

# **Cytomegalovirus in Immunosuppressed Patients**

Holger Hebart, MD

Department of Internal Medicine

Klinikum Schwaebisch Gmuend

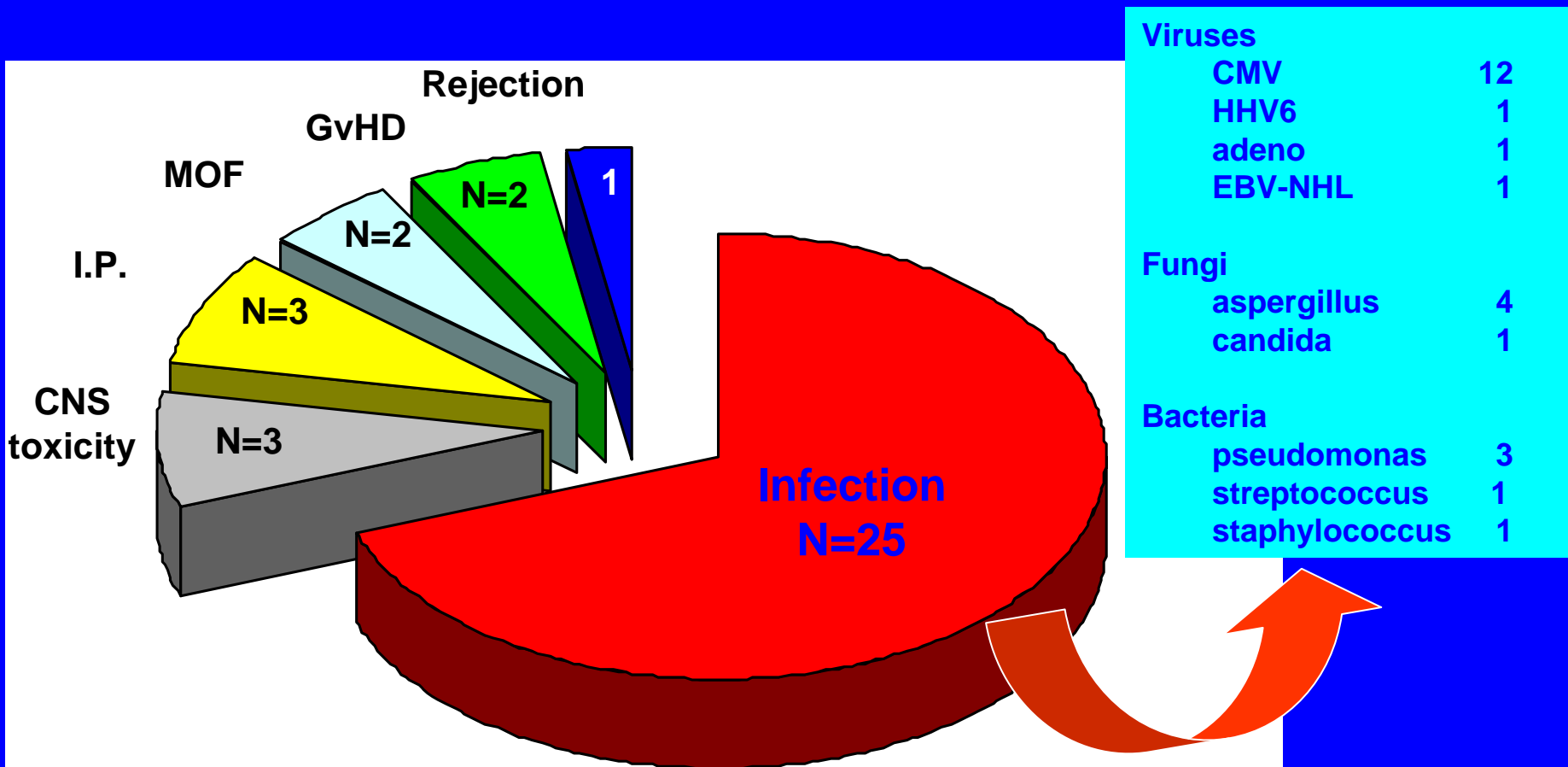
Germany

# Immunocompromised Patients at risk for CMV disease

- Inborn errors of immunodeficiency
- **Acquired immune defects**
  - Organ transplantation (solid organs,SCT)
  - Infections (AIDS, etc.)
  - Immunosuppressive drugs
    - nucleoside analogs
    - high-dose corticosteroids
    - anti-T-cell antibodies
  - Autoimmune diseases
  - Very low birth weight infants

# Allogeneic Stem Cell Transplantation

Transplantation-associated Mortality 36%



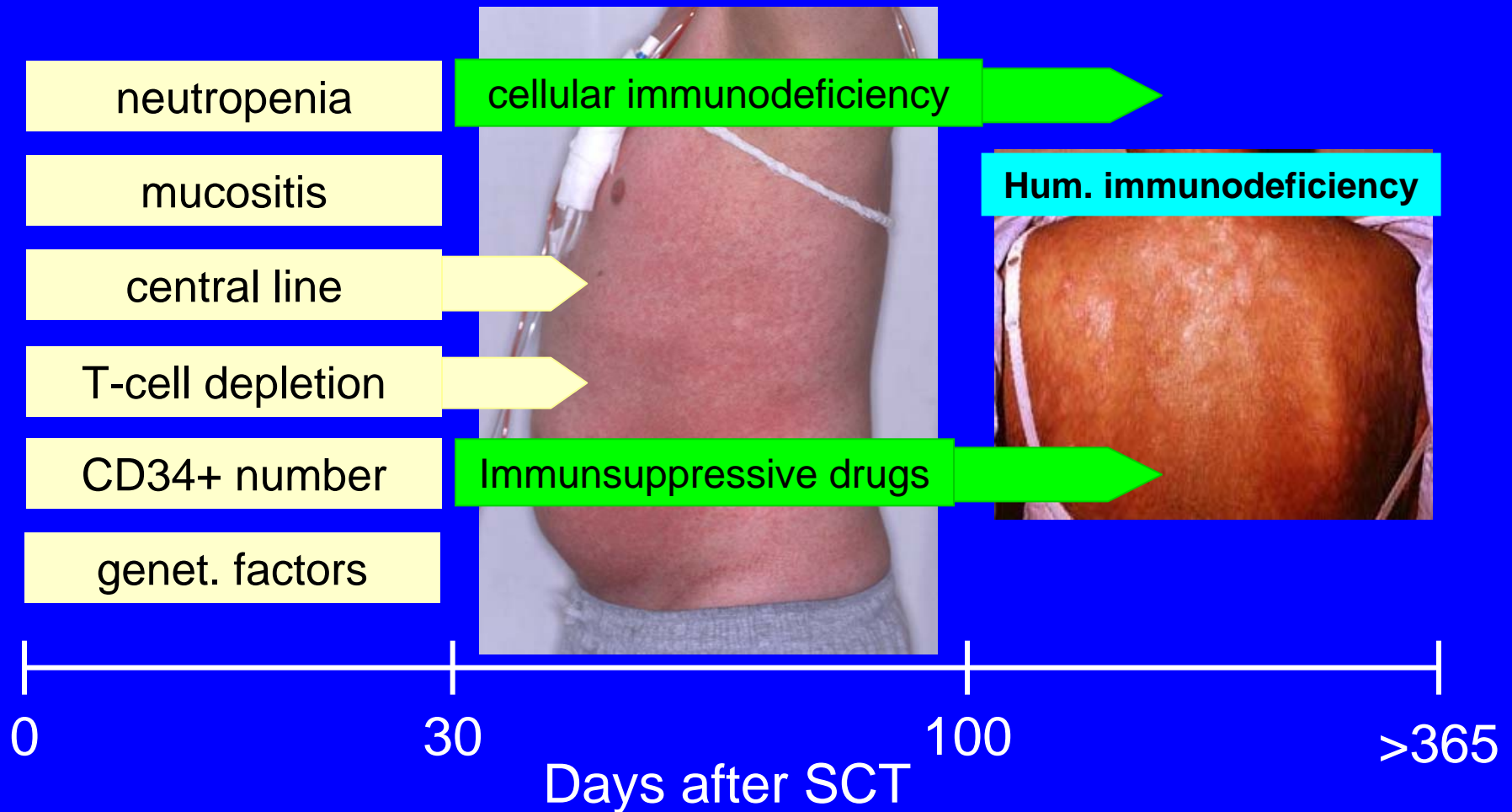
Cord Blood Transplantation: 77-100% CMV reactivation  
10-15% CMV-related mortality  
Prolonged antiviral Chemotherapy → secondary Infections↑↑

# Infectious complications after transplantation

- Major cause of transplant-related morbidity and mortality
  - Improvement in the management of infections → TRM ↓
    - Improved diagnostic methods → targeted therapy
    - effective prophylaxis
      - Primary (safer blood products)
      - Secondary (new drugs)
    - pre-emptive therapy (CMV)
- changes in the epidemiology
- emergence of antimicrobial resistance ↑

# Infectious complications after allogeneic SCT

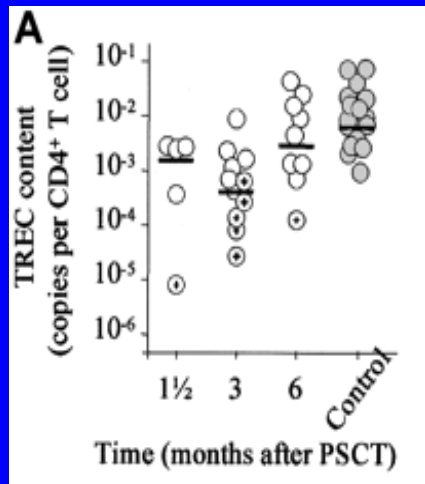
## risk factors



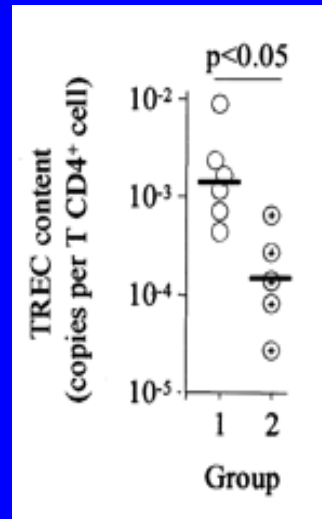
# Immune reconstitution after allogeneic SCT

## long lasting T-cell defect

### TREC analysis

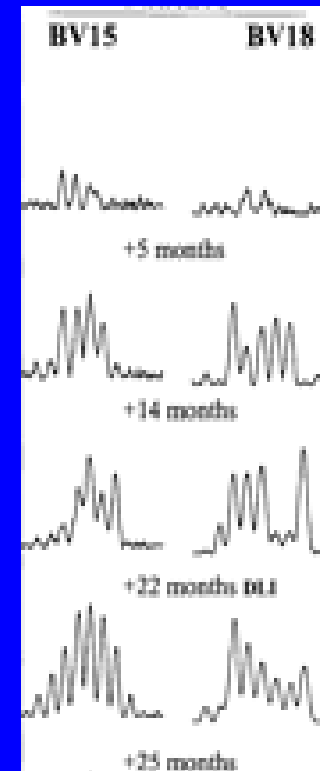
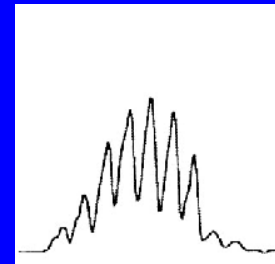


TRECs post  
allo SCT



Impact of GvHD /  
Infections

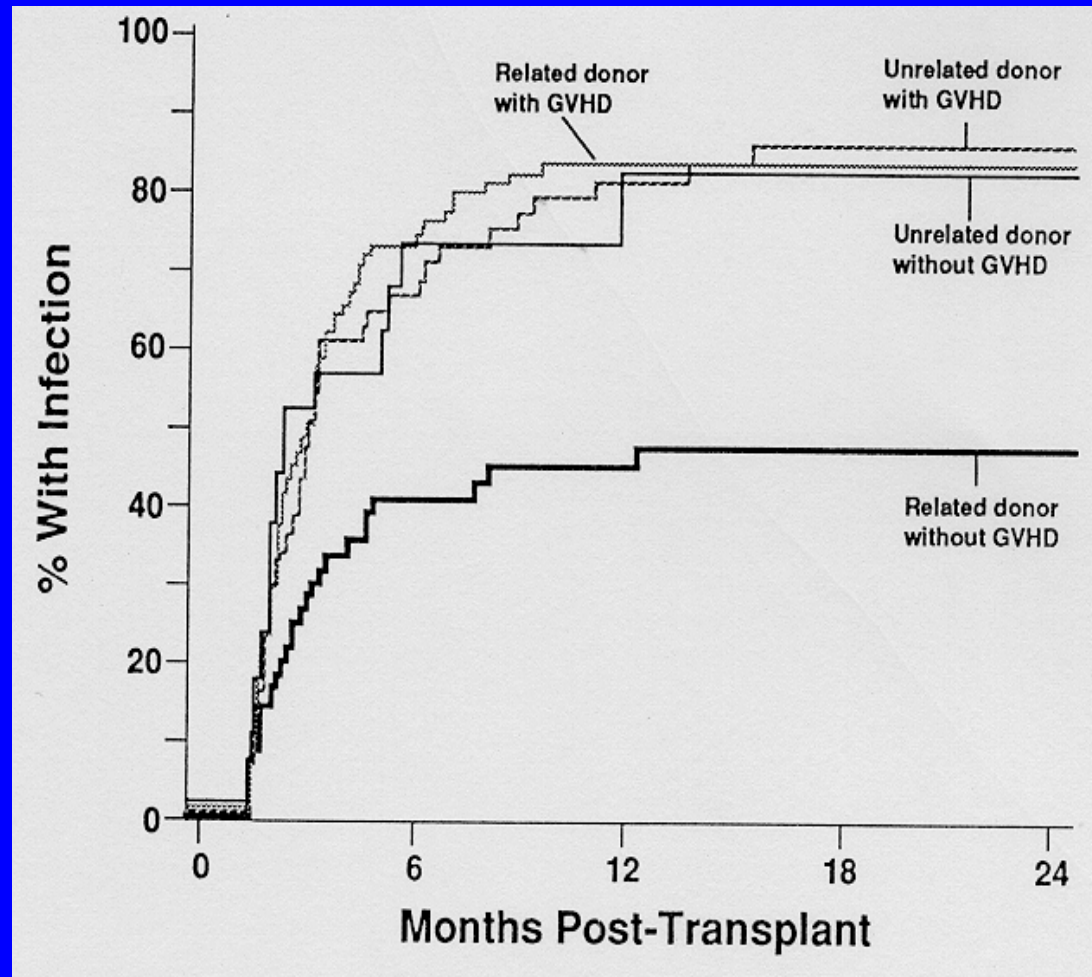
### CDR3-Spectratyping



Healthy ind.

Pat. after allo SCT

# Late infections after allogeneic SCT



# CMV-associated problems in immunosuppressed patients

- CMV disease:
  - e.g. interstitial pneumonia
- Immune suppression:
  - CMV-infection / GCV
- Early onset allograft rejection (kidney-Tx)
- Chronic allograft rejection

# CMV disease after transplantation

## Incidence

<u>Tx-Modality:</u>	<u>Incidence:</u>
kidney	8%
liver	15%
heart / lung	39%
auto SCT	2%
allo SCT	15% - 50%

# **CMV infection after allogeneic SCT**

## **Incidence according to D/R serostatus**

<b>D/R CMV Serostatus</b>	<b>CMV Infection</b>
<b>D-/R-</b>	<b>2,1%</b>
<b>D+/R-</b>	<b>11,8%</b>
<b>D-/R+</b>	<b>56%</b>
<b>D+/R+</b>	<b>57,6%</b>

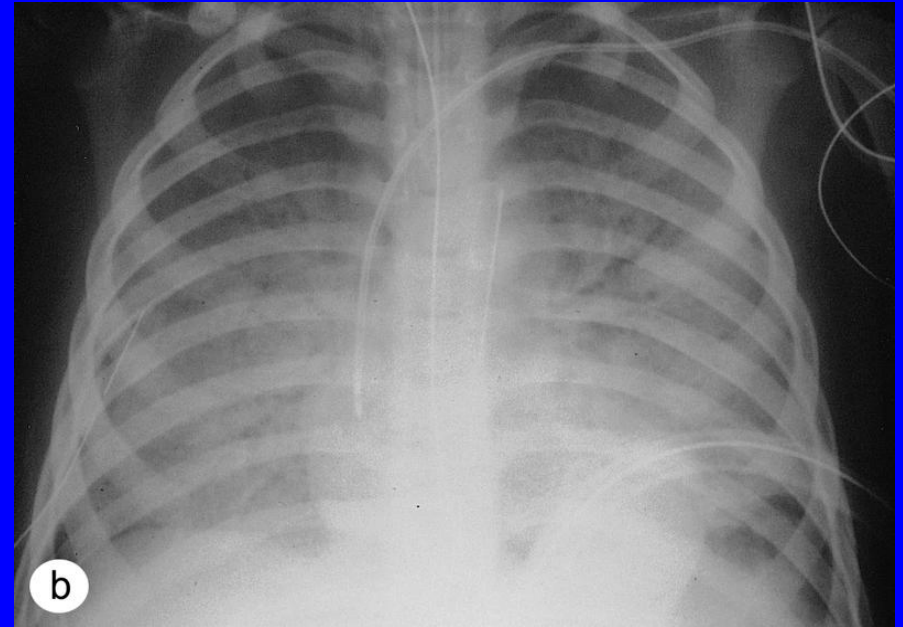
# Manifestations of CMV disease

- Interstitial Pneumonitis (IP)
- Enteritis
- Hepatitis
- CMV syndrome (pancytopenia, fever)
- Encephalitis
- Retinitis

# CMV-induced interstitial pneumonia

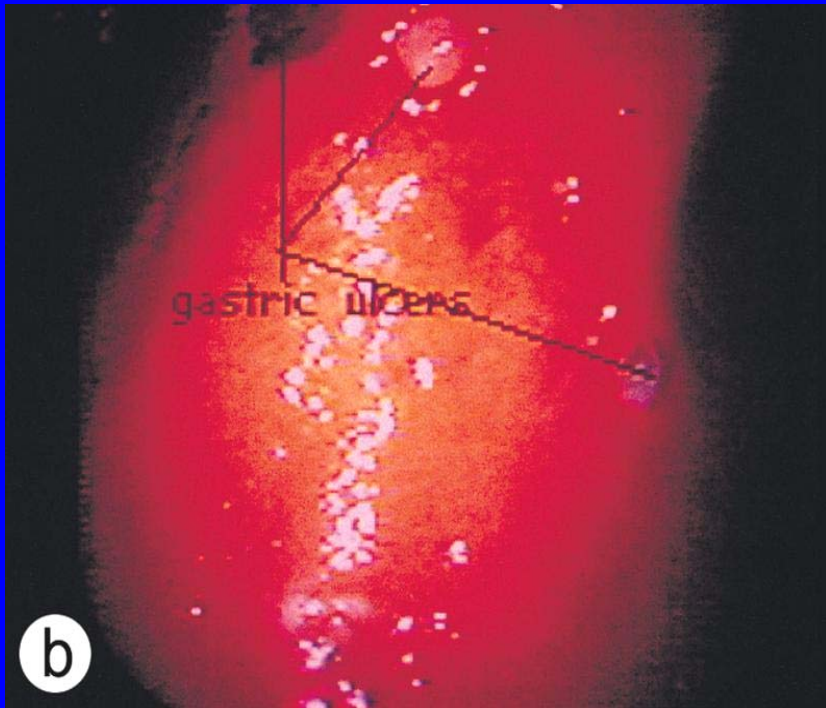


At onset

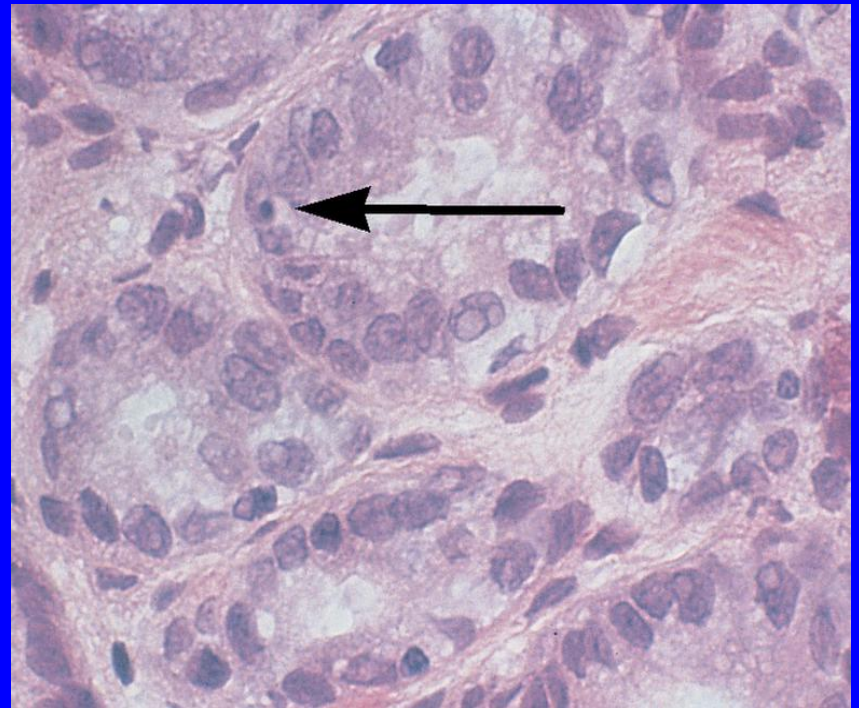


24 h later

# CMV-Gastritis



ulcers



CMV inclusion bodies

# CMV-Retinitis



*in „Infectious Diseases“, Eds Armstrong / Cohen*

## Definitions of CMV disease

- CMV IP                      Interstitial pneumonia + positive virus culture (BAL)
- CMV Enteritis              Enteritis + proof of local CMV infection by culture / in situ hybridization
- CMV Hepatitis              Hepatitis + proof of local CMV infection (in situ hybridization / histology)
- CMV Retinitis              Ophthalmological diagnosis
- CMV Encephalitis          CMV-DNA in cerebrospinal fluid

# Treatment of documented CMV disease

## Manifestation

## Therapy

IP

- GCV + Ig / CMV-Ig  
6 weeks + maintenance

Enteritis/Hepatitis

- GCV (+ Ig / CMV-Ig)  
6 weeks + maintenance?

Retinitis

- GCV / FC  
6 weeks (maintenance?)

CMV syndrome

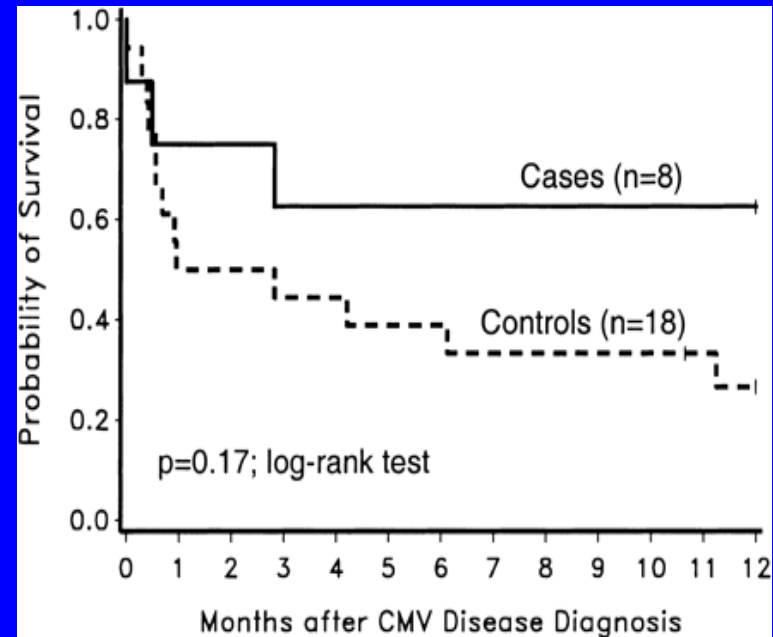
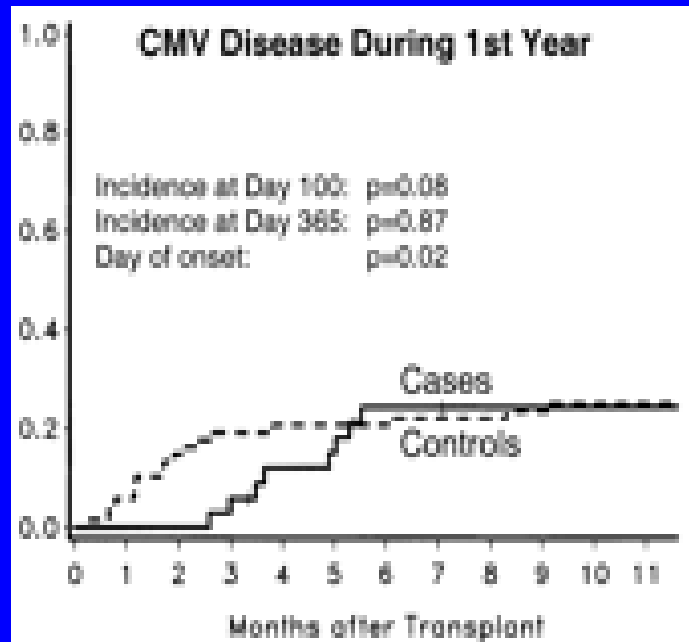
- FC + G-CSF  
4 weeks

# CMV-Disease Outcome

	Kidney-Tx Liver-Tx	Allo SCT
Response Rate	74%	60-80%
Survival	80%	31%

# CMV disease after allo SCT

## non-myeloablative vs myeloablative preparative regimen



- Incidence  $\uparrow$  with *in vivo* Campath-1H (Chakrabarti 2002)

Junghanss et al, Blood 2002

# Prevention of CMV disease in patients after allogeneic SCT

- seronegative patients
  - CMV-seronegative donor
  - „CMV-neg.“ blood products
- seropositive patients
  - Chemoprophylaxis
  - Preemptive antiviral therapy

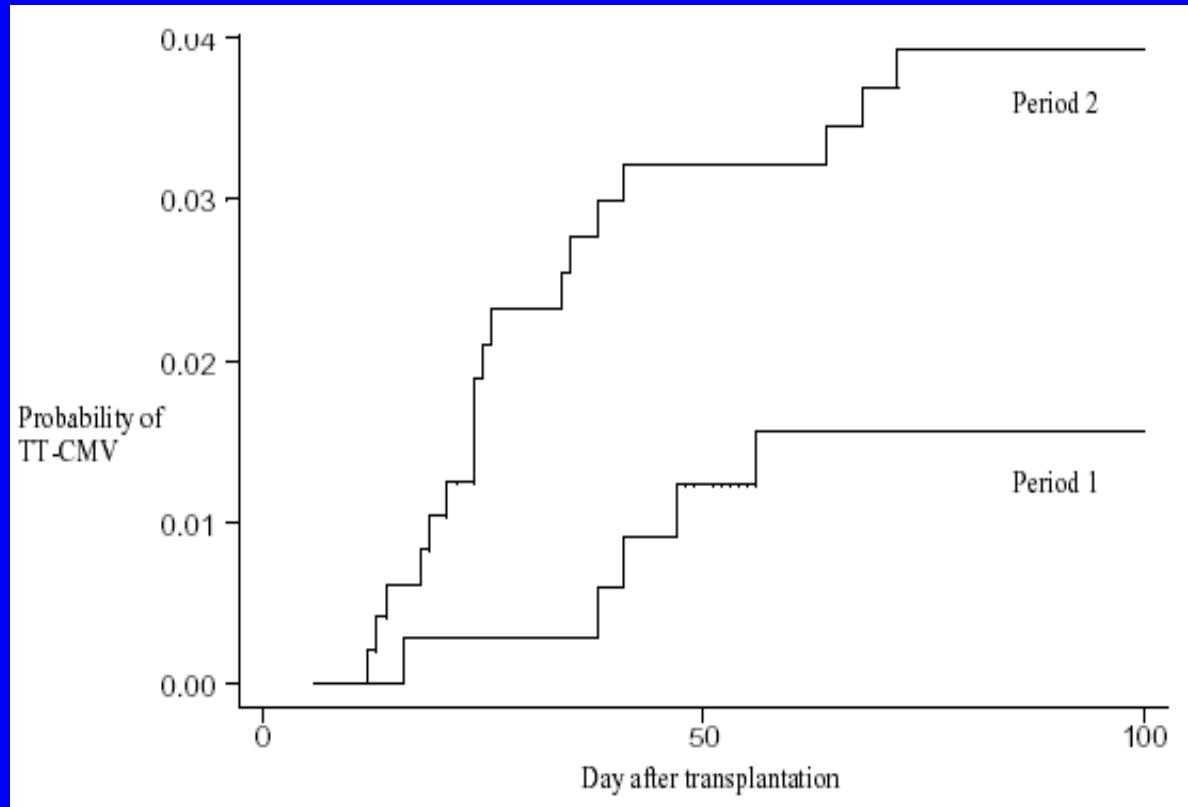
# Prevention of primary CMV infection

Leukocyte-depletion versus sero-negative blood products

CMV-Infection	Seroneg. BP (n=252)	Filtered BP (n=250)	P-Value
Day 21-100			
CMV-Infection	2 (1,3%)	3 (2,4%)	1,0
CMV-disease	0	3 (1,2%)	0,25
Day 0-100			
CMV-Infection	4 (1,4%)	6 (2,4%)	0,5
<b>CMV-disease</b>	<b>0</b>	<b>6 (2,4%)</b>	<b>0,03</b>
Survival	79%	82%	0,56

# Prevention of primary CMV infection

## Influence of transfusion policy



LD-BP



Sero-negative Donors

**TT-CMV 6/360 (1,7%, Period 1) vs 18/447 (4%, Period 2) (P<0.05)**

# Prevention of CMV infection after allo SCT

## TT-CMV versus no TT-CMV

Blood product	TT-CMV (N=24) (mean ± SE)	No TT-CMV (N=783) (mean ± SE)	P value
Total units*	55 ± 8	36 ± 2	0.04
Total CMV negative units	47 ± 7	34 ± 2	0.17
Total LR CMV positive units	7 ± 2	3 ± 0.3	0.01
Filtered RBC from CMV+ donor	0.9 ± 0.6	0.1 ± 0.04	0.002
Filtered PLT from CMV+ donor	0.3 ± 0.2	0.3 ± 0.1	0.92
LR Apheresis PLT from CMV+ donor	6 ± 2	2 ± 0.2	0.002

**Multivariate Analysis:** TT-CMV associated with filtered **Ery-Conc.** from CMV-seropos. Donors (RR 1,32, P=0.006)

# Secondary prophylaxis of CMV infection

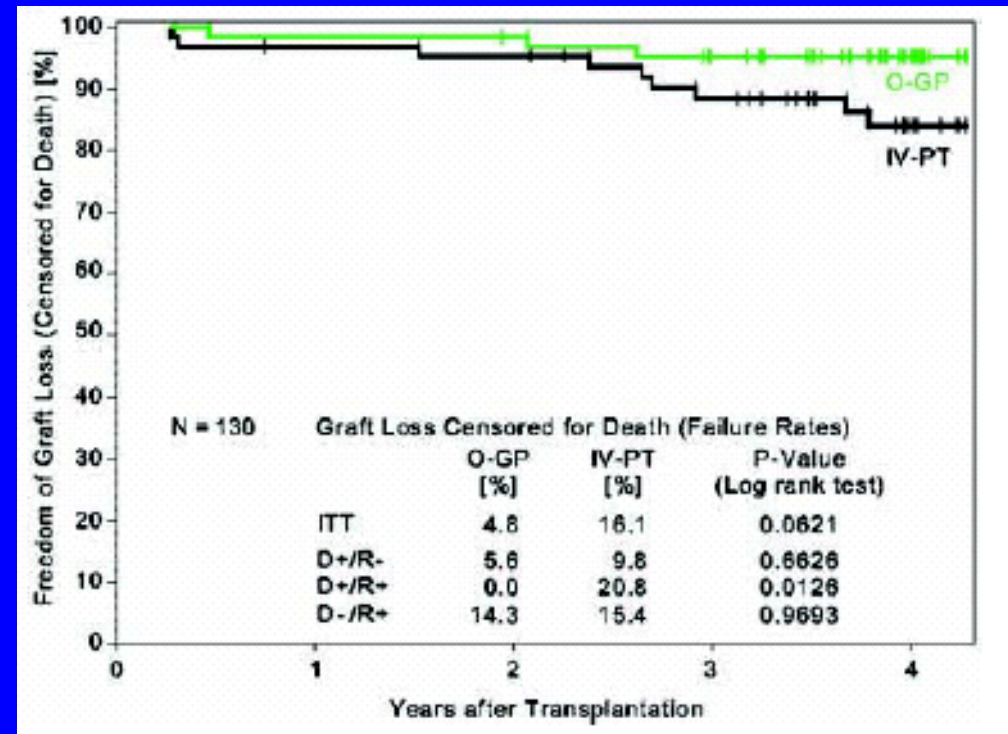
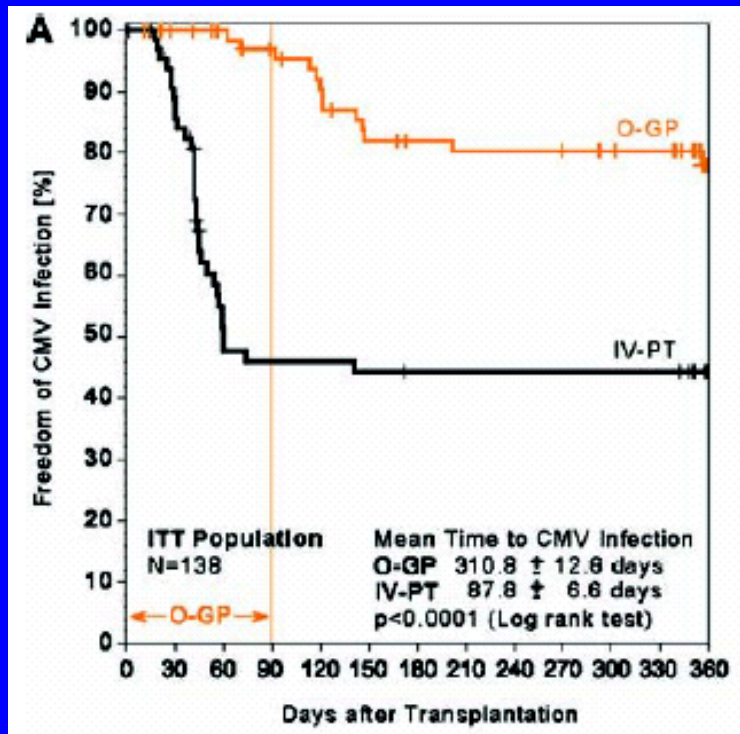
## Antiviral Chemoprophylaxis

	CMV infection	CMV disease	survival (100d)
Acyclovir (i.v.)	52%	9%	75%
Acyclovir (p.o.)	61%	12%	59%
Ganciclovir	20%	10%	70%
PCB	43%	24%	64%

*Prentice et al. 1994, Winston et al. 1995*

# Secondary prophylaxis of CMV infection after kidney-Tx

Antiviral Chemoprophylaxis with oral GCV



# Antiviral chemotherapy of CMV infection after allo SCT

Risk group:

R CMV-sero+ a./o. D CMV-sero+

Antiviral Strategy

prophylaxis

Tx

— Engraftment



GCV / FC

early intervention

Tx

PCR / Ag positive



negative

positive



Day 100

# Antiviral Therapy with Ganciclovir

Prophylaxis ↔ preemptive therapy

## Advantage

## Disadvantages

### Prophylaxis

highly effective  
no screening

overtreatment  
side effects ↑  
(neutropenia, infections)  
late onset CMV disease ↑  
high therapeutic costs

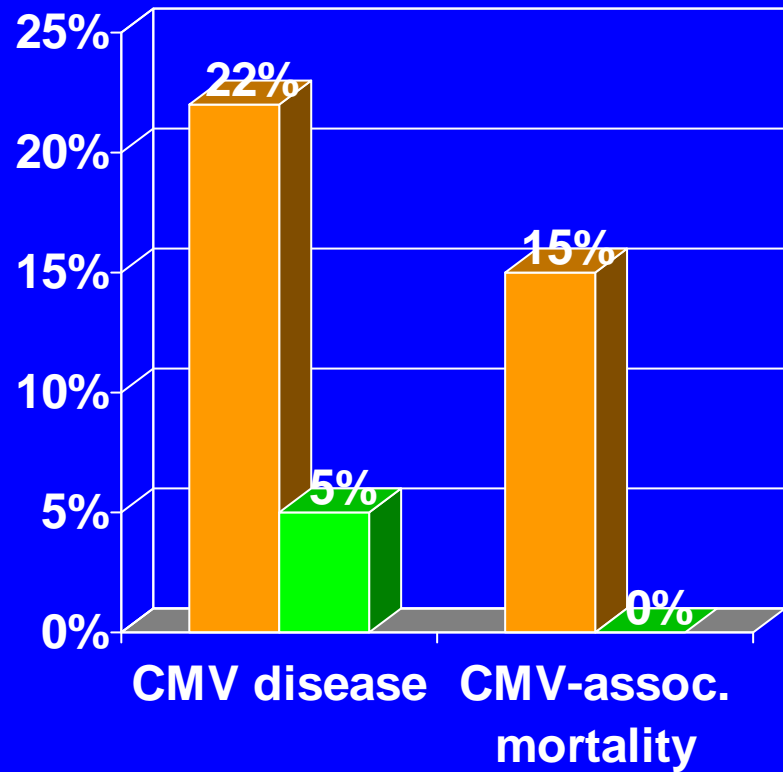
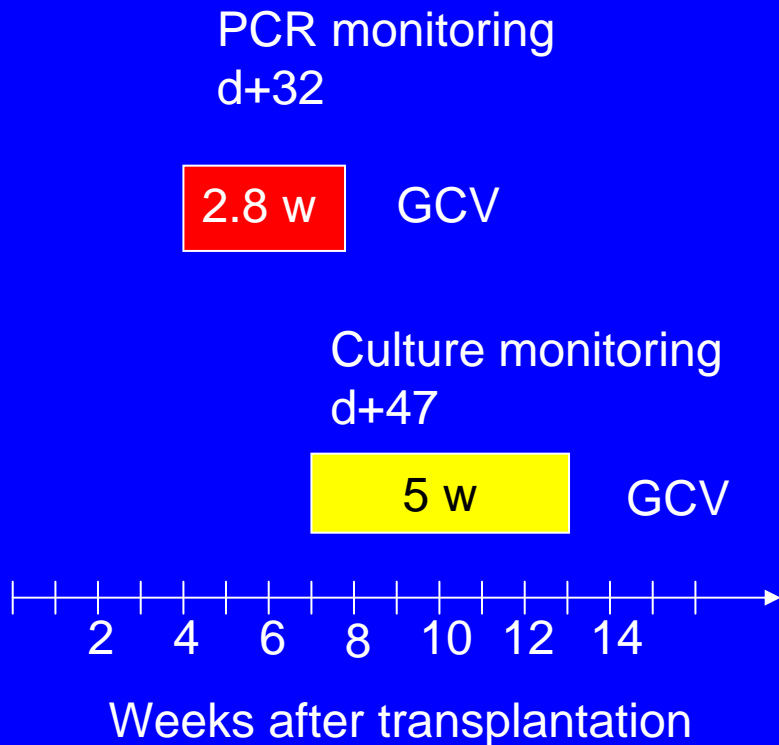
### Preemptive

targeted therapy  
highly effective  
less side effects

intensive screening  
late onset CMV disease ↑  
high costs for screening

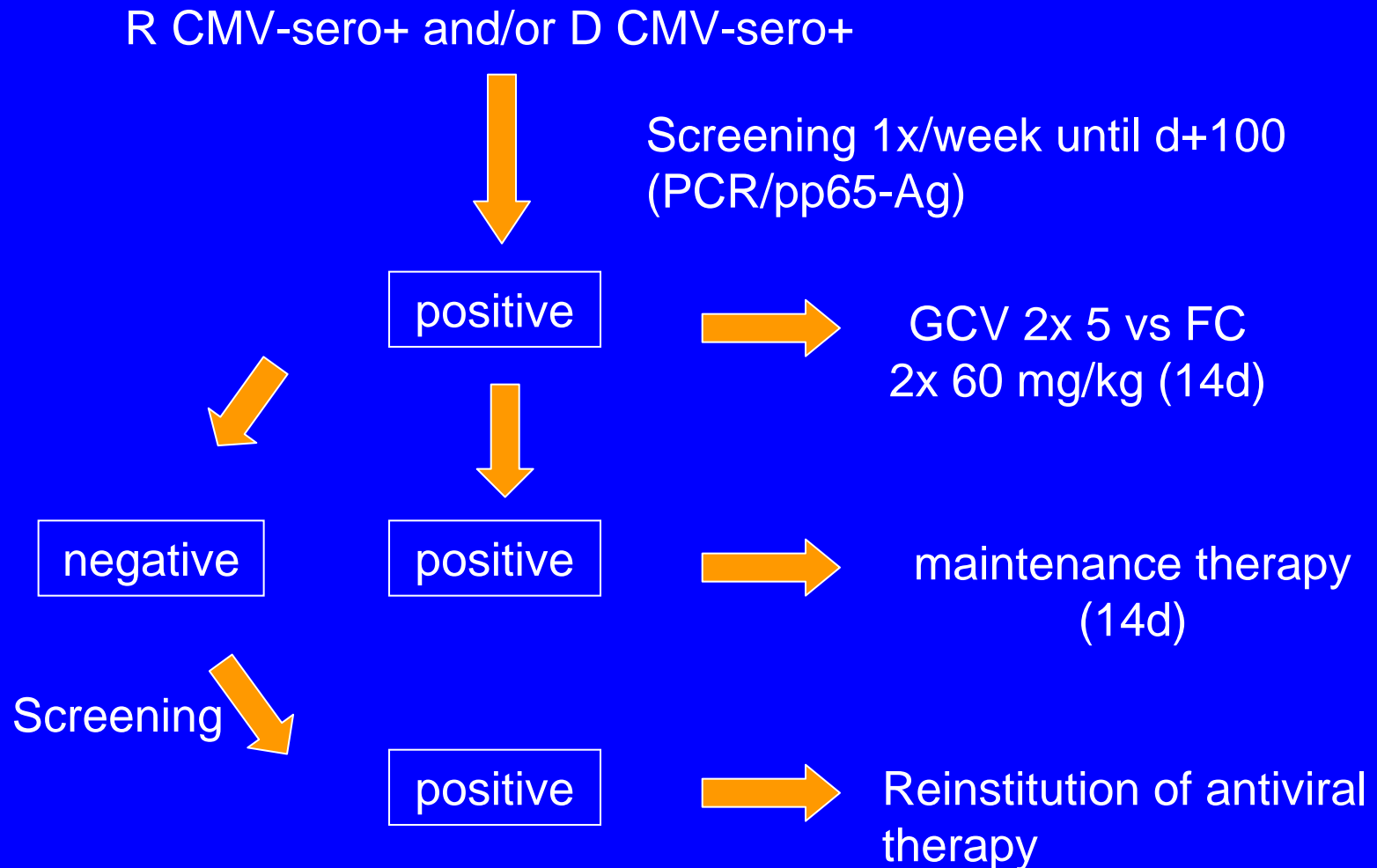
# Pre-emptive antiviral therapy

## PCR vs culture monitoring



# Preemptive antiviral therapy in patients after allogeneic SCT

Foscarnet vs. Ganciclovir (EBMT-Study)



## Foscarnet vs Ganciclovir after allo SCT

	Foscarnet (n=110)	Ganciclovir (n=103)
neg. after 14d GCV/FC	65,5%	51,5%
2nd treatment course (<d100)	35,4%	19,1%
median duration of therapy	16 d	16 d

## Foscarnet vs Ganciclovir after allo SCT

	Foscarnet (n=110)	Ganciclovir (n=103)
EFS	65,5%	72,8%
CMV disease	4,5%	4,9%
CMV-GI	1,8%	1,9%
CMV-IP	2,7%	1,9%
CMV-retinitis	0%	1,0%
day 100 mortality	26,4%	22,3%

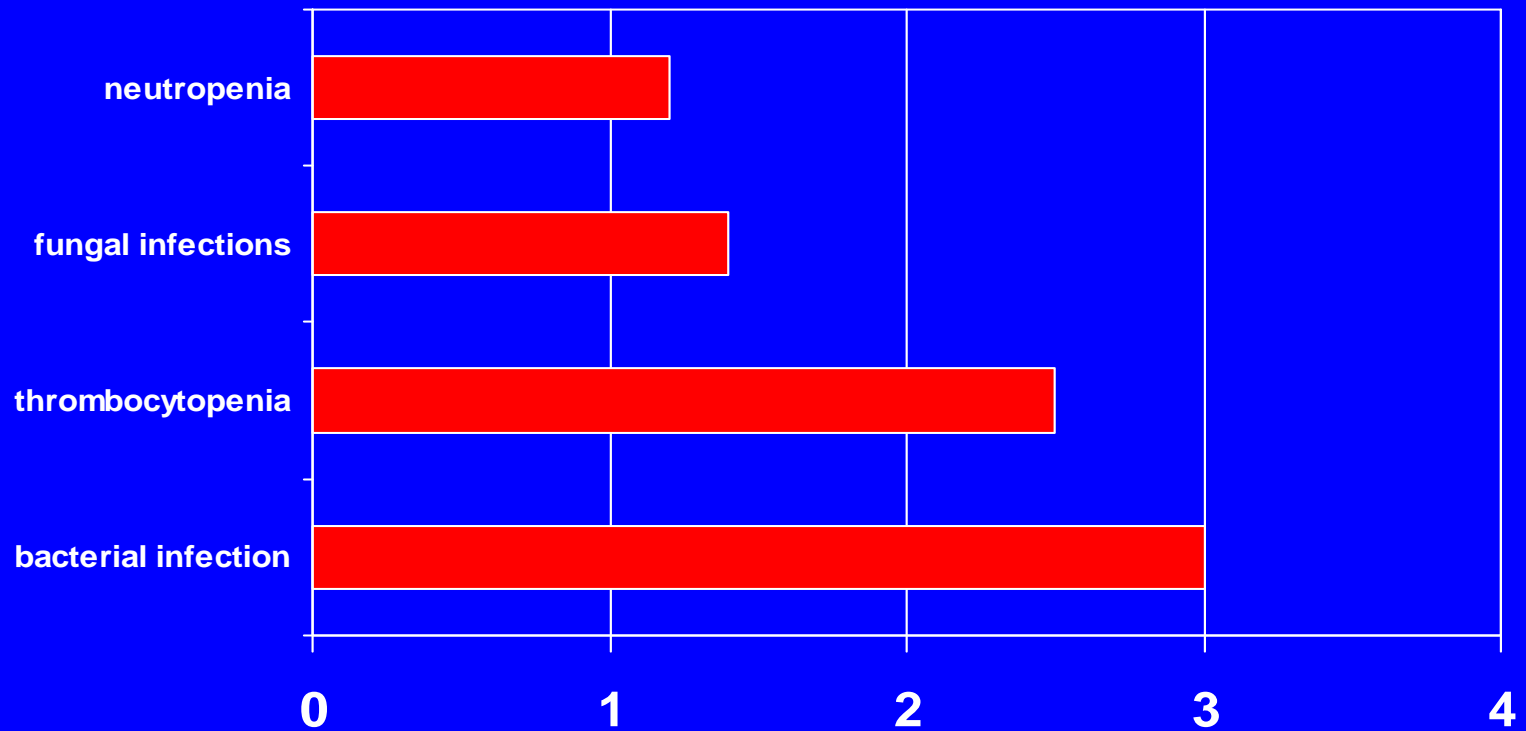
# Foscarnet vs Ganciclovir side effects

	FC	GCV	p-value
non-viral Infections (<d100)	25,5%	28,2%	n.s.
Neutropenia (<500/ $\mu$ l)	3,6%	10,7%	p=0.045
Creatinin $\uparrow$ ( $\geq$ 100%)	4,5%	1,9%	p=0.447
Hypocaliämia	9,1%	0%	p<0.05
$\downarrow$ Ca $^{++}$ $\downarrow$ Mg $^{++}$	25%	5%	p<0.05

# Side effects of antiviral therapy

Tübingen results

RR-Risk/ week of therapy

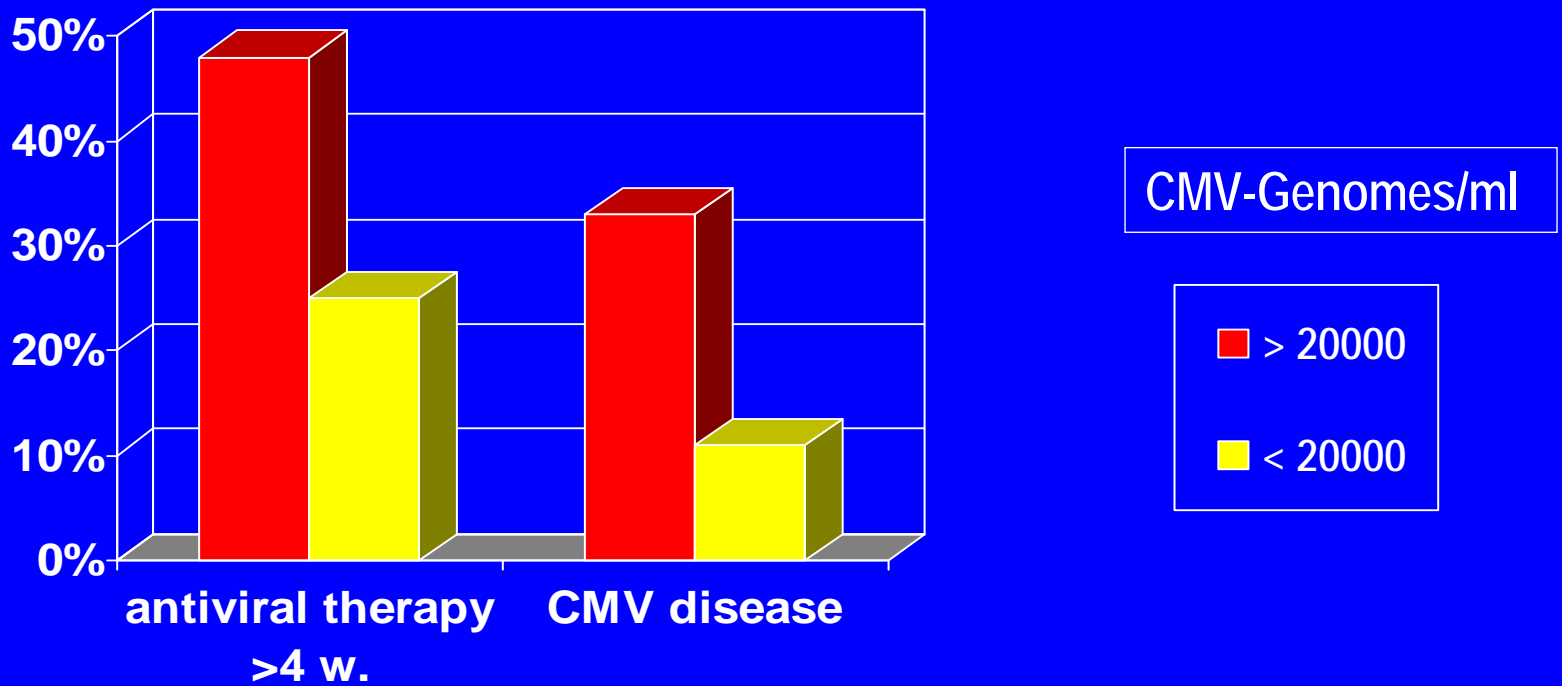


# How to improve pre-emptive antiviral therapy?

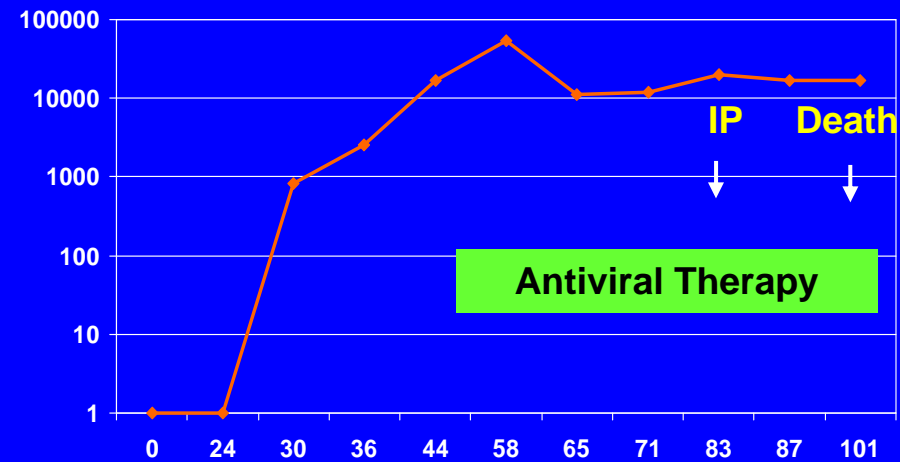
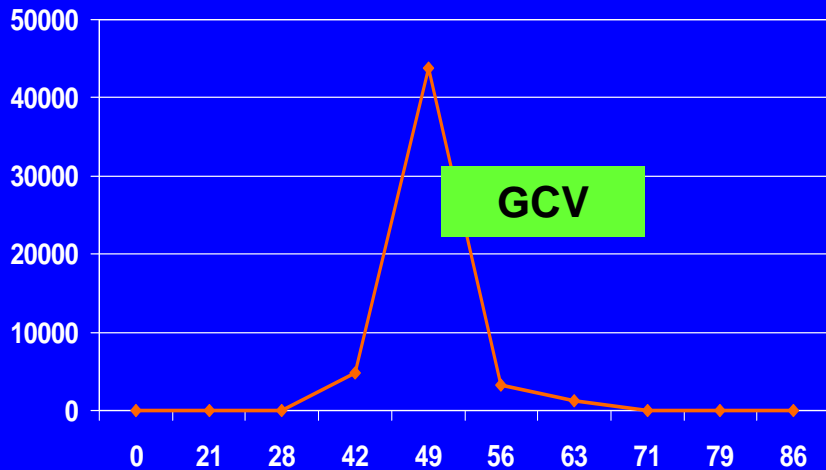
- **Better diagnostic methods**
  - Quantitative PCR assays?
  - Detection of active viral replication?
- **New treatments**
  - More effective and less toxic drugs?
  - Adoptive immunotherapy?

# Impact of viral load on duration of antiviral therapy and incidence of CMV disease

Tübingen Experience

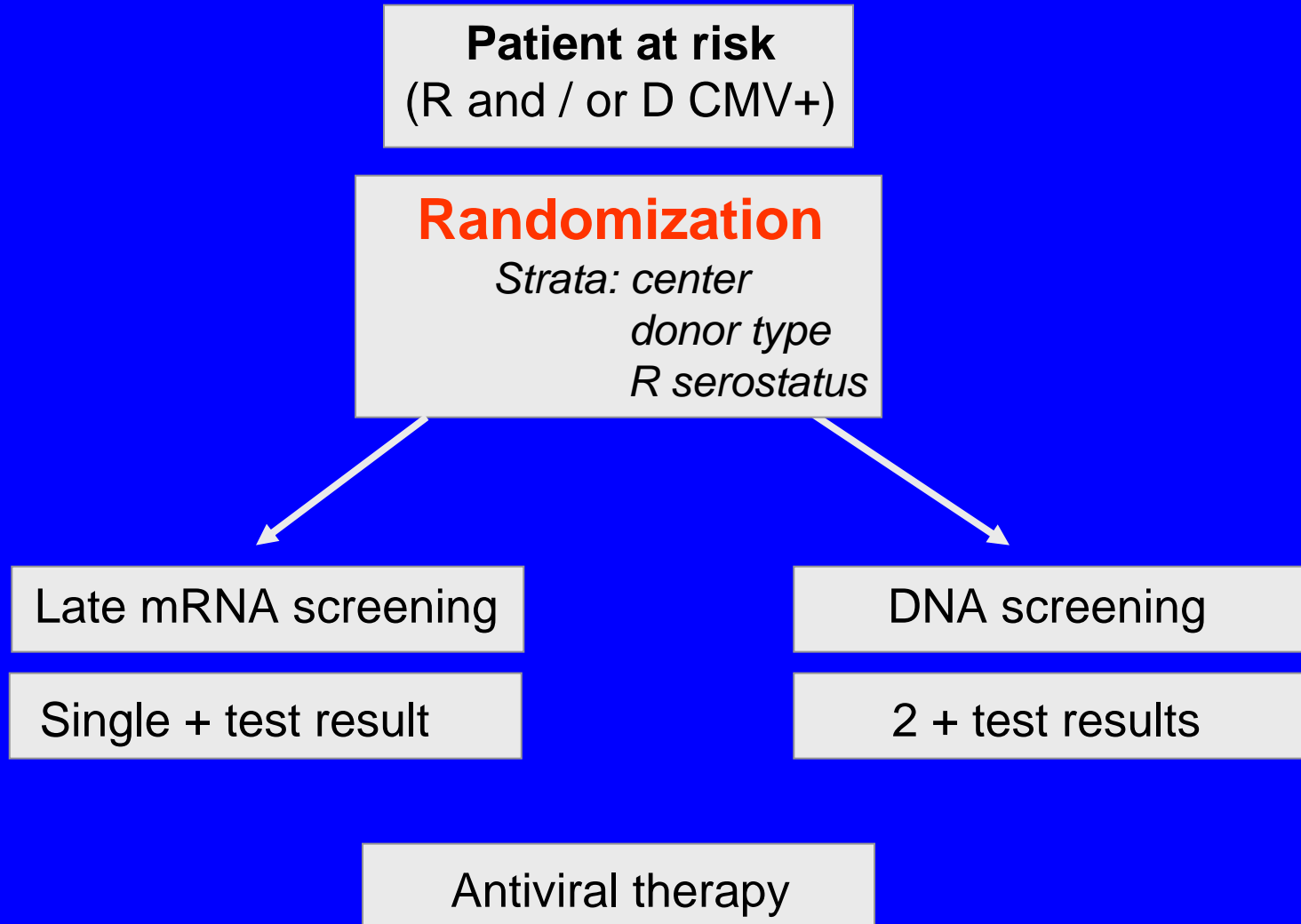


# Monitoring of antiviral therapy by quantitative PCR



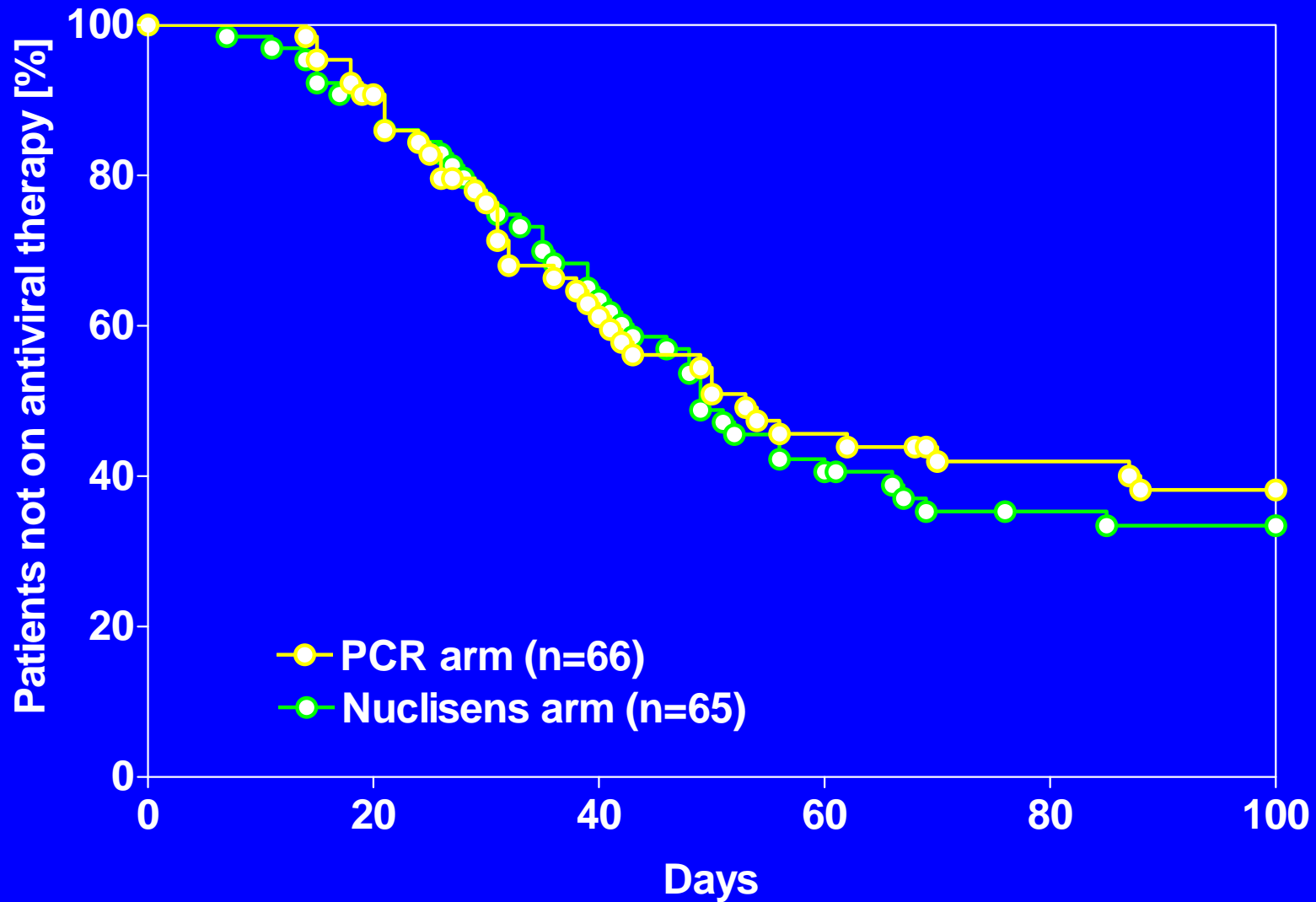
Days post-transplant

# Study design



# Event-free survival

"no antiviral therapy"



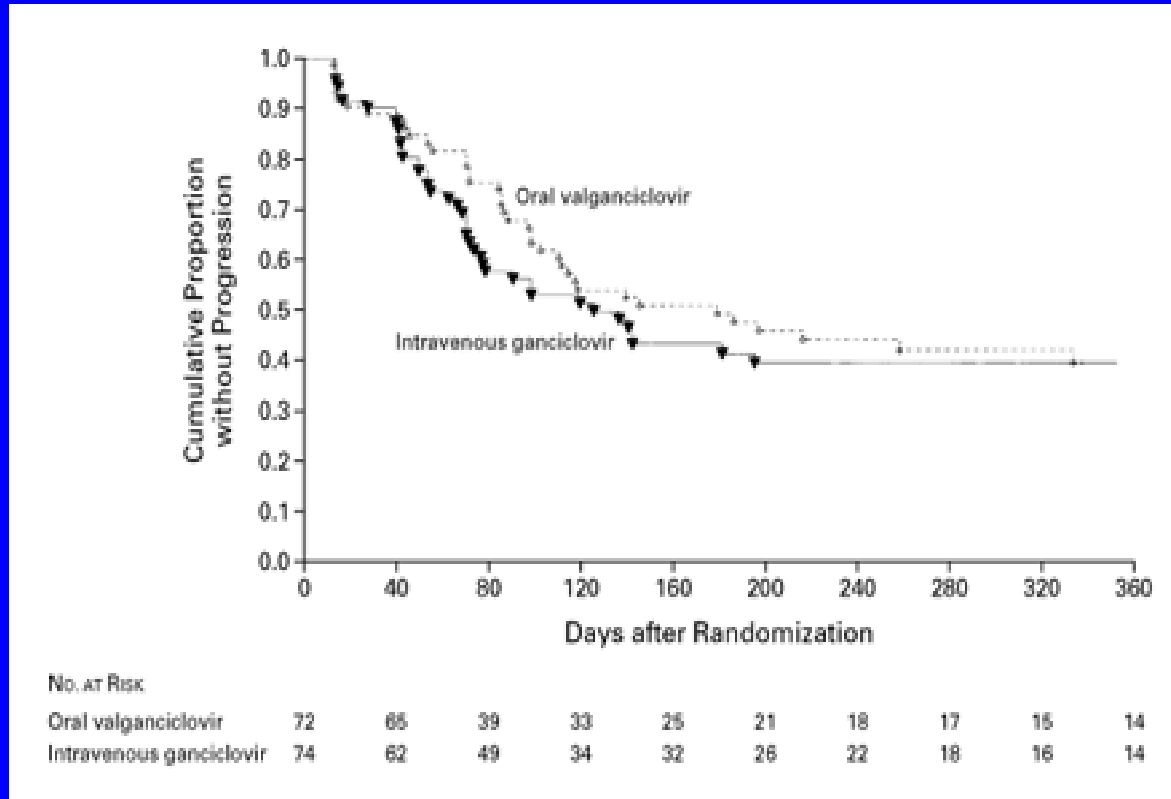
# Treatment of CMV Infection with Cidofovir

---

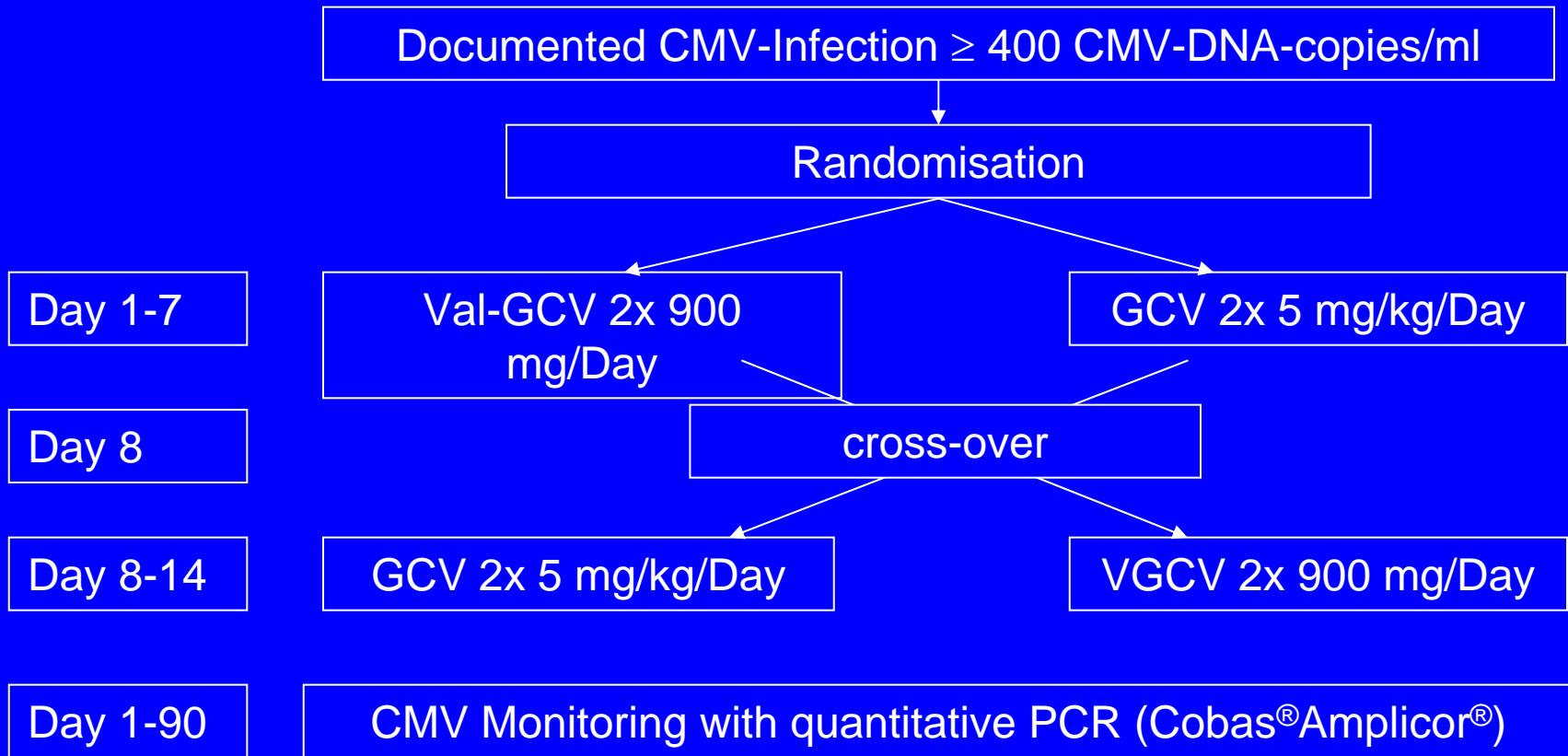
Indication	Patients [n]	Response [%]
CMV disease	20	10/20 [50%]
CMV pneumonia	16	9/16 [56%]
Pre-emptive relapse	38	26/38 [68%]
Pre-emptive 1st line	26	15/26 [58%]

---

# Ganciclovir versus Valganciclovir CMV-Retinitis



# Oral Pre-emptive Therapy with Val-GCV versus i.v. GCV



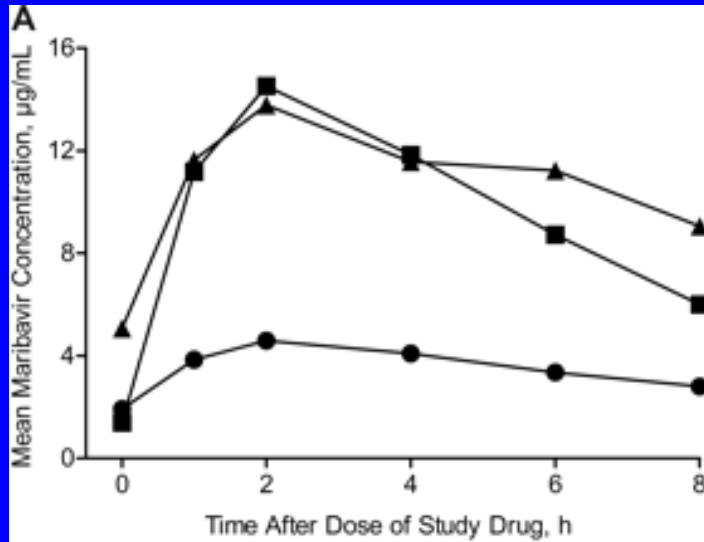
# Pharmacokinetic Parameters of Ganciclovir after Val-GCV versus i.v. GCV in SCT

	Valganciclovir (n = 23)	Ganciclovir (n = 23)
<b>AUC (0–12) (mg/L*h)</b>		
Mean (S. D./90 % CI)	54.1 (20.84)	40.1 (14.75)
Median	56.6	37.3
Min-Max	3.6–102.3	22.1–64.5
<b>C<sub>max</sub> (mg/l)</b>		
Mean (S. D./90 % CI*)	8.9 (2.86)	10.6 (2.40)
Median	8.0	10.4
Min-Max	0.7–13.8	7.3–14.6
<b>t<sub>1/2</sub> (hours)</b>		
Mean (S. D.)	4.1 (1.05)	3.2 (0.66)
Median	4.3	3.2
Min-Max	2.5–5.8	2.1–4.0

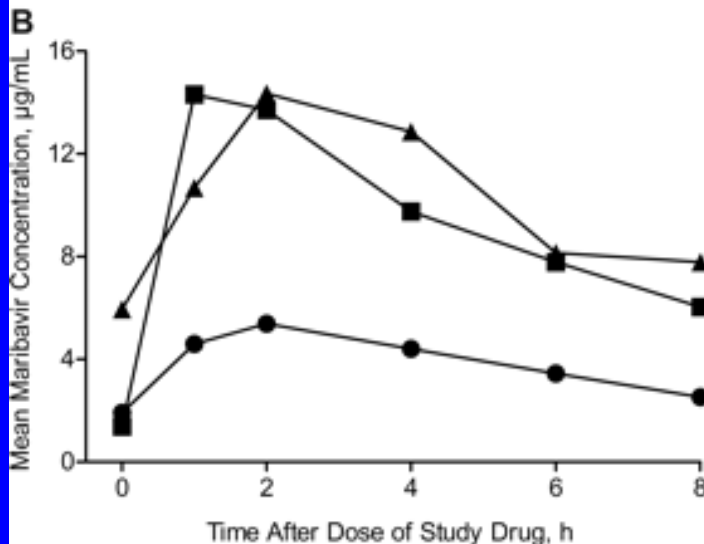
- Preliminary Data -

# Maribavir – Plasma levels

Phase II study in pts. after allogeneic SCT



Week 1

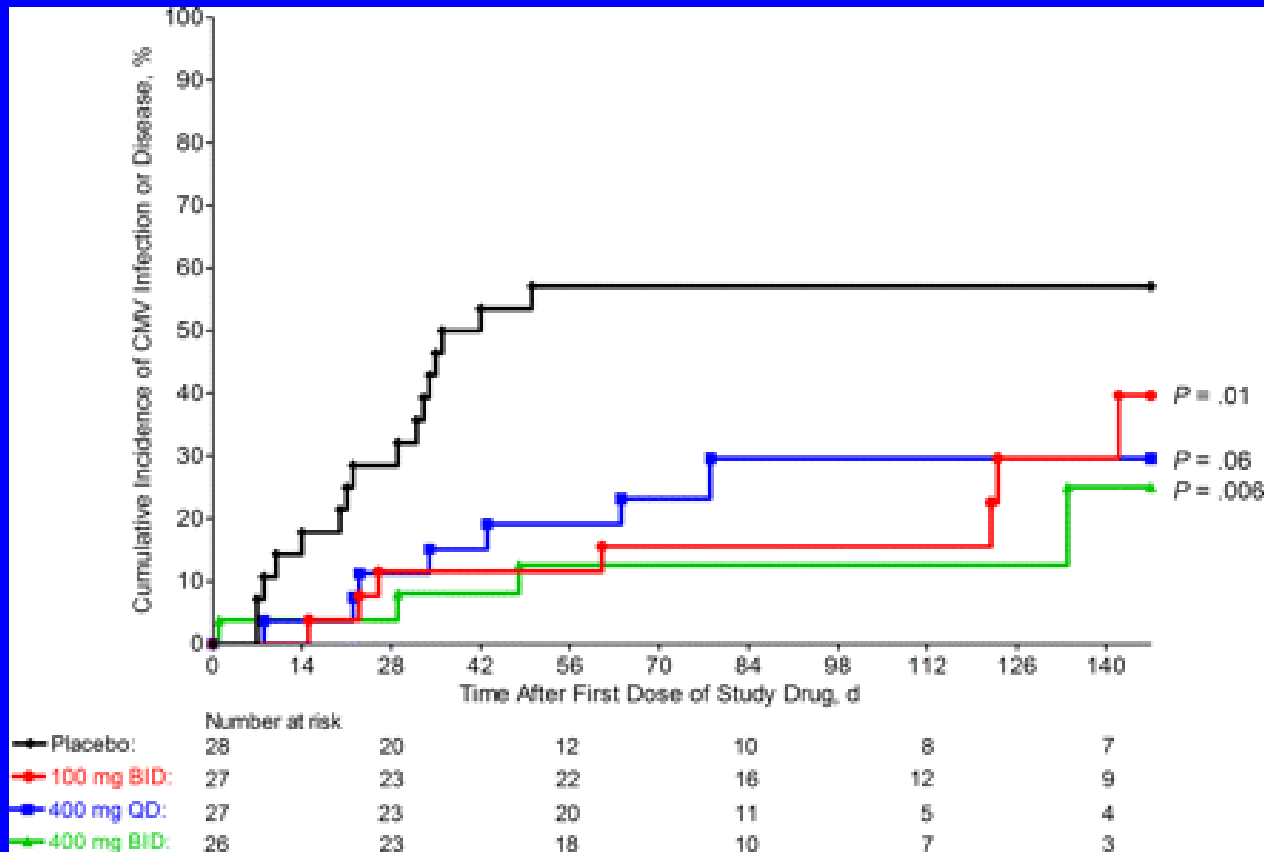


Week 4

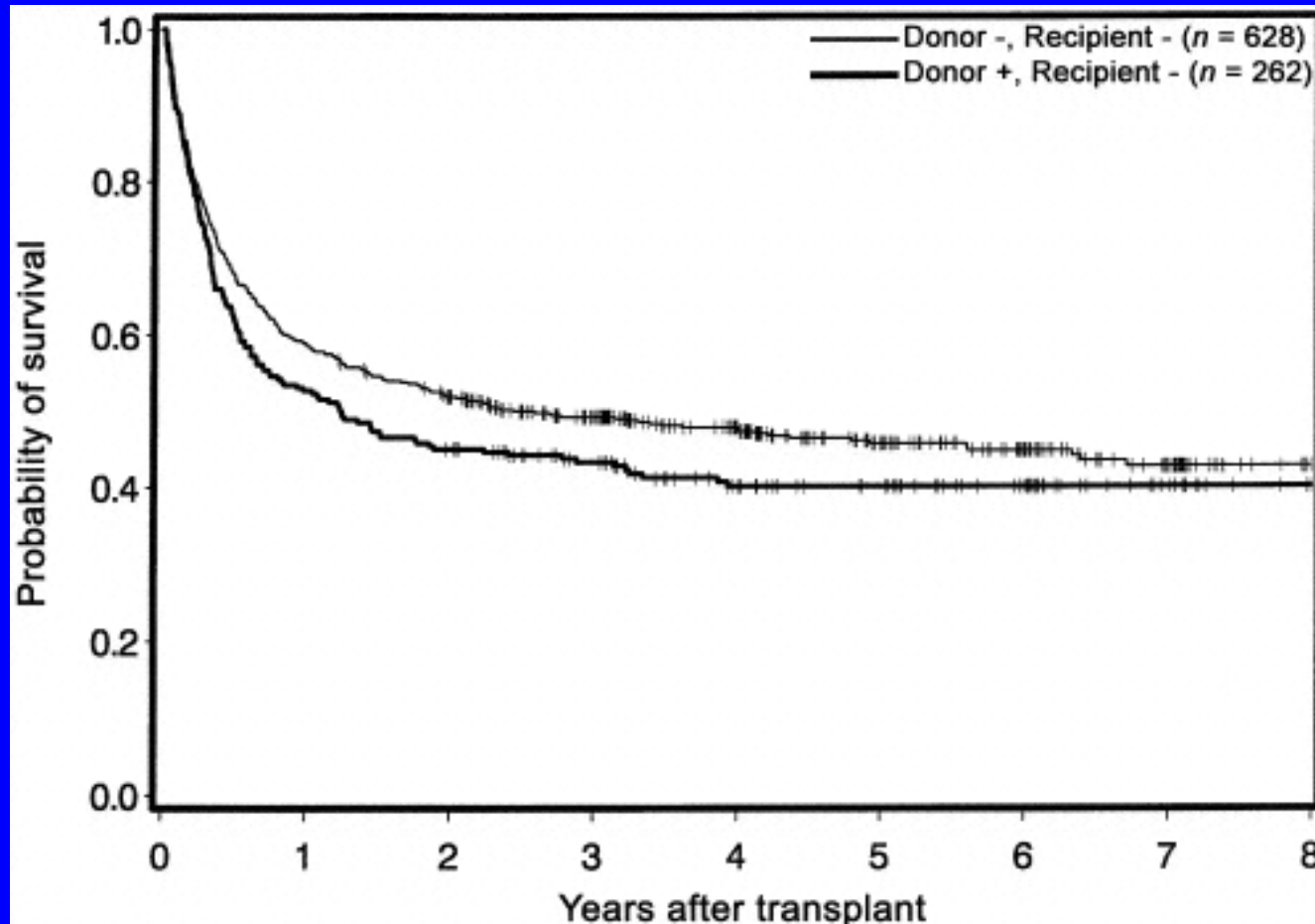
Winston et al, Blood 2008, 111:5403

# Maribavir – CMV infection and disease

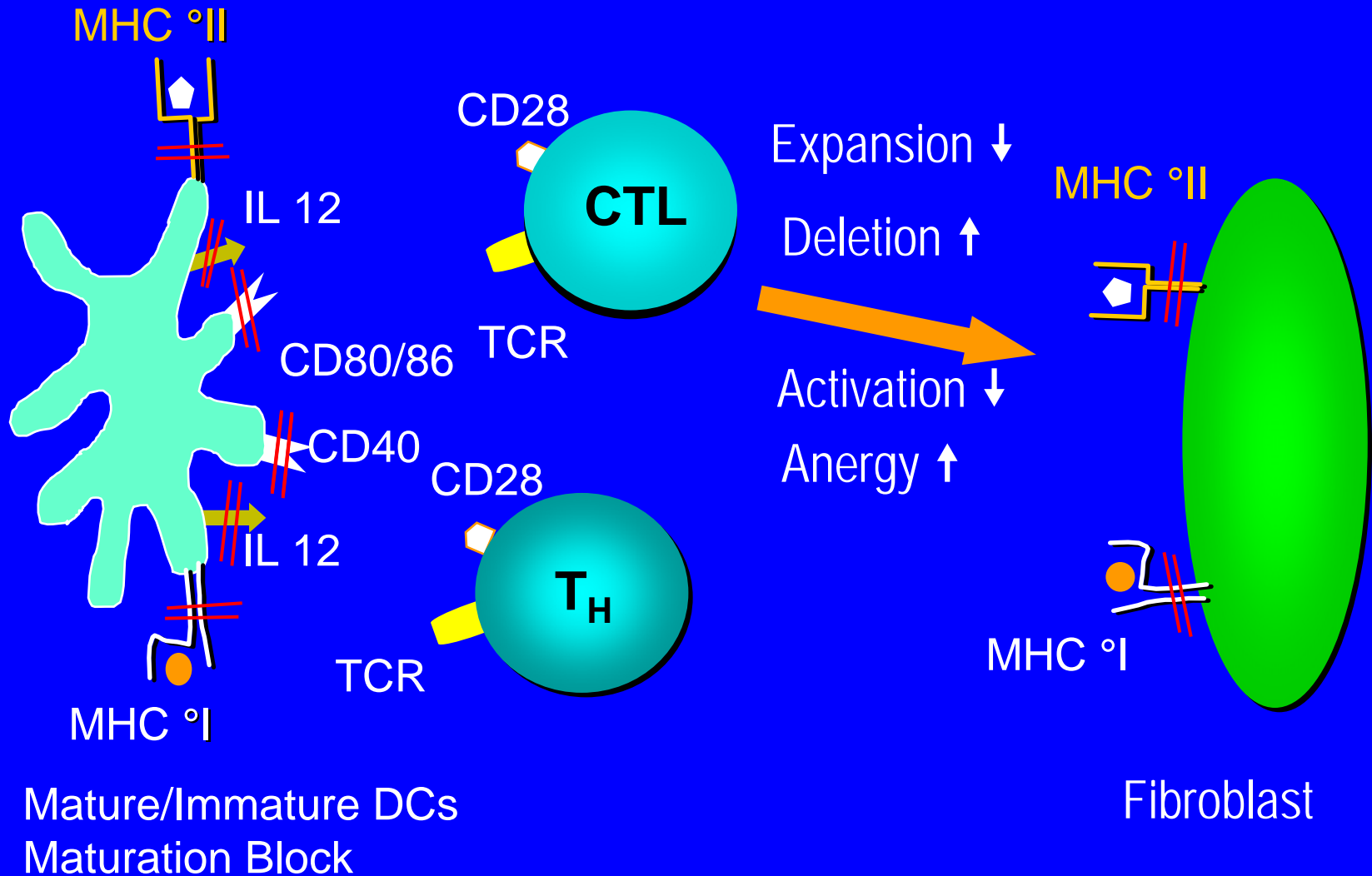
## Phase II study in pts. after allogeneic SCT



# Impact of Recipient CMV-Serostatus on Survival in the era of pre-emptive therapy

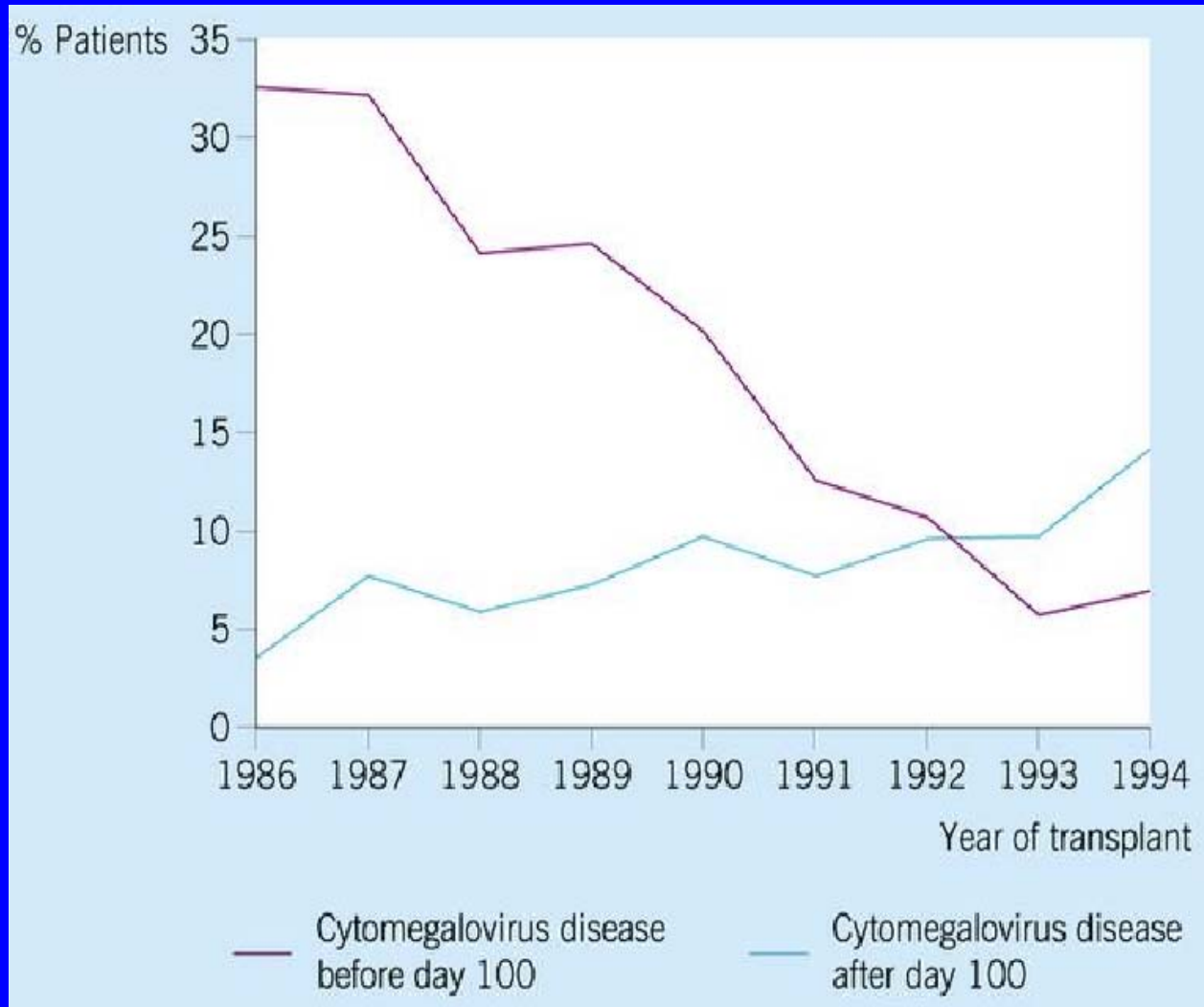


# CMV-DC Interaction

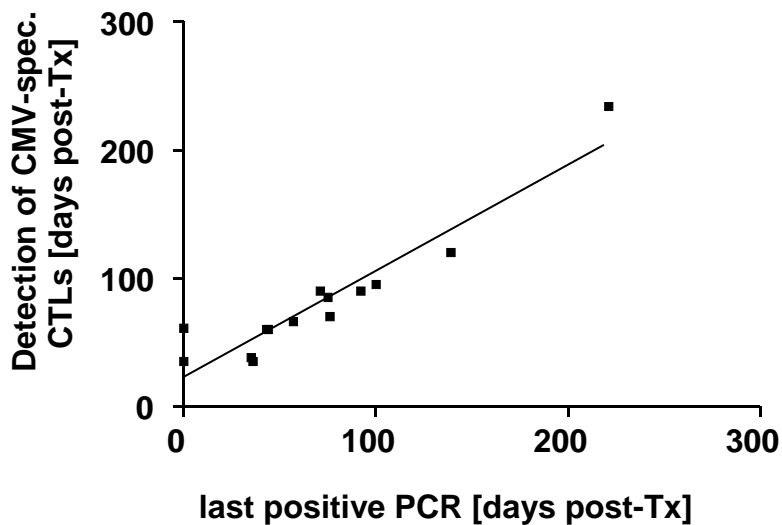


# Incidence of CMV disease after allo SCT

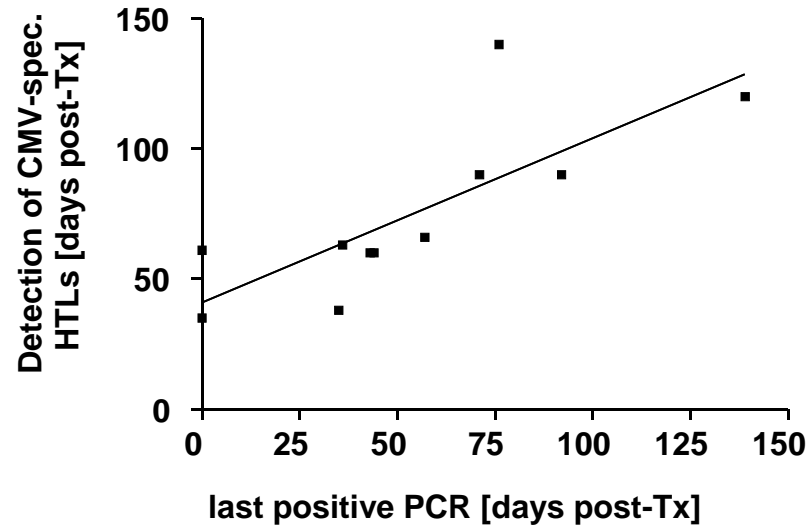
CMV-sero+ patients (n=1458)



# Reconstitution of CMV-spec. CD8+ and CD4+ T cells

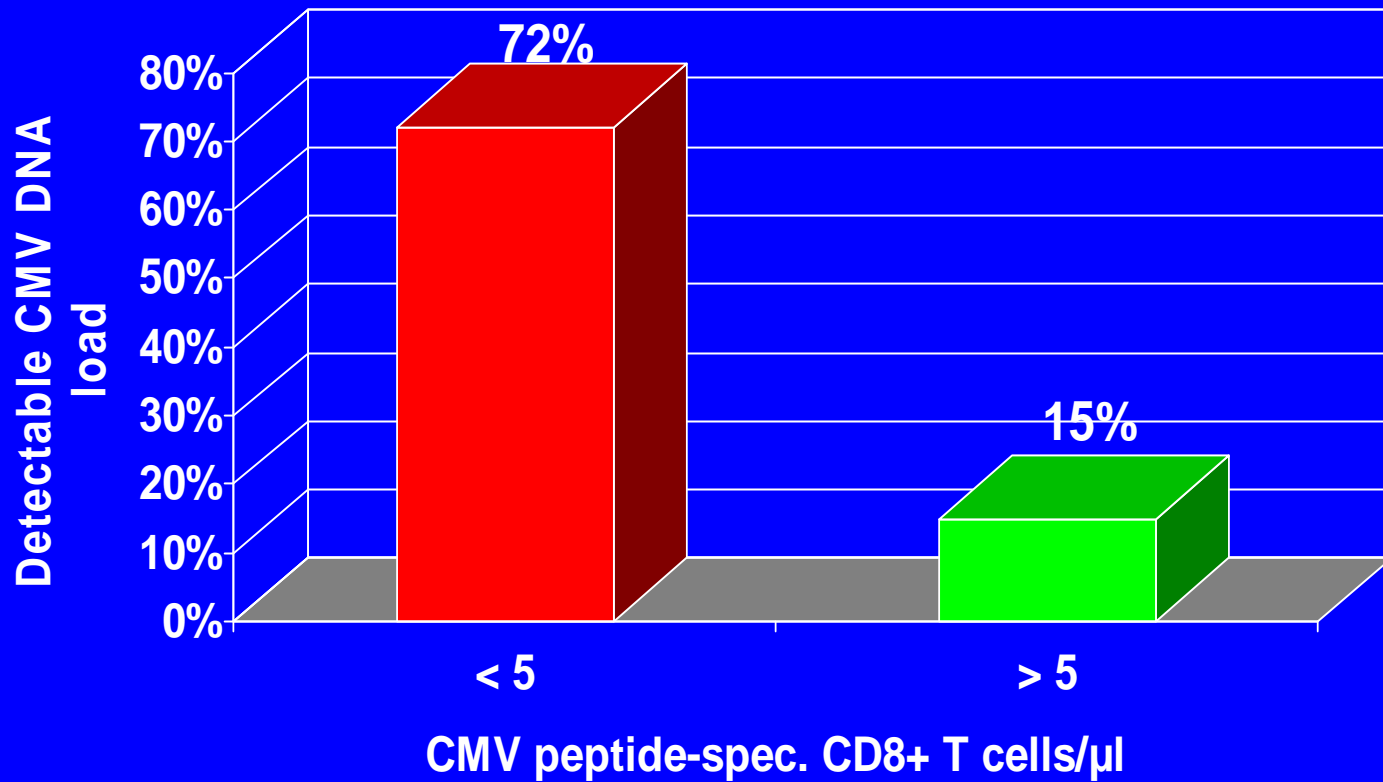


$P < 0.0001$

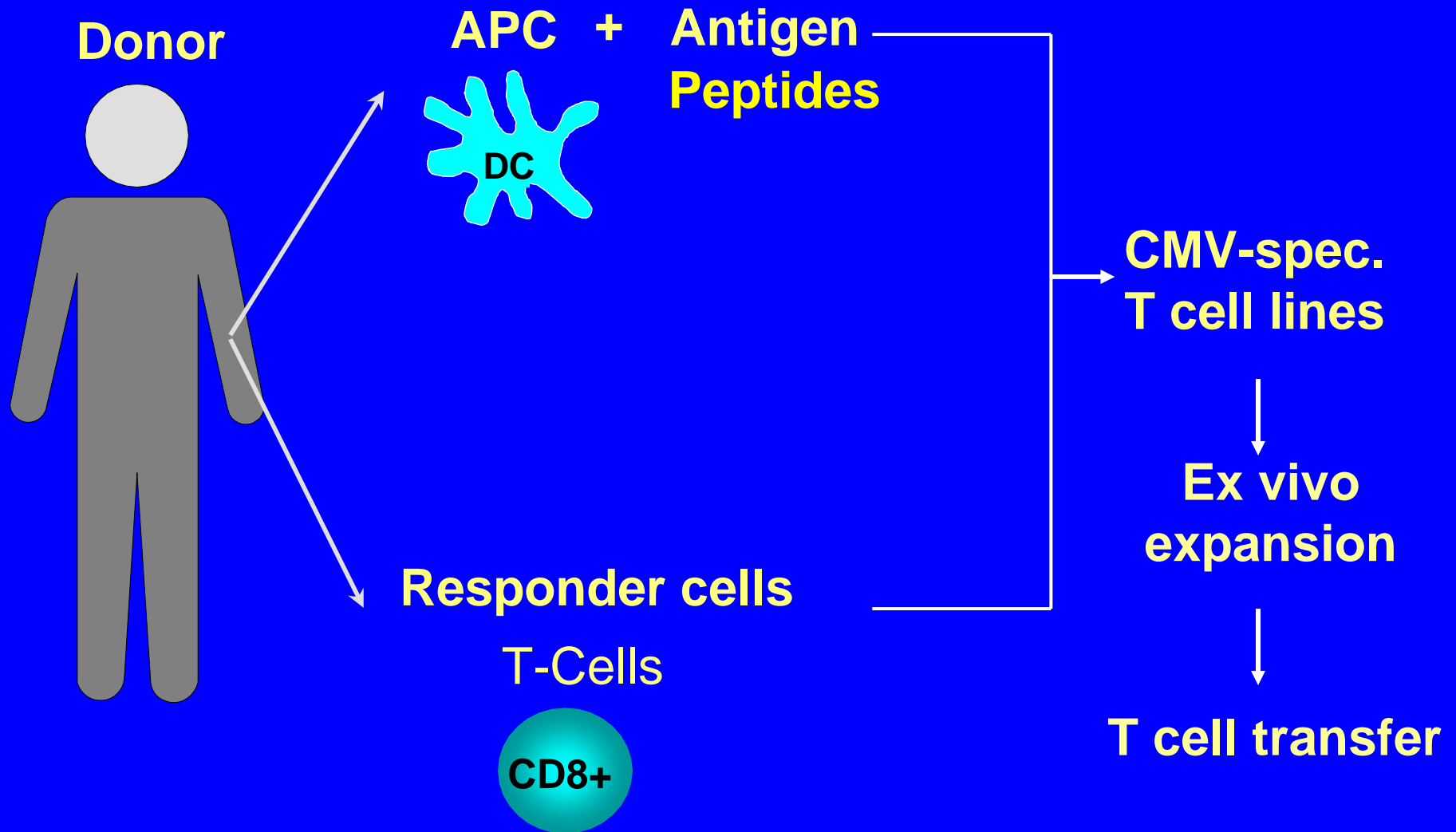


$P = 0.0045$

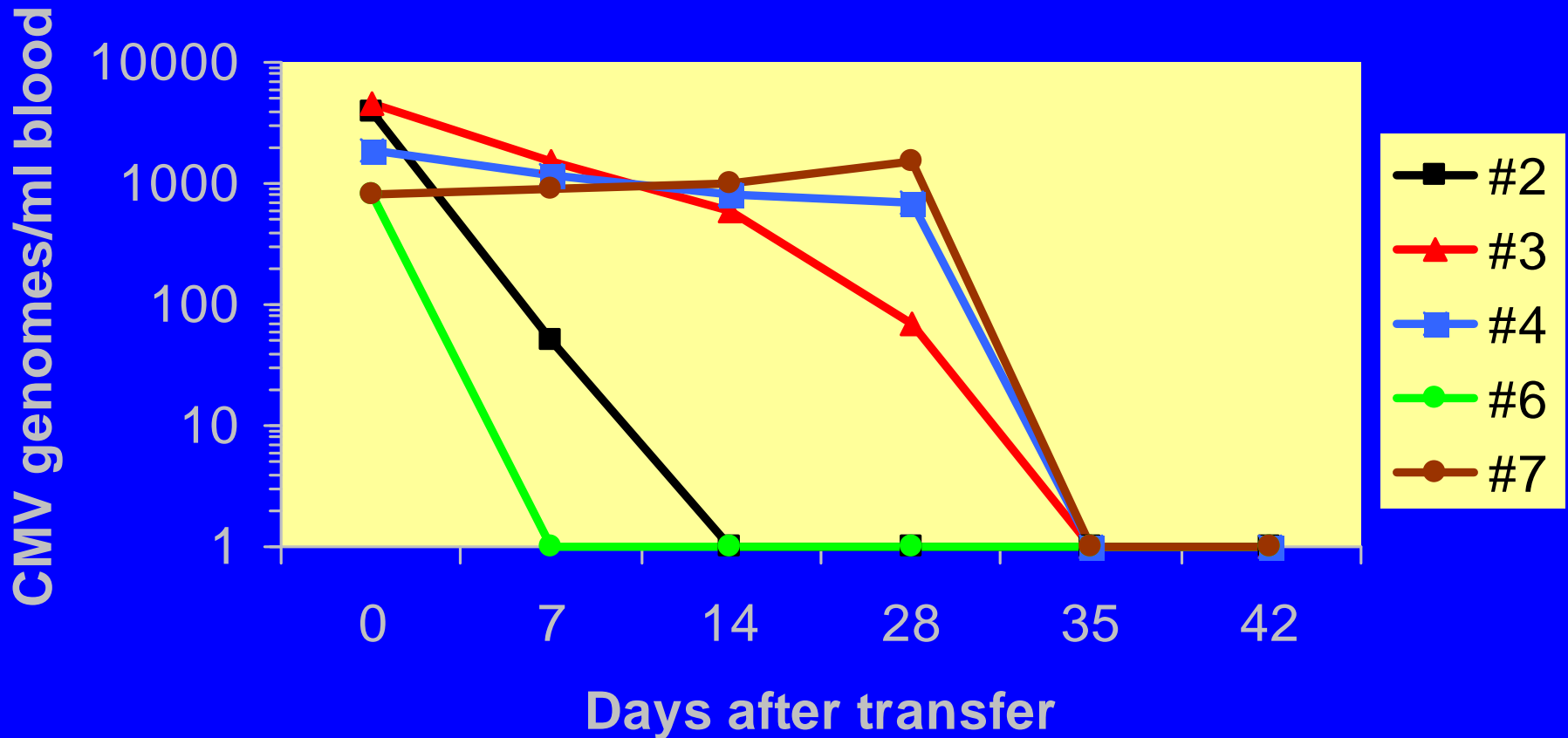
# CMV-DNAemia and CMV-peptide specific CD8+ T cells



# Generation of peptide-specific CTLs



# Viral load upon adoptive transfer of CMV-specific T cell lines



# CMV Infection after Transplantation

## Summary

- **Standard treatment early post-transplantation**
  - Pre-emptive strategy
  - Antiviral prophylaxis
  - Incidence of late CMV disease ↑
- **Treatment >day 100 post-transplantation**
  - Prolonged screening and pre-emptive treatment in patients lacking CMV-specific T cells
  - Adoptive immunotherapy
- **Perspective**
  - new drugs (Valganciclovir, maribavir)
  - Developments in adoptive immunotherapy