Antiviral therapy of neurotropic herpesviruses

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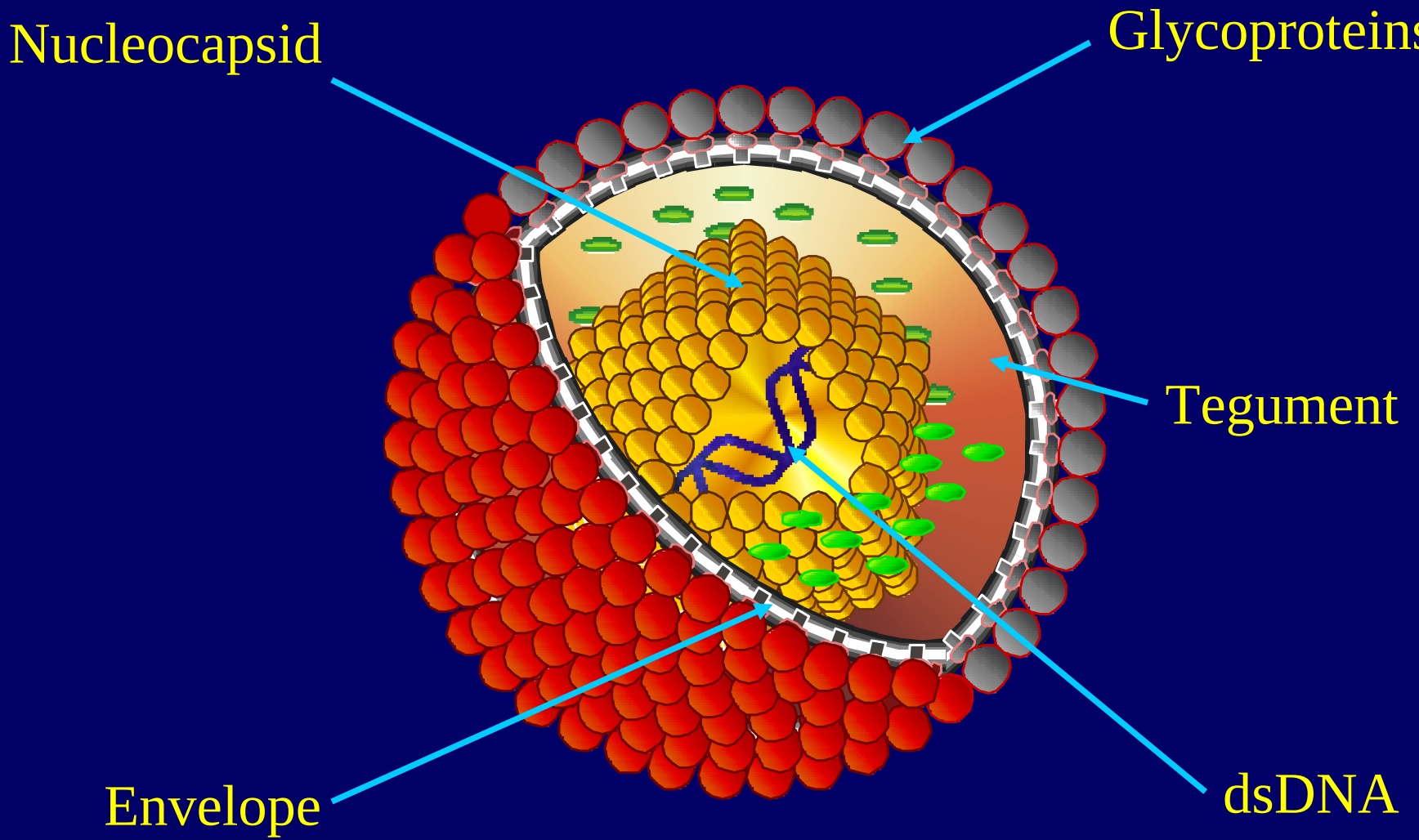
Structure of Herpesviruses



Treatment of Recurrent Genital Herpes

Three Options

- Episodic or (acute) intermittent treatment
- Chronic suppressive therapy
- Episodic suppressive therapy

Considerations for Suppressive Therapy

- Patient choice and willingness to take medication every day
- Frequent recurrences
- Severe recurrences (independent of frequency)
- Anxiety associated with recurrences
- Concern about preventing a recurrence
- Concern about impact of recurrences on sexual behaviour and social circumstances
- Transmission

Suppressive Management: Goals

- Enhance control of disease
- Reduce asymptomatic and symptomatic shedding
- Decrease risk of transmission of HSV virus
  - Person-to-person spread
  - Prevent neonatal transmission and/or need for Caesarean section
- Improve psychological well-being of HSV patients (reduce psychosexual morbidity)

Nationwide Survey

Many patients with recurrent genital herpes want suppressive therapy

- 80% of patients on episodic treatment wanted to learn about therapy to help prevent recurrences
- Nearly 40% with histories of 2–3 episodes/year would prefer daily treatment to help prevent recurrences
- Once-daily administration of medication is preferred
- But compliance drops over time -> breakthrough

Suppressive Therapy

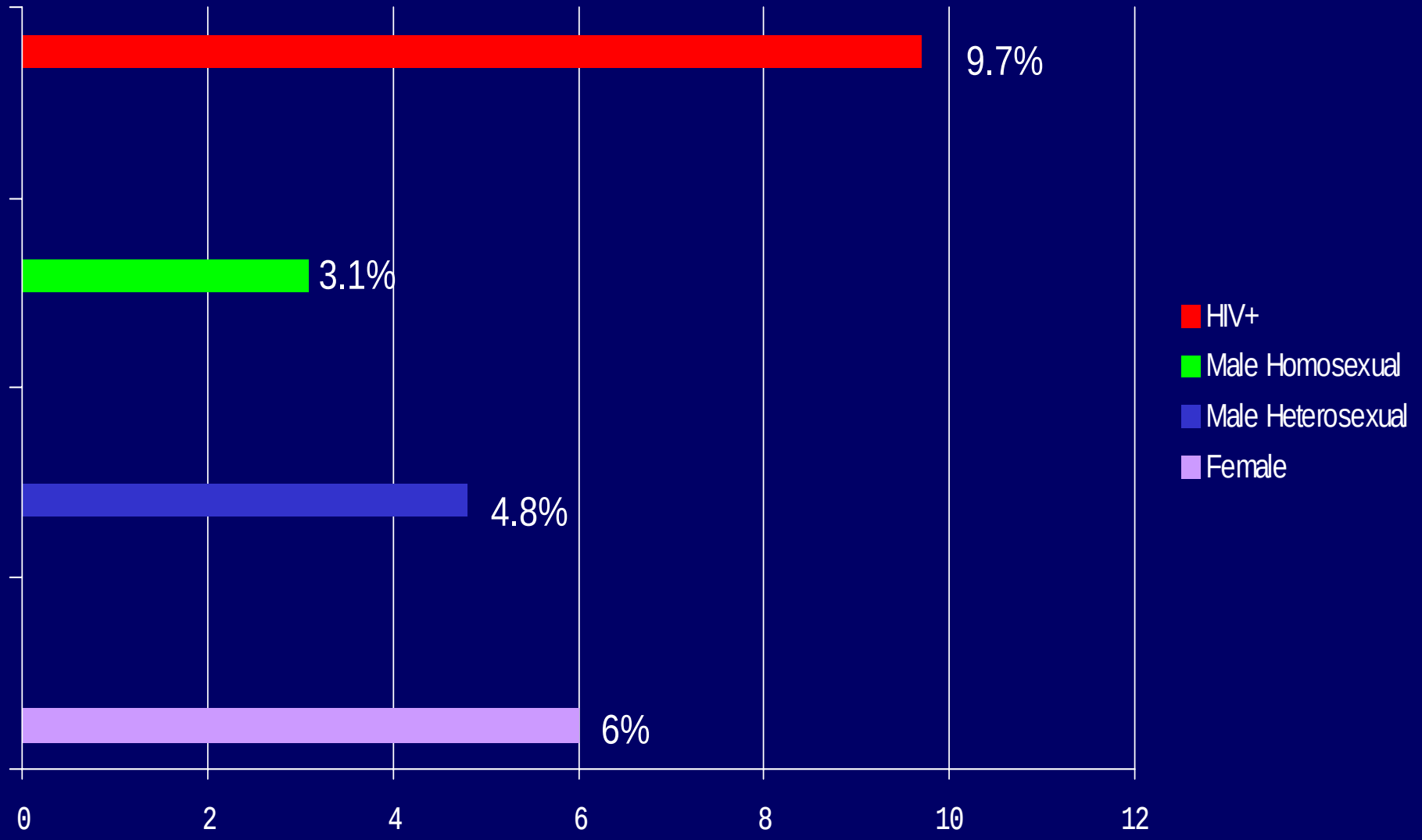
- Patient does not need to have >6 outbreaks in 12 months
- Discuss options for antiviral therapy at second visit
- Define impact of genital herpes on work, travel, family, personal relationships
- After a 6 months – one year on suppressive therapy, discuss whether to continue suppressive therapy & efficacy/ compliance

Episodic Suppression

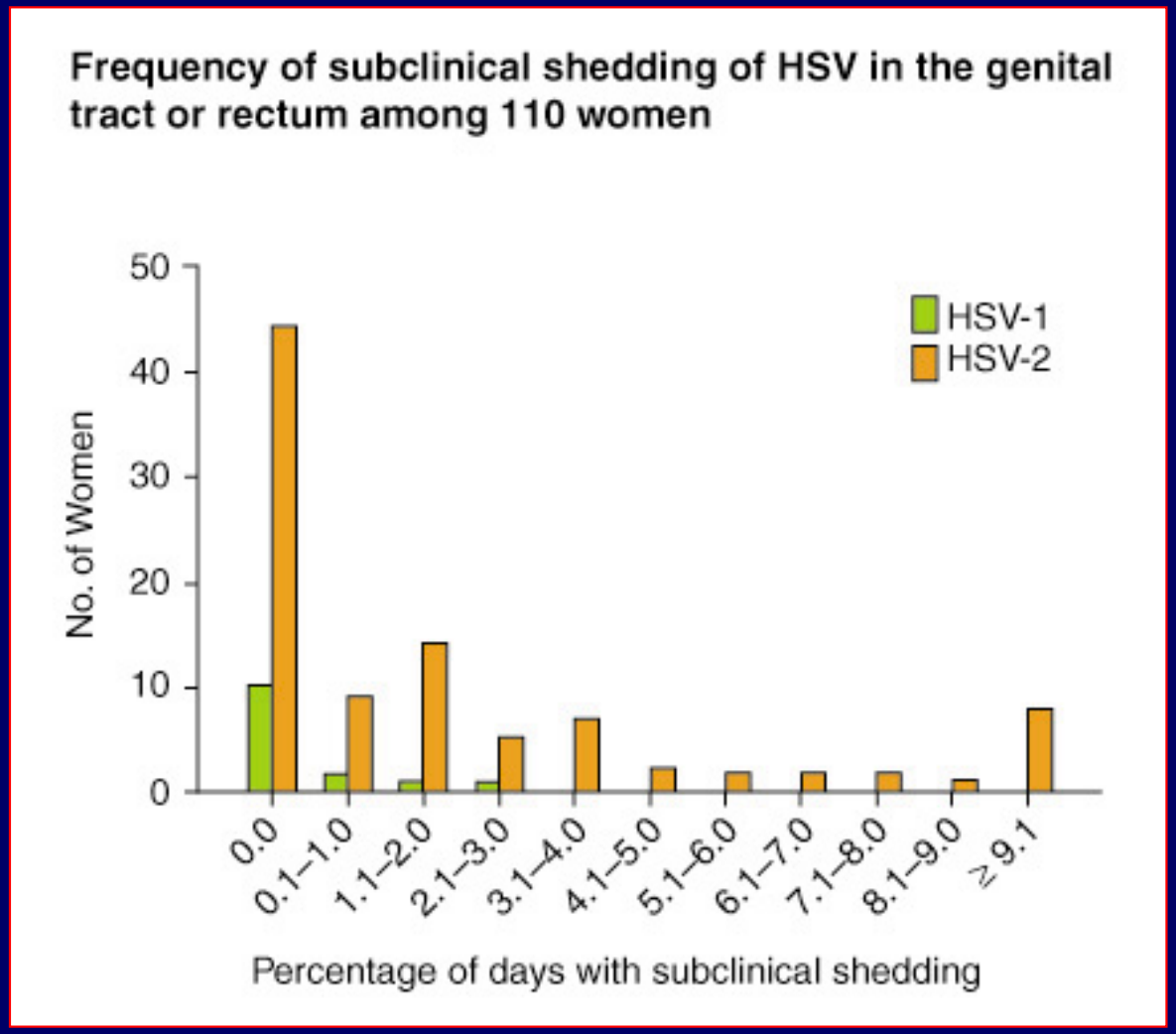
- Reasons:
  - New sexual relationship
  - Major life events i.e. weddings, final exams, vacations
  - To evaluate herpes symptoms or differentiate them from other symptoms
- Treatment must be initiated ~ 5 days in advance of desired event

Reducing the Risk of Transmission

Shedding of HSV2 (% of days)



Subclinical Shedding



Wald *N Eng J Med* 1995

Asymptomatic Viral Shedding

- The majority (>90%) of people with genital HSV-2 shed virus asymptomatically
- Genital herpes is frequently transmitted during periods of asymptomatic shedding – patients unaware
- Frequency of asymptomatic shedding is highest in first year after acquisition
- 75% of source partners find out about their own infection only when their newly-infected partner is diagnosed (Mertz, 1985)
- 60% of patients diagnosed only by serology learn to recognize their recurrent episodes (Langenberg, 1989; Wald, 2000)
- Uncommon with HSV-1 genital infection

Subclinical Shedding Studies

	Antiviral	Trial dose	Technique	ASx Reduction
Wald	Acyclovir	400 mg tid	PCR/ culture	71.3% (PCR), 95% (culture)
Sacks	Famciclovir	125 mg tid	culture	83%
Sacks	Famciclovir	250 mg tid	culture	87%
Wald	Acyclovir	400 mg bd	PCR/ culture	79% (PCR), 94% (culture)
Wald	Valacyclovir	500 mg bd	PCR/ culture	81% (PCR), 95% (culture)
Schacker (HIV)	Famciclovir	500 mg bd	culture	76%

Do Antivirals interrupt sexual transmission of HSV?

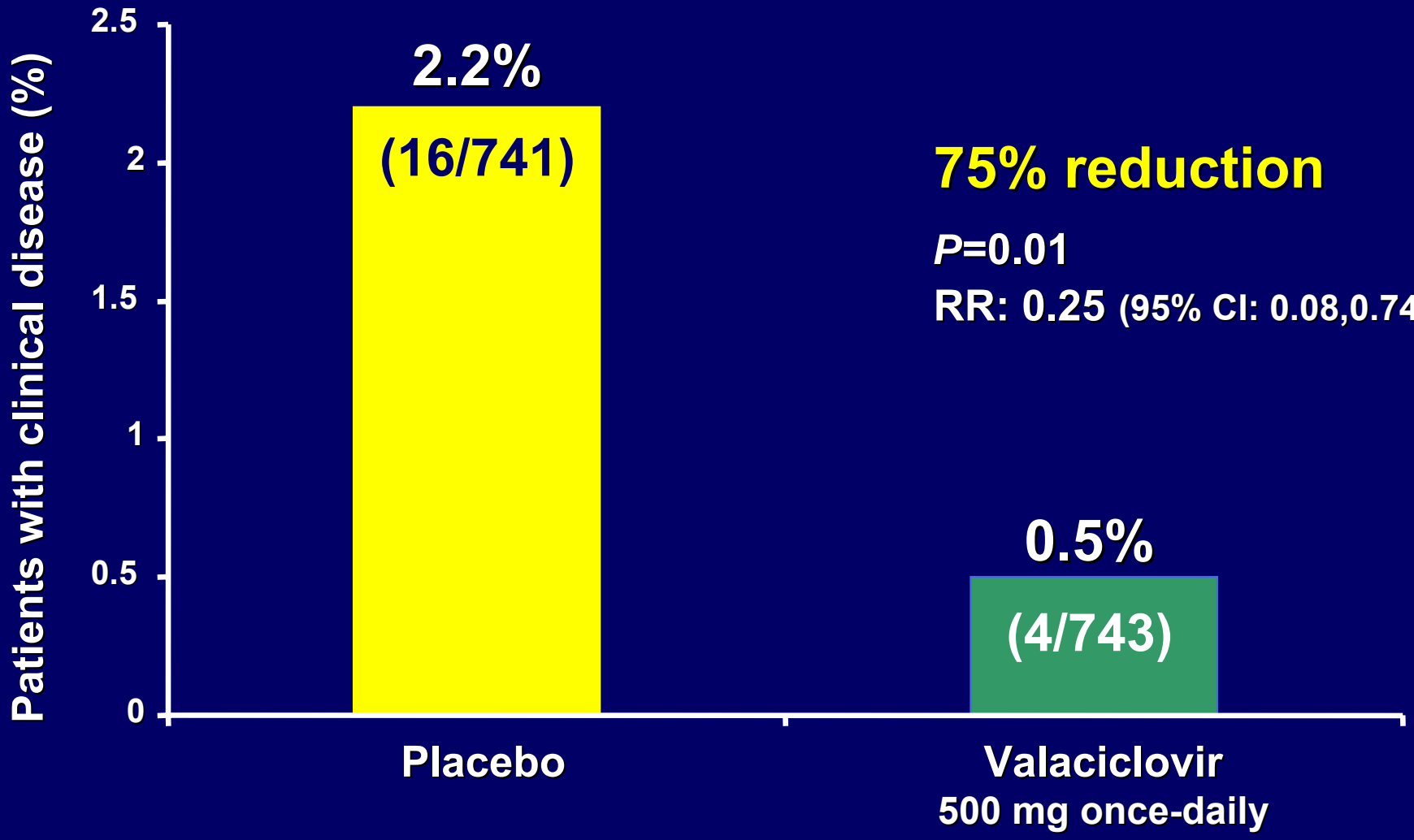
- 1500 couples in consort design
- Source partner:

  ≤ 9 episodes GHD per year

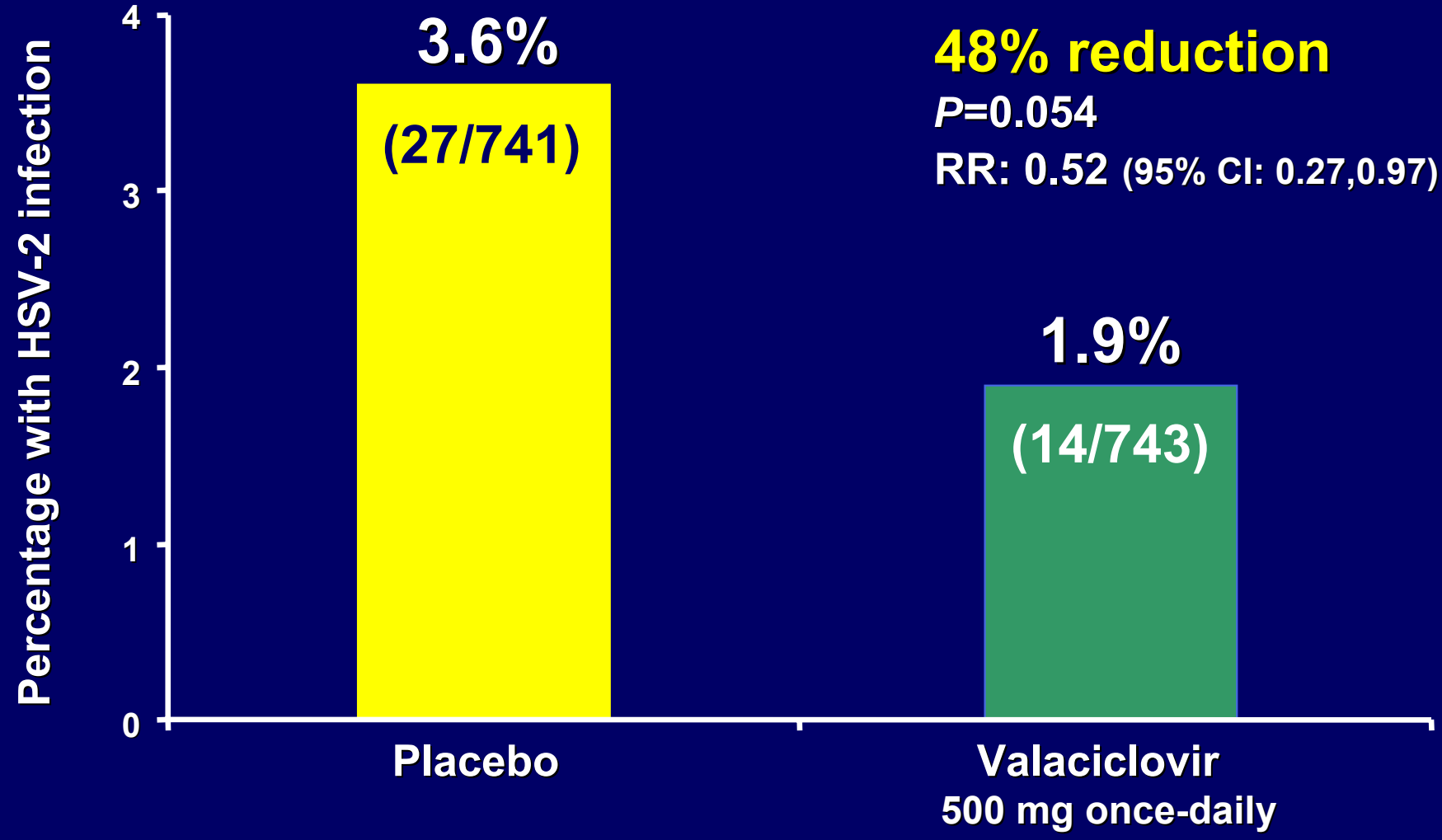
  allocated Placebo or Valtrex 500mg once daily[1]
- 8 months duration[2,3]

1. Reitano M, et al. JID 1998;178:603-610.
2. Corey L, et al. JAMA 1999;282:331-340.
3. Wald et al. JAMA 2001;285;3100-3106.

Proportion of Susceptible Partners With Symptomatic Genital Herpes



Proportion of Susceptible Partners Acquiring HSV-2 Infection



Clinical Messages

- Suppressive ACV, famciclovir and valaciclovir decreases symptomatic and asymptomatic shedding in immunocompetent persons.
- Famciclovir decreases HSV shedding in persons with HIV.
- Valaciclovir reduced transmission of HSV2 by ~50% and genital herpes by 75%
- In HIV+ patients HAART does not decrease HSV2 shedding

HIV and prior HSV2 infection

- Prior HSV2 infection (especially if recent) enhance HIV acquisition 3 fold (male to male/female)
- Several trials of ACV suppression in Africa, South America
- RDBPC trial of 821 HIV- HSV2+ female sex workers in Tanzania given ACV (400 mg bd) or placebo for 12-30 months
- No overall difference in acquisition of HIV 27/28)

Watson-Jones et al N Engl J Med 2008

Genital Herpes: Short Course Therapy

- 1,2,3 day courses = 5 day course of antivirals:

- Valaciclovir 3 days
- ACV 2 days
- FCV 1,2 days

Corey l et al Herpes 2007

Table 1: Short-course treatments for episodes of recurrent herpes genitalis

Reference	Treatment regimen	*n*	Episode length (days)	Healing time (days)	Duration of viral shedding (days)	Duration of pain (days)	Aborted lesions (%)
Wald[8]	ACV 800 mg bid, 2 days	30	4	4	1.04	-	27
	Placebo	47	6	6	2.44	-	5
Leone[6]	VCV 500 mg bid						
	3 days	402	4.4	4.4	-	2.9	25
	5 days	398	4.3	4.7	-	2.5	27
Strand[7]	VCV 500 mg bid						
	3 days	259	4.7	4.9	1.7	3	27
	5 days	272	4.6	4.5	1.8	2.8	21
Aoki[9]	FCV 1 g bid	163	-	4.3	-	0.9	23.3
	Placebo	166	-	6.1	-	1.5	12.7
FaST[10]	FCV 500 mg stat						
	+ 250 mg bid, 2 days	515	(24% [20, 28]* had lesions at 5.5 days)				7.6
	FCV 250 mg bid, 5 days	506	(28% [24, 32]* had lesions at 5.5 days)				9.5

ACV, aciclovir; bid, twice daily; FCV, famciclovir; VCV, valaciclovir.
*95% confidence interval.

Orolabial Herpes: Short Course Therapy

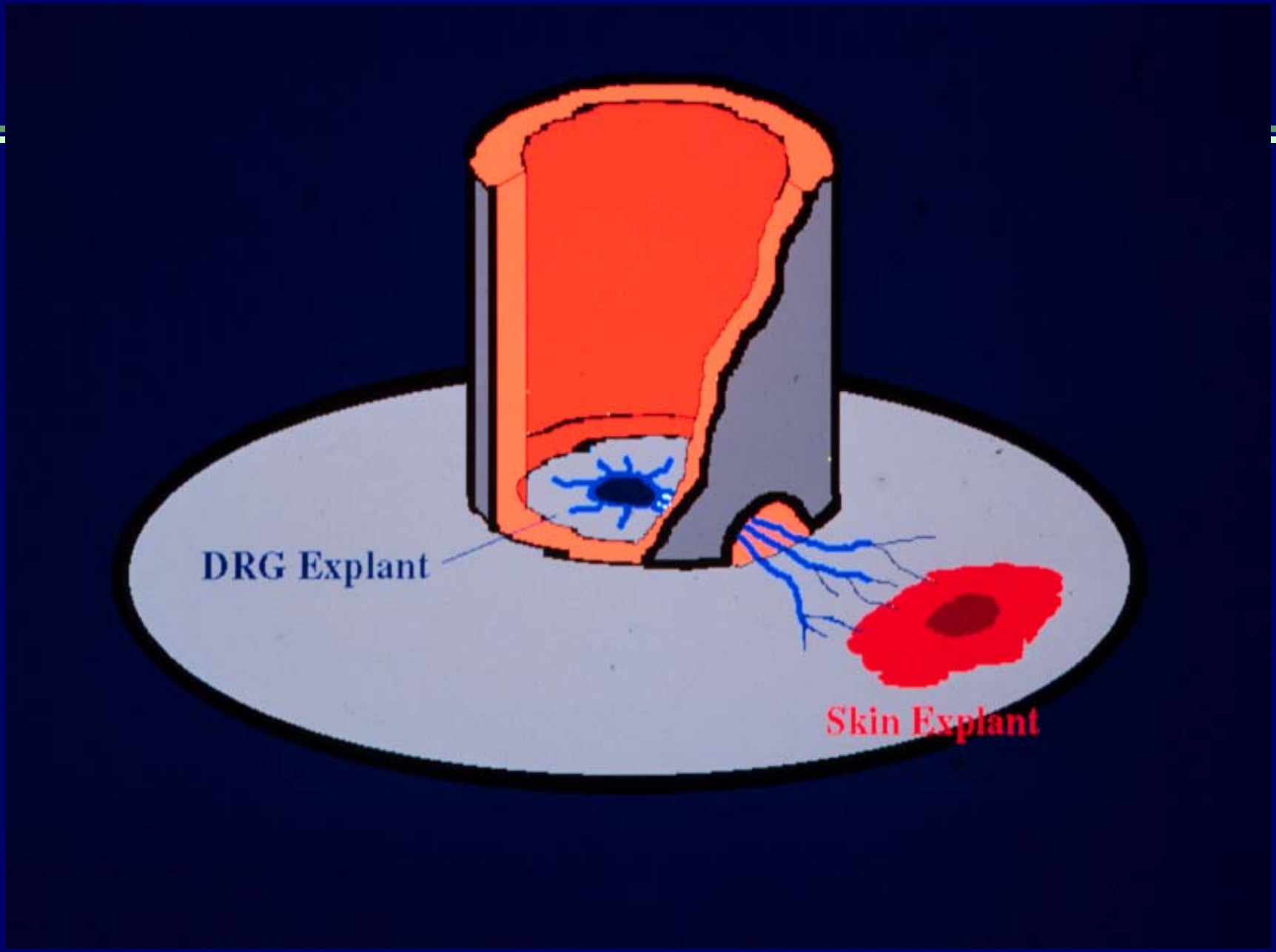
- Short course, high dose valaciclovir/famciclovir (1,2 or 4 dose): 1-2 days)
  - (? ± topical steroids)

  $\rightarrow\uparrow$ healing, $\downarrow$ pain, $\uparrow$ adherence to treatment
- ? Topical therapy (penciclovir, aciclovir) ± steroids may be useful
- Short term prophylaxis (Val, Fam): sun exposure, facial cosmetic procedures
- Long term prophylaxis: frequent episodes, erythema multiforme, severe facial atopic eczema

Gilbert et al Herpes 2007

Herpes Simplex infections: antiviral resistance

- In HSC/solid organ transplantation: up to 25% of HSV infections are ACV resistant
  - Thymidine kinase mutants (↓CMI) therefore susceptible to Foscarnet
- Rare HSV DNA polymerase mutants of HSV: resistant to Foscarnet
  - Remain susceptible to IV cidofovir but nephrotoxic (can use topical cidofovir with mucosal disease)


DRG Explant
Skin Explant

Herpes Simplex Encephalitis: little progress

- Genetic deficiency of Unc 93B and TLR3
  - $\rightarrow\uparrow$ susceptibility to HSE (? Via interferons/innate immunity)
- Exact role of adaptive immunity (CD4/CD8 lymphocytes) in immune control/immunopathology uncertain
  - ($\rightarrow$? Anti-inflammatory agents, anti-cytokine Mabs)
- Should therapy be prolonged (in newborn not adults – PCR evidence of disease persistence)
- NIAID trial of CSF VL and MRI for ,follow-up
  - $\rightarrow$? Prolonged oral VACV (high dose)

Whitley RJ Antiviral Research 2006

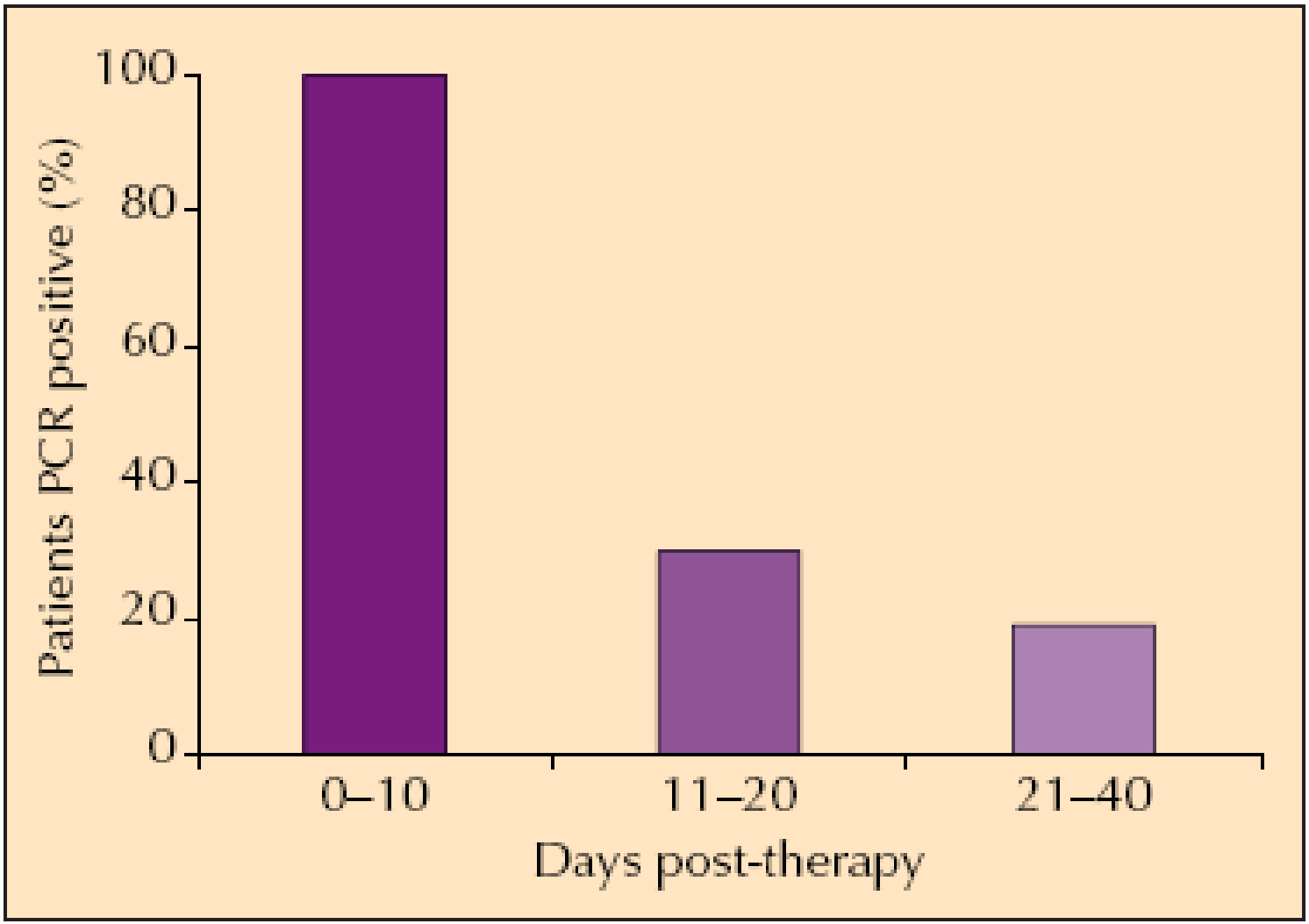
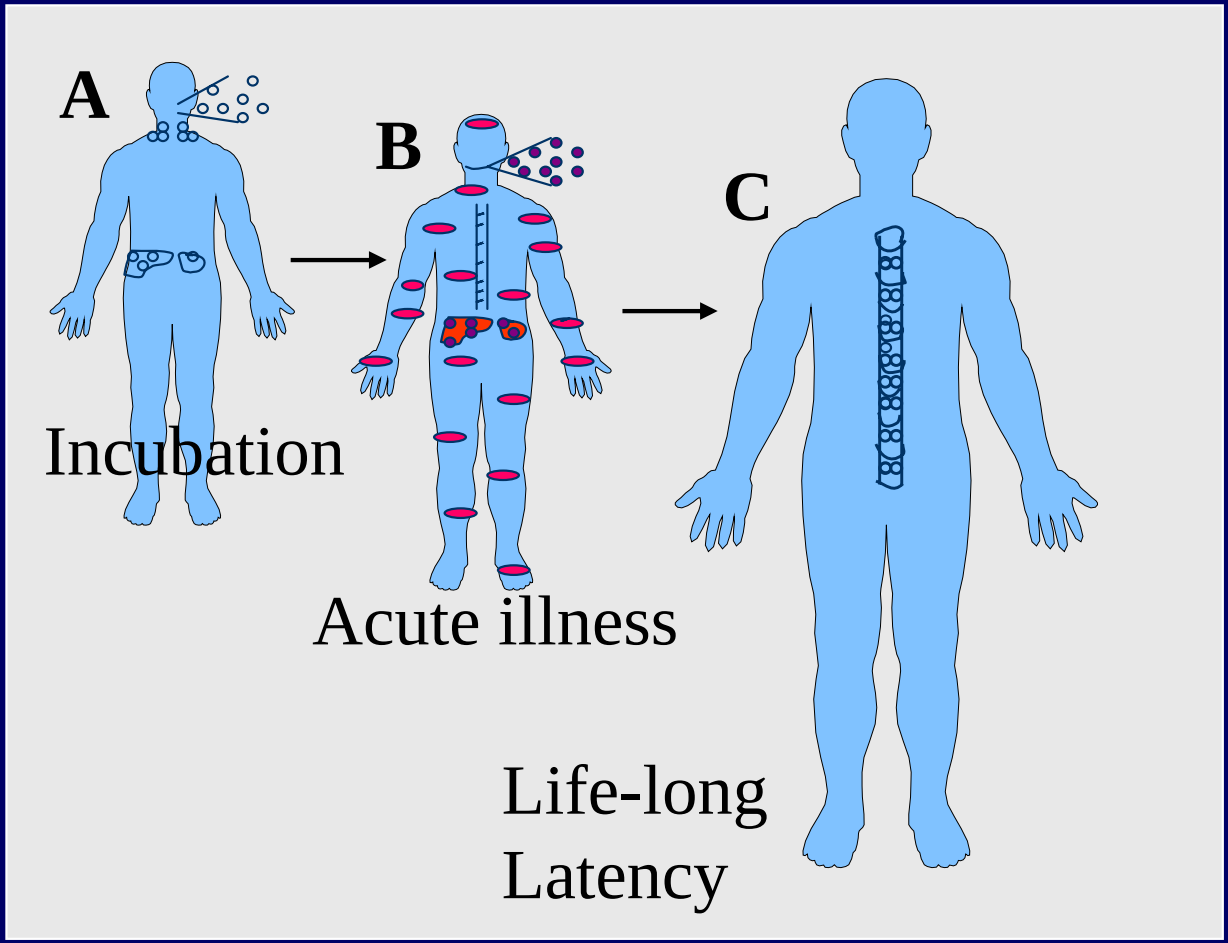


Figure 1:
Detection of HSV DNA in the CSF following onset of symptoms[23]

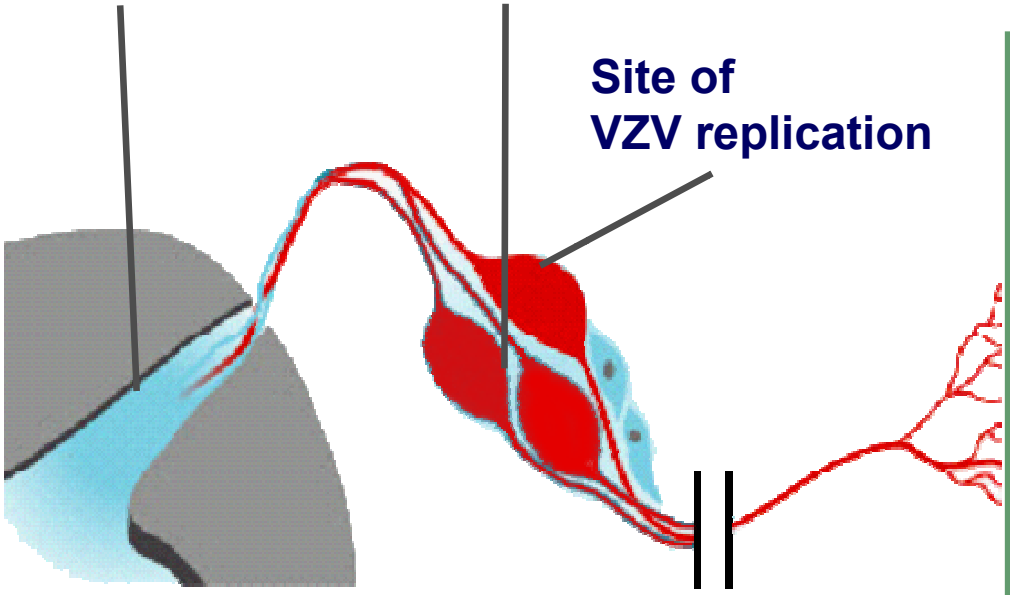
VZV pathogenesis



Courtesy C. Hood

- Entry through upper respiratory tract
- 10-21 day incubation
- Travels to regional lymph nodes, then liver spleen via Primary viremia
- Secondary viraemia (MN cells)- to skin/mucous membranes: vesicular rash
- Replication in epidermal cells, entry into nerve endings & transport to DRG to establish latency in sensory neurons
- Reactivation from DRG & transport to skin

Zoster: Latency and Reactivation



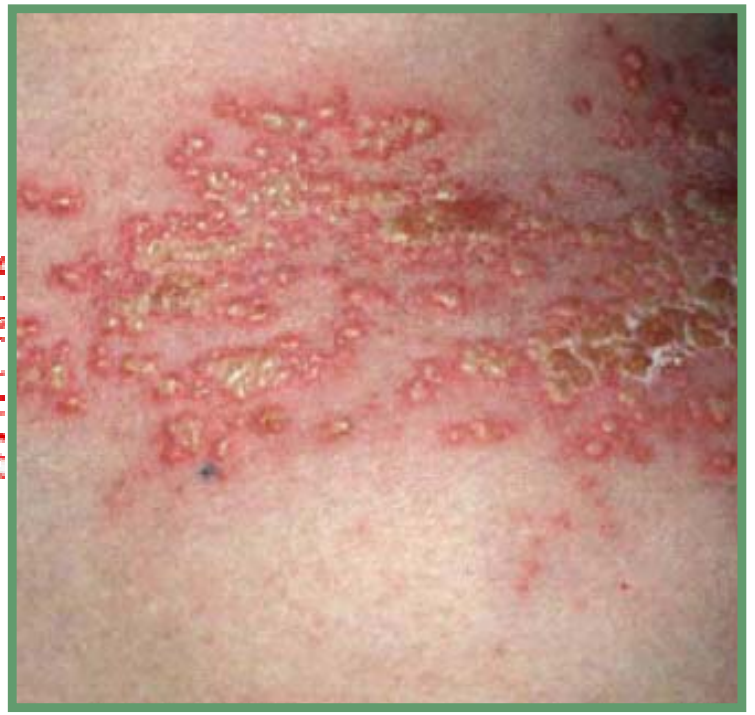
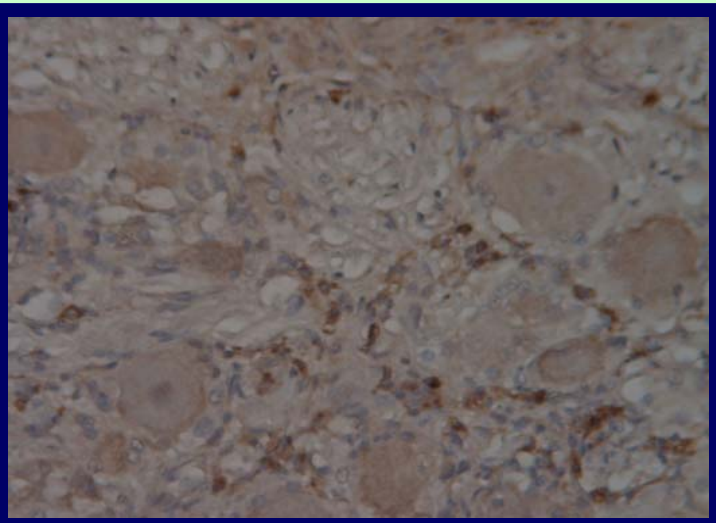
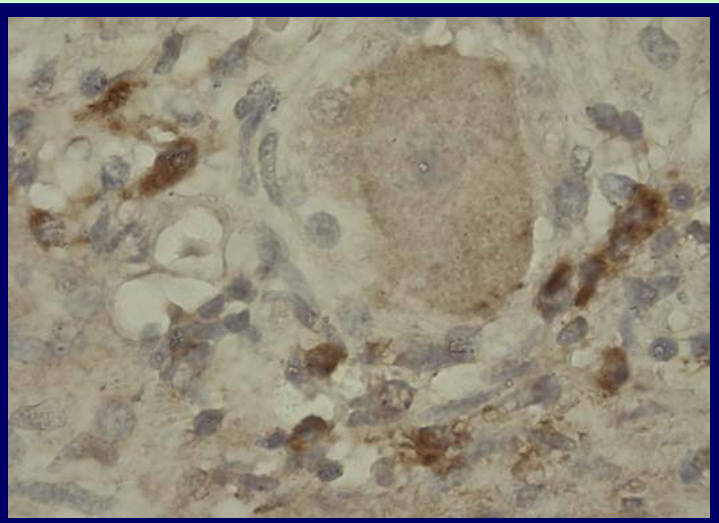


Image courtesy of Thomas P. Habif, MD.

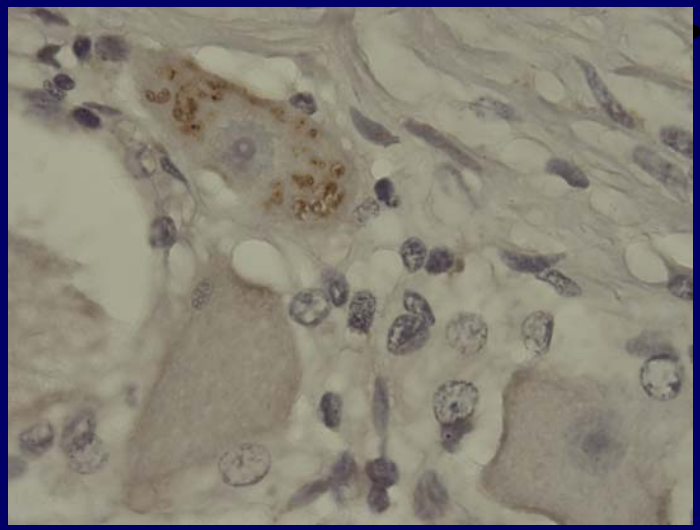
VZV expression in zoster ganglia

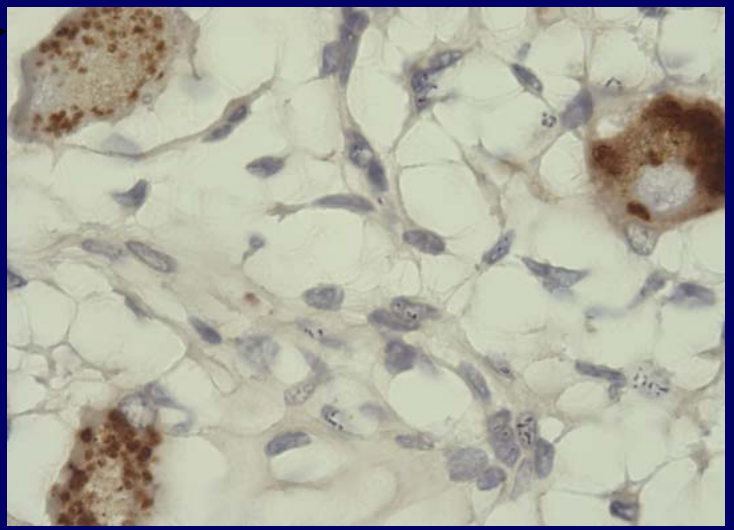
gB





gI



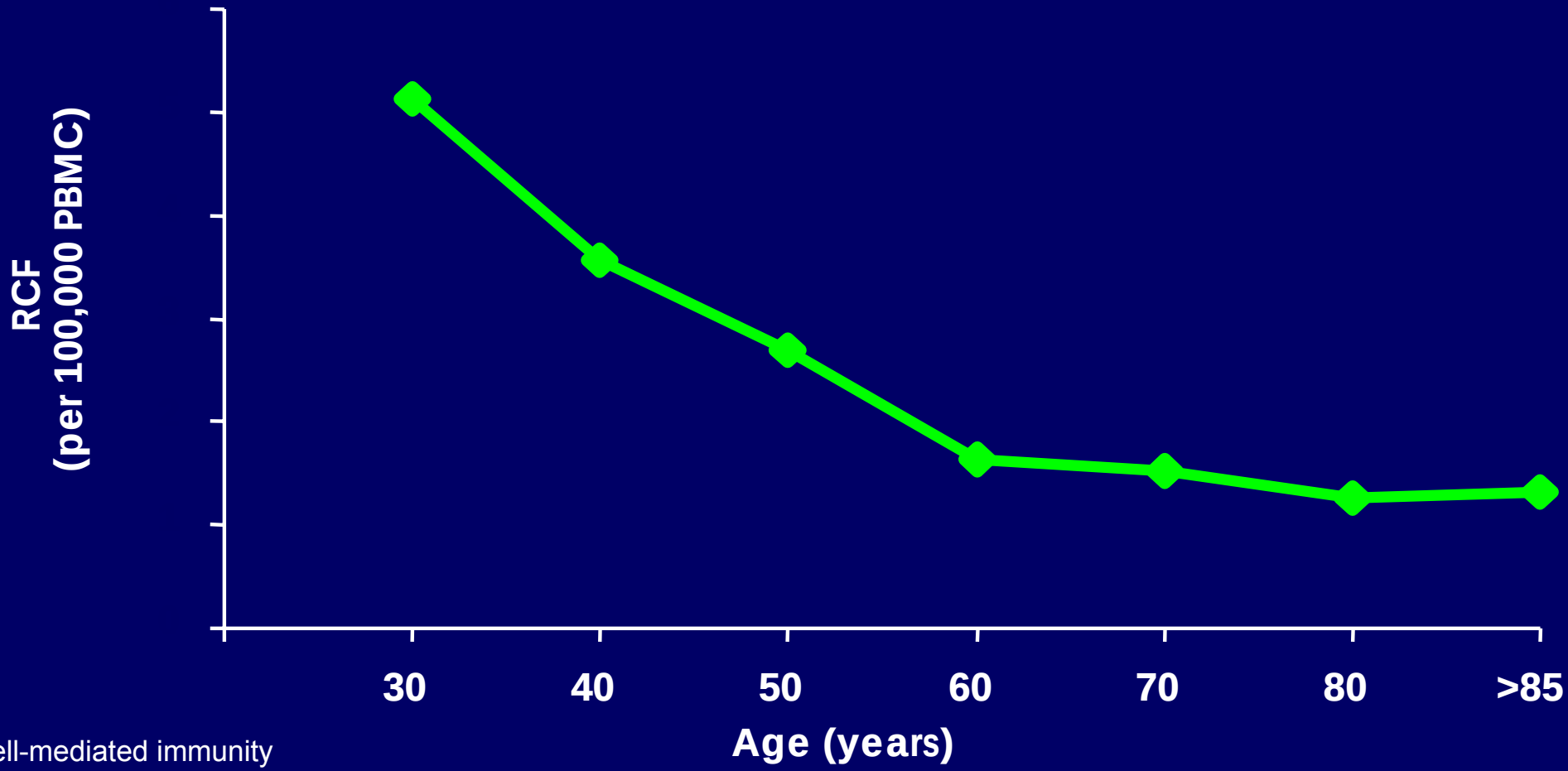


N3 (2.2%)

AI (22.3%)

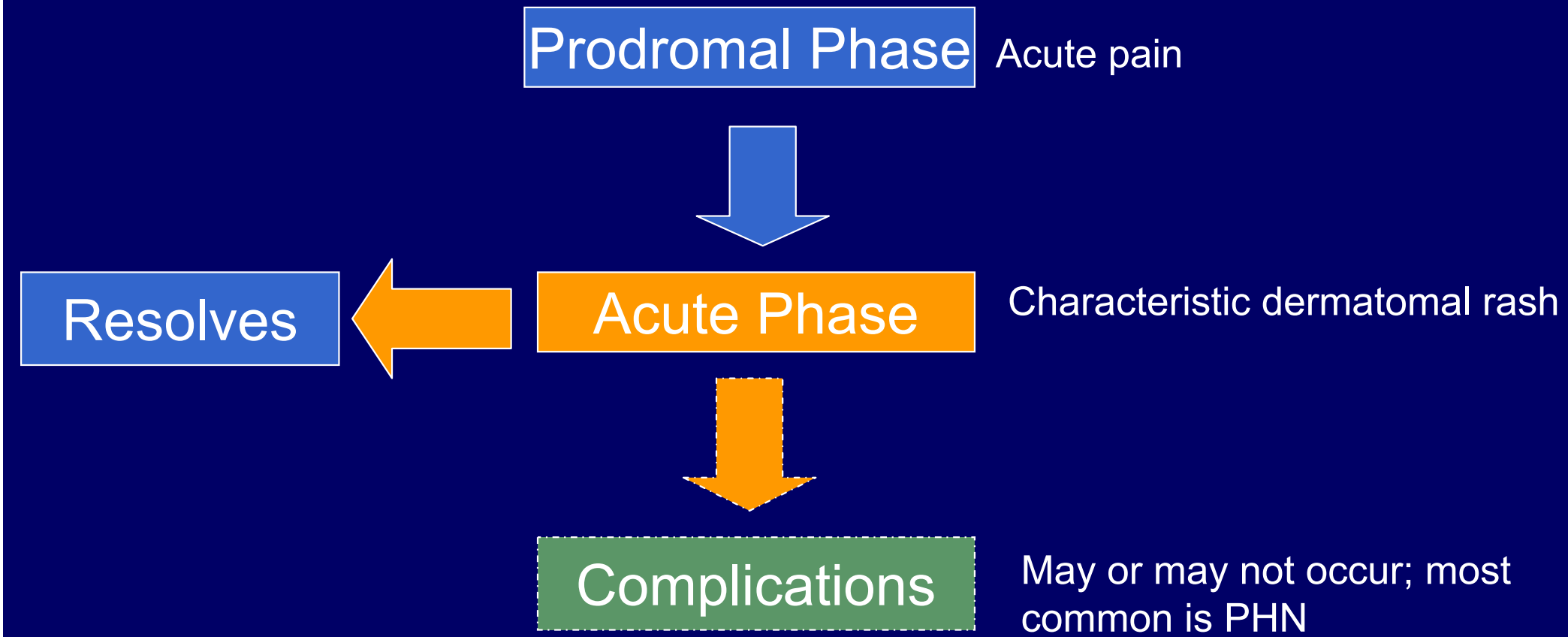
Glycoprotein expression is an indication of viral replication and productive infection. gI and gB are not expressed during latent infection.

CMI to VZV Decreases With Age



CMI=cell-mediated immunity
PBMC=peripheral blood mononuclear cell
RCF=responder cell frequency

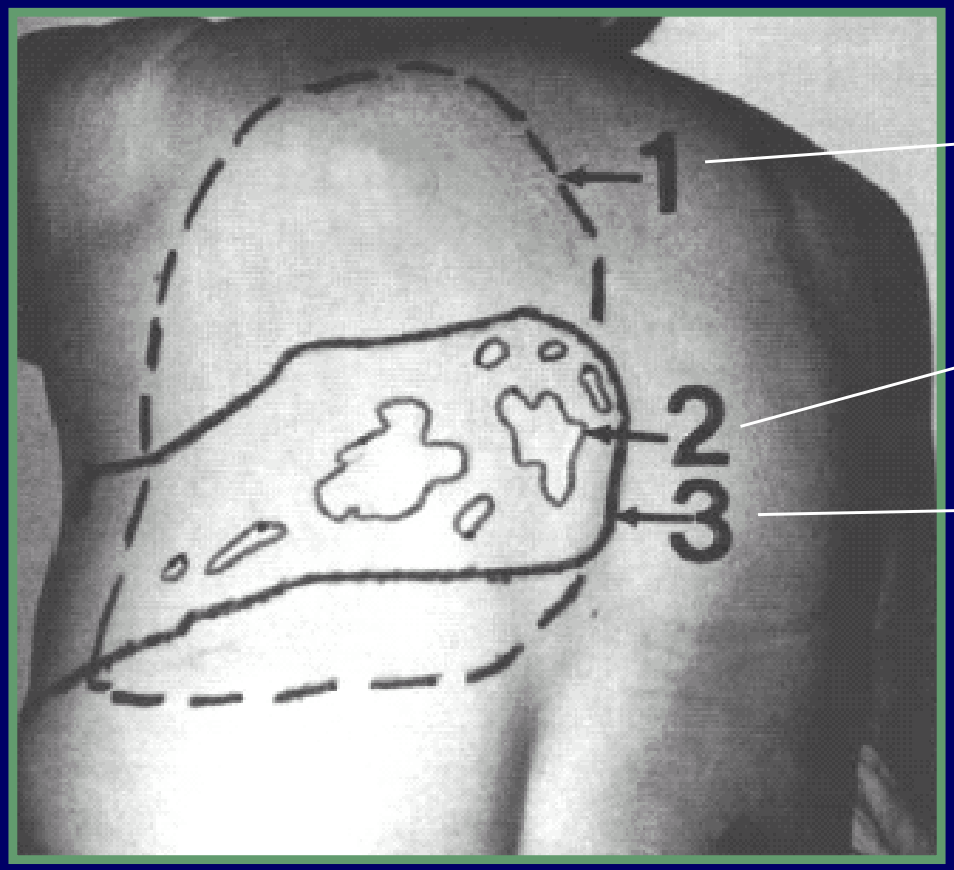
Clinical Manifestation of Zoster



1. Oxman MN. In: *Varicella-Zoster Virus: Virology and Clinical Management*. Cambridge: Cambridge University Press, 2000:246–275.

Zoster pain and Postherpetic Neuralgia

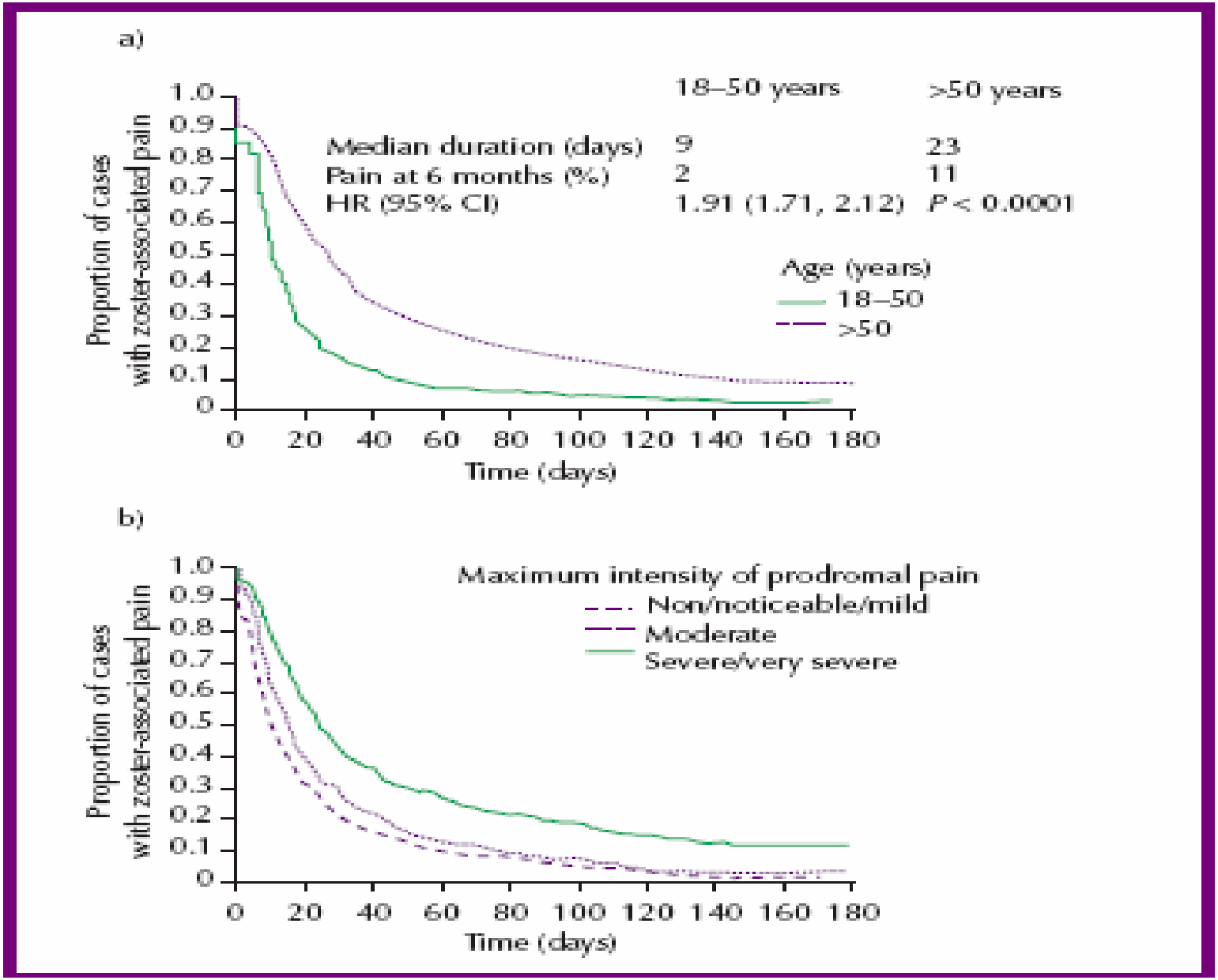
Map of Sensory Disturbances of PHN



- Allodynia
- Postherpetic scarring
- Reduced sensation to pinprick, temperature (cold), and touch

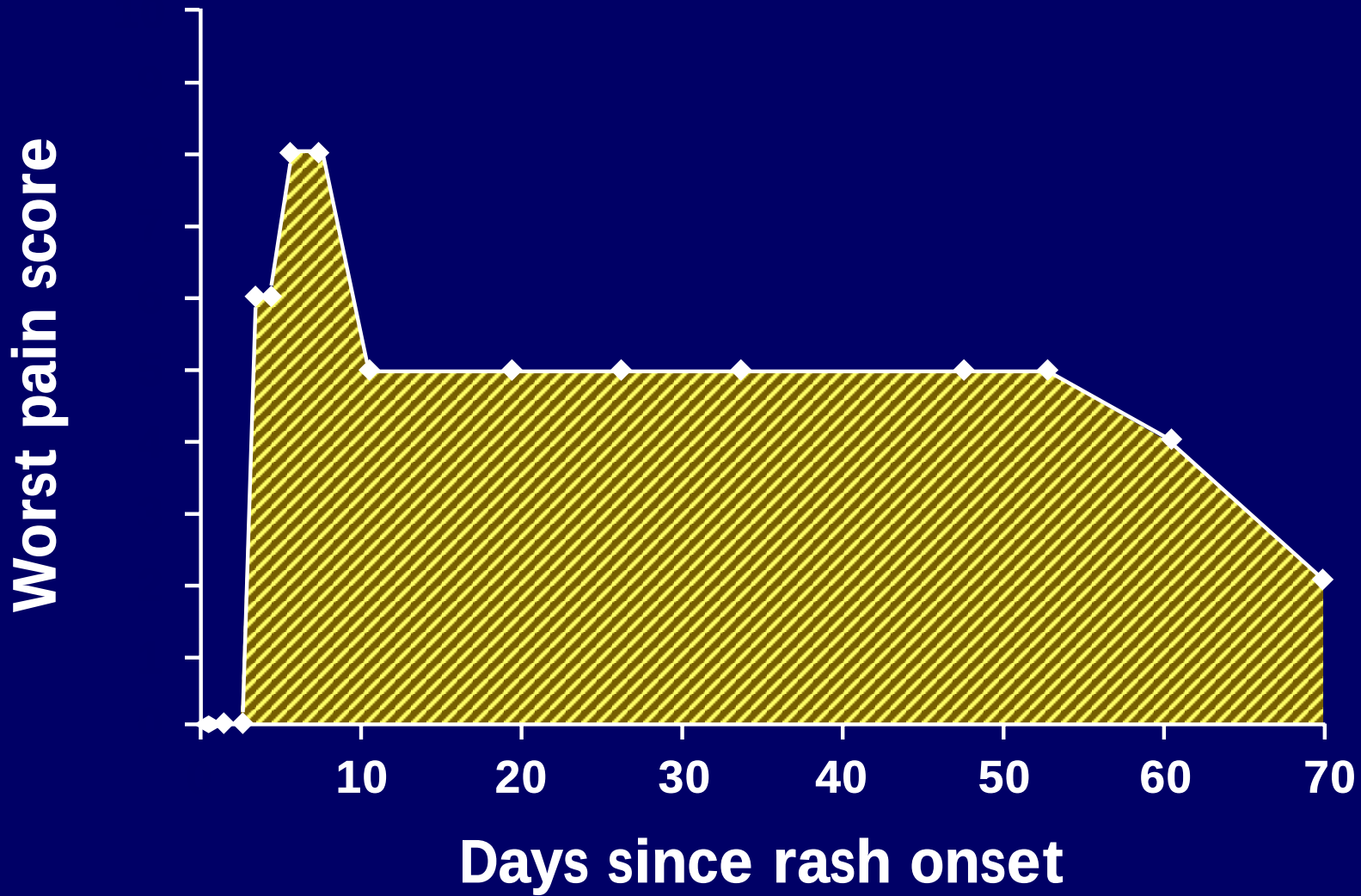
Reprinted from *Herpes Zoster and Postherpetic Neuralgia, 2nd Revised and Enlarged Edition*, Vol. 11, Watson CPN, Oaklander AL, Deck JH, The neuropathology of herpes zoster with particular reference to postherpetic neuralgia and its pathogenesis, pp167–182, 2001, with permission from Elsevier.

Natural history of zoster-associated pain



Decroix et al J Eur Acad Dermatol Venereal 2000;14(1):23-33

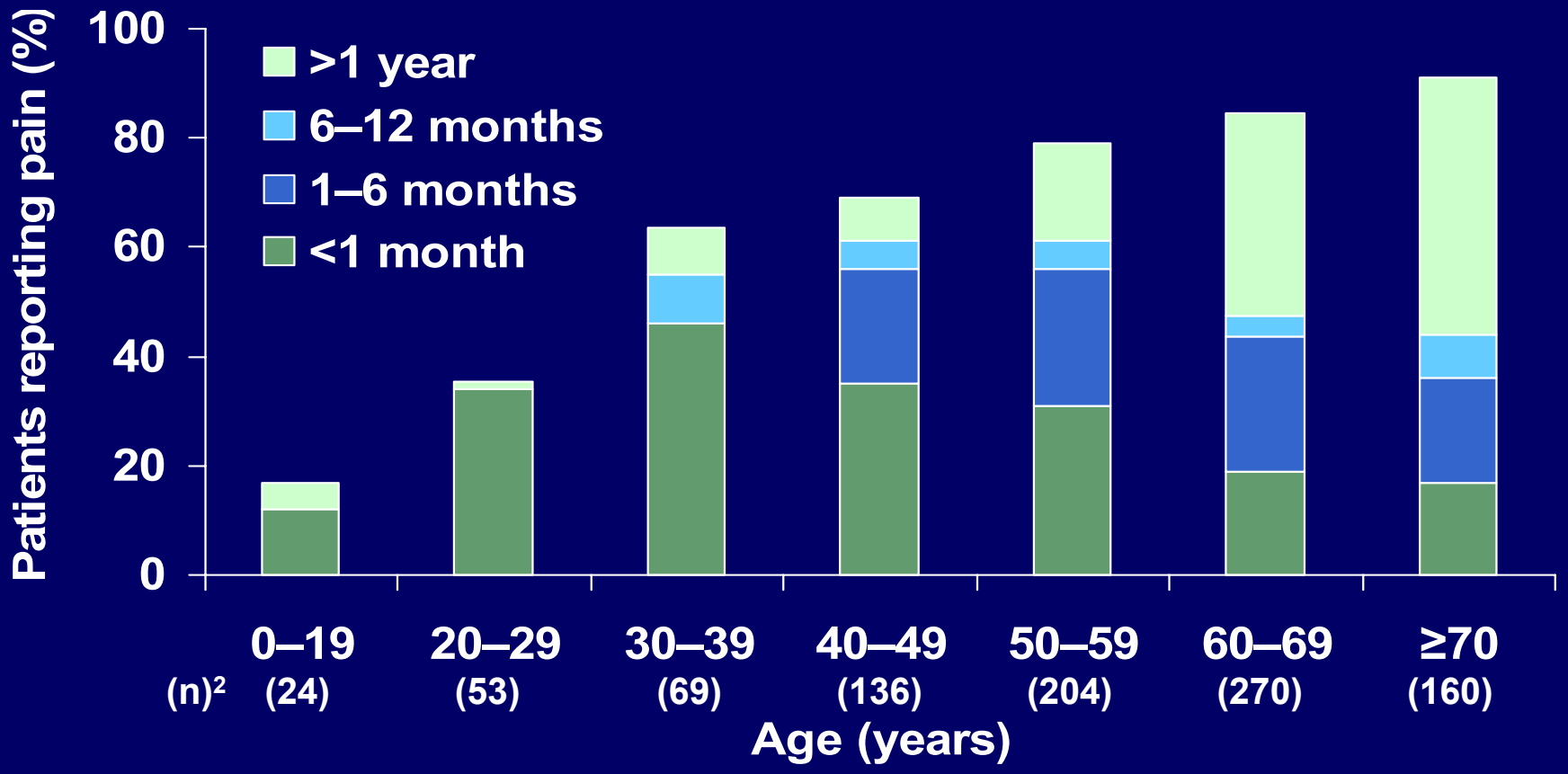
AUC of Worst Pain Scores Over Time



Definition of PHN

- Pain and Herpes Zoster
  - **Acute Herpetic Neuralgia**
    - Within 30 days following rash onset
  - **Sub acute herpetic neuralgia**
    - 30 days to 90 or 120 days after rash onset
  - **Post herpetic neuralgia (PHN)**
    - Pain Lasting longer than 90 or 120 days

Duration of Zoster-Associated Pain According to Age[1,2]



Adapted with permission from Kost RG et al.[1] © 1996 Massachusetts Medical Society.

1. Kost RG et al. *N Engl J Med* 1996;335:33–42. **2.** de Moragas JM et al. *AMA Arch Derm* 1957;75:193–196.

Treatment of Zoster and Postherpetic Neuralgia

Zoster: Goals of Therapy

- Major goals of therapy include:
  - Accelerating healing of zoster lesions[1]
  - Reducing viral replication and spread[2]
  - Limiting the duration and severity of acute and chronic pain[1]
  - Limiting other complications

1. Gnann JW Jr et al. *N Engl J Med* 2002;347:340–346. **2.** Straus SE et al. In: *Fitzpatrick's Dermatology in General Medicine*. 5th ed. Vol. 2. New York: McGraw-Hill, 1999:2427–2450.

Principles of Management

- Early presentation and clinical recognition
- Assess risk factors for PHN
- Antivirals
- Consider corticosteroids
- Aggressive pain management
- Referral for specific zoster syndromes
  - Ophthalmic
  - Disseminated

Dworkin RH et al. Antiviral Res 1997;33:73-85, Dworkin RH et al CID 2003;36:887-882, Cunningham AL et al BMJ 2000;321:778-9.

Antiviral Treatment

- Oral antivirals
  - Valaciclovir or Famciclovir >Aciclovir
  - within 72 hours
  - over 50 years
  - 7 days duration
    (laboratory resistance rare)
  - Reduce acute and prolonged pain by >40%

- Corticosteroids effective only for acute symptoms

  (Wood MJ et al NEJM 1994;330:896-900, Whitley RJ et al, Ann Intern Med 1996;125:376-383

- ? Do they have a practical role, especially in elderly

Continuing treatment problems & controversies

- How to improve uptake (only ~70%)
- Is FCV better than VACV?
  - Trial measurements
    - PHN, ZAP
    - Pain severity

    (approx equal)
- Treat after 72 hours of rash?

  (Decroix J et al J Eur Acad Dermatol Venerol 2000;14:23-33)
  - If severe pain?
  - If new vesicles?
- Antivirals for people <50 years?
- Do we need better antivirals?

Preventing PHN?

Antivirals[1]

Tricyclic Antidepressants[1]

Sympathetic blocks

1= controlled trials

Treatment of PHN: Evidence from Clinical Trials none[1], negative[2], inadequate[3], good [4]

TENS[1]
Sympathetic blocks[1]
Antidepressants[3]
Analgesics[1,4]
- opioids eg tramadol
Antiepileptic drugs[2,3]
carbamazepine, phenytoin, lamotrigine
Gabapentin, pregabelin [4]
NMDA antagonists[2]
Topical preparations (capsaicin, lignocaine)
Intrathecal steroids [4?]

Shingles Prevention Study (SPS)

- A double-blind, placebo-controlled trial
  - 22 Sites
- Live, attenuated VZV vaccine
  - Oka/Merck strain (Median = 24,600 pfu)
  - 14-fold greater titer than childhood vaccine
- Subjects = 38,500
  - Median age = 69 years
  - 60-69 years = 20,750
  - ≥ 70 years = 17,800 (46%)
  - ≥ 80 years = ~2500 (>6.5%)

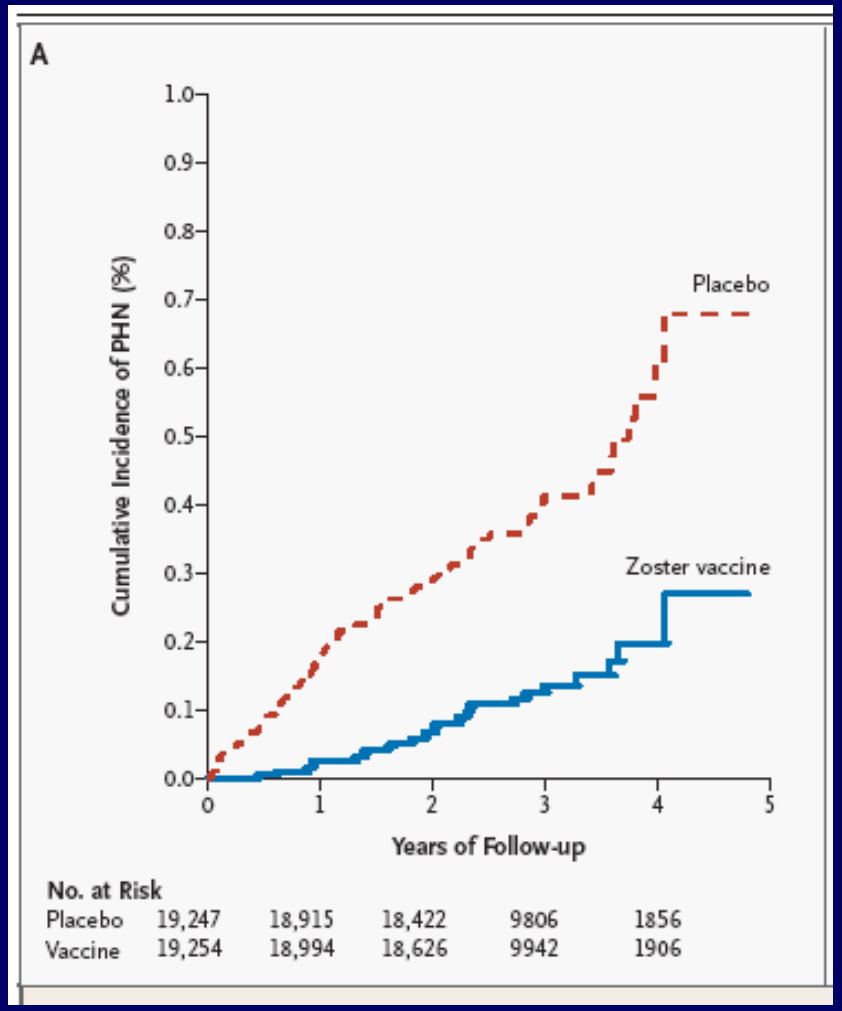
Efficacy*

- Burden Of Illness
  - 61.1% (51.1 – 69.1%)
- Post Herpetic Neuralgia
  - 66.5% (47.5 – 79%)
- HZ Incidence
  - 51.3% (44.2 – 57.6%)

Oxman M et al N Engl J Med 2007

Post herpetic neuralgia (PHN)

- **Definition**
  - Persistent pain &/or other sensory symptoms (including pain, allodynia, itching, or numbness) in the zoster dermatome
  - Definition of onset varies:
    > 30 days to > 90 days post onset of rash
  - ?Severity
- **Incidence**
  - 8-70%



Gnann & Whitley 2002 N Engl J Med. 2002 Aug 1;347(5):340-6:Helgason et al BMJ 2000;321:794-6; Dworkin et al Antiviral research 1997:33(2): 73-85; Choo et al Arch Int med 1997;157:1217-24

New Paradigm for management of Zoster

- Immunize all at age 60 (?earlier: 50 or 55)
- Treat breakthrough zoster or zoster in unimmunized with valaciclovir/famciclovir

Cytomegalovirus retinitis in the era of HAART

- Since HAART introduced in 1996 – marked ↓ CMV retinitis (CD4 counts <50)
- Now CMV retinitis in:
  - HAART naïve
  - HAART unresponsive/intolerant
- New challenges:
  - Drug resistant CMV
  - Immune recovery uveitis

Sobrin L et al Int Ophthalmol Clinic 2007

Treatment of CMV retinitis

- Induction phase:
  - IV ganciclovir for 2-3 weeks
  - Or Foscarnet
  - Or in some carefully selected cases (peripheral): valganciclovir 900mg daily for 3 weeks
- Maintenance phase:
  - HAART naïve: VGCV 900mg 0 daily (or IV GCV/foscarnet/cidofovir)
  - HAART unresponsive: ?GCV implant $\rightarrow \downarrow$ recurrence rate
  - Withdraw anti CMV maintenance treatment: once CD4 >150 for 3 months

CMV resistance to Ganciclovir

- 25-33% of patients after 9/12 treatment (i.e. unresponsive to HAART)

- Tests:

  Phenotypic testing: complex, slow

  - ?viral load helpful – if low resistance is unlikely
  - Direct sequencing for UL97 mutations?

Immune recovery uveitis

- Patients with pre-existing retinitis (active/inactive) $\rightarrow$ HAART $\rightarrow \uparrow$ CD4 counts: 5-30% $\rightarrow$ uvetis
  - 1-8 months after commencement
  - Immunopathologic response to CMV antigens
  - Floaters, loss of vision
  - Treatment: oral prednisone (no reactivation of retinitis)

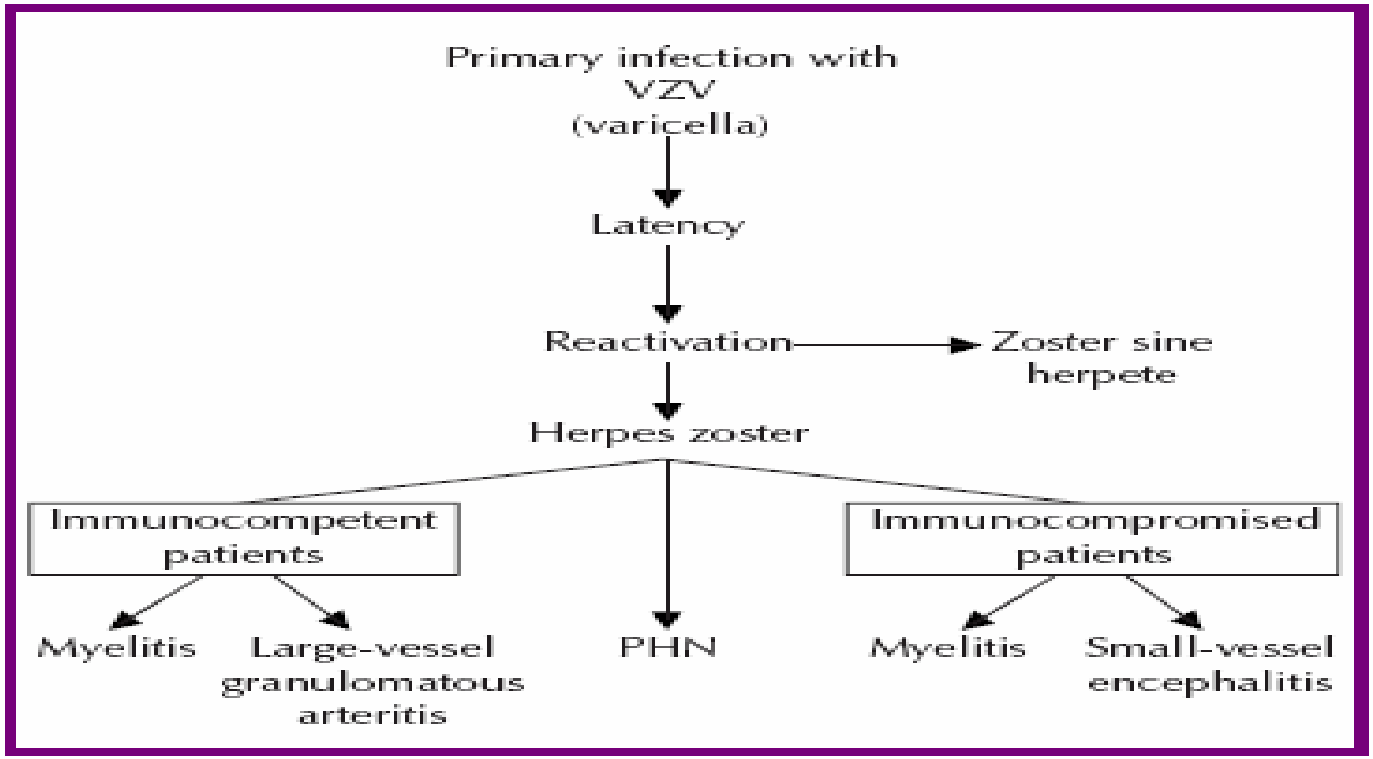
CMV retinitis after transplantation

- Risk factors
  - Haemopoietic stem cell transplant
  - CMV seropositive pre-treatment
  - CMV reactivation before day 100
  - Chronic GVHD
- Rare, often delayed (9/12 to 1 year)
- Asymptomatic to severe
- Part of multi-organ involvement, viraemia
- Variable response to antiviral therapy and high rate of recurrence (20%)
  - ? $\rightarrow$ prolonged oral VGCV

Eid AJ et al Transplant Infect Dis 2007

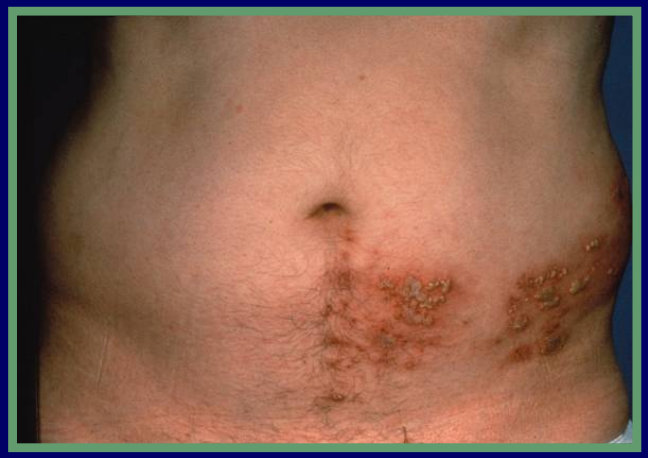
Natural history of zoster

FIGURE 1: Natural history of herpes zoster



Gilden et al NEJM 2000;342:635-45

Zoster: Dermatomal Distribution



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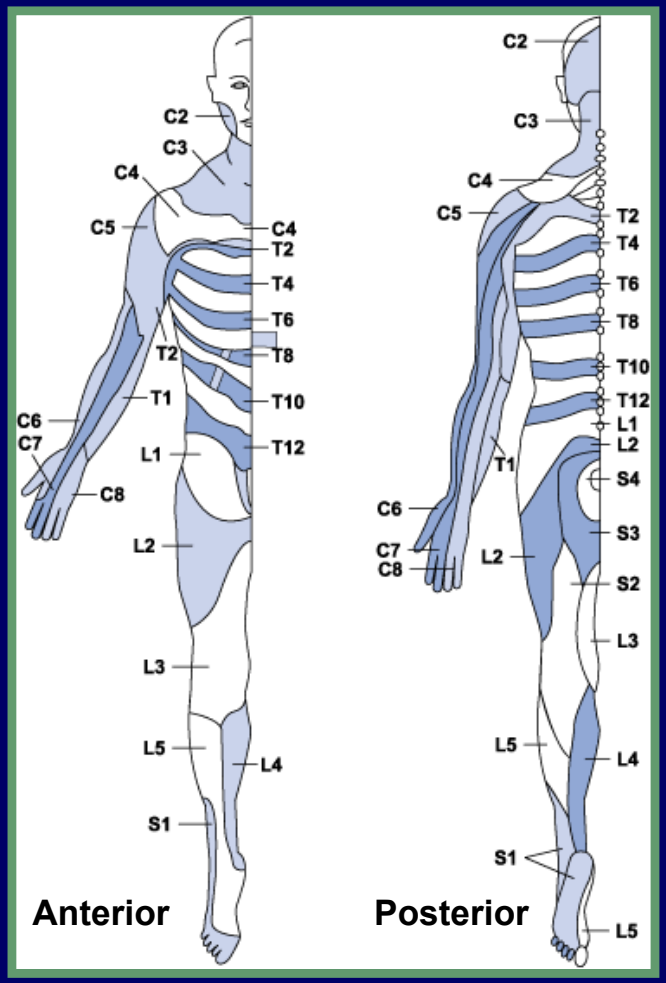


Asbury AK.[1] ©2001. Adapted with permission of McGraw-Hill.

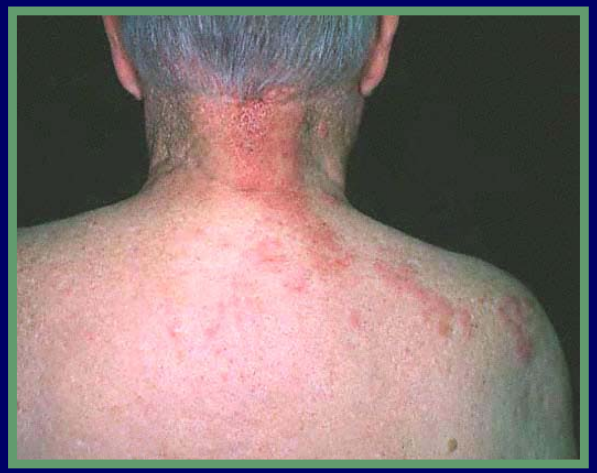


Image courtesy of Thomas P. Habif, MD.

1. Asbury AK. In: *Harrison's Principles of Internal Medicine*. 15th ed. New York: McGraw-Hill, 2001:128–132.

Genital Herpes: CDC Treatment Recommendations

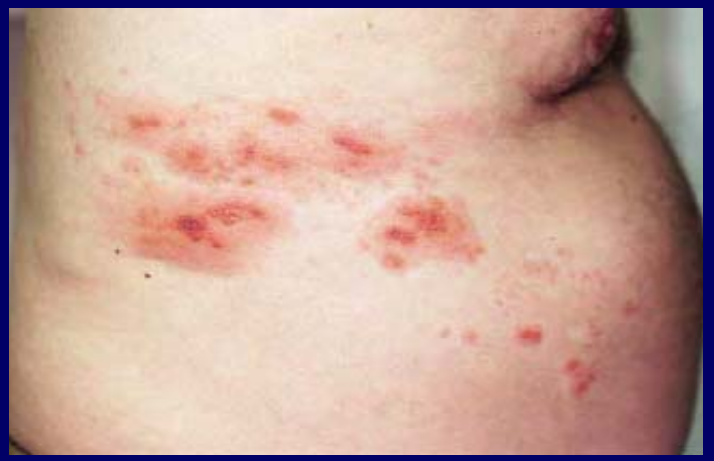
	First clinical genital herpes episode (mg for 7–10 days)	Recurrent genital herpes	
		episodic (mg × days)	suppressive (mg, daily)
Valaciclovir	1000 bid	500 bid (3†-5 d) 1000 qd (5 d)	500 qd‡ 1000 qd
Acyclovir	400 tid 200 5×/day	400 tid (5 d) 800 bid (5 d) 200 5×/day (5 d)	400 bid
Famciclovir	250 tid*	125 bid (5 d)	250 bid up to 1 year

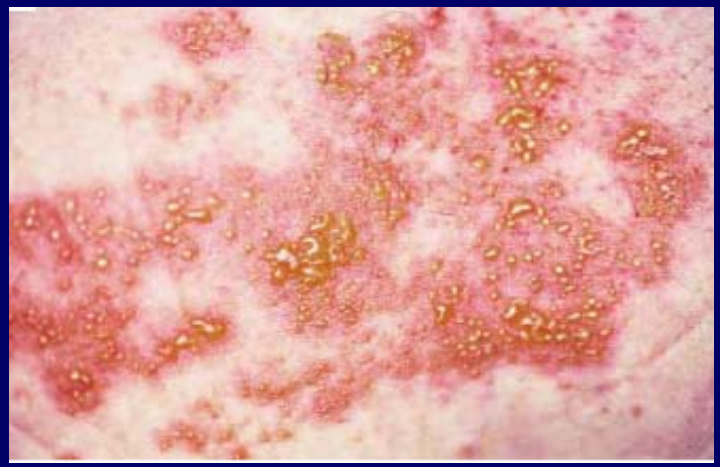
*Not FDA approved
†New FDA-approved dosing
‡May be less effective in patients who have very frequent recurrences (≥10 episodes/year)

Clinical Presentation

- **Prodrome**
  Headache, photophobia, malaise

- **Acute stage**
  Localised pain or other sensations
  (tingling, itching or burning or lancinating severe pain)
- **Rash**
  - Erythematous maculopapular rash → clusters of vesicles (over 3-5 days) → pustules, ulcers then crusts (7-10 days)→ healing (2-4 weeks)
  - Dermatomal and unilateral
  - Occasional (20%) overlap in dermatomes
  - Thorax> face> elsewhere
  - Occasional extradermatomal lesions





Gnann & Whitley 2002 N Engl J Med. 2002 Aug 1;347(5):340-6: Johnson and Patrick

Long-term Suppression: Safety

- Safety data available for up to 20 years of continuous use
- No routine safety tests (eg liver or kidney) needed