CMV EN TRANSPLANTATION RÉNALE: TRAITEMENT PRÉVENTIF OU PRÉEMPTIF ET NOUVELLES ALTERNATIVES

JOURNÉE G2I 31/3/2021

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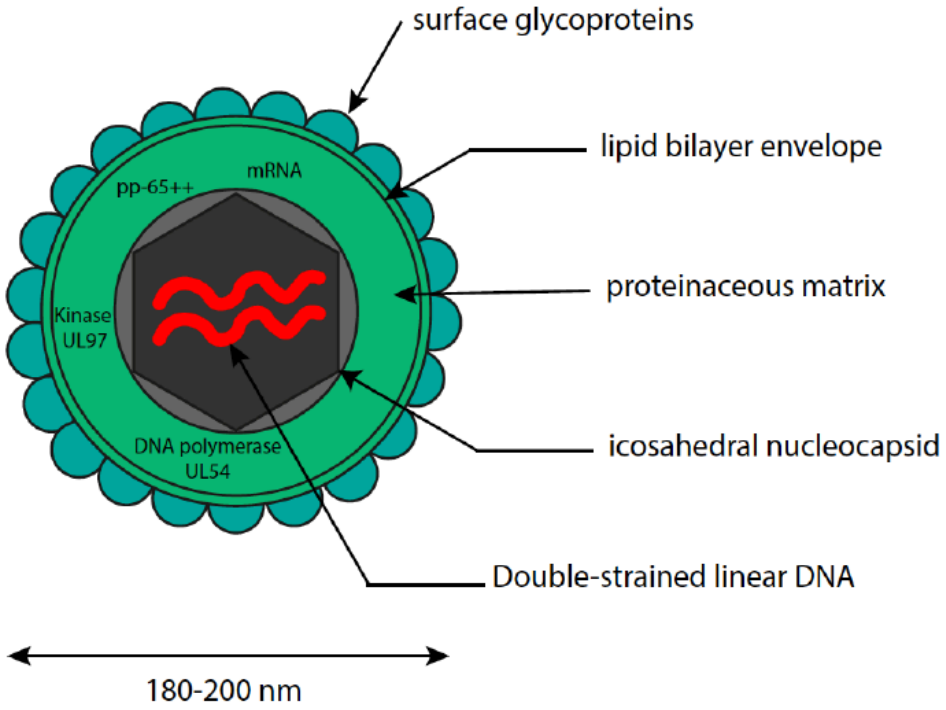
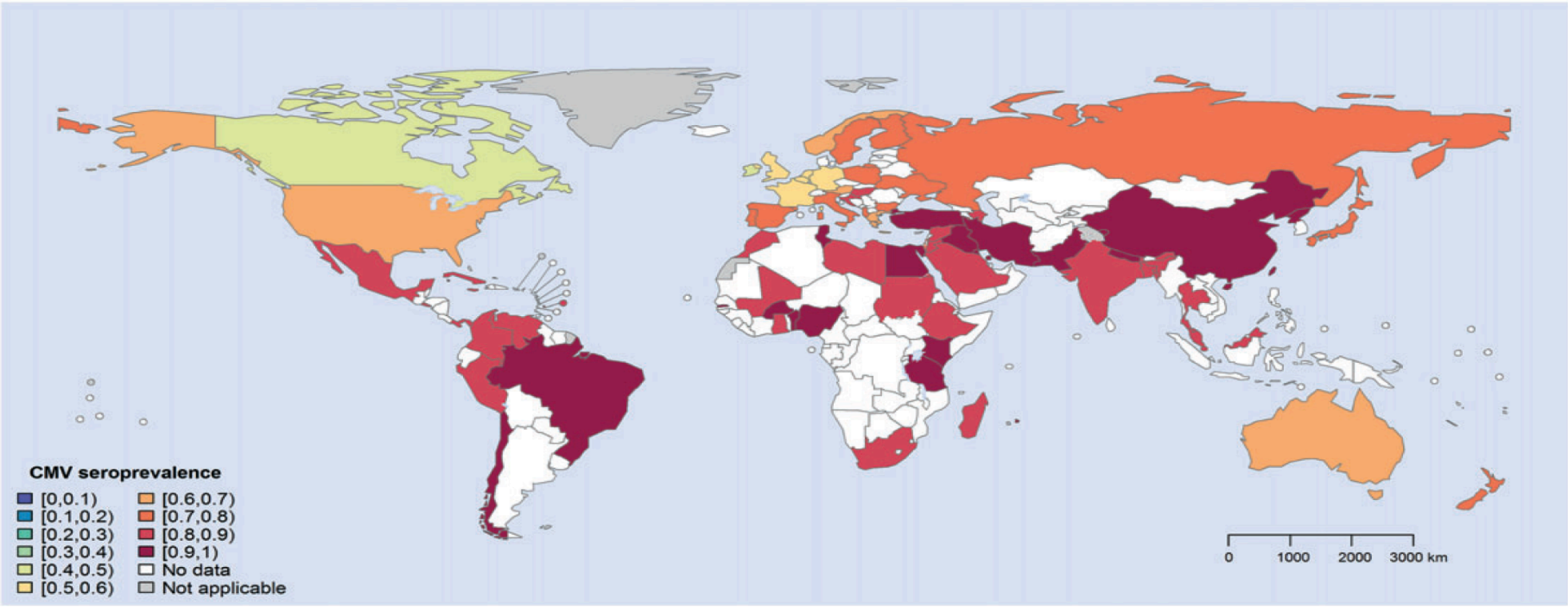
ImmunoConcEpT Immunology from Concept and Experiments to Translation

STRUCTURE, TRANSMISSION



- Herpesvirus
- Double strain DNA
- 235 KB et 165 genes
- 180-200 nm
- Icosahedral capsid
- Transmission: exclusively inter-human

WORLDWIDE SEROPREVALENCE OF CYTOMEGALOVIRUS



83% (95%UI: 78-88) in the general population,
86% (95%UI: 83-89) in women of childbearing age

86% (95%UI: 82-89) in donors of blood or organs
European region 66% (95%UI: 56-74).

Zuhair M, Rev in Med Virol, 2019

POPULATIONS AT RISK OF CMV DISEASE

Solid-Organ Transplant Recipients
► 126 670 transplanted organs in 2015 (+5.8%) worldwide

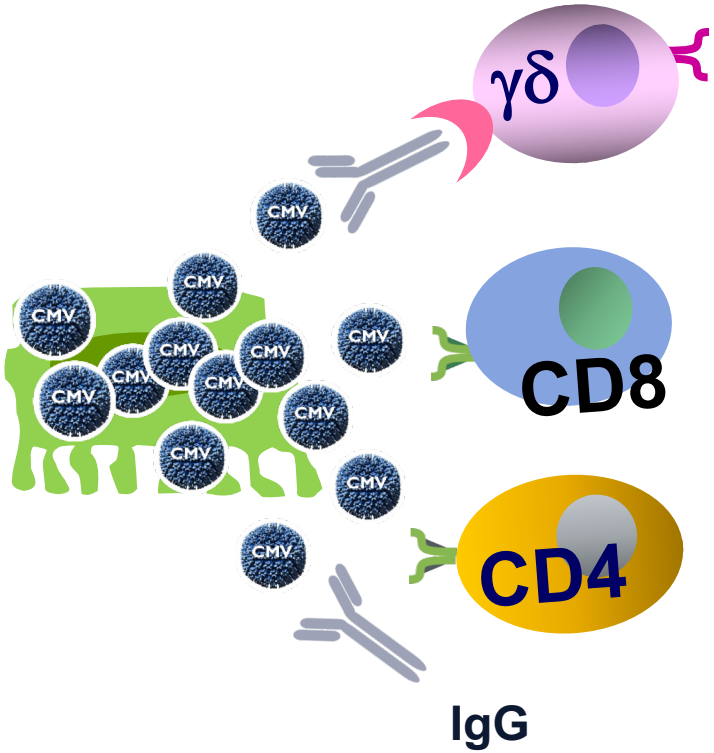
Hematopoietic-Cell Transplant Recipients
► more than 50 000 transplants each year

AIDS Patients
► 36.7 million

Newborns (congenital infections)

www.transplant-observatory.org
www.wbmt.org
www.avert.org/global-hiv-and-aids-statistics.org

ANTI-CMV IMMUNE RESPONSE

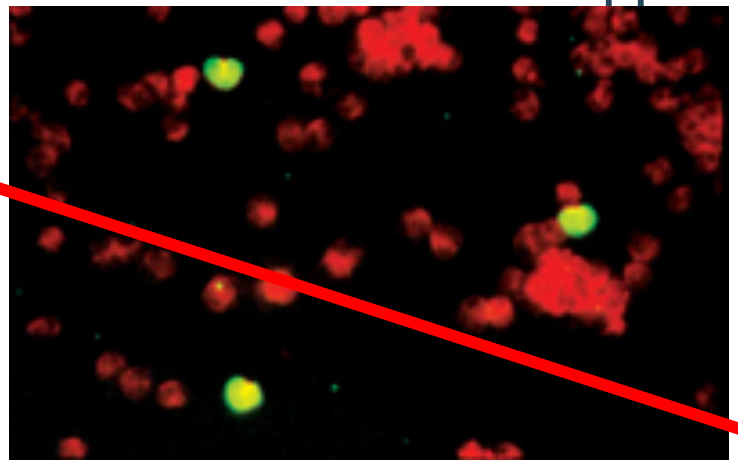


Healthy individuals

Dissemination and CMV disease in immunocompromised individuals

DEFINITIONS OF CMV INFECTION

- ***CMV antigenemia*** is defined as the detection of CMV pp65 antigen in PBMC.



- ***CMV DNAemia*** is defined as the detection of CMV DNA in samples of plasma, serum, whole blood.

Ljungman, Clin Infect Dis. 2017;64(1):87-91 (CMV Drug Development Forum)

CMV QUANTITATIVE ACID NUCLEIC TESTING *(QNAT)*

- Must be calibrated with the **WHO International Standard** for **Human CMV**
- Reported as **IU/ml, and** termed as **DNAemia** rather than viremia.
- **Highly sensitive QNAT : < 200 IU/ml (results given as $\log_{10}$ IU/ml)**
- Sensitivity: whole blood > plasma

- **In our center : whole-blood : sensitivity for positivity : 250 IU/ml** (WHO: since June 19, 2012)

Kotton, Transplantation. **2018** Jun;102(6):900-931

DEFINITIONS OF CMV INFECTION AND DISEASE

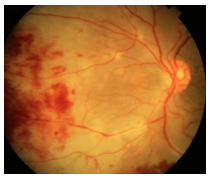
- **CMV infection** is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen, regardless of symptoms *(ie, CMV DNAemia ± symptoms)*

- **CMV disease**: Evidence of CMV infection with attributable symptoms. CMV disease can be further categorized as:
  - Viral syndrome
  - Tissue-invasive disease

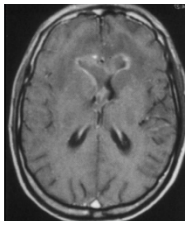
Ljungman, Clin Infect Dis. 2017;64(1):87-91 (CMV Drug Development Forum)

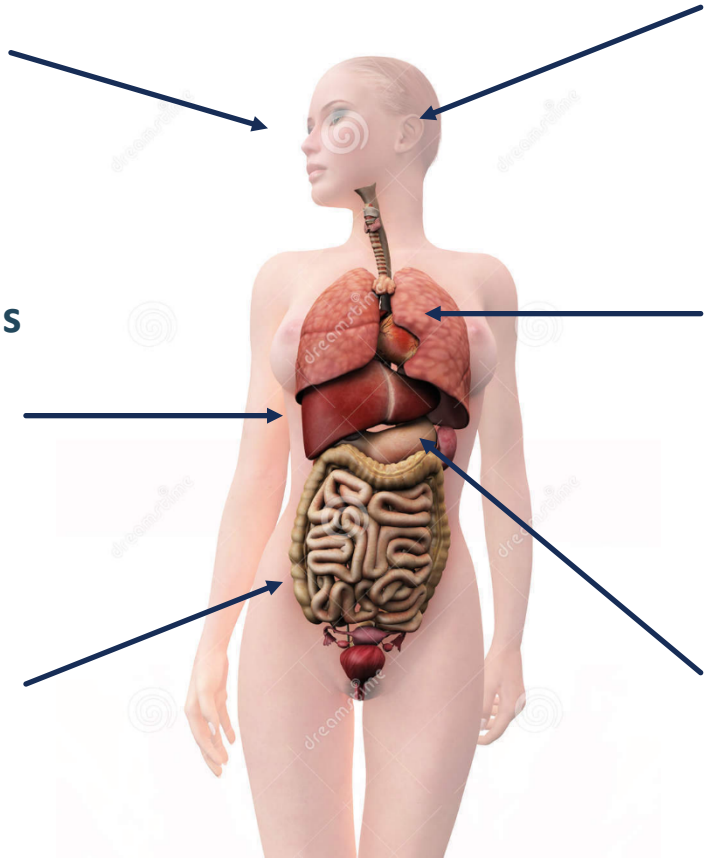
DEFINITIONS OF CMV DISEASE:
TISSUE INVASIVE (OR END-ORGAN) DISEASE

CMV retinitis

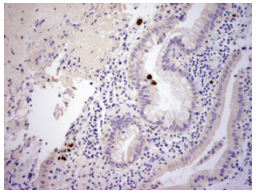


CMV encephalitis

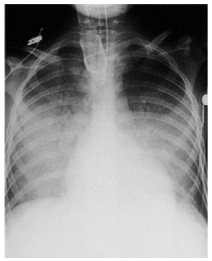




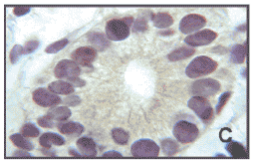
CMV cholecystitis



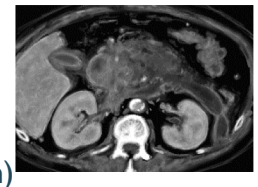
CMV pneumonia



CMV colitis



CMV Pancreatitis



Ljungman, Clin Infect Dis. 2017;64(1):87-91 (CMV Drug Development Forum)

RISK FACTORS OF CMV DISEASE

- **Risk of cytomegalovirus (CMV) infection** in solid organ transplant recipients is defined by:
  - Donor and recipient **CMV serostatus**

    D+R- > D+R+ > D-R+ > D-R-

    Atabani, Am J Transplant. 2012;12(9):2457-2464

  - The transplanted **organ**

    Lung > others

    Manuel, Am J Transplant. 2013;13(9):2402-2410

  - Additional **immunosuppressive** therapy
    - **Induction** :ATG > anti-IL2R in R+ patients but not in D+R-

      Webster, *The Cochrane Database of Systematic Reviews*, 2010
      Kaminski, J Inf Dis, 2019, 220(5):761-771

    - **Rejection**

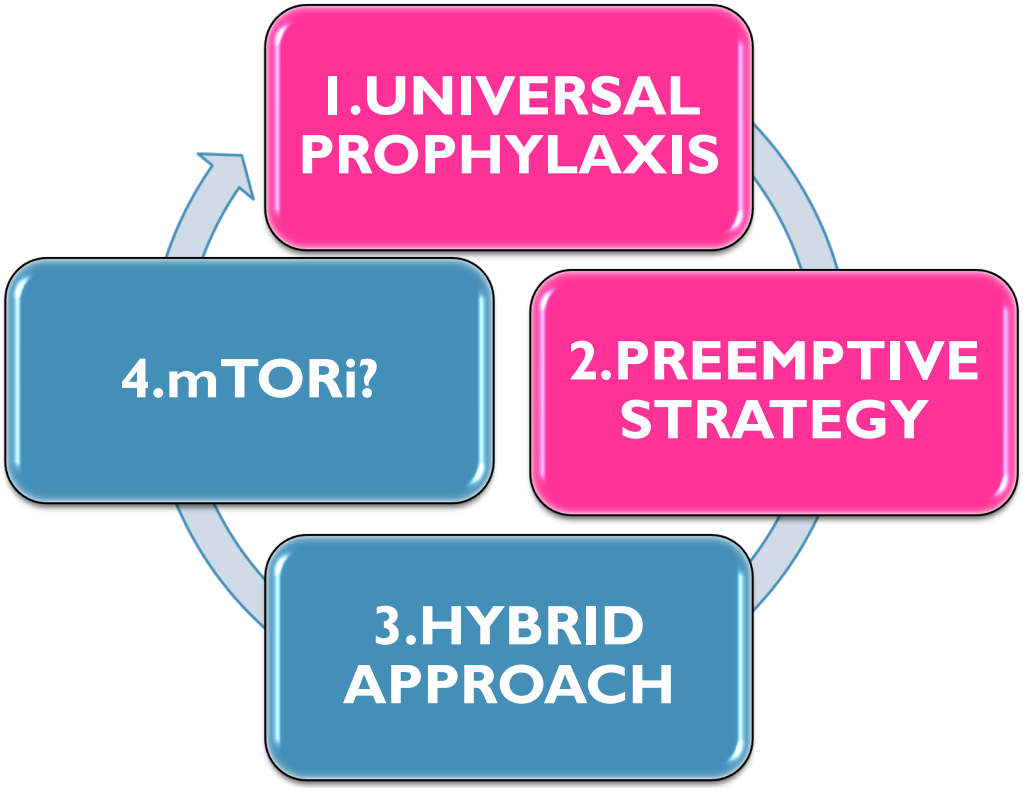
      Lee, Transpl Infect Dis. 2014;16(3):397-402.
      Santos, Transplantation. 2014;98(2):187-194

PREVENTION

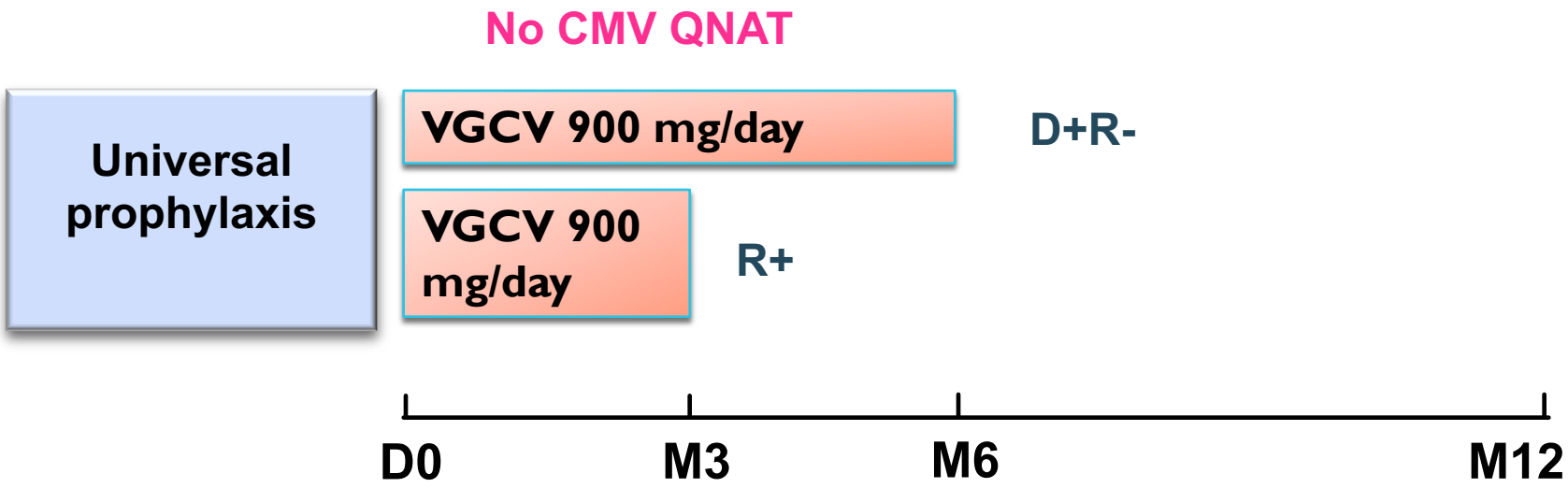
- **Risk of CMV infection** in solid organ transplant recipients is defined by:
  - donor and recipient **CMV serostatus**
  - the transplanted **organ**
  - and additional **immunosuppressive** therapy.

- these parameters are used to design the preventive strategy

CMV PREVENTION: FOUR STRATEGIES



CMV PREVENTION: UNIVERSAL PROPHYLAXIS

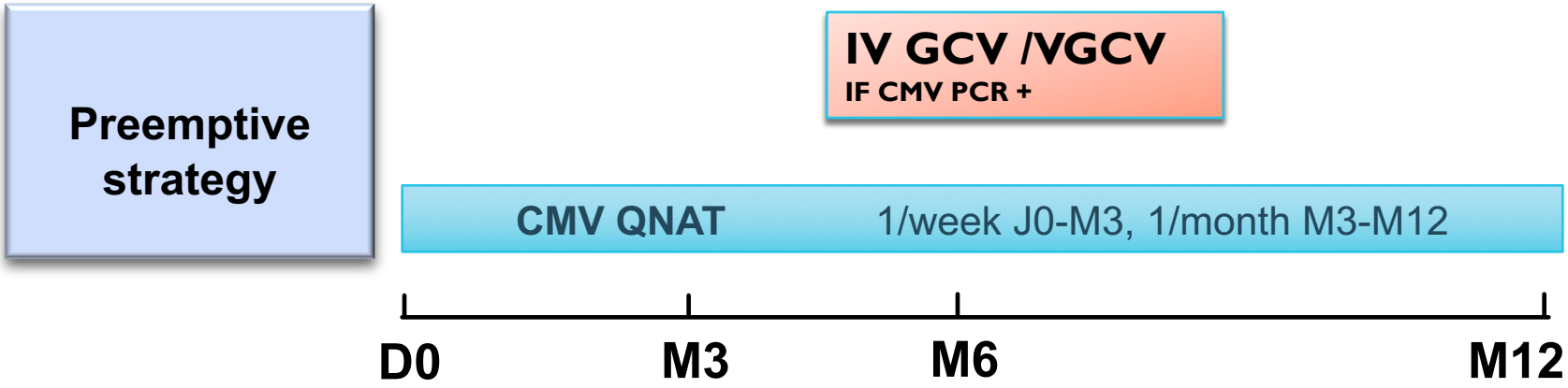


- **Valganciclovir**: most commonly used
- *High-dose valacyclovir (=valganciclovir)*

Humar, Am J Transplant. 2010 May;10(5):1228-37
Reischig, Clin J Am Soc Nephrol 2015;10(2):294-304

VGCV : Valganciclovir; GCV : Ganciclovir

CMV PREVENTION: PREEMPTIVE THERAPY



Kotton, Transplantation. 2013 Aug 27;96(4):333-60

VGCV : Valganciclovir; GCV : Ganciclovir

SUMMARY ON THE RATE OF INFECTION/DISEASE FOLLOWING STRATEGY

	No treatment			Références
	D+R-	D+R+	D-R+	
Infection/Disease	68 %	63 %	50 %	(1, 2, 3, 5, 8)
	Universal prophylaxis			
Infection	3 month : 51 % 6 month : 37 %	3 mois : 25 %	3 mois : 23 %	(1, 2, 3, 5, 6, 9)
Disease	3 month : 37 % 6 month : 16 %	3 mois : 7 %	3 mois : 2 %	(1, 6, 9)
	Preemptive strategy			
Infection	68 %	63 %	50 %	(1, 2, 3, 5, 8)
Disease	20 %	5 %	2 %	(1, 3, 6, 7, 8)

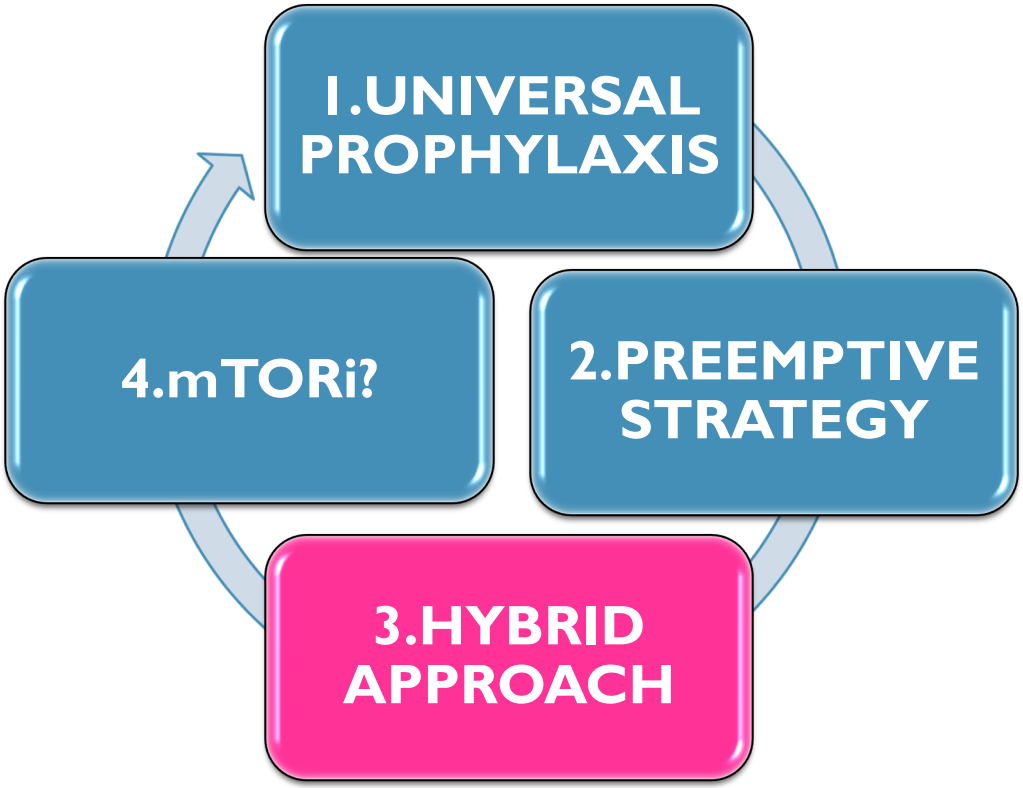
1. Khoury, Am J Transplant. 2006; 9:2134-43.
2. Kliem, Am J Transplant. 2008; 5:975-832008
3. Reischig, Am J Transplant. 2008, 1:69-77
4. Helentera, Am J Transplant. 2010, 9:2026-3
5. Van der Beek, Transplantation. 2010, 3:320-6
6. Couzi, Am J Transplant. 2012, 1:202-
7. Witzke, Transplantation. 2012, 1:61-8
8. Atabani, Am J Transplant. 2012, 9:2457-64
9. Humar, Am J Transplant. 2010, 10:1228-37

UNIVERSAL PROPHYLAXIS *VERSUS* PREEMPTIVE THERAPY

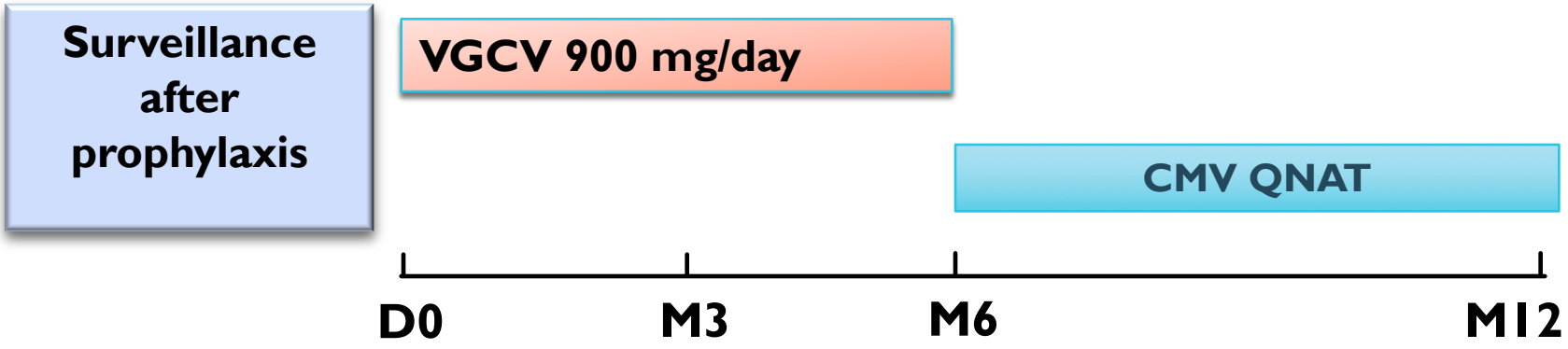
	Prophylaxis	Pre-emptive therapy
Early CMV DNAemia/ infection	Rare	**Common**
Prevention of CMV disease	Good efficacy	Good efficacy
Late CMV (infection/disease)	**Common**	Rare
Resistance	Uncommon	Uncommon (with weekly testing)
Ease of implementation	Relatively easy	**More difficult**
Prevention of other herpes viruses	Prevents HSV,VZV	**Does not prevent**
Other opportunistic infections	May prevent	Unknown
Costs	Drug costs	Monitoring costs
Safety	**Drug side effects**	Less drug toxicity
Prevention of rejection	May prevent	Unknown
Graft survival	May improve	May improve

Kotton, Transplantation. **2018** Jun;102(6):900-931 ; Florescu, Clinical Infectious Diseases 2014;58(6):785–803

CMV PREVENTION: FOUR STRATEGIES



SURVEILLANCE AFTER PROPHYLAXIS (OR "HYBRID APPROACH")



VGCV :Valganciclovir; GCV : Ganciclovir

SURVEILLANCE AFTER PROPHYLAXIS (OR "HYBRID APPROACH")

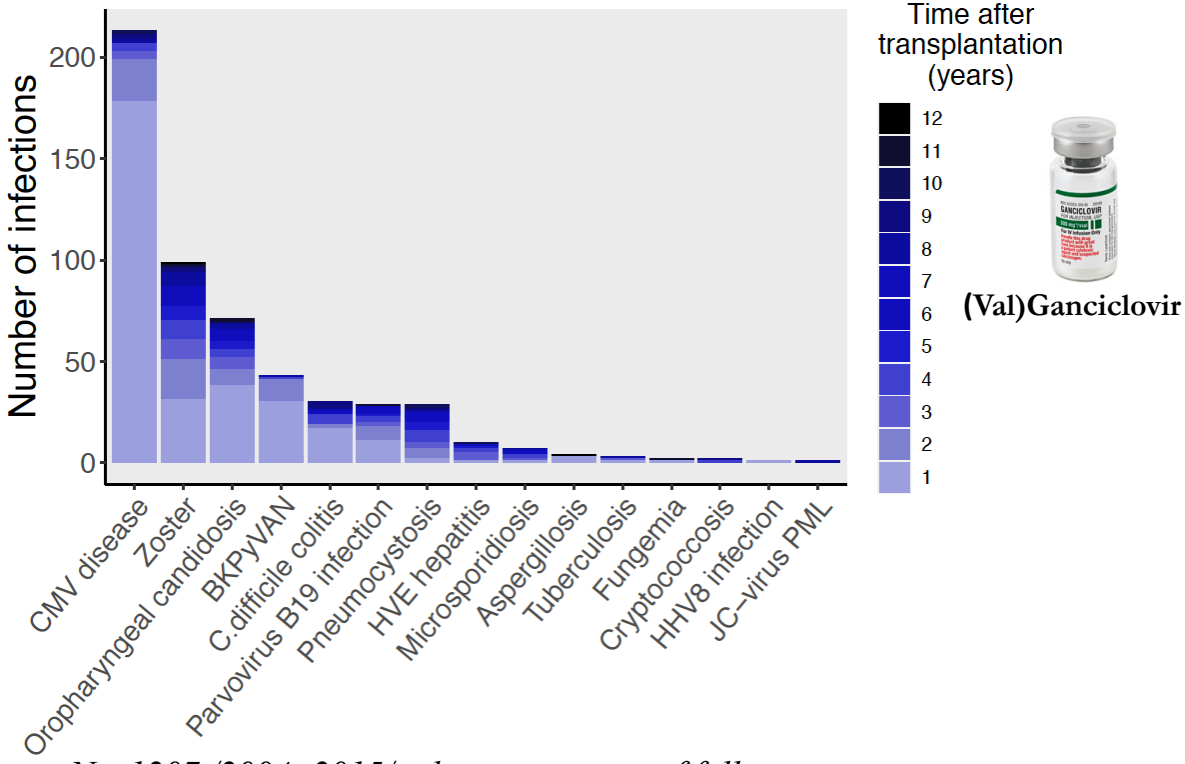
- **No RCT to support the use of a surveillance** after prophylaxis approach

- Use of surveillance after prophylaxis may be considered **in patients at increased risk for post-prophylaxis CMV disease**. The value is probably greatest if done weekly for 8-12 weeks.

Kotton, Transplantation. **2018** Jun;102(6):900-931

RCT : randomized control trial

CURRENT EPIDEMIOLOGY OF CMV INFECTION IN KIDNEY TRANSPLANT PATIENTS



(Val)Ganciclovir

CMV requiring treatment 17.5%

↓

Persistence 28.5%

↓

Clinical relapse : 20.7%

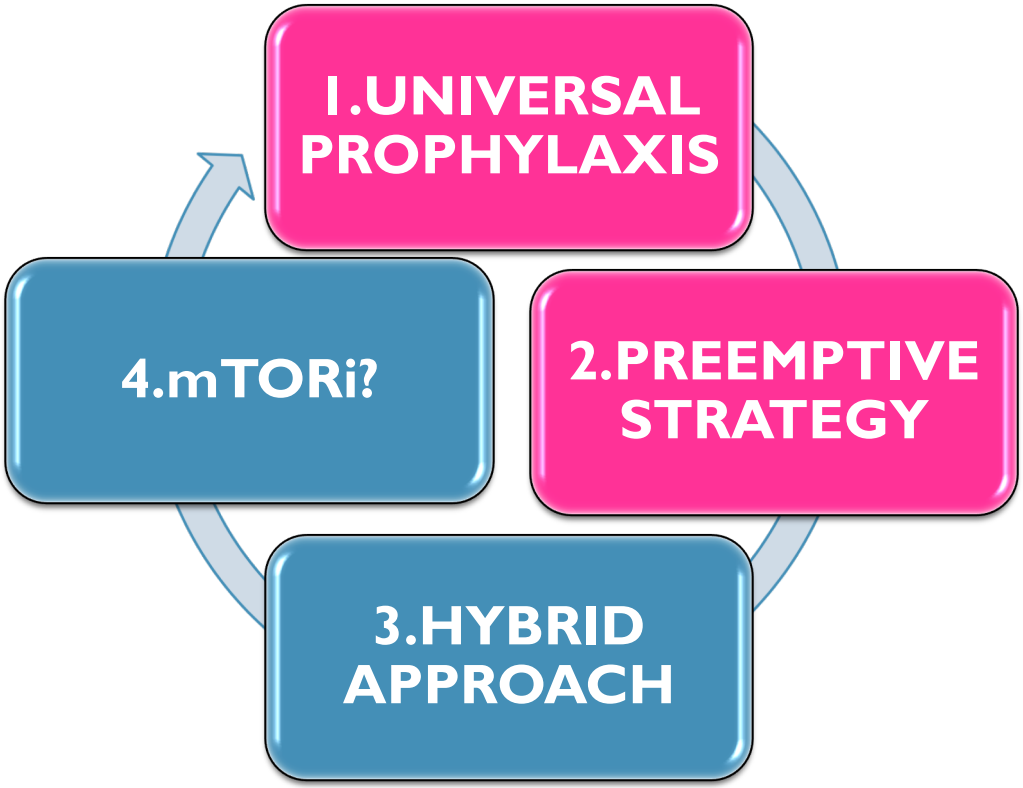
↓

CMV Mutant : 6%

N= 1207 /2004 -2015/at least two years of follow-up. Personal unpublished data P.Pfirmann-B.Taton-H.Kaminski

313 events among 1792 KTR 2004-2017 Personal unpublished data M.Acquier-H.Kaminski-L.Couzi

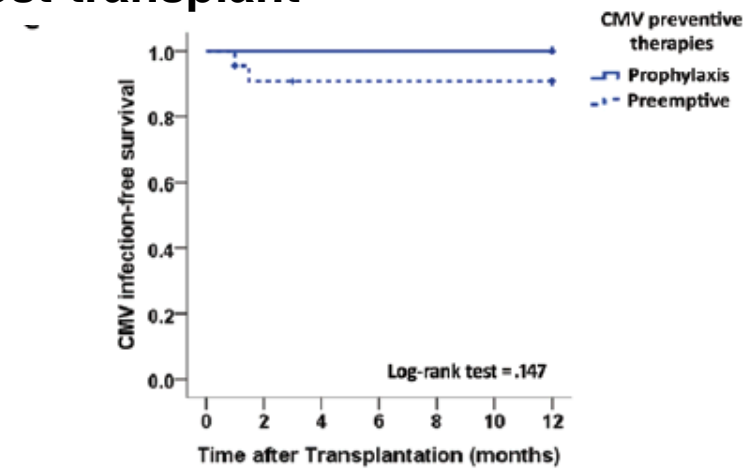
CMV PREVENTION: COULD IMMUNOMONITORING HELP?



CELLULAR IMMUNITY TO PREDICT THE RISK OF CMV INFECTION IN R+ KIDNEY TRANSPLANTATION

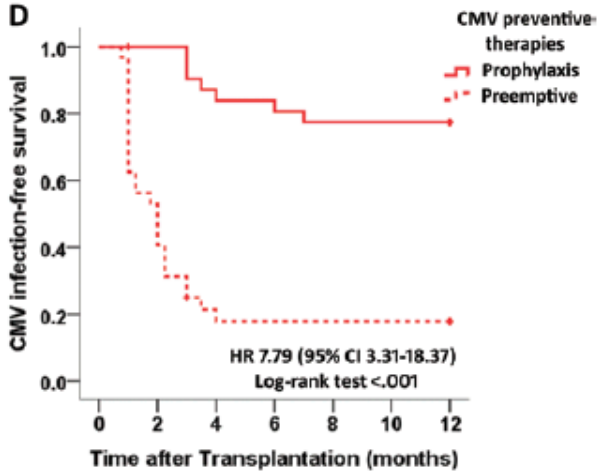
15-day post-transplant

CMV-specific T cell response



Prophylaxis (n)	22	22	22	22	22	22	22
Event-Free (n)	22	22	22	22	22	22	22
Preemptive (n)	22	19	18	18	18	18	18
Event-Free (n)	22	20	20	20	20	20	20

No CMV-specific T cell response

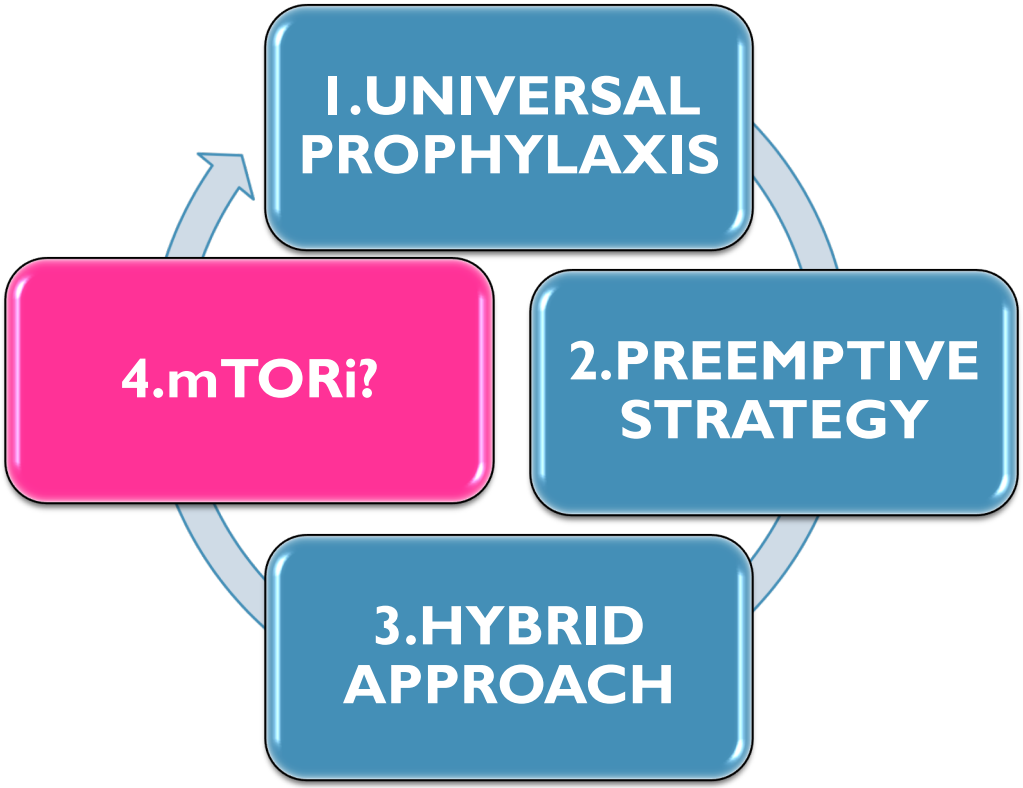


Prophylaxis (n)	32	31	26	25	24	24	24
Event-Free (n)	32	32	27	26	25	25	25
Preemptive (n)	32	13	5	5	5	5	5
Event-Free (n)	32	13	6	6	6	6	6

Jarque, *CLIN INFECT DIS*, vol. 357, pp. 2601–11, Feb. 2020.

ELISPOT

CMV PREVENTION: FOUR STRATEGIES

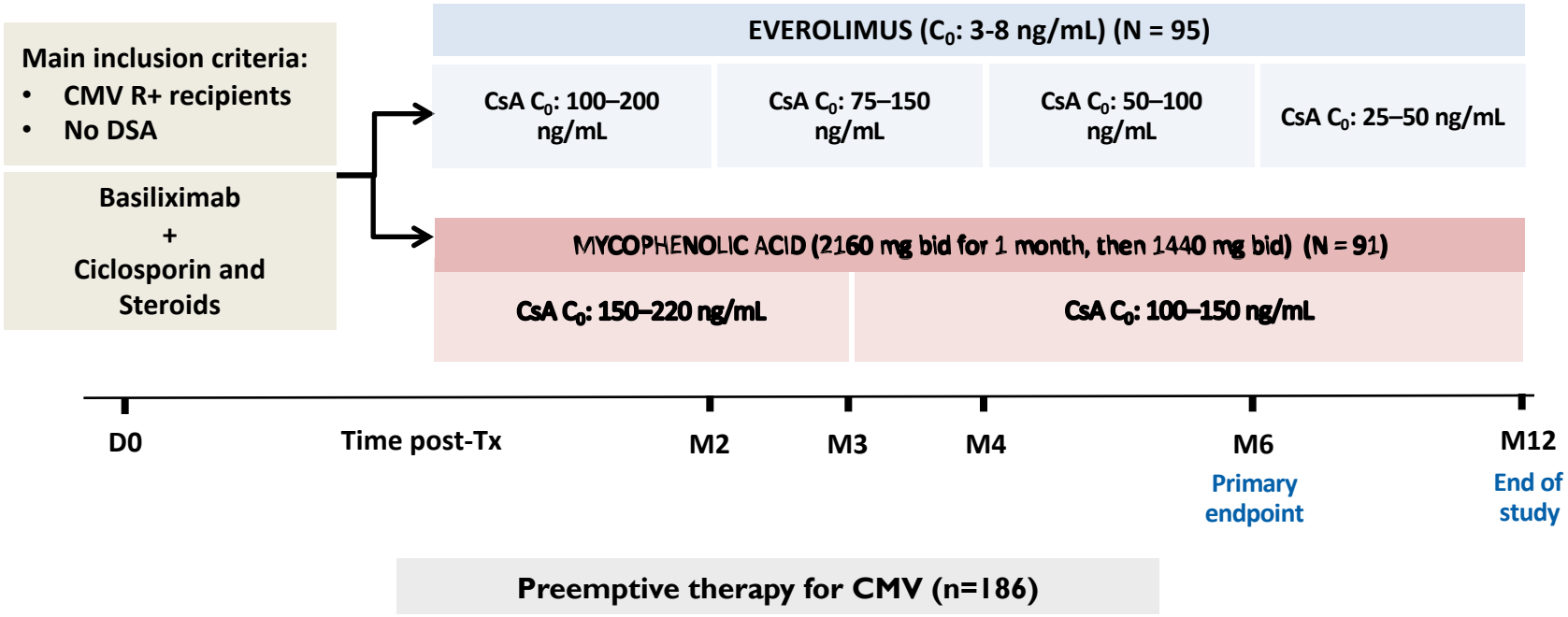


EVERCMV STUDY

First randomised, **multicenter**, open-label, parallel group study in CMV R+ kidney transplant recipients, comparing everolimus *versus* mycophenolic acid, with **CMV DNAemia** as a primary end-point

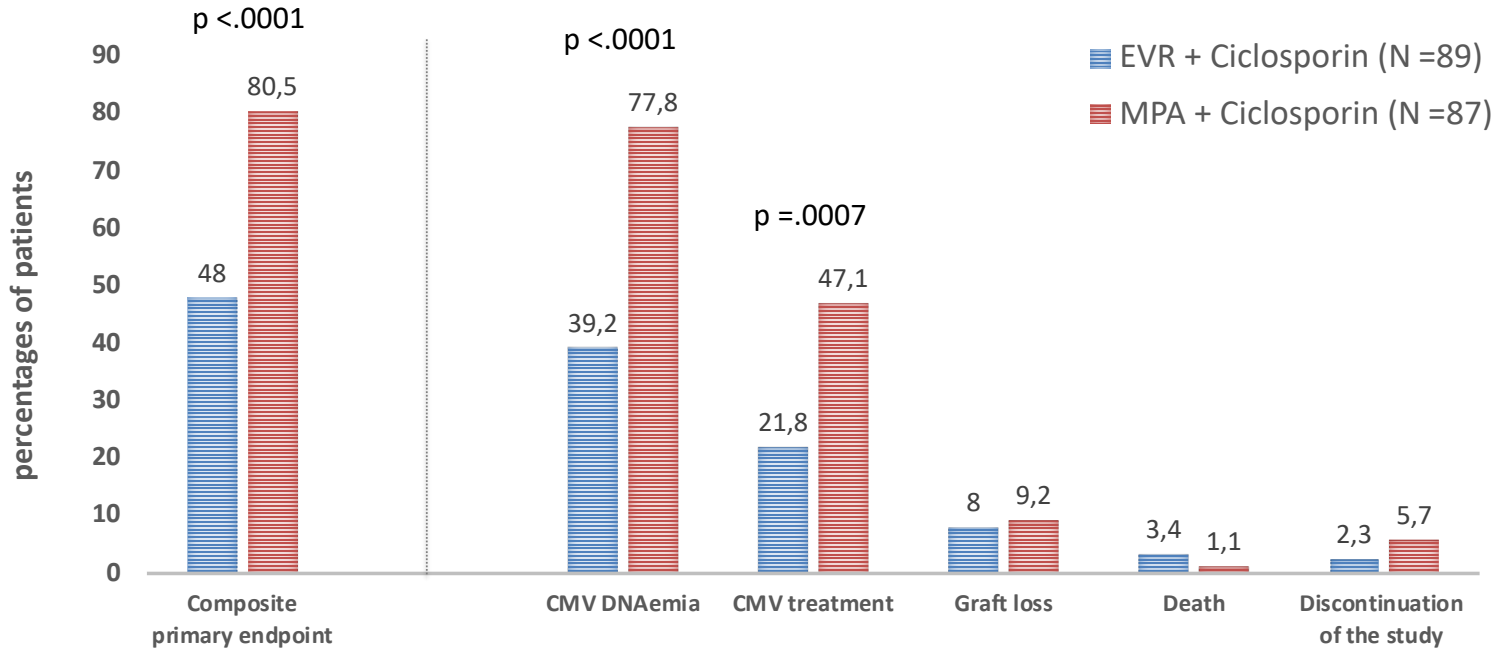
First draft : 2012…

STUDY DESIGN



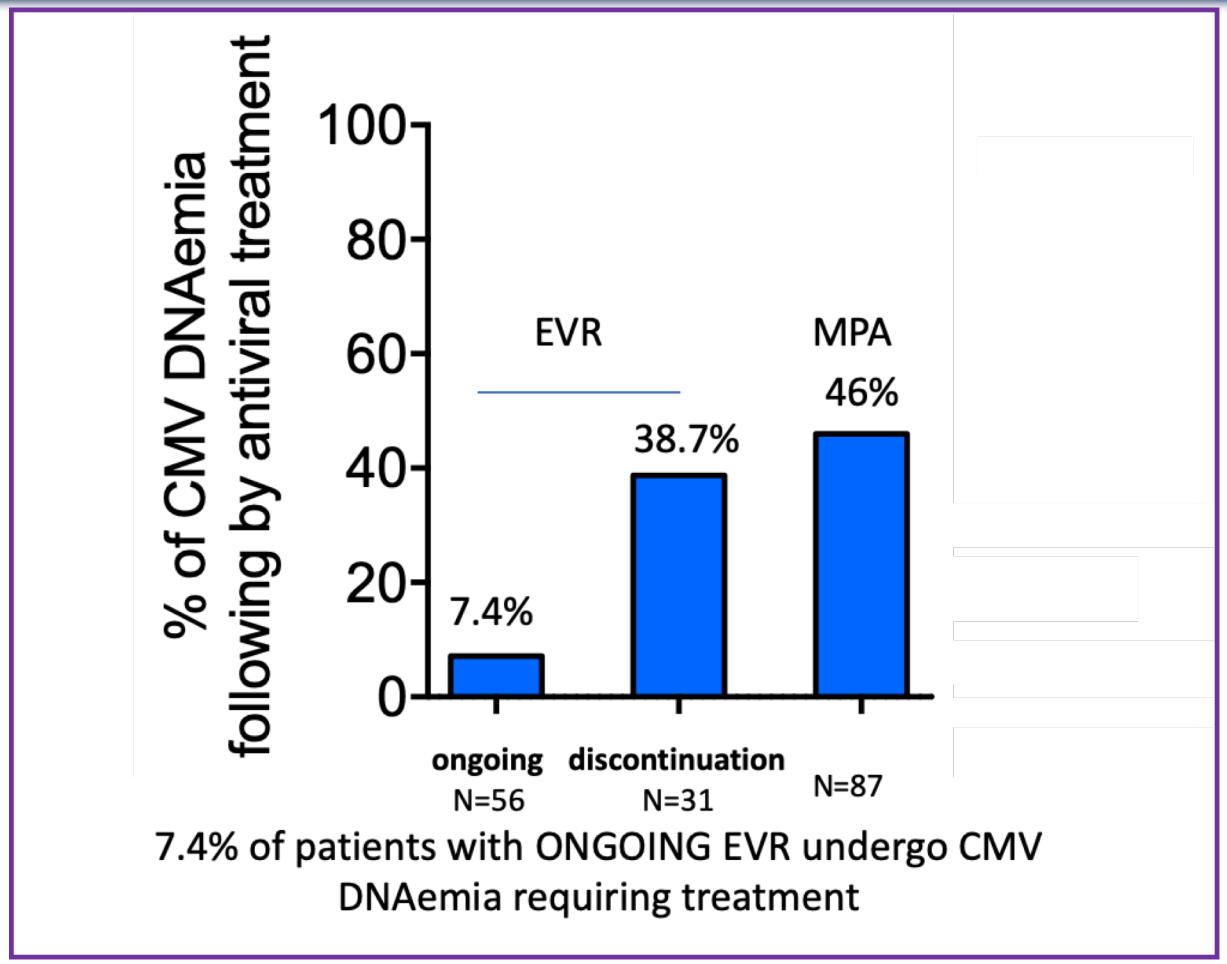
Inclusion: May 2014 - October 2017

PRIMARY ENDPOINT AT 6 MONTHS POST-TRANSPLANTATION



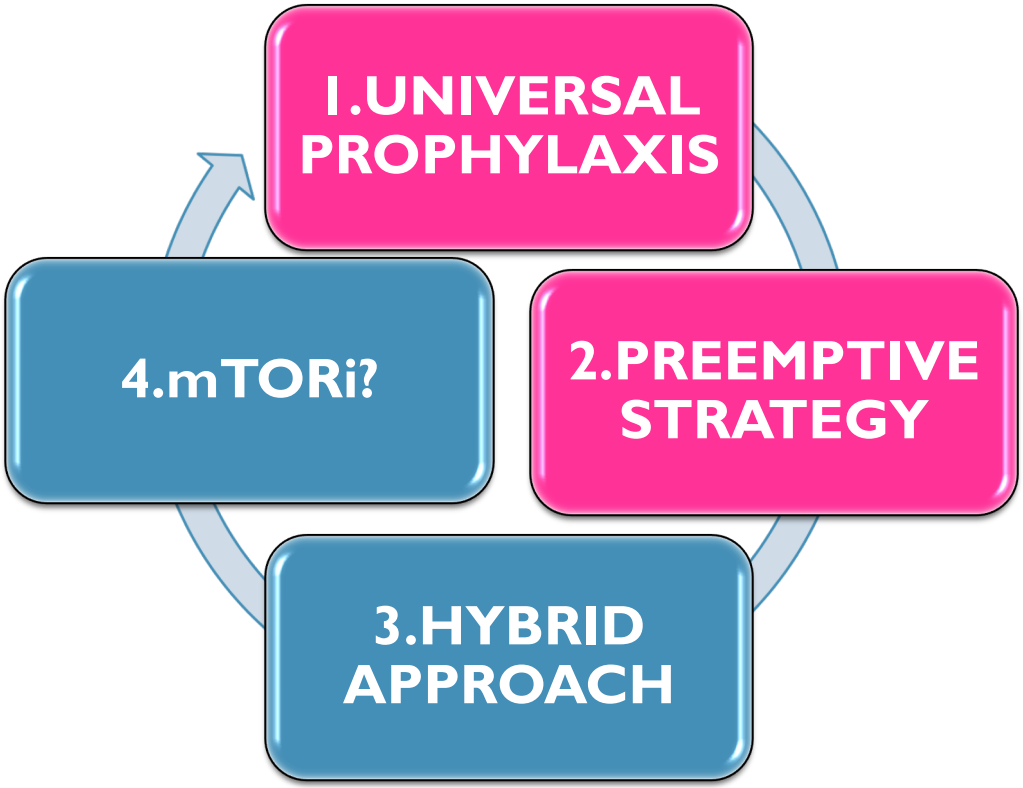
Kaminski et al, in prep.

ONGOING TREATMENT ANALYSIS



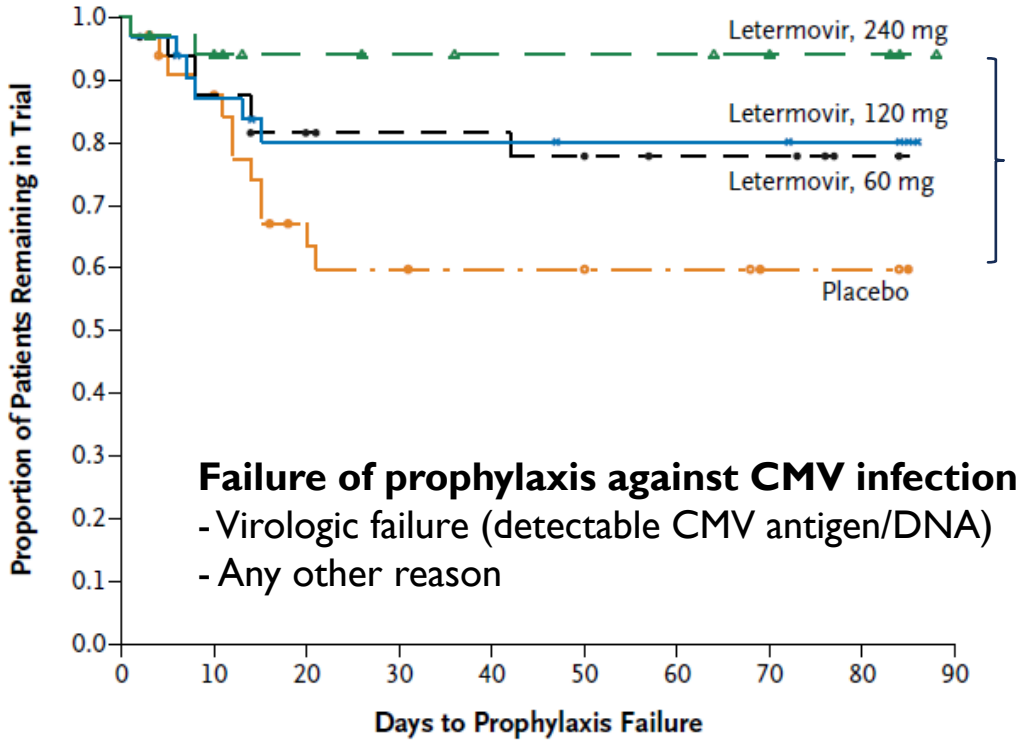
Kaminski et al, in prep.

CMV PREVENTION: ALTERNATIVE DRUGS



LETERMOVIR FOR CMV PROPHYLAXIS IN HEMATOPOIETIC-CELL TRANSPLANTATION (PHASE II)

n=133

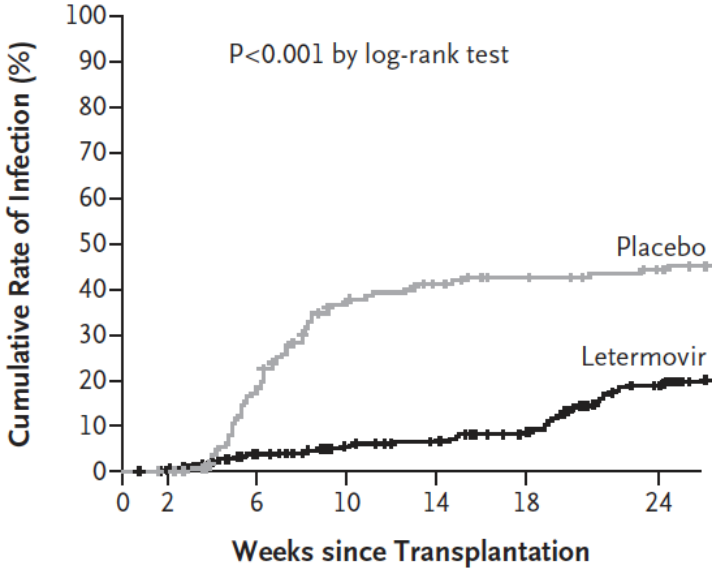


p = 0.002

Chemaly, N Engl J Med 2014;370:1781-9

LETERMOVIR FOR CMV PROPHYLAXIS IN HEMATOPOIETIC-CELL TRANSPLANTATION (PHASE III)

Clinically significant infection



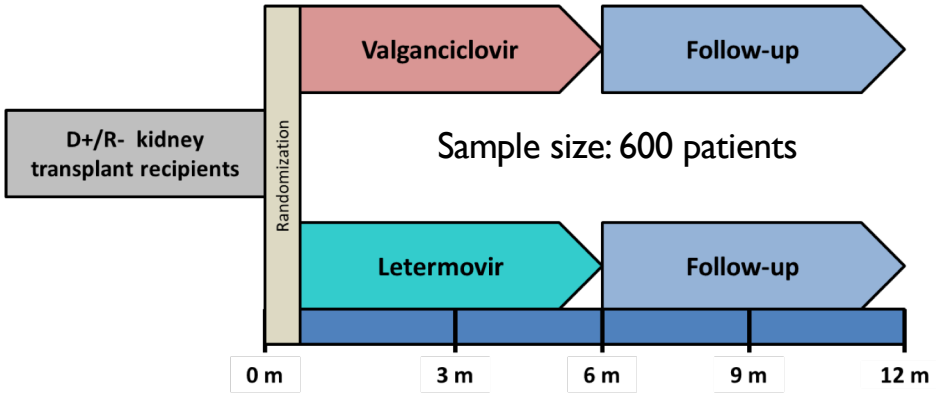
No. at Risk

Placebo	170	169	135	96	85	77	70
Letermovir	325	320	299	279	270	254	212

n=565 but 495
With undetectable CMV DNAemia at day 9

Marty, New England Journal of Medicine 2017 ,377(25), 2433–2444

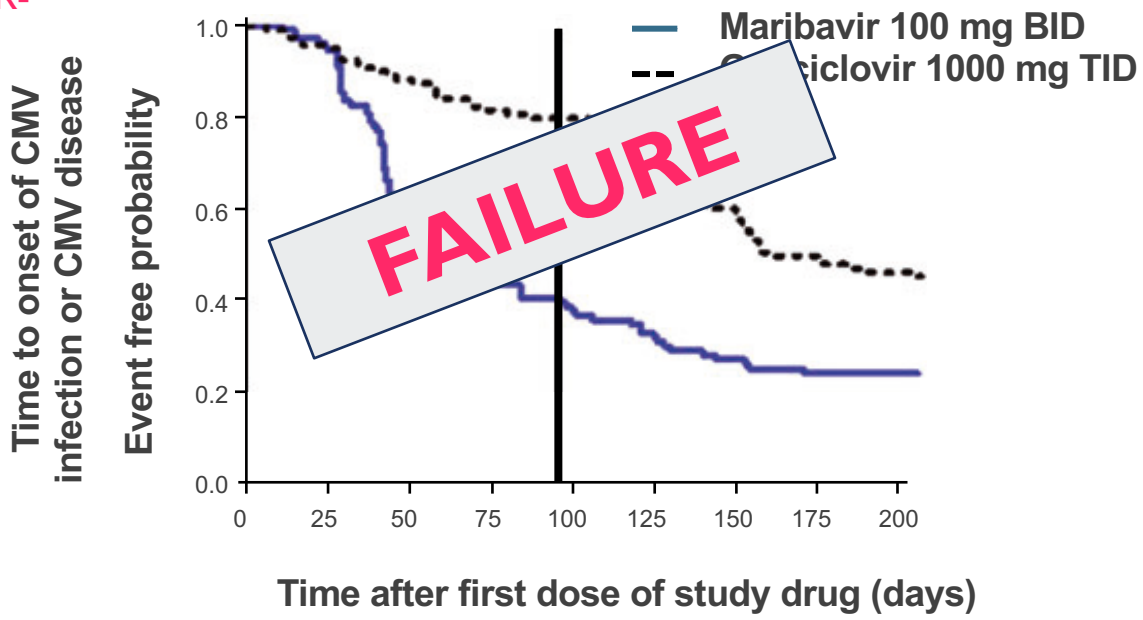
PHASE III in Kidney transplant recipients (MK-8228-002)



Recruiting D+R-
ClinicalTrials.gov NCT03443869

MARIBAVIR: PROPHYLAXIS IN LIVER TRANSPLANTATION

- Oral maribavir (n= 147, 100 mg twice daily) – 14 days
- Vs Oral ganciclovir (n=156, 1 g three times daily) - 14 days
- D+R-



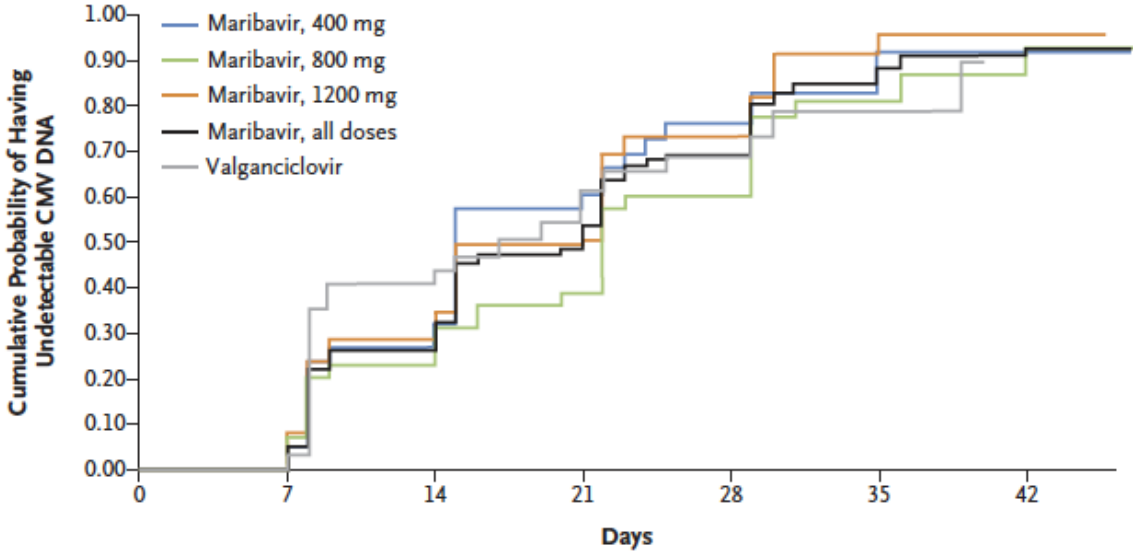
Winston, Am J Transplant. 2012 Nov;12(11):3021-3030

MARIBAVIR FOR PREEMPTIVE TREATMENT OF CYTOMEGALOVIRUS REACTIVATION (PHASE 2 STUDY)

Characteristic	Maribavir				Valganciclovir (N=40)
	400 mg (N=40)	800 mg (N=40)	1200 mg (N=39)	Overall (N=119)	
Age — yr					
Median (IQR)	56.5 (41–65)	58.5 (50–63)	58.0 (51–64)	58.0 (49–64)	58.5 (46–63)
Range	29–76	18–74	25–74	18–76	28–76
Male sex — no. (%)	22 (55)	27 (68)	22 (56)	71 (60)	27 (68)
Race — no. (%)†					
White	37 (92)	37 (92)	39 (100)	113 (95)	32 (80)
Asian	2 (5)	1 (2)	0	3 (3)	4 (10)
Black	1 (2)	2 (5)	0	3 (3)	3 (8)
Other	0	0	0	0	1 (2)
CMV serostatus — no./total no. (%)					
Hematopoietic-cell transplant					
Donor positive, recipient positive	6/20 (30)	9/21 (43)	13/20 (65)	28/61 (46)	8/21 (38)
Donor negative, recipient positive	13/20 (65)	12/21 (57)	7/20 (35)	32/61 (52)	13/21 (62)
Donor positive, recipient negative	1/20 (5)	0	0	1/61 (2)	0
Solid-organ transplant					
Donor positive, recipient positive	7/20 (35)	8/19 (42)	11/19 (58)	26/58 (45)	10/19 (53)
Donor negative, recipient positive	4/20 (20)	1/19 (5)	1/19 (5)	6/58 (10)	3/19 (16)
Donor positive, recipient negative	9/20 (45)	10/19 (53)	4/19 (21)	23/58 (40)	6/19 (32)
Donor negative, recipient negative	0	0	3/19 (16)	3/58 (5)	0
Most recent transplant — no. (%)					
Hematopoietic-cell transplant	20 (50)	21 (52)	20 (51)	61 (51)	21 (52)
Solid-organ transplant‡	20 (50)	19 (48)	19 (49)	58 (49)	19 (48)
Liver	6 (30)	6 (32)	6 (32)	18 (31)	7 (37)
Kidney	14 (70)	7 (37)	9 (47)	30 (52)	10 (53)
Other	0	6 (32)	5 (26)	11 (19)	3 (16)
Time from transplantation to first dose of trial treatment — days					
Mean	172.7±213.33	118.0±155.18	578.0±1956.13	287.1±1139.01	320.7±943.97
Median (range)	82.5 (25–854)	64.5 (13–836)	61.0 (21–9395)	65.0 (13–9395)	75.0 (20–5991)
Primary CMV infection — no. (%)§	29 (72)	34 (85)	34 (87)	97 (82)	27 (68)
Viral load at baseline — $\log_{10}$ copies/ml	3.56±0.853	3.69±0.966	3.64±0.919	3.63±0.908	3.57±0.840

Maertens, *N Engl J Med*, vol. 381, no. 12, pp. 1136–1147, Sep. 2019.

MARIBAVIR FOR PREEMPTIVE TREATMENT OF CYTOMEGALOVIRUS REACTIVATION (PHASE 2 STUDY)



No. at Risk							
Maribavir, 400 mg	39	38	26	15	7	4	2
Maribavir, 800 mg	40	39	30	23	14	6	3
Maribavir, 1200 mg	38	35	24	13	6	2	1
Maribavir, all doses	117	112	80	51	27	12	6
Valganciclovir	39	37	20	13	8	2	0

Maertens, *N Engl J Med*, vol. 381, no. 12, pp. 1136–1147, Sep. 2019.

UPDATE OF CMV GUIDELINES 2018

Organ	Serostatus	Risk Level	RECOMMENDED
All	D-/R-	Low	Monitoring for clinical symptoms; consider antiviral prophylaxis against other herpes infections
Kidney	D+/R-	High	6 months of GCV/VGCV OR Preemptive therapy
	R+	Intermediate	3 months of VGCV OR Preemptive therapy
Liver	D+R-	High	3 -6 months of VGCV OR Preemptive therapy
	R+	Intermediate	3 months of VGCV (VGCV not FDA approved in liver) OR Preemptive therapy
Pancreas	D+R-	High	3 -6 months of VGCV
	R+	Intermediate	3 months of VGCV OR Preemptive therapy
Islet	D+R-	Intermediate	3 months of VGCV
	R+	Intermediate	3 months of VGCV OR Preemptive therapy

Kotton, Transplantation. **2018** Jun;102(6):900-931

UPDATE OF CMV GUIDELINES 2018

Organ	Serostatus	Risk Level	RECOMMENDED
Heart	D+/R-	High	3-6 months of GCV/VGCV
	R+	Intermediate	3 months of GCV/VGCV OR Preemptive therapy
Lung	D+/R-	High	6-12 months of GCV/VGCV
	R+	Intermediate	Minimum 6 months of GCV/VGCV
Intestinal, composite tissue	D+/R-	High	Minimum 6 months GCV/VGCV +- surveillance after prophylaxis

CMV Ig is not generally recommended for use, although there may be specific circumstances, especially in thoracic organs, when used in combination with antivirals, in which some benefit has been demonstrated

Kotton, Transplantation. **2018** Jun;102(6):900-931

BIBLIOGRAPHY

The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation

Kotton et al, Transplantation. 2018 Jun;102(6):900-931

THANK YOU FOR YOUR ATTENTION!

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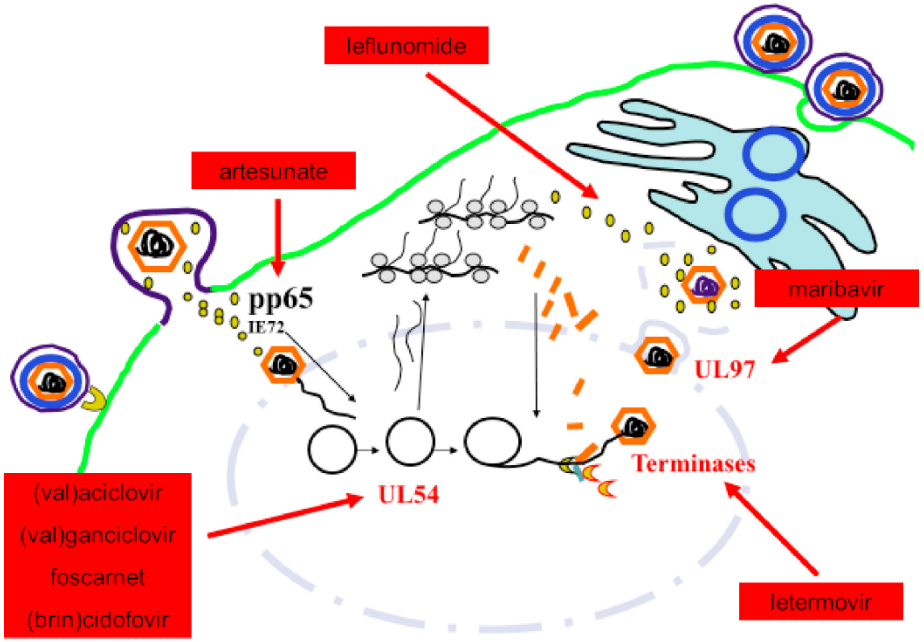
ImmunoConcEpT
Immunology from Concept and Experiments to Translation

MARIBAVIR: INHIBIT UL97



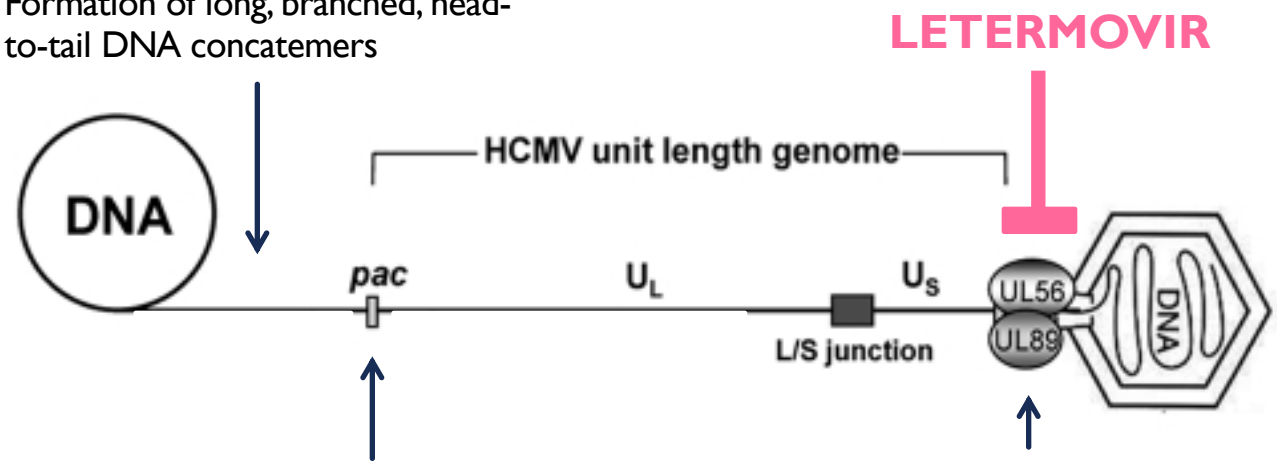
Activities of the UL97 kinase :

- stimulate the cell cycle to support viral DNA synthesis
- enhance the expression of viral genes
- promote virion morphogenesis
- facilitate the egress of mature capsids from the nucleus

Frange, Med Mal Infect. 2018 Dec;48(8):495-502
Prichard MN., *Rev Med Virol*. 2009;19(4):215–229. doi:10.1002/rmv.615

LETERMOVIR (AIC246): IMPACT ON HERPESVIRUS DNA REPLICATION

Formation of long, branched, head-to-tail DNA concatemers



pac indicates the terminase cleavage site at the genome terminus

The **HCMV terminase complex** is responsible for the **cleavage** of concatemeric progeny DNA to unit-length genomes and the **packaging** of those genomes into preformed procapsids.
Essential for virus replication

Goldner, J. Virol. 2011 Oct;85(20):10884-93