WHEN CMV IS PLAYING UNFAIR, HOW TO BREAKTHROUGH CMV RESISTANCE ?

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CMV Symposium
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Conflicts of interest

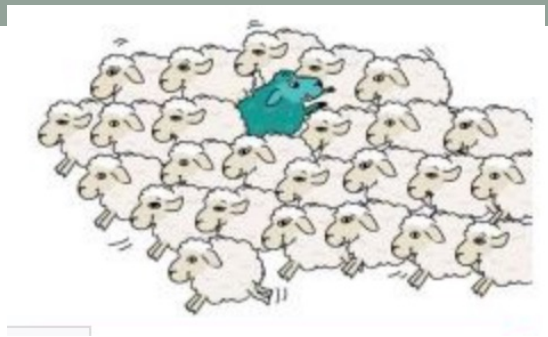
- No personal link
- Research funding as a scientific expert or site principal investigator:
- Altona, BioMérieux, Qiagen
- GlaxoSmithKline, Merck, Merck Sharp & Dohme, Biotest, Shire, a Takeda company (Primary investigator for SHP 303 study in France)
- Scientific expert and member of the advisory board for the QCMD
- ANSM expert for delivery of anti-CMV for compassionnate use in refractory/resistant patients

Why being concerned by drug-resistance ?

- **Resistance occur in highly immunocompromised patients**
- **Resistance alters the prognosis:**
- Prolonged treatments in deeply immunocompromised hosts with increased toxicity
- Risk of intolerance, interruption, and multidrug resistance
  - Increases frequency and duration of viremia whether disease or not.
  - Thus favouring CMV disease
  - And triggering graft rejection and graft loss
  - Increases CMV-associated morbidity
- **Alternatives to ganciclovir (foscarnet or cidofovir) are nephrotoxic and only parenteral**

(Eid, Clin transpl.2008, Fisher, CID 2017, Hantz, JAC 2010, Myrhe Transplantation 2011, Minces, AAC 2014, Avery RK Transplantation 2014,Kotton et al, Transplantation 2017)

The burden of CMV resistance to current antivirals



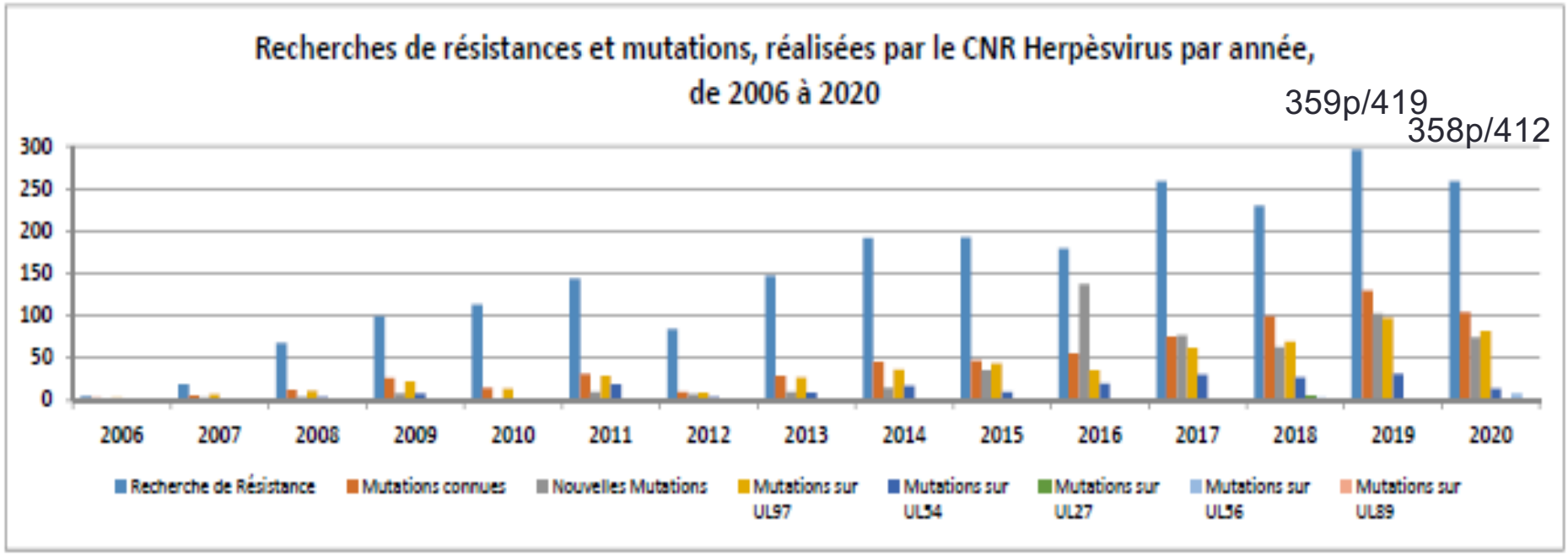
- Prevalence in treated patients :
- Solid organ recipients : (update from the consensus 2018)
  - 5% to 12% overall
  - Up to 18% in lung transplant recipients
  - 31% in intestinal and multivisceral organ transplant recipients
  - 0% to 3% range, for 100 to 200 days of ganciclovir or valganciclovir prophylaxis in D+/R- kidney recipient
  - 4% after valaciclovir prophylaxis
- Stem cell recipients :
  - 1- 3% (Orphavic French cohort and Campos 2017- 7/22 NR- in Portugal).

(Lurain, 2001 ; Alain 2004, Limaye, 2000 ; Boivin, 2004, 2009 ; Humar, 2005 ; Gruber, 2005, Hantz, 2009, Hantz 2010, Boivin 2010, Boivin 2012, Schubert BMJ 2013, kotton 2013, Campos 2016, Fisher 2017, Kotton 2017 and French CNR Data

New recommendations for valganciclovir prophylaxis prophylaxis did not prevent non response to therapy, nor resistance

		French cohort 2006-2010			French cohort 2012-2016 Orphavic (NCT02067169)			
	Chicago (Lurain, 2002)	680 pts virémiques	Resistance	Non-réponse Sans Resistance	371 pts virémiques	Resistance	Non-réponse Sans Resistance	**Victor Study (Boivin, 2009)**
Rein	2.2%	448	8.04 %	6.7%	162	7.4%	16.4%	3.7%
Foie	5.6%	42	7.14%	4.8%	7	14.3%	14.3%	4.3%
Coeur	5.3%	44	2.27%	13.6%	12	0	0	5%
Poumon	15.2%	18	27.8%	27.8%	3	0	0	17.6%
Total SOT	**9.5%**	**552**	**8.1%**	**7.8%**	**184**	**7.1%**	**14.1%**	**4.7%**
CSH	**/**	**128**	**3.1%**	**10.9%**	**187**	**1.1%**	**20.9%**	**/**
Global	/	**680**	**7%**	**15.6%**	**371**	**4%**	**17.5%**	**/**

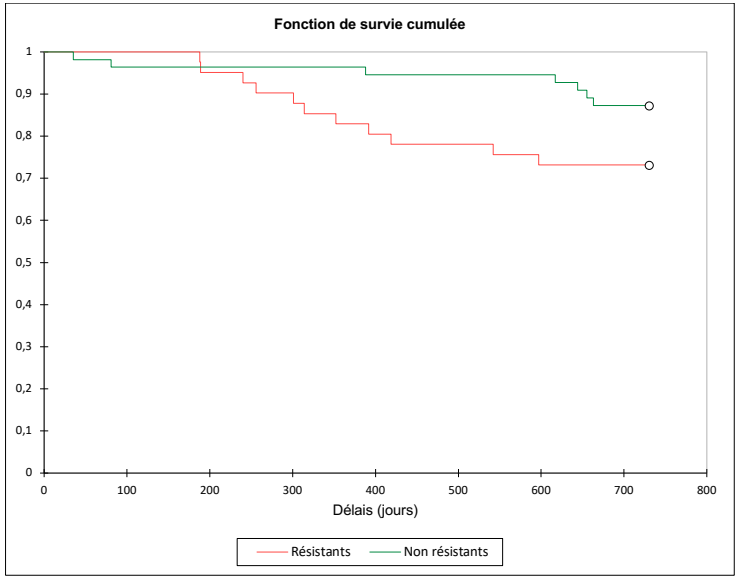
No real impact of Covid19 on the burden of resistance



Outcome of CMV resistance in French kidney recipients 2006-2010

41 resistant compared to
126 refractory without resistance

Figure présentant la survie sans événements (décès ou perte du greffon) chez les patients résistants au CMV N=41 (vert) et chez les patients non résistants N=55 (rouge)



Statistique	Valeur observée	Valeur critique	p-value	alpha
Log-rank	3,351	3,841	0,067	0,050
Wilcoxon	3,545	3,841	0,060	0,050
Tarone-Ware	3,454	3,841	0,063	0,050

(Unpublished data from CNR , Amal et al., pHD 2021)

HOW TO BREAKTHROUGH RESISTANCE?

1st: identify patients at risk and when to look for resistance

2nd: analyse and guide treatment by genotyping

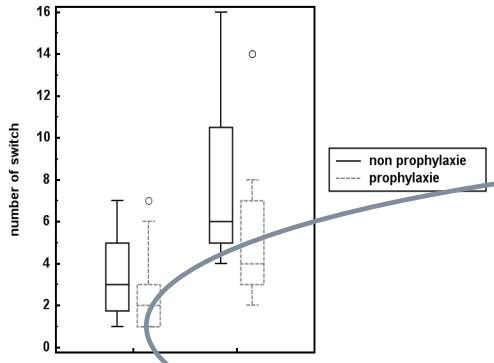
3rd: examine new therapeutic options in personalised medicine

1st identify patients at-risk for resistance

High risk for CMV infection/disease

Prolonged/inadequate exposure to treatment

Same risk factors for CDV-FOS resistance



Refractory non resistant

Resistant

(Data from the first French Observatoire, 350pts)

Risk factors in SOT:

Risk factors
Prolonged antiviral drug exposure (5 months for GCV)
Primary infection (D+/R-)
Strong immunosuppression including belatacept
Inadequate antivirak drug delivery
Same risk factors in paediatircs but lower incidence or resistance…
Ùultipe dose modifications, due to either problems of renal adaptation of dosages or haematological or renal intolerance
No clear difference between prophylaxis and preemptive tt.

(Kotton et al. Transplantation 2017
Bernard et al, 2019)

Immune evaluation (QF, Elispot…)

GCV dosage

Risk factors in SCT

Clinical Infectious Diseases
SPECIAL SECTION/INVITED ARTICLE
IDSA Infectious Diseases Society of America
hivma HIV medicine association

Definitions of Resistant and Refractory Cytomegalovirus Infection and Disease in Transplant Recipients for Use in Clinical Trials

Roy F. Chemaly,[1] Sunwen Chou,[2] Hermann Einsele,[3] Paul Griffiths,[4] Robin Avery,[5] Raymund R. Razonable,[6] Kathleen M. Mullane,[7] Camille Kotton,[8] Jens Lundgren,[9] Takashi E. Komatsu,[10] Peter Lischka,[11] Filip Josephson,[12] Cameron M. Douglas,[13] Obi Umeh,[14] Veronica Miller,[15] and Per Ljungman[16,17]; for the Resistant Definitions Working Group of the Cytomegalovirus Drug Development Forum

Risk Factor
Host factors
Prolonged antiviral CMV drug exposure (>3 mo)
Previous antiviral CMV drug exposure
Recurrent CMV infection
Inadequate antiviral CMV drug absorption and bioavailability
Inadequate antiviral CMV oral prodrug conversion
Variation in antiviral CMV drug clearance
Subtherapeutic antiviral CMV drug level
Poor patient compliance with antiviral drug regimen
T-cell depletion
Haploidentical, allogeneic, or cord blood HCT
Delayed immune reconstitution
CMV-seropositive recipient and CMV-seronegative donor
Treatment with antithymocyte antibodies
Active GVHD
Young age
Congenital immunodeficiency syndromes
Viral factors
CMV viral load rise while receiving treatment (after >2 wk of adequate dosing)
Failure of CMV viral load to fall despite appropriate treatment
Rise in CMV viral load after initial decline while receiving appropriate treatment
Intermittent low-level CMV viremia
High CMV viral loads

Abbreviations: CMV, cytomegalovirus; GVHD, graft-vs-host disease; HCT, hematopoietic cell transplantation.

[a]Modified with permission from El Chaer et al 1.

[b]Most of the risk factors for CMV resistance pertain to solid organ transplant recipients as well, in addition to graft rejection (instead of GVHD) and CMV-seropositive donor and CMV-seronegative recipient.

Clinical Infectious Diseases

SPECIAL SECTION/INVITED ARTICLE

When to ask for resistance genotyping ? Refractory CMV

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Table 2. Summary of the Definitions of Refractory Cytomegalovirus Infection and Disease and Antiviral Drug Resistance for Use in Clinical Trials

Term	Definition
Refractory CMV infection	CMV viremia that increases[a] after at least 2 wk of appropriately dosed antiviral therapy
Probable refractory CMV infection	Persistent viral load[b] after at least 2 wk of appropriately dosed antiviral therapy
Refractory CMV end-organ disease	Worsening in signs and symptoms or progression into end-organ disease after at least 2 wk of appropriately dosed antiviral therapy
Probable refractory CMV end-organ disease	Lack of improvement in signs and symptoms after at least 2 wk of appropriately dosed antiviral drugs
Antiviral drug resistance	Viral genetic alteration that decreases susceptibility to one or more antiviral drugs[c]

Abbreviation: CMV, cytomegalovirus.

[a]More than 1 $\log_{10}$ increase in CMV DNA levels in blood or serum and determined by $\log_{10}$ change from the peak viral load within the first week to the peak viral load at ≥2 weeks as measured in the same laboratory with the same assay.

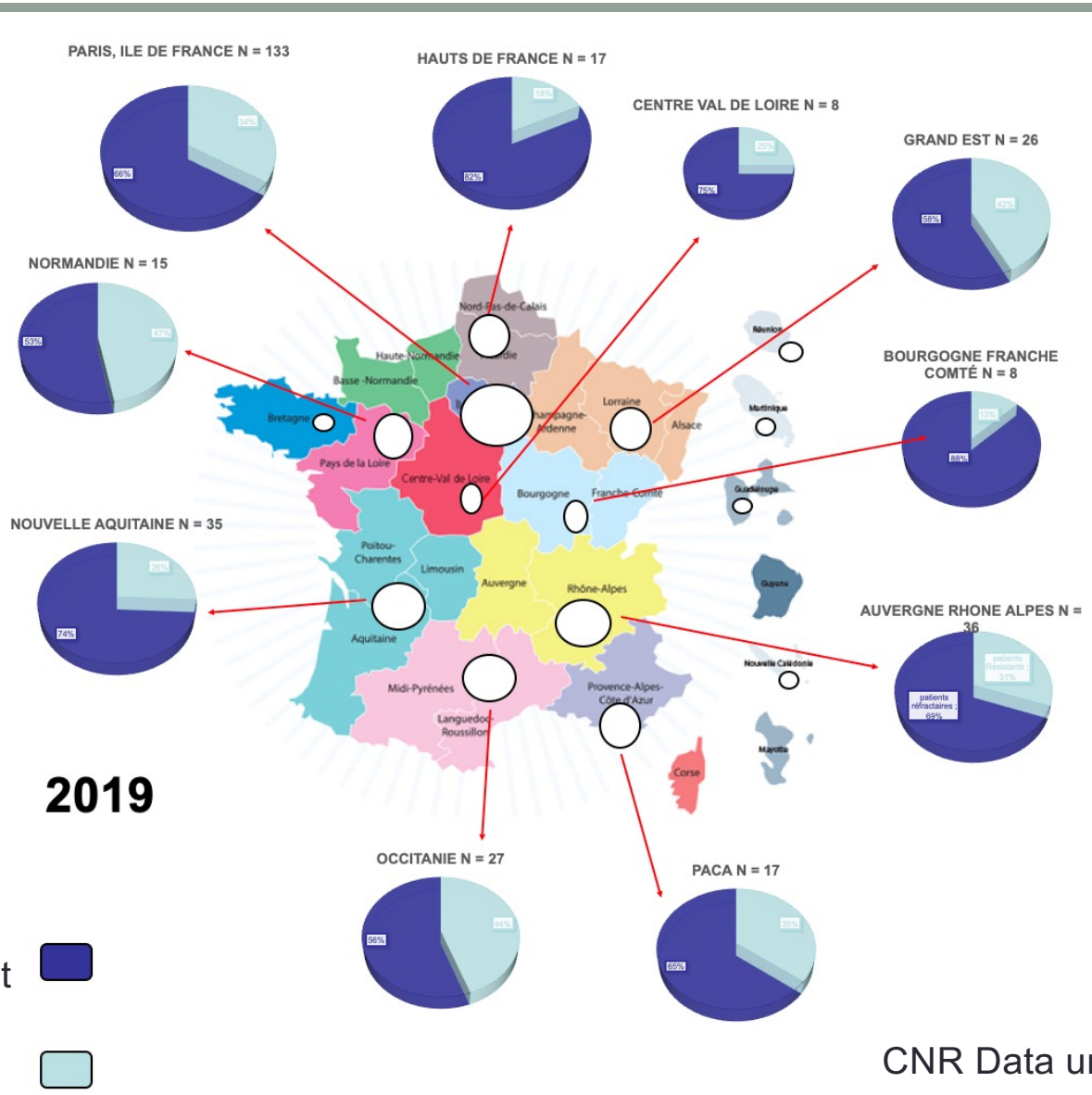
[b]CMV viral load at the same level or higher than the peak viral load within 1 week but <1 $\log_{10}$ increase in CMV DNA titers done in the same laboratory and with the same assay.

[c]Known examples involve genes involved in antiviral drug anabolism (eg, UL97-mediated phosphorylation of ganciclovir), the antiviral drug target (eg, UL54, UL97, UL56/89/51), or compensation for antiviral inhibition of biological function (eg, UL27).

Viral load usually decreases in a range of 0,5log /week
A rebound may occur at d 8-15
Except for high initial viral loads, undetectability is reached at d21
This has to be reconsidered for new antivirals with late stage action due to accumulation of viral DNA.

Proportion of antiviral resistance amongst refractory patients

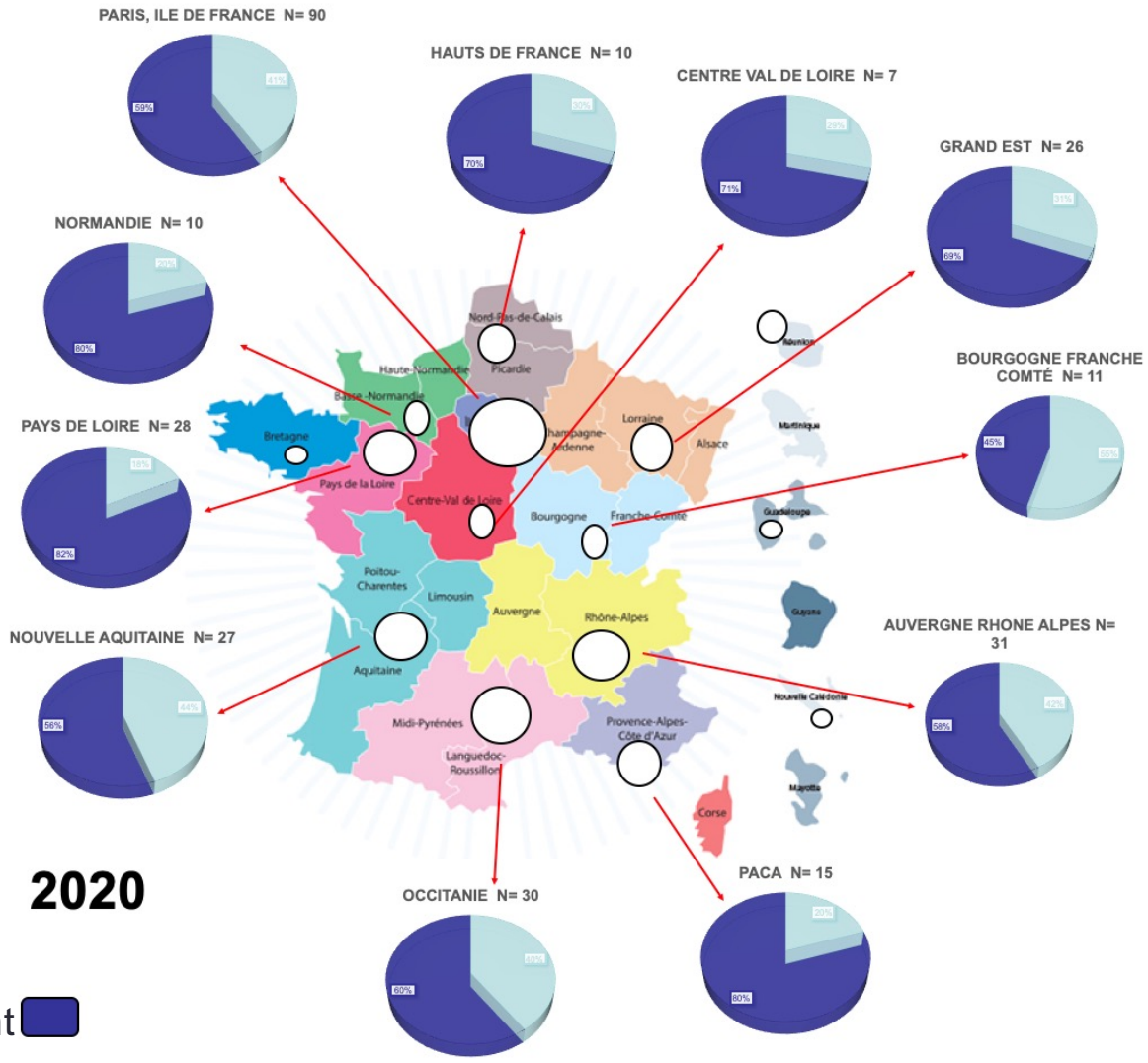
2019 : 32 %



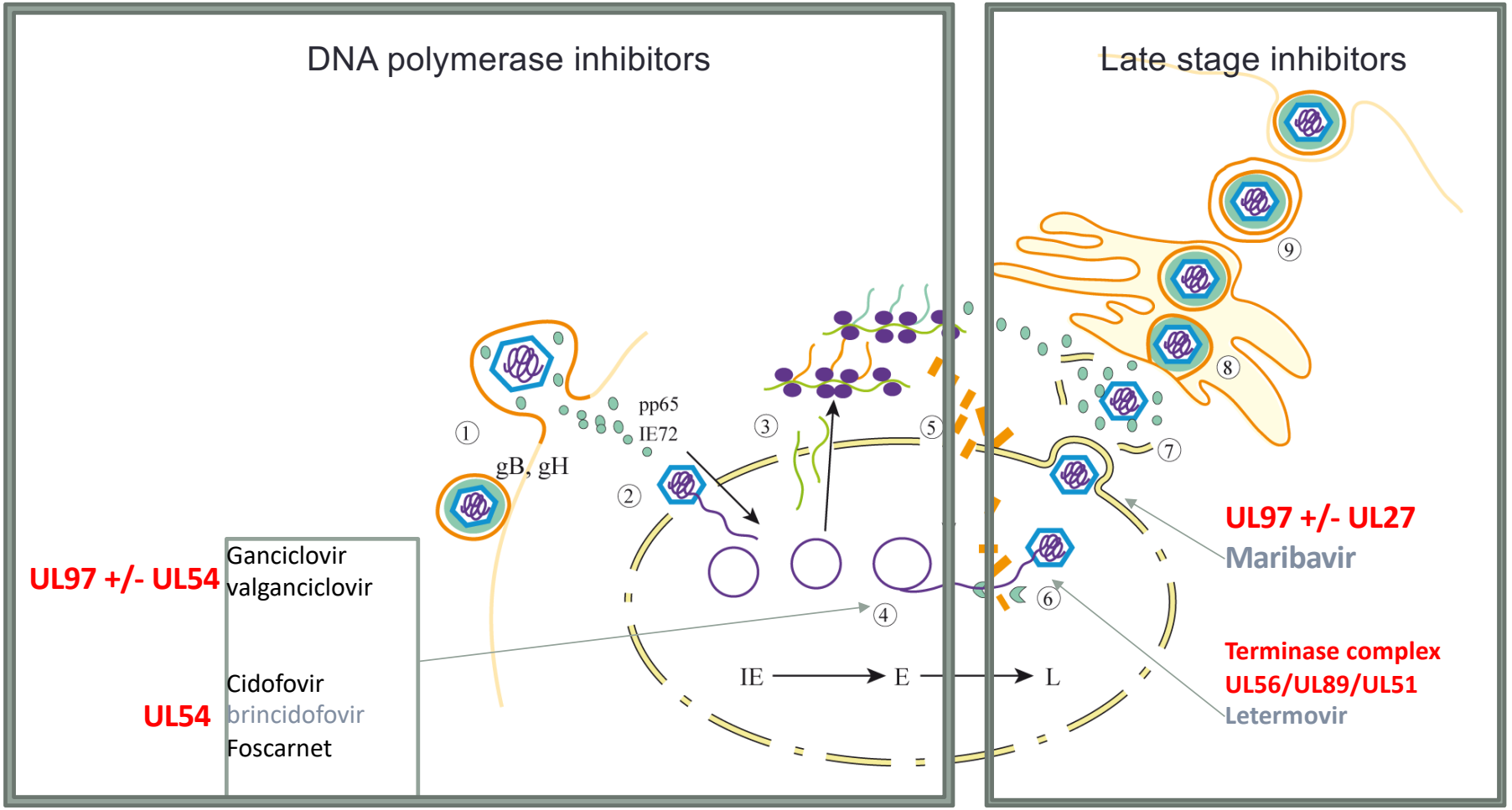
CNR Data unpublished

Proportion of virological resistance amongst refractory patients

2020: 34%



2nd identify the type of resistance: mechanisms of resistance



(Alain S, Garrigue I, Traité de virologie 2018)

How to identify resistance ?

- **Phenotype: needs viral isolation in culture** => reference laboratories
- **Genotype : Full-length Sanger sequencing of target genes** UL97+UL54 +/- UL56-89-51
  - need clinical information on treatment received and viral load (>1000U/mL)
  - Sensitivity : 17-20% , results within 3-5 days
  - now the reference, but not fully standardized, need databases

- **Reference/expert laboratories participating in quality controls** (ex: QCMD) and having clinical experience can give useful interpretation and counselling and identify new mutations of interest.
- Send **new mutations** to reference labs for recombinant **Bacmid phenotyping**

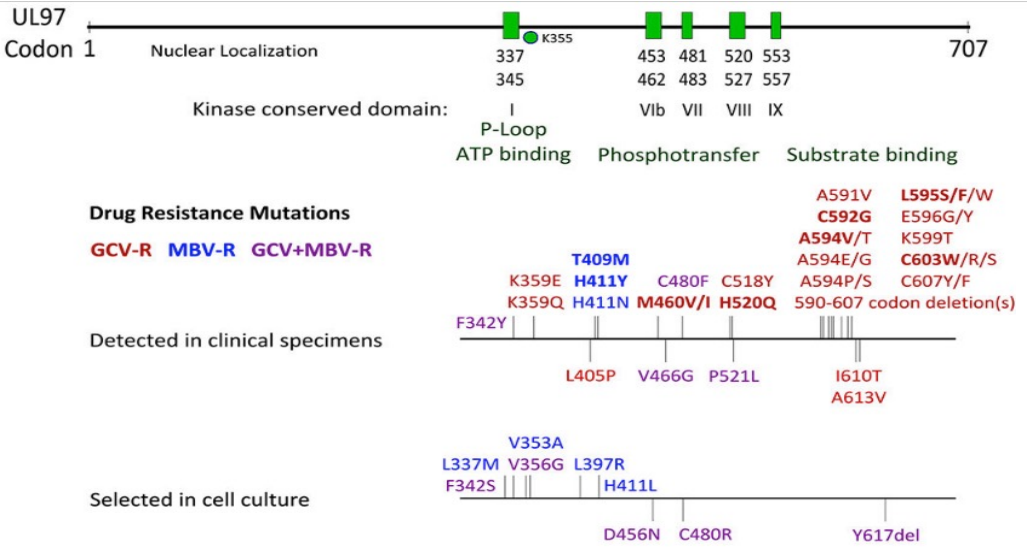
- **Input of NGS?**
  - Sensitivity is high (2-5%) but costful and significance of low-frequency mutants remains controversial .
  - Need controls, standardization and reproducibility.

  - Potential clinical impact when early detection of known mutants .(at best 8-15 days before Sanger)
  - Usefulness in retrospective analysis for kinetics of early emergence of mutants

(Chou S. Antiviral res. 2020 Alain et al. JAC 2020)

Evaluate the consequence of known mutations in UL97

- UL97 mutations conferring various levels of resistance to ganciclovir are the most frequent in the clinical setting, with a preserved viral fitness



Low resistance mutations may be overcome by GCV dose increase

Table 1.

Relative levels of drug resistance of CMV UL97 mutants

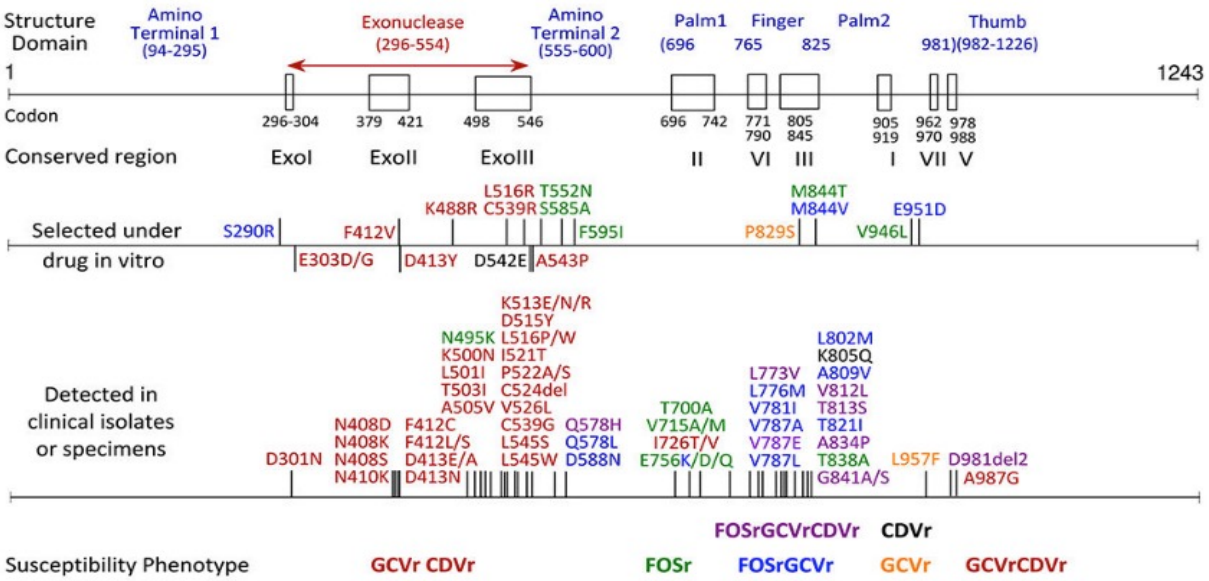
Fold-increase in EC50	<2.2	2.2 to 4.9	5 to 20	21-99	>100
Ganciclovir	T409M, H411Y, K599E/R, L600I, T601M, D605E	K359E/Q, L405P, C480F, A591V, **C592G**, A594E/S/T, E596G, E596del, L600del, L600del2, I610T, A613V	F342Y, M460V/I, V466G, C518Y, **H520Q**, P521L, A594V/G, **L595S/F/W**/del, E596Y, K599T, C603W/R, C607Y, A591del4, L595del, N597del3, T601del3		
Maribavir	M460V/I, H520Q, A594V, L595S, C603W	F342Y	V353A, **H411Y**, H411N	T409M, H411L	V466G, C480F, P521L
Filociclovir (cyclopropavir)	L595S	M460V, C592G, A594V, C603W	M460I, H520Q		

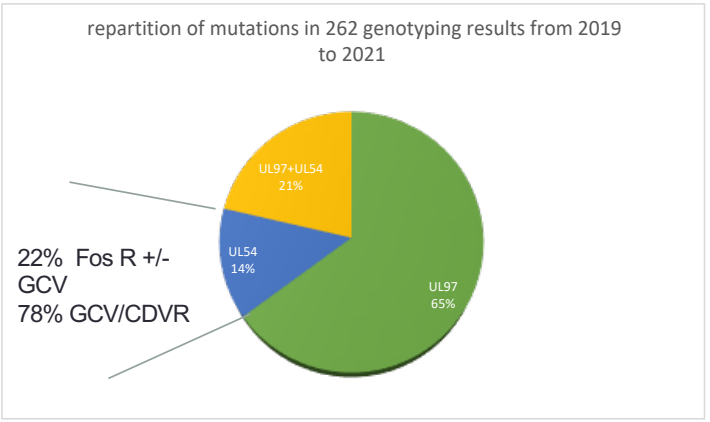
Drug susceptibility phenotypes of UL97 mutations observed in clinical specimens and transferred into baseline strains Amino acid substitutions most commonly observed after ganciclovir or maribavir therapy are shown in **bold**

del = in-frame codon deletion, with suffix indicating number of codons deleted if more than one

Chou et al. Antiviral Res. 2020

In the UL54 polymerase





CNR res survey 2019-2021

UL54 mutations are seldom detected as the initial genetic event in ganciclovir resistance,and usually but not always add to pre-existing UL97 mutations after prolonged therapy to multiply the level of drug resistance by several fold

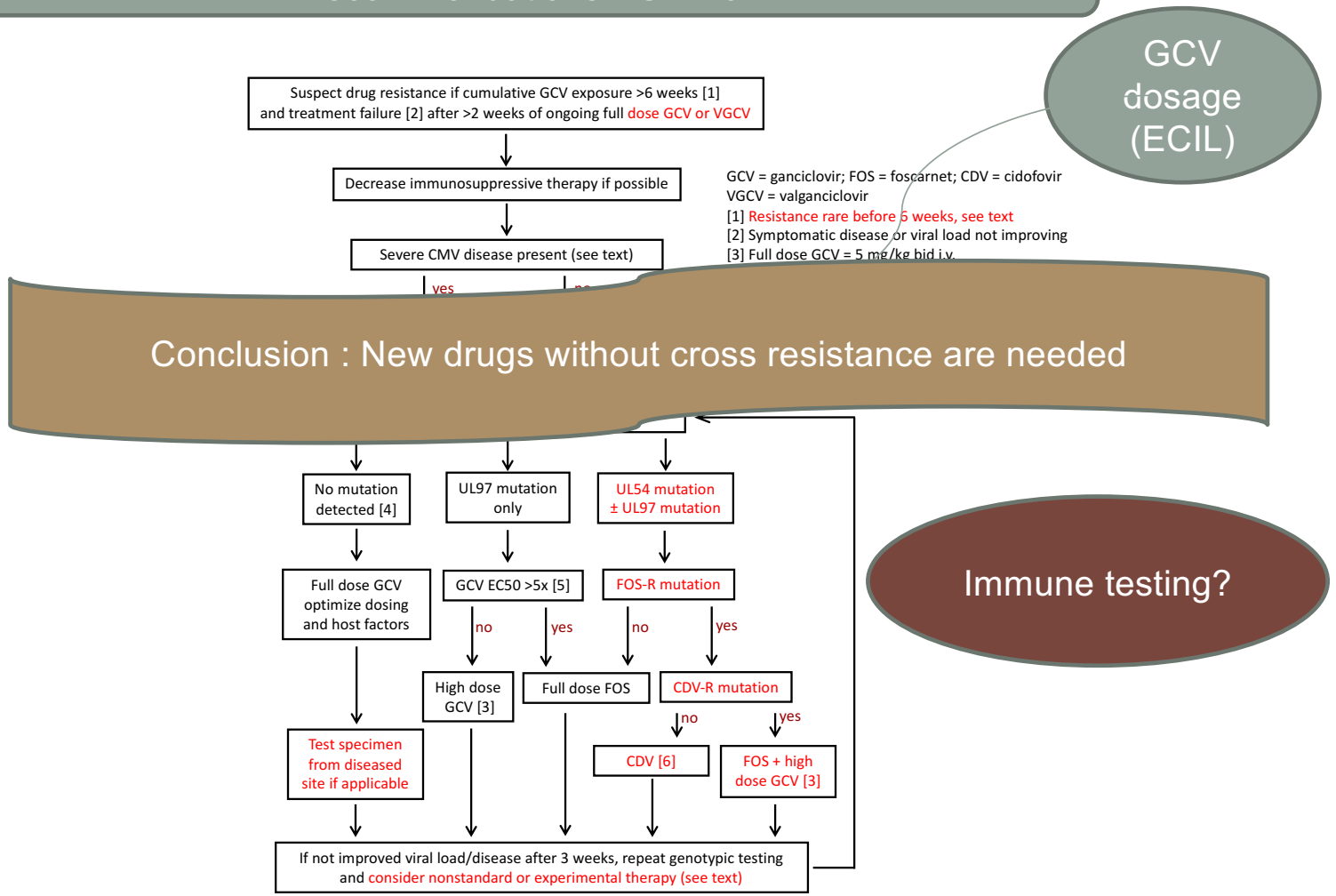
They can decrease viral fitness

They confer cross resistance to cidofovir, at various levels

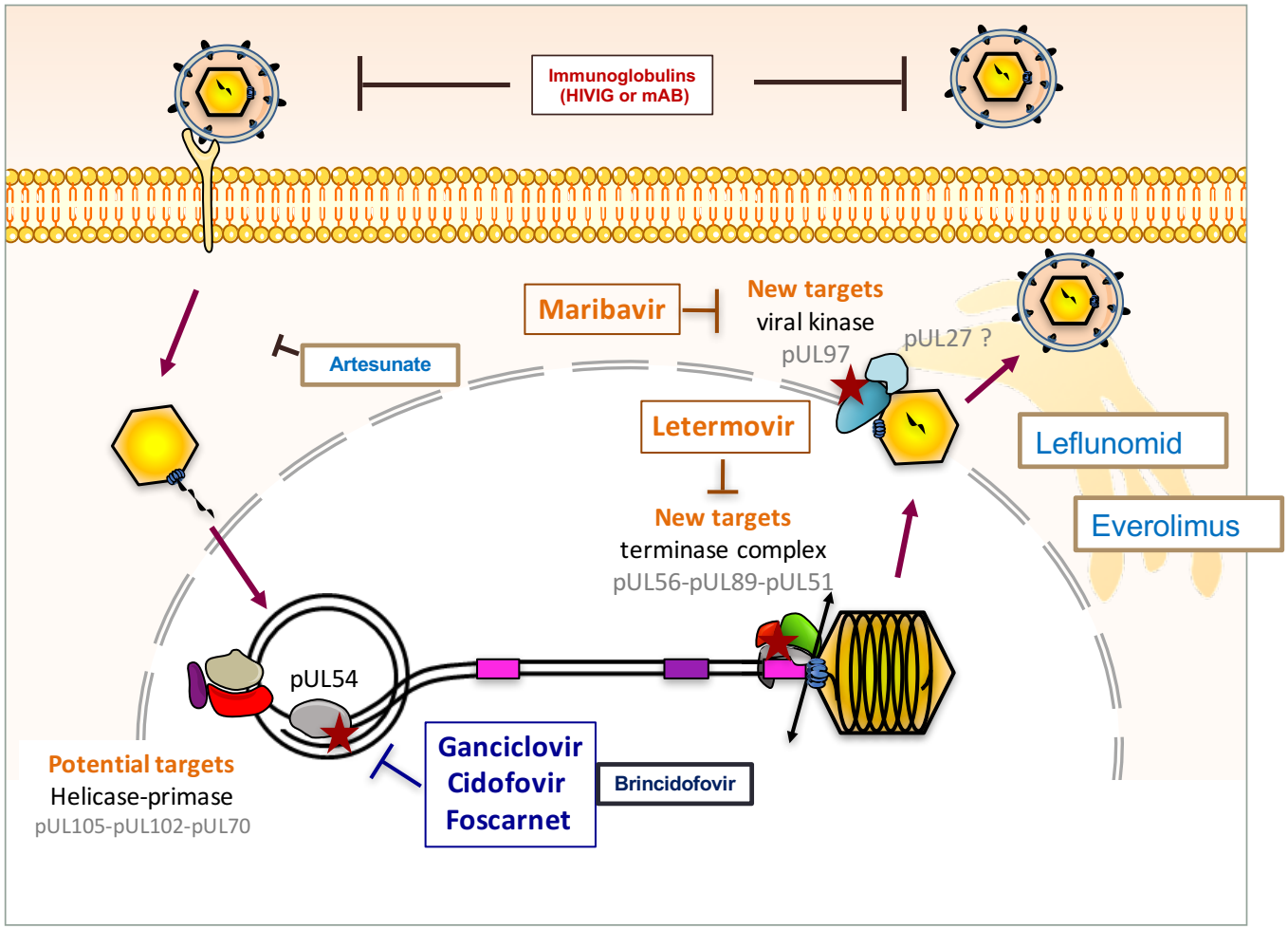
Resistance to foscarnet is less frequent

Chou et al. Antiviral Res. 2020

consensus SOT 2017
Recommendations ECIL 2017



Salvage therapies :



Ligat et aL, FEMS Microbiology reviews, 2018

Strengths and weaknesses of polymerase inhibitors

PRO

- Powerful molecules *in vitro* and *in vivo (*IC50 micromolar range),
- Rapid decrease of viral load (T1/2 24h), undetectability reached within1 à 3 weeks

- **CDV and FOS: high concentration in tissues and CSF, plus long half-life for CDV**

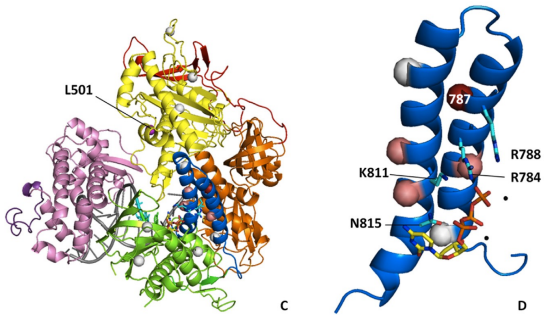
CON

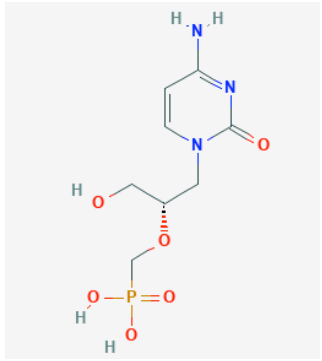
- GCV and VGCV haematologic toxicity (neutropenia) is the major problem in stem cell transplant setting, and in some other patients with nucleotides analogs intolerance

- Broad spectrum for CDV and FOS => toxicity
  - Specificity through preferential fixation on viral DNA polymerases
  - Renal elimination of active metabolites => renal toxicity
  - Long half-life of CDV

- CDV and FOS available exclusively under IV form

Cidofovir





pubchem.
ncbi.nlm.nih.gov

- Nucleotidic analog déoxycytosine monophosphate
- No viral phosphorylation needed by UL97

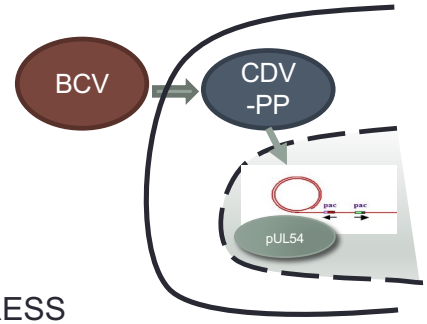
- Powerful competitive inhibitor of viral DNA polymerases
- 2 molecules => stop DNA synthesis
- IC50 0,1-0,4uM; IC90 1-2uM

- Broad spectrum CMV, HSV, Adénovirus, Poxvirus, BK-virus,
- **Renal toxicicty +++ up to 33 % in refractory SOT (Bonatti et al. Surg. Infect, 2017)**
- Only (IV), long half life (1 x 2 sem)

- **Higher genetic barrier than GCV but cross-resistance through viral polymerase mutations**

Brincidofovir

- New CDV prodrog : Hexadecyloxypropyl-CDV

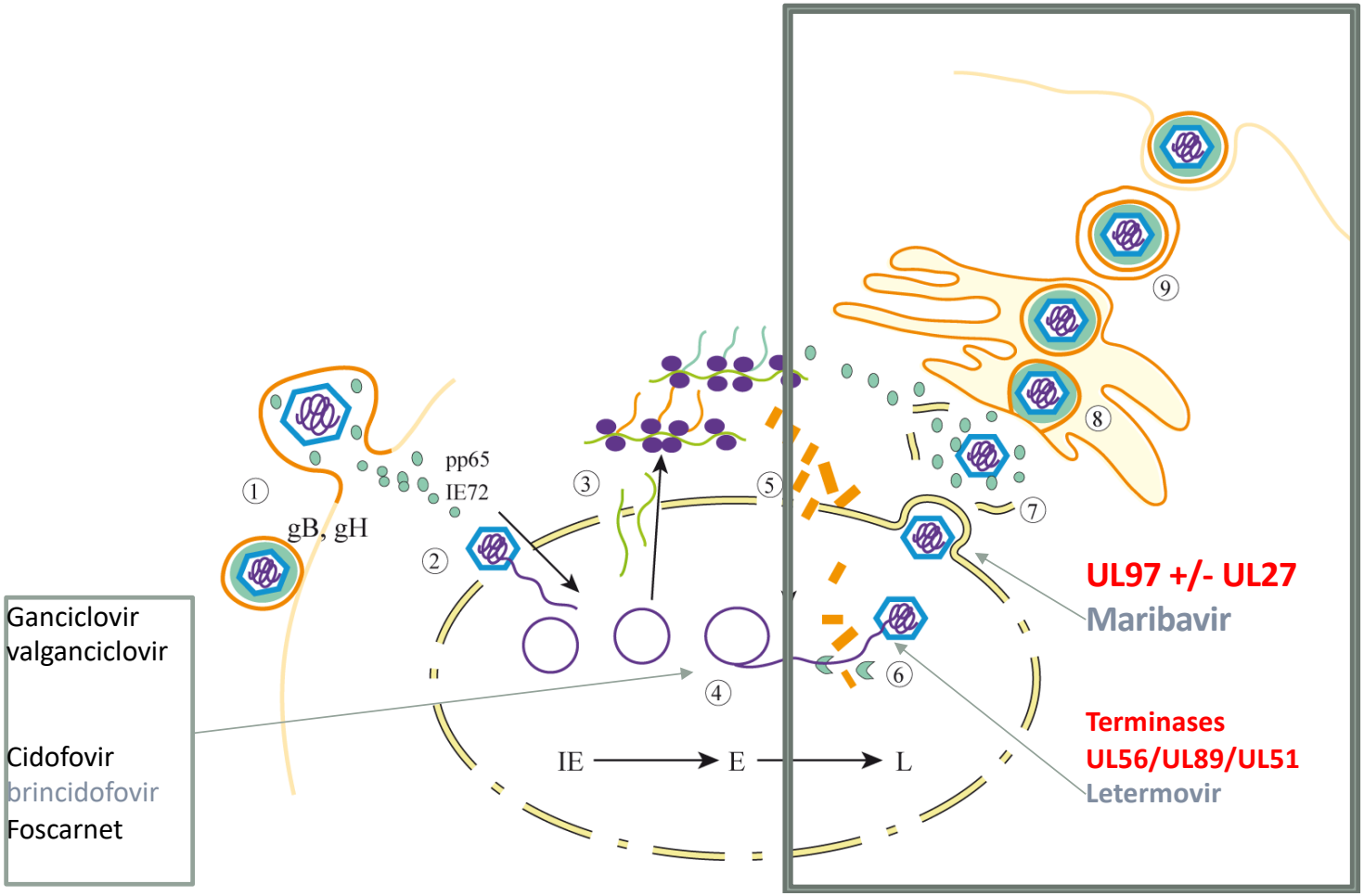


- Low renal toxicity by intracellular liberation of the active compound
- Digestive toxicity : diarrhea => Stop clinical phase III prophylaxis studies in CSH (SUPPRESS study) for increased GVHD symptoms ? Toxicity? And limited efficacy
- Still used for adenovirus infection
- 10x more efficient than CDV in vitro
  - (IC50 AD169 : BCV1nM, CDV 400nM,GCV 3800nM) *(Aldern et al., Mol. Pharmacol 2003)*
  - *Broad spectrum CMV, HSV, adenovirus, poxvirus*

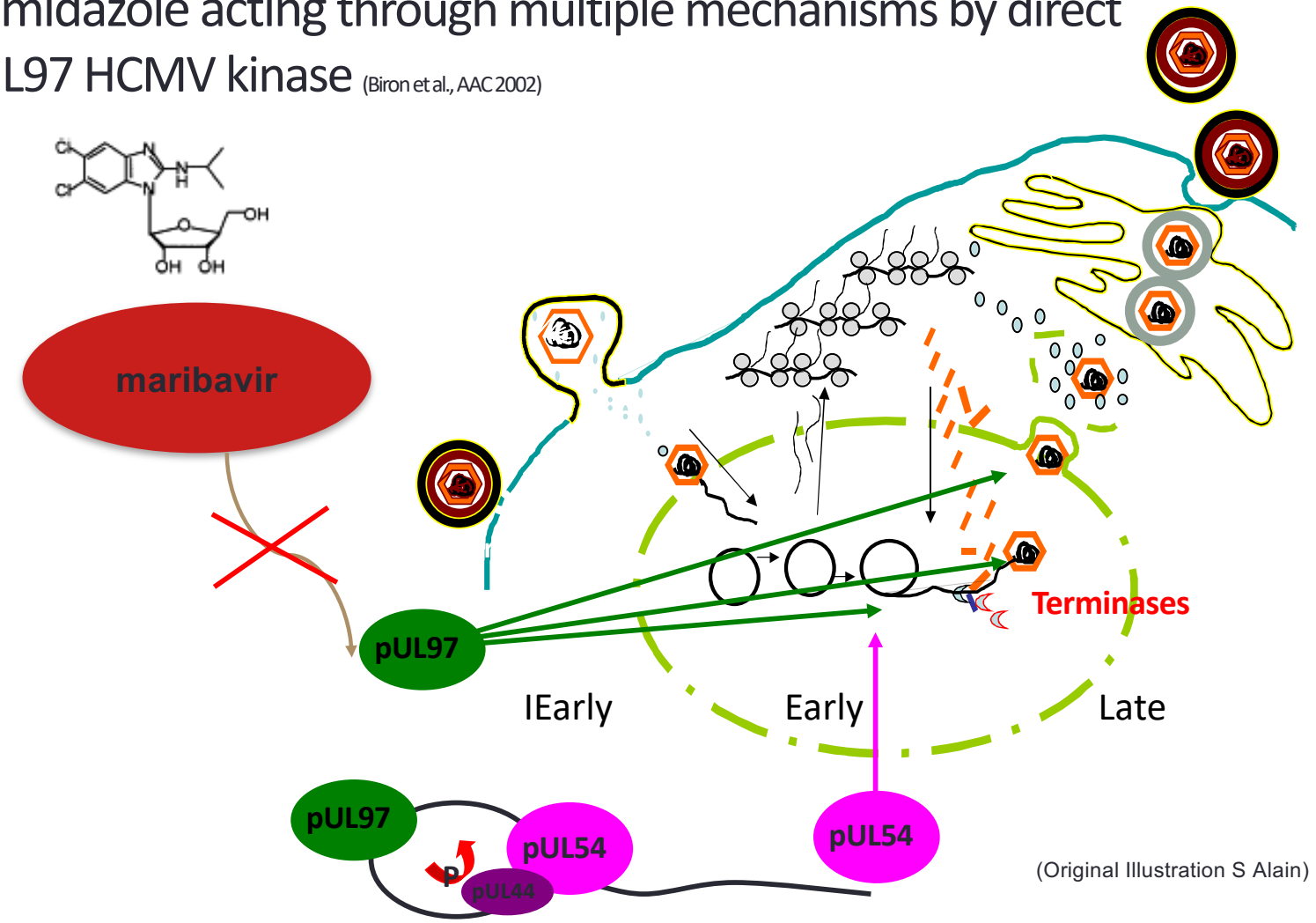
- Oral biodisponibility and long half life(1 x 2 sem),
- Ocular conentration
- Cross resistance CDV /GCV is the rule (*Chou S et al., Antiviral therapy 2020)*

- *Use of Rapid emergence of mutations when malabsorption*
- *Renal toxicity decribed post foscarnet tubulopathy (Vial et al., 2016, Faure et al., 2016)*

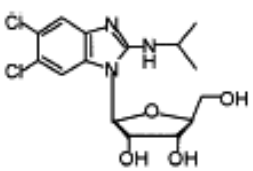
New anti-CMV molecules targeting the late stages of viral replication



Maribavir a benzimidazole acting through multiple mechanisms by direct inhibition of the UL97 HCMV kinase (Biron et al., AAC 2002)



Maribavir characteristics/Skills



- **The unique mode of action of maribavir confers**
  - **Specificity against CMV and thus low toxicity (no myelotoxicity at clinical doses)**
  - Short half life (2x per day) rapidly metabolised to less active, non cytotoxic compound
  - No need for renal function adaptation
  - **but does not cross the Blood Brain Barrier**

- **High efficacy and easy to use in clinical practice :**
  - 4x more active than ganciclovir (**ID50 0,12 - 0,56uM**)
  - **Oral biovailability (No IV)**
  - **No interaction/competition with other drugs (except ganciclovir) but possible interaction with tacrolimus blood levels**
  - **Possible synergy or additive effect (artesunate, foscarnet, terminase inhibitors)**

Maribavir inhibition site on UL97 is specific cross-resistance with ganciclovir is rare and selected by GCV

Maribavir Resistance

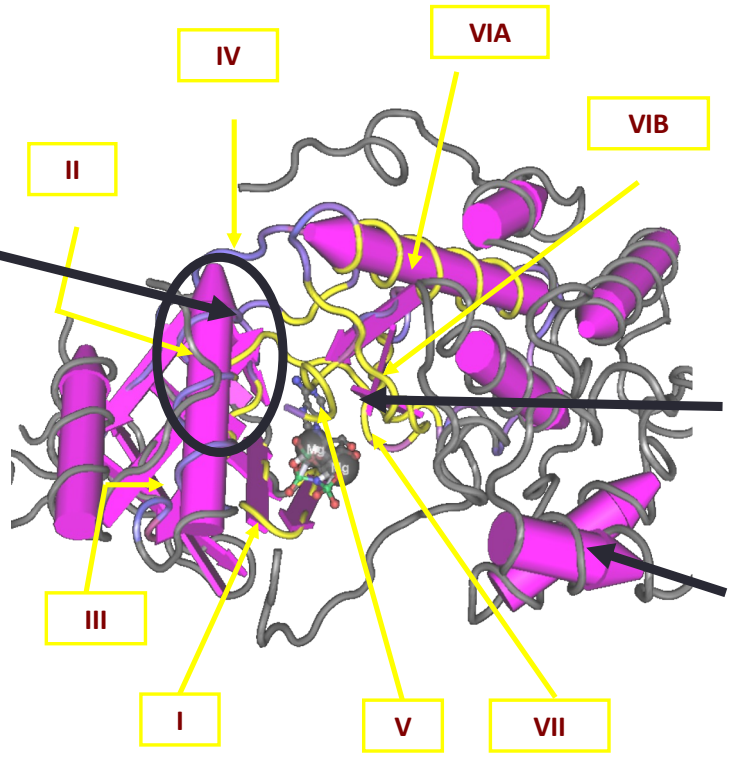
353

397

409

411

UL97 mutations: confer high level of resistance to MBV



GCV resistance

405, 460, 520

590–607

GCV/ MBV cross resistance

466, 480,

(original Illustration G Champier CNR Herpesvirus)

Chou *et al. Antiviral res. 2020*

Santos Bravo et al., JID 2021

Pharmacokinetics : maintain of high doses of MBV is mandatory

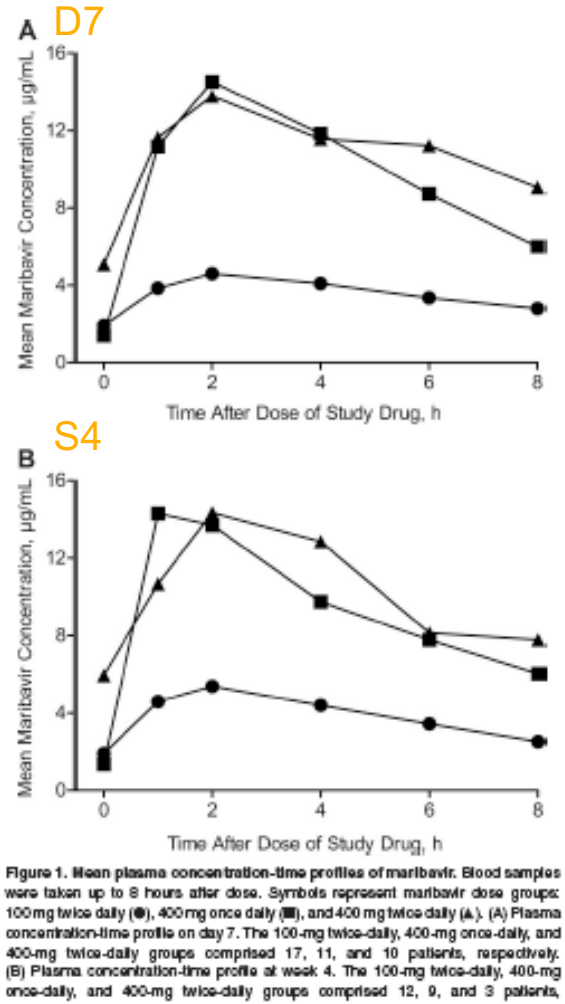


Figure 1. Mean plasma concentration-time profiles of maribavir. Blood samples were taken up to 8 hours after dose. Symbols represent maribavir dose groups: 100 mg twice daily (●), 400 mg once daily (■), and 400 mg twice daily (▲). (A) Plasma concentration-time profile on day 7. The 100-mg twice-daily, 400-mg once-daily, and 400-mg twice-daily groups comprised 17, 11, and 10 patients, respectively. (B) Plasma concentration-time profile at week 4. The 100-mg twice-daily, 400-mg once-daily, and 400-mg twice-daily groups comprised 12, 9, and 3 patients, respectively.

• ID50 for naive or GCV-resistant isolates :
0,2-0,8uM
Or 0,07-0,3 ug/mL

Covered by the lower dosage

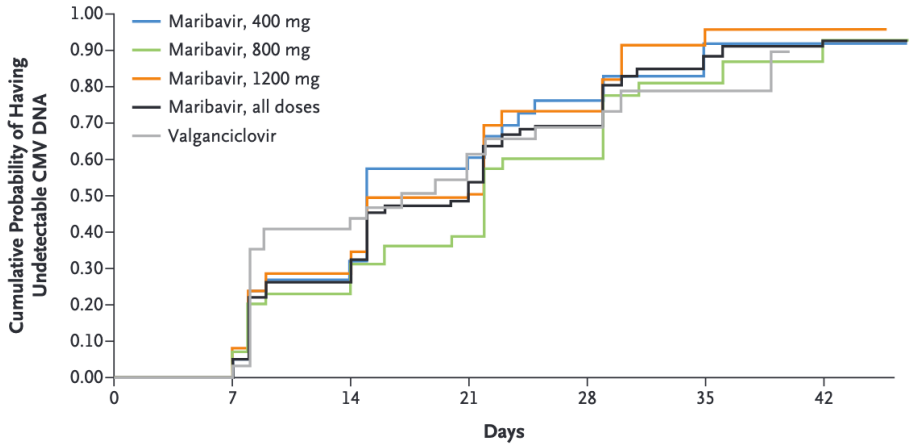
• ID90 for the same isolates : 20uM to 76uM (7,52-28,5 ug/mL)

Not covered by the lower dosage, partially covered by the high dosages

•As MBV is a direct inhibitor maintenance of a sufficient plasmatic level may be important

(Wang et al., AAC 2003),

Maribavir was as efficient as ganciclovir in preemptive tt **providing 6 weeks therapy** (diesel effect of late inhibitors)



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

Figure 2. Time to Confirmed Undetectable CMV DNA in Plasma within 6 Weeks (Intention-to-Treat Safety Population with Postbaseline CMV DNA Measurements).

The intention-to-treat safety population included all patients who underwent randomization and received at least one dose of trial drug. Confirmed undetectable CMV DNA in plasma was defined as two consecutive CMV DNA polymerase-chain-reaction assay values measured during treatment that were below the level of quantitation (i.e., <200 copies per milliliter according to the central laboratory) separated by at least 5 days.

(Papanicolaou et al.CID 2018)

Maribavir development in preemptive and salvage therapy

- **Failure of phase III prophylaxis low dose (100mg) and late administration SCT, Kidney-Liver**

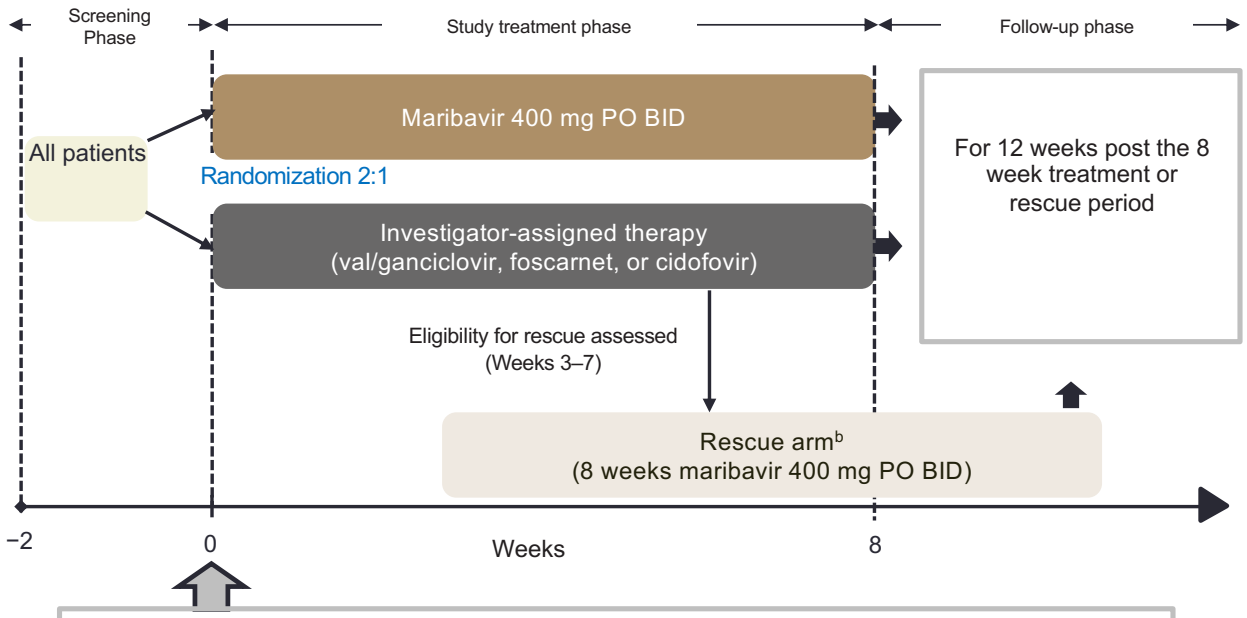
- **Efficacy preemptif: 3 doses 200 400 800mg/d**
  - 400mgx2 ⇔ valganciclovir (Obj CV <200UI/mL)
  - After 3 weeks tt 62%vs 56%, After 6 weeks TT 75% vs 67% RR 1,20 (0,9-1,51
  - Résistance 2/156 (1,58%)
- **Efficacy as salvage therapy for refractory/resistant patients**
  - **ATU Europe 800mgx2 At 3 weeks TT efficacy 56,7%** resistance 14%
  - **Phase II dose ranging 400 vs 800mg X2 6 weeks** efficacy 68%,- at 6 weeks - resistance 15%

ATU in non responders to 1st and 2nd line DNA pol inhibitors

- ***Phase III:*** *Solstice salvage TT randomized study: 400mg x 2 /d 8 weeks 55,7% overall efficacy analysis ongoing*

(Marty et al., NEJM 2011, Alain et al., Tr Proc. 2014 and CNR data, Papanicolaou et al.CID 2018, Maertens et al., NEJM 2019, Avery K et al., ESOT 2021, EBMT 2021)

Solstice clinical trial : Phase 3, Randomized, Open-label, Multicenter, Active-Controlled Study



Primary endpoint
Confirmed CMV clearance (plasma CMV DNA <137 IU/mL in 2 consecutive tests ≥5 days apart at central laboratory) at end of Week 8

Key secondary endpoint
Achievement of CMV clearance and symptom control at end of Week 8 and maintained through Week 16

Patients characteristics at baseline

	Maribavir (n=235)	IAT (n=117)
Median age (range), years	57 (19–79)	54 (19–77)
Received SOT,[b] n (%)	142 (60.4)	69 (59.0)
Kidney	74 (52.1)	32 (46.4)
Lung	40 (28.2)	22 (31.9)
Heart	14 (9.9)	9 (13.0)
Liver	6 (4.2)	1 (1.4)
Multiple	5 (3.5)	5 (7.2)
Pancreas	2 (1.4)	0
Intestine	1 (0.7)	0
CMV mutation resistant to ganciclovir/foscarnet/cidofovir,[c] n (%)	121 (51.5)	69 (59.0)

(Avery K et al., ESOT 2021, EBMT 2021)

Solstice/SHP 303 main results summary

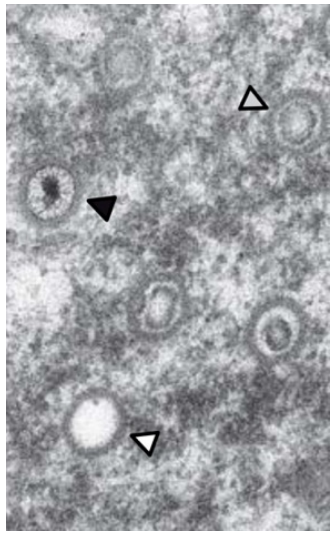
ENDPOINT	MARIBAVIR RM n=235	Investigator assigned therapy (IAT) n=117	Adjusted difference (95% CI)
PRIMARY : % VIREMIA CLEARANCE AT W8	55,7%	22,9 % p<0.001	32,8% (22,80-42,74)
HSCT SOT*	55,5% (79/142)	26,1% (18/69)	36,1% (20,92-51,37) 30,5% (17,31-43,61)
IAT=valganciclovir IAT=foscarnet			31,7% (18,63-44,78) 36,4% (23,37-49,40)
Resistant Non resistant			44,1% (31,3-59,64) 12,6% (6,24-31,43)
CMV CLEARANCE AND SYMPTOM CONTROL AT W8 AND W16	18,7%	10,3%	9,5% (2,0-46,9)
ADVERSE EVENTS Dysgueusia Neutropenia Acute kidney injury Anemia Serious AE leading to drug discontinuation	97,4% 35,9% 1,7% 1,7% 1,3% 8,5%	91,4 % 0,9% 13,8% 7,8% 7,8% 14,7%	Rates of treatment-related neutropenia, anemia, hypokalemia and renal events were lower with maribavir versus IAT Dysgueusia rarely resulted in discontinuation (2 [0.9%] patients in the maribavir arm)

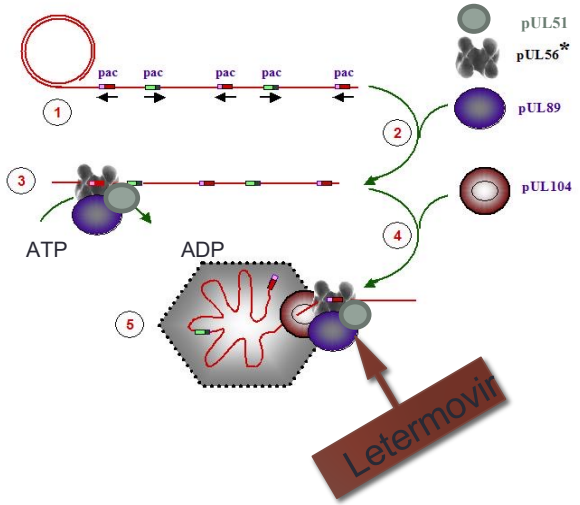
(Avery K et al., ESOT 2021, EBMT 2021)

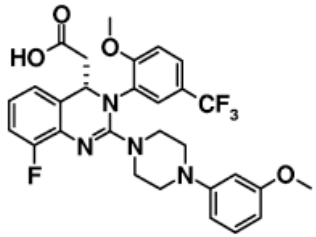
Letermovir: a quinazoline, targetting the viral HCMV terminase complex

- FDA approved for prophylaxis in stem cell recipients after phase III study (Marty et al. NEJM 2017)
- 100 days 480mg per day or 240mg per day in case of co administration of cyclosporin
- efficacy persists if low viral load at initiation (<1000IU/mL)
- Low toxicity profile
- Administration oral and IV
- Cross the BHE
- Largely marketed for prophylaxis of CMV in high risk HCT recipients but off-label use

Target:
U56, UL89, UL51.
No equivalent in mammalian cells







Specificity : no action on HSV VZV HHV6 or EBV
No cross resistance with other antivirals

Off-label use of letermovir as rescue therapy

N /type patients	LMV	LMV+GCV or FOS	Endpoint	% success	Delay of response	Refractory Resistance	Toxicity	Reference
27 SOT 21 HCT 13 centers 37 VL<1000IU/mL 8 resistant 10 VL>1000IU/ml 7/10 resistant	**480-960mgqd**	**/**	**VL< cut-off Or VL<1000 IU/mL**	**VL<1000IU/mL => undetectability : 71% VL>1000IU/mL => VL<1000IU/mL 60%**	**2-12w**	**None 1 C325W**	**Serious AE =2 Diarrhea Drug interaction with tacrolimus**	**Linder et al., Transpl. Infect. Dis. 2021**
28 LTR refractory or GCV-resistant 15/28 CMV disease			**VL clearance**	**23/28 (82,1%)**	**17d (14-27)**	**5 non-responders: 3 resistant (C325W)**	**Mild gastrointestinal**	**Voit et al., AJT 2021**
9 (3/9 refractory) SOT, HCT, TARFO, Castelman	**480**	**/**	**VL<200 IU/mL**	**77% (7/9)**	**23(8-83)d, after initial VL increase**	**2, NT**	**None**	**Schubert et al., Eu jMic 2021**
13 KTR 10/14 CMV disease VL<1000IU/mL	/	Step-down tt LMV+GCV in 4/13	Absence of VL relapse	0/4 but controlled by add-on VGCV	/	Only 1/4 needed to be re-treated by FOS for VL>10 000 IU/mL	NA	Rho et al., clin Transpl 2021
5 LTR refractory or resistant 3DNAemia, 1 pneumonia+colitis resistant 1CMV syndrom,	480 3/5 1 underdosed	1/5	VL clearance <200 IU/mL 2log reduction in viremia	3/5 (Asymptomatic) 1 (pneumonia/colitis clinical improvement but further decease)	4-6 weeks	1 (viral syndrome) No resistance	None	Phompoong et al., Transplantation 2020
14y-o girl HCT GCV/CDV/FOS R CMV disease	480 secondary prophylaxis	/	relapse			Relapse and resistance	NA	Kilgore et al. J Pediatric Infect Dis Soc.2020
14 HCT R CMV DNAemia	480 43-59 d	/	VL < cut-off	12/14 (85,7%)	16d (13-21)	1 clearance failure NT	1 LMV-related thrombocytopeni	Kachur et al., Transpl. Infect Dis 2021

Outcome in higher viral loads

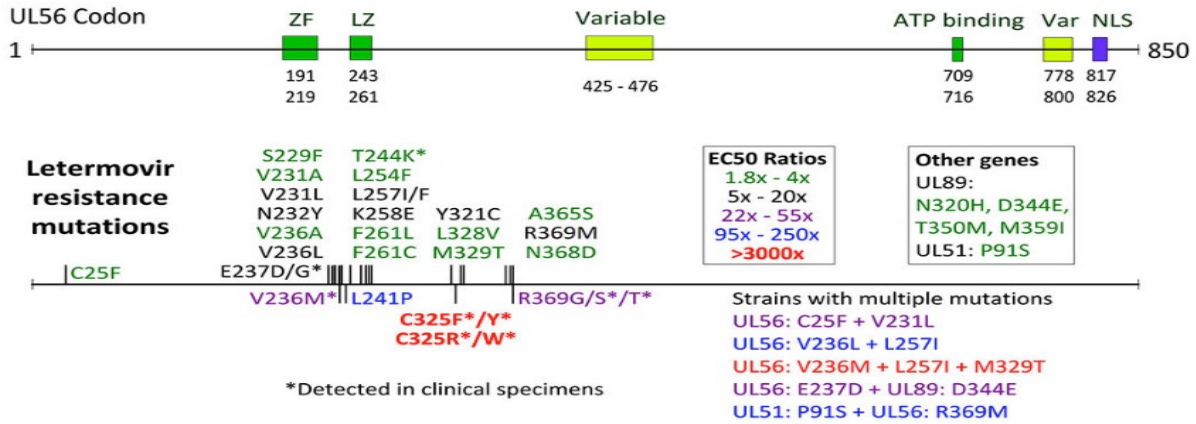
TABLE 4 Characteristics and outcomes of patients with CMV viral loads > 1000 IU/ml at letermovir initiation

Age	Gen	Race	Transpl	Days from transplant to CMV episode	CMV disease	Prior CMV treatments	Days from CMV diagnosis to LET	LET indication	LET dose	Other CMV agents used with LET	Mut	Viral load at LET start	Viral load wk 2–4	Viral load wk 5–8	Viral load wk 9–12	Duration LET wks	Viral load < 1000 at LET end	Last known status
50	M	Black	Lung	272	GI (probable)	(val)gan, fos	15	resistance, toxicity	480 mg qd; increased to 960 mg qd	(val)gan	UL97	23854	10975	85257	2939	19.4	Yes	Alive
29	M	White	Intestine	1753	GI (proven)	(val)gan, fos	36	Resistance	480 mg qd	None	UL97	2000	NA	NA	NA	1.14	No	Dead
63	F	White	Lung	136	GI (probable)	(val)gan, fos	123	Toxicity	480 mg qd	None	None	2350	BLQ	167	BLQ	46.4	Yes	Alive
65	F	Black	Lung	415	None	(val)gan, fos	318	Resistance, toxicity	480 mg qd	None	UL97	18270	4788	4662	4473	> 52 (ongo-ing)	NA	Alive
55	M	Black	Kidney	68	None	(val)gan	20	Refractory, toxicity	480 mg qd	None	None	4000	BLQ	BLQ	BLQ	26.4	Yes	Alive
50	M	Black	Kidney	214	None	cdv, CMV IgG	49	Resistance, toxicity	480 mg qd	None	UL97	41923	41736	43109	NA	11.0	No	Alive
35	M	White	Stem cell	190	Lung (probable)	fos	10	Combination therapy	480 mg qd	fos	None	160000	BLQ	NA	NA	2.3	Yes	Dead
56	M	White	Kidney	97	None	(val)gan	286	Resistance, oral preferred	720 mg qd	None	UL97, UL54	4318	NA	BLQ	NA	>22 (ongo-ing)	NA	Alive
70	F	White	Lung	260	Lung (proven), GI (proven)	(val)gan, fos, CMV IgG	77	Resistance	720 mg qd, increased to 960 qd	CMV IgG	UL54	994000	5950	1100	7690	18	No	Dead
50	M	Asian	Lung	735	GI (possible), retina (proven)	(val)gan, fos, mbv, CMV IgG, i.v. gan, i.v. fos	163	Resistance, toxicity	720 mg qd	CMV IgG, lefluno-mide	UL54	1657	701	1246	5548 (C325 LET)	15.7	No	Alive

Abbreviations: BLQ, below the limit of quantitation; cdv, cidofovir; CMV, cytomegalovirus; fos, foscarnet; GI, gastrointestinal; IgG, immunoglobulin; i.v., intravitreal; LET, letermovir; mbv, maribavir; mut, mutation; NA, not applicable; qd, daily; transpl, transplant; (val)gan, (val)ganciclovir; wk, week.

Linder et al., Transpl. Infect. Dis. 2021

Letermovir resistance in the clinical setting



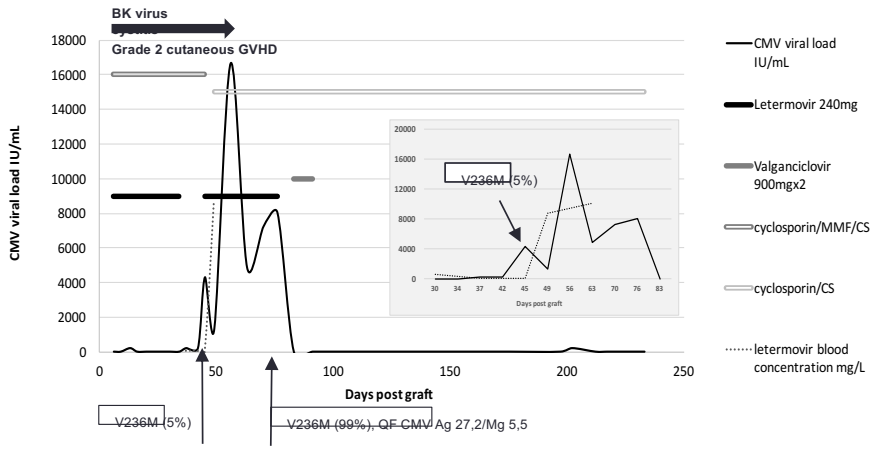
- Resistance detected in 7-8% of breakthrough
  - Phase II : 1/12 pUL56 V236M (60mg) 8,3%
  - Phase III : 2/28 pUL56 V236M and 1 C325W 7,4%
  - Overall France 2018-2020 : 13/181 7,18%
  - Rescue ttt : Case R C325Y, within 10 weeks of tt
  - Rescue tt: 4 retinitis 3 tested 2/3 C325F and C325Y
  - Prophylaxis : Case R. J142 450mg/d C325F
- Prevalence of R in prophylaxis : 1-5,5%
  - Secondary prophylaxis 4/80 5,5%
  - Primary Prophylaxis: 0/123

Lischka J I D 2016
(www.accessdata.fda.gov, Reference ID 4179078).
Alain et al. CNR data
Cherrier et al., Am J Transpl. 2018
Turner et al., AAC 2019
Knoll, BMT 2018

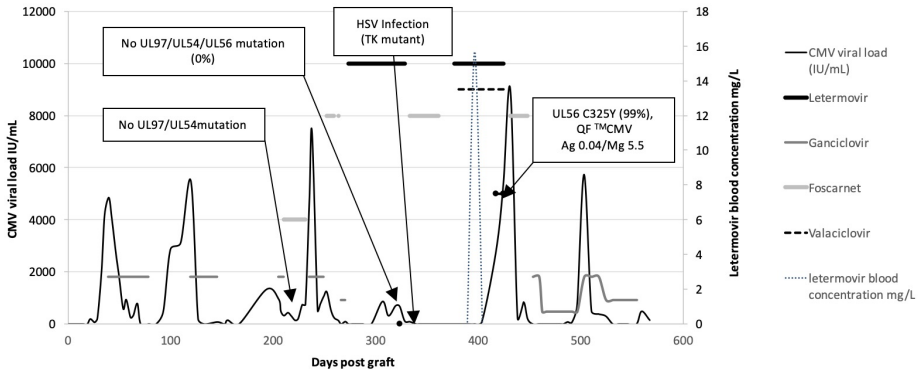
Alain et al. Jac 2019, Robin et al., BBMT 2020
Sassine et al., CID 2021

letermovir resistance may rapidly emerge if non observance or treatment interruption . Plasmatic concentration may help

Case 1



Case 2

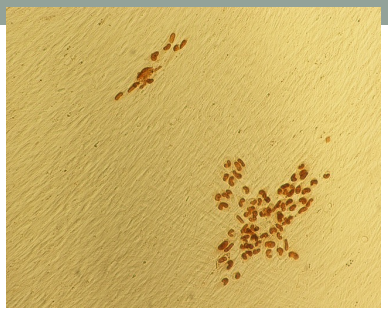


(Alain et al., JAC 2019)

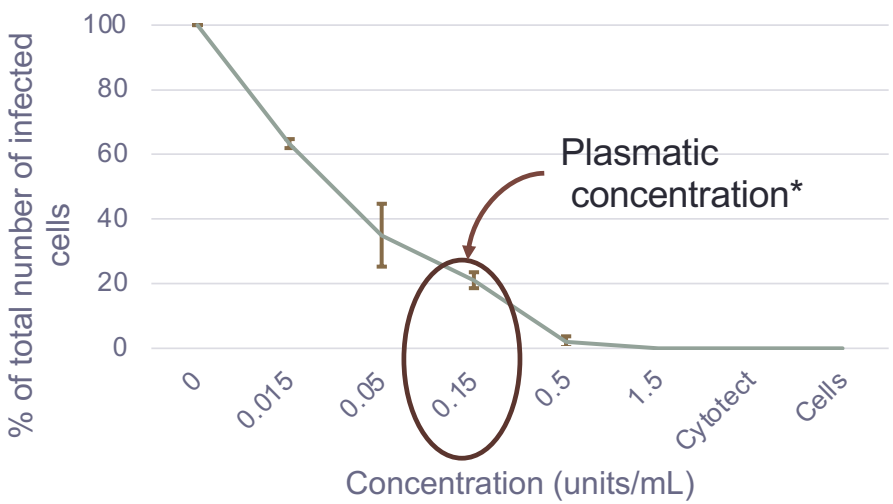
HIVIg for transplanted patients with CMV infection as adjuvant treatment ?

- **Posology of Human CMV Ig for IV use (100 U/mL):**
  - **Prophylaxis**: **1 mL/kg** in 6 times every 2 or 3 weeks
  - **Preemptive**: **4 mL/kg** at days 0, 4 and 8 follow by **2ml/kg** at days 12 and 14
  - **Curative: 2x** (**4 mL/kg** at days 0, 4 and 8 follow by **2ml/kg** at days 12 and 14)

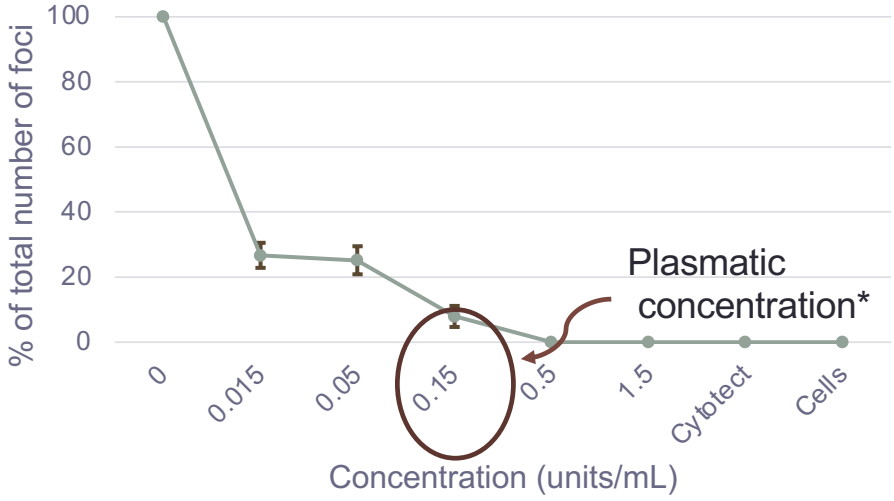
Neutralizes the virions



Merlin (MOI 0.1) at 24h (infection)



Merlin (MOI 0.1) at 5 days (viral multiplication)



	24H	5 days
IC50 Units/mL	0.04 (±0.0015)	0,014 (±0,0013)
IC90 Units/mL	0,19 (±0,04)	0,12 (±0,06)

* For preemptive treatment

Salvage therapy in HCT

Viral load

- 78% response (18/22 evaluables)
- 20 patients received preemptive dosage:
- 16/20 undetectability (15j, 3-51j)
- 1/20 VL decrease 4,8-->3,6 log
- 3 patients secondary prophylaxis: 1/3 persistant undetectability

Bone Marrow Transplantation (2018) 53:1328–1335
https://doi.org/10.1038/s41409-018-0166-9

ARTICLE

Cytotect®CP as salvage therapy in patients with CMV infection following allogeneic hematopoietic cell transplantation: a multicenter retrospective study

Tamim Alsuliman[1,2] · Caroline Kitel[1] · Rémy Dulery[3] · Thierry Guillaume[4] · Fabrice Larosa[5] · Jérôme Cornillon[6] · Helene Labussière-Wallet[7] · Clémence Médiavilla[8] · Stéphanie Belaiche[9] · Jeremy Delage[10] · Sophie Alain[11] · Ibrahim Yakoub-Agha[1,12]

Survival :

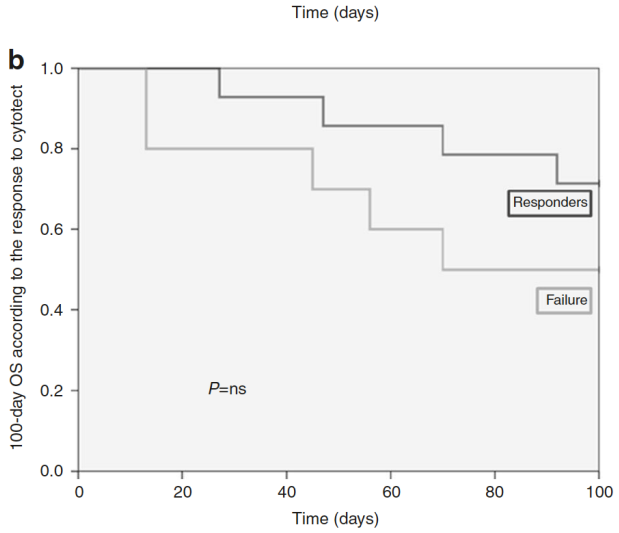


Fig. 1 Overall survival in 23 patients 100 days after outset of Cytotect®CP (2 deaths were related to CMV while 6 others were unrelated to CMV). **a** 100-day from the onset of CytotectCP® overall survival in the 23 patients. (2 deaths were related to CMV while 6 others were unrelated to CMV). **b** 100-day overall survival according to the response to CytotectCP®

(Alsuliman et al., Bone Marrow Transplantation 2018)

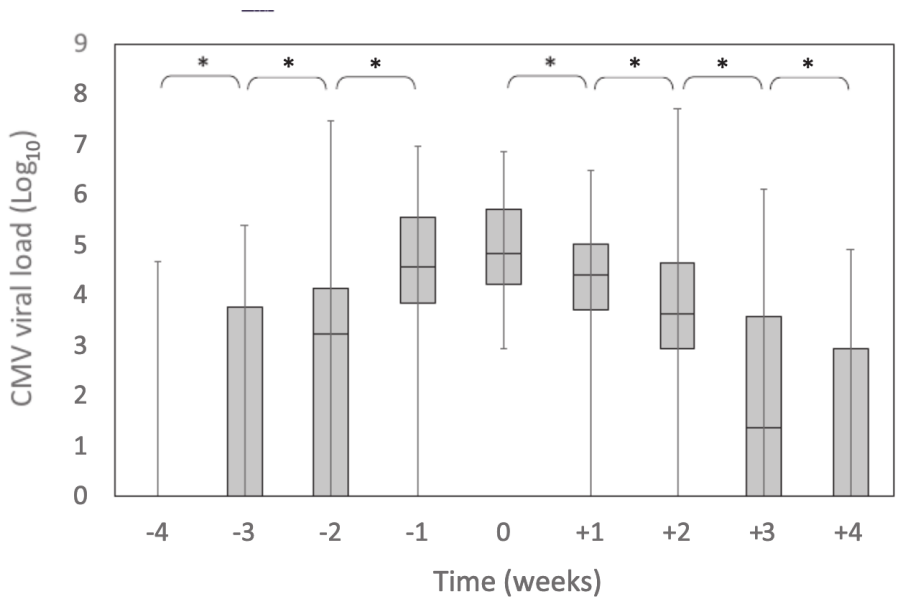
Salvage therapy in SOT

- 35 heart/ung recipients, monocentric
- CMVIg rescue therapy :
  - CMVIg (Cytotect CP® Biotest, 2-3 mL/kg)
  - with antiviral therapy (GCV/VGCV) adjusted to renal function.
  - Leflunomide 20 mg BD instead of standard antiviral therapy if CMV resistance was noted.
- Frequency of CMVIg doses adjusted based on the viral load (expressed in $\log_{10}$ copies/mL):
  - >5.2: bi-weekly;
  - 4.6-5.2: weekly;
  - 4.3-4.6: fortnightly;
  - <4.3 not required).

(Santhanakrishnan et al. Clin Transplant, 2019)

CMV Ig rescue therapy was safe, well tolerated and effective at controlling viral replication

Viral loads :



Adverse events :

- 2 patients with severe renal impairment
- Fluid retention , ankle oedema and increase of creatininemia

(Santhanakrishnan et al. Clin Transplant, 2019)

Cytotect in French lung transplant recipients

	INFECTION N= 22	DISEASE N=6
Death, n (%)	2 (9%)	2 (33%)
Relapse under Cytotect®	0 SP no association	NRD
Success, n (%) Negativation of the viral load or Clinical improvement	15 (83%) of the 18/22 avalaible data	4 (66%)
Relapse after discontinuation of Cytotect®	0	2 (33%) (1 had an incomplete cure)
Median Follow up of 174 days after initiation (18-682 d) **Adverse Effect : one case of pruritus without anaphylactic symptomes**		

Success Rate of Cytotect® is :
83% for **infection**
66% for **CMV disease**

Courtesy of Pr A Roux, Foch, Suresn

Take home messages :

- The burden of refractory infections and resistance is still an unmet need
- New therapeutic and more personalized approaches combining new non toxic direct antivirals and potent adjunctive therapies such as HIVIG will enhance the prognosis of these patients
  - New antivirals development give access to non toxic, oral direct antivirals but only maribavir has been tested in randomized trials
  - The place of letermovir either in salvage therapy or as secondary prophylaxis in SOT deserves clinical tevaluation
  - In absence of resistance or if QF testing is low we can propose HIVIG in adjunction to current tt
  - In case of CNS/eye involvement : no maribavir, add Letermovir?
  - Leflunomid, Everolimus to discuss (at any stage?)
  - Cell therapy at the end of the pathway
- Good quality genotyping, repeated if necessary, is mandatory for all antivirals

⌘ To all the patients, and our colleagues clinicians and virologists ….

UMR-S 1092, Univ Limoges

CNR Herpesvirus, CHU Limoges