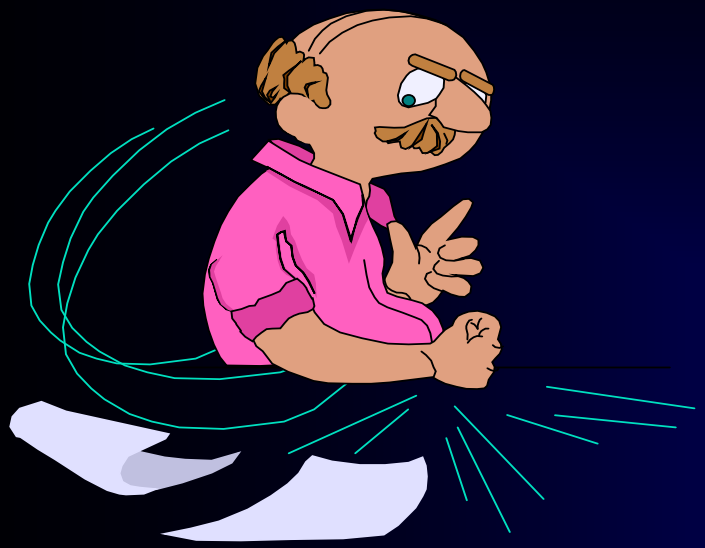
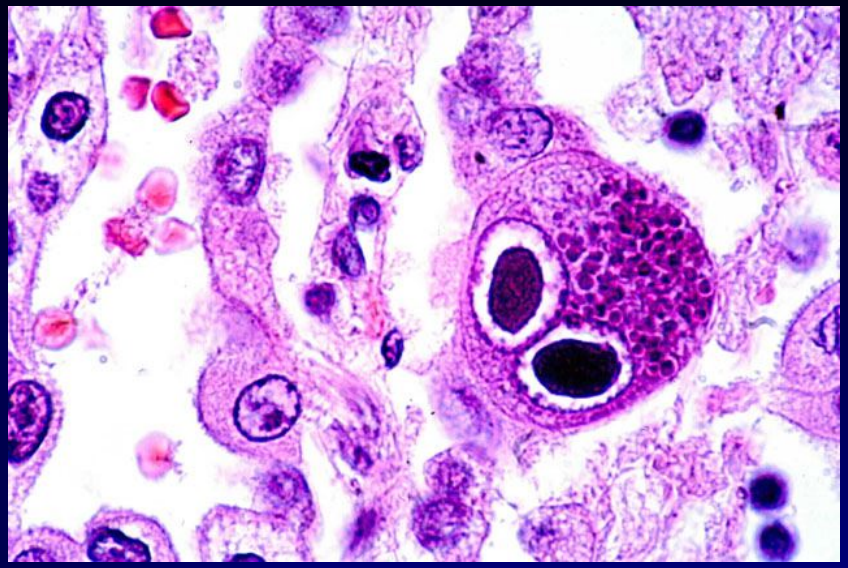
Advances in clinical management and endpoints





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CMV and allogeneic HSCT in 2014

- CMV remains an important pathogen
- CMV serological status influences outome after especially high risk HSCT
- Management options, although having improved a lot, still have important limitations
- Data support a relationship between CMV reactivation and reduced risk for leukemic relapse

Association of CMV Serostatus with Patient Survival

	Number of patients	Underlying disease	CMV-seropositive recipients compared with CMV-seronegative recipients with a seronegative donor
Broers, 2000	115	Mixed	24% absolute decline in OS (p=0.01)
McGlave, 2000	1423	CML	20% relative decline in DFS (p=0.002)
Cornelissen, 2001	127	ALL	38% relative decline in DFS (p=0.05)
Craddock, 2001	106	CML	22% absolute decline in OS (p=0.006)
Kroger, 2001	125	Mixed	41% absolute decline in OS (p,0.001)
Castro-Malaspina, 2002	510	MDS	46% relative decline in DFS (p=0.001)
Doney, 2003	182	ALL	99% relative rise in TRM (p=0.01)
Yakoub-Agha, 2006	236	Mixed	16.4% absolute decline in OS (p=0.01)
Craddock, 2011	168	Primary refractory AML	13% absolute decline in OS (p=0.09)

[1]Table modified from Boeckh, M and Nichols, WG Blood, 15 March 2004

Indirect effects of CMV in transplantation

GVHD (?)

Acute allograft rejection (bidirectional relationship)

Chronic allograft rejection and dysfunction

- TCAD – transplant coronary vasculopathy
- BOS – bronchiolitis obliterans syndrome
- TIF/CAN – chronic allograft nephropathy

Opportunistic infections

Leukemia relapse

Mortality

Rubin RH et al. JAMA 1985

Razonable RR and Limaye AP. *Transplant Infectious*

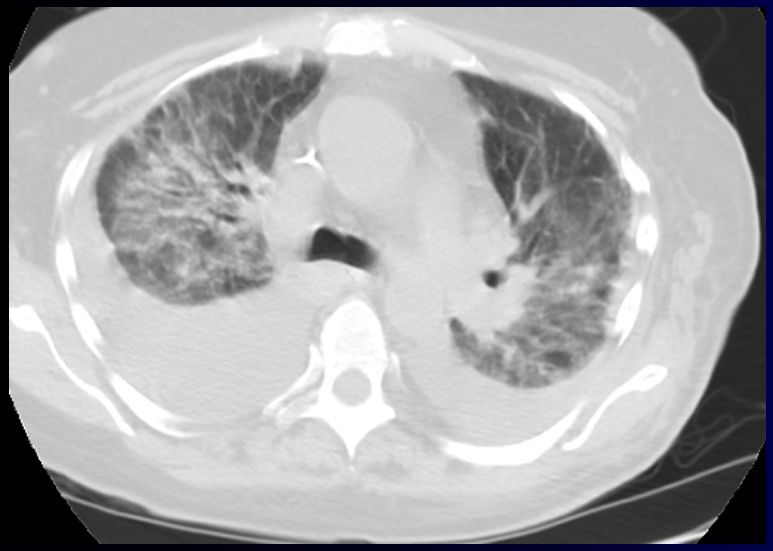
What are the “new” options in 2014?

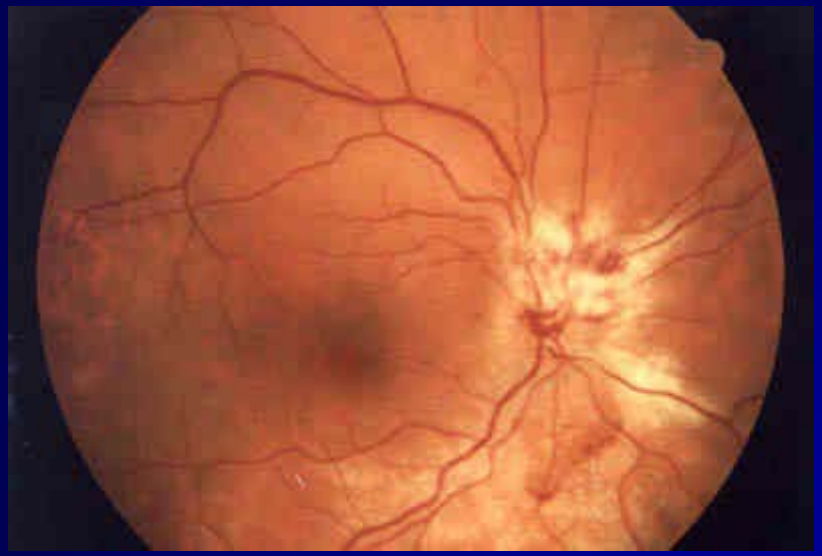
- WHO standard for testing
- New CMV antivirals
- New CMV vaccines
- Adoptive T-cell therapy

Treat established CMV disease

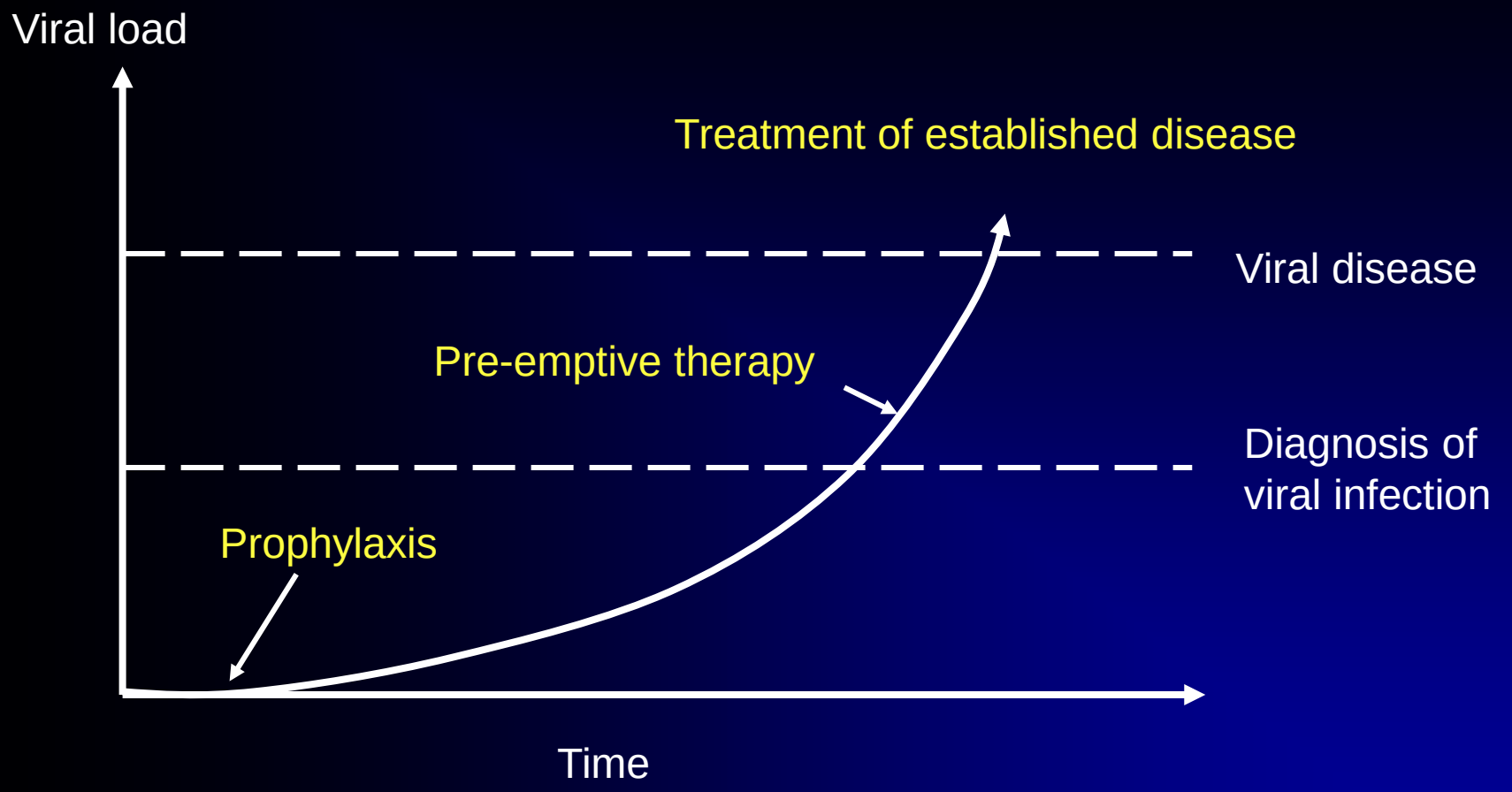
- A failure of strategy

- Associated with significant mortality in the most severely immunosuppressed HSCT patients





Timing of management options



Where are the advances in management?

- Sensitive diagnostic tests are available
- Possibility to judge responses by viral load measurements
- Reduction in the rates of CMV end-organ disease
- Easy access to safe blood products

Where are the major challenges?

- No real impact has been achieved in managing CMV disease
- The drugs are still too toxic
- High risk patients have problems with immune reconstitution and no drug alone can solve that problem

Potential groups to target in prospective studies

- High risk tx patients for prophylaxis
- Standard risk patients for preemptive therapy
- Patients who are refractory/resistant to standard therapy

What is the rationale for prophylaxis?

- To prevent CMV disease we should prevent CMV replication
- CMV seropositivity in the patient decreases survival
- CMV is associated with indirect effects most likely based on the replication itself
- Placebo controlled studies are ethical

The maribavir story

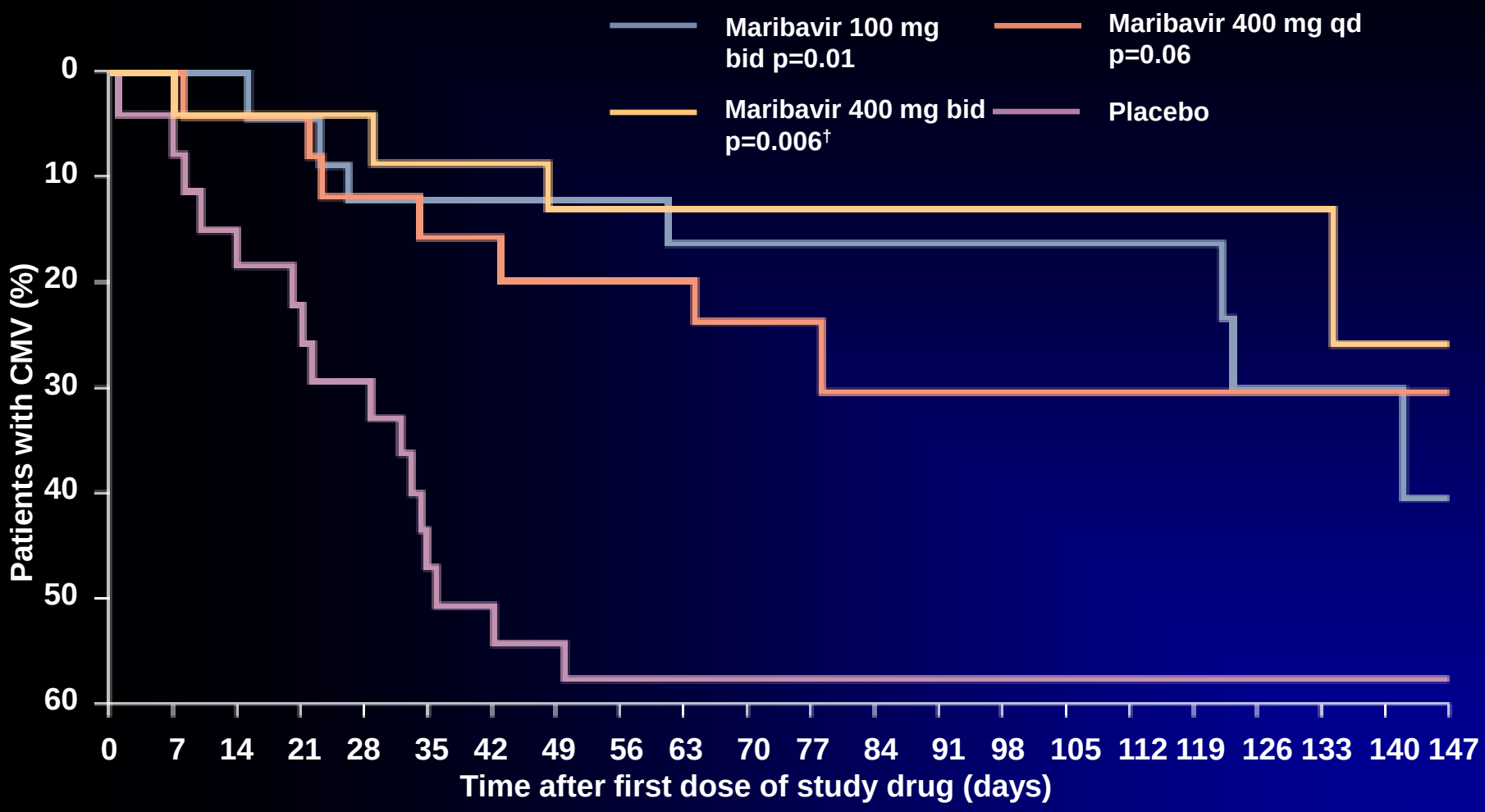
- Very promising phase II results
- Failure of the phase III studies

CMV infection or disease ≤100 days after transplant (Phase II)

		CMV infection n (%)			CMV disease n (%)
	ITT population n (evaluable, n)	pp65 antigenaemia	Plasma CMV DNA PCR	Initiation of anti-CMV therapy	
Placebo	28 (28)	11 (39)	13 (46)	16 (57)	3 (11)
Maribavir					
100 mg bid	28 (27)	4 (15) *p=0.046*	2 (7) *p=0.001*	4 (15) *p=0.001*	0 (0)
400 mg qd	28 (27)	5 (19)	3 (11) *p=0.007*	8 (30)	0 (0)
400 mg bid	27 (26)	4 (15)	5 (19) *p=0.038*	4 (15) *p=0.002*	0 (0)

Winston *et al. Blood* 2008

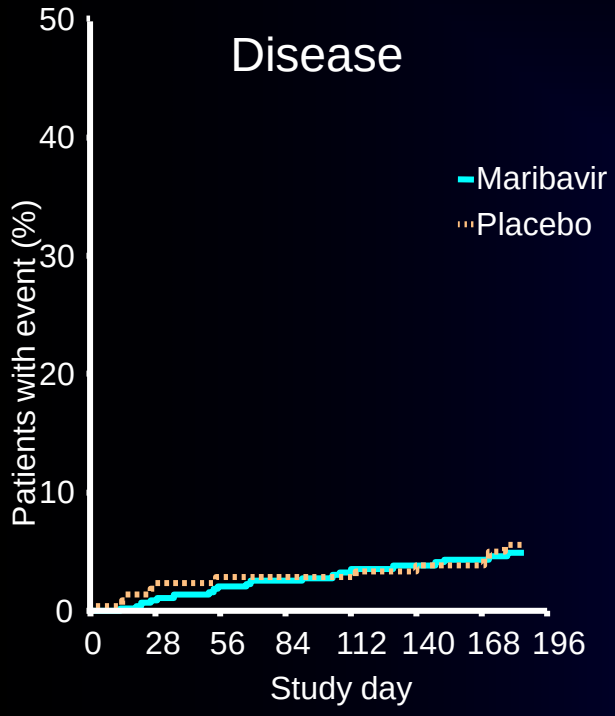
Time to onset of CMV infection or disease

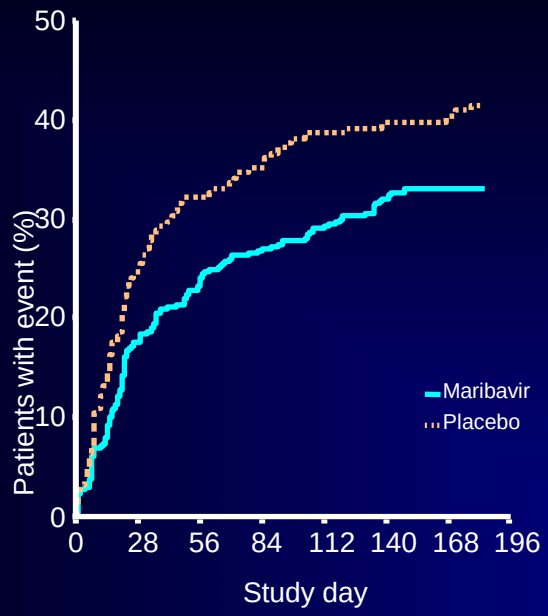


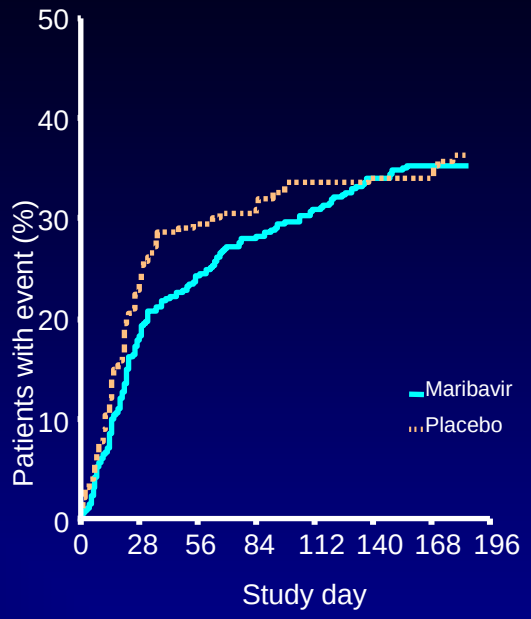
†Cox proportional model hazard regression model

Winston *et al. Blood* 2008

Maribavir phase III results







Marty et al, Lancet ID 2011

Lessons for endpoints

- CMV disease can not be used as the primary endpoint in HSCT studies

- Techniques for diagnosing CMV infection are criticial

What are critical CMV assay requirements?

Test sensitivity and specificity

Conserved target not affected by variant and mutant species

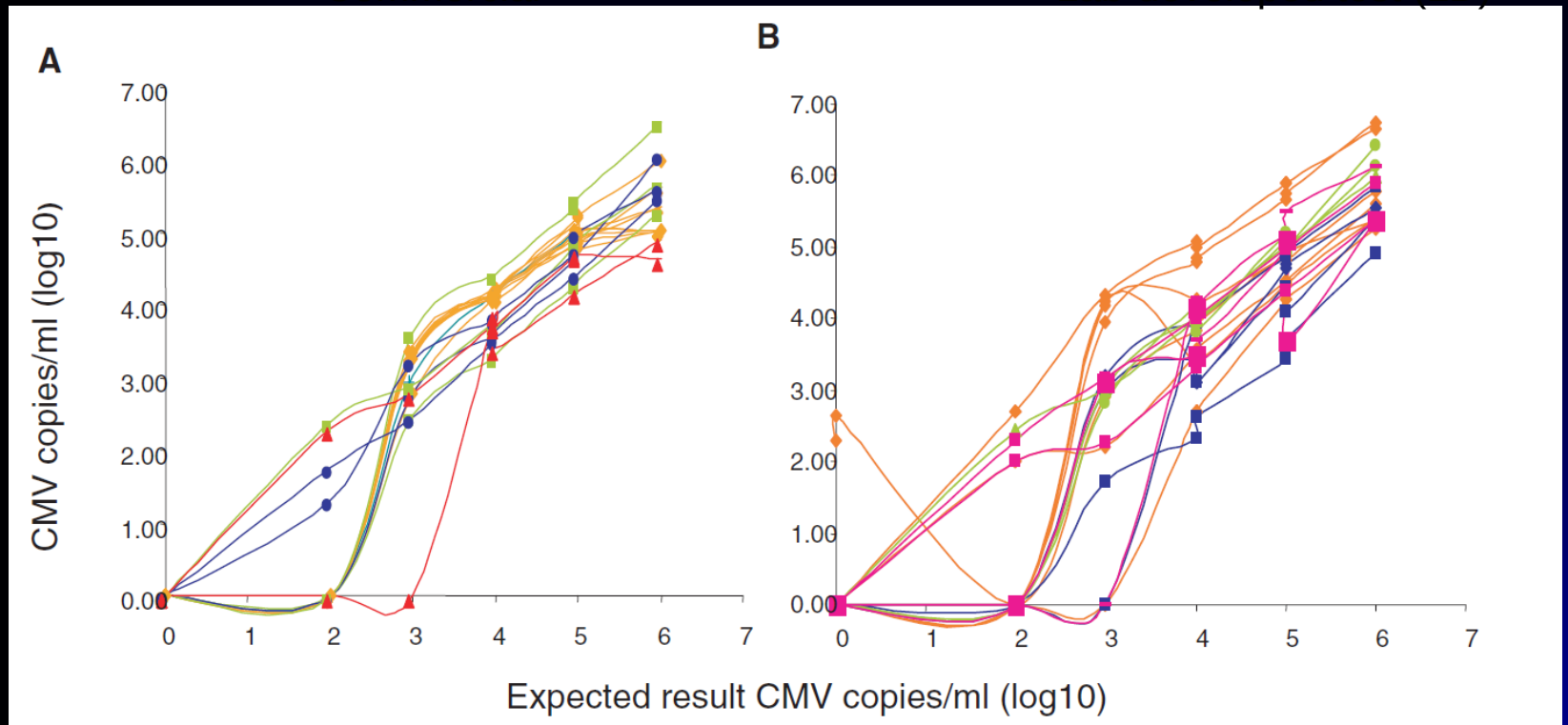
Relevant specimen e.g. whole blood or plasma

Precision such that changes in values represent biologically and presumably important changes in viral replication

Accuracy to trigger start and stop of antiviral therapy

Linearity throughout important medical decision points

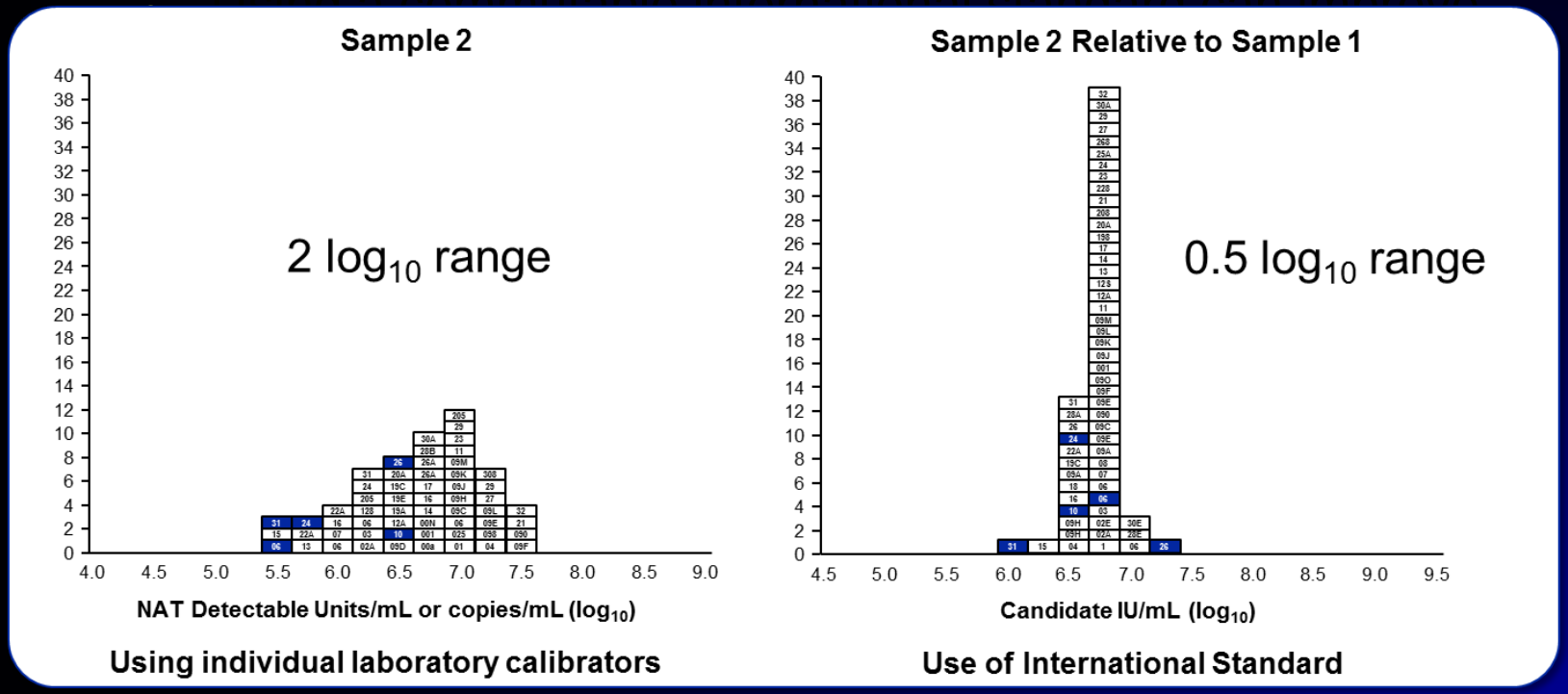
Interlaboratory comparison of non-standardized QNAT for CMV in plasma



e 3: Result linearity over dynamic range for 35 panels from 33 laboratories. Each line represents results from one panel. (A) mercial assays (n = 17) and (B) Laboratory-developed assays (n = 18). The x-axis shows expected results based on stock quantified ference laboratories

Pang et al. 2009 Am J Transplant 9:258

What is the impact of an international standard?



Fryer JF et al. (2010) Collaborative study to evaluate the proposed 1st WHO International Standard for human cytomegalovirus (HCMV) for nucleic acid amplification (NAT)-based assays. WHO ECBS Report 2010; WHO/BS/10.2138.

What the (potential) problems with prophylaxis?

- Patients are treated that don’t need the drug
- Will effective prophylaxis prevent adequate CMV-specific immune reconstitution?
- Can complete prevention increase the risk for relapse?

CMV replication och relapse

British Journal of Haematology, 1986, **63**, 671–679

Reduced risk of recurrent leukaemia in bone marrow transplant recipients after cytomegalovirus infection

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blood

2011 118: 1402-1412
Prepublished online May 3, 2011;
doi:10.1182/blood-2010-08-304121

Early human cytomegalovirus replication after transplantation is associated with a decreased relapse risk: evidence for a putative virus-versus-leukemia effect in acute myeloid leukemia patients

Ahmet H. Elmaagacli, Nina K. Steckel, Michael Koldehoff, Yael Hegerfeldt, Rudolf Trenschel, Markus Ditschkowski, Sandra Christoph, Tanja Gromke, Lambros Kordelas, Hellmut D. Ottinger, Rudolf S. Ross, Peter A. Horn, Susanne Schnittger and Dietrich W. Beelen

Regular Article

TRANSPLANTATION

CMV reactivation after allogeneic HCT and relapse risk: evidence for early protection in acute myeloid leukemia

Margaret L. Green,[1,2] Wendy M. Leisenring,[3,4] Hu Xie,[3] Roland B. Walter,[2,3] Marco Mielcarek,[2,3] Brenda M. Sandmaier,[2,3] Stanley R. Riddell,[2,3] and Michael Boeckh[1,2,3]

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CMV and relapse

- CMV replication reduces the risk for leukemia relapse at least in myeloid malignancies
- Unclear if this is a direct effect or an effect mediated through an imune phenomenon
- The effect occurs early after HSCT
- The potential positive effect on survival is counterbalanced by an increased non-relapse motality

What endpoints would I then like to see?

- A clear reduction in the risk for detecting CMV replication
- Introduction of preemptive therapy could be included but should not be necessary
- An innovative way to look at viral replication. AUC? Proportion to reach certain cut-offs
- Safety is paramount
- Supportive evidence on prevention of indirect effects

What is the rationale and requirements for monitoring and preemptive treatment

- Only patients developing CMV replication are subjected to treatment

- A sensitive diagnostic test must be available
- A positive result is predictive for development of disease
- Early intervention can prevent disease
- An effective (and safe) antiviral drug is available

Preemptive therapy today; HSCT

- Proven efficacy
- Allows short treatment courses
- Low risk for CMV disease
- Standardized monitoring techniques are now available

Viral load and CMV disease

Initial viral load correlate with CMV disease

Liver tx (OR 1.82 [1.11-2.98; p=0.02)

Renal tx (OR 1.34 [1.07-1.68], p=0.01)

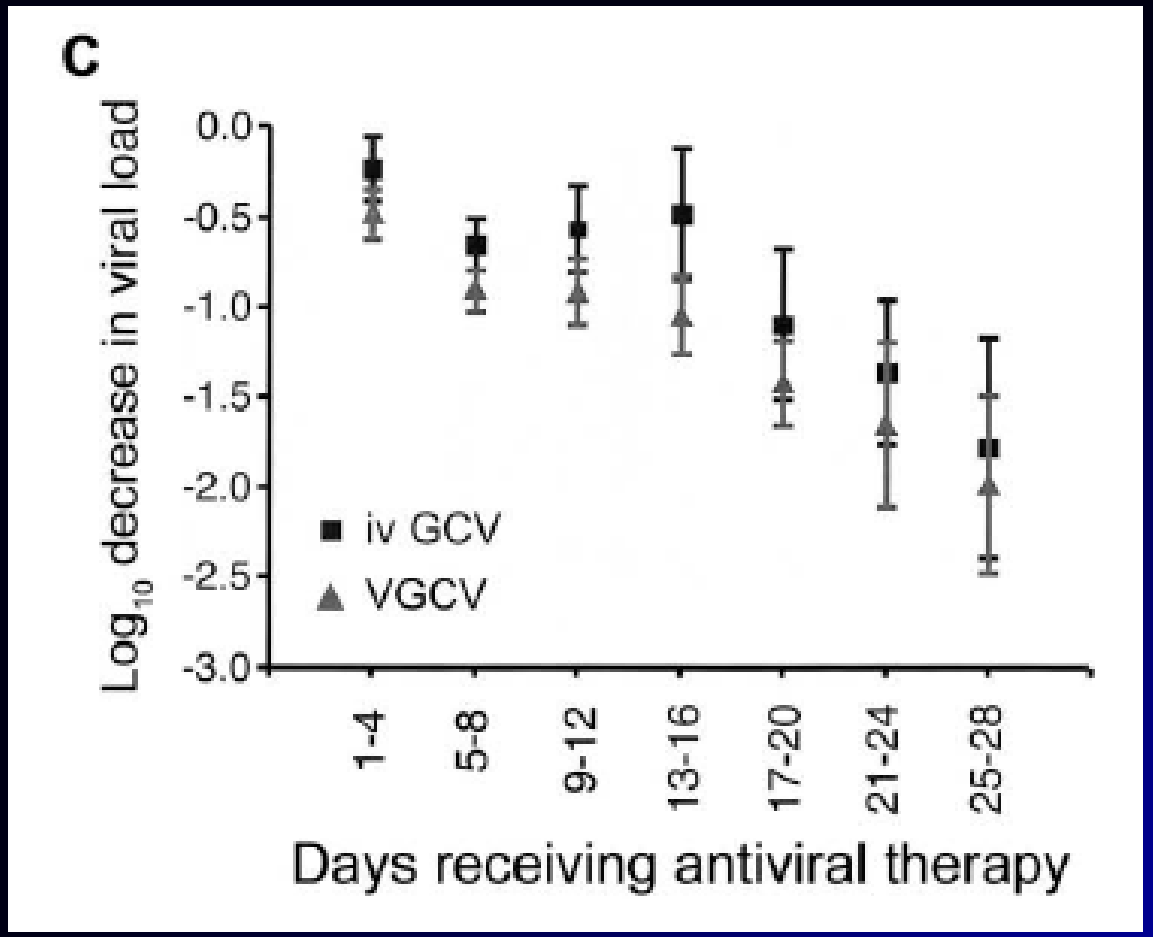
HSCT tx (OR 1.52 [1.13-2.05], p=0.006)

per 0.25 log10 increase in viral load

The rate of increase in CMV load correlates with CMV disease (0.33 log10 vs 0.19 log10 genomes/mL daily, $p<0.001$)

Emery et al; Lancet 2000

Effects on antiviral therapy on viral load



Mattes et al JID 2005

Response to therapy and CMV disease

Analysis of first course response

Patients w/o CMV disease		0.7 log/decrease/week
Patients who developed CMV disease		0.4 log/decrease/week

Multivariate analysis

Quick decrease in viral load	RR	0.08 (0.01-0.8; p=.03)
Acute GVHD II-IV	RR	11.2 (1.2-73; p=.009)

Ljungman et al Haematologica 2006

Requirements and questions for preemptive studies

- Can an antiviral effect be used as primary endpoint?
- What about CMV disease in this setting?
- What should a new drug be compared to?
  - Iv GCV? Valganciclovir? Local standard?

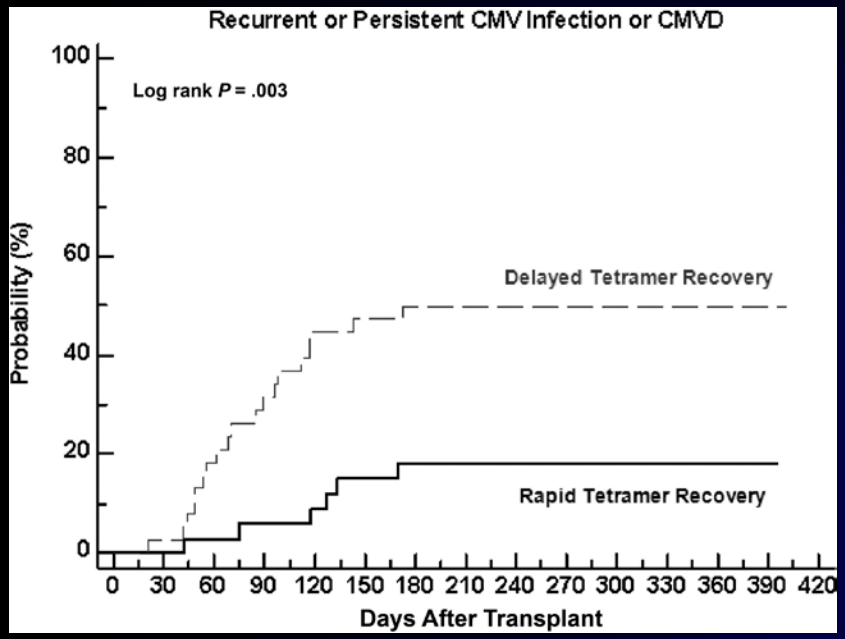
What endpoints would I then like to see?

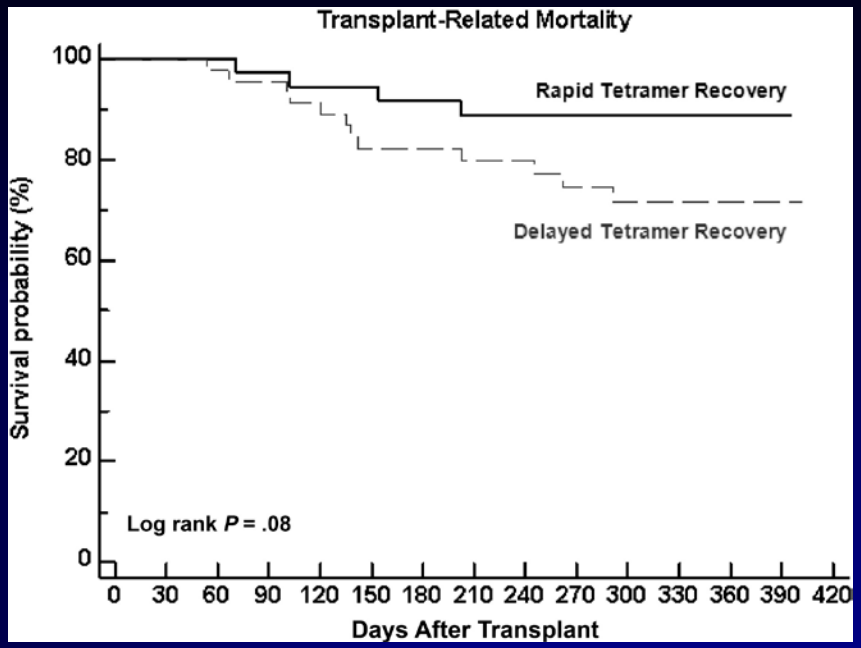
- Quick and reproducible reduction in viral load when antiviral therapy is introduced
- Safety is important should be better than today's drugs
- No increase in the risk for CMV disease
- Comparator?

Management of repeated CMV replication episodes

- More common in high risk patients
- Concomitant problems such as GVHD are common
- Associated with poor T-cell control of CMV
- Frequently poor activity/tolerability of existing antiviral drugs
- Clinical/viral resistance
- Unmet medical need

Immunological monitoring might add important information for management



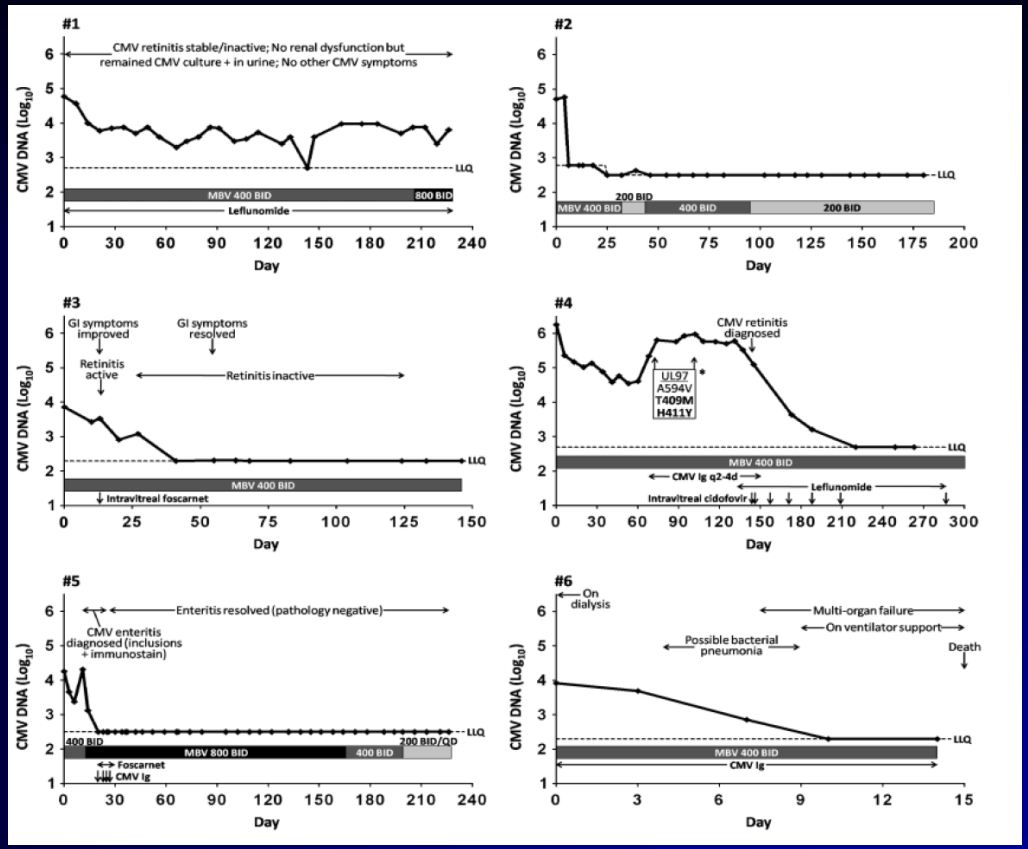


Gratama J W et al. Blood 2010;116:1655-1662

Treatment of refractory patients

6 treated patients
6 CMV disease
Median 4 prev. agents
4 proven resistant

4 cleared virus
5 survived
1 developed resist.



Avery et al; TID 2010

What endpoints would I then like to see?

- Quick and reproducible reduction in viral load when antiviral therapy is introducted
- Low risk for progession to disease
- Low risk for development of resistance
- Compared to what?
- How to deal with inmovative approaches? T-cells

Karolinska Institutet

Thank you for your attention!