

Infections virales des immunodéprimés

B. Henry

6 février 2025

Au menu (théorique)

Herpesviridae

CMV
EBV
HSV
VZV
HHV6
HHV8

Polyomaviridae

BK virus
JC virus

Autres

Parvovirus B19
Hépatites virales
Adenovirus
...



Arbovirus

Dengue
Chikungunya
Zika
...

Virus respiratoires

Myxovirus
influenza
Rhinovirus
SARS-CoV2
...

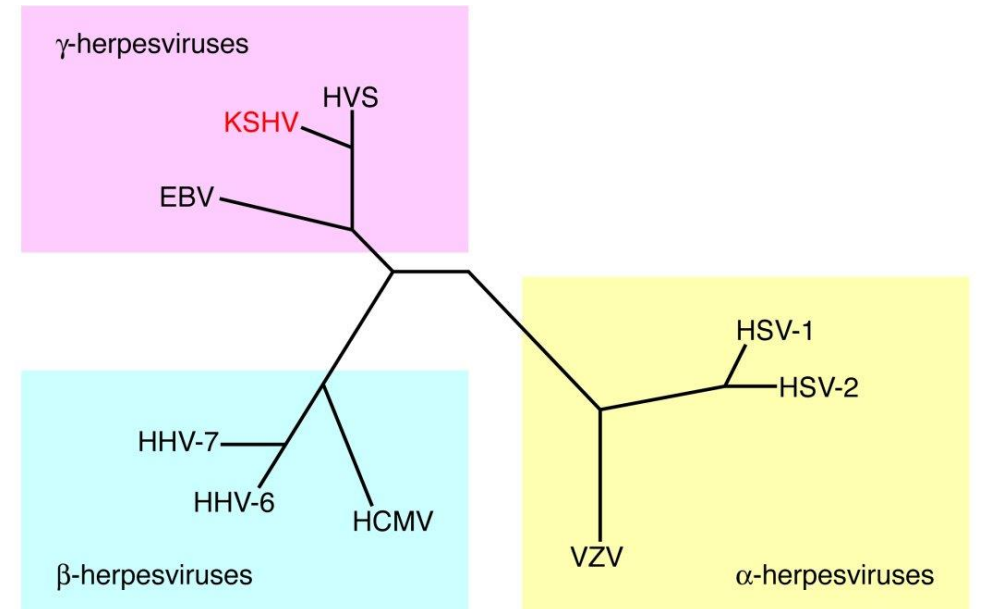
Virus entériques

Norovirus
Astrovirus
Calicivirus
...

Herpesviridae

Virus à ADN enveloppés
 Très prévalents
 Human only
 Latence

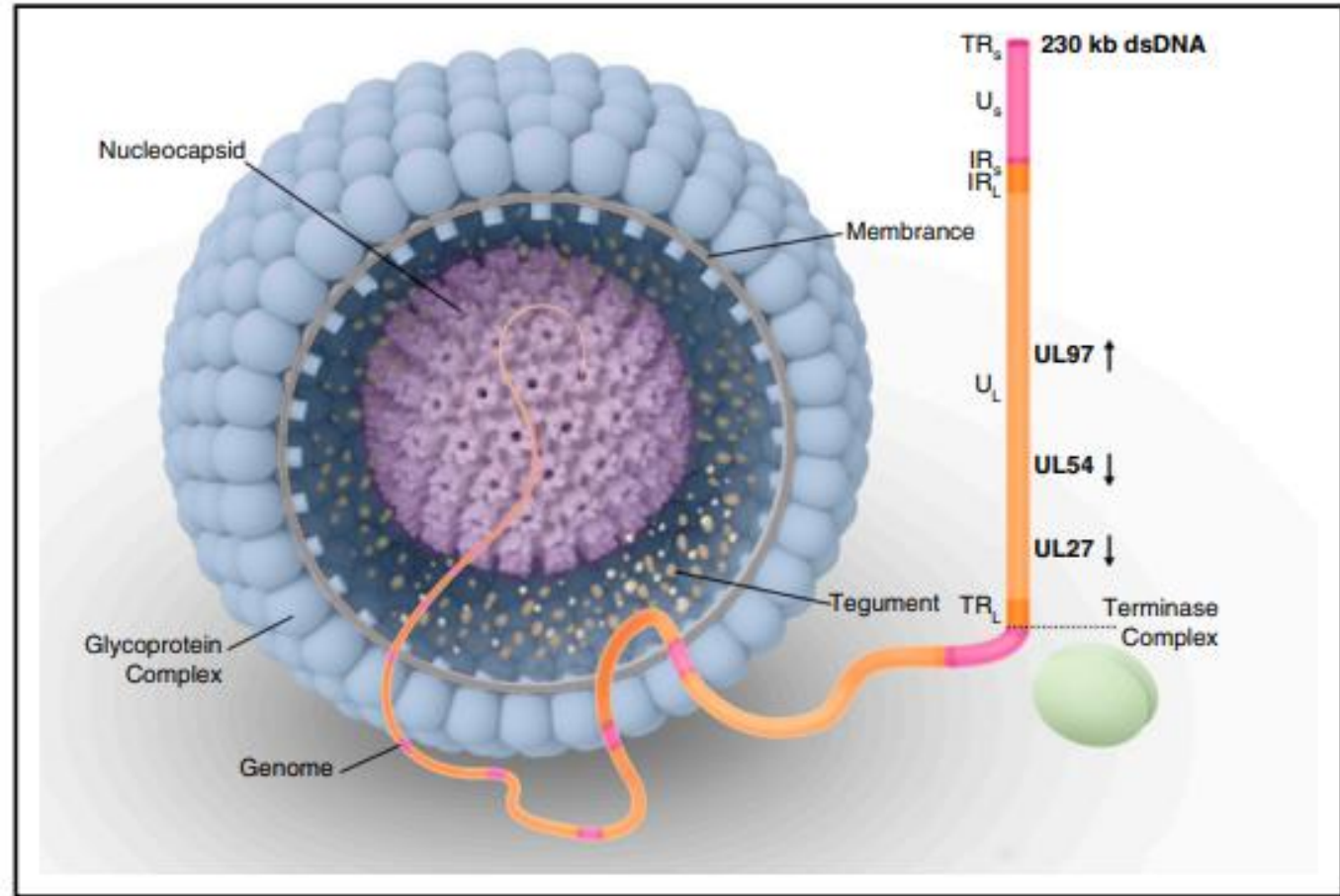
CMV	EBV	HSV	VZV	HHV6	HHV8
Progéniteurs myéloïdes Monocytes	Lym Bm/T/NK Cellules épith. Myocytes	Ganglions nerveux (trigéminé/sacré)	Ganglions nerveux (racines post.)	Nombreux	Cellules endoth. Monocytes Lymphocytes B



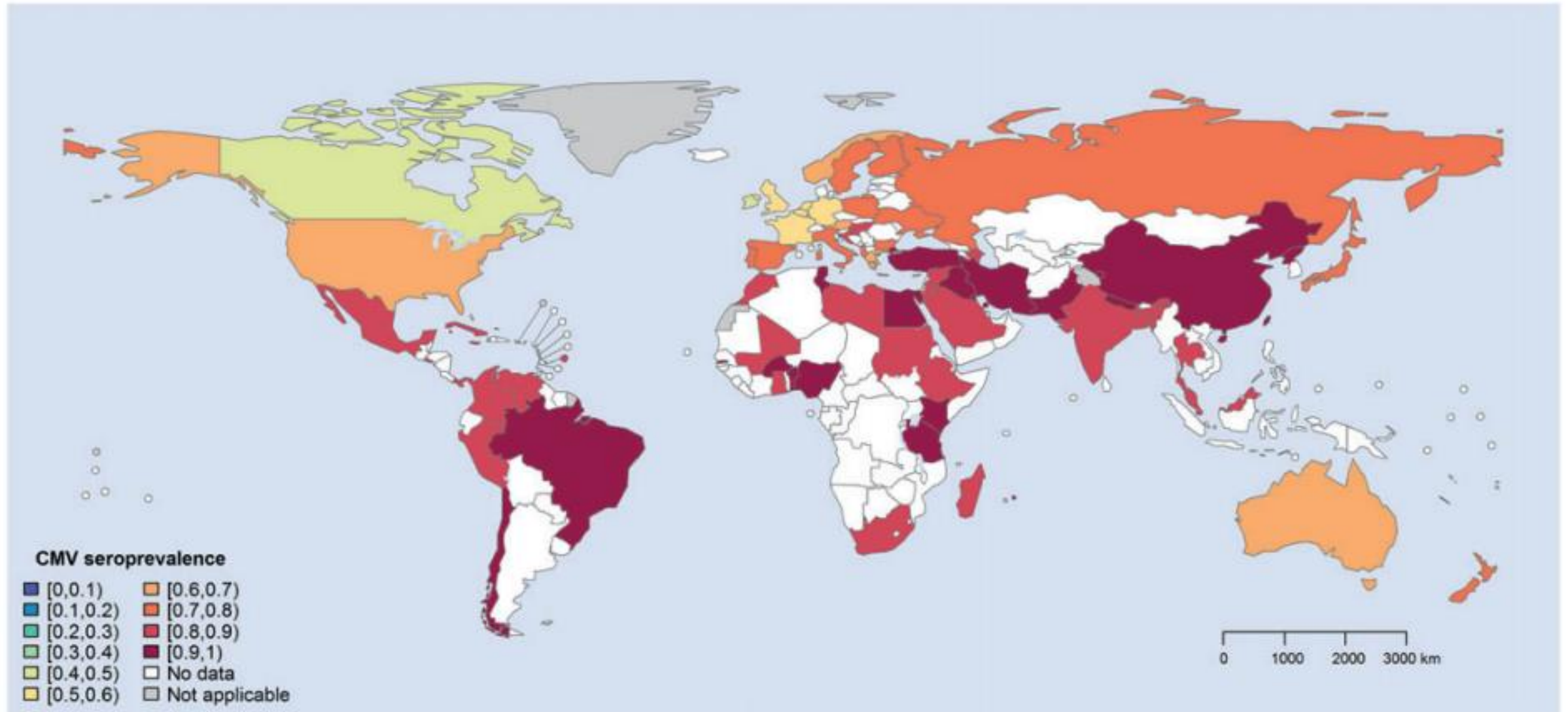
CMV

CMV: le virus

- β herpes virus (HHV5)
- ADN, enveloppé
- Humain strict
- Latence (CD34+)
- Génome: UL, US et TR
- Transmission via les fluides corporels



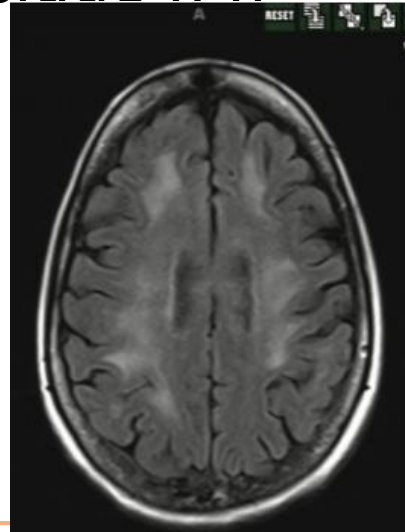
CMV: séroprévalence



Les pathologies

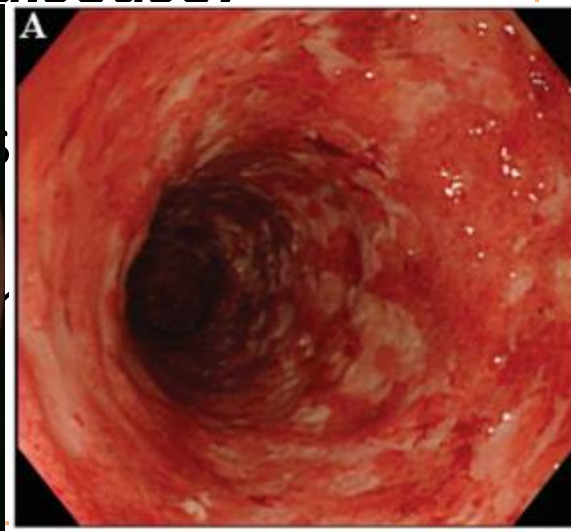
Immunocompétent

- *rien*
- syndrome mononucléosique (PI)



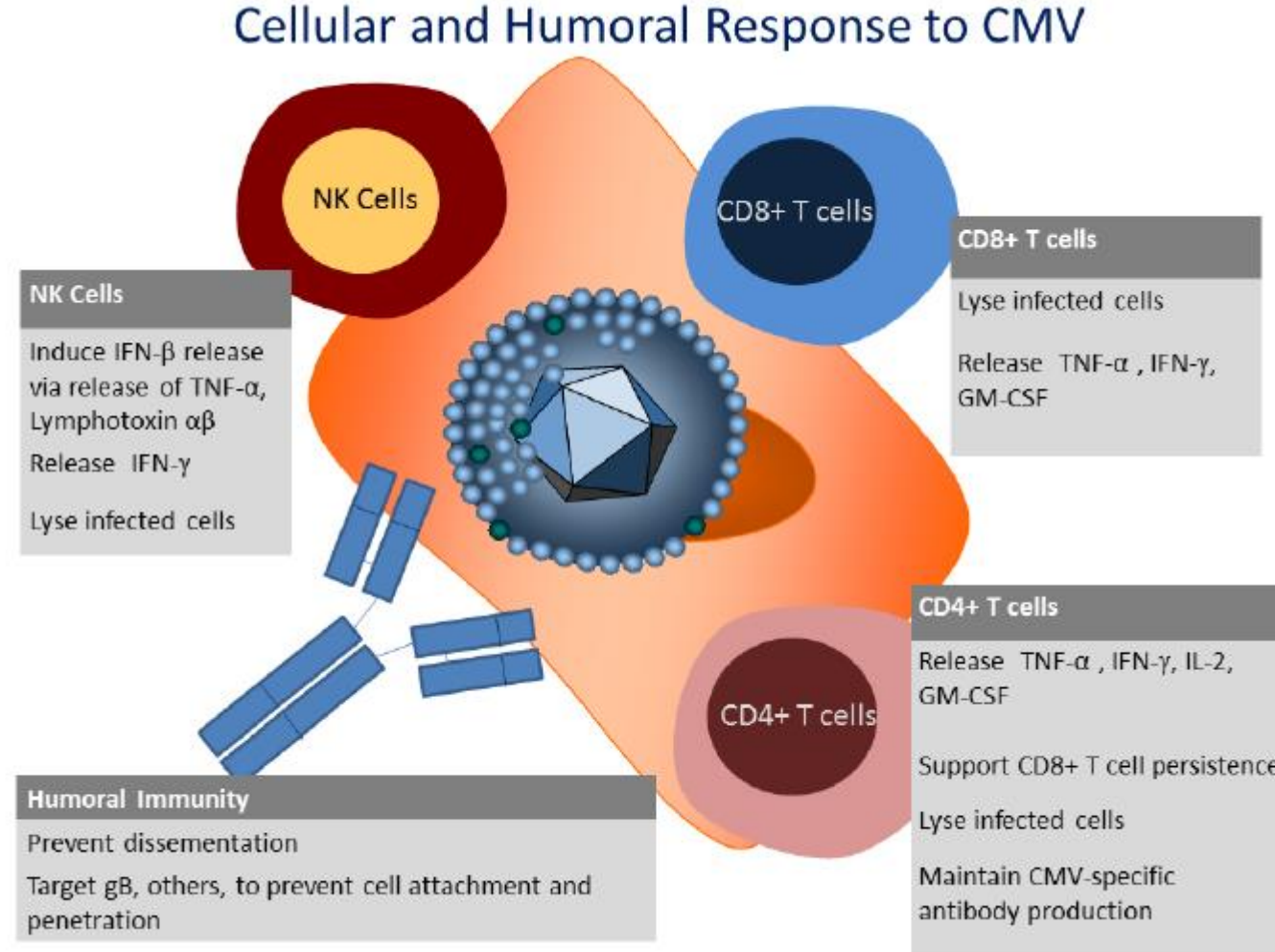
Immunodéprimé

- *Virémie (infection)*
- *Atteinte d'organe (disease)*



Femme enceinte
Embryofœtopathie

Types d'immunodépression concernés



Trois populations principales:

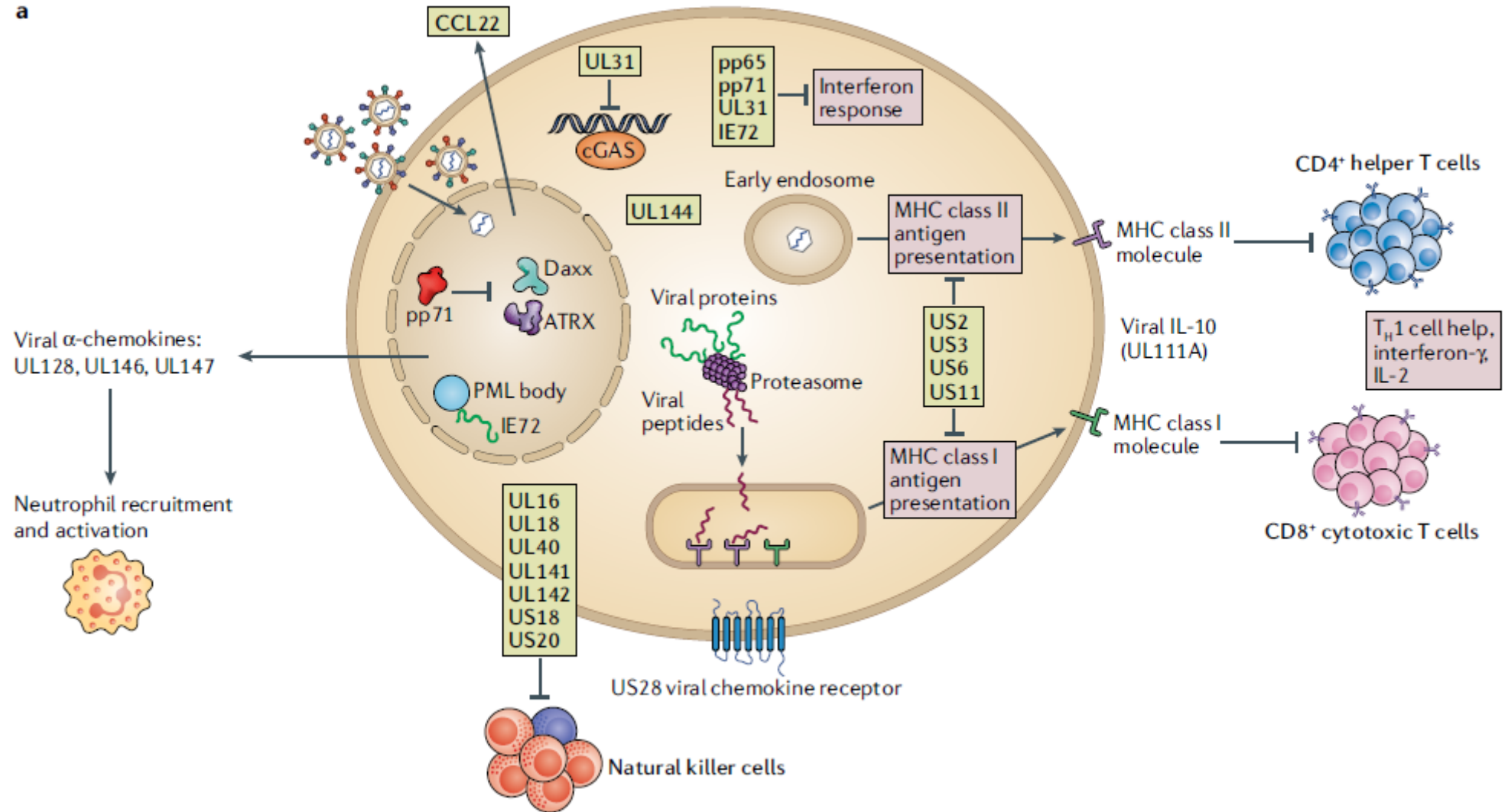
TOS

HSCT

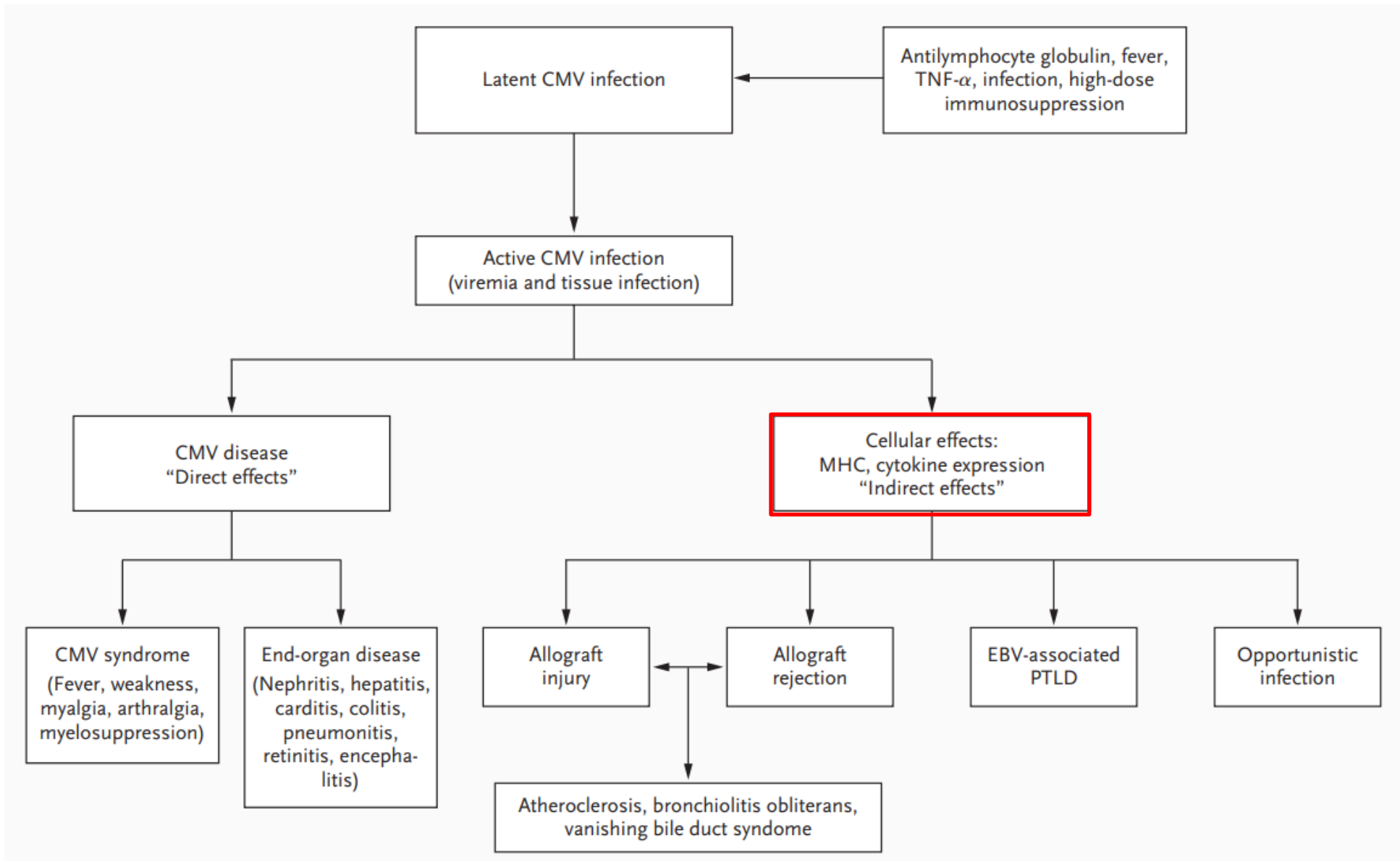
VIH

Evasion immunitaire

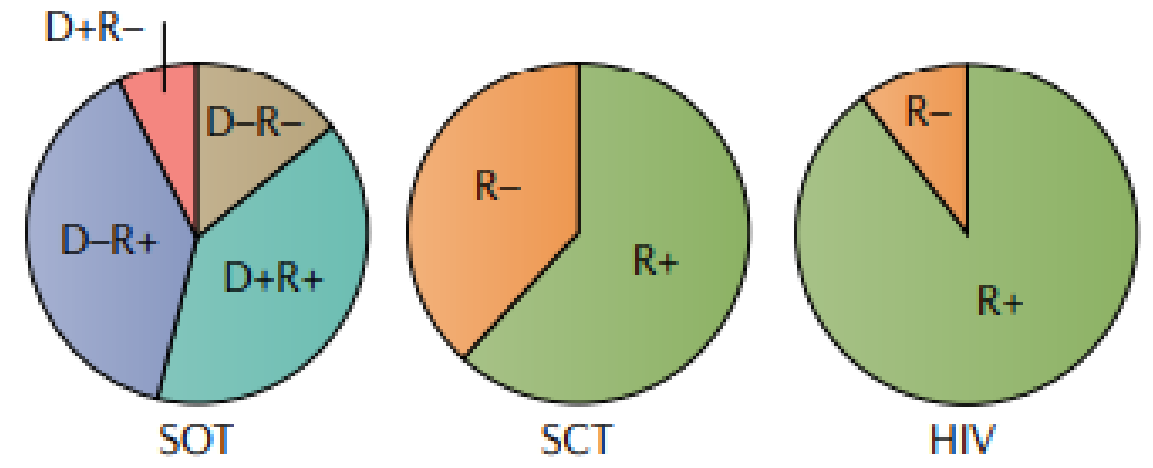
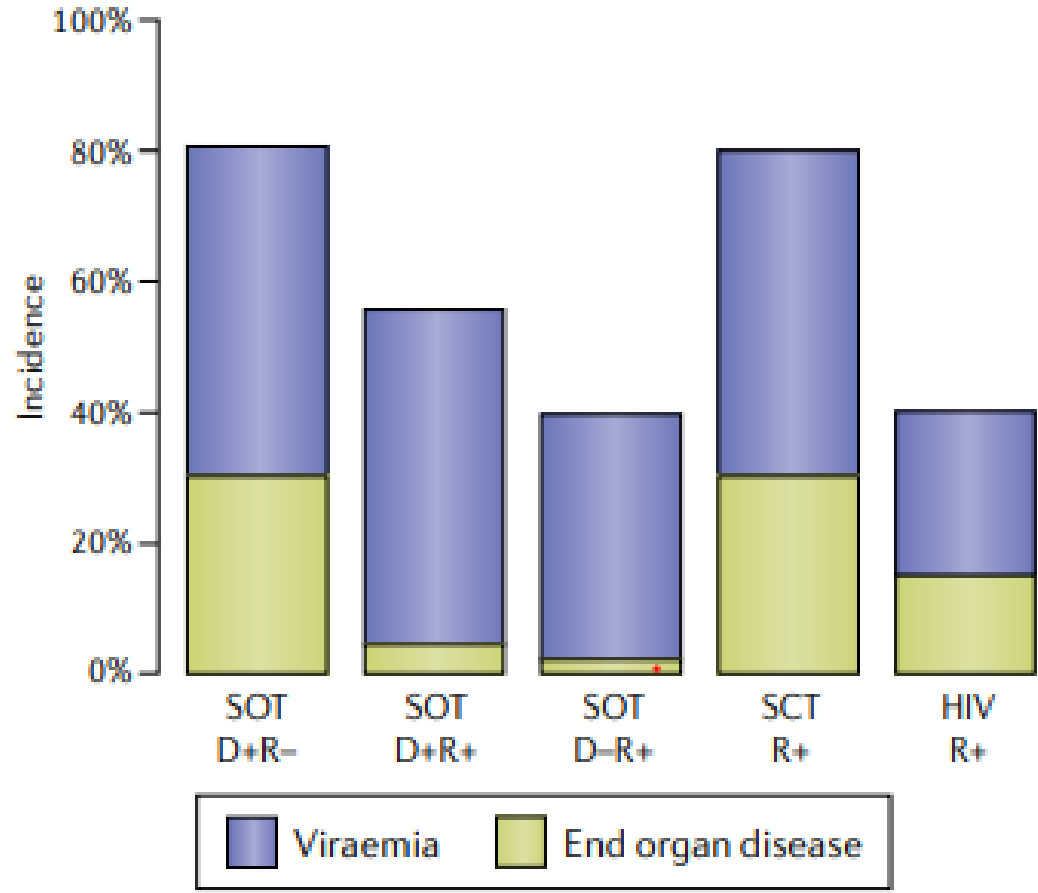
a



Effets indirects du CMV



Virémie et atteinte d'organe: amplitude du problème

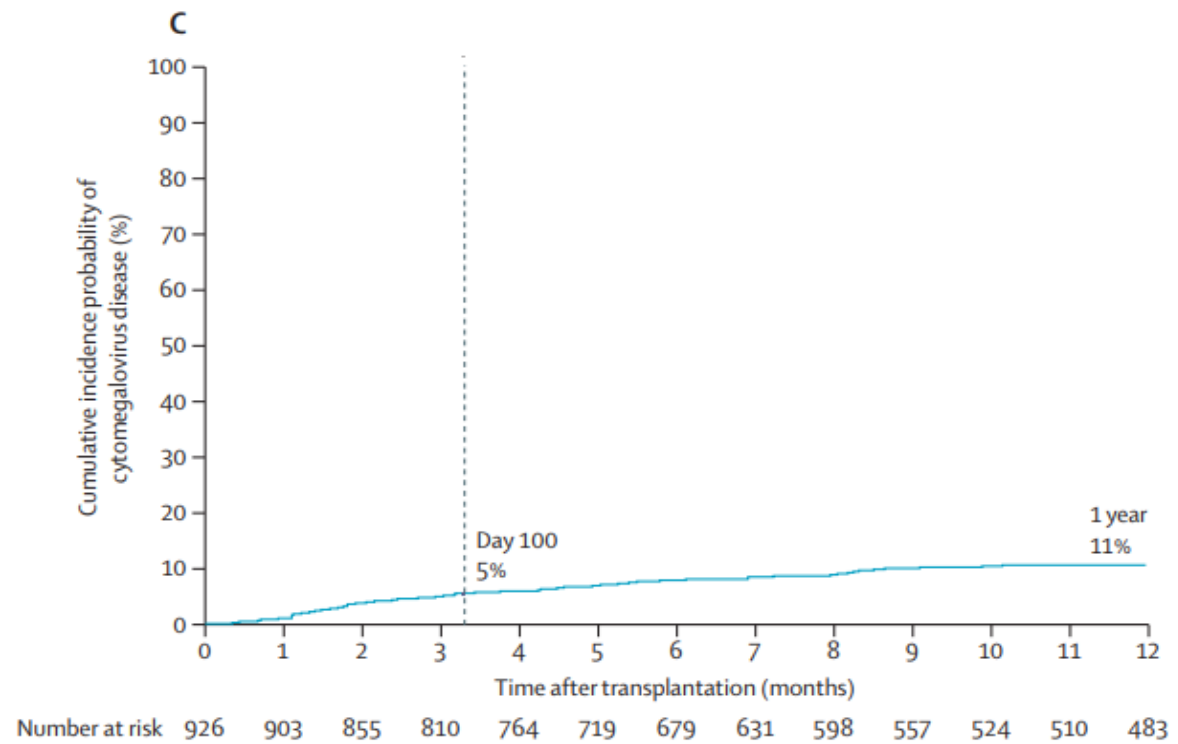
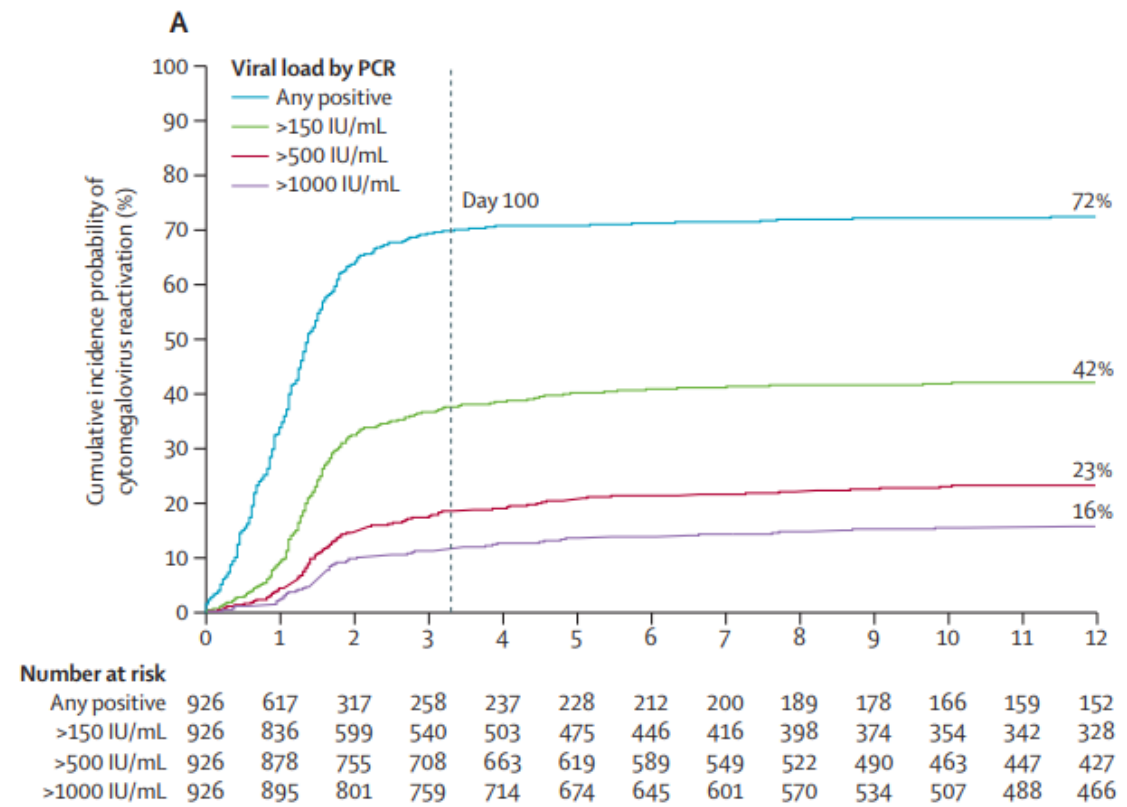


CMV: beaucoup plus de virémies que d'atteintes d'organe



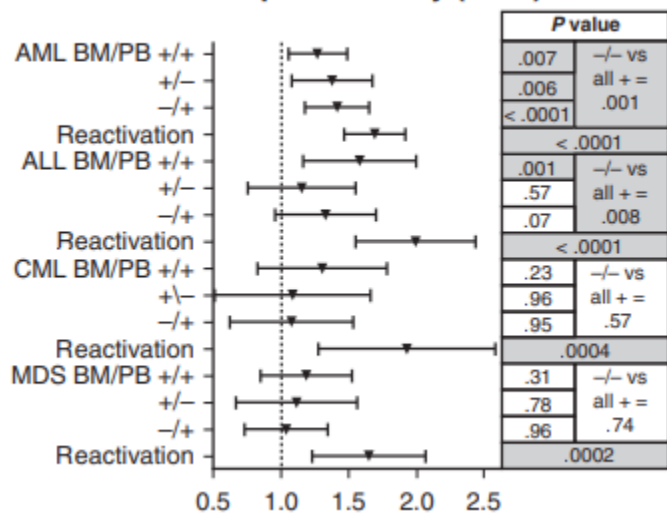
Infection (ADNémie)

Atteinte d'organe

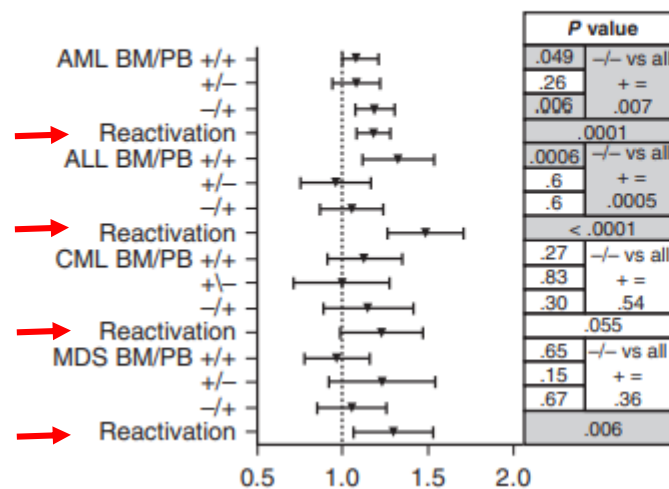


L'impact du CMV: HSCT

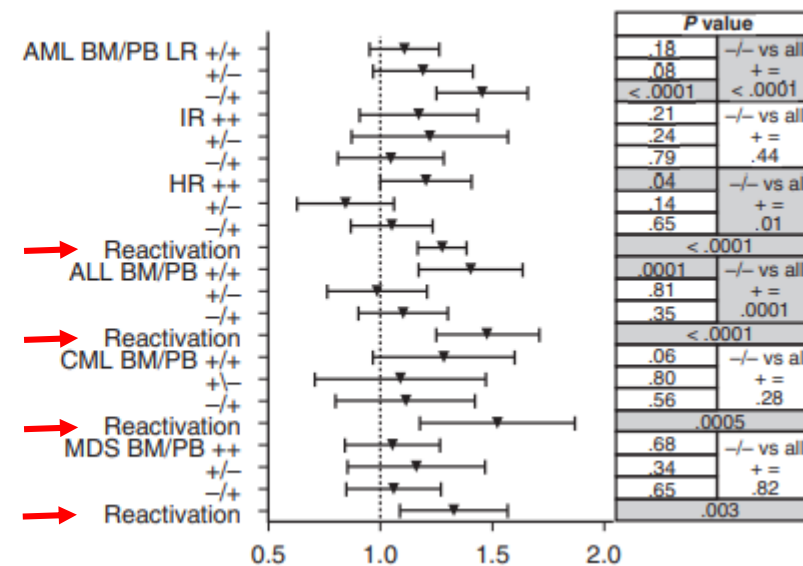
Non relapse mortality (NRM)



E Disease free survival (DFS)



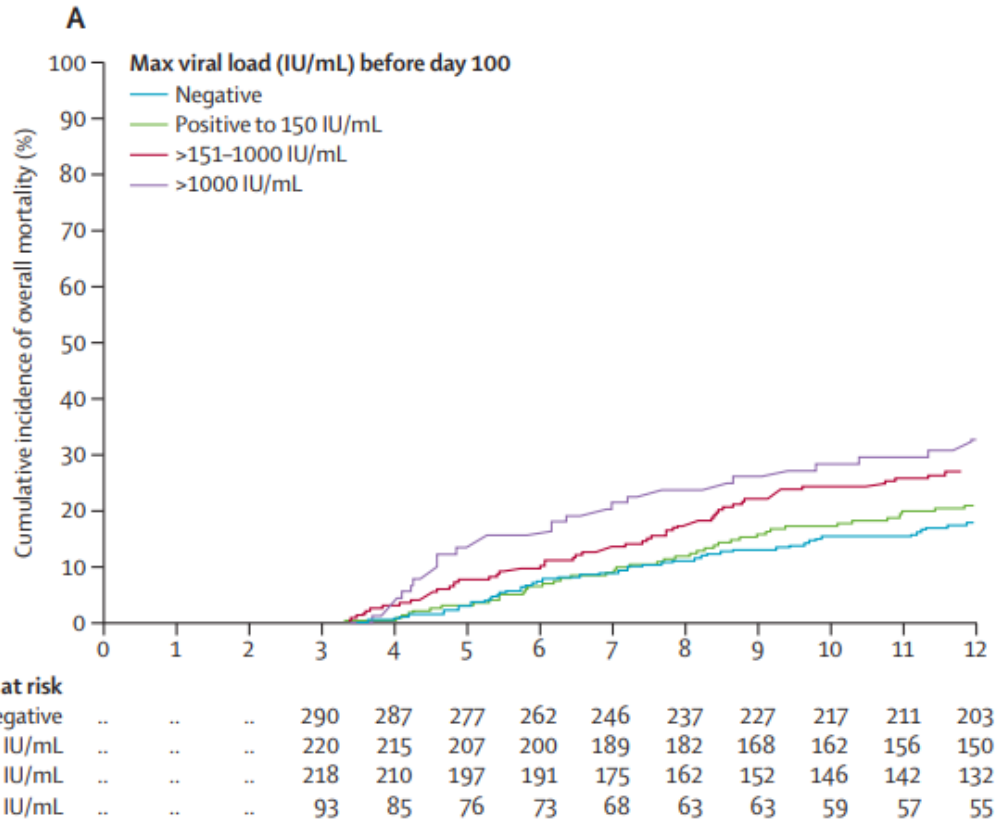
F Overall survival



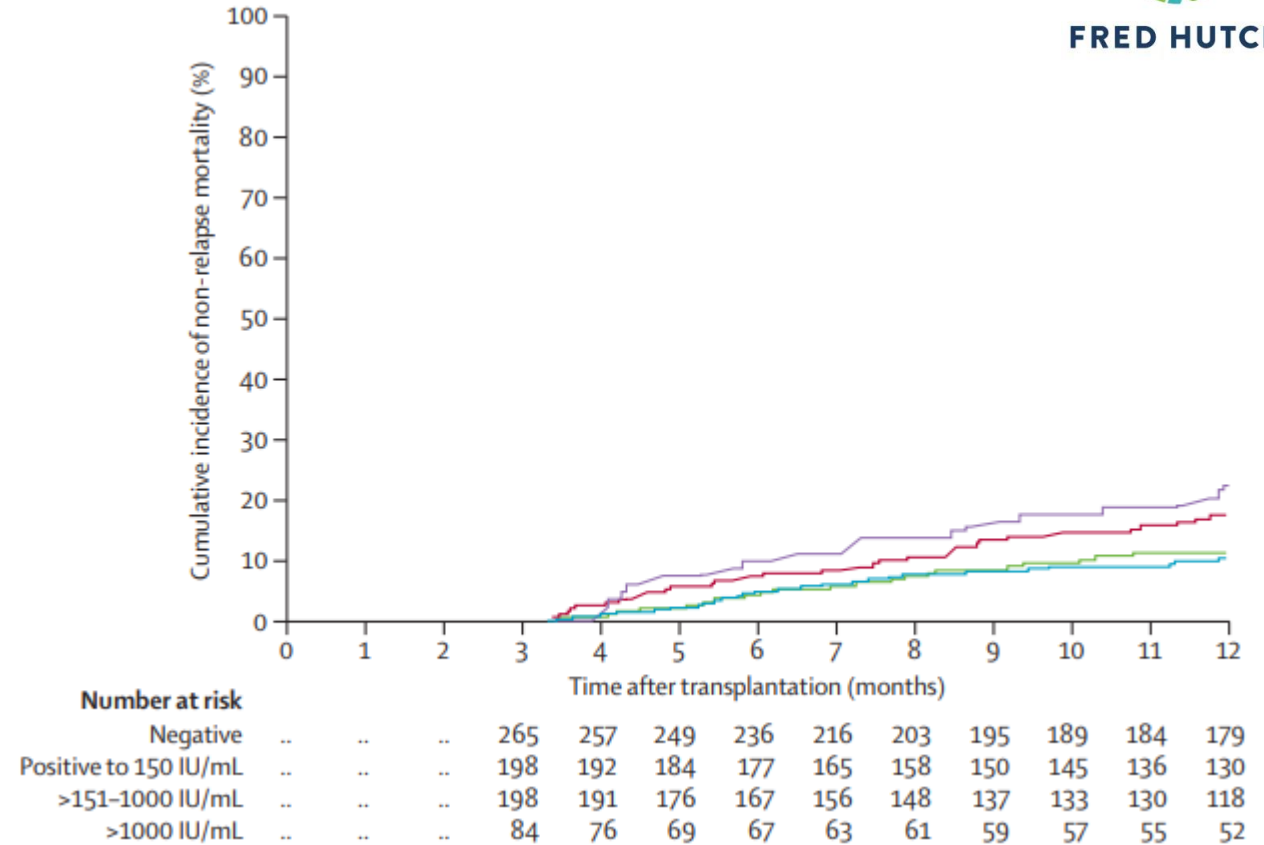
9469 SCT patients, 2003-2010

L'impact du CMV: HSCT

Mortalité globale

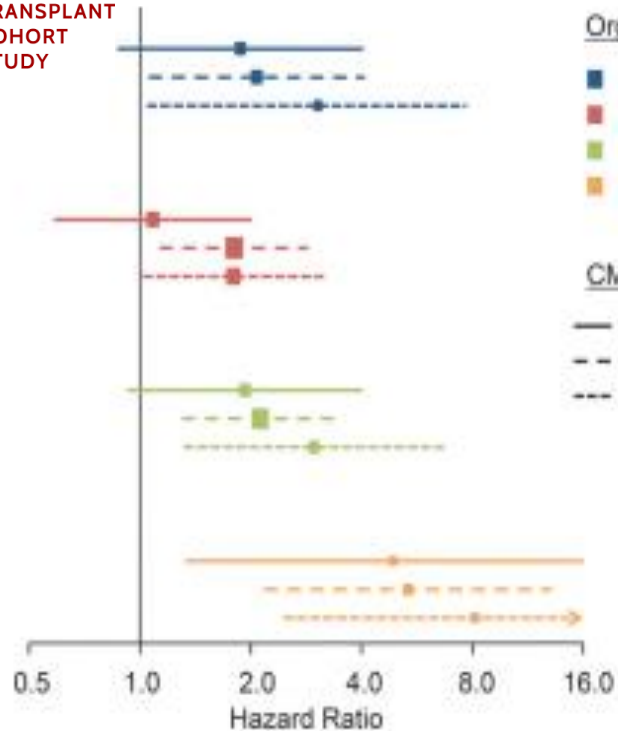


Mortalité non liée à la rechute



FRED HUTCH™

L'impact du CMV: transplantation d'organe



N=1414
Rejet dans les 30 j
après réplcation CMV

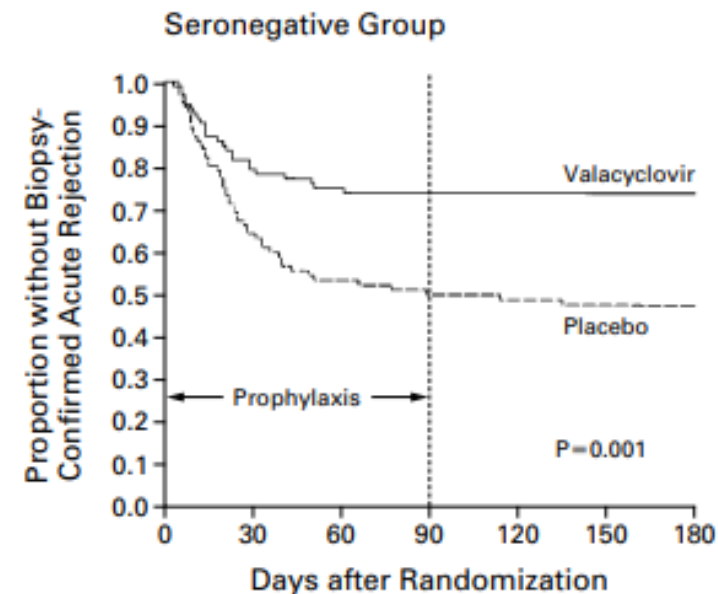
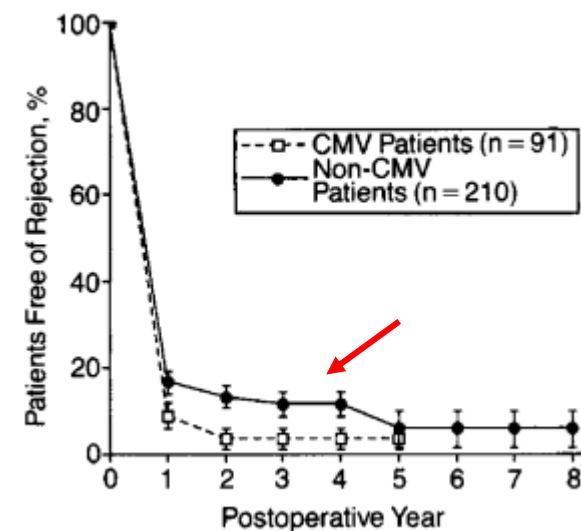
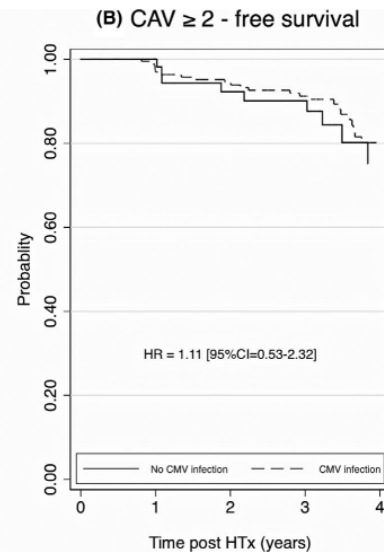
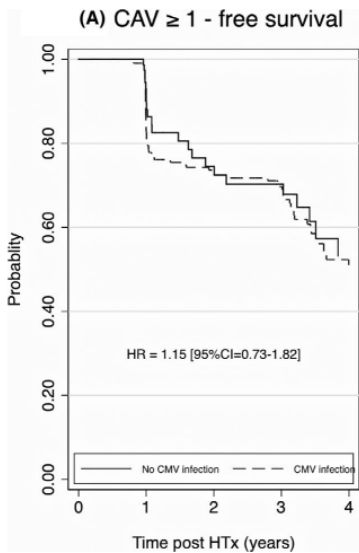
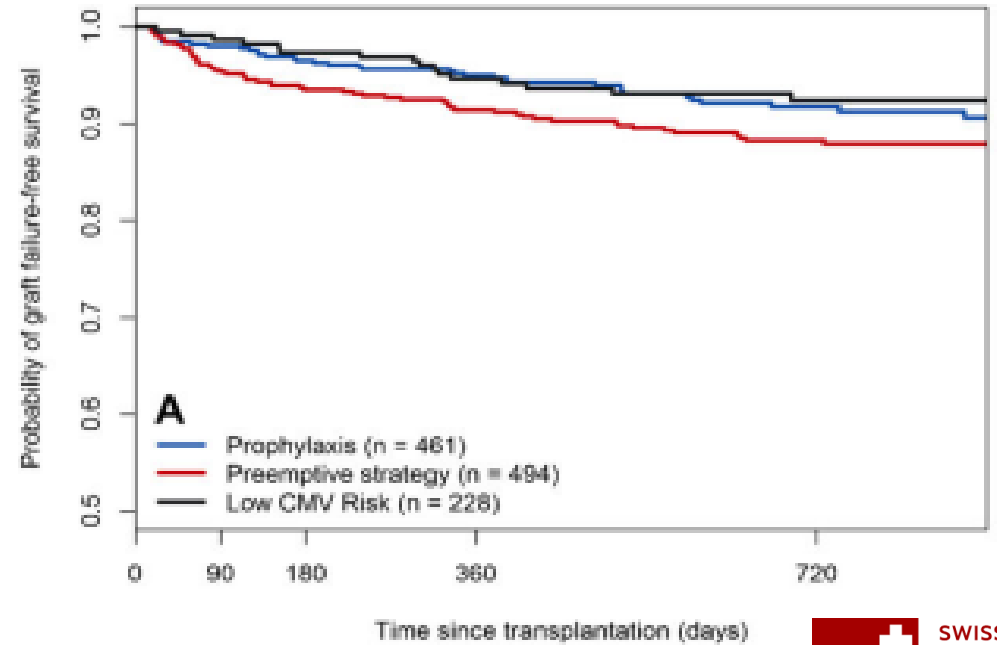
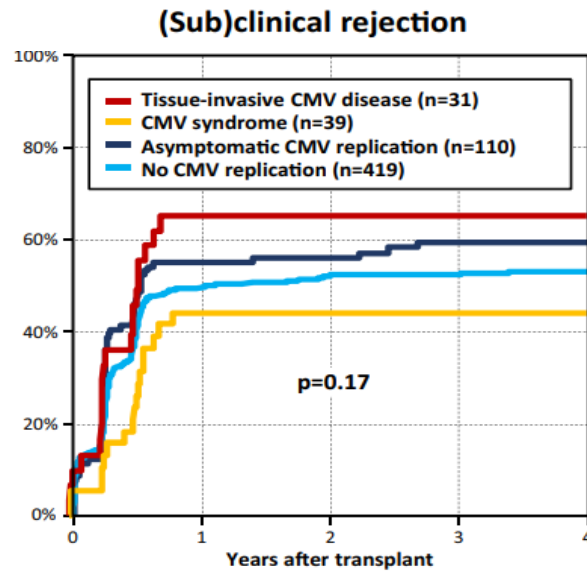
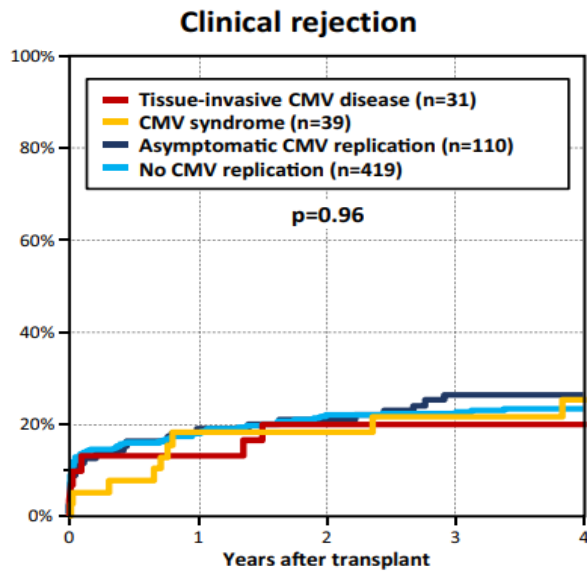


Table 3. Multivariate Model of Risk Factors for Biopsy-Proven Rejection

Factor	RR	95% CI	P Value
Donor age*	1.20	1.06-1.36	0.004
Recipient age*	0.78	0.63-0.96	0.02
Bacteremia†	3.57	1.39-9.36	<0.008
Initial immunosuppression cyclosporine Versus tacrolimus	1.98	1.27-3.09	0.002
Three months ganciclovir prophylaxis group	0.51	0.33-0.79	0.003



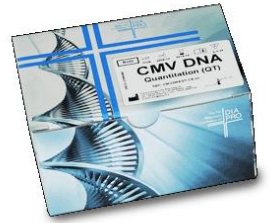
L'impact du CMV: transplantation d'organe: not so sure...



Lack of Association Between β -herpesvirus Infection and Bronchiolitis Obliterans Syndrome in Lung Transplant Recipients in the Era of Antiviral Prophylaxis

Oriol Manuel,¹ Deepali Kumar,¹ George Moussa,² Maggie H. Chen,³ Joseph Pilewski,⁴ Kenneth R. McCurry,⁵ Sean M. Studer,⁴ Maria Crespo,⁴ Shahid Husain,^{6,7} and Atul Humar^{1,7}

Le diagnostic biologique



Détection virémie: qPCR (Ag pp65)

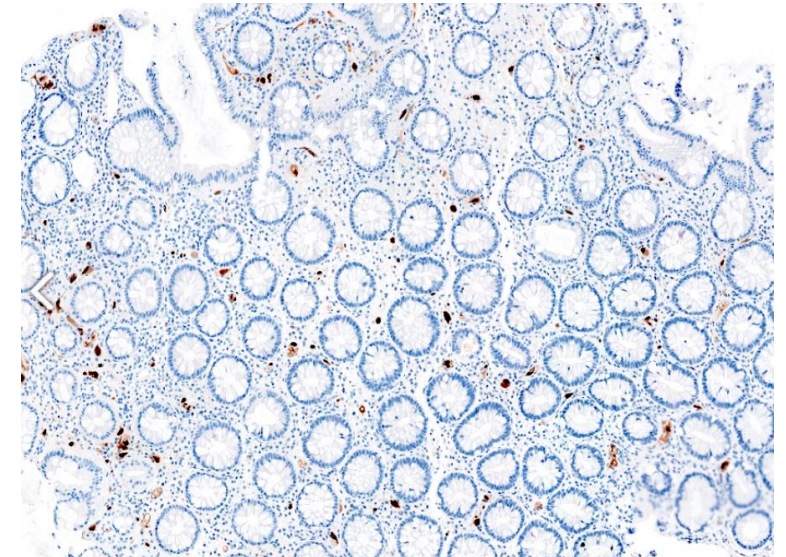
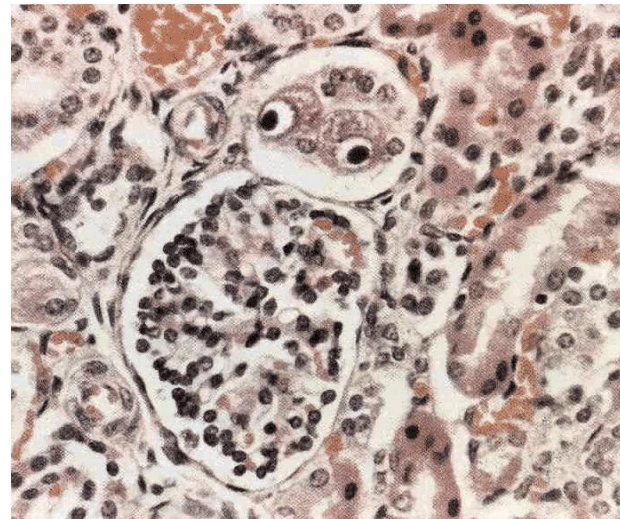
PCR: variabilité inter technique et inter échantillon: maintenir la même technique

Avenir: dried blood spots?

Atteinte d'organe: histologie, PCR, IHC

La question du seuil est non résolue

NB: la virémie peut manquer (GI)



La virémie est un bon marqueur indirect

The Journal of Clinical Investigation

CLINICAL MEDICINE

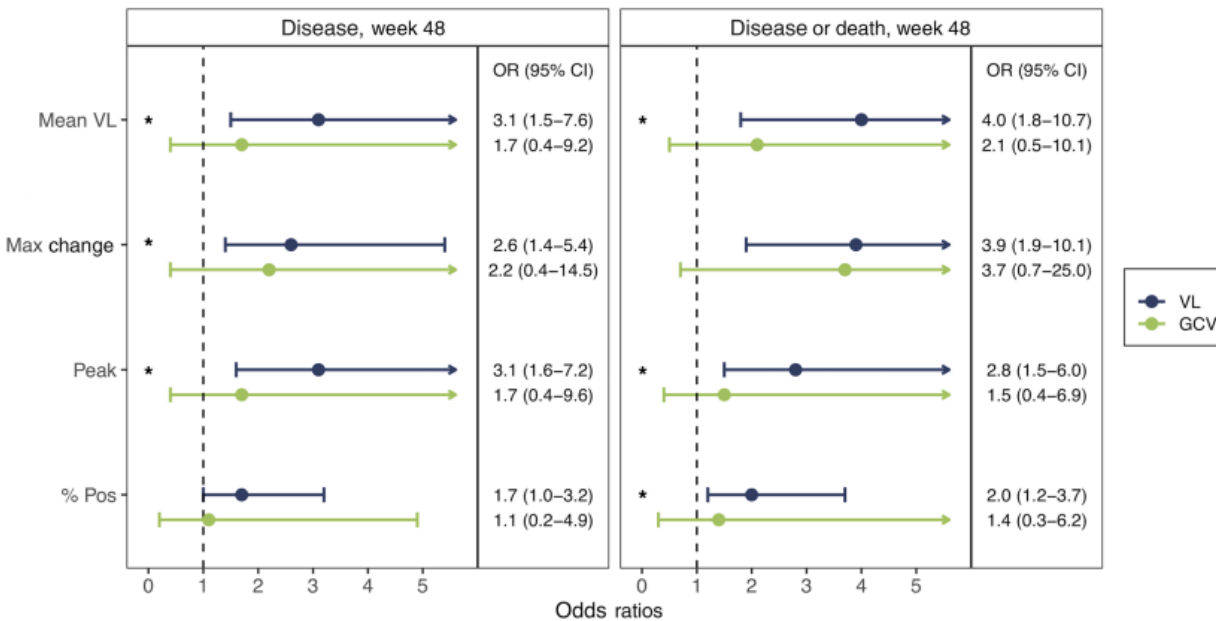
CMV viral load kinetics as surrogate endpoints after allogeneic transplantation

Elizabeth R. Duke,^{1,2} Brian D. Williamson,¹ Bhavesh Borate,¹ Jonathan L. Golob,^{1,2} Chiara Wychera,¹ Terry Stevens-Ayers,¹ Meei-Li Huang,² Nicole Cossrow,³ Hong Wan,³ T. Christopher Mast,³ Morgan A. Marks,³ Mary E. Flowers,^{1,2} Keith R. Jerome,^{1,2} Lawrence Corey,^{1,2} Peter B. Gilbert,^{1,2} Joshua T. Schiffer,^{1,2} and Michael Boeckh^{1,2}

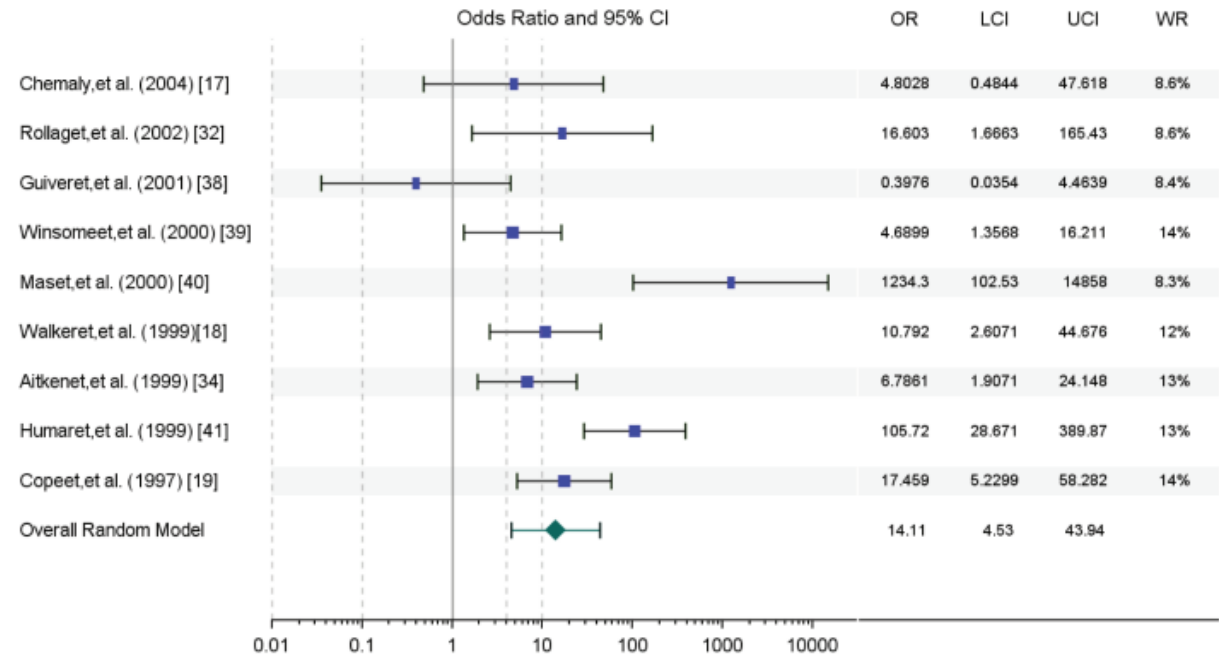
Clinical Infectious Diseases

Use of Viral Load as a Surrogate Marker in Clinical Studies of Cytomegalovirus in Solid Organ Transplantation: A Systematic Review and Meta-analysis

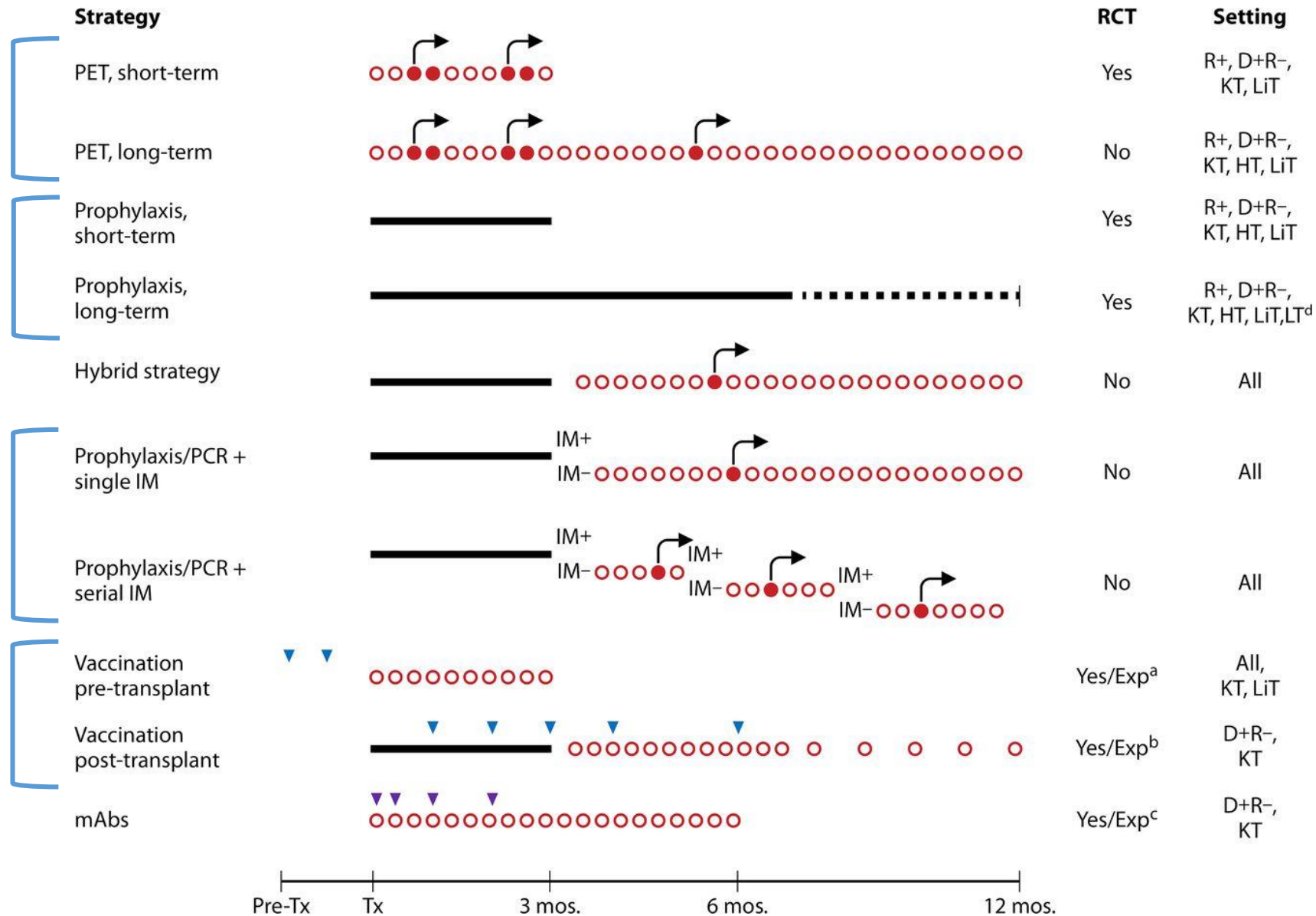
Yoichiro Natori,¹ Ali Alghamdi,^{1,2} Mahmood Tazari,¹ Veronica Miller,³ Shahid Husain,¹ Takashi Komatsu,⁴ Paul Griffiths,⁵ Per Ljungman,⁶ Ani Orchanian-Cheff,⁷ Deepali Kumar,^{1,8} and Atul Humar^{1,8}; for the CMV Consensus Forum^b



Relationship Between CMV Viral Load and Disease In Solid Organ Transplant Recipients by Study (NATURAL)



Stratégies thérapeutiques

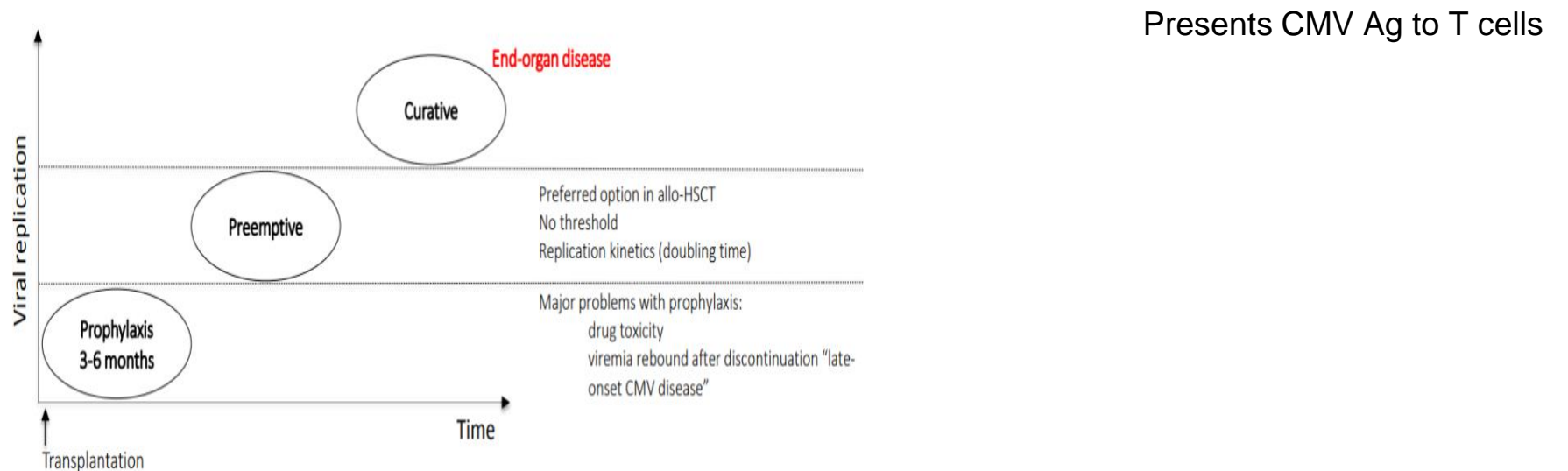


Les anti CMV

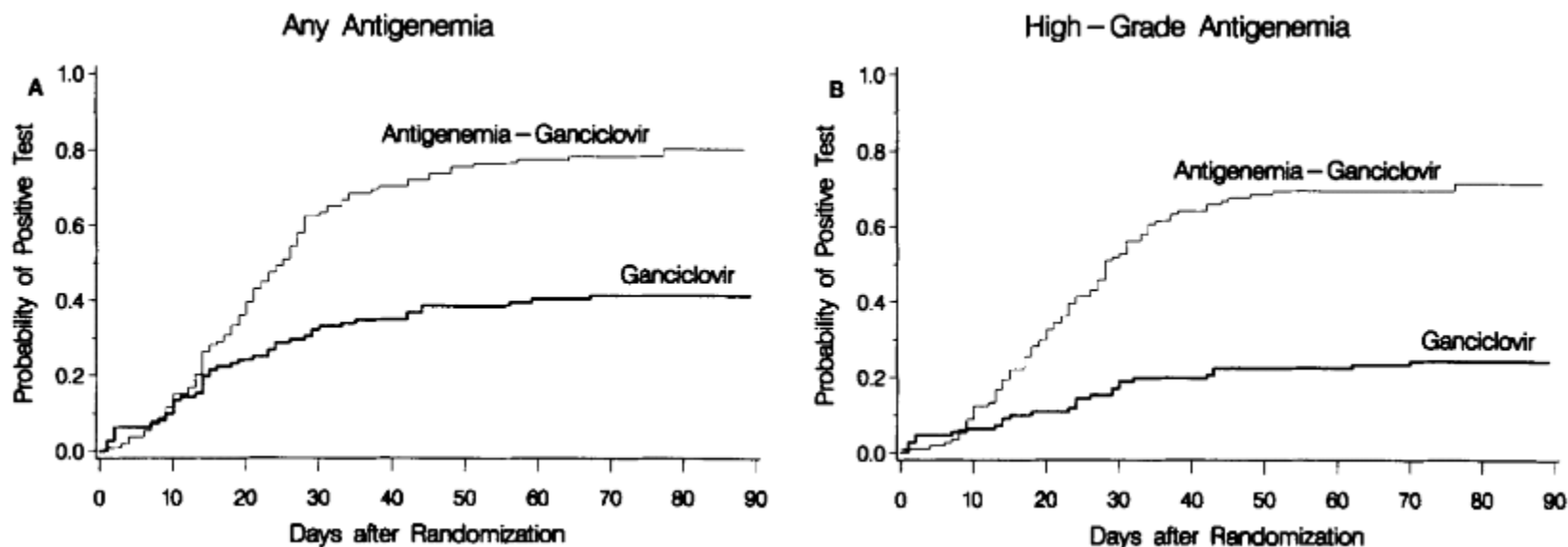
	Ganciclovir	Valganciclovir	Foscarnet	Cidofovir	Letermovir	Maribavir
<i>Voie</i>	IV	PO	IV	IV	IV/PO	IV/PO
<i>Posologie curative</i>	5 mg/kg/12h	900 mg/12h	180 mg/kg/j	5 mg/kg/sem	480 mg/j Ciclo: 240	400 mg/12h
<i>Posologie prophylaxie</i>	5 mg/kg/j	900 mg/j			480 mg/j Ciclo: 240	
<i>Adaptation fonction rénale</i>	Oui	Oui	Oui	Oui	Non	Non
<i>Adaptation obésité</i>	Plutôt non	?	IBW? AdjIBW?	?	?	?
<i>Toxicités</i>	Cytopénies	Cytopénies	Tubulopathie Veinite Muqueuse	Tubulopathie		Dysgueusie

Stratégies thérapeutiques

	Prophylaxis	Preemptive 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



Prophylaxie vs préemptif: HSCT

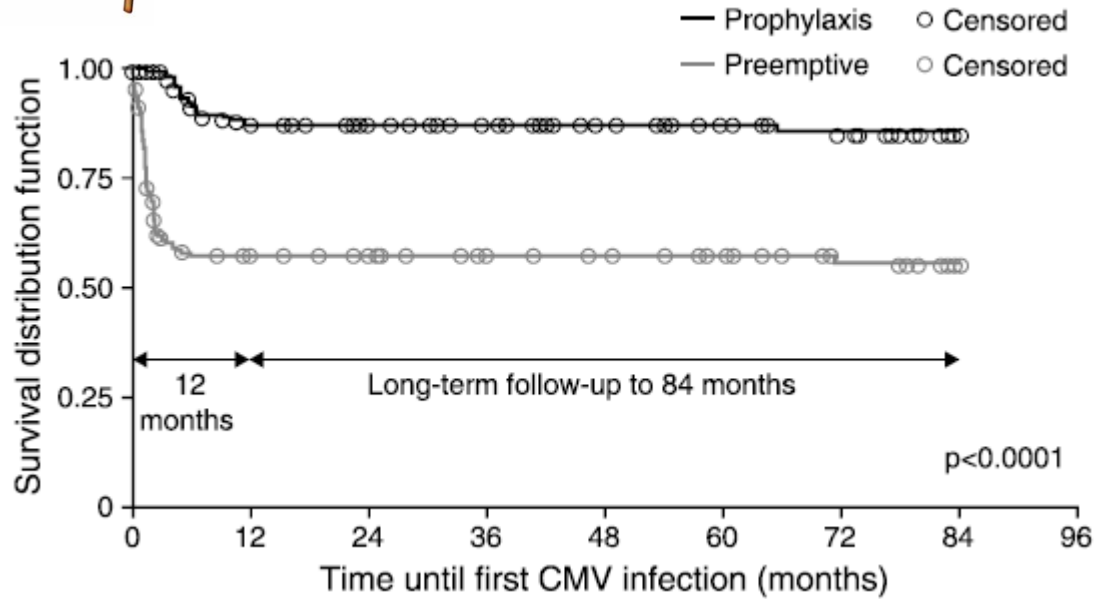


ganciclovir was neutropenia. Neutropenia requiring interruption of study drug (usually a fall in the neutrophil count to less than $1.0 \times 10^9/L$) occurred in 13 of 47 placebo patients (28%) receiving post-transplant study drug and in 25 of 43 ganciclovir patients (58%) receiving post-transplant study drug (CI, -50% to -11%; $P = 0.005$).

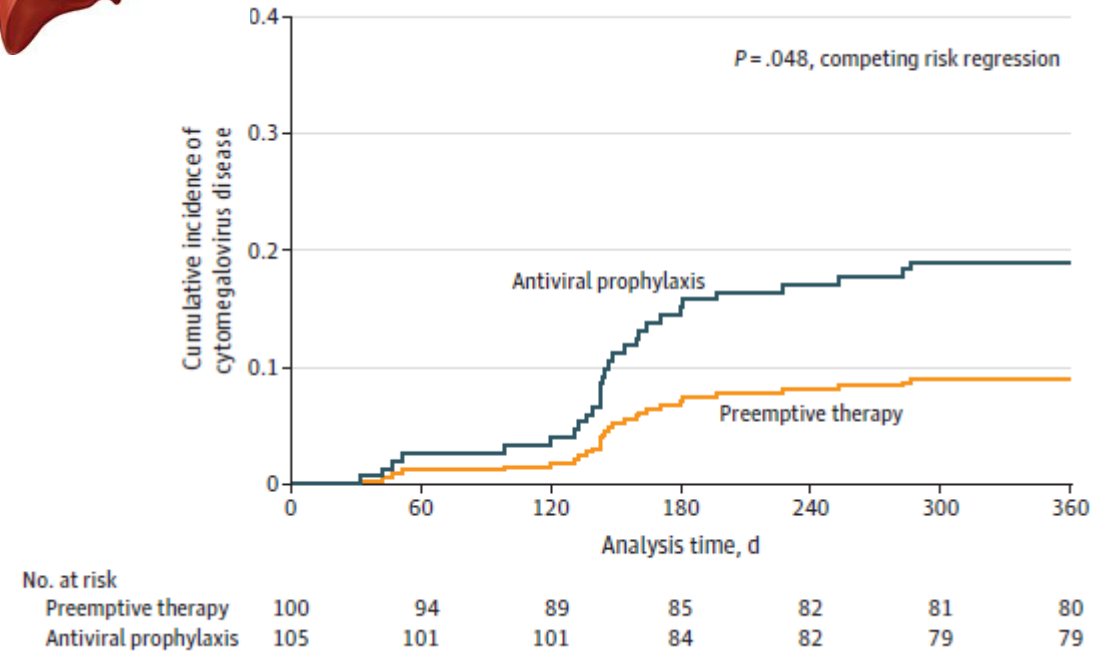
ASC + imp VGCV

Hématotoxicité du GCV/V-GCV  préemptif favorisé

Prophylaxie vs préemptif: SOT



N=299, R+, V-GCV 100 j vs préemptif V-GCV puis prophylaxie II^{aire}



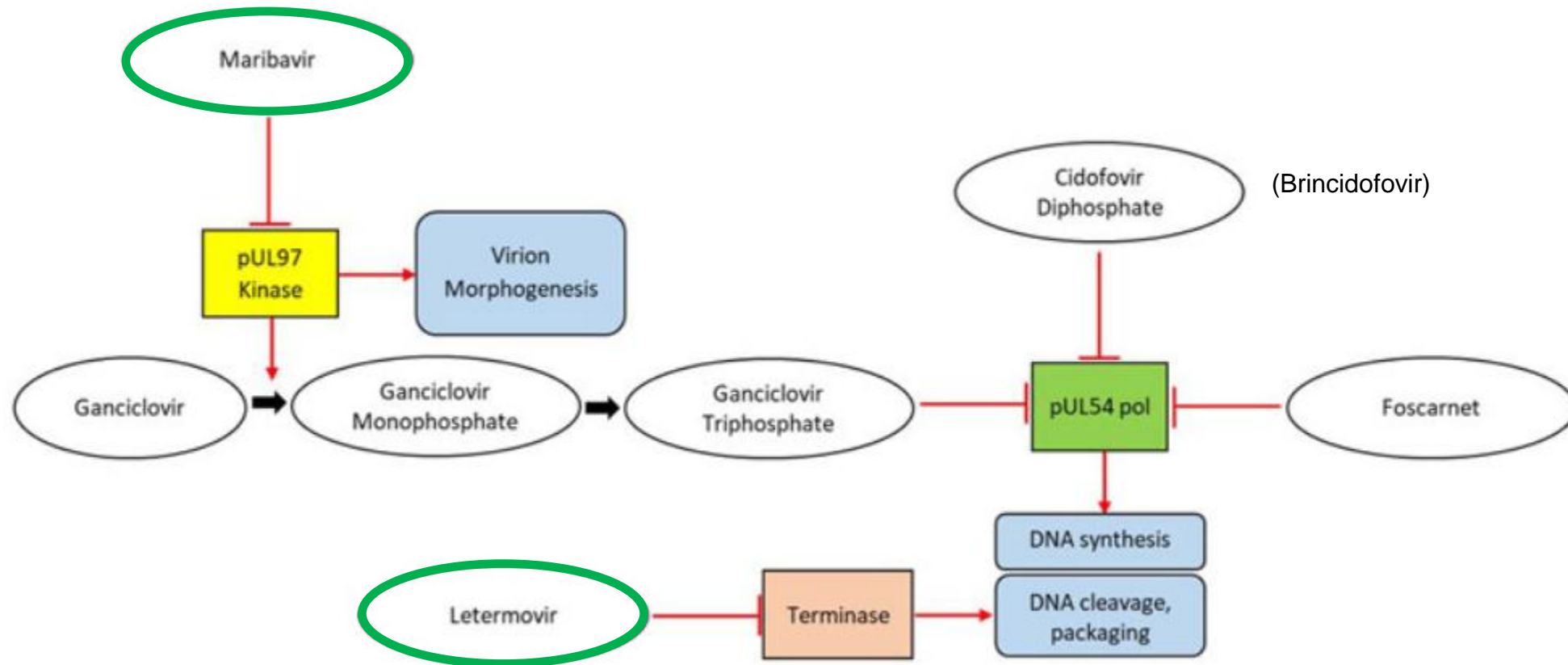
N=205, D+/R-, V-GCV 100 j vs préemptif V-GCV



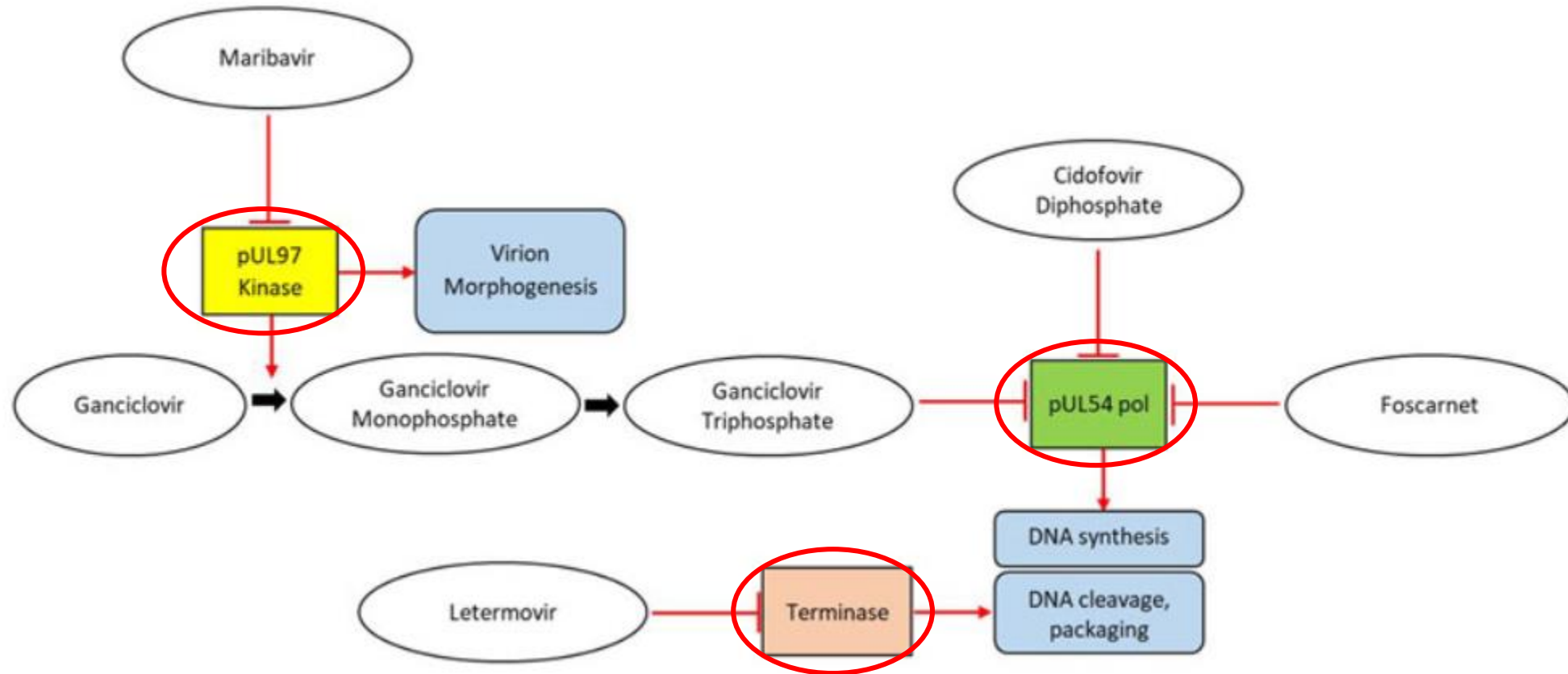
Pas de franc consensus chez SOT

Molécules disponibles

Deux problèmes persistent: toxicité et résistance



Résistance du CMV



Infections CMV réfractaires/résistantes

Infection **réfractaire**: non-décroissance de la CV ou échec clinique.

Résistance virologique: présence de mutations conférant résistance phénotypique

Amplitude du problème: 1% SOT (4,1% si D+/R-), 0 à 8% HSCT

France: 10% des référés au CNR réfractaires; R génotypique 49% des réfractaires

Facteurs De Risque:

D+/R- (SOT), D-/R+ (HSCT)

Poumon vs autres (SOT)

SAL, T déplétion, haplo, CBT, GVHd (HSCT)

Intensité de l'immunosuppression

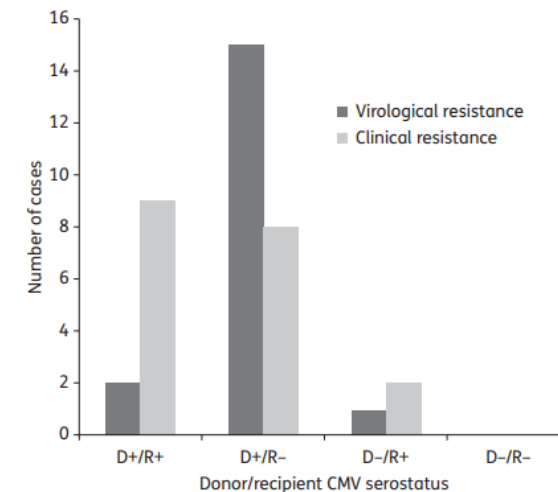
Exposition prolongée et sous dosage en antiviraux

Pic de charge virale

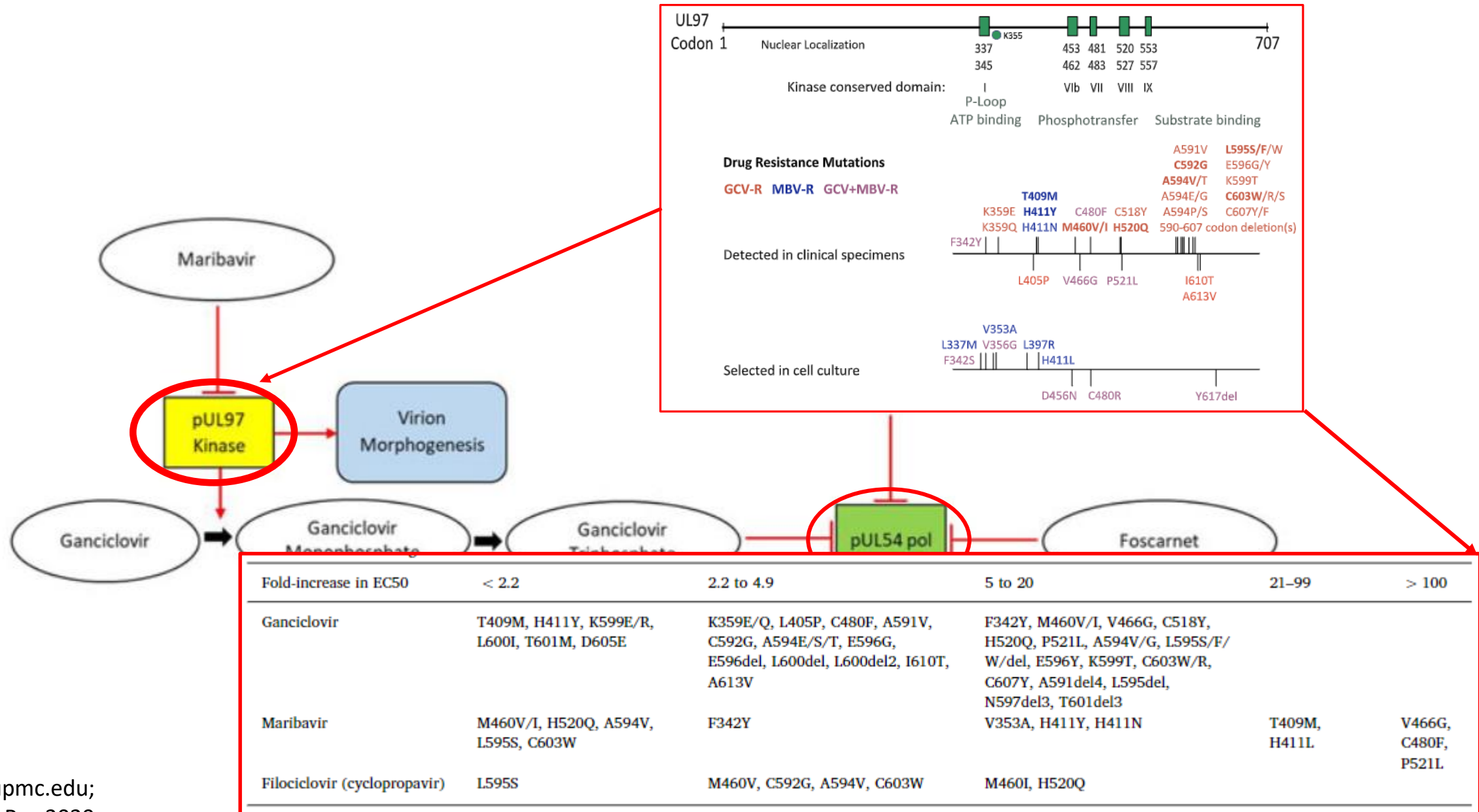
Effet délétère sur la survie

« Sanctuaires » possibles

Détection: séquençage des sites cibles

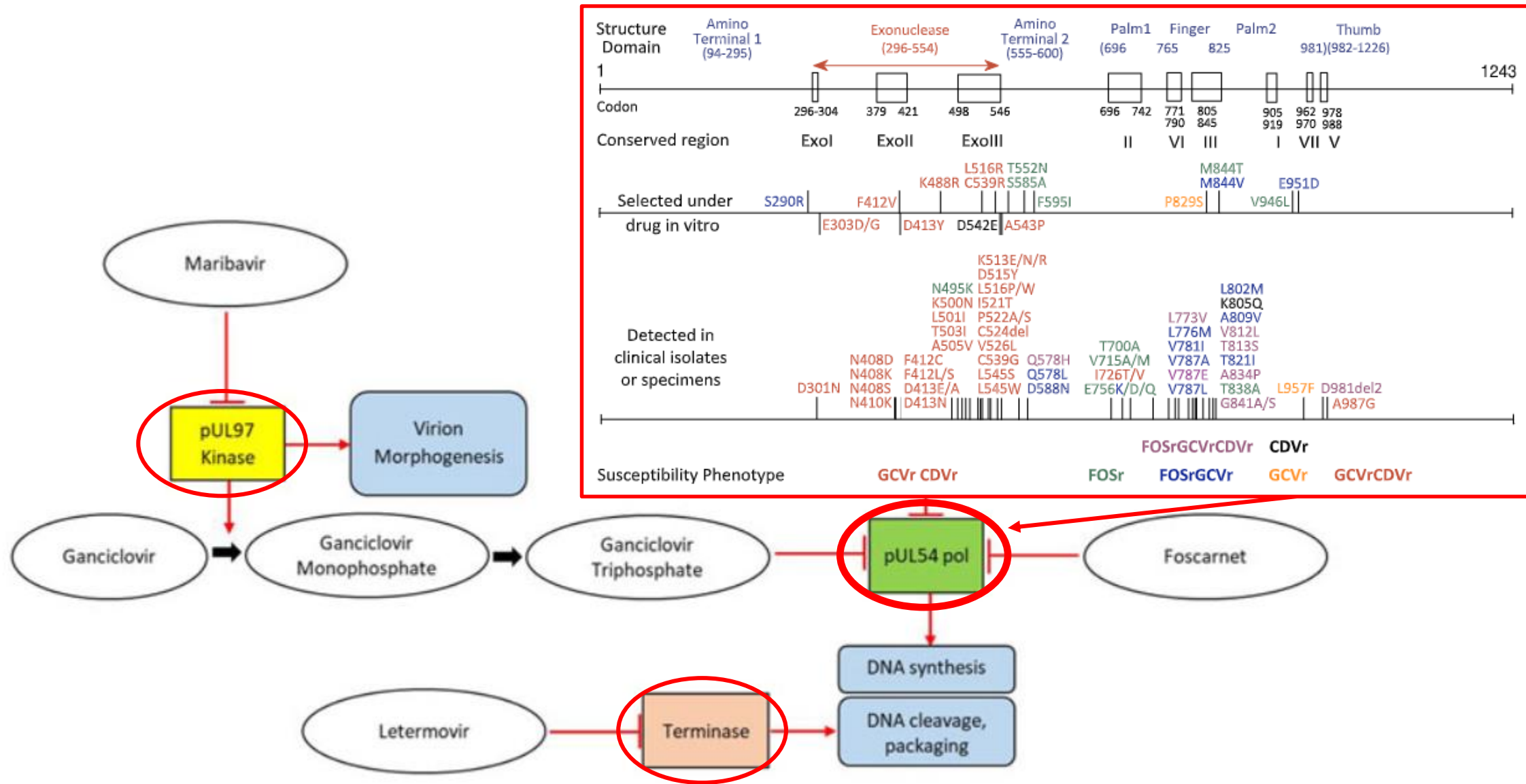


Résistance du CMV

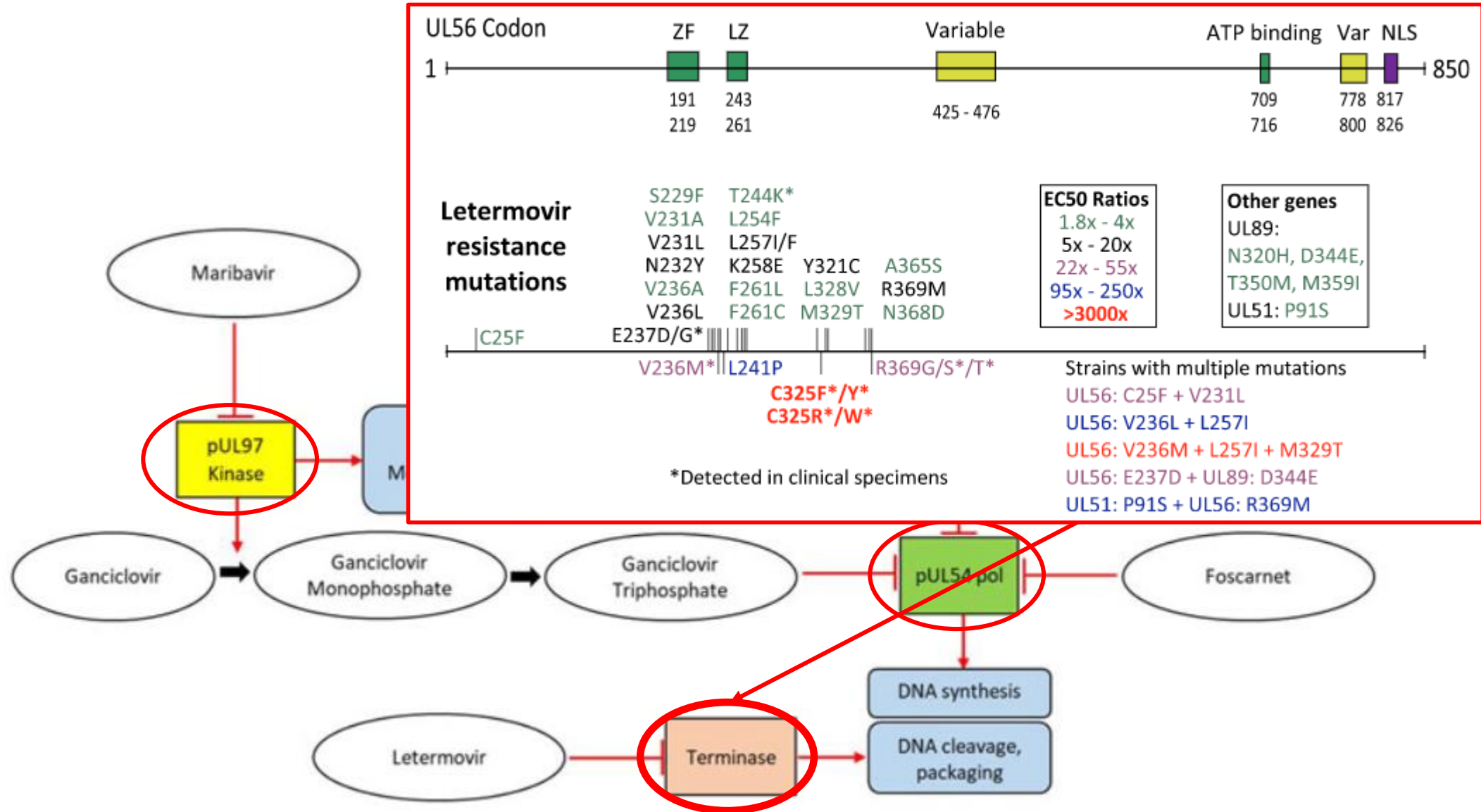


	Fold-increase in EC50	< 2.2	2.2 to 4.9	5 to 20	21-99	> 100
Ganciclovir		T409M, H411Y, K599E/R, L600I, T601M, D605E	K359E/Q, L405P, C480F, A591V, C592G, A594E/S/T, E596G, E596del, L600del, L600del2, I610T, A613V	F342Y, M460V/I, V466G, C518Y, H520Q, P521L, A594V/G, L595S/F/W/del, E596Y, K599T, C603W/R,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

Résistance du CMV

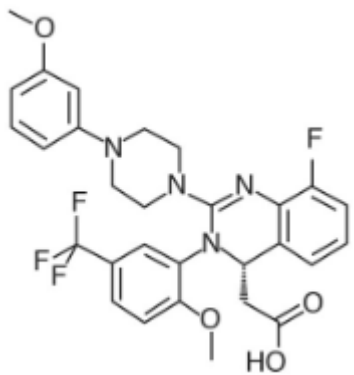


Résistance du CMV



Parfois:
UL89
UL51

Letermovir (MSD)



Oral et IV

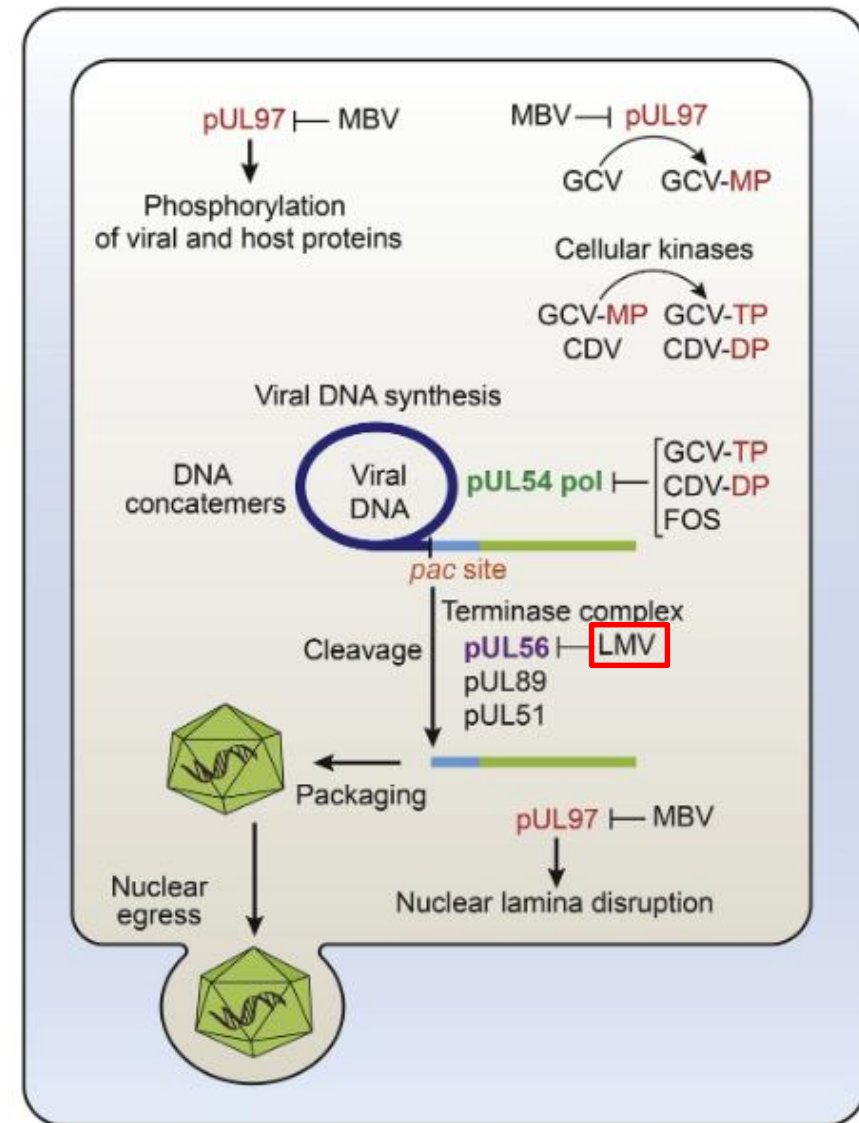
Biodisponibilité 35% sans cyclo (85% sujets sains)

Peu toxique (tr digestifs)

Interactions: **cyclosporine**, VCZ, tacrolimus

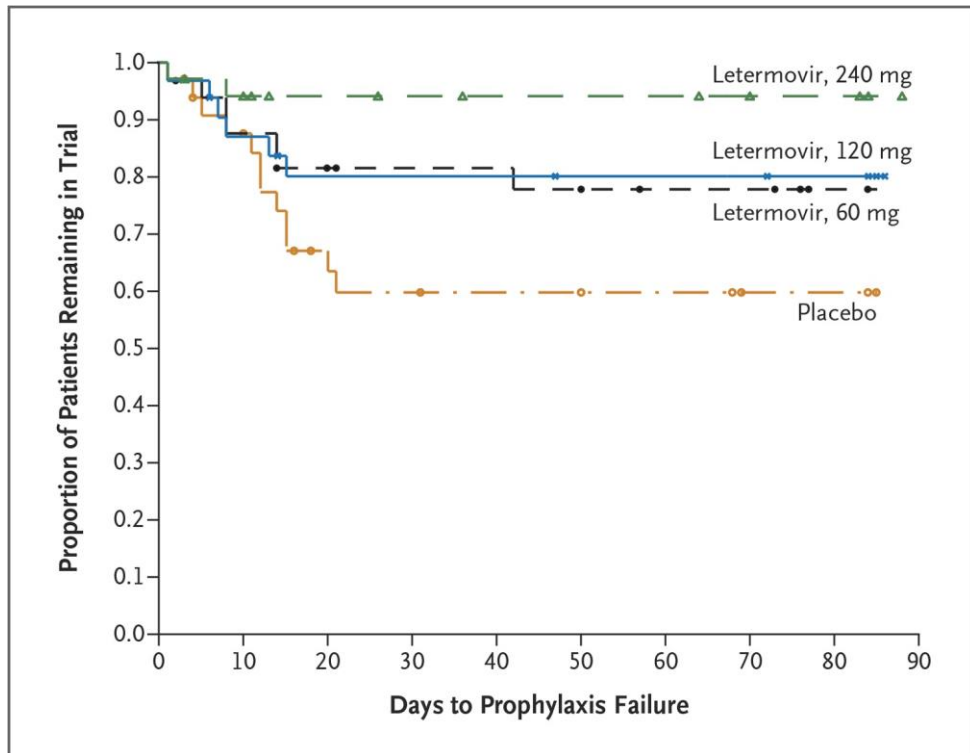
Inactif sur autres Herpesviridae

Site d'action tardif: attention à l'interprétation de certaines CV



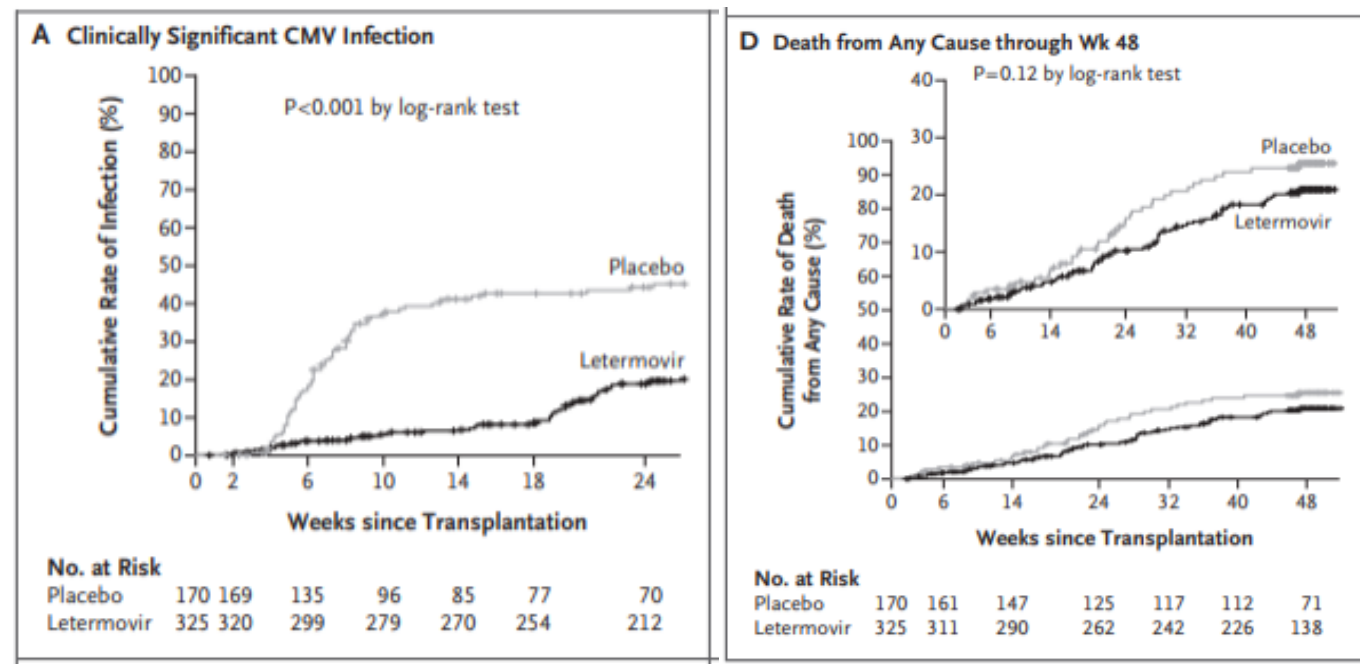
Letermovir en prophylaxie: HSCT

Phase II



131 alloHSCT, R+, letermovir 3 mois

Phase III



570 alloHSCT, letermovir 14 semaines

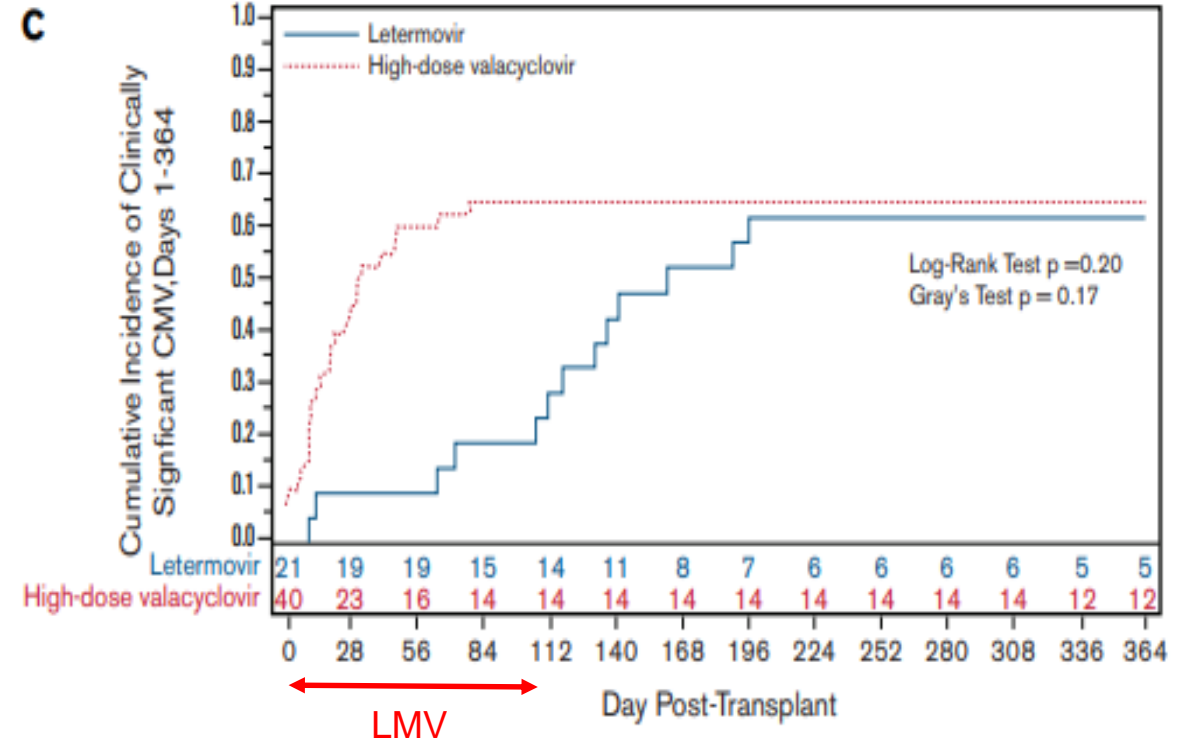
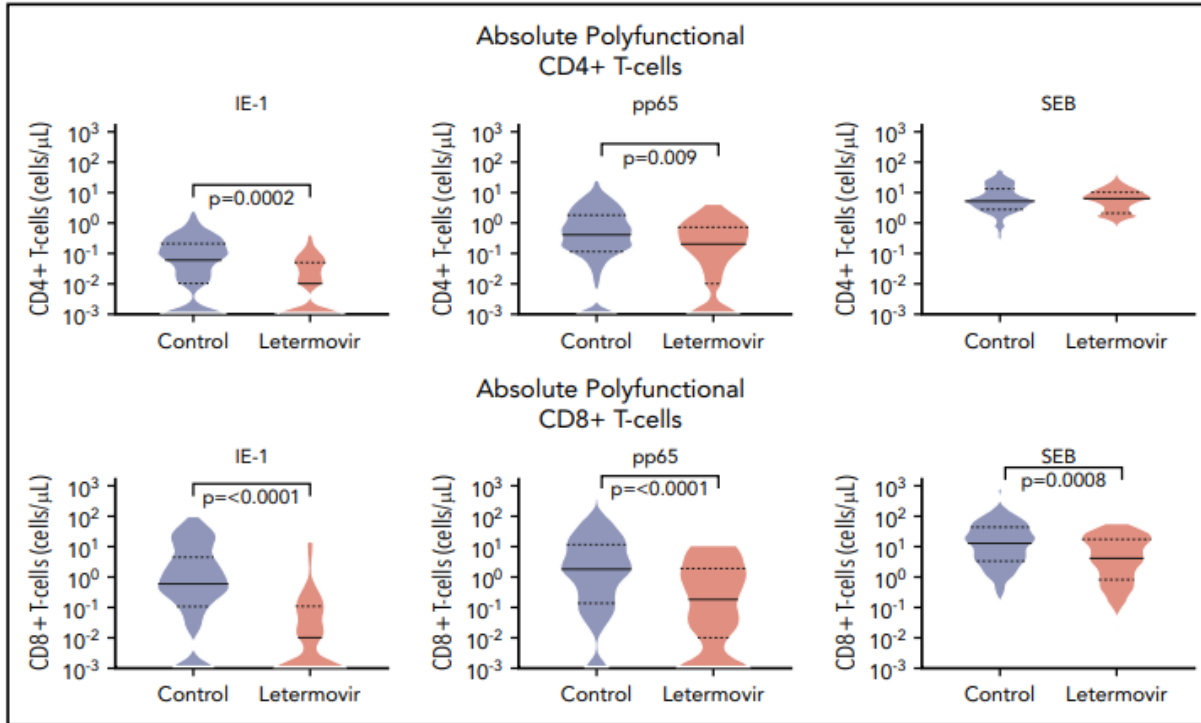
Letermovir prophylactique: les problèmes

FDR d'échec de prophylaxie: CV positive à l'initiation et aGVHd

Royston L *et al.* Immun Inflamm Dis 2021

Retarde l'apparition de l'immunité anti CMV à M3?

En allogreffe de cordon, transitoirement efficace



Letermovir en curatif (rescue) chez SOT

Auteur	Journal	Année	Population	N	Situation	Résultat
Jorgenson M	Transpl Infect Dis	2021	Tx rein	8	Infections R/R	Inefficace
Linder K	Transpl Infect Dis	2021	SOT/HSCT	48	R/R/I	Efficace si CV < 1000
Veit T	Am J Transplant	2021	Tx pulmonaire	28	R/R/I	82% réponse
Phoompoung P	Transplantation	2020	SOT/HSCT	6	R/R	66% réponse
Veit T	Transplantation	2020	Tx pulmonaire	4	R/R/I	100% réponse
Aryal S	Transpl Infect Dis	2019	Tx thoracique	2	R	50% réponse
Turner N	AAC	2019	Tx thoracique	4	Résistant	Réponse clinique mais rebond de CV

➔ La barrière génétique semble faible
Résistances: UL56 > UL89
Rôle du sous dosage? Alain S *et al.* JAC 2020

Prudence pour l'instant

Peut être pas en monothérapie...PHRC LUCY (Necker)

Letermovir en prophylaxie secondaire

SOT

Type of transplant	Age	Sex	CMV status	Immunosuppression (at time of letermovir initiation)	Ganciclovir resistance	Reason for (val)ganciclovir discontinuation	Outcome
Single lung transplant	69	M	D+/R-	Tacrolimus, prednisone	No	Leucopenia	Successful
Bilateral lung transplant	60	M	D+/R+	Cyclosporine, prednisone	No	Leucopenia	Successful
Single lung transplant	68	F	D+/R-	Tacrolimus, prednisone, mycophenolate mofetil	No	Leucopenia	Successful
Bilateral lung transplant	59	F	D+/R-	Tacrolimus, prednisone	No	Leucopenia	Failure
Bilateral lung transplant	63	F	D+/R-	Tacrolimus, prednisone	No	Leucopenia	Failure
Single lung transplant	67	F	D+/R-	Tacrolimus, prednisone	Yes (UL97, not specified)	Resistance	Failure
Heart transplant	60	M	D+/R-	Tacrolimus, prednisone	Yes (UL97 C603W)	Resistance	Successful

Pourrait aider à installer l'immunité anti CMV...

Jorgenson M *et al.* TID 2022

Hofmann *et al.* Transpl Infect Dis 2021, Boignard A *et al.* Antivir Ther 2022

HSCT

Série **SFGM-TC**: 5,5% échec (n=80)

Médiane 3 mois

Tolérance acceptable

Robin C *et al.* BBMT 2020

Série **EBMT**: 10,1% échec (n=49)

Médiane 3 mois

Styczynski J BMT 2021

Série **MSKCC**: aucun échec (n=14)

Lin A *et al.* Transpl Infect Dis 2019

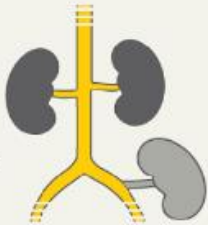
Letermovir en prophylactique chez SOT

QUESTION Is letermovir noninferior to valganciclovir prophylaxis for cytomegalovirus (CMV) disease prevention in high-risk adult CMV-seronegative kidney transplant recipients who receive an organ from a CMV-seropositive donor?

CONCLUSION Letermovir was noninferior to valganciclovir for prophylaxis of CMV disease over 52 weeks among adult CMV-seronegative recipients who received an organ from a CMV-seropositive donor.

POPULATION

422 Men
167 Women



Adult CMV-seronegative kidney transplant recipients receiving an organ from a CMV-seropositive donor

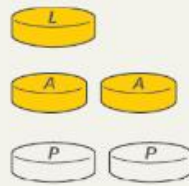
Mean age: 50 years

LOCATIONS

94
Hospitals
worldwide



INTERVENTION

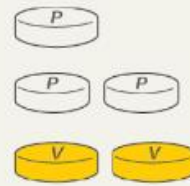


601 Patients randomized
586 Patients analyzed

301

Letermovir

480 mg of letermovir orally daily,
400 mg of acyclovir twice daily,
and a valganciclovir placebo



300

Valganciclovir

900 mg of valganciclovir orally daily with letermovir and acyclovir placebos

PRIMARY OUTCOME

CMV disease through 52 weeks after transplant

FINDINGS

Patients with committee-confirmed CMV through week 52

Letermovir

10.4% (30 of 289 patients)

Valganciclovir

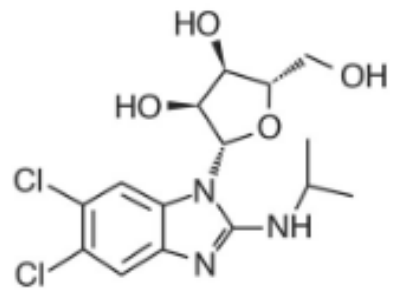
11.8% (35 of 297 patients)

Letermovir was noninferior to valganciclovir:

Stratum-adjusted difference, **-1.4%**
(95% CI, -6.5% to 3.8%)

© AMA

Maribavir (Takeda)



Oral et IV

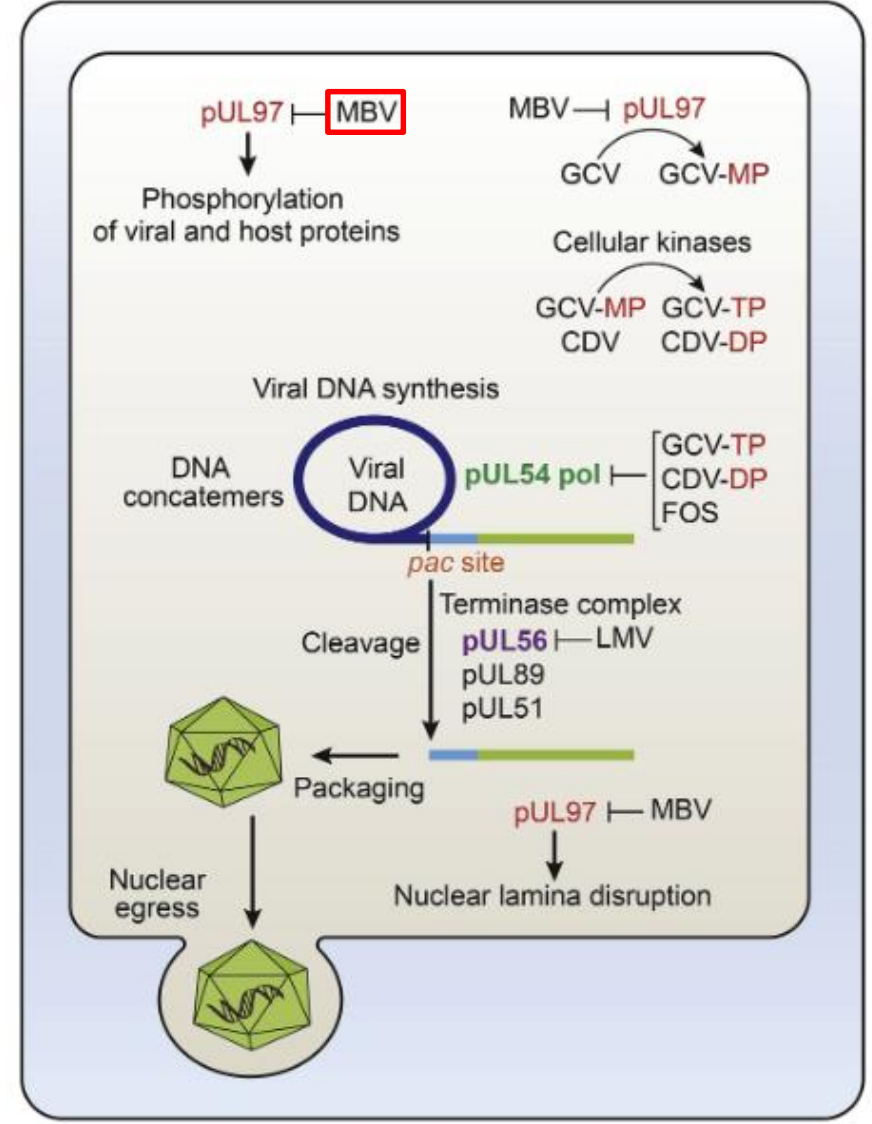
Biodisponibilité bonne (40%)

Peu toxique (dysgueusie) et non hématotoxique

Interactions: tacrolimus

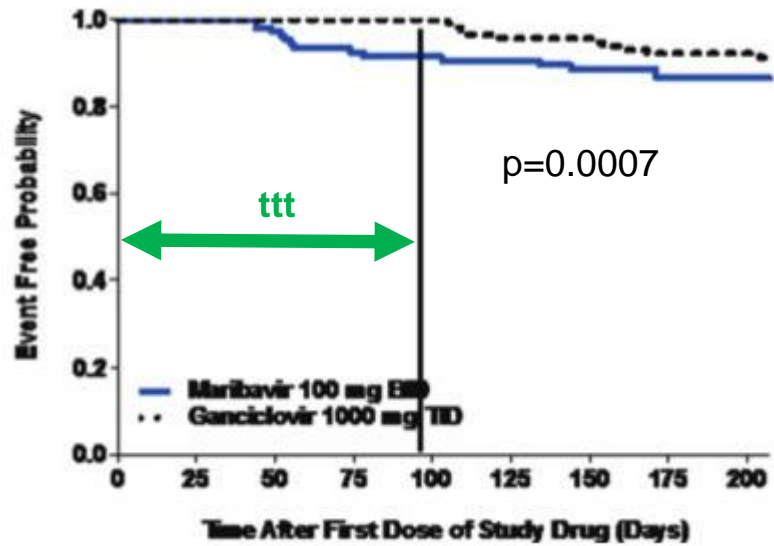
Ne passe pas la BHE

A ne pas associer au GCV

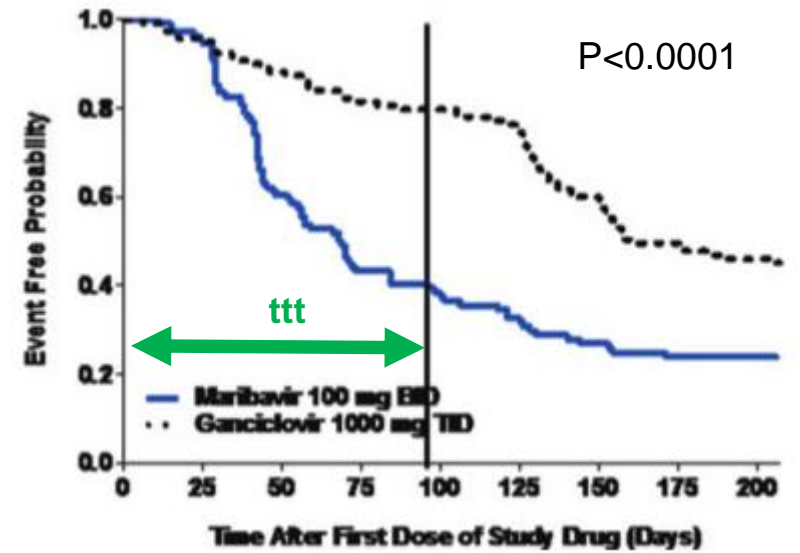


Maribavir en prophylaxie: SOT

N=303 Tx hépatiques D+/R-, maribavir 100 mg/12h vs GCV 1 g/8h durant 14 semaines



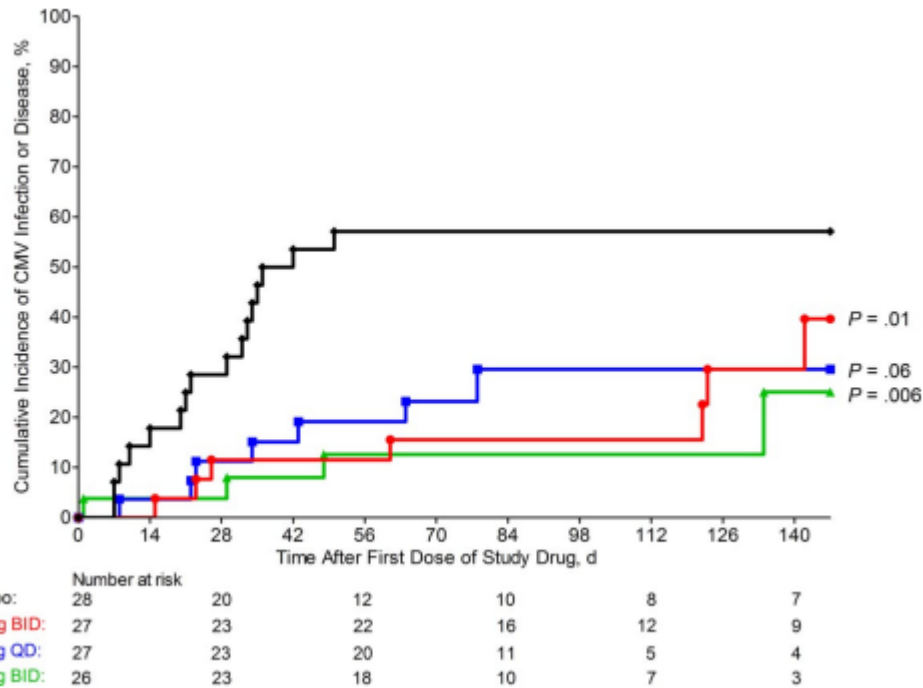
CMV infection



CMV disease

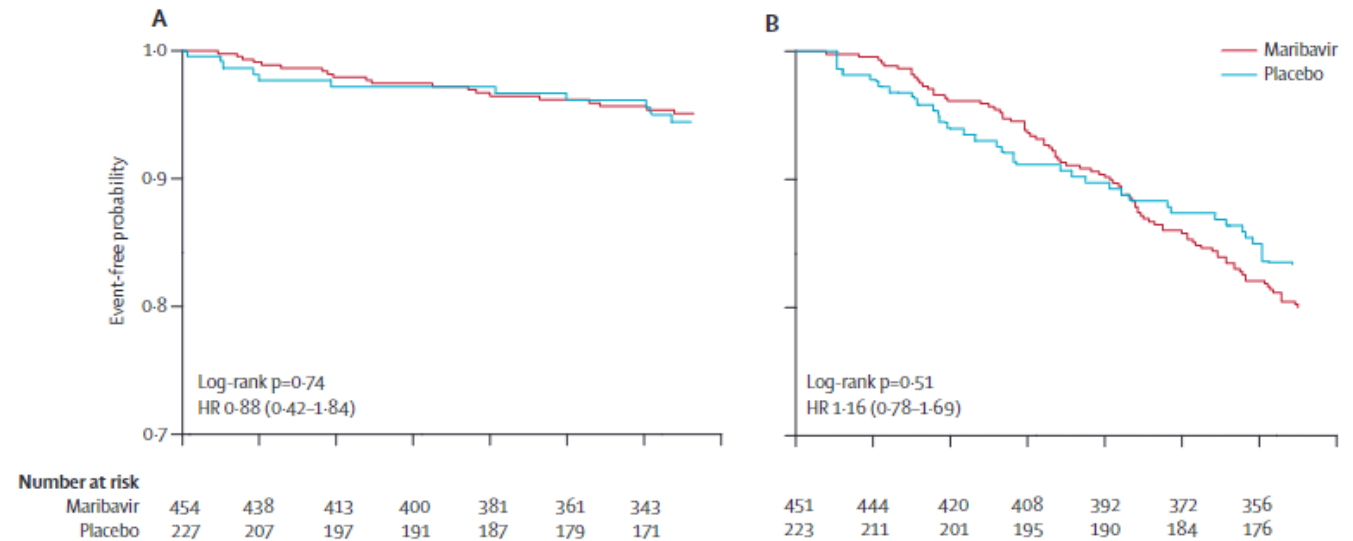
Maribavir en prophylaxie: HSCT

Phase II



111 alloHSCT, R+, maribavir 200 à 800 mg/j, 100 jours

Phase III



N=681, R+ et/ou D+, Maribavir 100 mg/12h, 3 mois



Pas de place à ce jour en prophylaxie

Maribavir en préemptif: SOT/HSCT

Table 1. Patient Demographic Characteristics (Intention-to-Treat Safety Population).*

Characteristic	Maribavir			Overall (N=119)	Valganciclovir (N=40)
	400 mg (N=40)	800 mg (N=40)	1200 mg (N=39)		
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

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Denominators for the calculation of percentages are the numbers of patients in the intention-to-treat safety population (i.e., all patients who underwent randomization and received at least one dose of trial drug) unless otherwise specified. CMV denotes cytomegalovirus, and IQR interquartile range.

† Race was reported by the patient.

‡ Denominator is the number of solid-organ transplants. Because patients may have had more than one solid-organ transplant, percentages may not total 100%.

§ Primary CMV infection was defined as the first known CMV infection since the date of the most recent transplantation.

Phase II

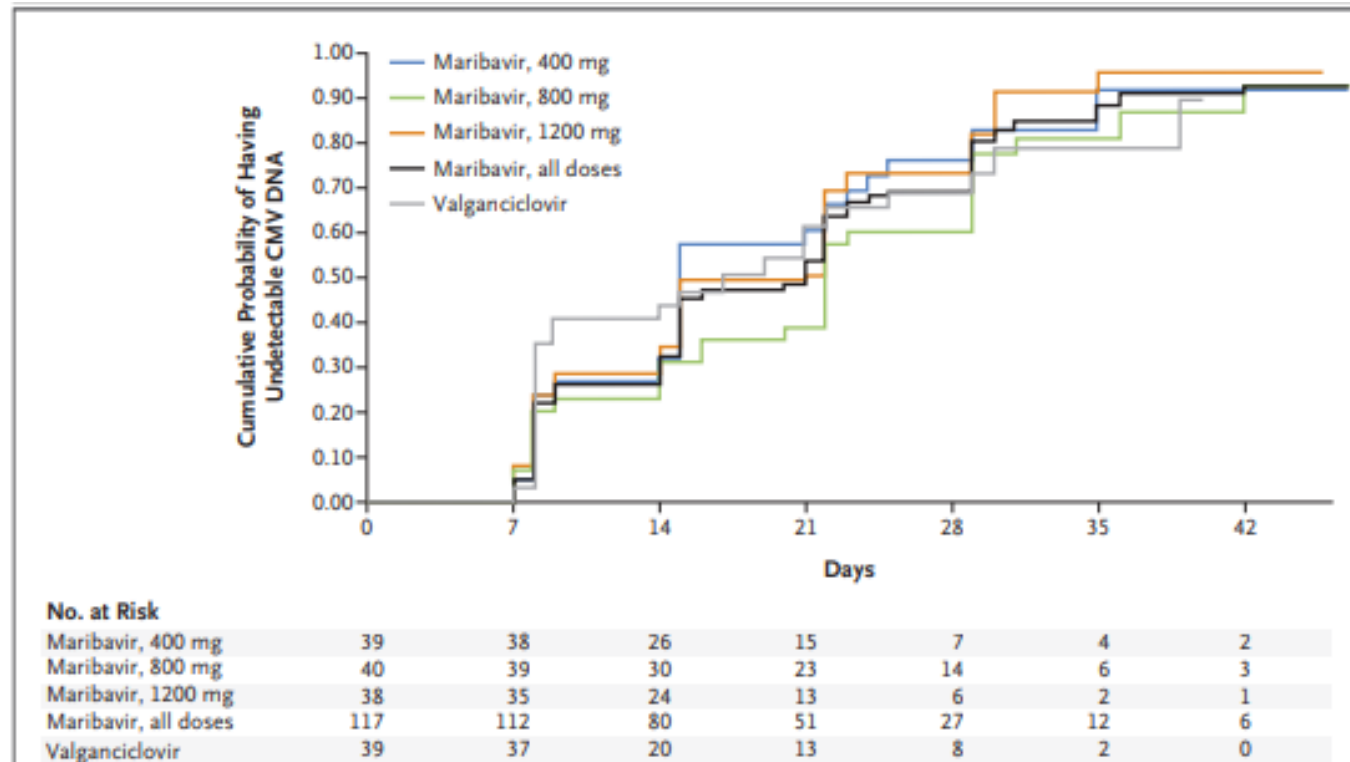


Figure 2. Time to Confirmed Undetectable CMV DNA in Plasma within 6 Weeks (Intention-to-Treat Safety Population with Postbaseline CMV DNA Measurements).

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.

Maribavir en sauvetage: SOT/HSCT

Response to maribavir (MBV) treatment for refractory cytomegalovirus (CMV) infection

Patient no./ transplant type	Baseline CMV DNA blood level (copies/mL)	Other CMV therapy within first 6 weeks of MBV	Days on MBV until CMV undetectable	Total days of MBV treatment	MBV PK: C_{min} ($\mu\text{g/mL}$)	Developed genotypic resistance to MBV
1/Kidney	58,500	LEF	–	228	0.35 (400 mg b.i.d.) 0.70 (800 mg b.i.d.)	No
2/Lung	50,947	CsA switched to sirolimus	6	186	4.9 (400 mg b.i.d.)	No
3/Lung	7200	Intravitreal FOS	41	147	3.4 (400 mg b.i.d.)	No
4/Heart	1,811,171	–	–	376	10.1 (400 mg b.i.d.)	Yes (UL97:T409M, H411Y)
5/Small intestine	18,203	IV FOS, CMVlg	20	227	2.2 (400 mg b.i.d.)	No
6/Stem cell	8283	CMVlg	10	15 ¹	15.3 (400 mg b.i.d.)	No

¹Patient died of progressive CMV pneumonitis and multiorgan failure.
MBV, maribavir; CMV, cytomegalovirus; PK, pharmacokinetics; C_{min} , minimum concentration of drug; LEF, leflunomide; b.i.d., twice per day; CsA, cyclosporine; FOS, foscarnet; IV, intravenous; CMVlg, cytomegalovirus immune globulin.

Réponse à 6 semaines: 4/6

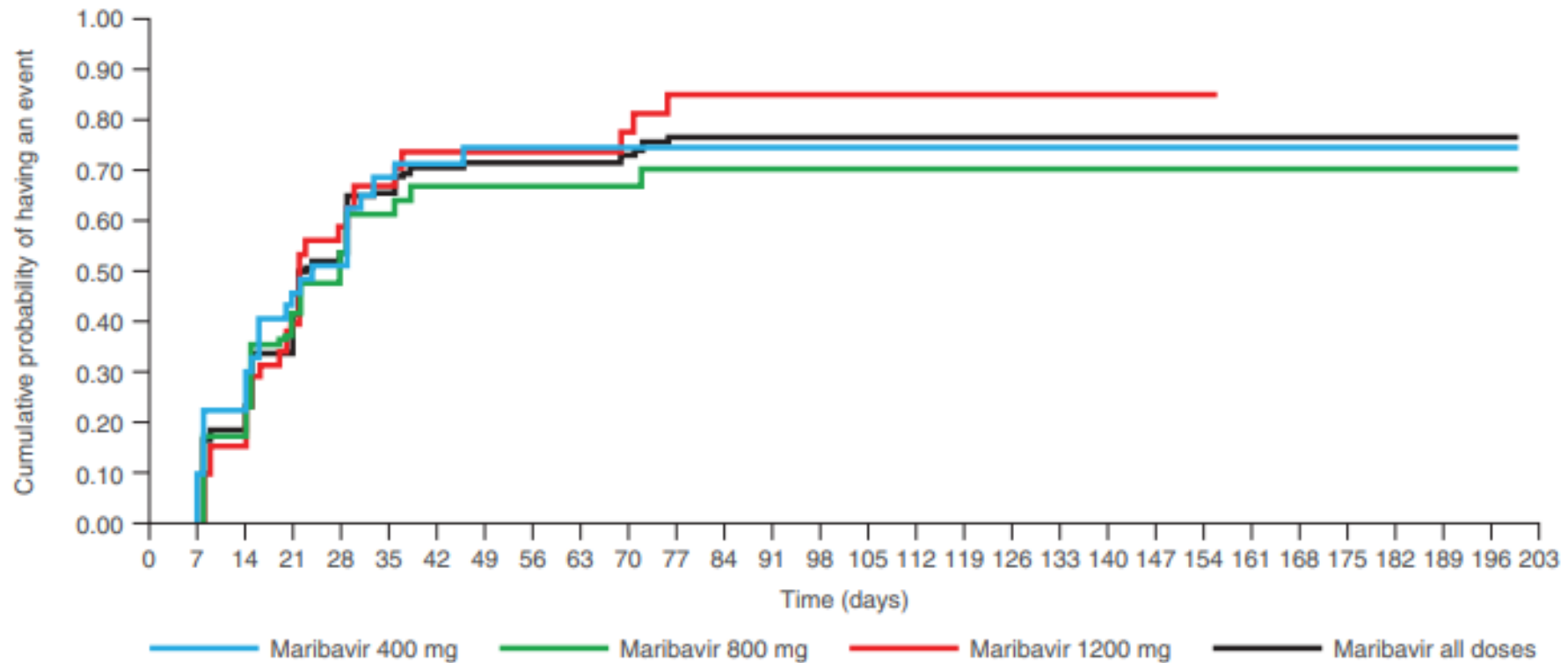
Maribavir en sauvetage: SOT/HSCT

Phase II

N=120, 60% HSCT, 40% SOT

Infections à CMV résistantes et/ou réfractaires

Maribavir 400 vs 800 vs 1200 mg/12h



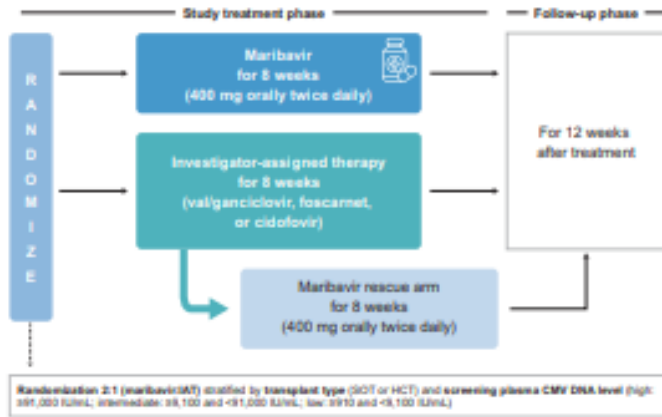
Maribavir en sauvetage: RCT

INTRODUCTION

This was a phase 3, multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir compared with IAT in HCT and SOT recipients with CMV infections refractory to most recent treatment, with or without resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir.



STUDY DESIGN



STUDY ENDPOINTS



The primary endpoint was confirmed CMV viremia clearance at the end of Week 8 (regardless of premature treatment discontinuation).



The key secondary endpoint was a composite of confirmed CMV viremia clearance and symptom control at the end of Week 8, maintained through Week 16 after receiving exclusively study-assigned treatment.

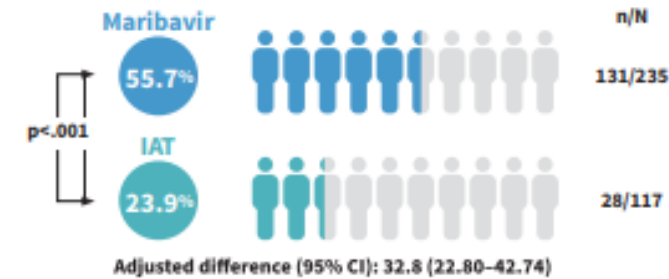
CMV, cytomegalovirus; HCT, hematopoietic-cell transplant; IAT, investigator-assigned therapy; SOT, solid-organ transplant; TEAE, treatment-emergent adverse event.
ClinicalTrials.gov: NCT02931539
This study was funded by Takeda Development Center Americas, Inc., Lexington, MA

RESULTS

352 patients were randomized (maribavir, n=235; IAT, n=117)

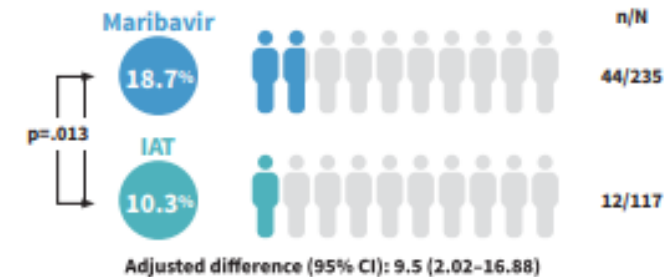


PRIMARY ENDPOINT (WEEK 8)



A significantly higher proportion of patients treated with maribavir achieved the primary endpoint of confirmed CMV viremia clearance at Week 8 compared with IAT.

KEY SECONDARY ENDPOINT (WEEK 16)



A greater proportion of patients treated with maribavir achieved the composite key secondary endpoint of CMV viremia clearance and symptom control at Week 8, with maintenance through Week 16 compared with IAT.

SAFETY



Median (range) duration of exposure was 57 (2–64) days with maribavir and 34 (4–64) days with IAT.



Fewer patients discontinued maribavir than IAT due to TEAEs (13.2% vs 31.9%).



Dysgeusia was the most frequently reported TEAE in the maribavir group (maribavir: 37.2%; IAT: 3.4%).



Maribavir was associated with less acute kidney injury versus foscarnet (8.5% vs 21.3%) and neutropenia versus valganciclovir/ganciclovir (9.4% vs 33.9%).



One patient per treatment group had fatal treatment-related TEAEs.

CONCLUSIONS

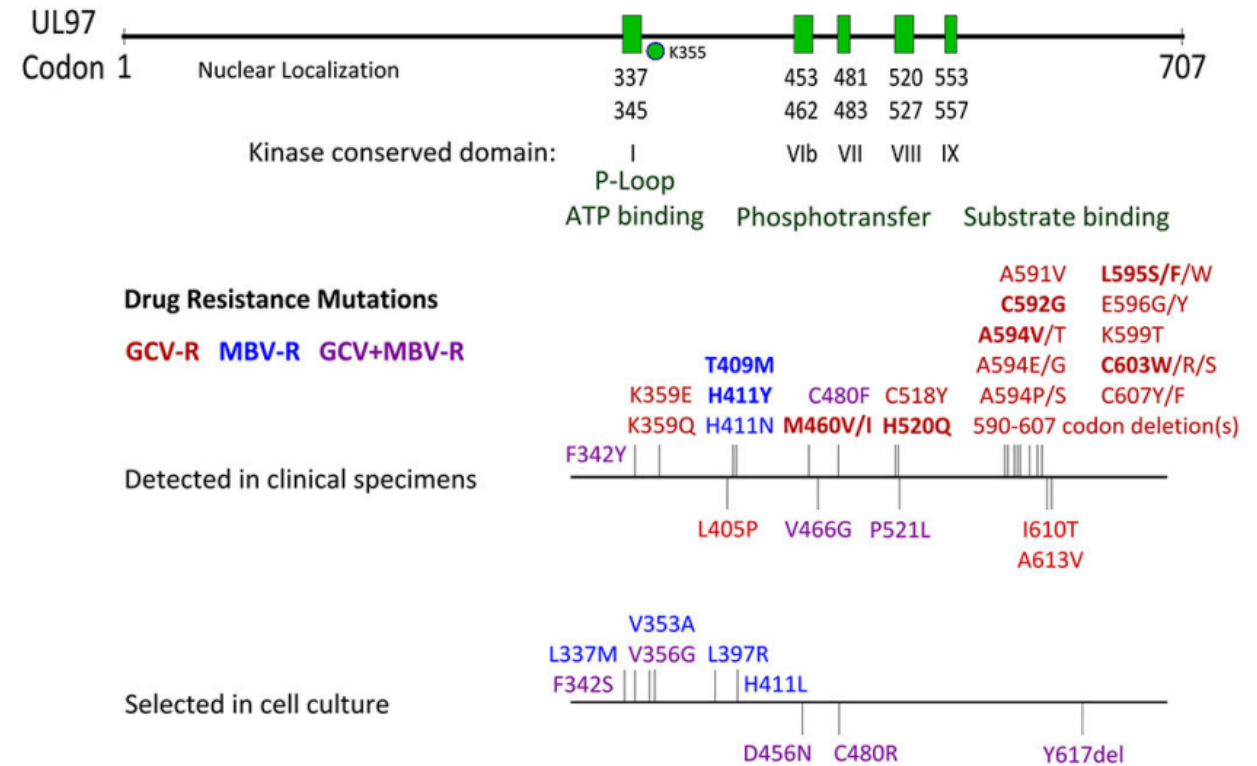
Maribavir was superior to IAT for cytomegalovirus viremia clearance, and viremia clearance plus symptom control, with maintenance of these effects post-therapy in transplant recipients with refractory cytomegalovirus infections with or without resistance.

Maribavir demonstrated an improved safety profile versus valganciclovir/ganciclovir for myelotoxicity and versus foscarnet for nephrotoxicity, with fewer patients discontinuing maribavir than IAT.

The availability of an orally bioavailable therapy without the tolerability issues associated with current therapies may confer patient management benefits.

Résistances au maribavir

Fréquence de mutations: 1% environ
Papanicolaou G *et al.* CID 2019



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
Filiciclovir (cyclopropavir)	L595S	M460V, C592G, A594V, C603W	M460I, H520Q		

En résumé

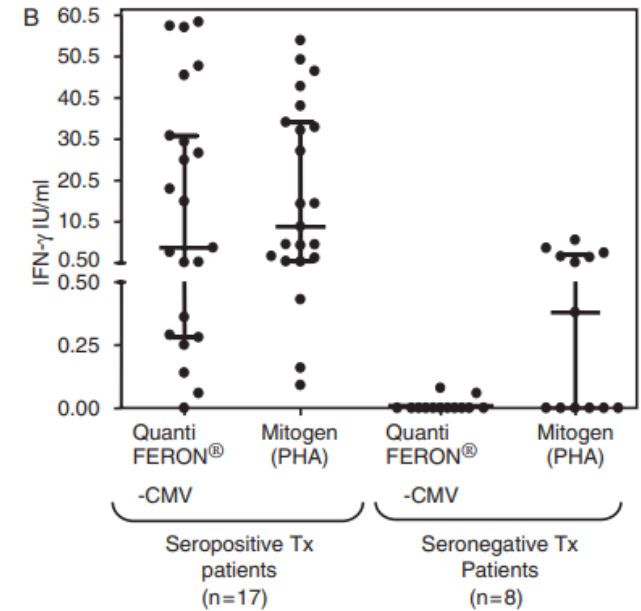
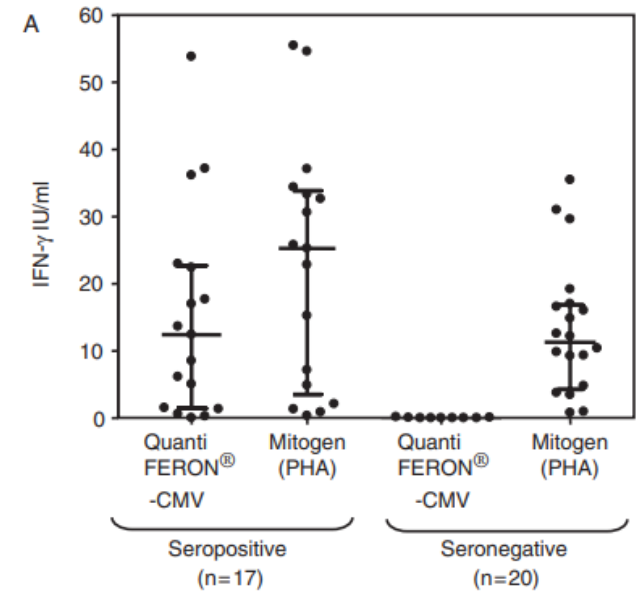
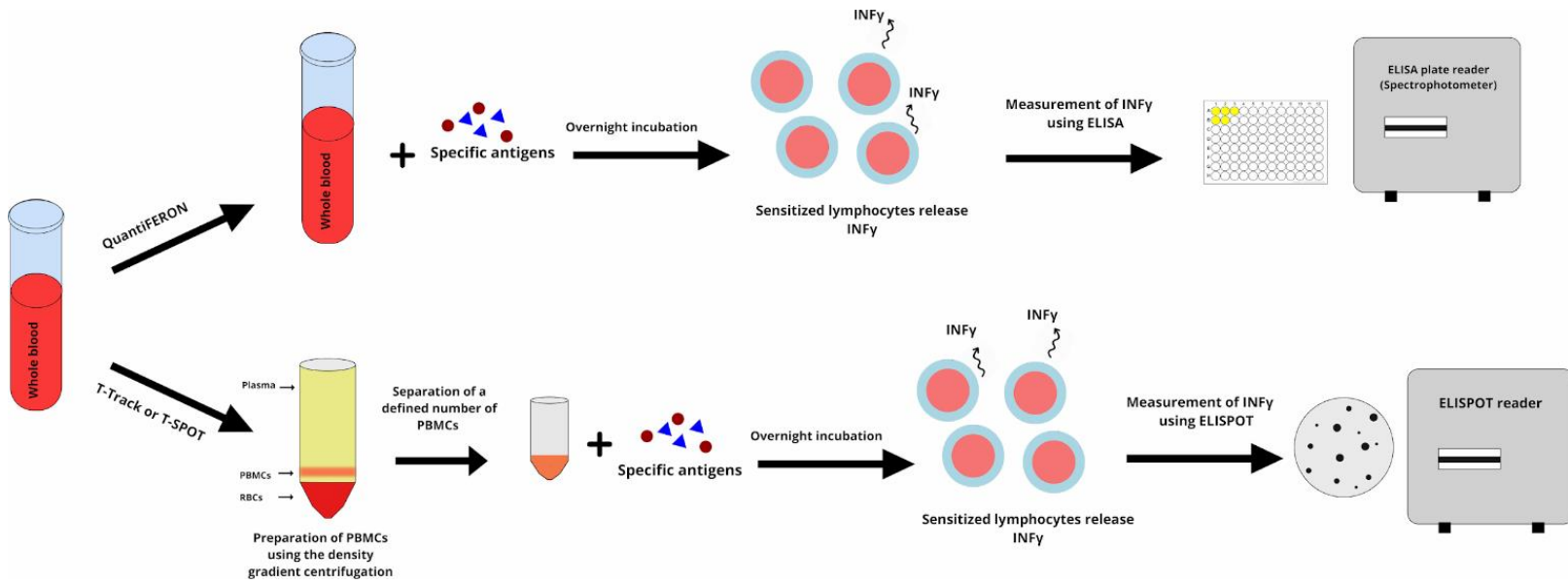
Transplantation d'organes solides

	Prophylaxie	Préemptif	Sauvetage	Prophylaxie II ^{aire}
GCV/V-GCV				
FOS		Mais non fait		
Letermovir	(Kidney)		Trial ongoing	Trial ongoing
Maribavir				

Transplantation de CSH

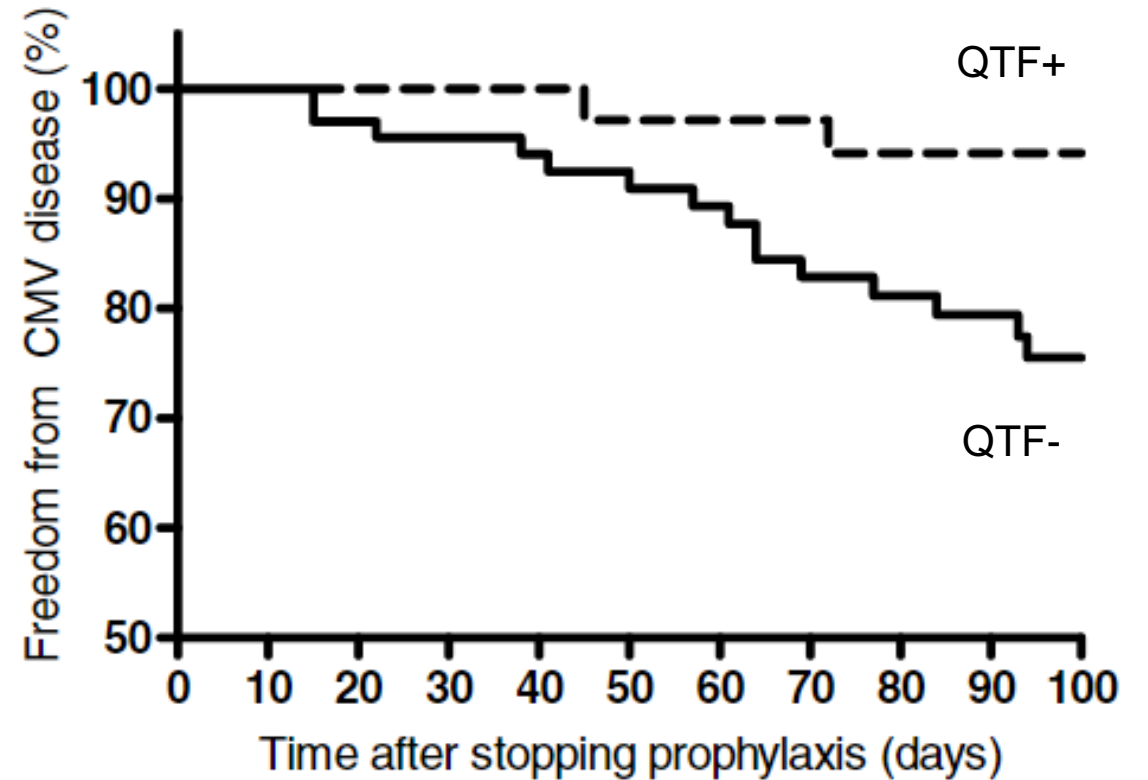
	Prophylaxie	Préemptif	Sauvetage	Prophylaxie II ^{aire}
GCV/V-GCV	Mais non fait...			
FOS		Mais non fait		
Letermovir	100 ou 200 jours?		Trial ongoing	
Maribavir				

IGRA CMV



Quantiferon CMV: études pionnières (SOT)

Characteristic	All (n = 108)	CMV disease (n = 18)	No CMV disease (n = 90)
Age (years; mean ± SD)	49.7 ± 14.0	52.5 ± 15.5	49.2 ± 13.8
Gender (male/female)	61/47	10/8	51/39
Type of transplant			
Lung	48 (44.4%)	7 (38.9%)	41 (45.6%)
Kidney	32 (29.6%)	3 (16.7%)	29 (32.2%)
Liver	19 (17.6%)	6 (33.3%)	13 (14.4%)
Kidney–Pancreas	4 (3.7%)	1 (5.6%)	3 (3.3%)
Other	5 (4.6%)	1 (5.6%)	4 (4.4%)
Pretransplant CMV donor (D)/recipient (R) serostatus			
D+/R–	35 (32.4%)	11 (61.1%)*	24 (26.7%)
D–/R+	34 (31.5%)	2 (11.1%)	32 (35.6%)
D+/R+	39 (36.1%)	5 (27.8%)	34 (37.8%)
Duration of antiviral prophylaxis (median, interquartile range), days	94 (86–109)	98 (86–109)	93 (86–109)
Induction therapy (thymoglobulin) (%)	39 (36.1%)	5 (27.8%)	34 (37.8%)
Maintenance immunosuppression			
Corticosteroids	96 (88.9%)	15 (83.3%)	81 (90.0%)
Calcineurin inhibitor	93 (86.1%)	17 (94.4%)	76 (84.4%)
Mycophenolate mofetil	59 (54.6%)	10 (55.6%)	49 (54.4%)



Quantiferon CMV: SOT

Author	Journal	Study	Tx	Status	N	When?	Main findings
Manuel O	CID 2013	P	All	D+/R-	127	End of prophylaxis	6.4% 22.2%
Lisboa L	Transplantation 2012	P	All	All	42	Viremia	92% clearance 46% clearance
Lochmanova A	Transplant Proc 2010	P	Kidney	All	14	?	? ?
Tarasewicz A	Transplant Proc 2016	R	Kidney	All	25	4.4 Mo post Tx	50% 54.5%
Lee H	PLoS One 2017	P	Kidney	D+/R+	124	1 Mo post Tx	QTF not predictive, ELISPOT predictive
Sood S							Weak associated with
De Gracia-Guinda							is protective for infection
Deborska-Materkowska D							is associated with
Chiereghin A	J Clin Microbiol 2018	P	Heart	R+	44	Multiple	Positive QTF associated with control of infection
Andreani M	Transplant Proc 2020	P	Kidney	D+/R-	12	End of prophylaxis	Positive QTF predicts spontaneous clearance
Sood S	Transpl Infect Dis 2018	P	Liver	All	59	6 Mo post Tx	Negative QTF associated with late infection
Altaf M	JID 2021	P	Lung	All	39	Pre Tx	Negative QTF associated with infection
Poglajen G	JHLT 2020	P	Heart	All	154	D100	QTF-guided prophylaxis decreases

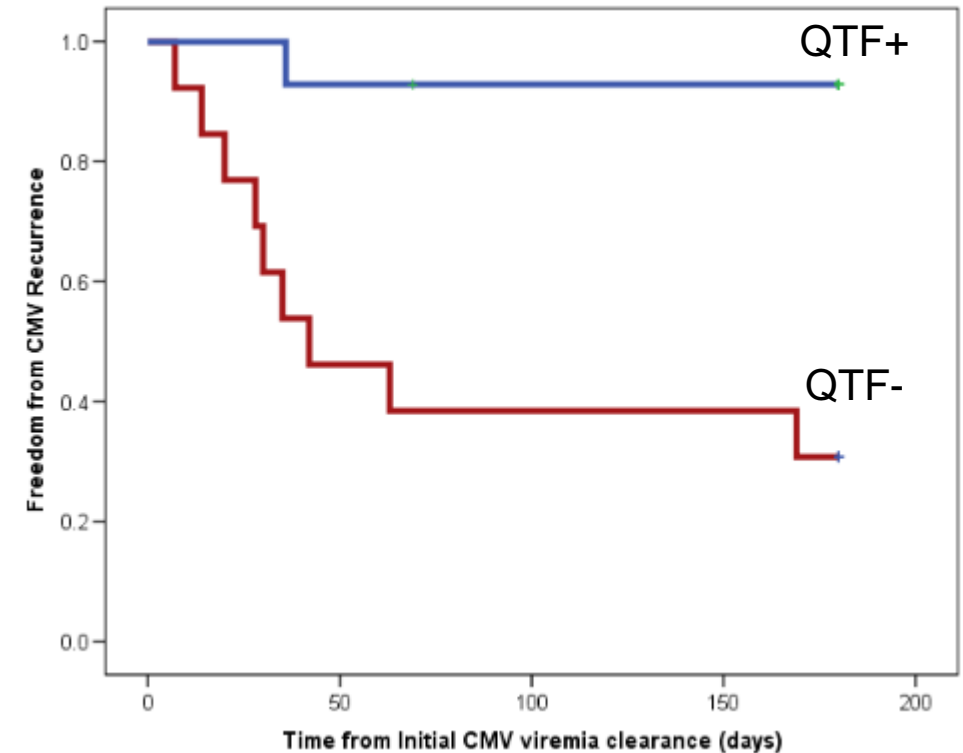
Positivité du QTF signe l'acquisition d'une immunité durable et est associé à un faible risque de réactivation CMV

Quantiferon CMV: étude interventionnelle non randomisée

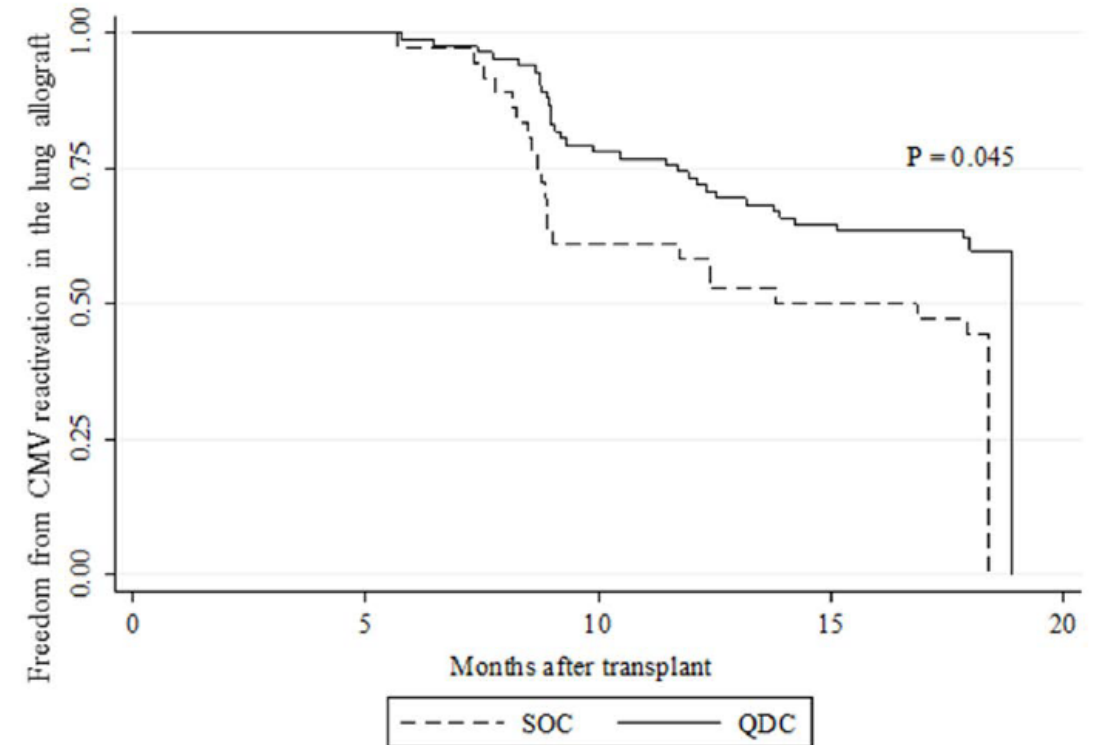
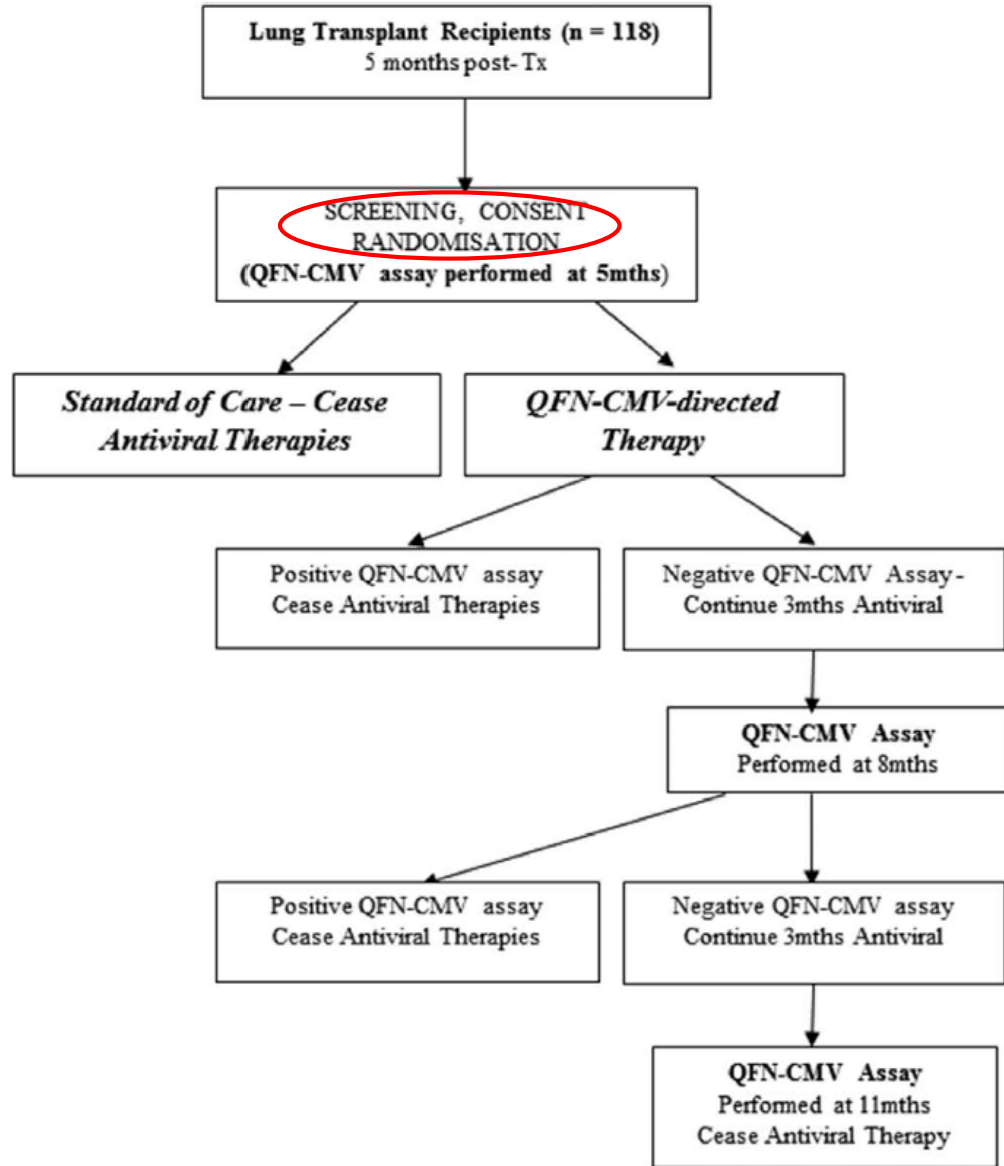
Tx poumons/reins/foie, virémie CMV et QTF au contrôle de la virémie: QTF+: observation

QTF-: prophylaxie II^{aire}

Variable	CMV-CMI positive N = 14	CMV-CMI negative N = 13	p-value
Age (years); median (range)	59 (29-86)	57 (33-76)	0.69
Gender (male/female)	8/6	7/6	0.86
Type of transplant			
Kidney	4 (28.6%)	3 (23.1%)	0.99
Liver	7 (50.0%)	3 (23.1%)	0.24
Lung	1 (7.1%)	5 (38.5%)	0.08
Combined	2 (14.3%)	2 (15.4%)	0.99
Time from transplant (to CMV) (days); median (range)	149 (29-14671)	177 (28-1434)	0.79
CMV serology			
D+/R-	7 (50.0%)	5 (38.5%)	0.70
R+	6 (42.9%)	7 (53.8%)	0.71
D-/R-	0 (0)	1 (7.7%)	0.48
Unknown	1 (7.1%)	0 (0)	0.99
Primary antiviral prophylaxis ¹	10 (71.4%)	10 (76.9%)	0.99
Duration of prophylaxis (months); median (range)	3 (1-12)	3 (2-9)	0.48
Anti-thymocyte globulin use in prior 1 year	3 (21.4%)	3 (23.1%)	0.99
Immunosuppression			
Prednisone	12 (85.7%)	10 (76.9%)	0.43
Calcineurin inhibitor	10 (71.4%)	13 (100%)	0.22
Mycophenolate	10 (71.4%)	3 (23.1%)	0.99
Azathioprine	1 (7.1%)	3 (23.1%)	0.33
Sirolimus	1 (7.1%)	0 (0)	0.99
GFR < 30 mL/min	5 (35.7%)	2 (15.4%)	0.39

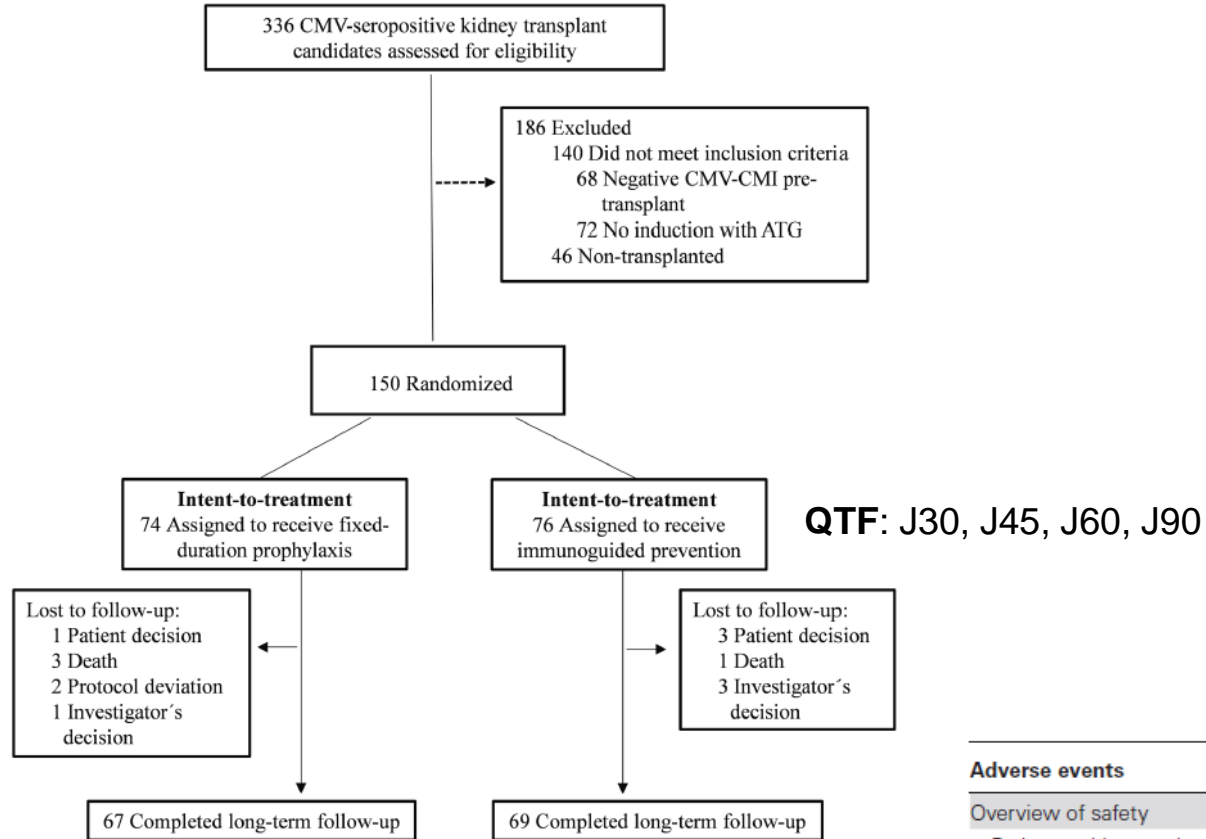


Quantiferon CMV: études randomisées

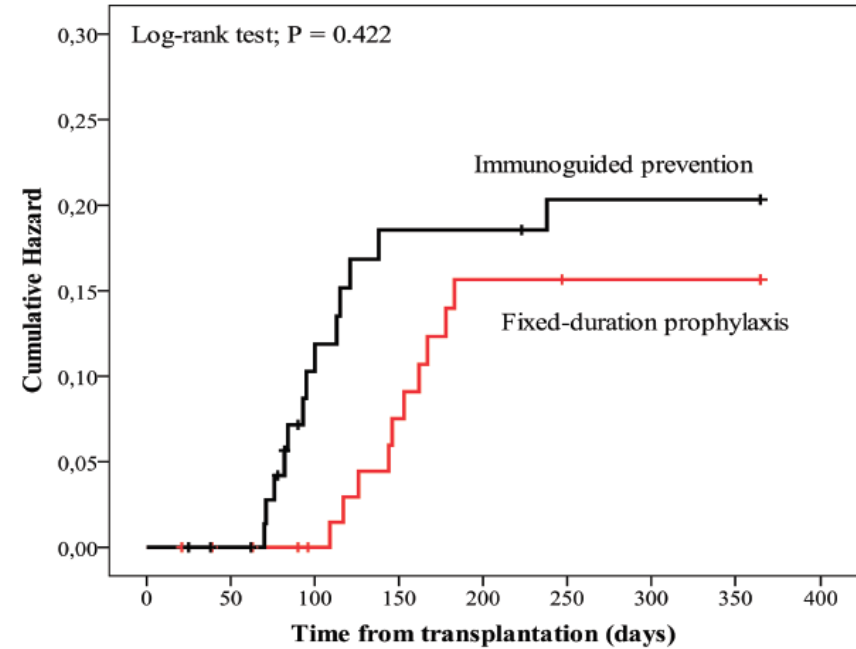


	Standard of care (n = 36)	QFN-CMV directed (n = 82)	Odds ratio (95% CI)	P
BAL				
CMV PCR <600 copies/mL	15	52	0.41	0.03
CMV PCR >600 copies/mL	21	30	(0.17–0.99)	
CMV PCR <10 000 copies/mL	32	73	0.99	0.98
CMV PCR >10 000 copies/mL	4	9	(0.25–4.71)	
Blood				
CMV PCR <600 copies/mL	24	63	0.60	0.25
CMV PCR >600 copies/mL	12	19	(0.24–1.59)	
CMV PCR <10 000 copies/mL	29	75	0.39	0.09
CMV PCR >10 000 copies/mL	7	7	(0.11–1.43)	

Quantiferon CMV: RCT in kidney Tx



Prophylaxis (standard vs immunoguided) followed by preemptive



Adverse events	Immunoguided Prevention (n = 76)	Fixed-Duration Prophylaxis (n = 74)	PValue ^a
Overview of safety			
Patients with any adverse event	44 (57.9)	51 (68.9)	.161
Patients with serious adverse events	14 (18.4)	18 (24.3)	.378
All-cause mortality at 12 months	1 (1.3)	3 (4.1)	.363
Common adverse events^b			
Neutropenia ^c	7 (9.2)	28 (37.8)	<.001
Increased blood creatinine ^d	23 (30.3)	19 (25.7)	.532
Urinary tract infection ^e	12 (15.8)	11 (14.9)	.875
Biopsy-proven acute rejection	12 (15.8)	8 (10.8)	.370
Diarrhea	8 (10.5)	4 (5.4)	.248

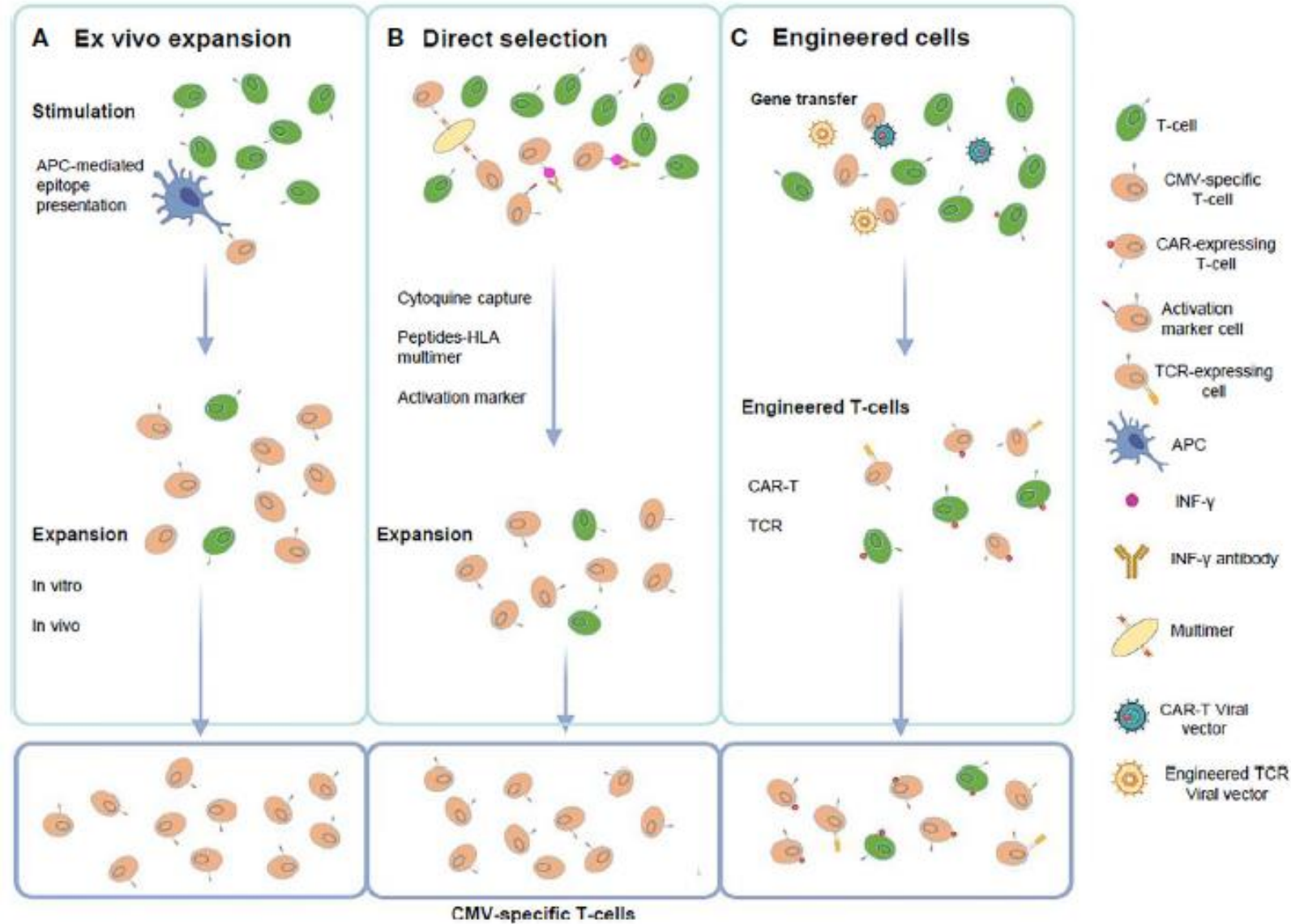
Quantiferon CMV: HSCT

Author	Journal	Study	Status	N	When?	Neg	pos
Tey S	PLoS One 2013	Prospective	All	41	Multiple	65%	27%
Bono P	J Clin Virol 2016	Prospective	All	22	Multiple	Positive QTF associated with spontaneous clearance	
Yong M	JID 2017	Prospective	All	89	Multiple	Negative QTF associated with viremia/disease	
Krawczyk A	J Clin Virol 2018	Prospective	All	34	Multiple	Positive QTF is protective	
Douglas A	Transpl Infect Dis 2020	Prospective	All	40	Multiple	Negative QTF associated with viremia/disease	
Thompson G	Transpl Infect Dis 2022	Prospective	All	46	D100/D150	Excellent PPV (poor NPV)	

Immunothérapie adoptive

Sources:

Donneur (HSCT)
Third party
Autologues



Les Ig spécifiques anti CMV (Cytogam[®], Cytotect[®]CP)

Etudes anciennes en prophylaxie: abandonné sauf dans de rares cas de D+/R- SOT

Un RCT pour la prophylaxie de l'infection congénitale: inefficace Revello M et al. NEJM 2014

En traitement conventionnel, préemptif ou curatif: non recommandé

Plutôt dans les situations difficiles (pneumonie) et en association aux antiviraux

Série en sauvetage chez les **allogreffés**: n=23, en association n=16

78% réponse, mais 4 rechutes à distance

Pas d'effet sur la survie globale

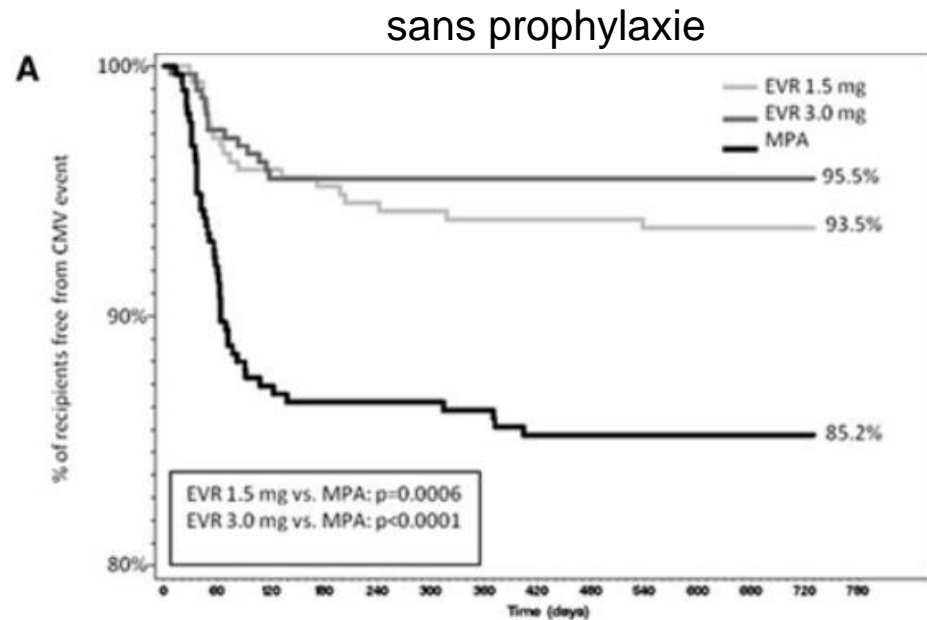
Série en **Tx pulmonaire**: n=22, 68% traitement, 32% prophylaxie II^{aire}

68% réponse

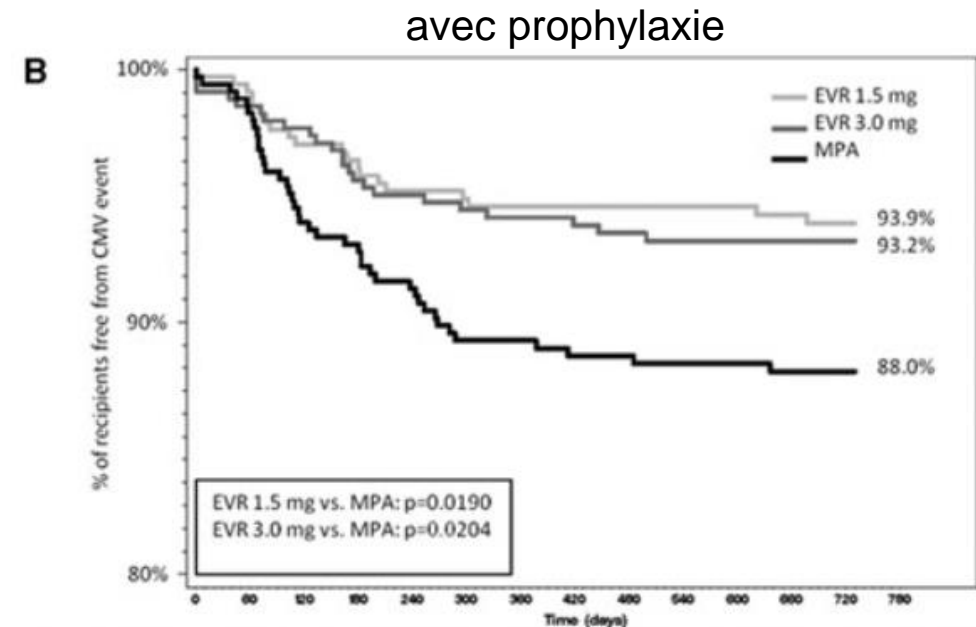
Modulation de l'immunosuppression

A toujours négocié (diminution/arrêt MMF)

Bénéfices potentiels du switch antimétabolites → mTOR inhibiteurs (si R+)



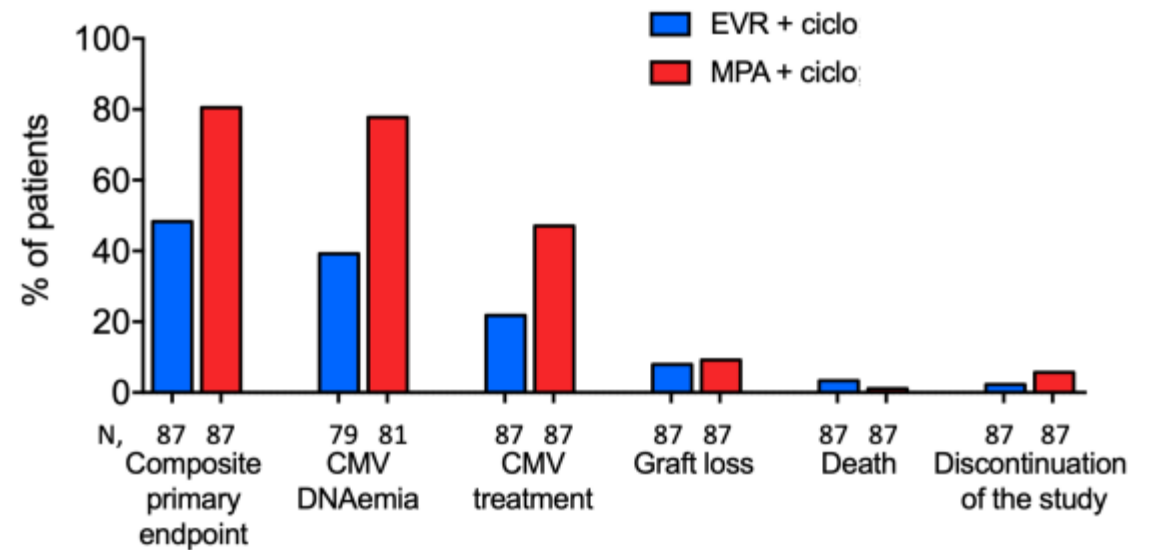
	Total number at risk at Day 0	Total number failed (with event)	Total number censored
MPA	318	46	272
EVR 1.5 mg	319	20	299
EVR 3.0 mg	323	16	307



	Total number at risk at Day 0	Total number failed (with event)	Total number censored
MPA	351	41	310
EVR 1.5 mg	345	22	323
EVR 3.0 mg	348	23	325

Modulation de l'immunosuppression: everolimus

	EVR (n = 87)	MPA (n = 87)
Recipients		
Age (years), mean (SD)	63.0 (14.1)	61.5 (14.7)
Male, n (%)	58 (66.7)	62 (71.3)
Donors		
Age (years), mean (SD)	59.3 (15.2)	56.9 (18.2)
Male, n (%)	51 (58.6)	46 (52.9)
Living donor, n (%)	9 ^a (10.7)	3 ^b (3.6)
Expanded criteria deceased donor, n (%)	51 (58.6)	47 (54.0)
Cold ischemia time (hours), mean (SD)	12.3 ^a (6.2)	13.4 ^b (5.9)
HLA-sensitized recipients, n (%)	8 ^c (9.3)	10 (11.5)
HLA A mismatches, n (0/1/2)	7/39/41	13/41/33
HLA B mismatches, n (0/1/2)	3/32/52	6/29/52
HLA DRB1 mismatches, n (0/1/2)	21/43/23	25/36/26
HLA DQB1 mismatches, n (0/1/2)	21/50/16	29/38/20
CMV seropositive donors, n (%)	47 (54.0)	48 (55.2)



Cumulative incidence (95% CI)	EVR (n = 87)	MPA (n = 87)	Log-rank
12-month borderline rejection	8.8 (4.0-18.5)	13.6 (7.3-24.6)	0.39
12-month acute T cell-mediated rejection	13.8 (7.7-24.2)	17.9 (10.6-29.4)	0.57
12-month active antibody-mediated rejection	3.3 (0.8-12.5)	2 (0.3-13.1)	0.63
12-month graft loss	9.4 (4.8-17.9)	10.8 (5.8-19.8)	0.99
12-month death	6.3 (2.7-14.6)	1.2 (0.2-8.1)	0.11
12-month CMV disease or syndrome	5.0 (1.9-12.8)	11.2 (6.0-20.5)	0.14

Bénéfices des mTOR inhibiteurs

mTOR Inhibitors Prevent CMV Infection Through the Restoration of Functional $\alpha\beta$ and $\gamma\delta$ T Cells in Kidney Transplantation

JASN[®]

JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

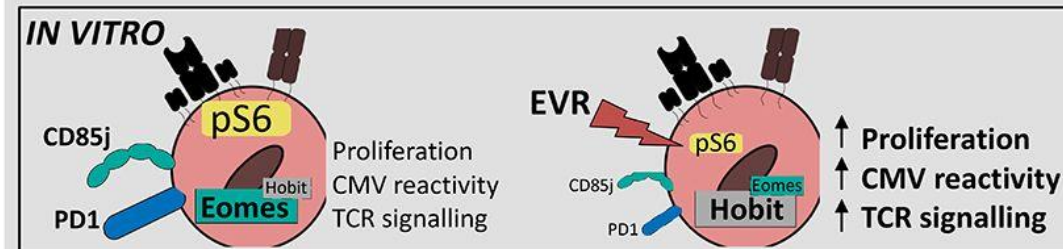
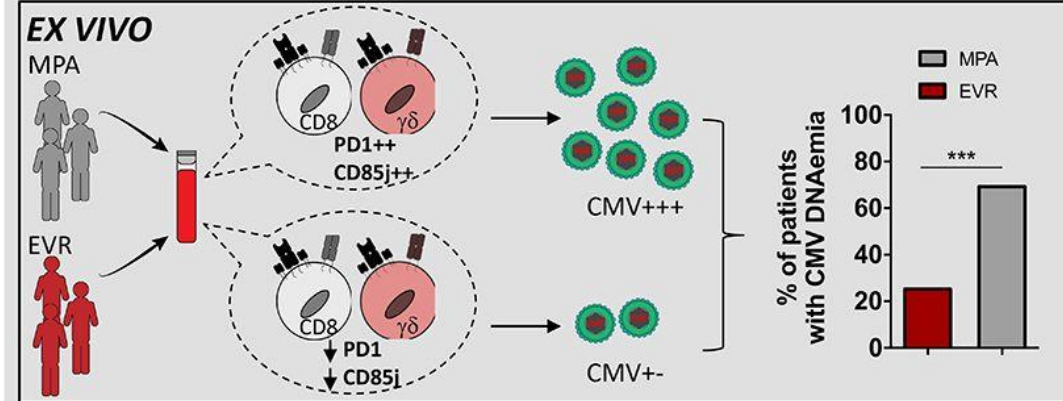
CMV-pos (R+) kidney transplant recipients undergoing or not CMV infection

Description of $\alpha\beta$ and $\gamma\delta$ T cell profile at day 0 of transplantation

Effect of EVEROLIMUS (EVR) on $\alpha\beta$ and $\gamma\delta$ T cells

- *Ex vivo* profile after transplantation and impact on CMV events
- *In vitro* effect of EVR on inhibitory receptors, transcription factors, CMV-reactivity, and mTOR signaling

OUTCOME



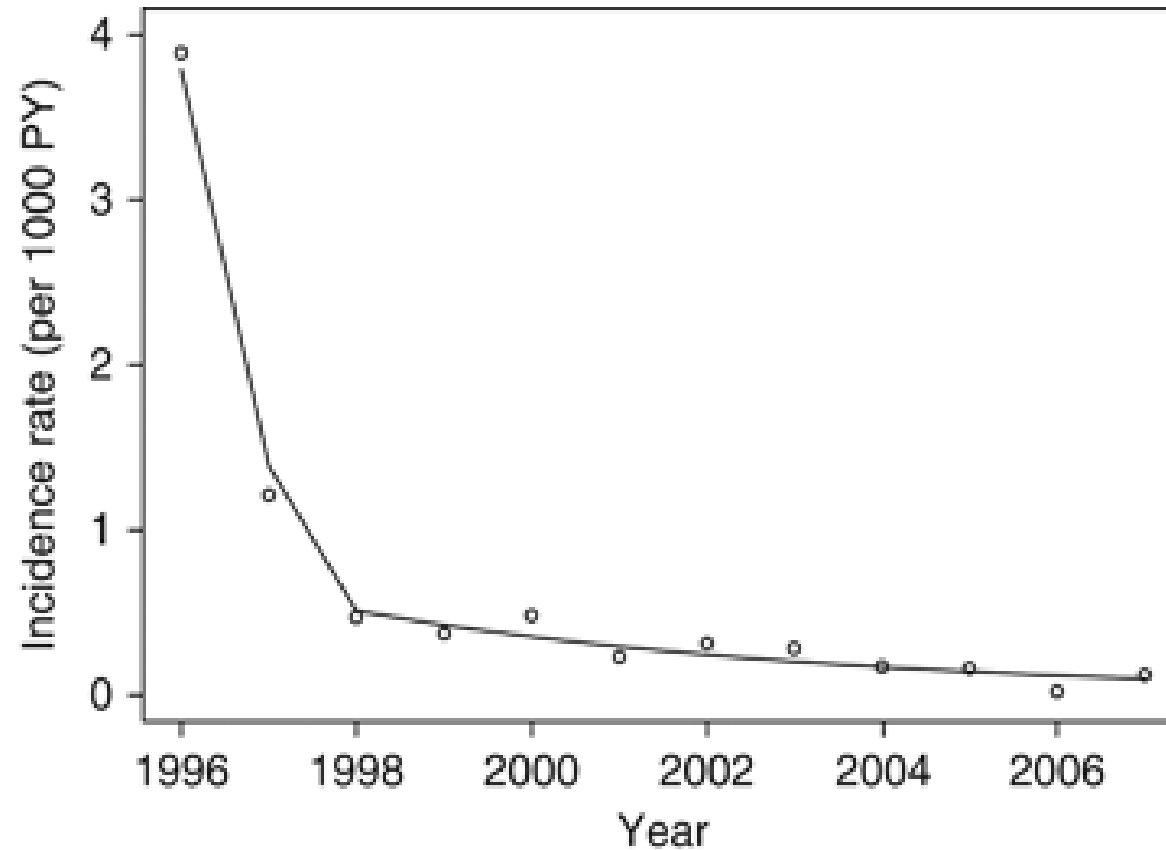
Conclusion

1. Severe CMV replication is associated with a dysfunctional T-cell profile
2. mTORi improve T-cell fitness in association with a better control of CMV .

doi: 10.1681/ASN.2020121753

CMV et VIH: beaucoup plus rare

Incidence des CMV EOD chez les PVV suisses

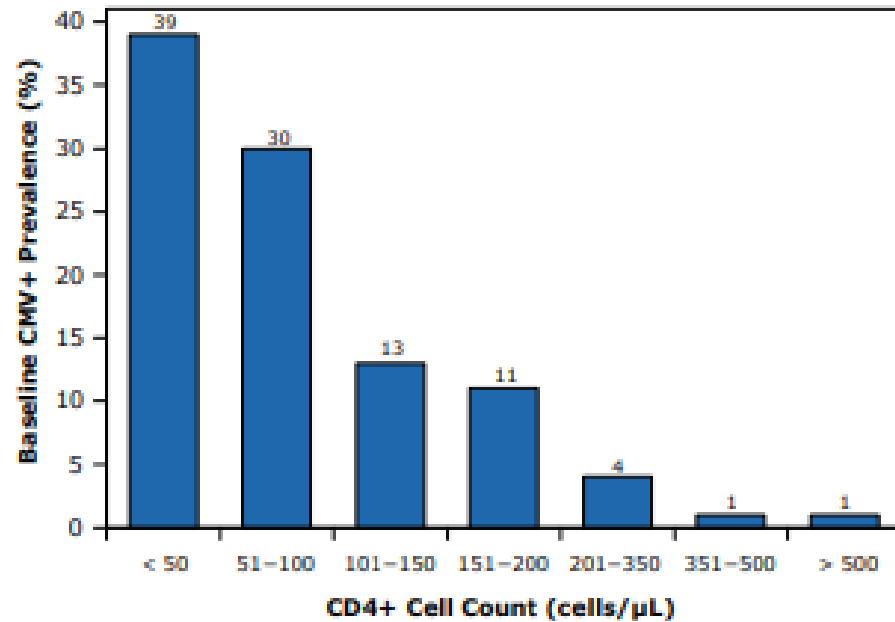


Virémie CMV : Reflet de l'immunodépression

	2009/2011	1999/2002	2002/2006	2009/2013
Characteristic	ANRS REFLATE TB (<i>n</i> = 137)	FIRST (<i>n</i> = 1169)	SMART (<i>n</i> = 54)	START (<i>n</i> = 1816)
Age (years)	38 (30,44)	38 (31, 43)	36 (31, 41)	36 (29, 44)
Female, <i>n</i> (%)	37 (27.0)	252 (21.5)	21 (38.9)	485 (26.7)
Black race, <i>n</i> (%)	46 (33.6)	614 (52.5)	9 (16.7)	545 (30.1)
CD4 ⁺ T-cells/ μ l	140 (58, 302)	153 (34, 318)	429 (380, 535)	648 (585, 759)
HIV RNA (copies/ml)	87000 (27022, 294479)	143843 (38654, 400147)	17012 (4040, 61200)	13480 (3440, 43759)
CMV-specific IgG ^a , <i>n</i> (%)				
Positive	136 (99.3)	1102 (94.4)	51 (94.4)	1752 (96.5)
Negative	1 (0.7)	66 (5.6)	3 (5.6)	64 (3.5)
CMV viremia prevalence ^b , <i>n</i> (%)				
Positive	35 (25.6)	201 (17.1)	0 (0)	15 (0.8)
IU/l (median, IQR)	361 (159–2381)	543 (184–2124)	–	88.5 (88.5–740)
Negative	102 (74.4)	968 (82.9)	54 (100)	1801 (99.2)

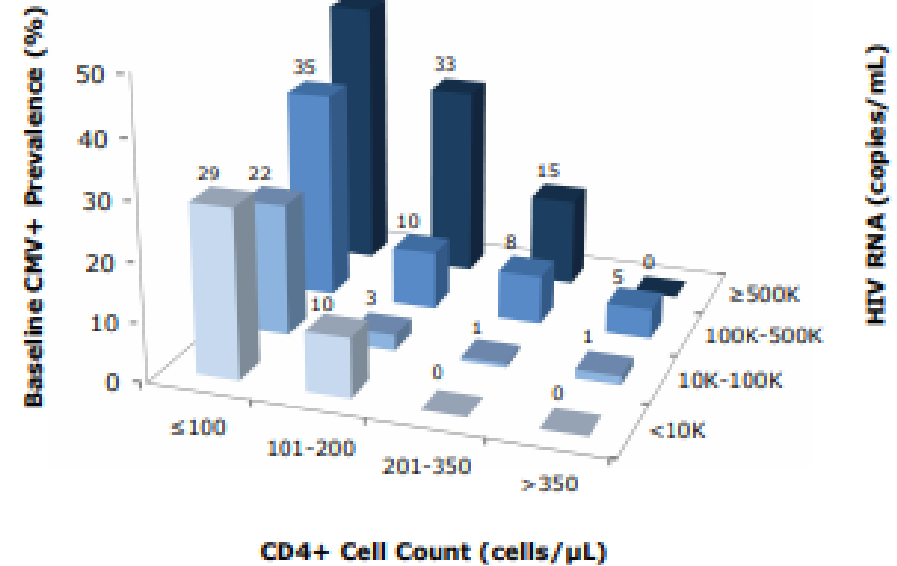
Virémie CMV : Reflet de l'immunodépression

A. By baseline CD4+ cell count pooled across the 4 trials (n=3176)



No. group:	382	148	122	99	289	195	1941
No. CMV+:	149	44	16	11	11	2	18

B. By baseline CD4+ cell count and HIV RNA among participants in FIRST and REFLATE (n=1306)



Denominator in each CD4+ group with increasing HIV RNA:

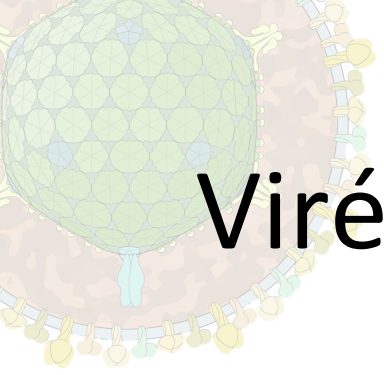
CD4+ ≤ 100:	14, 98, 237, 181
CD4+ 101-200:	10, 74, 91, 46
CD4+ 201-350:	30, 154, 85, 20
CD4+ > 350:	60, 134, 58, 14

Virémie CMV : Facteur de risque de gravité

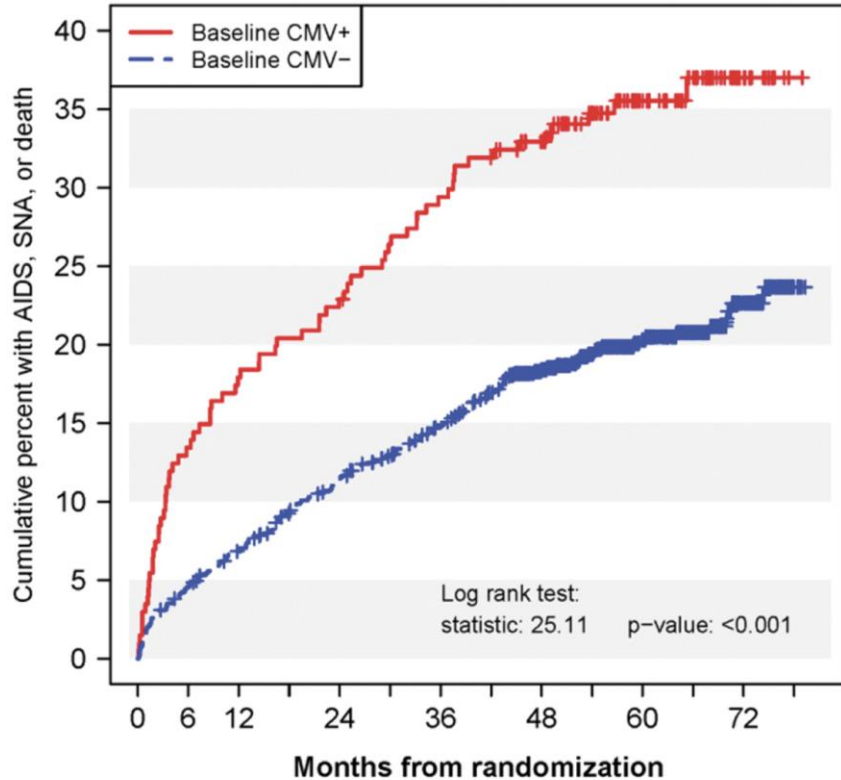
Characteristic	ANRS REFLATE TB (<i>n</i> = 137)	FIRST (<i>n</i> = 1169)	SMART (<i>n</i> = 54)	START (<i>n</i> = 1816)
Age (years)	38 (30,44)	38 (31, 43)	36 (31, 41)	36 (29, 44)
Female, <i>n</i> (%)	37 (27.0)	252 (21.5)	21 (38.9)	485 (26.7)
Black race, <i>n</i> (%)	46 (33.6)	614 (52.5)	9 (16.7)	545 (30.1)
CD4 ⁺ T-cells/ μ l	140 (58, 302)	153 (34, 318)	429 (380, 535)	648 (585, 759)
HIV RNA (copies/ml)	87000 (27022, 294479)	143843 (38654, 400147)	17012 (4040, 61200)	13480 (3440, 43759)
CMV-specific IgG ^a , <i>n</i> (%)				
Positive	136 (99.3)	1102 (94.4)	51 (94.4)	1752 (96.5)
Negative	1 (0.7)	66 (5.6)	3 (5.6)	64 (3.5)
CMV viremia prevalence ^b , <i>n</i> (%)				
Positive	35 (25.6)	201 (17.1)	0 (0)	15 (0.8)
IU/l (median, IQR)	361 (159–2381)	543 (184–2124)	–	88.5 (88.5–740)
Negative	102 (74.4)	968 (82.9)	54 (100)	1801 (99.2)



M0 : Virémie CMV 17,1%
M8 : Virémie CMV 5%

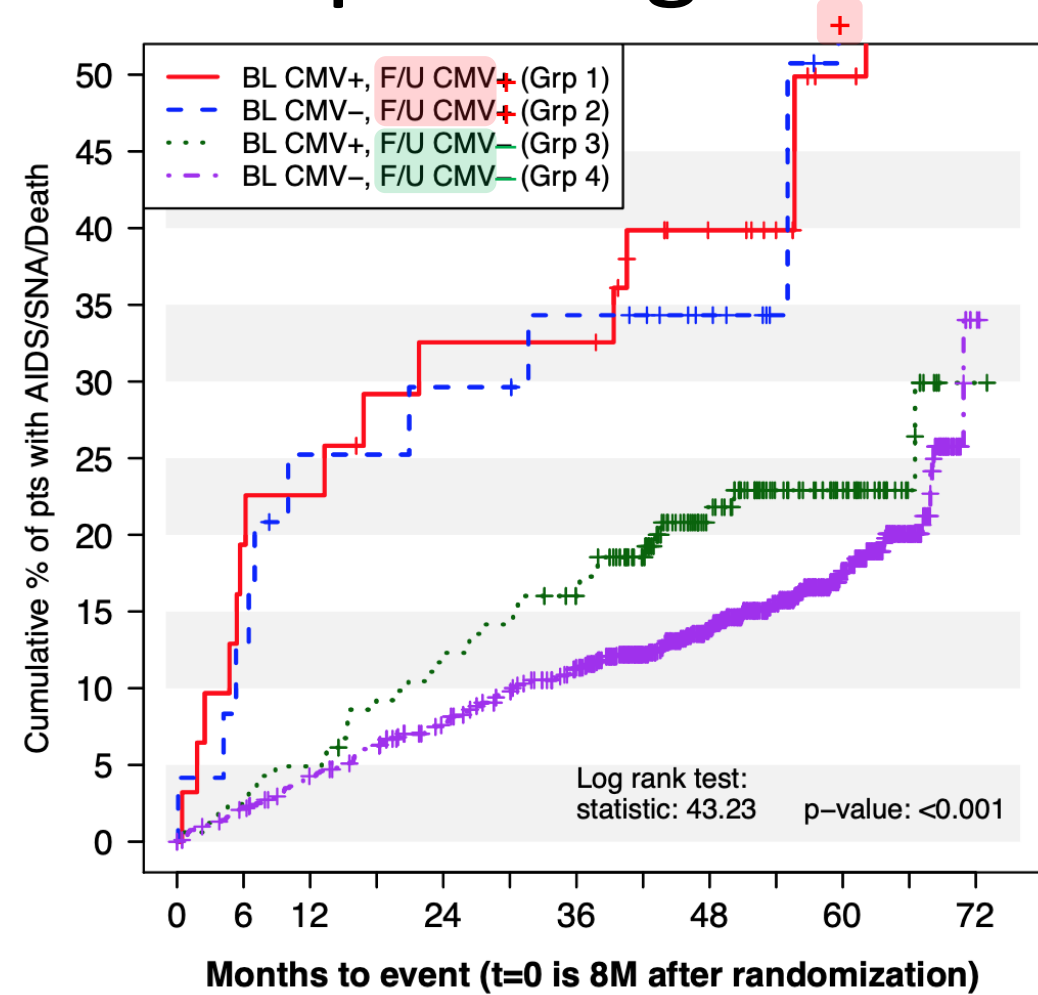


Virémie CMV : Facteur de risque de gravité



No. at risk:

BL CMV+:	201	174	165	160	155	147	141	135	124	90	62	40	17	1
BL CMV-:	968	922	895	863	839	815	787	753	659	515	374	245	123	12



Critère composite : événement classant SIDA, événement non-SIDA, décès

Virémie CMV : Facteur de risque de gravité

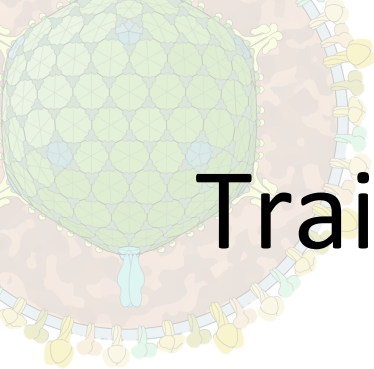
Table 2. Hazard ratios (HRs) for the risk of the composite outcome of death, AIDS, or serious non-AIDS events during follow-up in FIRST.

Subgroup	N in Grp.	N. Evt.	Rate (100 PY)	HR (95% CI)		
				Unadjusted	Adjusting for BL CD4	Adjusting for BL CD4 and HIV RNA
<i>Using all follow-up for time-to-first-event</i>						
BL CMV+	201	71	9.4	1.98 (1.51, 2.60) <i>P</i> = <0.001	1.22 (0.92, 1.64) <i>P</i> = 0.17	1.15 (0.86, 1.54) <i>P</i> = 0.36
BL CMV-	968	193	4.7	– ref –	– ref –	– ref –



Donc

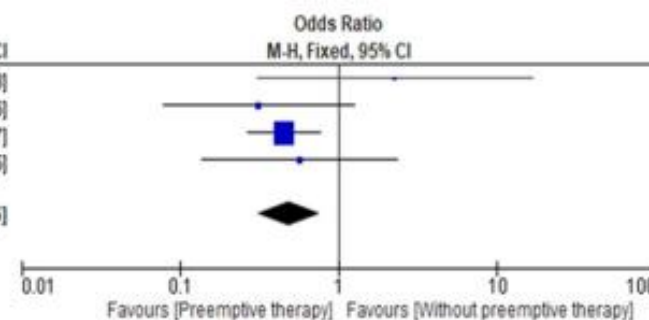
- Virémie CMV au diagnostic de VIH reflète la sévérité de l'immunodépression
- La persistance de la virémie CMV sous ARV est associée à une majoration de la morbi-mortalité



Traitement anti-CMV : méta-analyse

(a) CMV EOD

Study or Subgroup	Preemptive therapy		Without preemptive therapy		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Balfour 1996 (1)	12	20	2	5	2.4%	2.25 [0.30, 16.63]
Salmon-Ceron 1999 (2)	12	21	17	21	13.7%	0.31 [0.08, 1.26]
Spector 1998 (3)	49	191	39	90	74.2%	0.45 [0.27, 0.77]
Wohl 2009 (4)	4	24	6	23	9.6%	0.57 [0.14, 2.35]
Total (95% CI)		256		139	100.0%	0.49 [0.31, 0.76]
Total events	77		64			
Heterogeneity: $\text{Chi}^2 = 2.76$, $\text{df} = 3$ ($P = 0.43$); $I^2 = 0\%$						
Test for overall effect: $Z = 3.13$ ($P = 0.002$)						

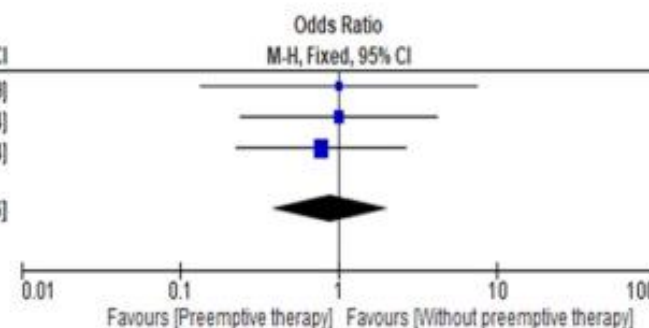


Footnotes

- (1) Foscarnet vs No treatment
- (2) Foscarnet vs No treatment
- (3) Ganciclovir vs Placebo
- (4) Valganciclovir vs Placebo

(b) All-cause mortality

Study or Subgroup	Preemptive therapy		Without preemptive therapy		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Balfour 1996 (1)	12	20	3	5	16.7%	1.00 [0.14, 7.39]
Salmon-Ceron 1999 (2)	16	21	16	21	33.1%	1.00 [0.24, 4.14]
Wohl 2009 (3)	7	24	8	23	50.3%	0.77 [0.23, 2.64]
Total (95% CI)		65		49	100.0%	0.89 [0.38, 2.06]
Total events	35		27			
Heterogeneity: $\text{Chi}^2 = 0.09$, $\text{df} = 2$ ($P = 0.96$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.28$ ($P = 0.78$)						

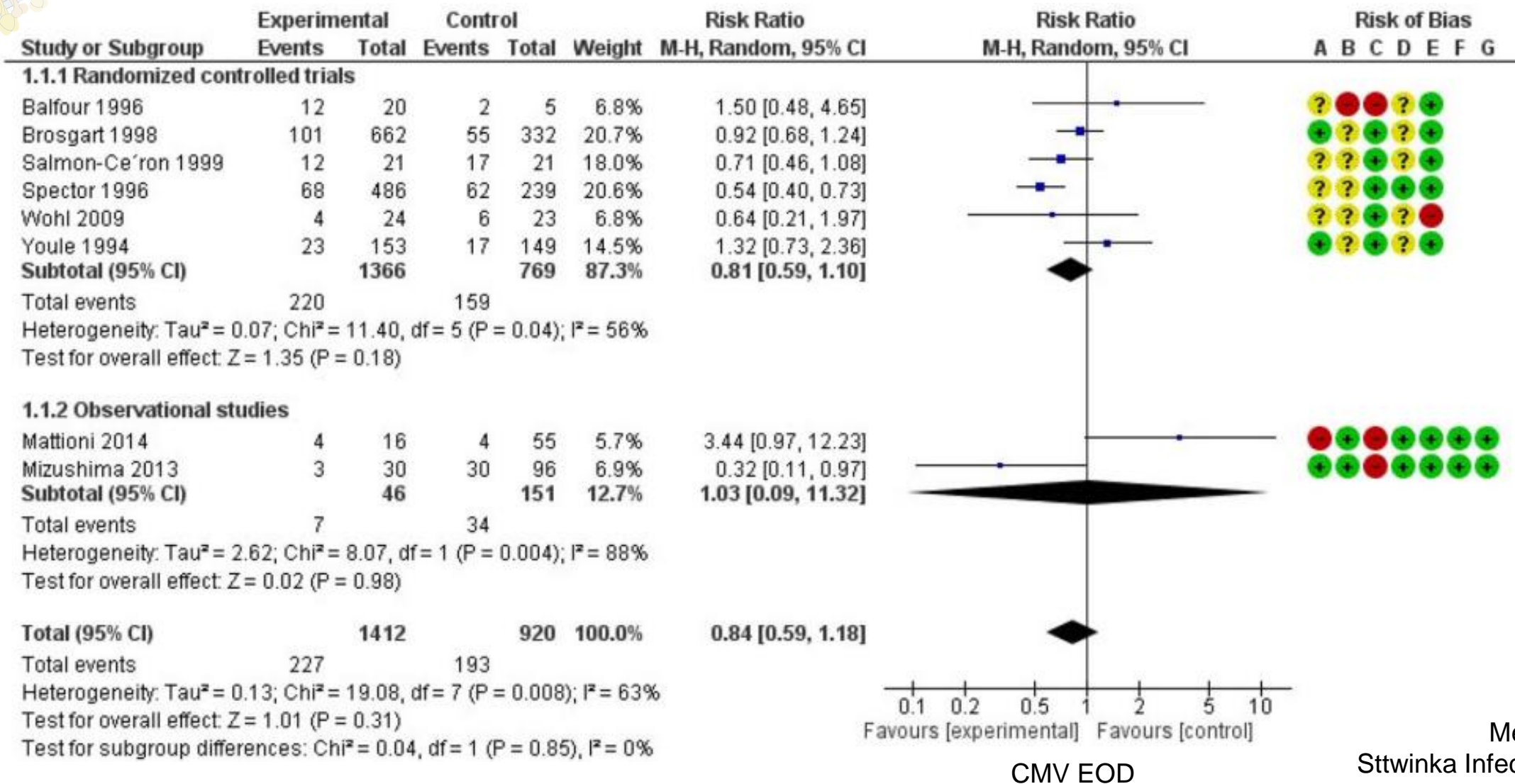


Footnotes

- (1) Foscarnet vs No treatment
- (2) Foscarnet vs No treatment
- (3) Valganciclovir vs Placebo

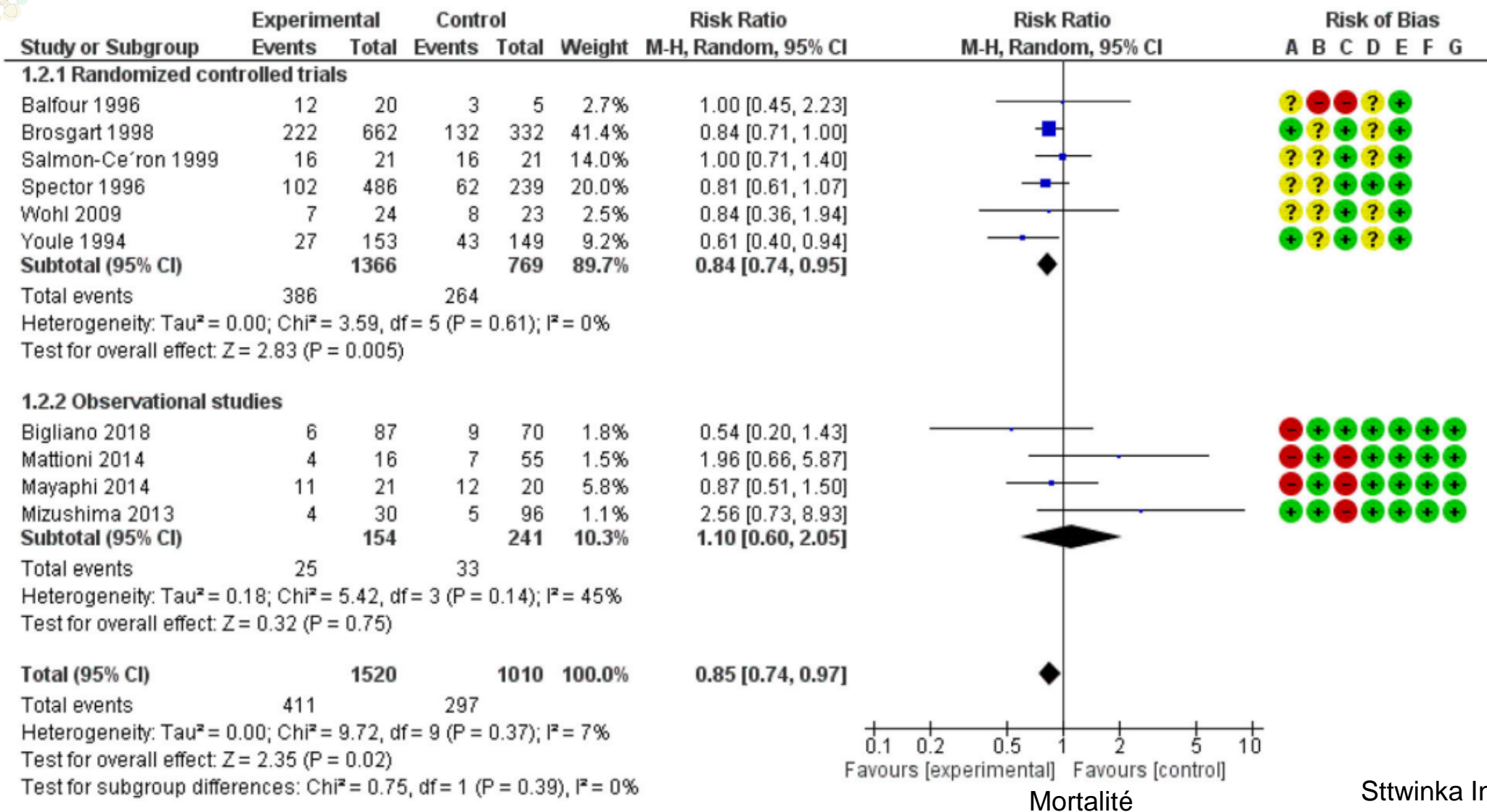


Traitement anti-CMV : méta-analyse





Traitement anti-CMV : méta-analyse





Donc

- Traitement semble réduire le risque de maladie à CMV
- Maladie à CMV = évènement rare
- Pas de bénéfice démontré des traitements actuellement notamment en terme de mortalité
- Risque d'évènements indésirables (23% leucopénie grade 3-4,

Mizushima *et al.* PloS one 2013)

Vous allez échapper à...

Immunothérapie adoptive

Techniquement complexe

Relancé par CRISPR CAS9?

Patients sous immunosuppresseurs

Beaucoup moins d'études « solides »

Risque proportionnel aux traitements lymphotoxiques

Prophylaxies hétérogènes

Vaccin

Beaucoup de recherches infructueuses

Plusieurs en développement (I/II)

Ac monoclonaux

Un essai prometteur en Tx rénale Ishida J *et al.* AAC 2017

Recommandations disponibles

Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7)



Lancet Infect Dis 2019

Per Ljungman, Rafael de la Camara, Christine Robin, Roberto Crocchiolo, Hermann Einsele, Joshua A Hill, Petr Hubacek, David Navarro, Catherine Cordonnier, Katherine N Ward, on behalf of the 2017 European Conference on Infections in Leukaemia group*

Original Clinical Science—General



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

Camille N. Kotton, MD,¹ Deepali Kumar, MD,² Angela M. Caliendo, MD, PhD,³ Shirish Huprikar, MD,⁴ Sunwen Chou, MD,⁵ Lara Danziger-Isakov, MD, MPH,⁶ and Atul Humar, MD⁷
on behalf of the The Transplantation Society International CMV Consensus Group

Transplantation ■ June 2018 ■ Volume 102 ■ Number 6

Guideline

American Society for Transplantation and Cellular Therapy Series: #4 - Cytomegalovirus treatment and management of resistant or refractory infections after hematopoietic cell transplantation

Michelle K. Yong^{1,2,3,*}, Terri Lynn Shigle⁴, Yae-Jean Kim⁵, Paul A. Carpenter⁶, Roy F. Chemaly⁷, Genovefa A. Papanicolaou⁸



Clinical TRANSPLANTATION

The Journal of Clinical and Translational Research

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice

Raymund R. Razonable ✉, Atul Humar

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Published NEW JOURNAL, 8/18/2020



CMV: en résumé

Reste un problème majeur en transplantation et en hématologie

Le letermovir en prophylaxie en alloHSCT et Tx rénale

Plus d'options en cas d'infections R/R/I: maribavir, voire letermovir

Démocratisation des IGRA après les essais de plus grande envergure?

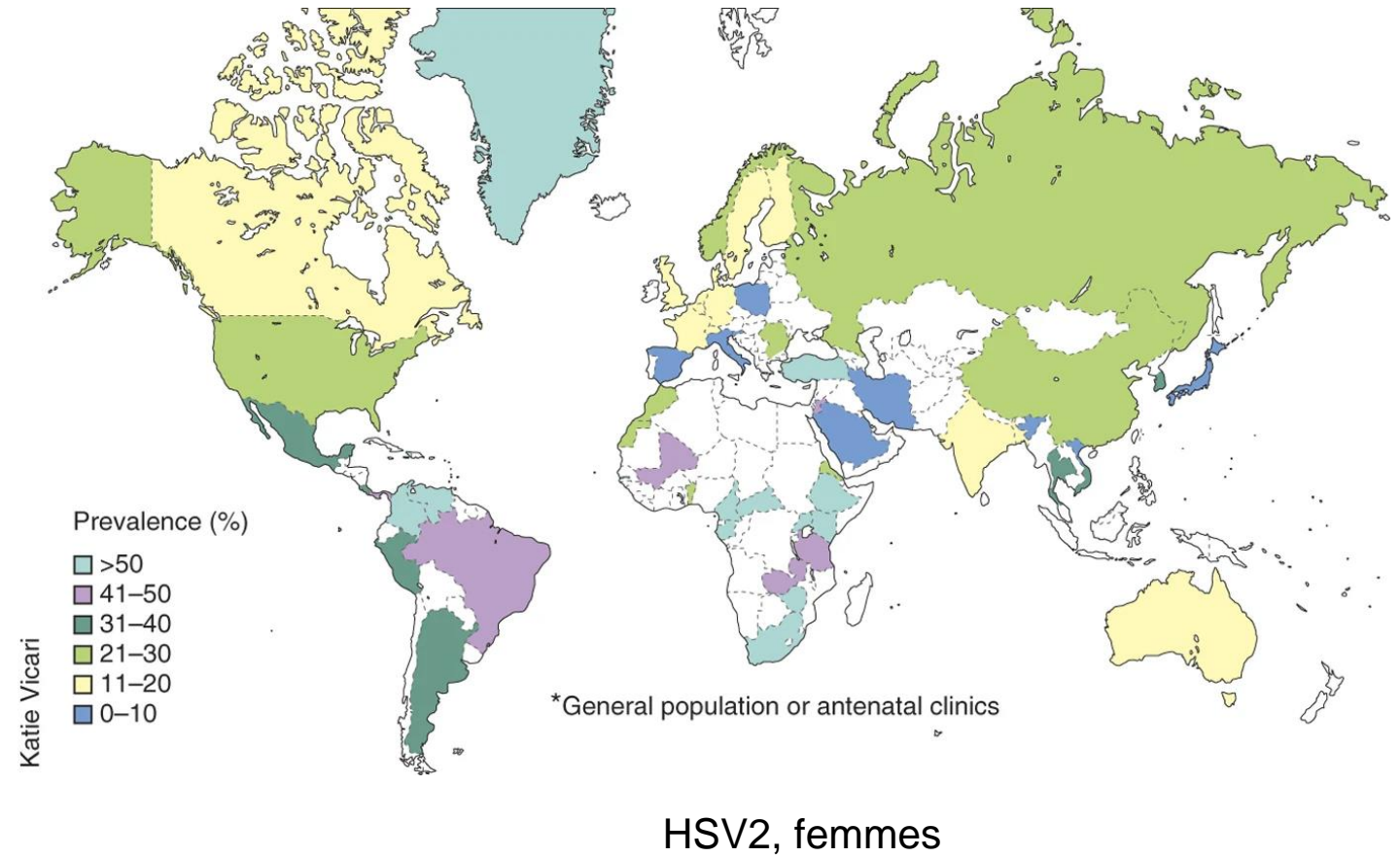
Place des CTL mal définie

Traiter, mais aussi tenter de réduire l'immunosuppression!

Si problème: CNR Herpesviridae à Limoges

HSV 1/2

Séroprévalence globale 67%
Variations géographiques
Transmission muqueuse
Latence: ganglion nerveux



HSV: amplitude du problème

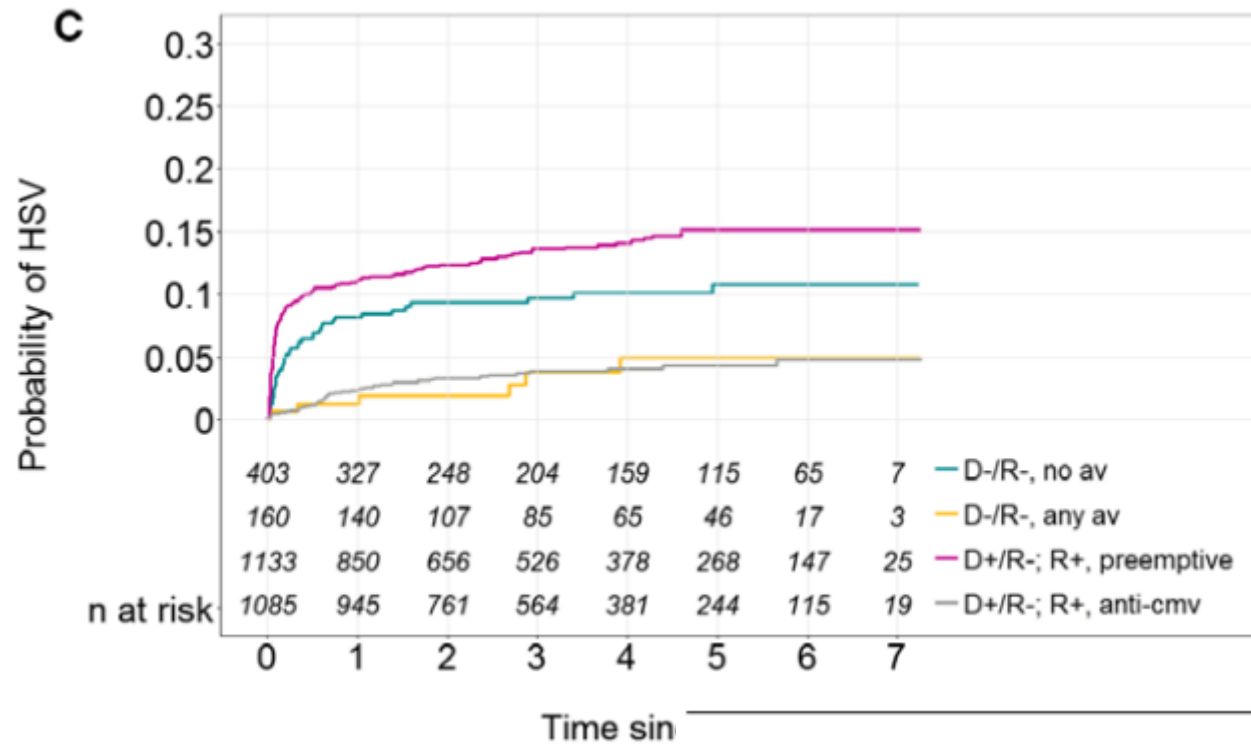
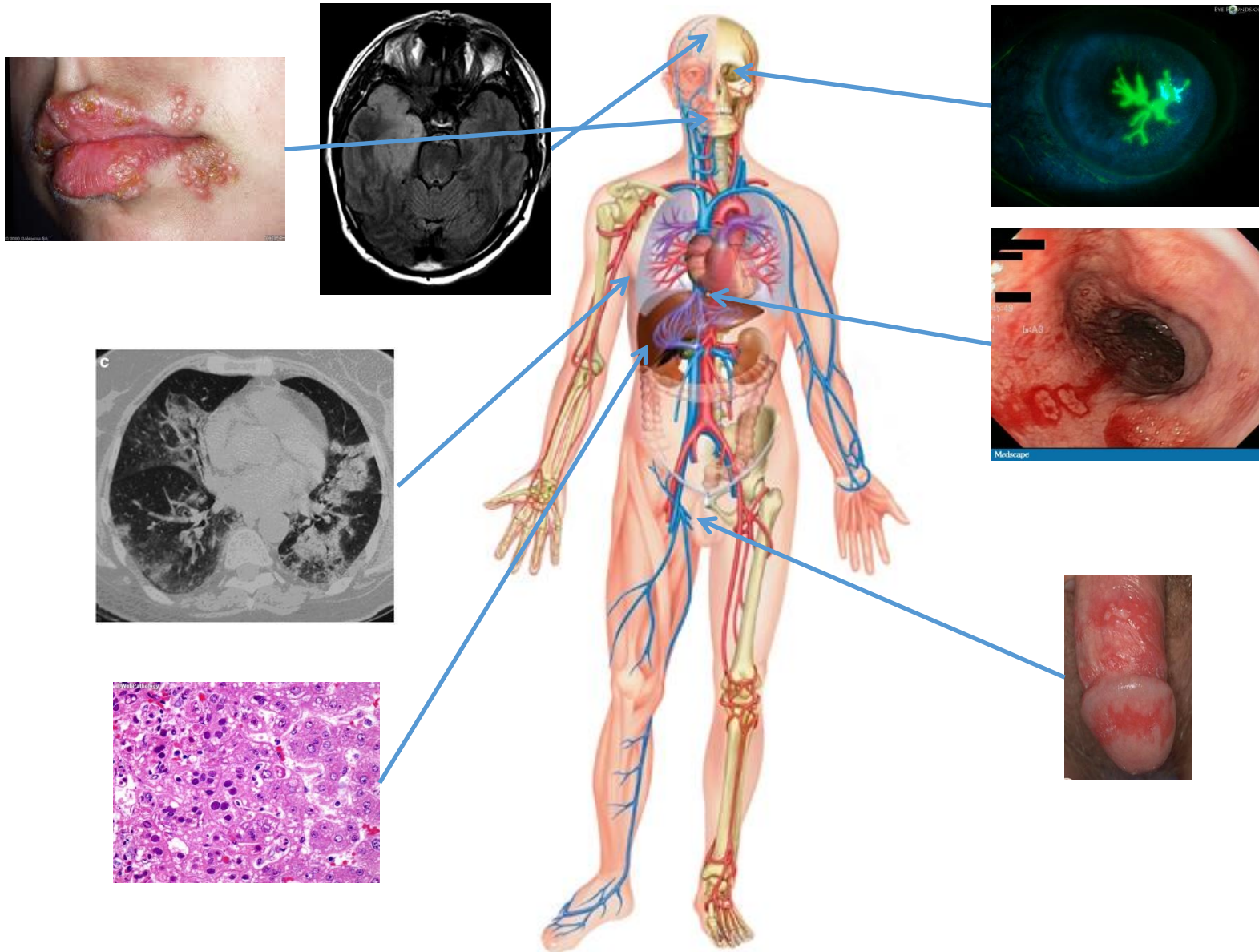


Table 2. Herpes simplex virus (HSV) cultures by site and CD4+ cell count.

	CD4+ cell count ($\times 10^6/l$)						P value
	< 50			> 50			
	+	-	% +	+	-	% +	
Oronasal	21	14	60	8	49	14	< 0.0001
Perianal	29	14	67.4	12	24	33.3	= 0.007
Genital	4	6	40	4	13	23.5	NS
Other	2	6	25	3	14	17.6	NS

	Initial visit			Follow-up visit		
	Adolescents* n = 24	Adults n = 119	Total n = 143	Adolescents* n = 22	Adults n = 103	Total n = 125
Trichomoniasis	4 (16.7)	12 (10.1)	16 (11.2)	5 (22.7)	18 (17.5)	23 (18.4)
Gonorrhea	4 (16.7)	1 (0.8)	5 (3.5)	5 (22.7)	4 (3.9)	9 (7.2)
Genital herpes	1 (4.3)	7 (5.9)	8 (5.6)	2 (9.1)	18 (17.5)	20 (12.4)
Chlamydia	3 (12.5)	2 (1.7)	5 (3.5)	1 (4.5)	4 (3.9)	5 (3.5)
Syphilis	1 (4.2)	8 (6.3)	9 (5.9)	0	7 (7.4)	7 (5.6)
Genital warts	2 (8.7)	0	2 (1.4)	3 (13.6)	4 (3.8)	7 (6.1)
Pelvic inflammatory disease	1 (4.2)	0	1 (0.7)	1 (4.5)	3 (2.9)	4 (3.3)
Any sexually transmitted disease	9 (37.5)	27 (22.7)	36 (25.2)	11 (50.0)	42 (40.8)	53 (42.4)
Pregnancy	9 (37.5)	20 (16.0)	29 (19.7)	1 (4.2)	10 (9.0)	11 (9.0)

HSV: tableaux cliniques



Terrains

VIH

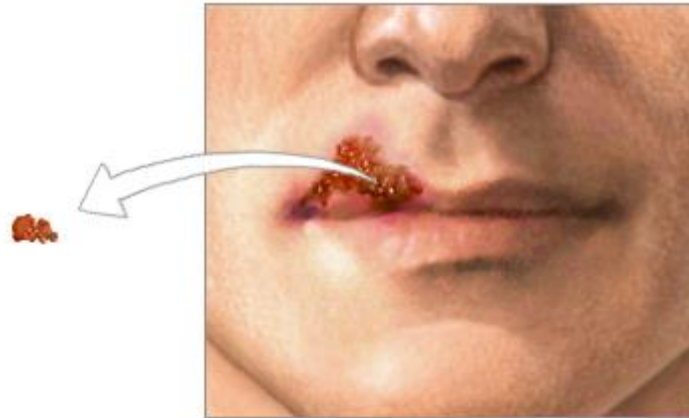
Transplantation

Pathologies systémiques

DIP

...

Herpès cutanéomuqueux des immunodéprimés



Spécificités des ID
Evolution plus longue
Présentation atypique
Résistance ACV

Diagnostic: clinique
si doute: PCR locale
PCR sang peu utile

HSV: quelques formes viscérales

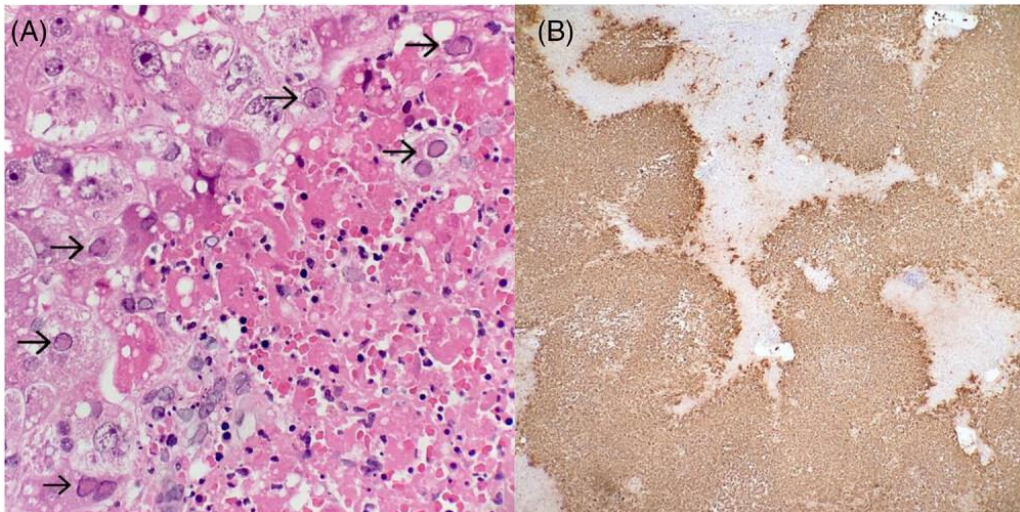
Hépatite à HSV (1/2)

Terrain: grossesse, VIH, corticothérapie, néoplasie

Présentation: hépatite fébrile (98%), très sévère
CIVD (84%), choc
lésions cutanées < 50%

Immunodépression: facteur de risque d'évol. défav.

Valeur de la PCR HSV sang?



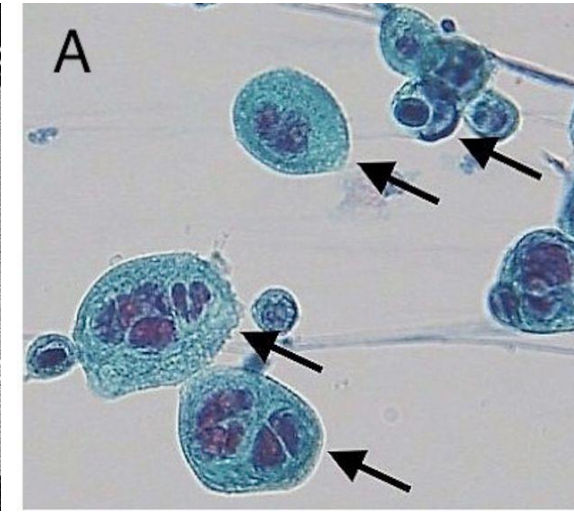
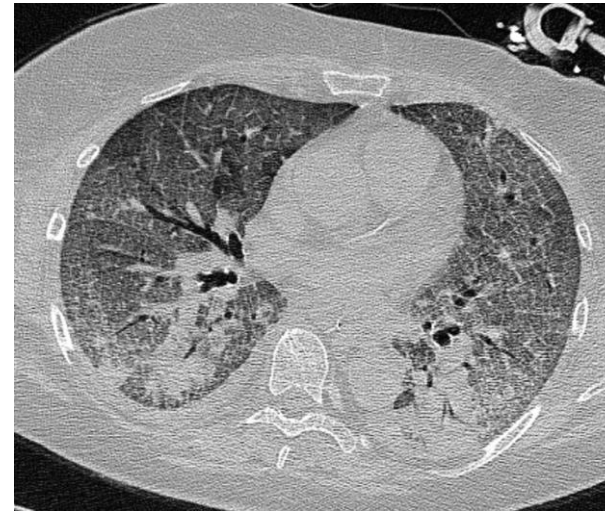
Pneumonie à HSV (1/2)

Terrain: VM, immunodépression cellulaire

Présentation: pneumonie interstitielle
lésions cutanées ?

Anapath: effet cytopathogène

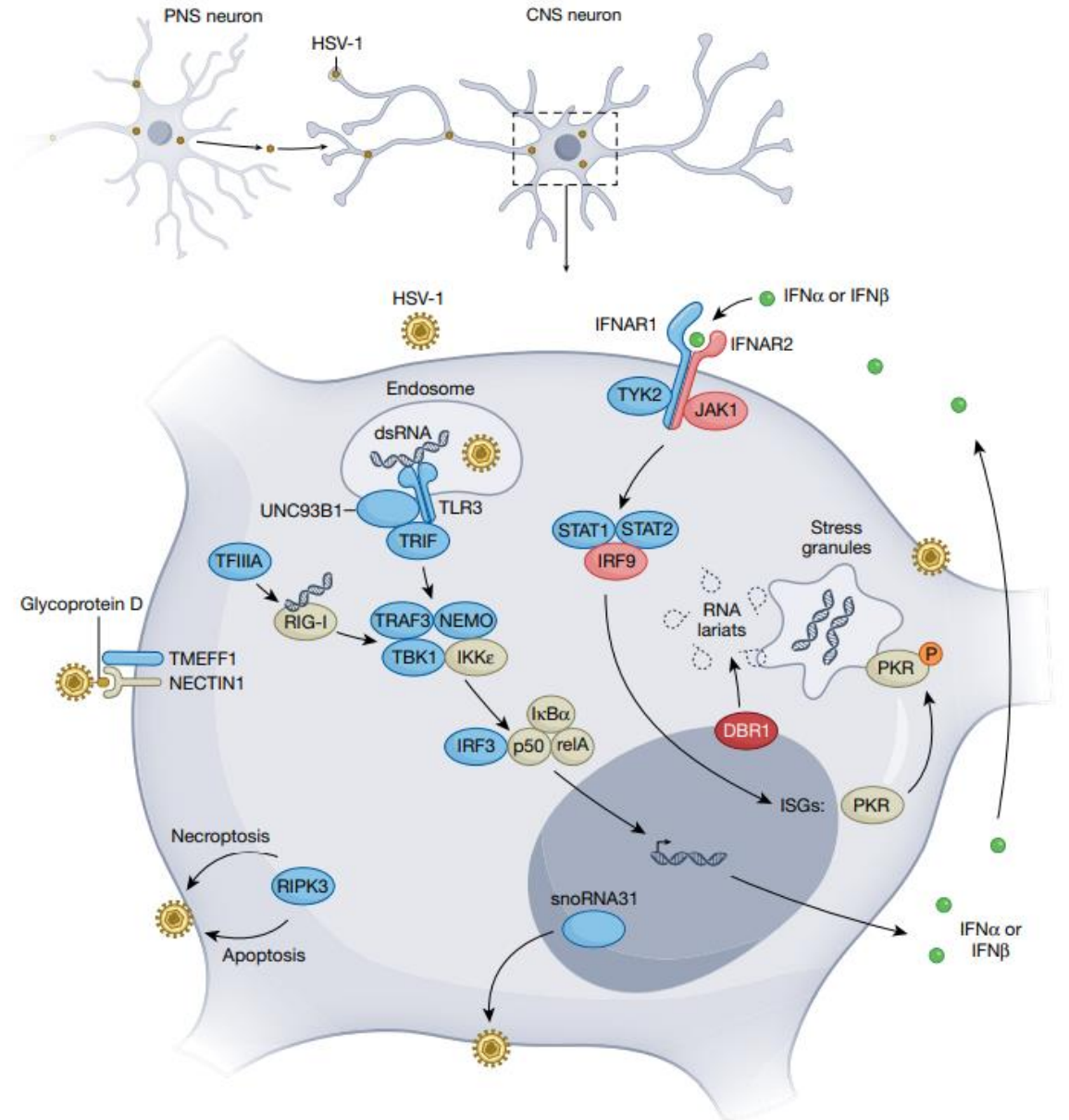
Valeur de la PCR HSV sang?



HSV : traitement et prophylaxies

	VIH	SOT	HSCT
<i>Curatif</i>	V-ACV PO 1000 mg/12h 7-10 j	V-ACV PO 1000 mg/12h 7 j au moins ACV IV 5 mg/kg/8h	
<i>Prophylaxie primaire</i>	Non	Si R+: cf CMV (sauf letermovir!) Sinon V-ACV PO 500 mg/12h ACV PO 400-800/12h Famciclovir PO 500 mg/12h	
<i>Prophylaxie secondaire</i>	V-ACV PO 500 mg/12h	Non	Non
<i>Curatif viscéral</i>	ACV IV 10 mg/kg/8h	ACV IV 5-10 mg/kg/8h	

Encéphalite herpétique et DIP



Mechanism of antiviral immunity

Response to type I interferon

Gene	OMIM no.	Mode of inheritance
<i>IFNAR1</i>	IMD106 (619935)	AR
<i>IFNAR2</i> ^a	IMD45 (616669)	AR
<i>TYK2</i>	IMD35 (611521)	AR
<i>JAK1</i> ^a	JAK1 (*147795)	AR
<i>STAT1</i>	IMD31B (613796)	AR
<i>STAT2</i>	IMD44 (616636)	AR

Production of type I interferon

<i>IRF9</i> ^a	IMD65 (619648)	AR
<i>TLR3</i>	IMD83 (613002)	AR
<i>UNC93B1</i>	IIEA1 (610551)	AR
<i>TRIF</i>	IIEA6 (614850)	AR
<i>TRAF3</i>	IIEA5 (614849)	AD
<i>TBK1</i>	IIEA8 (617900)	AD
<i>IRF3</i>	IIEA7 (616532)	AD
<i>NEMO</i>	IP (308300)	XR

Type I interferon-independent cell-intrinsic antiviral immunity

<i>GTF3A</i>	GTF3A (*600860)	AR
<i>RIPK3</i>	RIPK3 (*605817)	AR
<i>SNORA31</i>	IIEA10 (619396)	AD
<i>TMEFF1</i>	TMEFF1 (*603421)	AR
<i>DBR1</i>	IIEA11 (619441)	AR

HSV: les résistances virales

TK virale inactive

TK virale moins active

Modifications ADNpol virale

95%

5%

FDR: profondeur de l'immunodépression
durée de l'exposition aux antiviraux

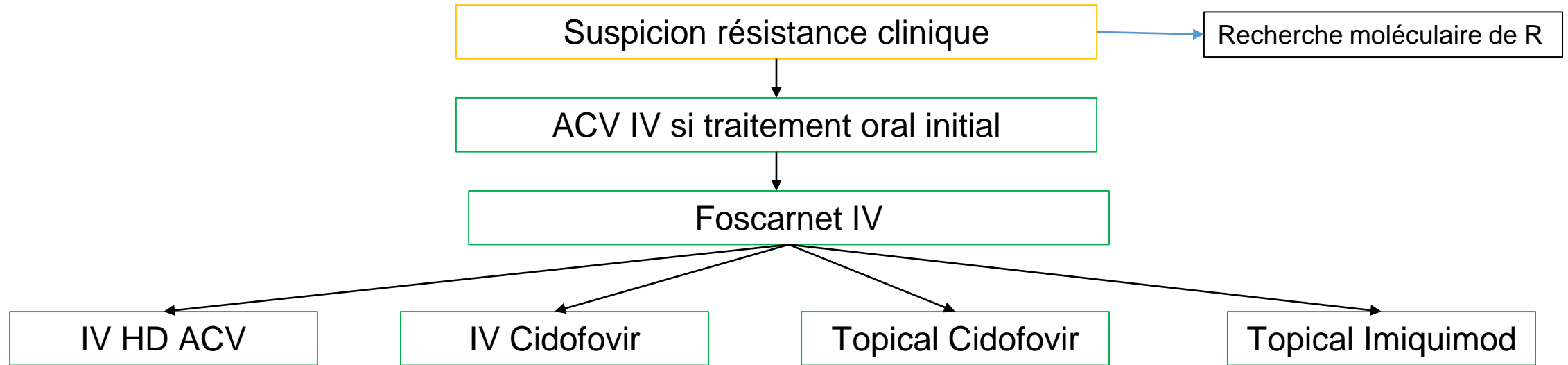
Clinique: non-réponse vers J7-10

Virus excreted	Immunocompetent patients		Immunocompromised patients		Total patients
	No. of patients ^a	No. of strains	No. of patients	No. of strains	No. of strains
HSV-1	1,237 (3 [0.2%])	1,326	1,168 (36 [3%])	2,405 (39 [1.6%])	2,848
HSV-2	618 (3 [0.5%])	664	334 (18 [5.4%])	952 (21 [2.2%])	1,075
Total	1,855 (6 [0.3%])	1,990	1,502 (54 [3.6%])	3,357 (60 [1.8%])	3,923

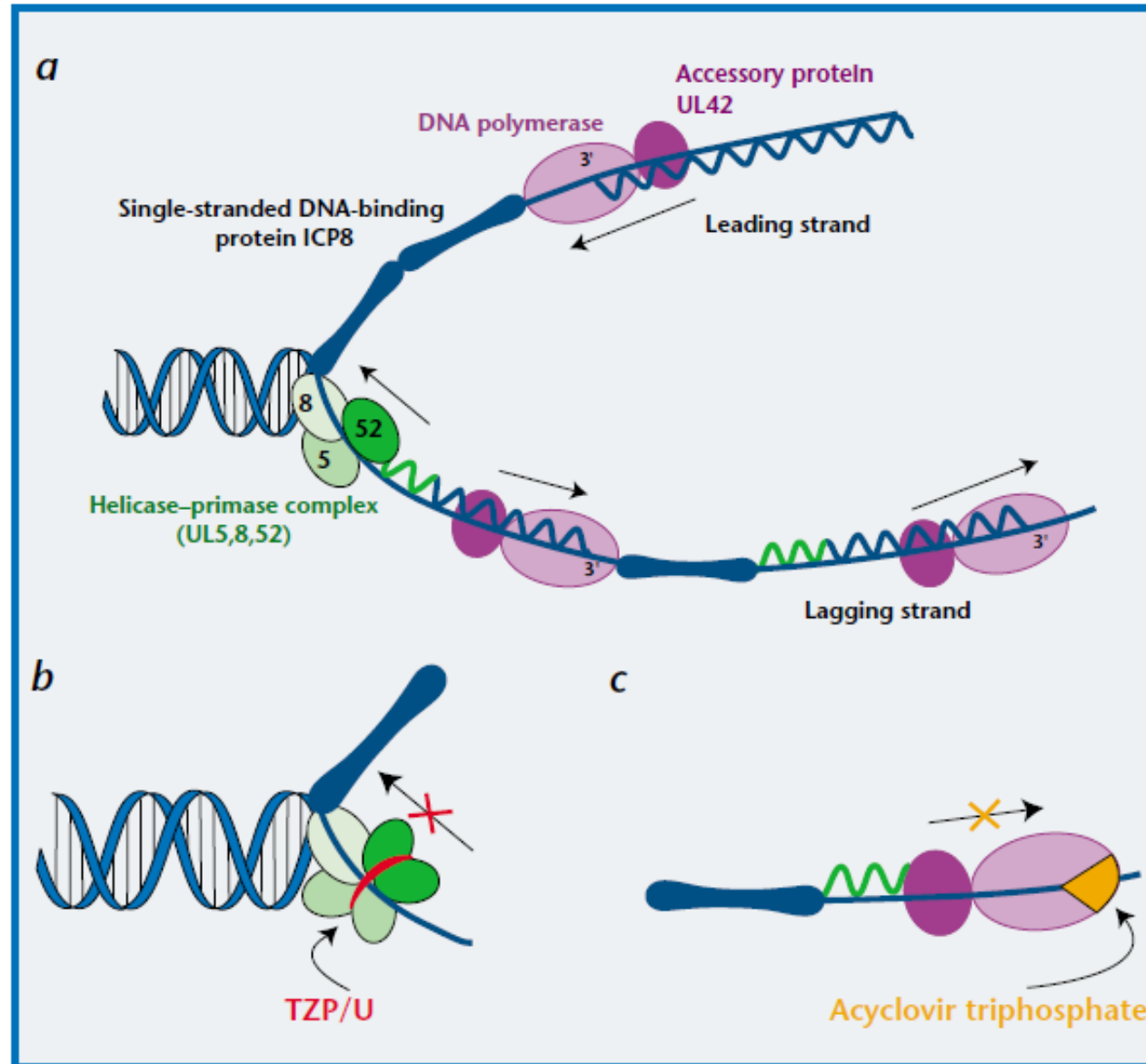
Immune status of the patient	No. of patients	No. of patients with resistant HSV (%)	No. of isolates	No. of resistant HSV isolates
Immunocompetent				
Total	368	1 (0.27)	389	1
Immunocompromised				
HSCT	28	4 (14.3)	34	5
HIV	51	2 (3.92)	59	3
Malignancy	26	1 (3.85)	36	2
SOT	17	0 (0.00)	17	0
Other	6	2 (na) ^a	7	2
Total	128	9 (7.03)	153	12
Grand total	496	10 (2.02)	542	13

Cause of immunosuppression	No. (%) of patients excreting:					
	HSV-1		HSV-2			
	ACV sensitive	ACV resistant	ACV sensitive	ACV resistant		
Bone marrow transplant	160	22 (12.1)	19	201	10.9	
HIV infection	133		164	13 (7.5)	310	4.2
Hemopathies	464	9 (1.9)	37	2 (5.1)	512	2.1
Organ transplant	164	4 (2.4)	32	1 (3.1)	201	2.5
Miscellaneous ^a	90	1 (1.1)	26	2 (7.1)	119	2.5
Cancer	62		22		84	
Corticotherapy	47		11		58	
Burns	24		0		24	
Nonspecified	24		5		29	
Total	1,132	36	316	18	1,502	3.6

HSV résistant: traitement



HSV: inhibiteurs de l'hélicase-primase



Pritelivir

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

JANUARY 16, 2014

VOL. 370 NO. 3

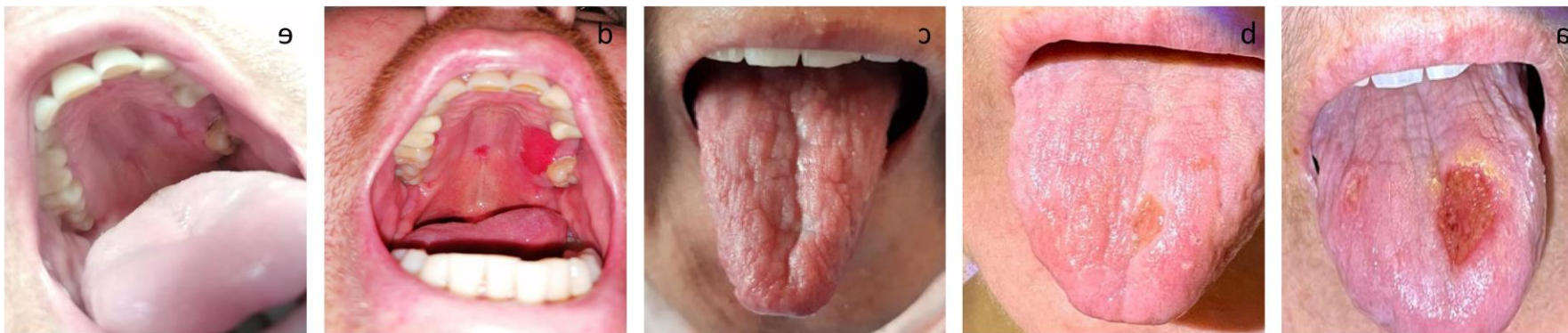
Helicase–Primase Inhibitor Pritelivir for HSV-2 Infection

Anna Wald, M.D., M.P.H., Lawrence Corey, M.D., Burkhard Timmler, M.D., Amalia Magaret, Ph.D., Terri Warren, M.N., Stephen Tyring, M.D., Ph.D., Christine Johnston, M.D., M.P.H., John Kriesel, M.D., Kenneth Fife, M.D., Ph.D., Lawrence Galitz, M.D., Susanne Stoelben, M.D., M.P.H., Meei-Li Huang, Ph.D., Stacy Selke, M.A., Hans-Peter Stobernack, D.V.M., Helga Ruebsamen-Schaeff, Ph.D., and Alexander Birkmann, Ph.D.

JAMA | Original Investigation

Effect of Pritelivir Compared With Valacyclovir on Genital HSV-2 Shedding in Patients With Frequent Recurrences A Randomized Clinical Trial

Anna Wald, MD, MPH; Burkhard Timmler, MD; Amalia Magaret, PhD; Terri Warren, ANP; Stephen Tyring, MD, PhD; Christine Johnston, MD, MPH; Kenneth Fife, MD, PhD; Stacy Selke, MA; Meei-Li Huang, PhD; Hans-Peter Stobernack, PhD; Holger Zimmermann, PhD; Lawrence Corey, MD; Alexander Birkmann, PhD; Helga Ruebsamen-Schaeff, PhD

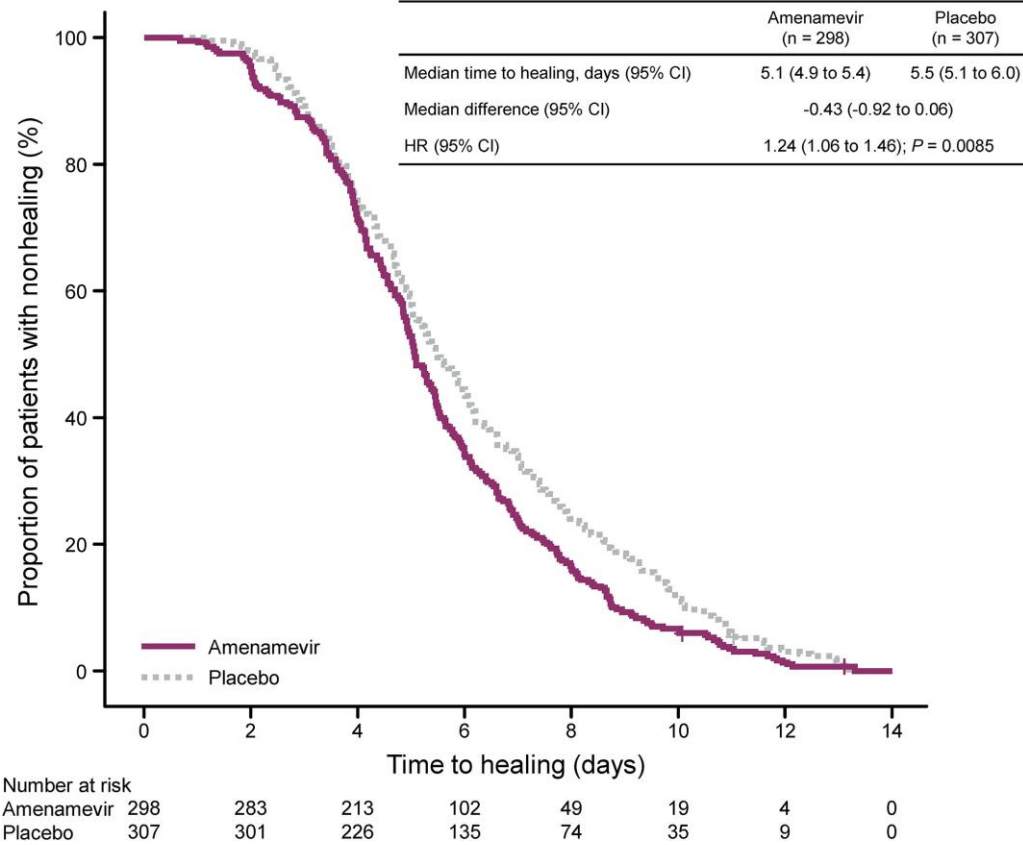


Chez l'immunodéprimé

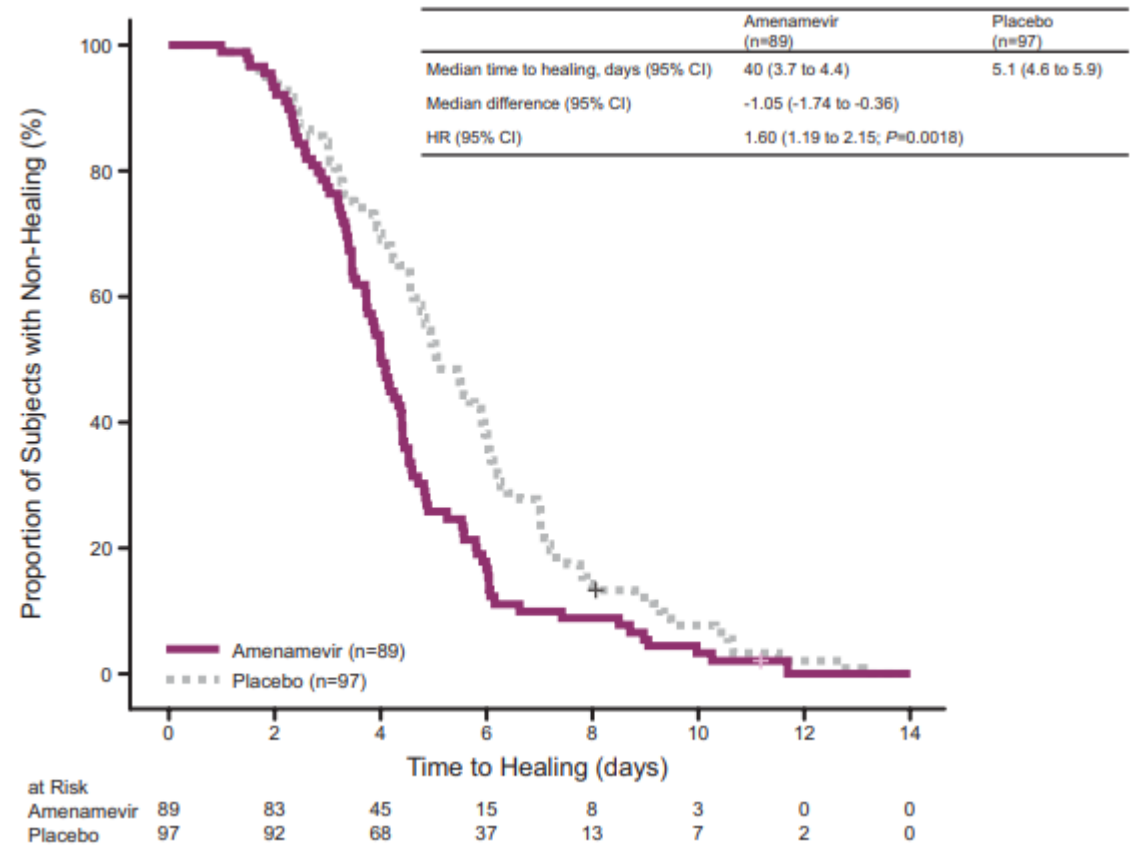
N=4, allogreffés

Amenamevir

Herpès oral



Herpès génital



Immunodéprimés: 3 case reports chez des allogreffés

HSV des immunodéprimés: en résumé

Encore très fréquent, notamment VIH / transplantation

Très majoritairement cutanéomuqueux

Clinique parfois atypique

Plus d'options en cas d'infections R/R/I: pritelivir, voire amenamevir

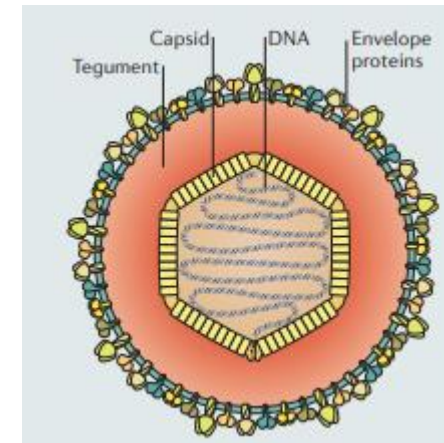
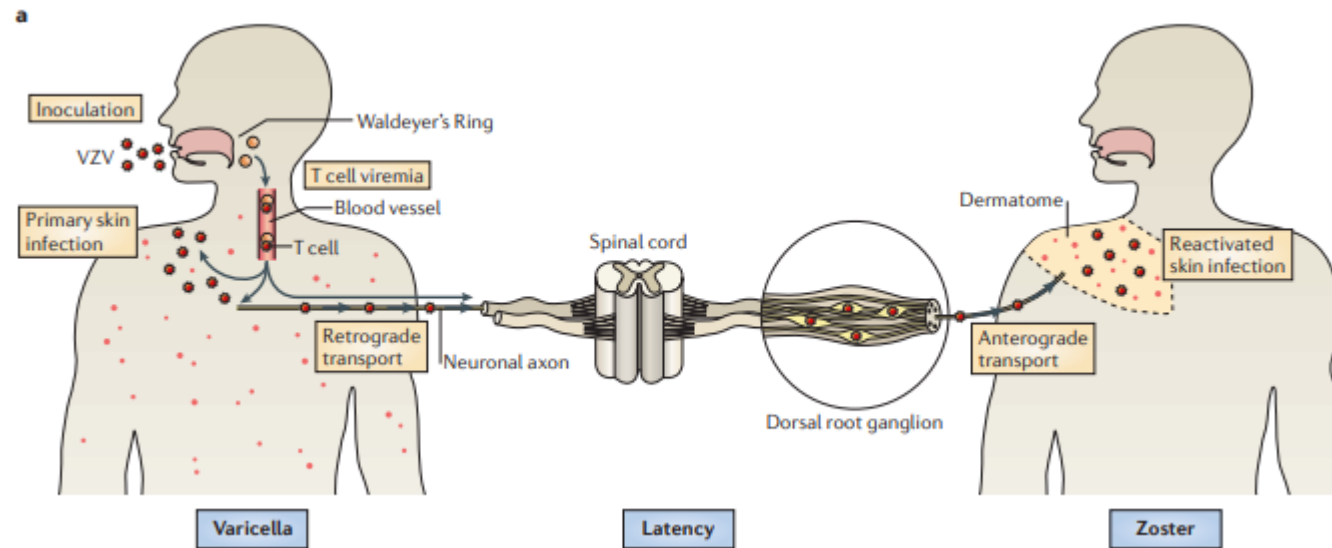
Les schémas prophylactiques sont bien établis

CNR: laboratoire associé GHPS

VZV

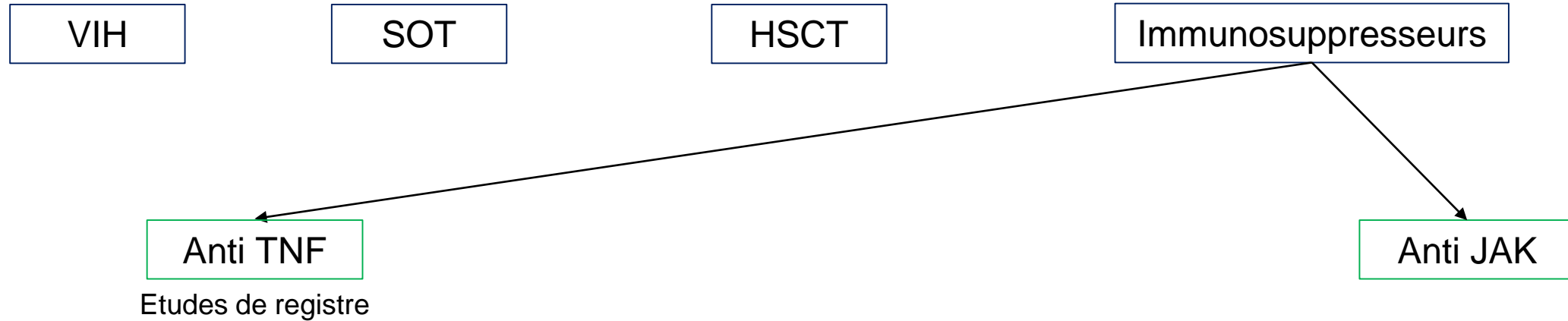
Séroprévalence globale très élevée

ID: 0.1% des varicelles, mais 25% des DC associés, avant l'ère des vaccins



Réactivation du VZV: terrains à risque

Immunodépression cellulaire



Strangfeld A JAMA 2009	Allemagne	PR	aHR 1,82 (1.05-3.15)
Galloway J ARD 2013	UK	PR	aHR 1,8 (1,2-2,8)
Serac G J Invest Dermatol 2012	France	PR, pso, MICI	aOR 3,49 (1,12-10,9) mAbs vs etanercept
Garcia-Doval I ARD 2010	Espagne	Rhumatismes	Hospit pour zona: 32/100000 PA vs 3,4/100000 PA

Type of infection	Number of studies	Random-effects model			Fixed-effects model		
		Relative risk	95% CI	P value	Relative risk	95% CI	P value
Overall							
Infections overall	26	1.39	1.096-1.76	.0067	1.58	1.42-1.74	<.0001
Viral infections overall	16	1.42	0.75-2.68	.27	1.77	1.25-2.52	.0012
Fungal overall	3	1.14	0.24-5.28	.86	1.24	0.28-5.41	.76
Herpes simplex virus	10	1.02	0.45-2.32	.95	1.53	0.93-2.51	.093
Herpes zoster virus	15	1.71	0.84-3.51	.13	2.37	1.25-4.49	.0075
Nasopharyngitis	19	1.15	0.87-1.52	.31	1.33	1.33-1.57	.0005
Respiratory tract infection	18	1.06	0.71-1.58	.76	1.11	0.92-1.34	.27
Pneumonia	7	0.95	0.29-3.11	.93	1.18	0.38-3.60	.77
Urinary tract infection	10	0.93	0.54-1.62	.81	1.10	0.65-1.85	.71
Folliculitis	9	1.12	0.30-4.18	.85	1.68	1.03-2.77	.039

Réactivation du VZV: clinique



Forme « classique »

APZ: 15% globalement
FDR: âge
immunosuppression

Forme compliquée

Formes faciales



Formes neurologiques

Méningite
Myélite
Encéphalite
Vasculopathie cérébrale
Guillain-Barré
Mononeuropathie

Formes disséminées



+ Atteinte viscérale

Formes surinfectées

VZV: traitement chez les immunodéprimés

VARICELLE	VIH	SOT	HSCT
Curatif	CD4 > 200: V-ACV 1 g/8h, 10 j CD4<200/atteinte viscérale: ACV IV 10 mg/kg/8h	ACV 10 mg/kg/8h Relais po possible	ACV IV 10 mg/kg/8h

ZONA	VIH	SOT	HSCT
Curatif	V-ACV PO 1000 mg/8h 7-10 j Voire ACV IV	Monométamérique V-ACV PO 7 j Sinon ACV IV 10 mg/kg/8h	
Curatif viscéral	ACV IV 10 mg/kg/8h		

Mesures associées

Précautions complémentaires air + contact

VZV: prévention chez les immunodéprimés

Antiviraux

VARICELLE	VIH	SOT	HSCT
<i>Prophylaxie primaire</i>	Non	Cf CMV (sauf letermovir)	
<i>Prophylaxie secondaire</i>	Non	Non	



Vaccin vivant atténué

Avant immunosuppression:

VZV IgG+: Zostavax © 2 doses si pas de CI

VZV IgG-: CI

Après immunosuppression:

Vaccin contre-indiqué

Abandonné

Vaccins

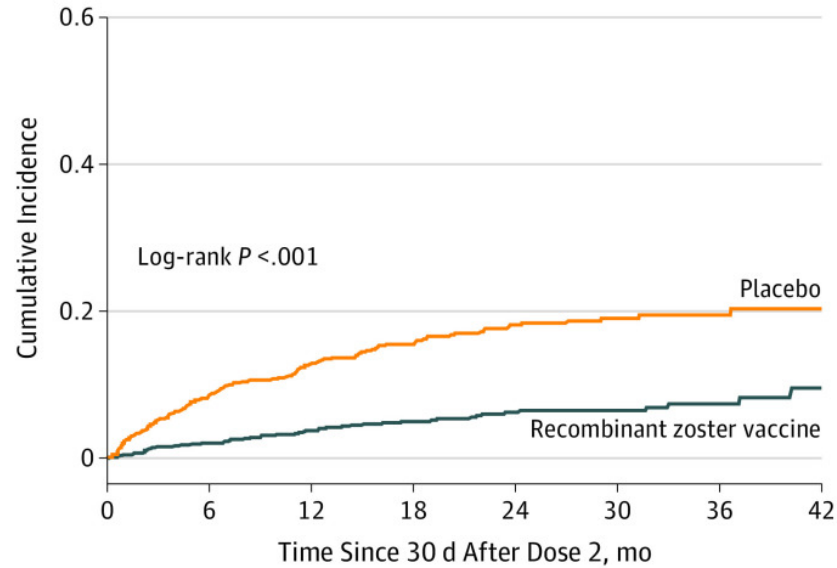


Vaccin recombinant adjuvanté

La vaccination contre le zona est également recommandée avec le vaccin SHINGRIX (vaccin zona recombinant avec adjuvant) chez les sujets âgés de 18 ans et plus, dont le système immunitaire est défaillant, en raison des pathologies innées (par exemple un déficit immunitaire primitif) ou acquises (par exemple immunodépression liée à l'infection par le VIH) ou d'un traitement (par exemple la corticothérapie au long cours ou les traitements immunosuppresseurs). Il est à noter que la vaccination des immunodéprimés fera l'objet de recommandations spécifiques.

Vaccin VZV recombinant chez les immunodéprimés

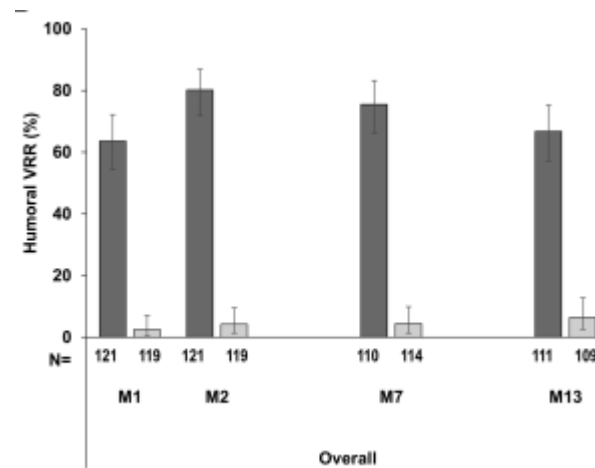
ASCT



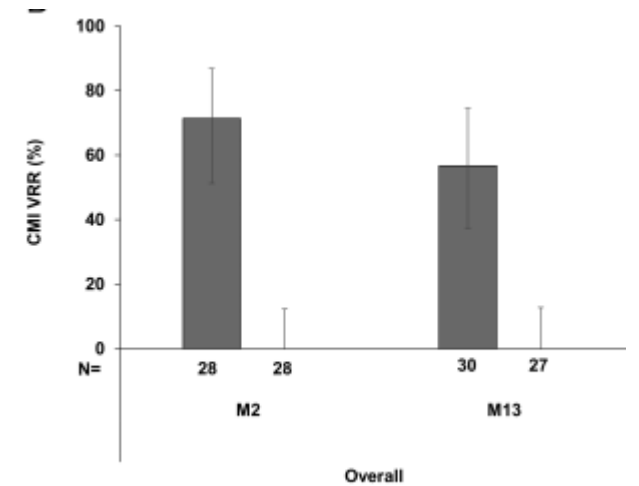
No. at risk		0	6	12	18	24	30	36	42
Placebo	851	704	604	464	337	209	112	40	
Recombinant zoster vaccine	870	779	682	537	396	268	141	49	

No. with ≥ 1 herpes zoster episode		0	6	12	18	24	30	36	42
Placebo	0	69	100	117	130	133	134	135	
Recombinant zoster vaccine	0	17	30	38	44	45	47	49	

Tx rénale



Réponse humorale



Réponse cellulaire

HHV6

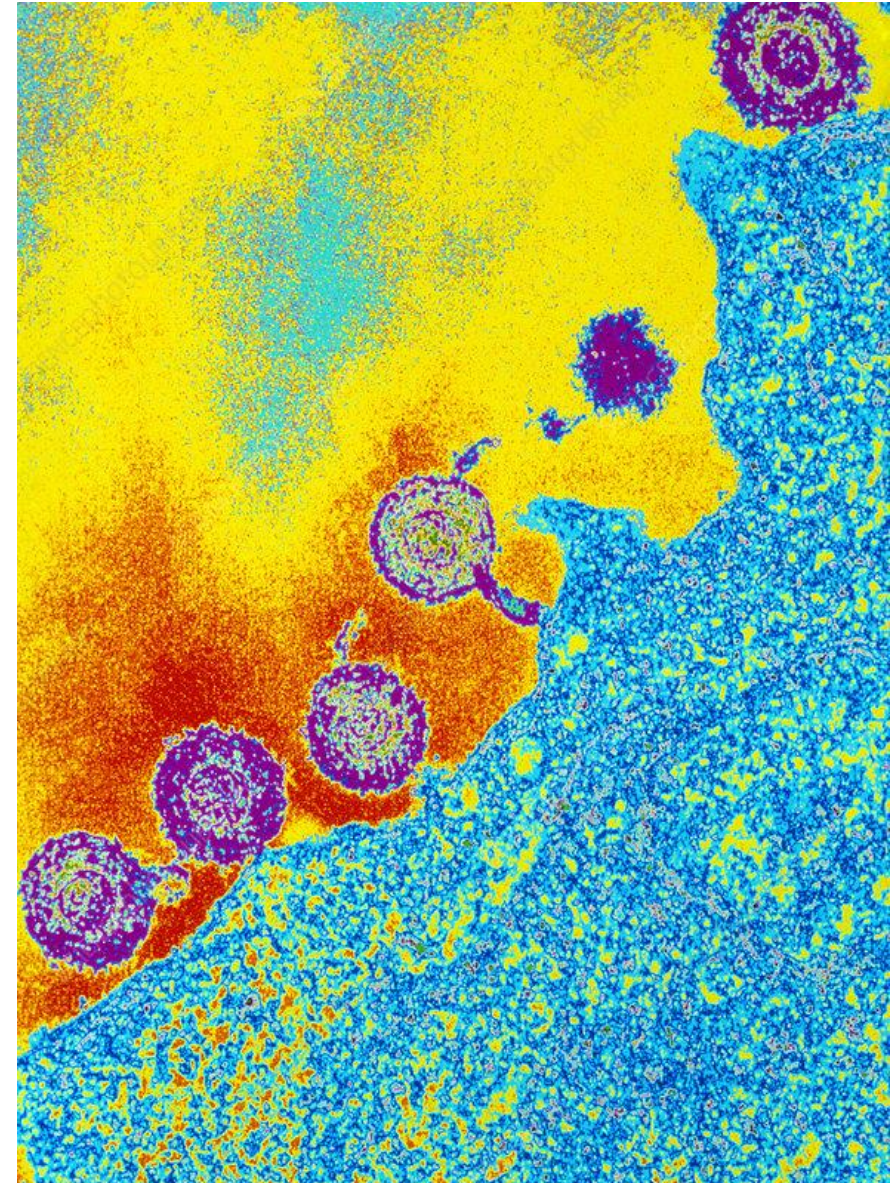
Virus à **ADN** enveloppé double brin

Deux **variants**: HHV6 B > A

Tropisme: lymphocytes T
cellules NK
astrocytes, cellules gliales
mégakaryocytes

Séroprévalence élevée (72-95%)

Transmission salivaire surtout



HHV6: tableaux cliniques chez l'immunodéprimé

Réactivation

Fréquente après *H SCT*: 42% après auto/allo Hentrich M *et al.* BJH 2005

Plus rare après *SOT*: 14% après Tx rénale Yoshikawa *et al.* Transplantation 1992

Tableaux cliniques convaincants:

Encéphalite de l'allogreffé de CSH

Pneumonie?

Myélosuppression?

Hépatite?

Associations non formellement prouvées:

SEP

Fatigue chronique

Myocardite

DRESS

...

HHV6: encéphalite limbique post allogreffe de CSH

FDR: âge, NK cell count Yu Y *et al.* BMT 2024
Sang de cordon Hill J *et al.* BBMT 2012

Rare

Délai 1 à 2 mois

Virémie concomitante

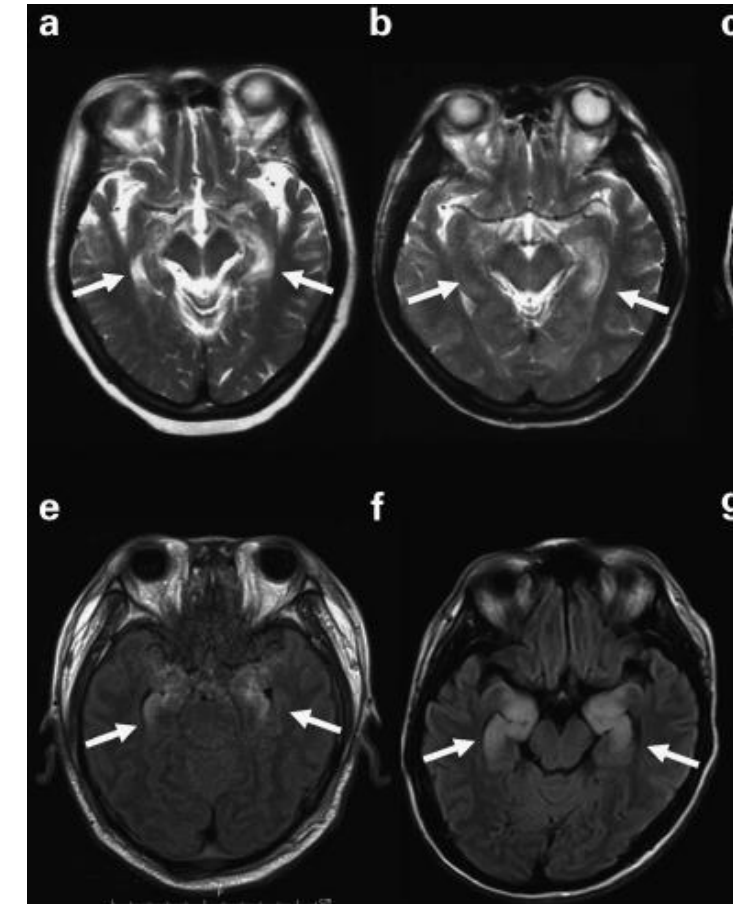
Atteinte limbique

Diagnostic sur faisceau d'arguments

Pronostic médiocre

Disease onset	Usually 2-6 weeks post HSCT, but can be later
Symptoms/signs	Confusion, encephalopathy, short-term memory loss, SIADH, seizures, insomnia
Brain MRI ^a	Often normal. Typically but not exclusively, circumscribed, non-enhancing, hyperintense lesions in the medial temporal lobes (especially hippocampus and amygdala)
Cerebrospinal fluid	HHV-6B DNA, +/- mild protein elevation, +/- mild lymphocytic pleocytosis
Prognosis	Memory defects and neuropsychological sequelae in 20-60%. Death due to progressive encephalitis in up to 25% of all HSCT recipients and up to 50% of cord blood recipients

HSCT: hematopoietic stem cell transplantation; SIADH: syndrome of inappropriate antidiuretic hormone secretion; MRI: magnetic resonance imaging; HHV6B: human herpesvirus 6B. ^aFeatures of T2, fluid attenuation, inversion recovery (FLAIR) and diffusion weighted-imaging sequences. Modified from Hill and Zerr.⁹⁹



HHV6: le problème de l'intégration chromosomique

Environ 1% en population générale

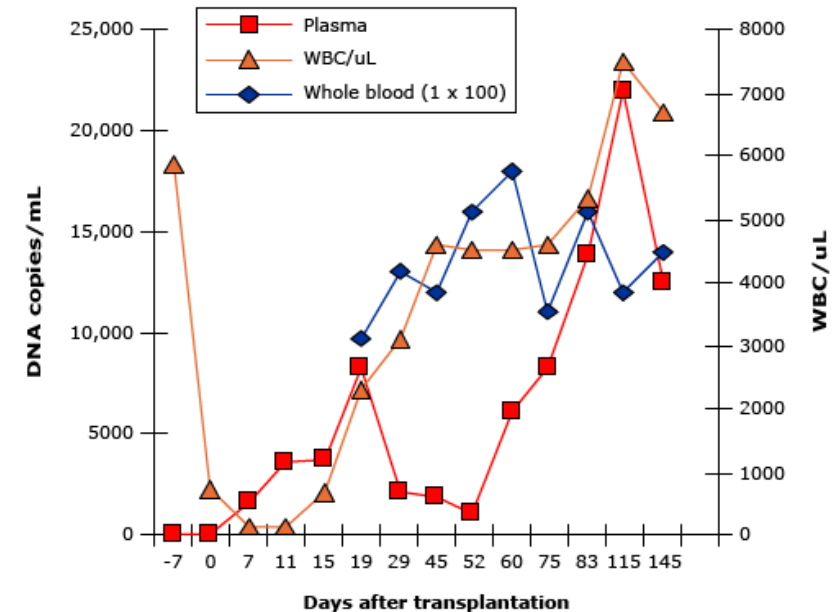
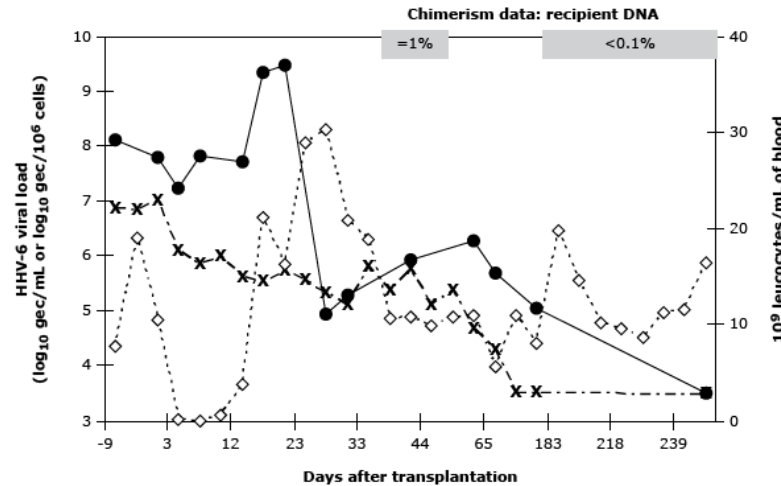
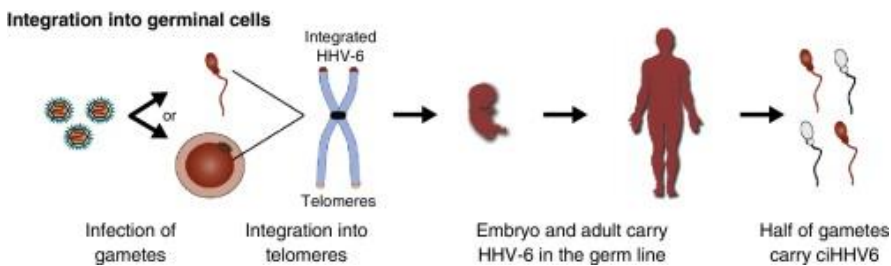
Intégration dans la lignée germinale

Charge virales très élevées, persistantes, sans effet des antiviraux
Sang total > plasma



Pour confirmer: FISH

mesure dans les follicules pileux
et PCR



HHV6: traitement

Aucun essai contrôlé

FOS 90 mg/kg/12 h

ou

GCV 5 mg/kg/12h

Durée: au moins 3 semaines

Négativation de la CV

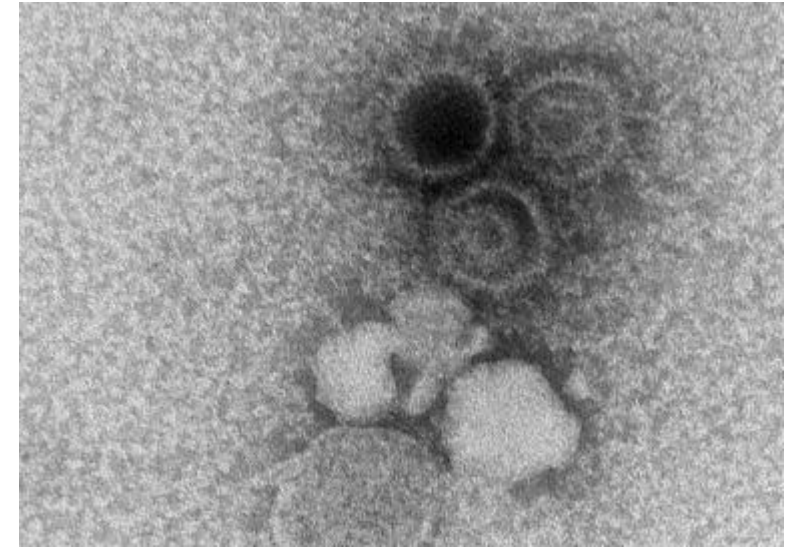
Diminution de l'immunosuppression si possible

Cidofovir: rares case reports

EBV

Transmission salivaire

Pouvoir **oncogène**: immortalise les cellules B
résiste à l'apoptose

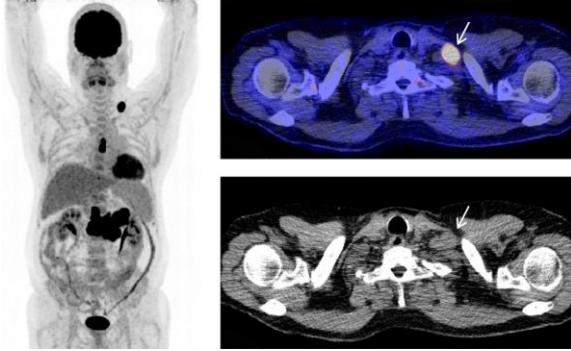


EBV: tableaux cliniques

Primo-infection



PTLD (SOT/HSCT)



Surtout 1^{ère} année (puis 7-10 ans)
D+/R-
Grêle>Poumon>Cœur>Foie>Rein
Age

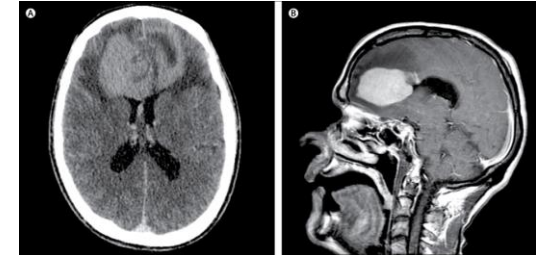
Leucoplasie
chevelue



CAEBV



GL



LNH
VIH

Quand est-il utile de rechercher l'EBV chez 1 immunodéprimé(e)?

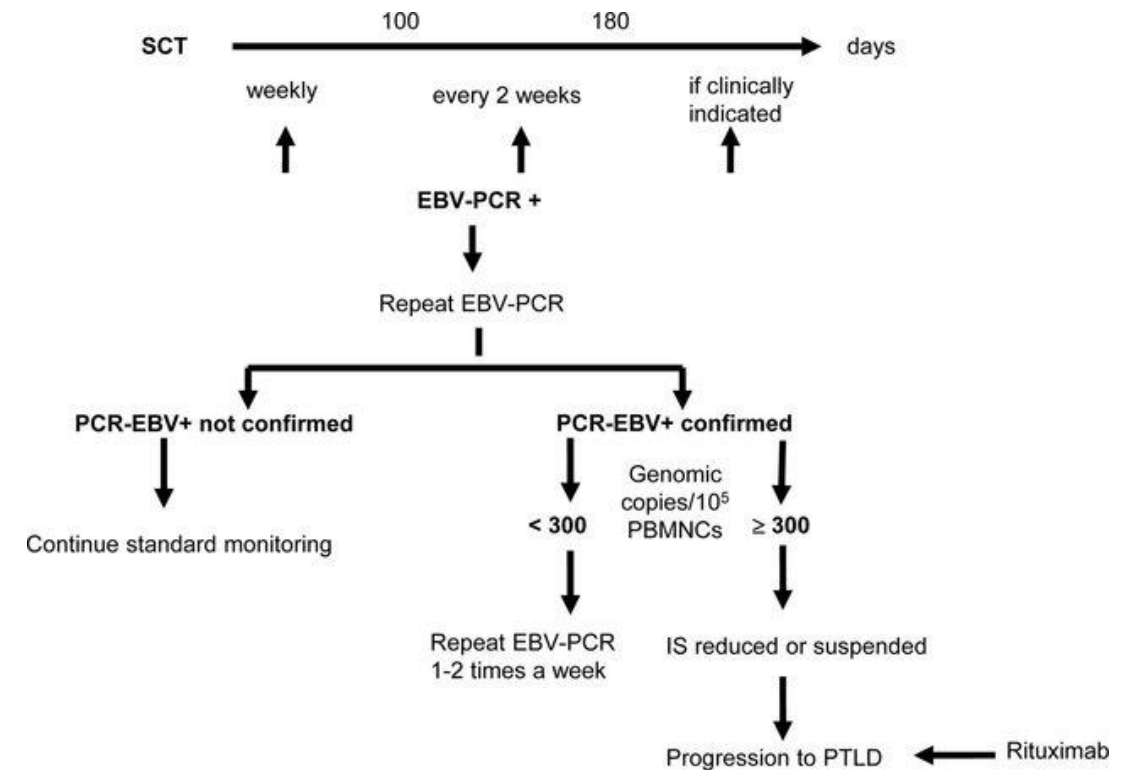
VIH: si suspicion de LNH notamment SNC

TOS: monitoring; parfois seuil d'intervention pour PTLD

HSCT: oui: traitement préemptif par RTX si positivité persistante

DIP: ?

Pathologies autoimmunes: ?



Utilisation de greffons VHC+

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

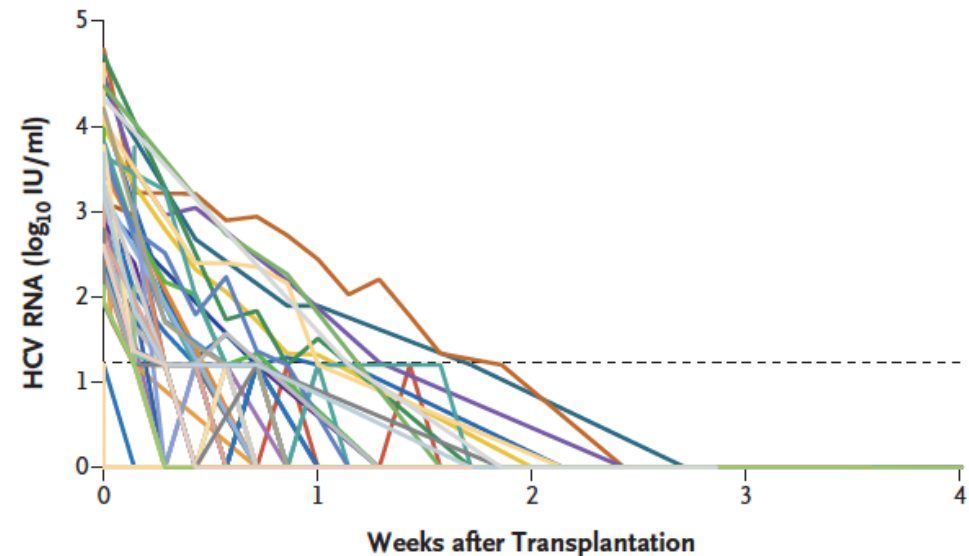
Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients

Ann E. Woolley, M.D., Steve K. Singh, M.D., Hilary J. Goldberg, M.D.,
Hari R. Mallidi, M.D., Michael M. Givertz, M.D., Mandeep R. Mehra, M.D.,
Antonio Coppolino, M.D., Amanda E. Kuztos, B.S., Megan E. Johnson, B.A.,
Kaiwen Chen, B.S., Esther A. Haddad, M.D., John Fanikos, R.Ph.,
David P. Harrington, Ph.D., Phillip C. Camp, M.D., and Lindsey R. Baden, M.D.,
for the DONATE HCV Trial Team*

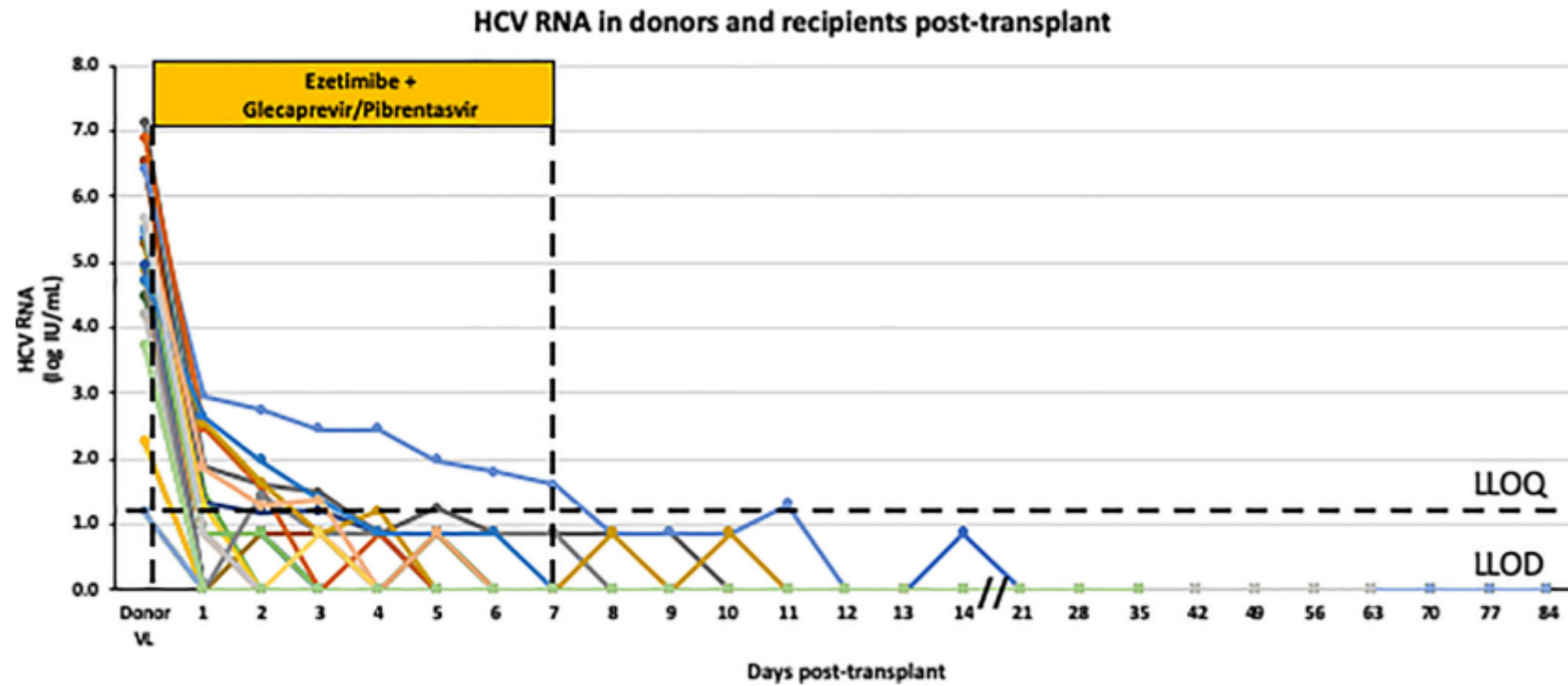
2019

Transplantation de poumons (n=36) et
cœurs (n=8) provenant de patients HCV +

4 semaines Sofosbuvir–velpatasvir



Utilisation de greffons VHC+: encore plus fort



Hépatites E en transplantation: formes chroniques

Table 3. Patients with Resolving HEV Infection and Those in Whom the Infection Evolved to Chronic Hepatitis.

Variable	Patients with Resolving Infection (N = 6)	Patients with Chronic Infection (N = 8)	P Value
	<i>median (range)</i>		
At diagnosis			
Time since transplantation — mo	78.5 (25–168)	37.5 (6.0–63.0)	0.03
Leukocyte count — $\times 10^{-3}/\text{mm}^3$	8.85 (6–9.66)	4.31 (2.19–7.20)	0.004
Lymphocyte count — $\times 10^{-3}/\text{mm}^3$			
Total	1.73 (1.12–2.33)	0.75 (0.63–1.04)	0.004
CD2+	1.59 (0.84–2.25)	0.66 (0.58–0.92)	<0.001
CD3+	1.54 (0.70–1.88)	0.61 (0.49–0.79)	0.01
CD4+	0.93 (0.49–1.07)	0.22 (0.16–0.40)	0.004
Platelet count — $\times 10^{-3}/\text{mm}^3$	261 (190–285)	155.5 (75.0–250.0)	0.01
Serum creatinine — mg/dl*	2.15 (1.31–2.84)	1.33 (1.08–1.89)	0.01
At last follow-up			
Aspartate aminotransferase — IU/liter	25.5 (7–35)	55.5 (39.0–238.0)	0.002
Alanine aminotransferase — IU/liter	25 (13–45)	108.0 (59.0–298.0)	0.002

Merci!

Herpesviridae et immunodépression

Problème restant fréquent

Immunodépressions cellulaires: transplantation, VIH

Des schémas prophylactiques bien codifiés

La résistance virale reste marginale actuellement

Vaccination VZV inactivée