Genitale Herpes-Infektionen

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Joint Symposium
PEG/DGN/DSTDG

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Der Herpes genitalis

E.E.Petersen (Gynäkologie), H.W.Doerr (Virologie G.Gross (Dermatologie/Venerologie) et al.. Deutsches Ärzteblatt 96(1999), A-2359-64
i.A. des Deutschen Herpes Management Forums der PEG

Genital herpes

R.Gupta, T.Warren, A.Wald
Lancet 370(2007), 2127-37

Primärerkrankung:

- Frühsymptome: Brennen beim Wasserlassen.
- Bläschen und Erosionen sind über weite Teile des Genitales gestreut. Regionale LK++.
- Schmerzhaftigkeit.
- Zu 2/3 der Fälle systemische Symptome wie Fieber, Kopf-/Rücken-/Muskelschmer-zen. Dauer bis zu drei Wochen.
- Manifestationsindex allgemein: 50%
- Manifestationsindex typ. Symptome: 30%

Cave sub partu graviditatis: Hohes Risiko für Herpes neonatorum generalisatus

Der Herpes genitalis II

Rezidivsymptomatik

- Umschriebene, gruppierte Bläschen und Erosionen
- Lymphknoten (+) oder + Schmerzhaftigkeit
- Dauer: 2-7 Tage
- Manifestationsindex: 85% der Patienten mit primärem H.g
- Rezidivhäufigkeit 1- >12/J.

Sub partu graviditatis: Risiko des Herpes neonatorum generalisatus

Petersen et al., 1999; Gupta et al. 2007

Herpes genitalis III

Differentialdiagnose:

Candida albicans Vulvitis, Behcet-Syndrom, Trichomoniasis, Verletzungen, Vulvitis/Balanitis plasmacellularis, **Zoster progenitalis**,

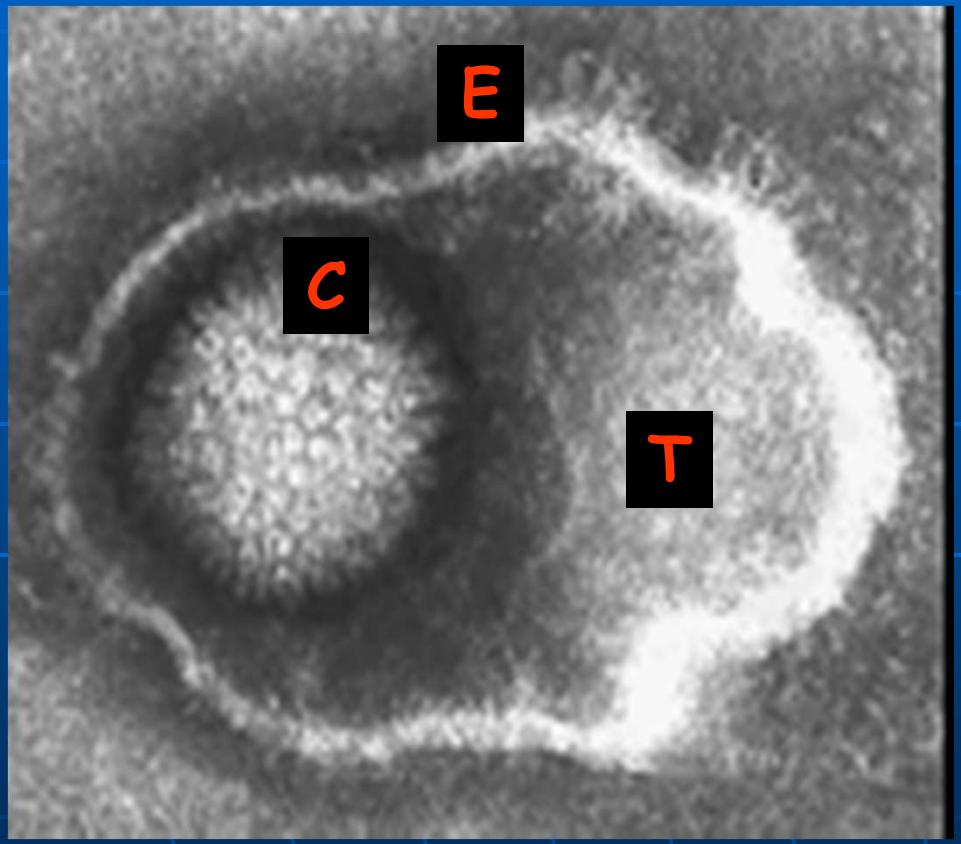
Pemphigus vulgaris, bullöses Pemphigoid, Molluscum contagiosum.

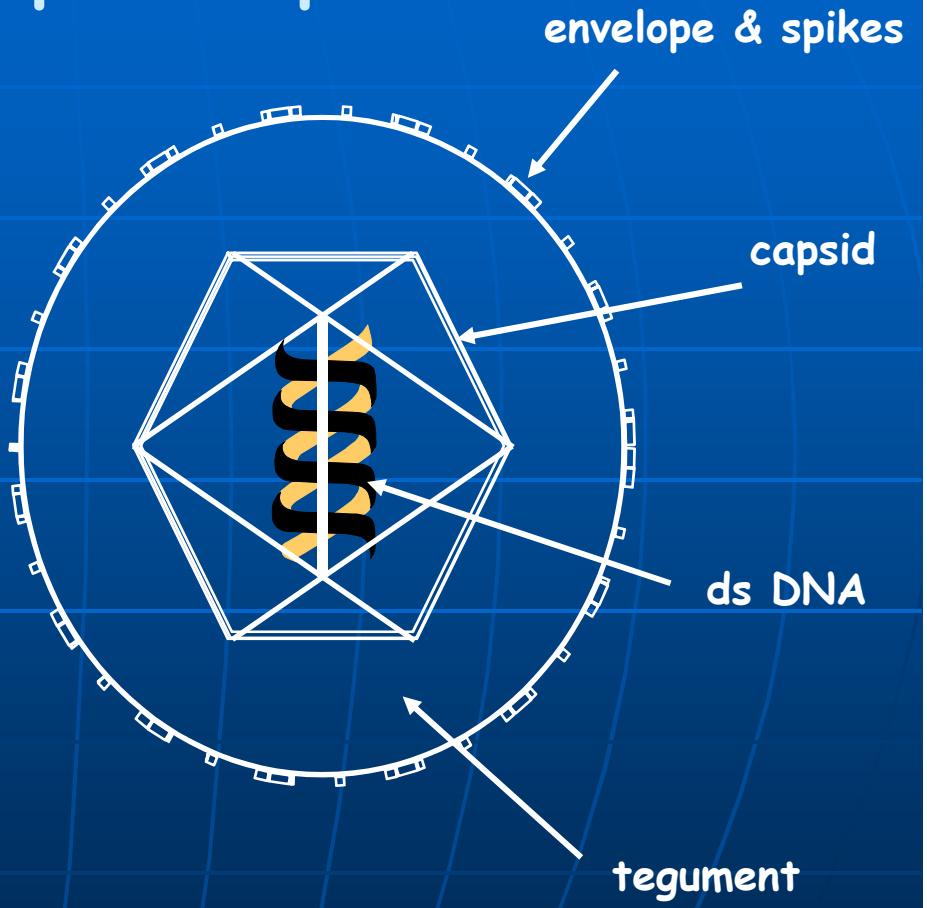
Lues (PA), Urethritis/Zystitis, Kontaktdermatitis

Petersen et al., 1999; Gupta et al. 2007

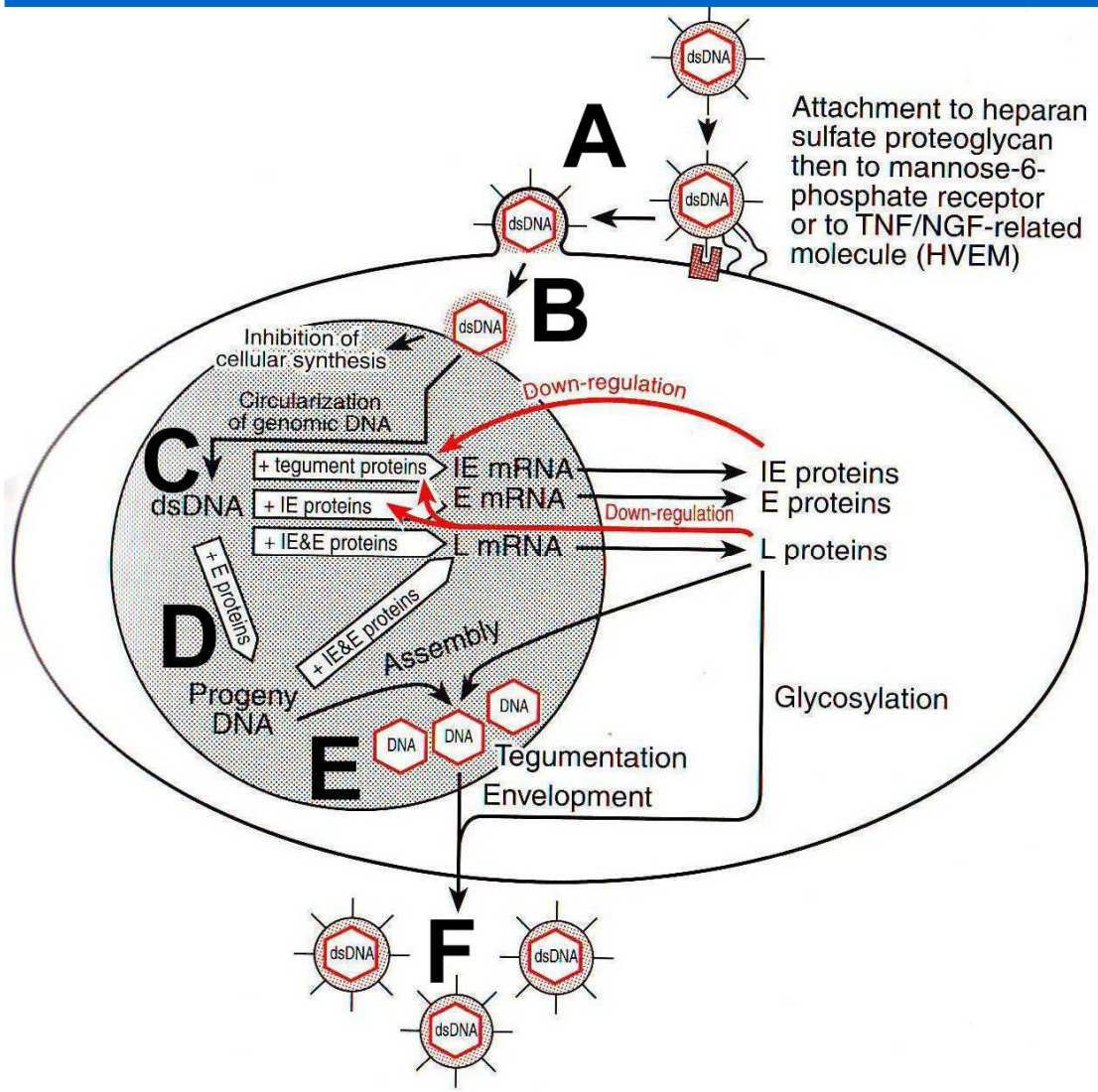
H.Genitalis - Ätiologie

Morphologie der Herpes simplex Virus





HSV-Replikation



a) Virusadsorption: Andocken und feste Bindung an einen Zellrezeptor

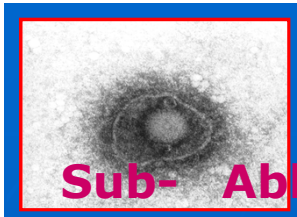
b) Penetration: Endozytose mit oder ohne Fusionierung der Zellmembran mit dem viralen Envelope

c) Auflösung des viralen Kapsides („uncoating") und Freisetzung des viralen Genomes

d) Transkription der Gene (NS = regulatorisch aktive Gene, S = Gene der viralen Strukturbausteine) zur mRNA und Transkription des ganzen Virusgenoms zur Reduplikation („progeny")

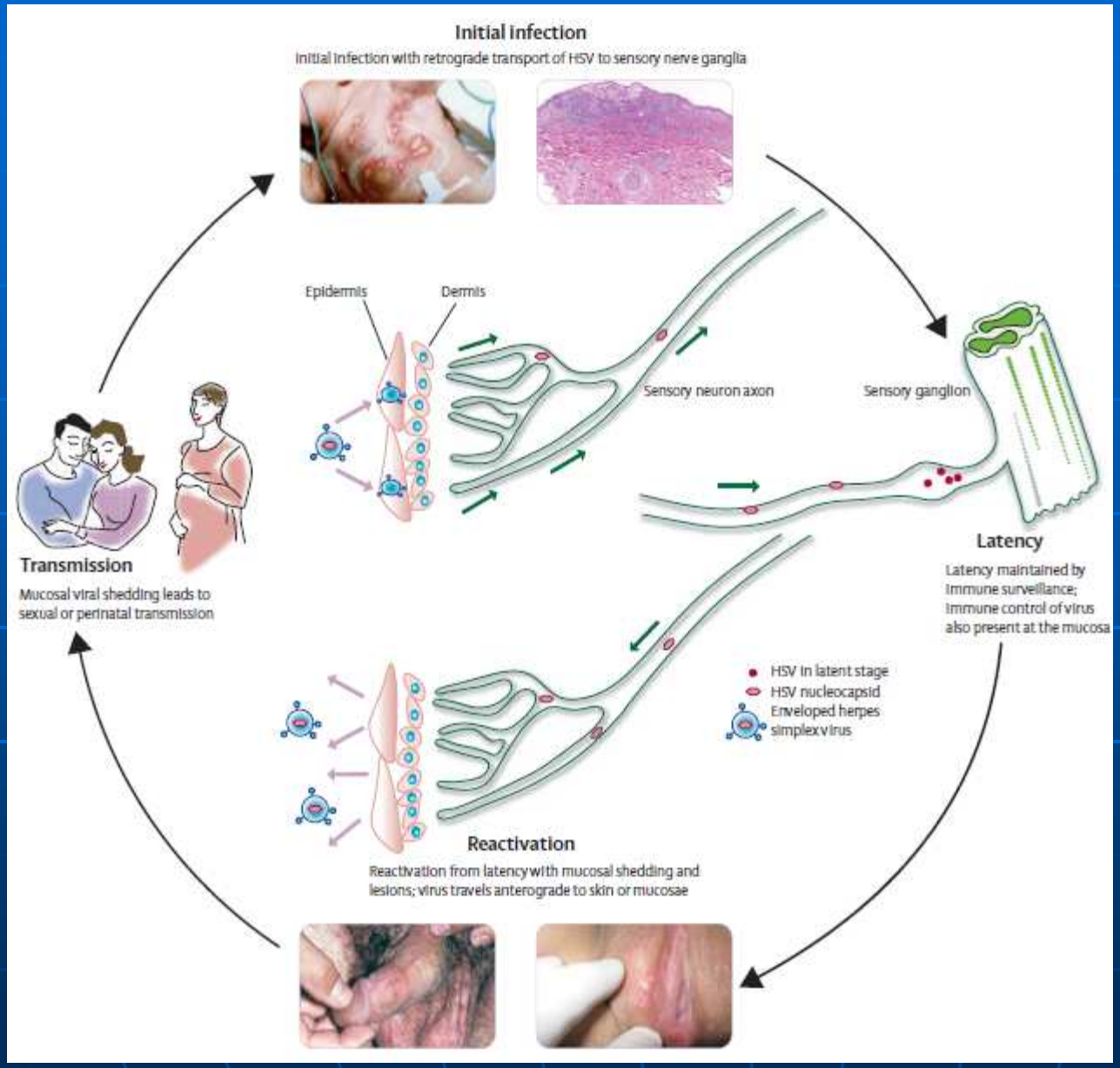
e) Spleißen und Translation der mRNA zu NS- und S-Proteinen („early" und „late antigens" – EA, LA)

f) Prozessierung und Zusammenbau der Strukturproteine („assembly") Freisetzung („release") oder Ausschleußung („budding") der neuen Viruspartikel. Komplette infektionstüchtige Viren = Virionen, defekte und interferierende Viren = DI-Partikel



Humane Herpesviren

Sub-fam.	Abk.	Name	Latenzort	Erkrankung
α	HSV-1	Herpes simplex-V. Typ 1	sensor.	H. labialis, Encephalitis
α	HSV-2	Herpes simplex-V. Typ 2	Ganglien des	H. genitalis, H. neonatorum
α	VZV	Varizella-Zoster-Virus	Rückenmarks	Windpocken, H. zoster
γ	EBV	Epstein-Barr-Virus	B-Lymphoz.	infekt. Mononukl., NPC, Burkitt-Lymphom, PTLD
β	CMV	Zytomegalievirus	Epithelzellen, Leukozyten	kongenitale Erkr., Retinitis (AIDS), Pneumonitis (Transpl.)
β	HHV-6	humanes Herpesvirus 6	T-Lymphoz.	Dreitagefieber = Exanthema subitum
β	HHV-7	humanes Herpesvirus 7	T-Lymphoz.	?
γ	HHV-8, KSHV	Kaposi-Sarkom-assoziiertes Herpesvirus	B-Lymphoz.	Kaposi-Sarkom, Lymphome (M. C.)



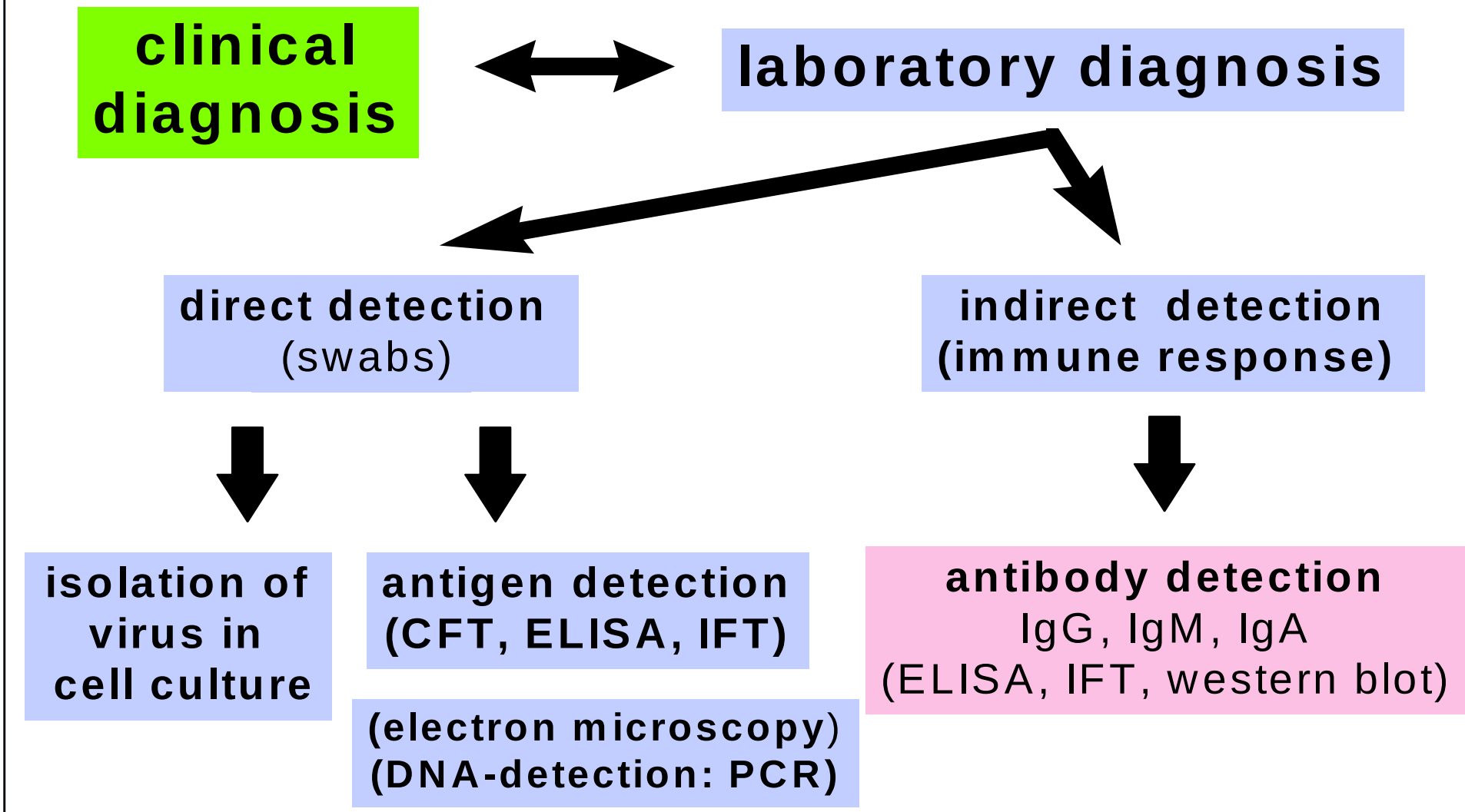
Gupta, Warren, Wald (2007) Genital herpes Lancet; 370: 2127-2137

Labordiagnostik des Herpes genitalis

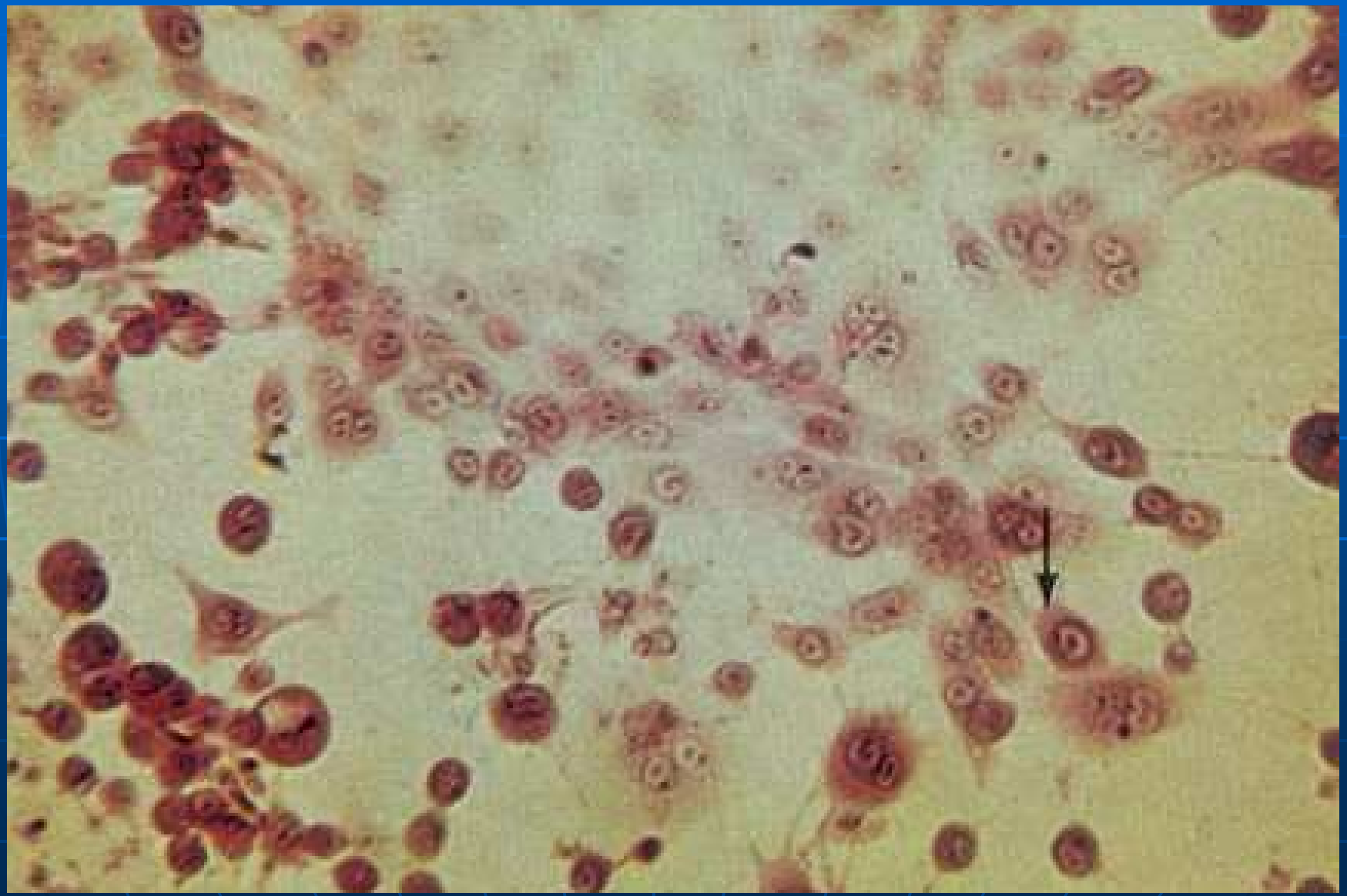
- Erregernachweis aus Abstrich
  - Virusisolierung in Zellkultur
  - Antigentest
  - DNA-PCR

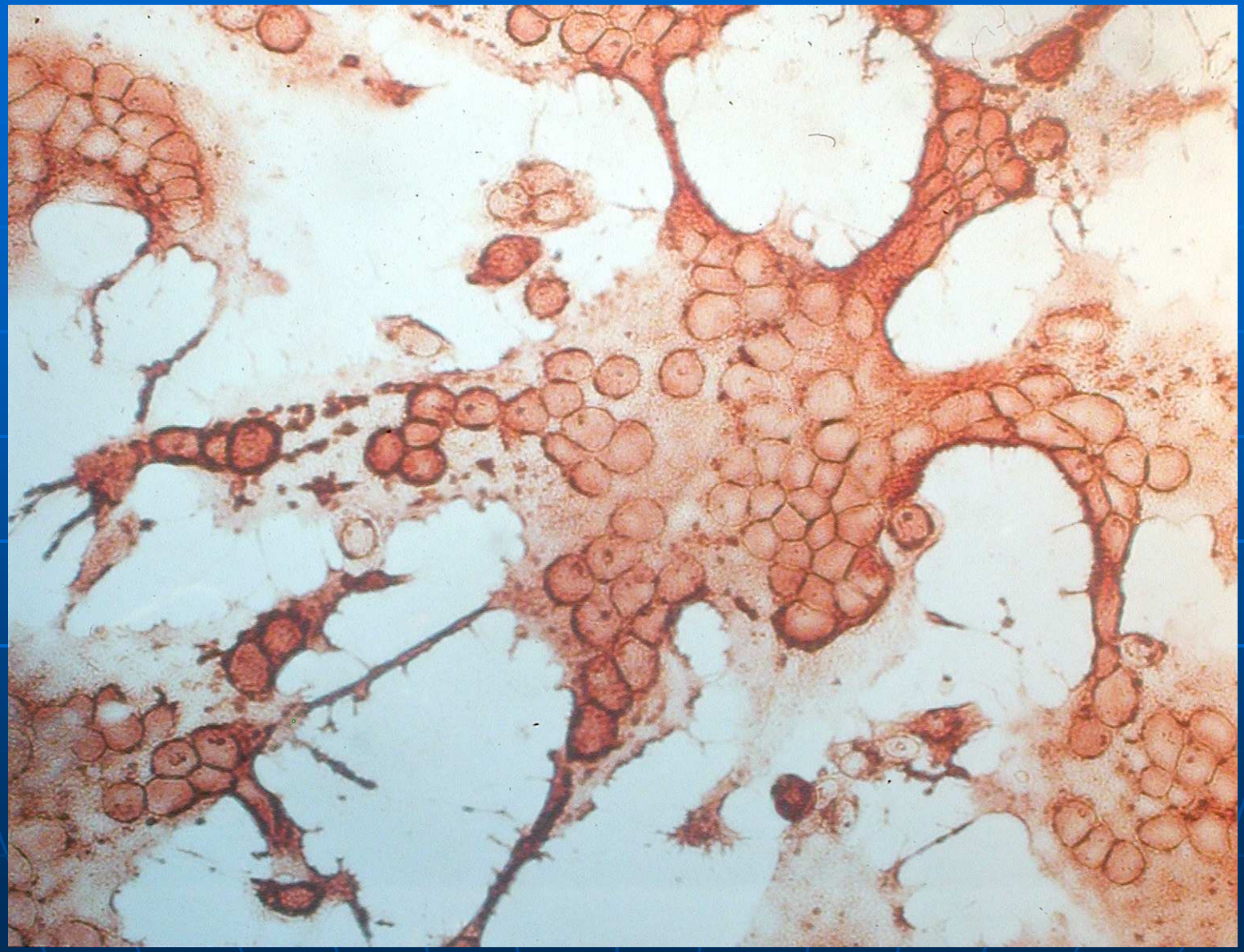
Erregeridentifikation
  - Serotypisierung
  - Genotypisierung (RFLP, Sequenzrg.)
  - Phänotypisierung (Zellkultur + Brivudin)

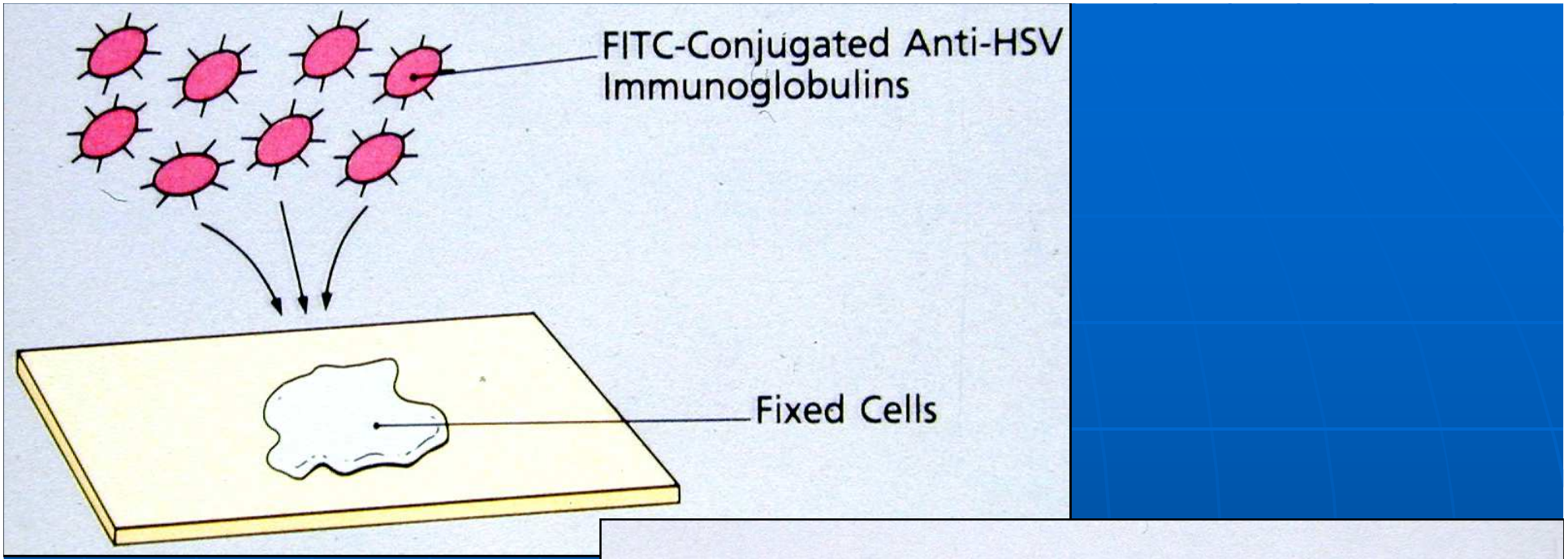
Diagnostic of Herpes genitalis

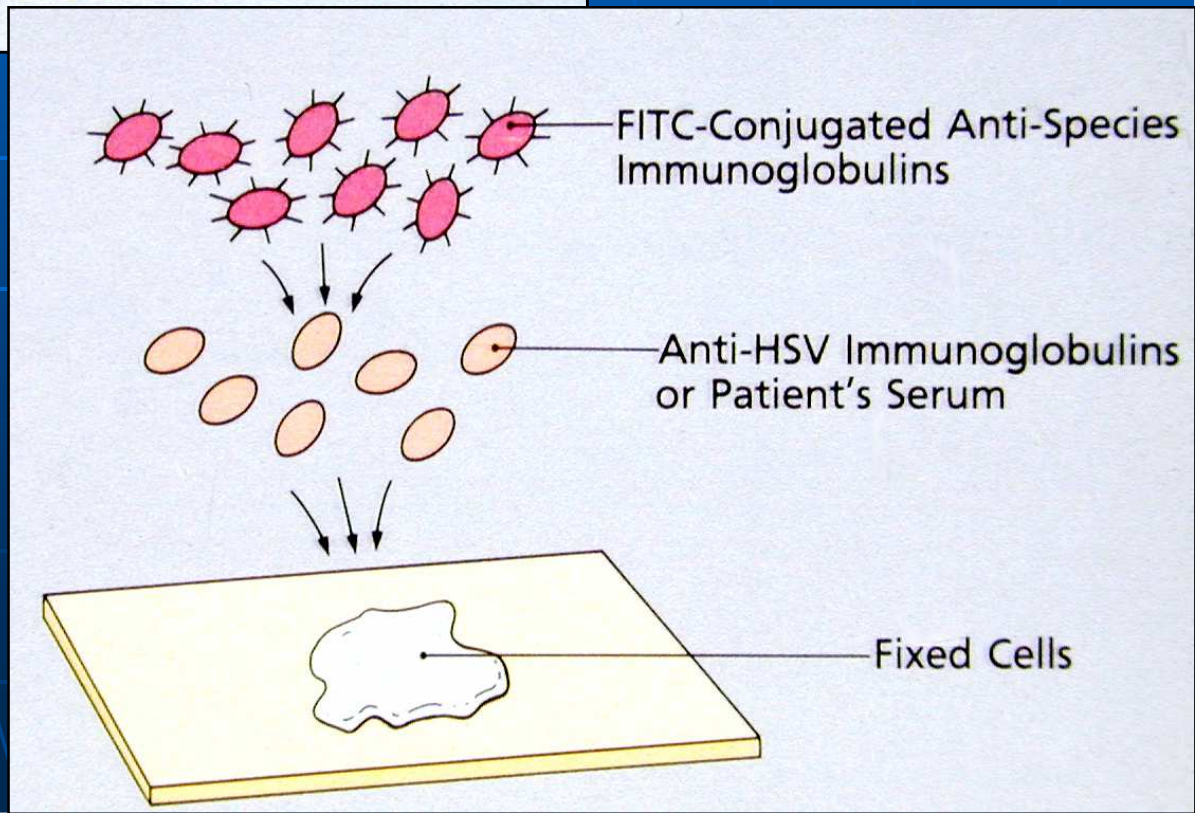


HSV-infizierte Zellkultur






FITC-Conjugated Anti-HSV
Immunoglobulins
Fixed Cells


FITC-Conjugated Anti-Species
Immunoglobulins
Anti-HSV Immunoglobulins
or Patient's Serum
Fixed Cells

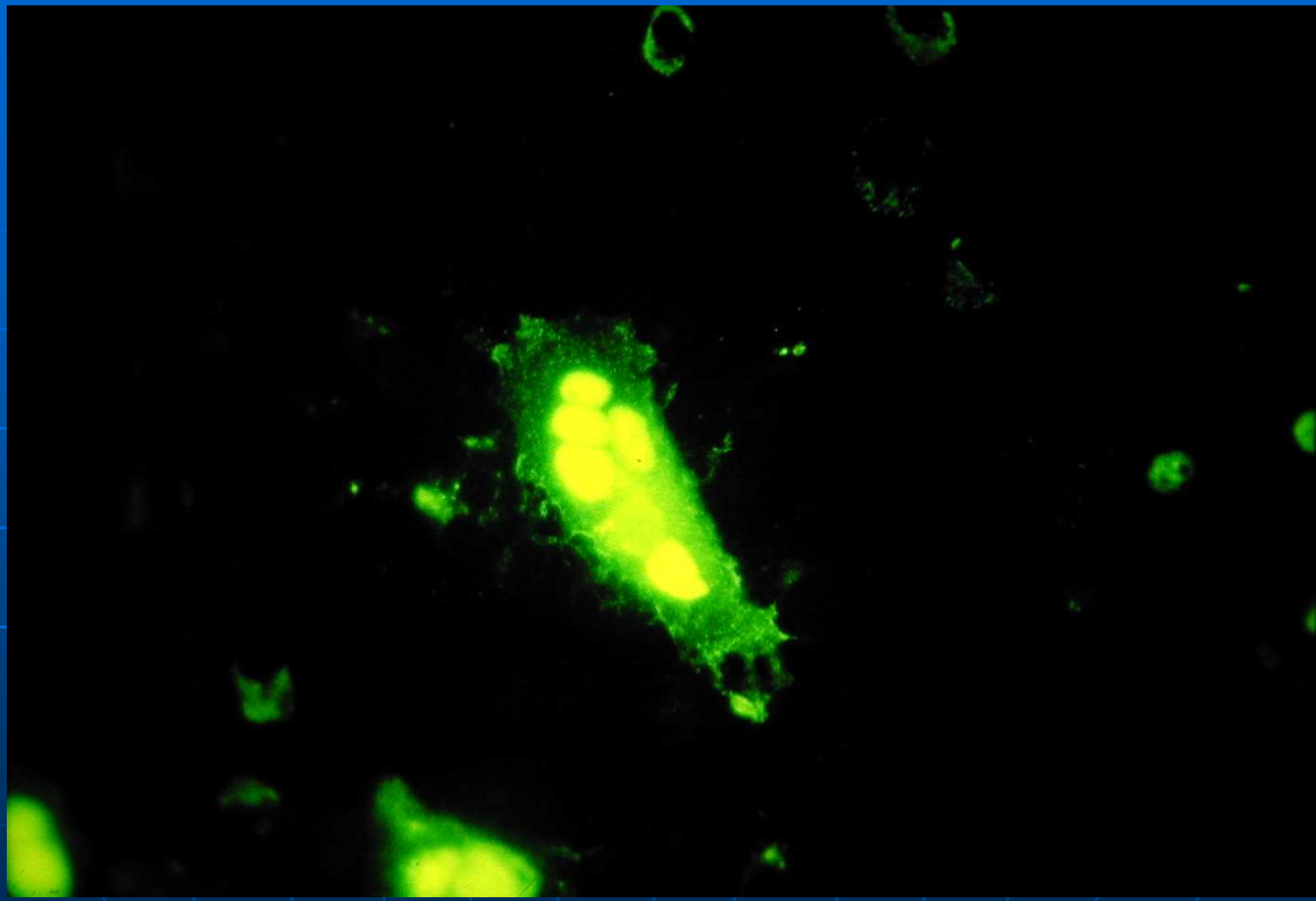
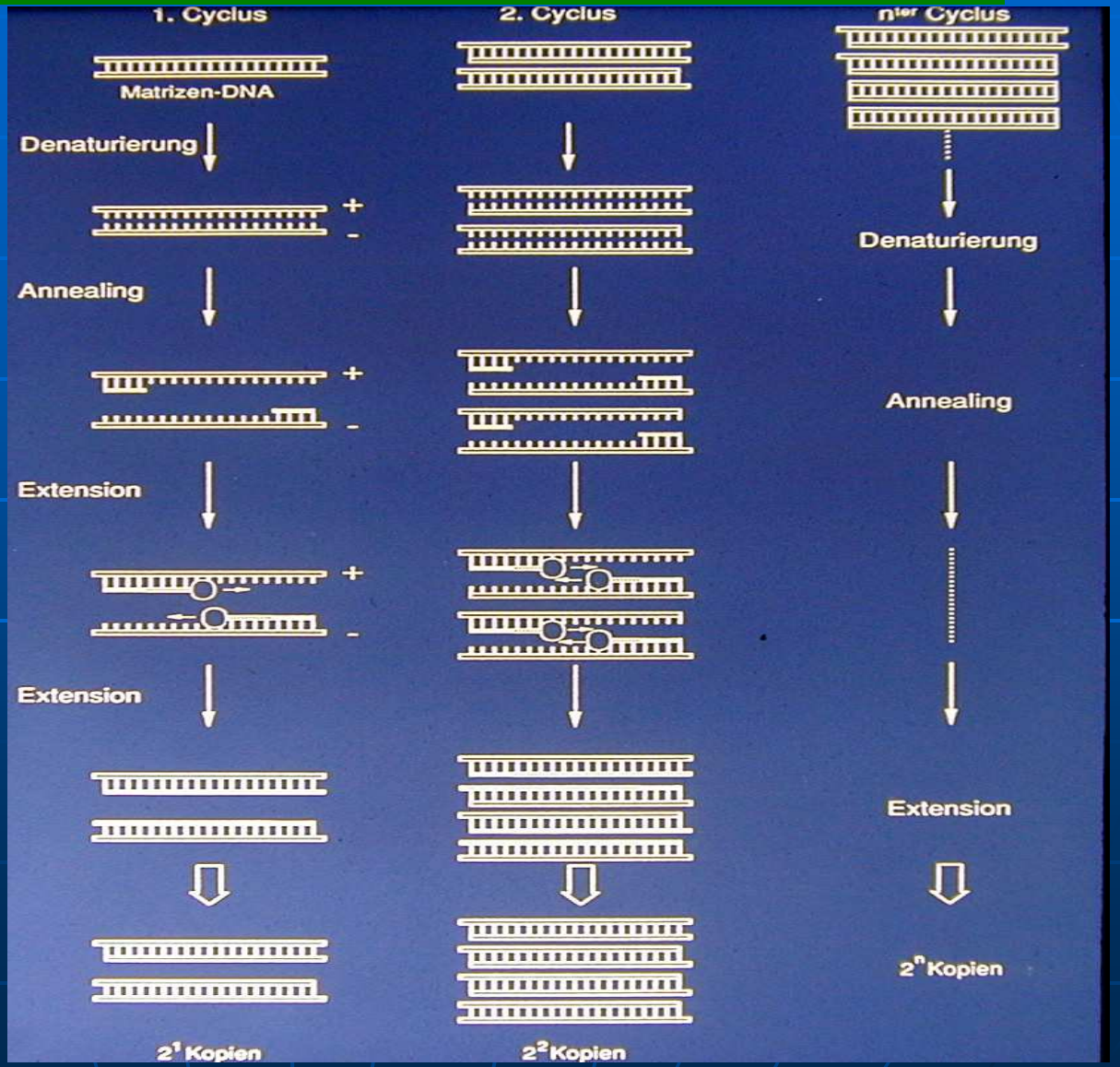


Fig: Differenzierung zwischen HSV Typ I und Typ II mittels Restriktionsenzym-Analyse mit Hind III

HSV-PCR

Sakrauski A, Weber B, Kessler HH, Pierer K, Doerr HW: J.Virol Meth 50(1994), 175-184

Ethidiumbromid-Gelelektrophorese von PCR-Produkten



RFLP-Analyse klinischer HSV-1 Stämme

Vogel JU, Weber B, Doerr HW: Int.J.Med.Microbiol. 281(1994), 502-512

Rsa I Verdau von HSV-1 TK Produkten
nach PCR-Amplifikation

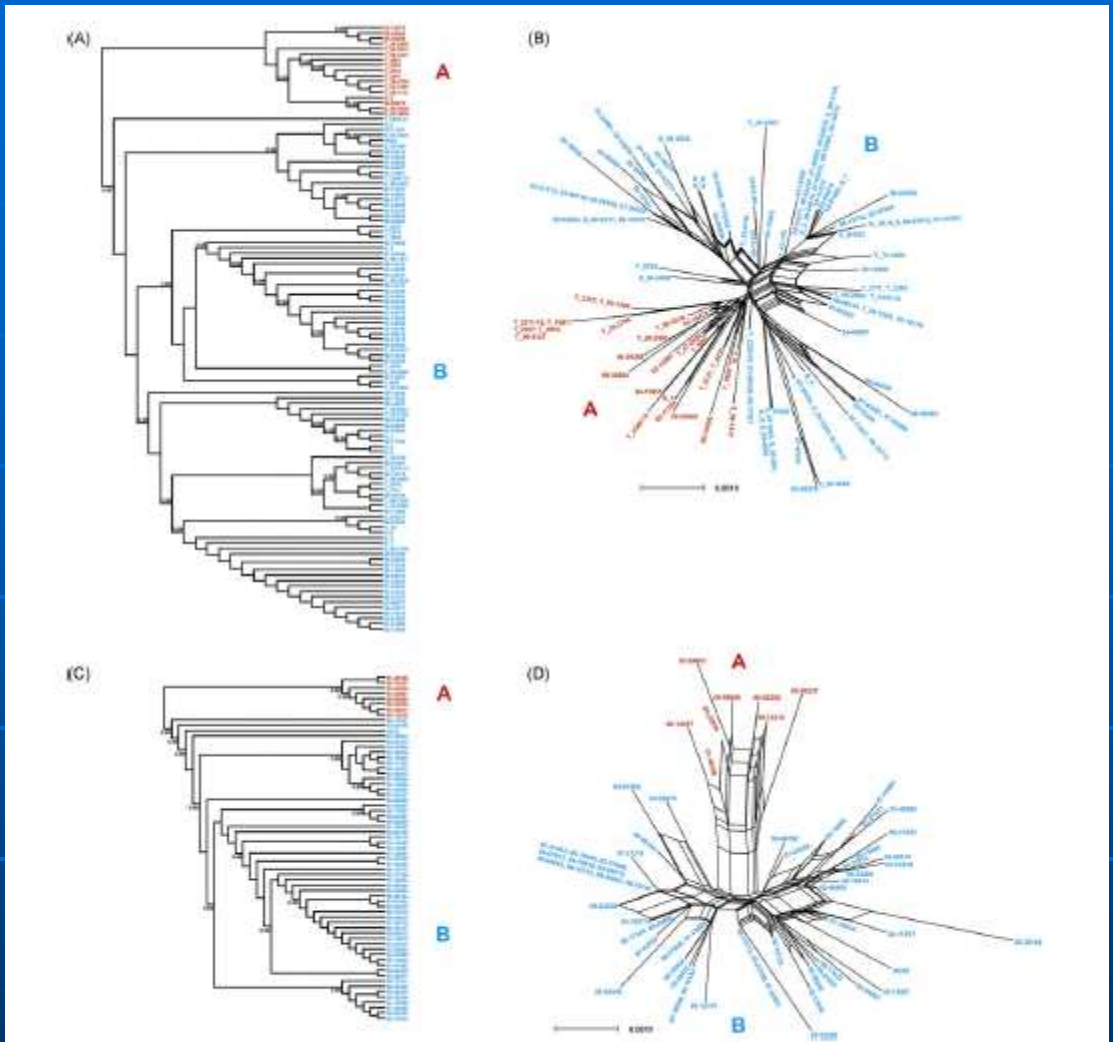


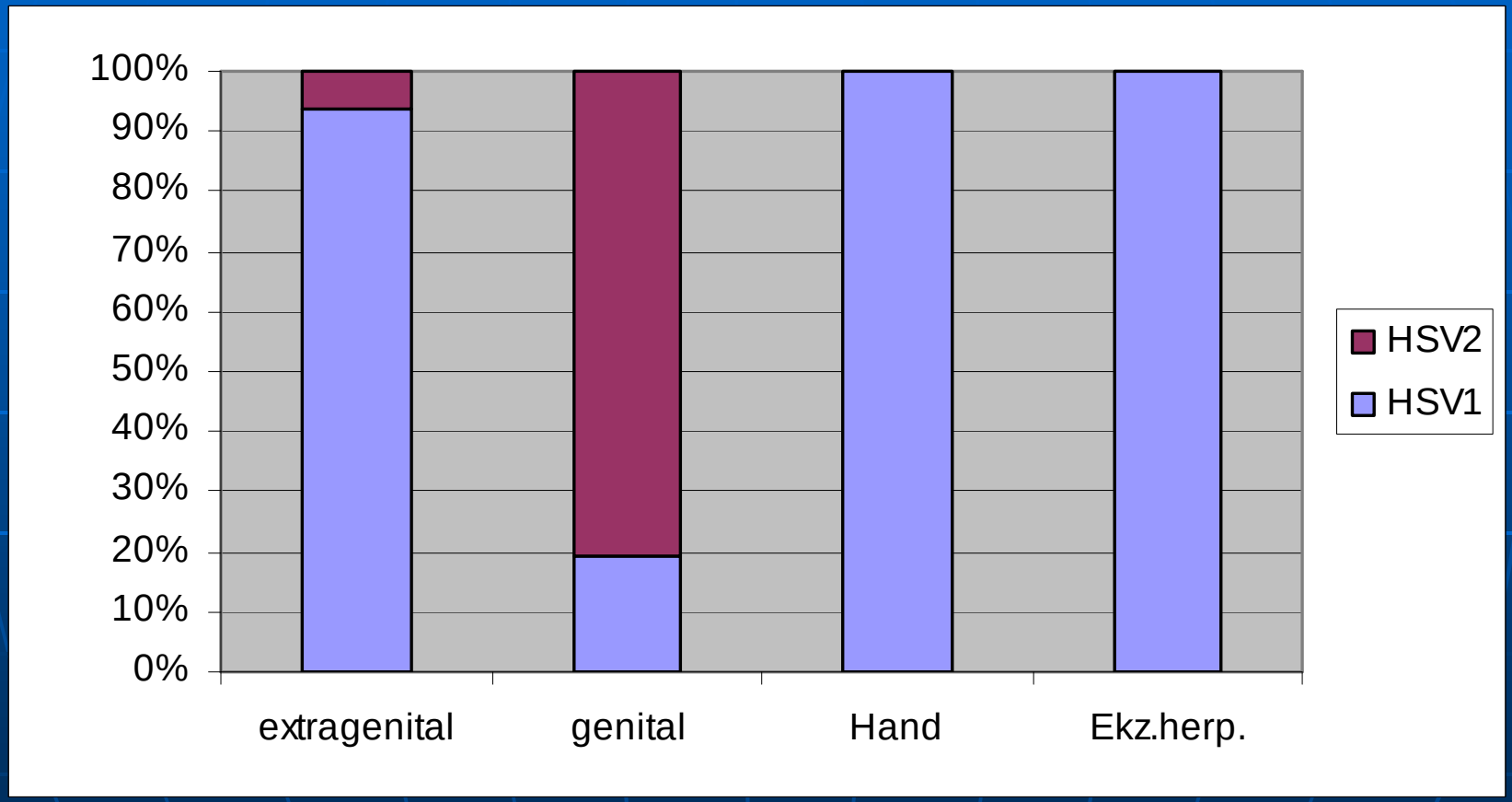
Fig. 1. Maximum-likelihood (ML) phylogenetic trees (A and C) and corresponding Neighbor-net networks (B and D) of 64 novel (GenBank accession numbers HM011303-HM011430) and 48 previously described (GenBank accession numbers EU106374, EU106421 and Z86099) gC (A and B) and gB (C and D) gene sequences of clade A (red) and B (blue) HSV-2 strains. The HSV-2 strain HG52 (Z86099) was used as reference for clade B. Chi^2-based probabilities are shown on each node of the ML trees if values were higher than 0.98.

Schmidt-Chanasit J, Bialonski A, Heinemann P, Ulrich RG, Günther S, Rabenau HF, Doerr HW. A 12-year molecular survey of clinical herpes simplex virus type 2 isolates demonstrates the circulation of clade A and B strains in Germany. J Clin Virol. 2010;48(3):208-11

HSV bei Männern: FfM-Studie

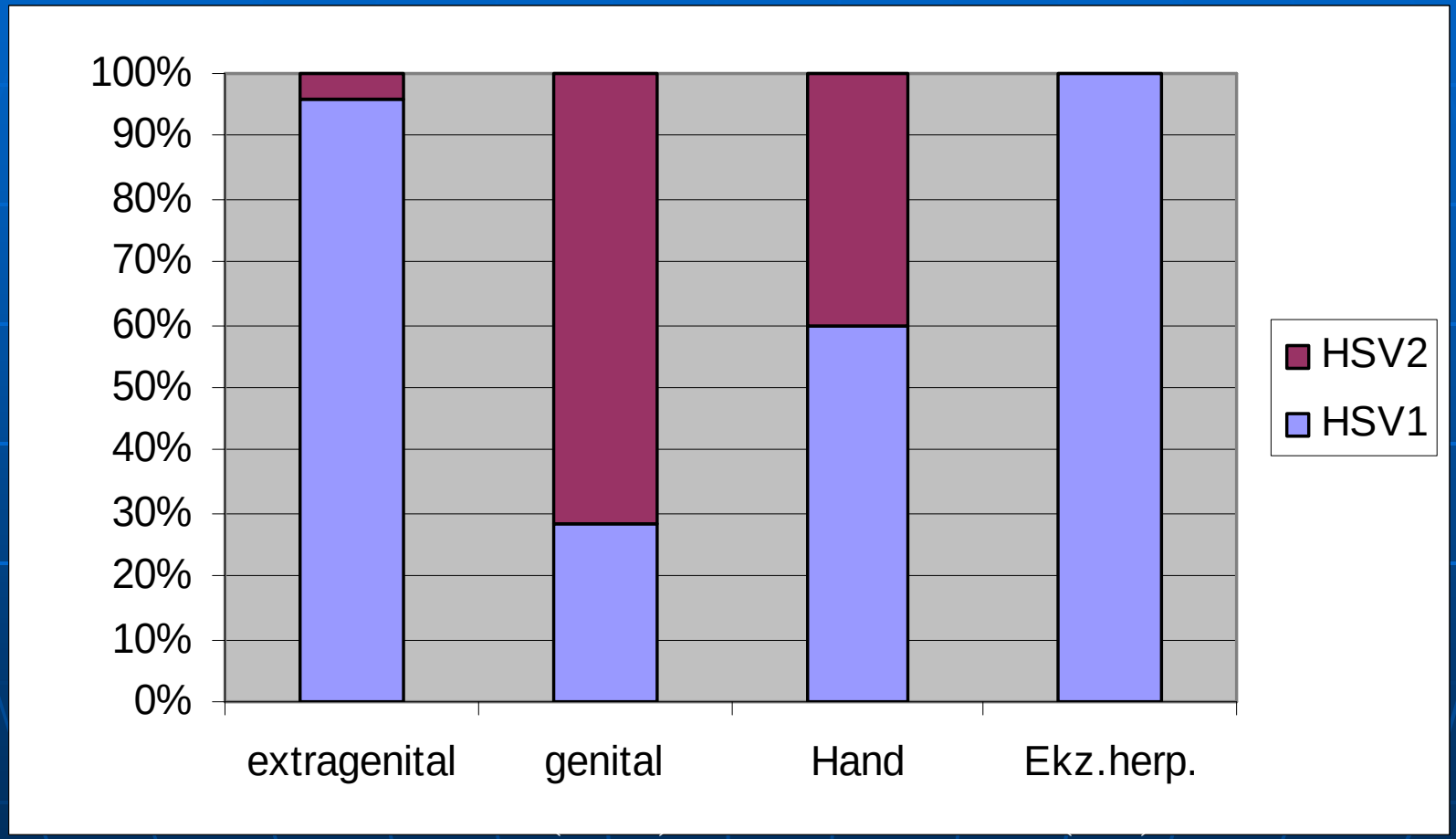
Buxbaum S, Geers M, Gross G, Schoefer H, Rabenau HF, Doerr HW: Epidemiology of HSV-1 and HSV-2 in Germany: What has changes? Med.Microbiol.Immunol. 192(2003), 177-181

n = 121 60 1 7



HSV bei Frauen: FfM-Studie

Buxbaum et al., 2003



Labordiagnostik des Herpes genitalis II

HSV-Serologie

Typ nicht differenzierender Ak-Test (KBR, IFT, ELISA)

Aussagewert: Auschlußdiagnose

Typ 1/2 differenzierender Ak-Test

ELISA mit typ-spez. Gp-Antigen

Typ 1/2 differenzierender Immuno-blot

Aussagewert des HSV-2 Ak-Nachweises: Warnung in der Schwangerschaftsüberwachung

Kommerzielle Testkits vorhanden. Typ nicht differenzierender Test ist etwas sensitiver wegen breiten Antigenspektrums

Chenot JF, Rabenau HF, Doerr HW: Laboratory diagnosis of herpes genitalis. J.Lab.Med. 25(2001), 223-225

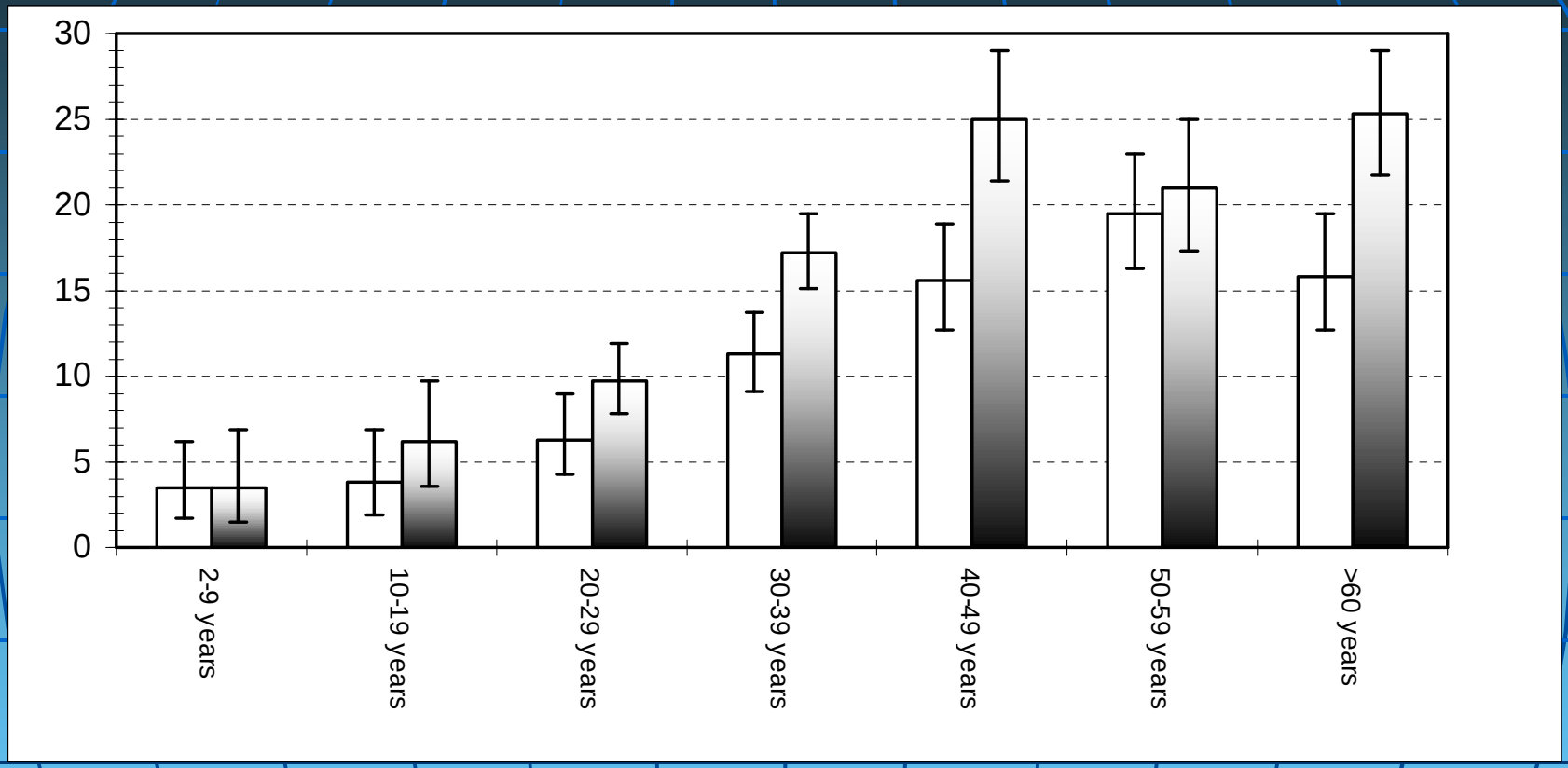
	HSV-2 positive by culture, antigen detection, or PCR	Type-specific HSV-1 IgG antibody	Type-specific HSV-2 IgG antibody	Interpretation
First assessment of genital lesions	Positive	Positive or negative	Negative	Acute HSV-2 infection; can check convalescent HSV-2 antibody
	Positive	Positive or negative	Positive	Recurrent HSV-2 infection with HSV-2 infection acquired at least 6 weeks ago
No lesions	n/a	Negative	Negative	At risk for orolabial or genital HSV-1 infection and HSV-2 infection; if healed genital lesions or new sexual exposure, check convalescent HSV-1 and HSV-2 serology
	n/a	Positive	Negative	At risk for acquiring HSV-2 infection; if healed genital lesions or new sexual exposure, check convalescent HSV-2 serology
	n/a	Positive	Positive	HSV-1 and HSV-2 infection
Recurrent genital lesions	Positive	Positive or negative	Positive	Recurrent HSV-2 infection
	Negative	Negative	Positive	Recurrent HSV-2 infection; need to consider other potential causes of genital ulcerative disease

n/a=not applicable.

Table 1: Virological and serological approach to HSV-2 diagnosis in the presence and absence of genital lesions

Gupta, Warren, Wald (2007) Genital herpes Lancet; 370: 2127-2137

Alters- und geschlechtsabhängige HSV-2-IgG Seroprävalenz in Deutschland



weiße Balken = männl. Patienten
graue Balken = weibl. Patienten

Patienten der J.W. Goethe-Universitätsklinik **Frankfurt zwischen 1993 -1998** (n = zwischen 226 und 1181)

HSV-2 Prävalenz in einem „Normalkollektiv„: 15,1%

(18% bei ♀ u. 13,8% bei ♂ >15-Jahre)

Rabenau et al. (2002) Seroprevalence of herpes simplex virus types 1 and type 2 in the Frankfurt am Main area, Germany. MMI 190, 153-160

Trends in der HSV-1/-2 Seroprävalenz in Deutschland

Investigator	Test method	Collective	Age group (years)	Seroprevalence anti-HSV-1/2 IgG	Seroprevalence anti HSV-2 IgG
Doerr et al. [3], Freiburg 1977	CFT (NT)	Probands, not selected	5–10	36% (40%) (CI: 30–56%)	
			20–40	72% (76%) (CI: 58–88%)	---/(16%)
Dannenmaier et al. [2], Heidelberg 1985	ELISA	Control group	17–61	65.6% (CI: 56.7–73.8%)	7.2% (CI: 3.4–13.3%)
		Prostitutes		93.2% (CI: 86.9–97%)	38.5% (CI: 29.7–48%)
Enzensberger et al. [5], Frankfurt/Main 1991	ELISA	Control group	>13	81.2% (CI: 80.4–81.9%)	
		HIV positives		93.4% (CI: 90.6–95%)	
Bahrdt et al. [1], Frankfurt/Main 1992	ELISA, Western blot	Control group	20–59		21.6% (CI: 17.2–26.1%)
		HIV positives			38.9% (CI: 32.5–45.5%)
		Prostitutes			65% (CI: 40.8–84.5%)
		Gynecological patients			26.3% (CI: 19.6–33.7%)
Enders et al. [4], Stuttgart 1998	ELISA	Pregnant women			8.9% (CI: 7.7–10.3%)
Wutzler et al. [22], Jena 2000	ELISA, Immuno blot differentiation of type is possible	Blood donors and hospital patients[a]	20–39	77.1% (CI: 74.9–79.3%)	14.8% (CI: 13.0–16.7%)
		HIV positives		91.1% (CI: 87.8–93.8%)	47.9% (CI: 42.8–53%)
Rabenau et al. [16], Frankfurt/Main 2002	ELISA differentiation of type is possible	Control group	5–14	48–51% (CI: 41–58%)	
			15–39	68% (CI: 66–70%)	13% (CI. 12–14%)
		Organ transplant recipients	15–39	84% (CI: 60–97%)	11% (CI: 1–33%)
		HIV positives		86% (CI: 78–92%)	61% (CI: 50–71%)
		Prostitutes			78% (CI: 73–83%)

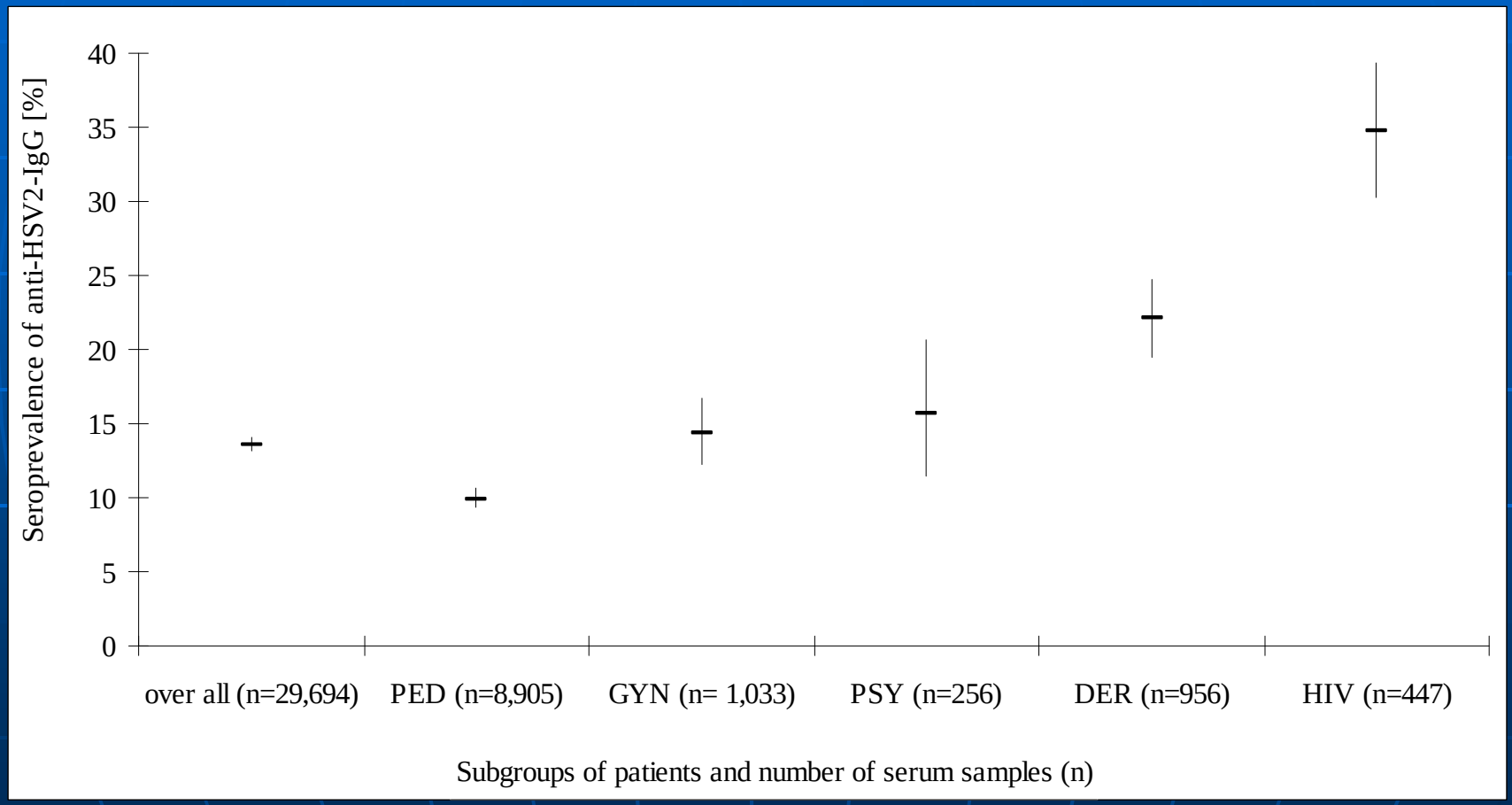
In: Buxbaum S, Geers M, Gross G, SchoeferH, Rabenau HF, Doerr HW (2003): Epidemiology of herpes simplex virus type 1 and 2 in Germany: what has changed? MMW, 192(3), 177-181

Neu: Sauerbrei et al.: HSV-1 and -2 seroprevalence in Thuringia (G) 1999-2006. Eurosurv. 3(2011), pii:20005

Reinheimer C, Doerr HW: Seroprevalence of HSV-2 in different risk groups 30 years after the onset of HIV. Intervirology, in press

HSV 2- Seroprävalenzstudie Frankfurt a.M. 2001 - 2011

PED/GYN/PSY/DER/HIV = Pädiatrische/gynäkologische/psychiatrische/dermatologische und HIV-Patienten



Reinheimer C, Doerr HW: Seroprevalence of HSV-2 in different risk groups 30 years after the onset of HIV. Intervirology, in press

Weltweite HSV-2-Seroprävalenz

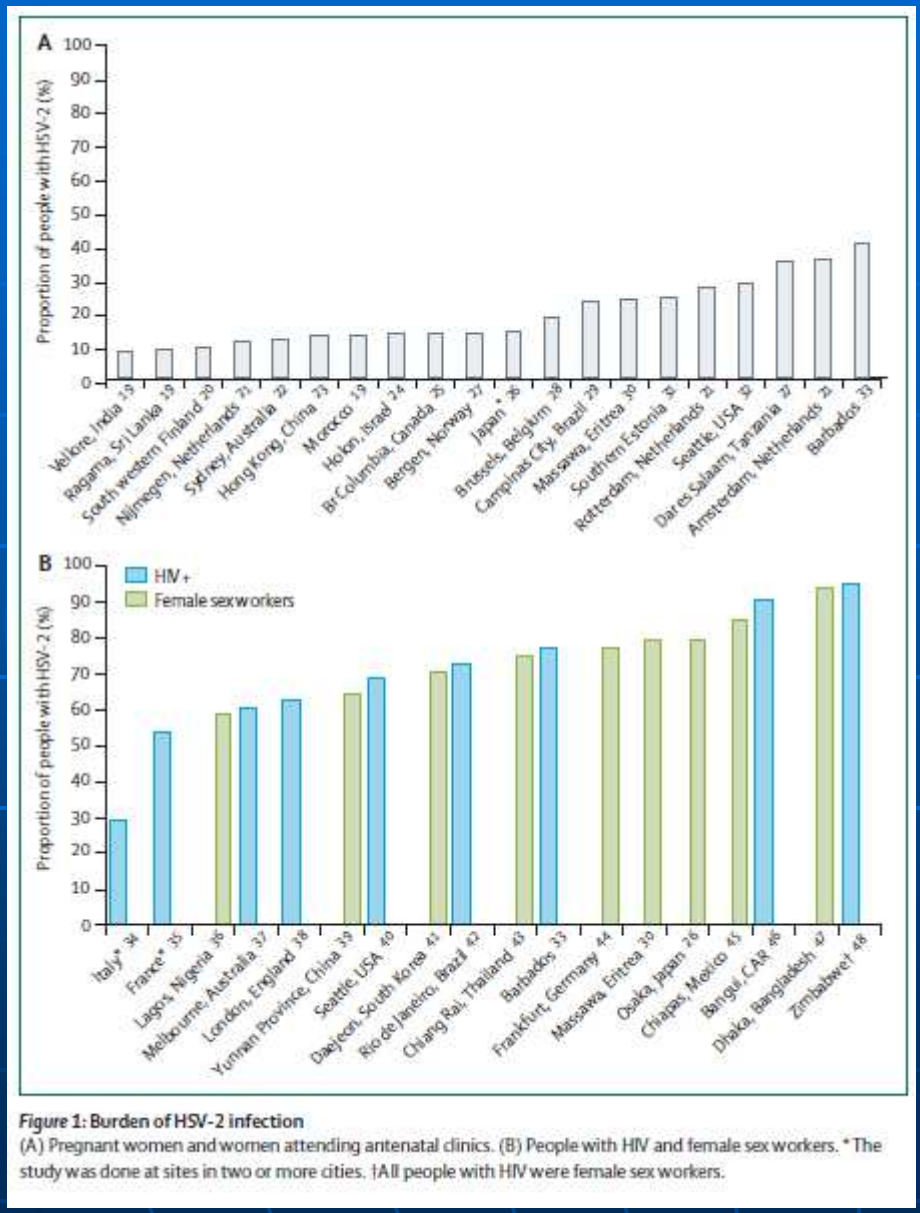


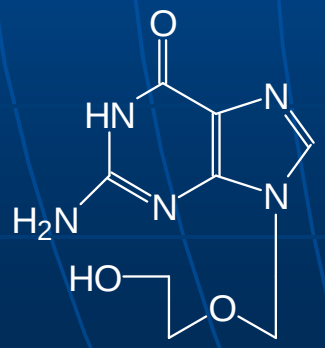
Figure 1: **Burden of HSV-2 infection**
(A) Pregnant women and women attending antenatal clinics. (B) People with HIV and female sex workers. * The study was done at sites in two or more cities. †All people with HIV were female sex workers.

Gupta, Warren, Wald (2007)
Genital herpes Lancet;
370: 2127-2137

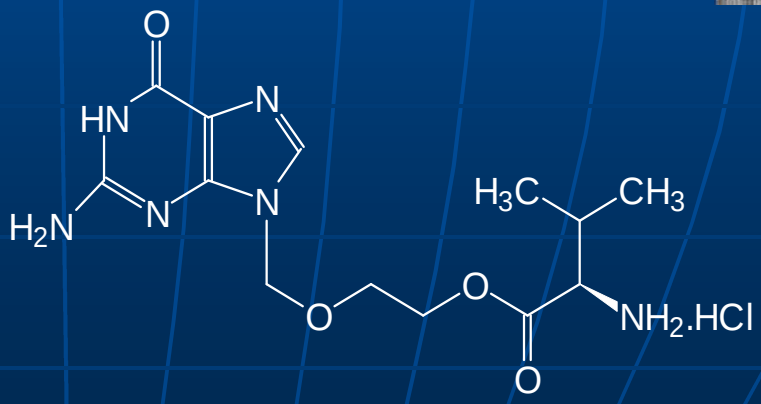
Antivirale Chemotherapeutika in Deutschland

α-Herpesviren: HSV-1, HSV-2, VZV - Systemica:

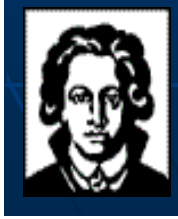
Acyclovir (ACV)	**Zovirax ® (GlaxoSmithKline) u. v. a.**
Valaciclovir	**Valtrex ® (GlaxoSmithKline / Cascan)** **(orales Prodrug von Acyclovir)**
Famciclovir	**Famvir ® (Novartis Pharma)** **(orales Prodrug von Penciclovir)**
Brivudin	**Zostex ® (Berlin Chemie)**



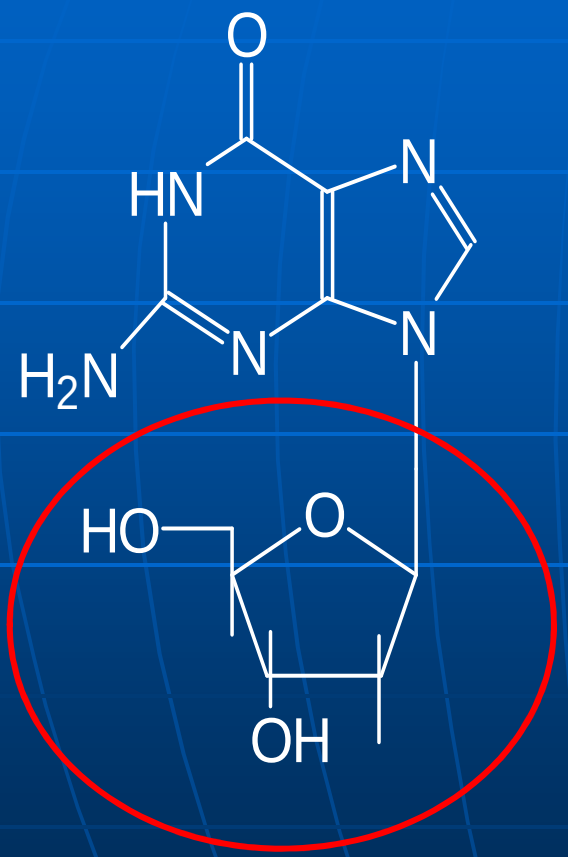
ACV



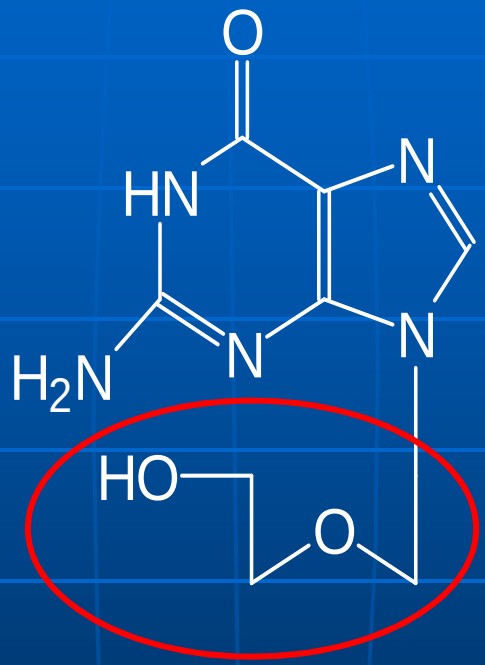
Val-ACV



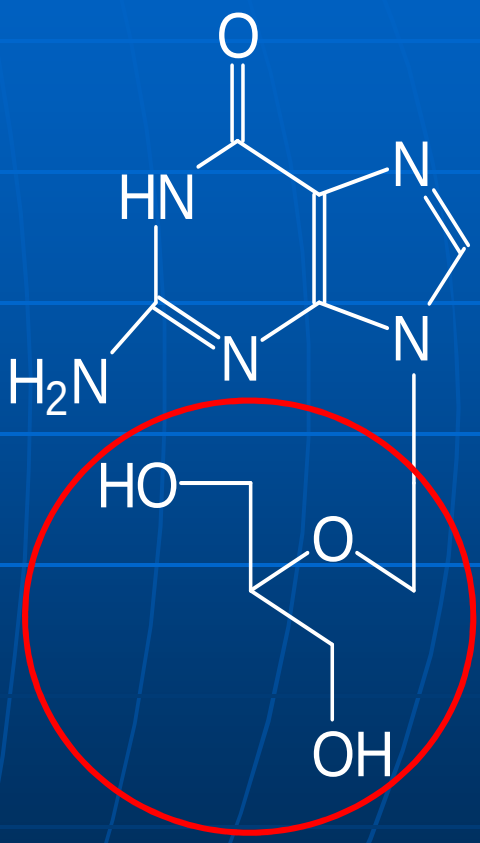
Desoxyguanosin



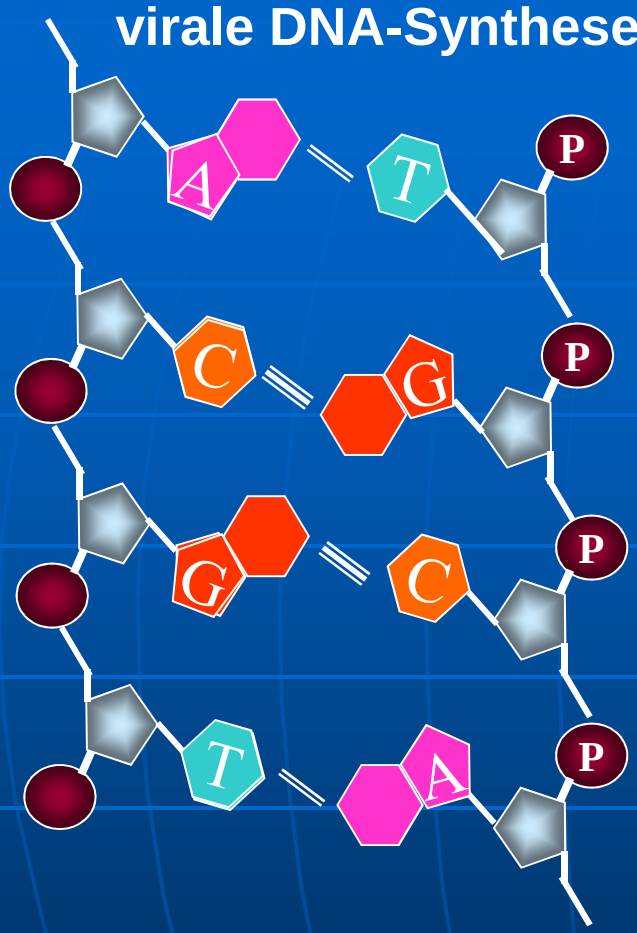
Acyclovir

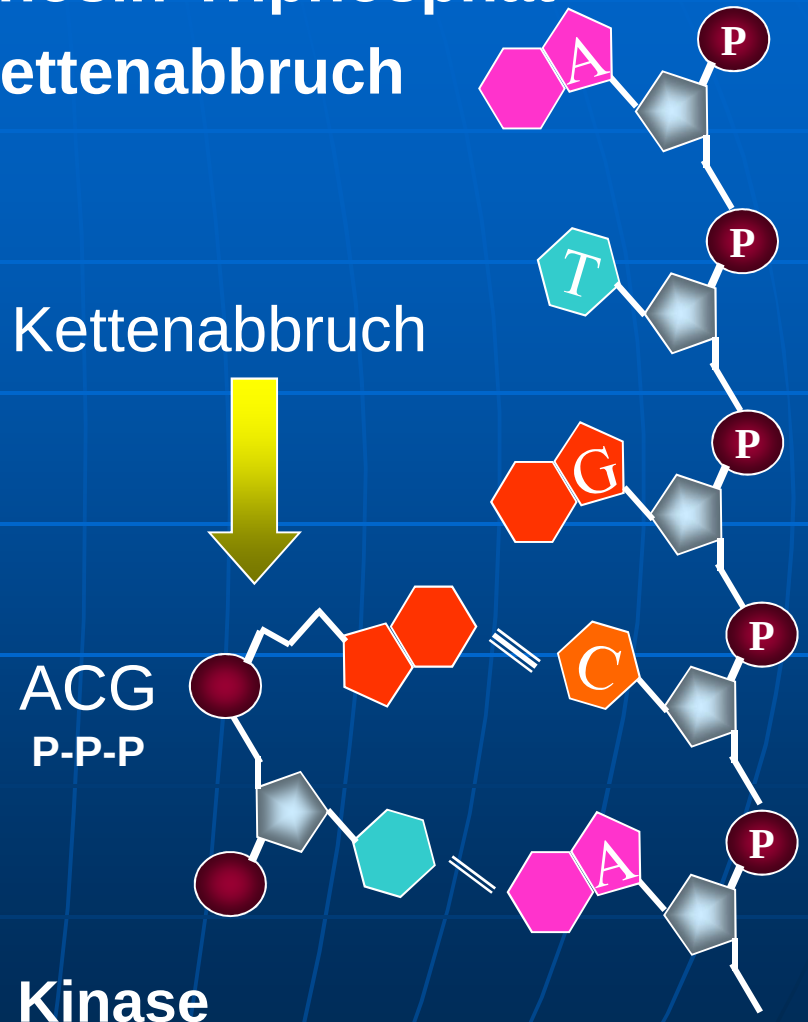


Ganciclovir



Wirkmechanismus von ACV: Kompetition mit Guanosin-Triphosphat ⇒ Kettenabbruch



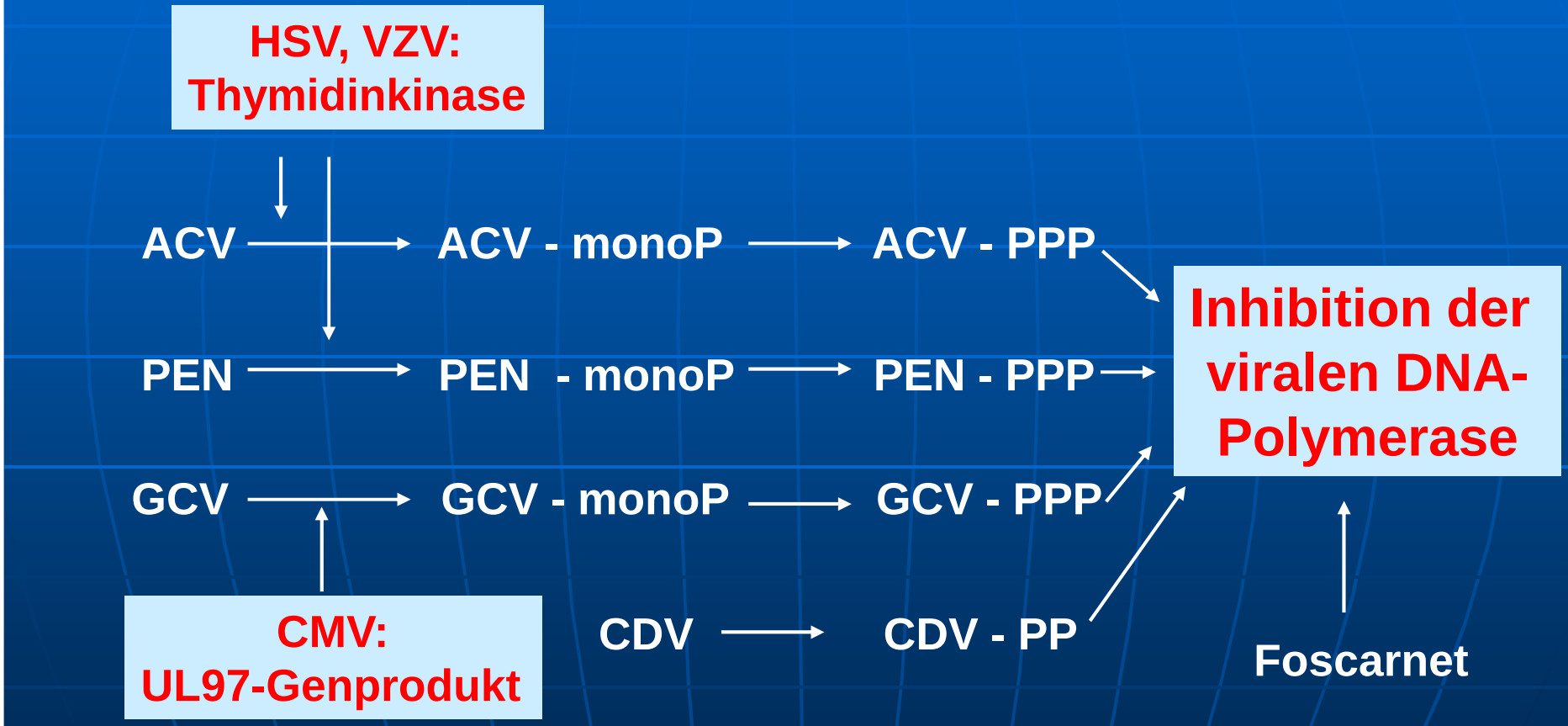


Selektivität von ACV durch:

1. Phosphorylierung durch virale Kinase

2. virale Polymerase empfindlicher gegenüber ACV als zelluläre

Antivirale Therapie der Herpesviren: intrazelluläre Phosphorylierung



ACV: Aciclovir
PEN: Penciclovir
GCV: Ganciclovir
CDV: Cidofovir

	Aciclovir	Valaciclovir	Famciclovir	Comments
Genital HSV Infection				
First episode*	400 mg three times a day for 7–10 days 200 mg five times a day for 7–10 days 5 mg/kg intravenously every 8 hours for 5–7 days, for severe disease, then change to oral therapy	1000 mg twice a day for 7–10 days	250 mg three times a day for 7–10 days	Screen for HIV and other STIs Counselling
Recurrent episode	400 mg three times a day for 5 days 800 mg three times a day for 2 days 800 mg twice a day for 5 days	500 mg twice a day for three days 1000 mg once a day for 5 days	125 mg twice a day for 5 days 1000 mg twice a day for 1 day	Assess need for suppressive therapy
Suppressive therapy	400 mg twice a day	500 mg or 1000 mg once a day† 250 mg twice a day	250 mg twice a day	Reassess the need to continue every year
Immunocompromised patients				
Episodic	400 mg three times a day for 5–10 days 200 mg five times a day for 5–10 days	1000 mg twice a day for 5–10 days	500 mg twice a day for 5–10 days	Assess need for suppressive therapy
Suppressive therapy	400–800 mg two to three times a day	500 mg twice a day	500 mg twice a day	

*Duration of therapy can be lengthened if healing is not complete after 10 days. †Valaciclovir 1000 mg dose is recommended for patients with >9 recurrences per year.

Table 3: **Treatment regimens for genital HSV infection**

Gupta, Warren, Wald (2007) Genital herpes Lancet; 370: 2127-2137

In vitro Inhibition der Herpes simplex-Virus-Vermehrung auf Monolayer-Zellkulturen. Aktivitätsvergleich von Aciclovir mit anderen antiviral wirksamen Substanzen (Plaques-Reduktions-Methode)

Kontrolle	Idoxuridin 50 µg	Vidarabin 50 µg	Aciclovir 0,5 µg	Aciclovir 1,25 µg

Resistenztestung bei HSV

Sauerbrei A, Deinhardt S, Zell R, Wutzler P: Antiviral Res. 86(2010), 246-252 und Virulence 1(2011), 55-557

Genotypisierung:

PCR-Amplifikation und Sequenzierung des

TK Genes: (partielle Deletionsmutanten)

HSV-Thymidinkinase aktiviert (phosphoryliert) die nukleosidalen Herpesvirostatika (Val)acyclovir, Famcyclovir, Brivudin)

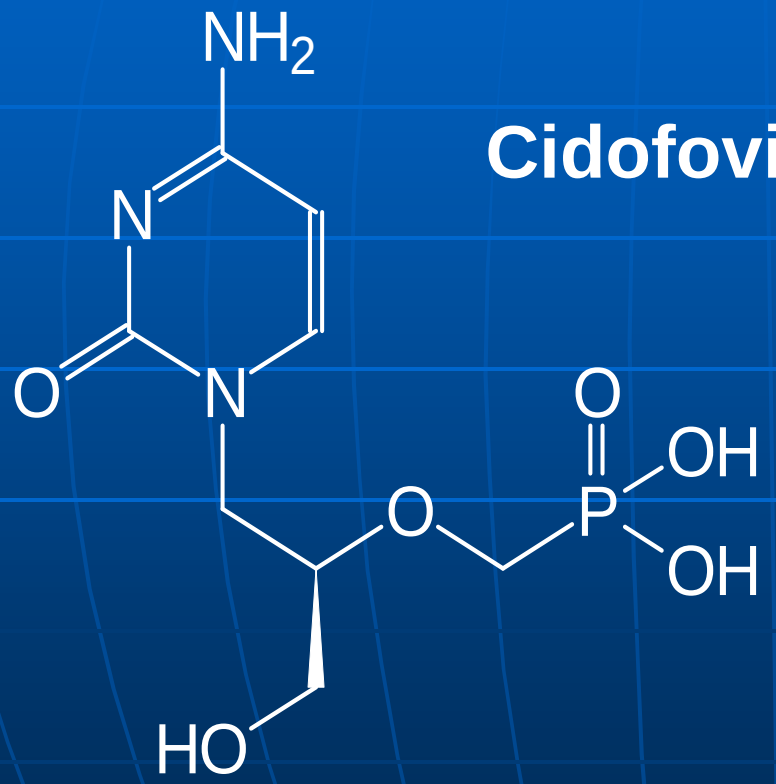
Pol Genes (partielle Deletionsmutanten)

HSV-Polymerase baut die nukleosidalen Herpesvirostatika in die HSV-DNA ein: Kettenabbruch und Pol-Fixation.

Foscarnet

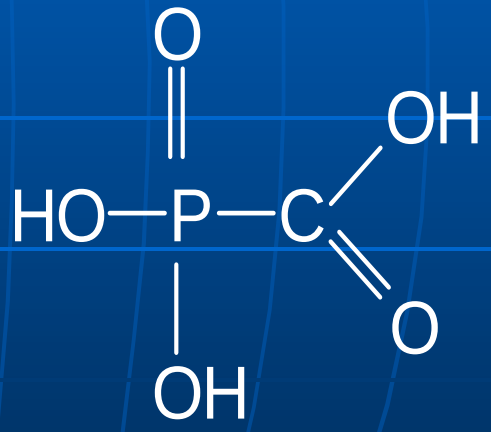
inhibiert/fixiert die HSV-Polymerase direkt.

Umgehung der Monophosphorylierung



Cidofovir

Foscarnet



Prävention des Herpes genitalis

- Expositionsprophylaxe
- Chemoprophylaxe
- Vakzination in Entwicklung unter Verwendung rekombinater Typen-spezifischer HSV-2 Glykoproteine. Erfolg fraglich.