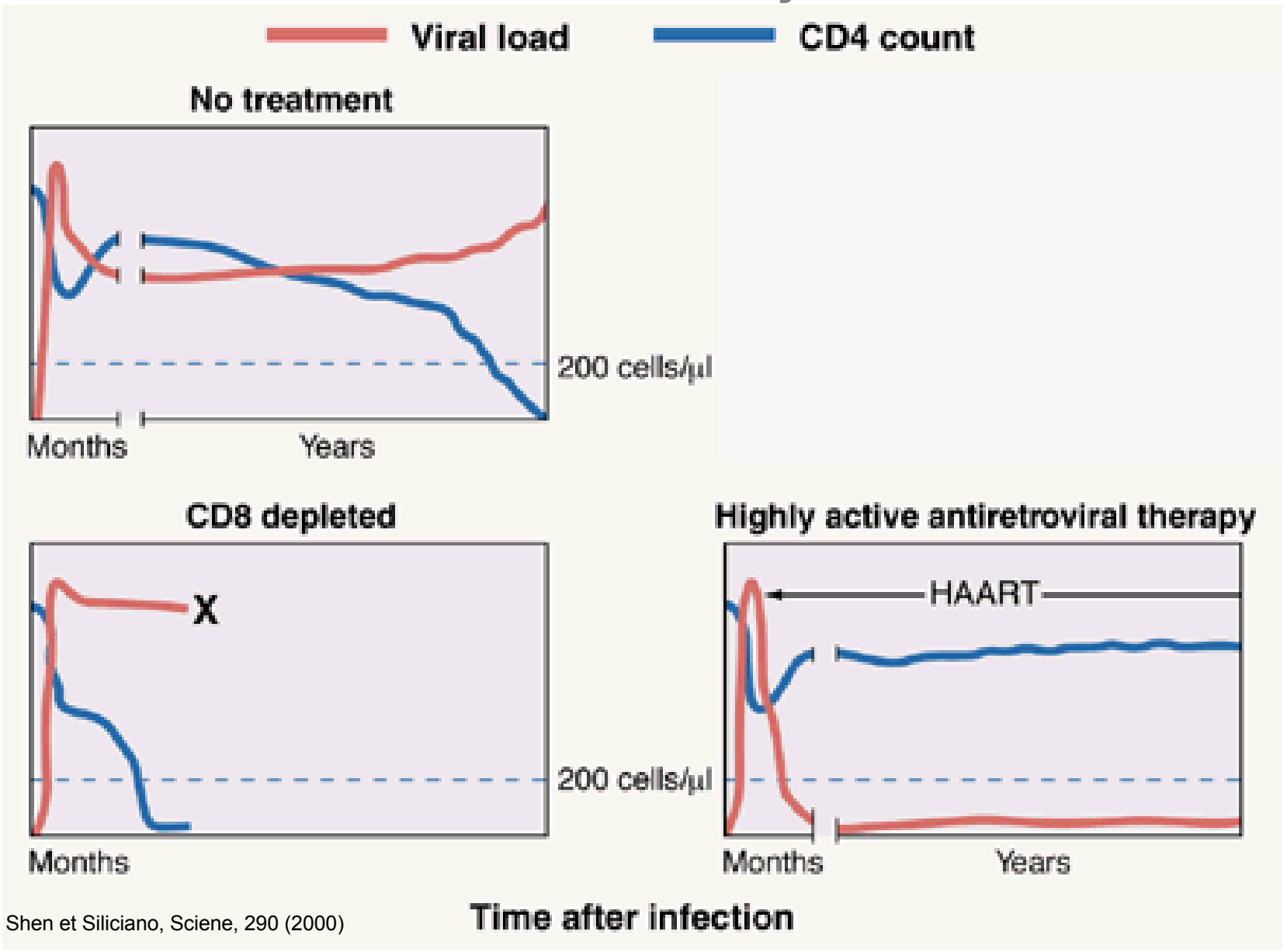
Preventing AIDS but not HIV-1 Infection with a DNA vaccine by inducing strong TH1- and specific CTL response in rhesus monkeys



Shen et Siliciano, Sciene, 290 (2000)

PRAXIS

Als Betriebsarzt eines Universitätsklinikums untersuchen Sie eine einzustellende 23-jährige Op-Schwester. Alle klinischen und paraklinischen Untersuchungen sind o.B. Bei der Inspektion des Rachenraumes findet sich eine 1.2 cm große Leukoplakie. Die Frau macht psychisch einen auffälligen Eindruck. Sie bestätigt auf Nachfrage, etwas verblüfft, dass Personen in ihrer Umgebung eine Wesensänderung an ihr seit einem halben Jahr feststellten.

Welchen Verdacht müssen Sie ausschließen?

Welche Kollegen sollten sie konsultieren?

Welche Diagnostik wollen Sie einleiten?

Was ist dazu notwendig?