

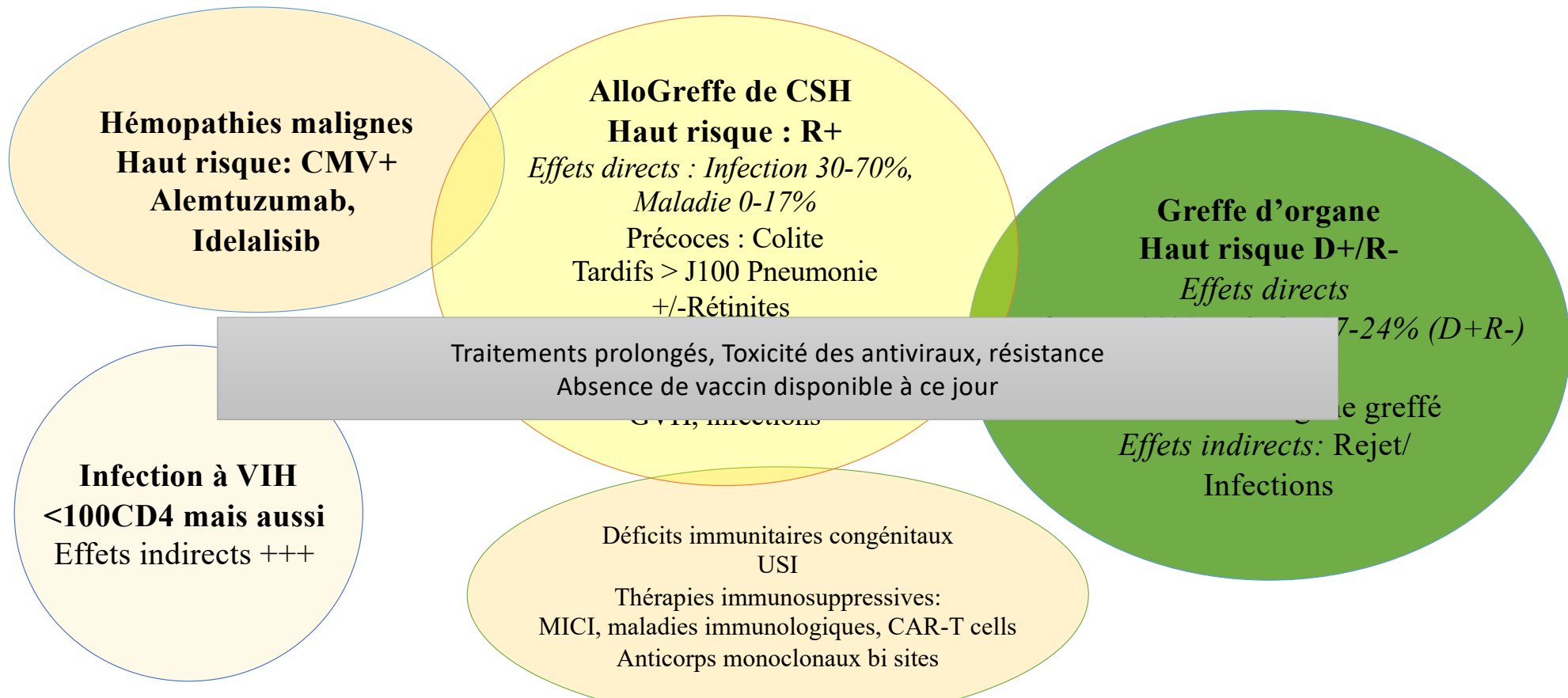
Immunomonitoring CMV : quels outils pour quelles questions ?

**Journée nationale du DES de maladies infectieuses
S. Alain
5 octobre 2026**

Objectifs :

- L'infection à CMV et la réponse immune,
- Méthodes de mesure de la réponse immunitaire cellulaire
- Recommandations 2025 utilisation des tests en transplantation d'organe et allogreffe de CSH
- Etudes majeures et nouvelles études 2025-2026
- Conclusions et perspectives

Impact du CMV en cas d'immunodéficience :



- Kotton C et al., Fourth IntL consensus guidelines on the management of cytomegalovirus in solid organ transplantation. Transplantation 2025
- Ljungman P. et al., Recommendations from the 10th European Conference on Infections in Leukaemia for the management of cytomegalovirus in patients after allogeneic haematopoietic cell transplantation and other T-cell-engaging therapies . Lancet ID 2025

Transplantation d'organe solide

(Source : ABM 2023)

- Un risque infectieux permanent lié à l'immunodéficience cellulaire
- Prophylaxie par valganciclovir ou letermovir (depuis 2024)

Allogreffe de cellules souches hématopoïétiques

- Des receveurs plus âgés, c'est-à-dire davantage de receveurs séropositifs pour le CMV (> 60 %) = patients à haut risque
- Une période à haut risque après la greffe, marquée par une reconstitution immunitaire progressive
- Une prophylaxie par letermovir disponible depuis 2018

Facteurs influant sur les conséquences de l'infection à CMV

- Charge virale initiale et augmentation de la charge virale

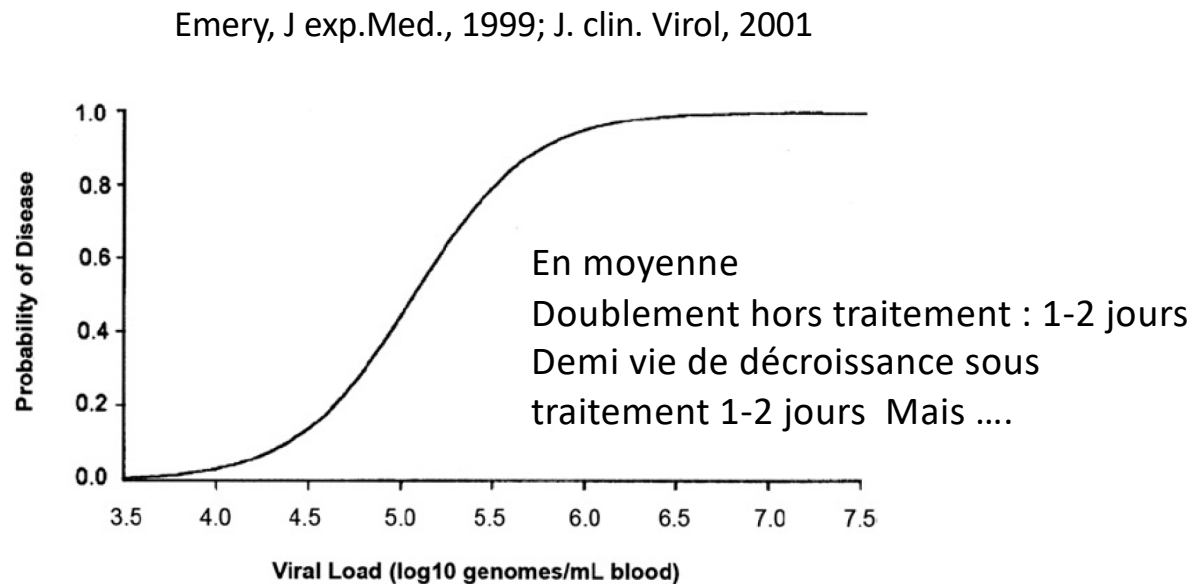
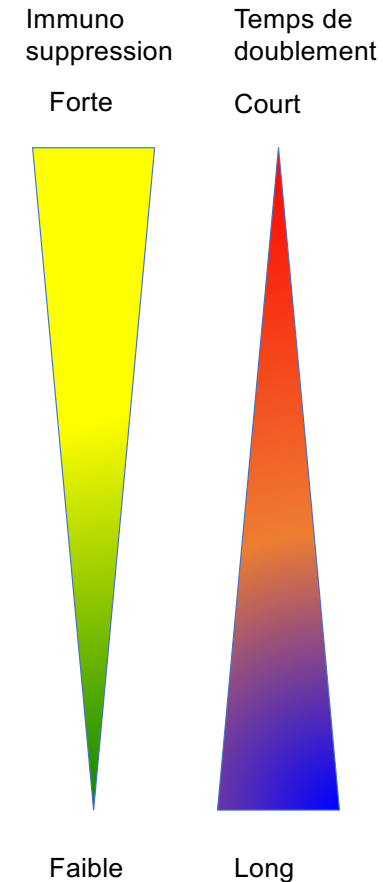


Fig 2. Association between cytomegalovirus viral load and disease probability.¹¹ (Adapted with permission from Cope AV et al. *J Infect Dis.* 1997;176:1484-1490.)

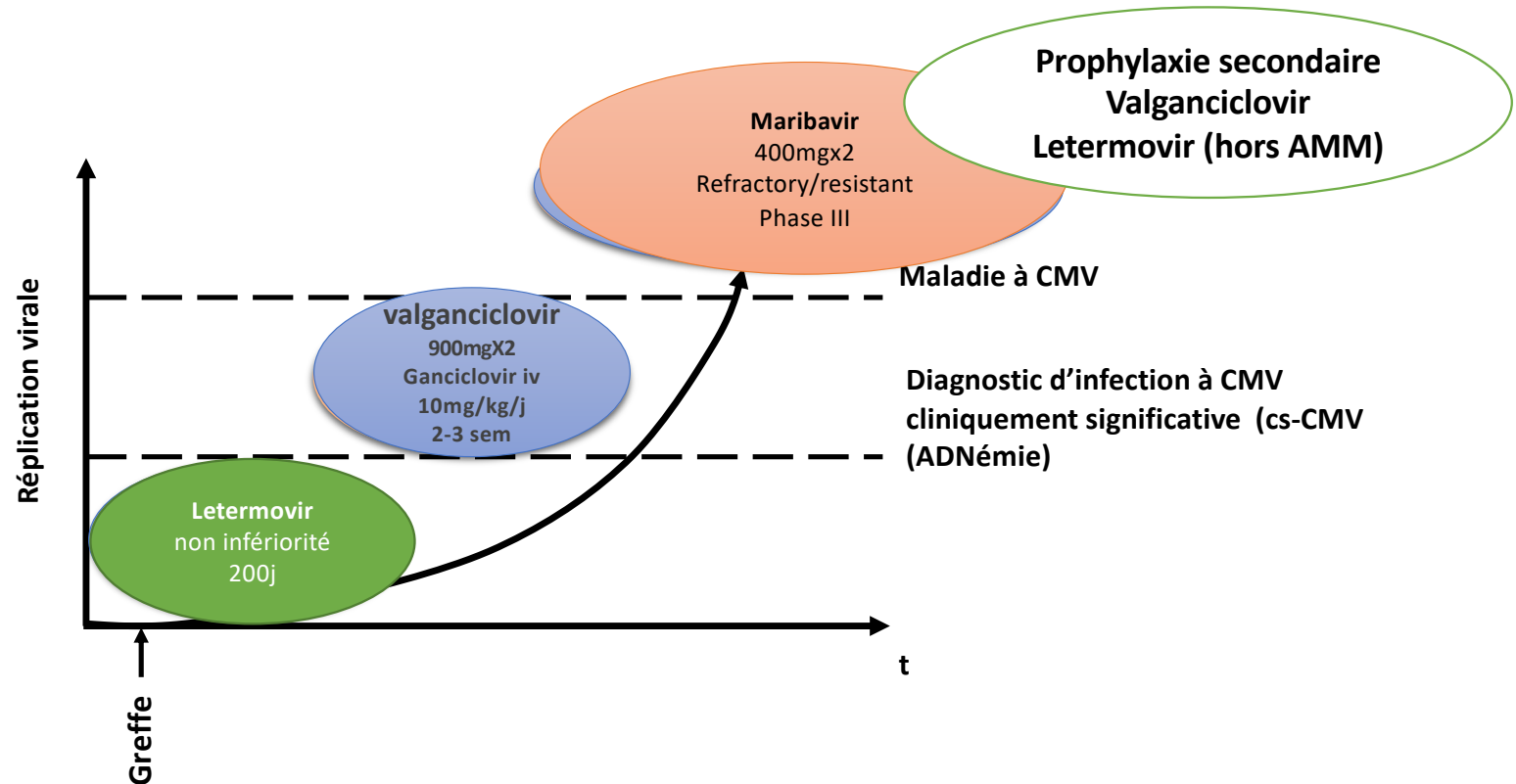
- Contrôle immunitaire

=> Ne pas laisser « exploser la charge virale »



Emery et al (2000) *Lancet* 355:2032-36
Boeckh et al., (2010)

Traitement de l'infection à CMV post greffe



Kotton C et al., Third IntL consensus guidelines on the management of cytomegalovirus in solid organ transplantation, Transplantation 2018, [revues 2024](#)

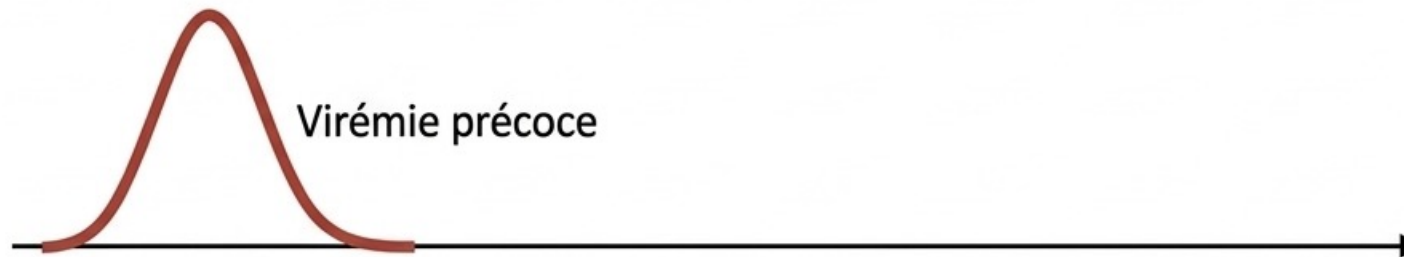
Avery RK, et al., Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial. *Clin Infect Dis.* 2022.

Marty FM et al., Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation *NEJMed* 2017

L'Impact de la Prophylaxie sur la Cinétique de l'Infection

La prophylaxie universelle retarde la reconstitution immunitaire spécifique, déplaçant le risque vers une maladie à révélation tardive (late-onset disease).

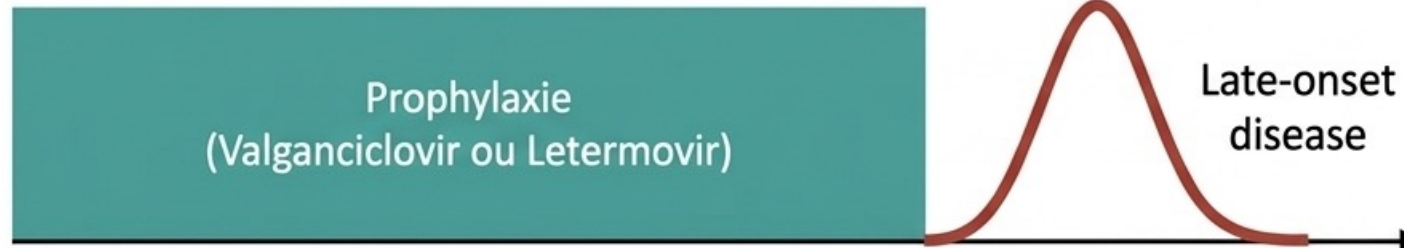
Scénario A : Sans Prophylaxie (Préemptif)



Transplantation d'Organes Solides (SOT)

- Prophylaxie par valganciclovir (3 à 6-12 mois selon le statut D/R).

Scénario B : Prophylaxie Universelle

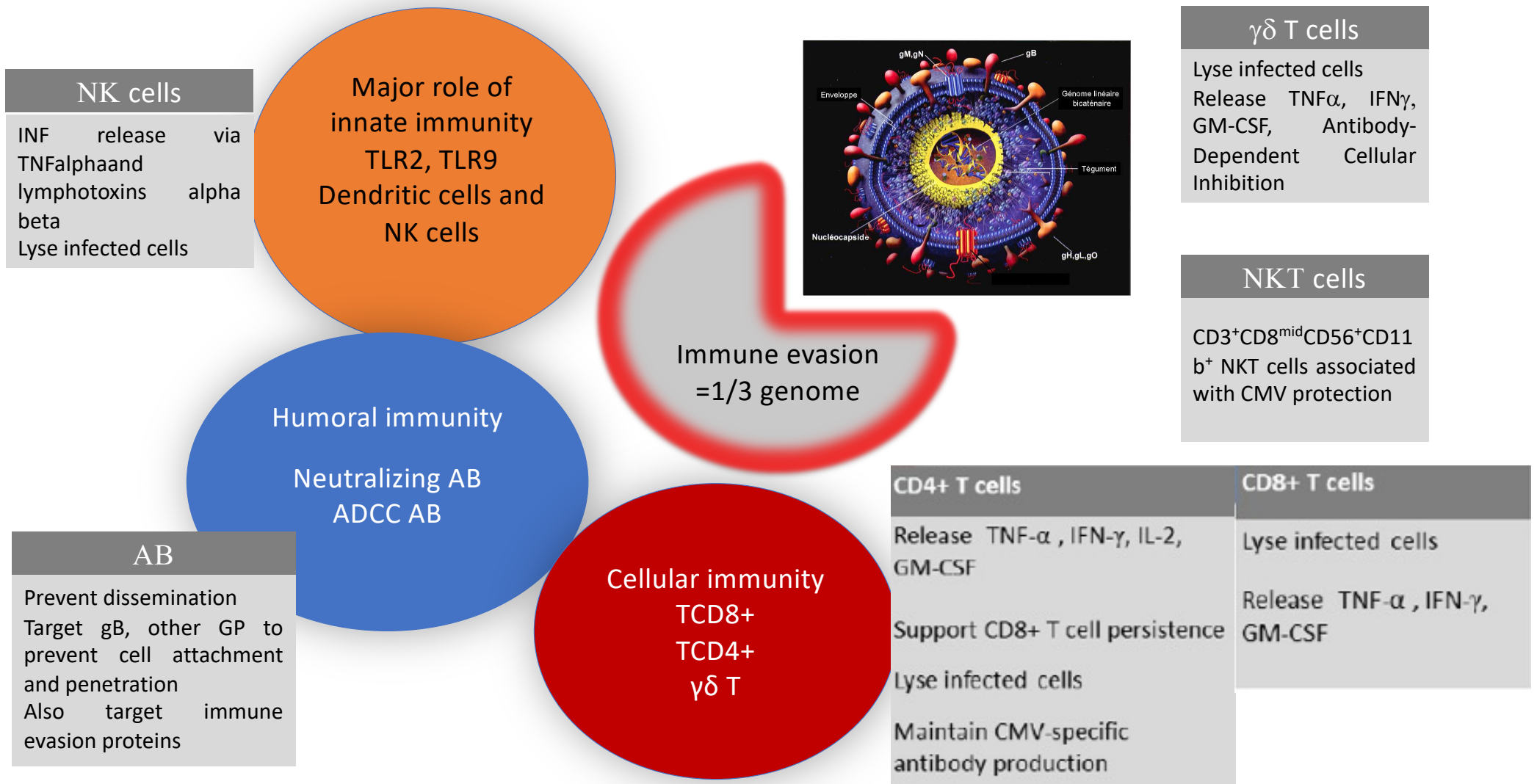


Cellules Souches Hématopoïétiques (HSCT)

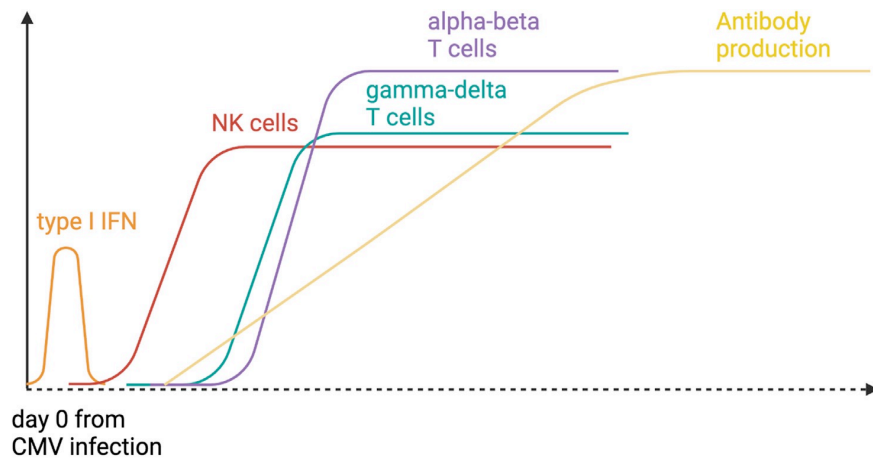
- Prophylaxie par Letermovir (J100 à J200).

Besoin Clinique : Nécessité absolue d'un **biomarqueur** pour guider la durée de la prophylaxie et anticiper la maladie tardive.

Immunité anti-CMV : un équilibre entre contrôle et échappement



Réponse immune anti-CMV post-greffe d'organe



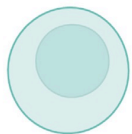
Patient greffé : prévenir la
réplication et la maladie à CMV

Immunité cellulaire +++ > Humorale



NK cells

- memory characteristics
- CD94/NKG2C⁺CD57⁺FcεR1γ



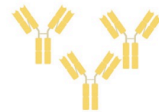
gamma-delta T cells

- memory characteristics
- TEMRA cells
- TCR ligand CMV-induced
- CMV control



CD4⁺/CD8⁺ alpha-beta T cells

- memory inflation
- TEMRA/TCM CD8⁺ cells
- effector memory CD4⁺ cells
- long term control of infection

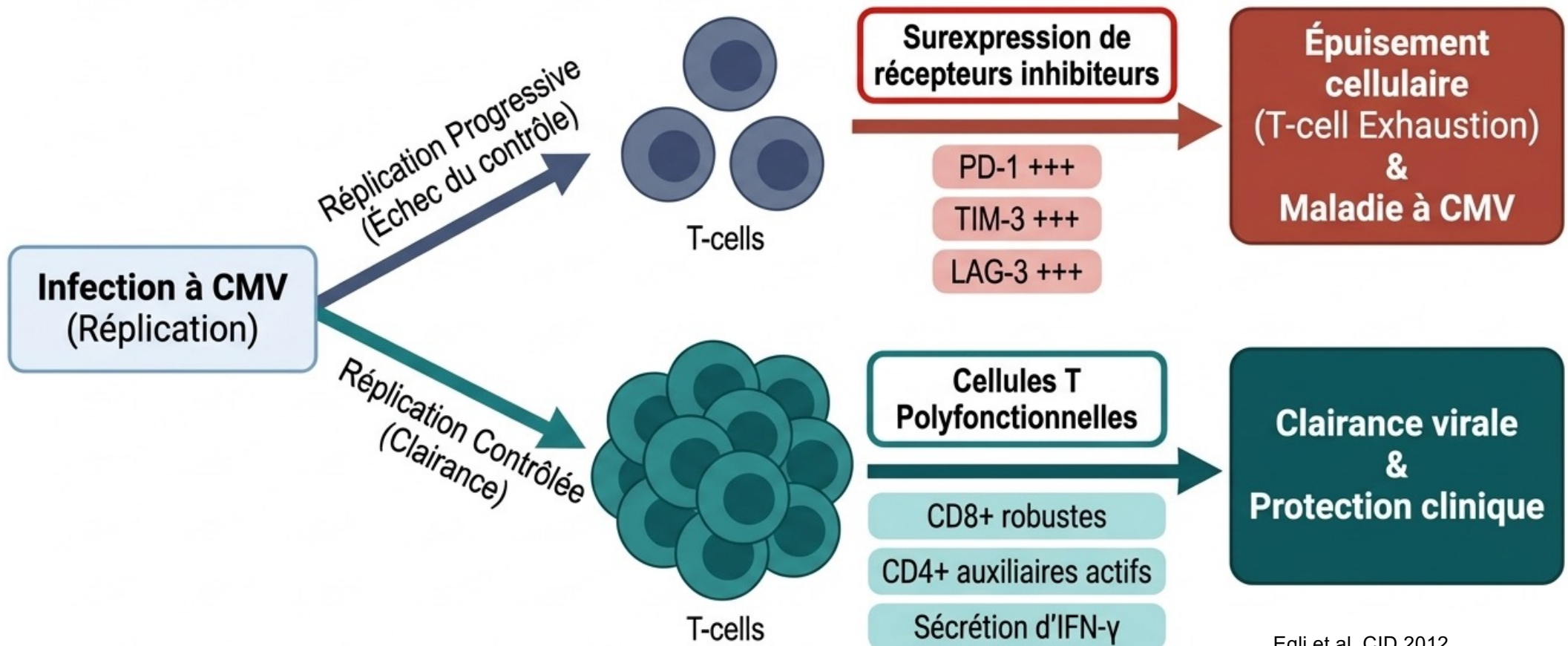


antibody production

- gB, gH, gL, pUL 128-131
- restricting viral dissemination
- limiting viral entry into host cells

Dynamique et Épuisement de la Réponse T-Spécifique

La simple présence de lymphocytes T ne suffit pas ; il est crucial de mesurer leur fonctionnalité *ex-vivo*.



Egli et al. CID 2012
Forconi et al., 2017

Un répertoire CTL très large, avec deux épitopes dominants

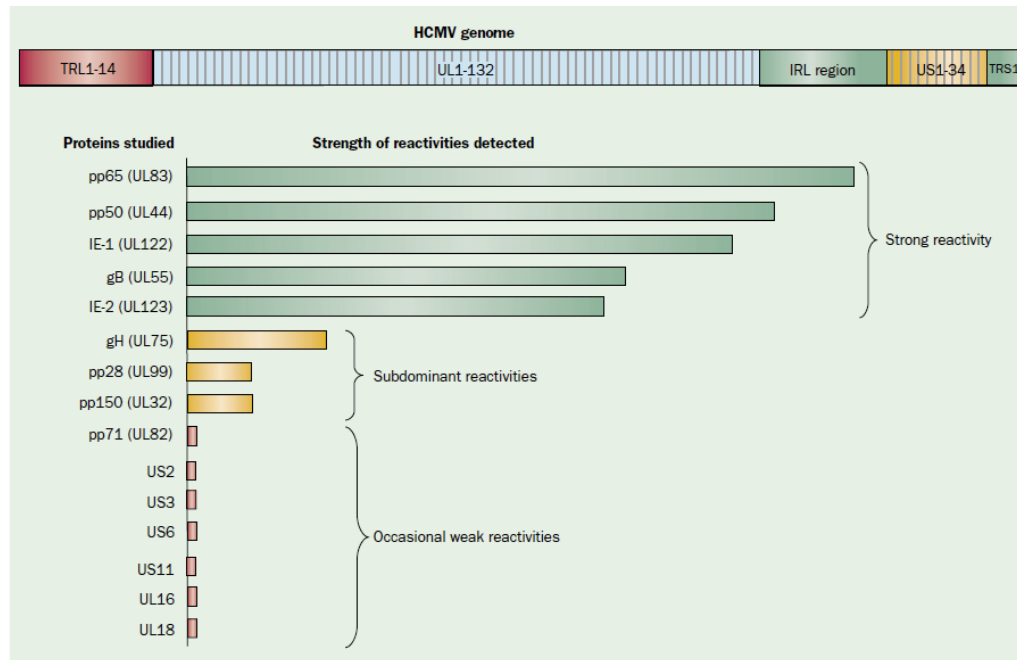
Epitopes majeurs chez les donneurs de sang séropositifs :

pp65 (UL83)

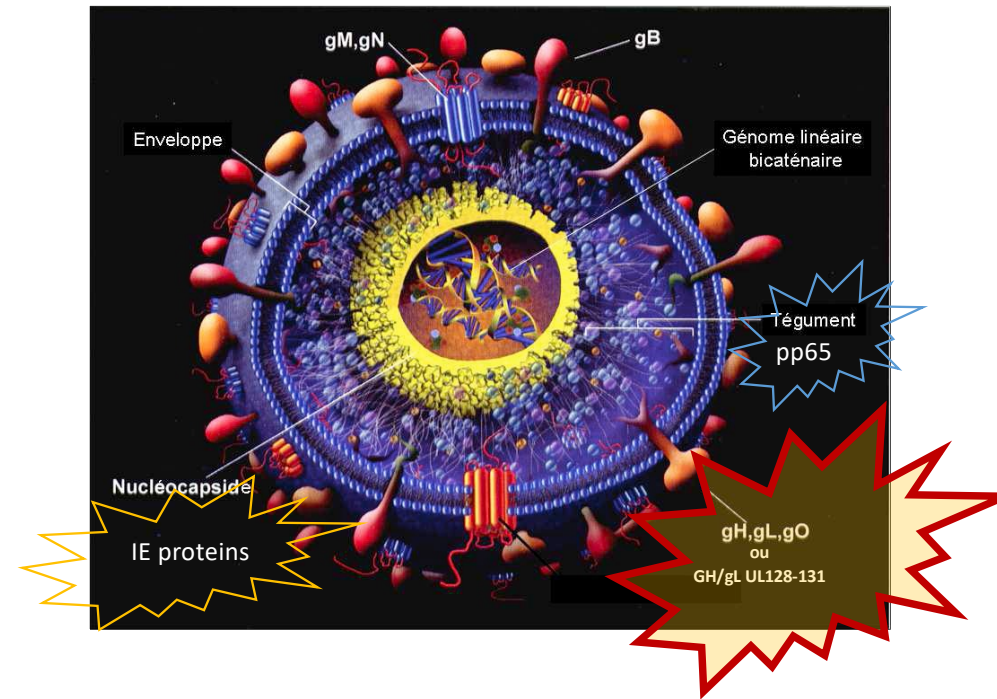
IE1 (UL123) : 40% des séropositifs

+ protéines immunomodulatrices et d'enveloppe

pp28, pp50, US2, US3, US5 et UL18, gH, gB,



Gandhi et Khanna, review, 2007



Reddehase. *Molecular Biology and Immunology* 2006

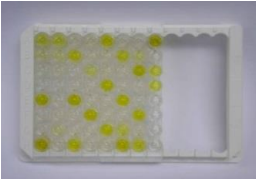
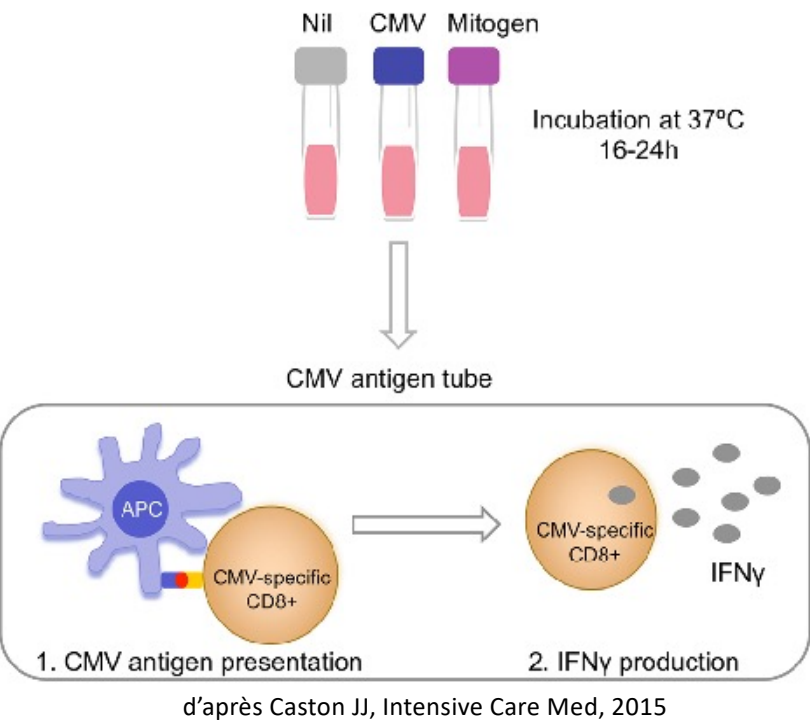
Tests disponibles : les seuls marqués CEIVD sont les tests IGRA (INF Gamma Release Assay)

Table 2
Overview of commercially available functional methods for measuring CMV-specific T-cell mediated immune response.

Assays	Brand names	Sample required	Turnaround time	Target cells	CMV stimulating antigen	Advantages	Disadvantages
ELISpot (IGRA)	T-SPOT.CMV® T-Track CMV®	PBMCs (10 mL)	24–48 h	CD4+/ CD8+/ NK/ NKT	Immunogenic peptides or proteins covering Pp65 and IE-1 proteins (separately)	Measures both CD4+ and CD8+ response Not limited by HLA CE marking	Requires ELISpot reader Requires PBMC isolation procedure Lack of cut-off standardization Unable to differentiate between CD4+ or CD8+ response
ELISA (IGRA)	QuantiFERON-CMV®	Whole blood (3–5 mL)	24 h	CD8+	Immunogenic peptides mapped within pp65, IE-1, IE-2, pp50	Standardized Simple to perform in laboratories Full automation CE marking	HLA Class I restricted Sensitive to lymphopenia Only measures CD8+ T cells (not CD4+ T cells)
VIDAS CMV IGRA	Sang total (3mL)	CD4+ et CD8+	Lysat ou peptides chevauchants	Totalement indépendant du phénotype HLA.			
ICS by flow cytometry	Viracor® CMV T-cell Immunity Panel (TCIP)	PBMCs or whole blood (1-2 mL)	8–10 h	CD4+/ CD8+	Usually pp65, IE-1, gB immunogenic peptides (overlapping peptides libraries) or pp65/IE-1/gB proteins	Differentiates between CD4+ and CD8+ response Allows phenotypic characterization Potential to measure a variety of cytokines and cell surface markers	Requires flow cytometer High cost Lack of technical standardization Labour-intensive No CE marking

CE, European conformity; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immunoabsorbent spot assay; gB, glycoprotein B; HLA, human leukocyte antigen; ICS, intracellular cytokine staining; IE, immediate-early; IGRA, Interferon-gamma release assay; NK/NKT, Natural Killer/Natural Killer T Cells; PBMCs, peripheral blood mononuclear cells; pp65, phosphoprotein 65.

QuantiFERON® CMV (Qiagen)



Lecture ELISA=> U INF/mL automatisée sur Liaison XL (Mafi et al., JCV 2023)

Marqué CEIVD
Sur sang total Faible volume de sang (3x1ml)
CD8+ uniquement
Pool de 22 peptides issus de pp65, IE1, IE2, pp50, gB, pp28
Impact du nombre de leucocytes totaux
=> Nombreux tests indéterminés notamment après allogreffe de CSH

Intérêt du test mitogène

ANTIGENE (UI/ml d'IFN)	MITOGENE (UI/ml d'IFN)	RESULTAT	INTERPRETATION
< 0,2	≥ 0,5	Non réactif	Réponse immunitaire aux antigènes de CMV non détectée
≥ 0,2	Tous	Réactif	Réponse immunitaire aux antigènes de CMV détectée
< 0,2	< 0,5	Indéterminé	Impossibilité de détection de réponse immunitaire aux antigènes de CMV et au mitogène

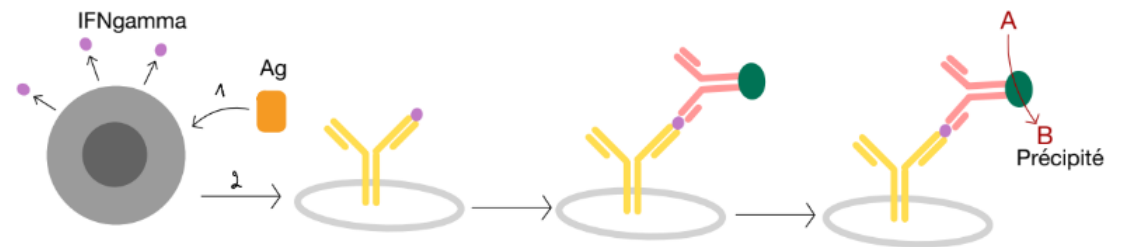
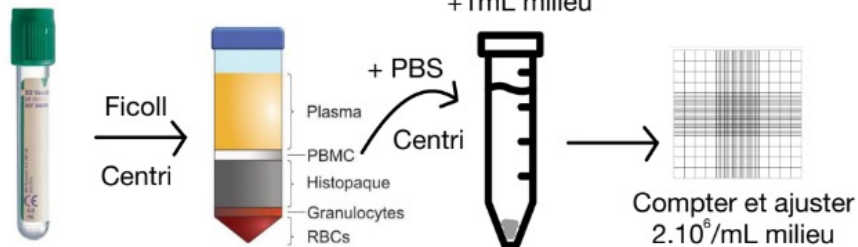


ELISpot

Dénombrer LcT CD4+/CD8+/NK après lavage puis stimulation

Ag IE et pp65

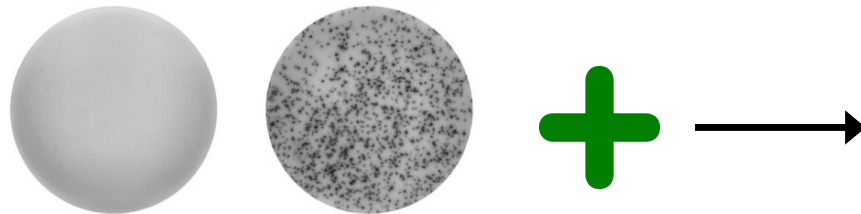
Héparinate de lithium
7,5mL sang



Analyse séparément les réponses

IE1 (UL123) : Ag très précoce du CMV

pp65 (UL83) : Ag précoce-tardif du CMV



≥ 10 SFC/200 000 cell mononucléées

Seuil fournisseur utilisé

Recommandations 2025 et au-delà ...

- Kotton C et al., Fourth IntL consensus guidelines on the management of cytomegalovirus in solid organ transplantation. Transplantation 2025
- Ljungman P. et al., Recommendations from the 10th European Conference on Infections in Leukaemia for the management of cytomegalovirus in patients after allogeneic haematopoietic cell transplantation and other T-cell-engaging therapies . Lancet ID 2025

Les Nouveaux Référentiels (2025) : SOT vs. Allo-HSCT

SOT (Kotton 2025 - 4^e Consensus International)



Prophylaxie : Valganciclovir (référence).
Letermovir si intolérance.



Stratégie CMI : Levée d'équivoque
sérologique en pré-greffe.



Arrêt Précoce : Test CMI à M1 post-
greffe chez les receveurs R+. Si le test
est réactif -> **arrêt précoce de la
prophylaxie et passage en stratégie
préemptive.**

Allo-HSCT (ECIL-10 2025)



Prophylaxie : Letermovir en 1^{ère} ligne
chez les receveurs R+ (jusqu'à J100,
extension possible à J200).

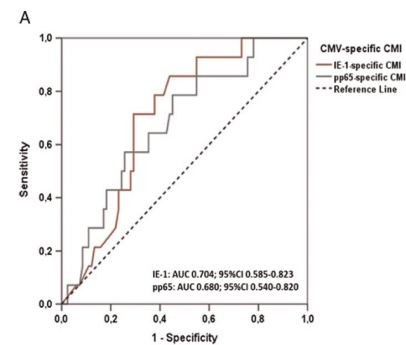
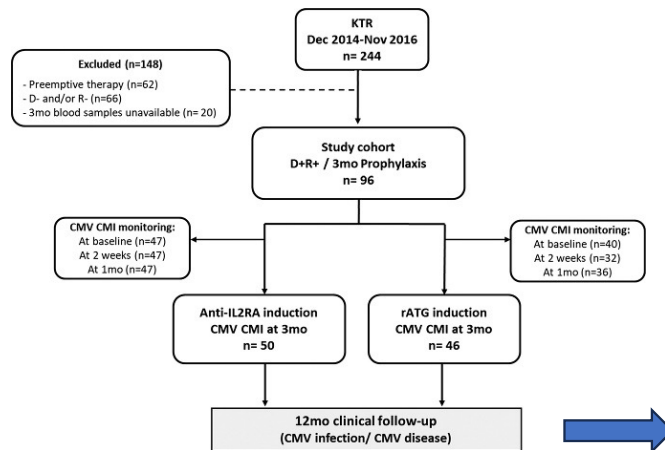


Suivi : La CMI est recommandée pour
stratifier le risque infectieux en post-
prophylaxie.



Nouveauté ECIL-10 : Intégration de
protocoles de suivi spécifiques pour les
patients sous CAR-T cells et anticorps
bispécifiques.

Valeur prédictive de l'ELISpot pour l'infection tardive à CMV chez les receveurs de rein séropositifs en fin de prophylaxie

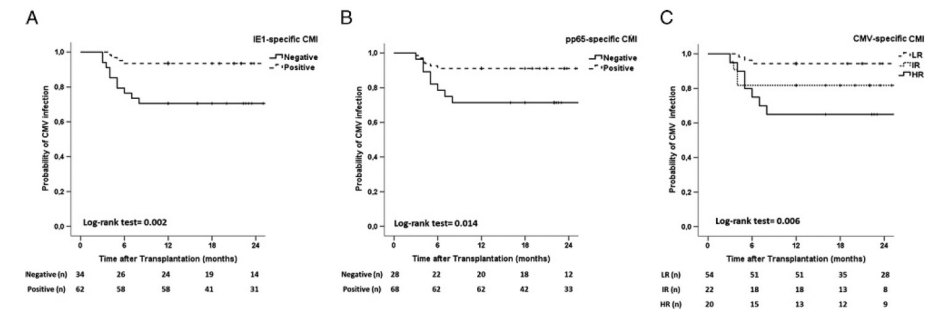


Seuils IE1 et pp65 à 25 et
130 IFN- γ spots/3.105 PBMC

CMV-specific Cell-mediated Immunity at 3-month Prophylaxis Withdrawal Discriminates D+/R+ Kidney Transplants at Risk of Late-onset CMV Infection Regardless the Type of Induction Therapy

Marta Jarque, MS,¹ Edoardo Melilli, MD, PhD,² Elena Crespo, PhD,¹ Anna Manonelles, MD,² Nuria Montero, MD,² Joan Torras, MD, PhD,^{1,2} Josep M. Cruzado, MD, PhD,^{1,2} Sergi Luque, MS,¹ Salvador Gil-Vernet, MD,² Josep M. Grinyó, MD, PhD,^{1,2} and Oriol Bestard, MD, PhD^{1,2}

Transplantation ■ November 2018 ■ Volume 102 ■ Number 11

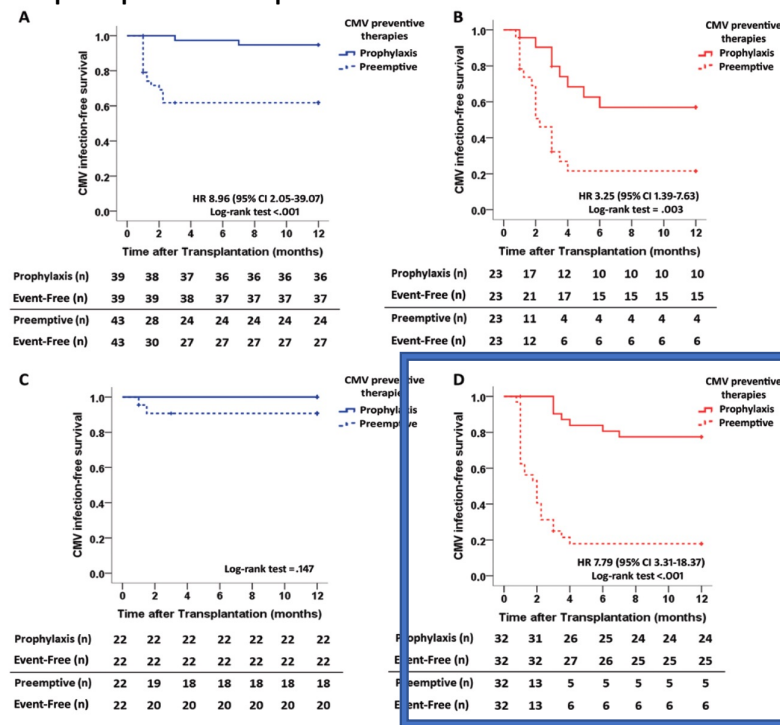
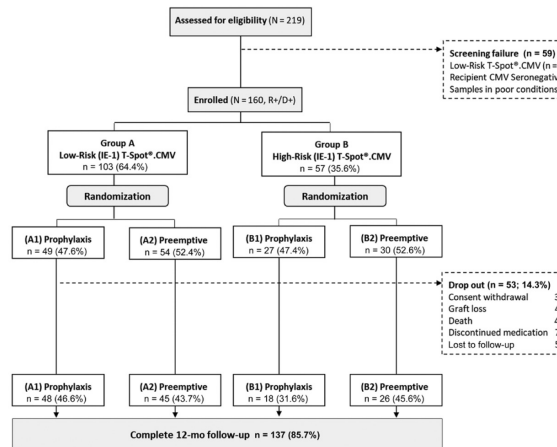


La réponse IE1(>130 spots) est le meilleur prédicteur à M3 avec un OR de 5.5
A M3 post greffe, l'impact des anticorps anti thymocytes(ATG)utilisés pour l'induction est minime

1^{er} essai randomisé : 160 patients receveurs de rein D+/R+ randomisés entre préemptif et prophylaxie et stratifiés en fonction de leur résultat ELISpot

Low risk (Tspot +) High risk (Tspot -)

T Spot pré-transplantation



T Spot J15 post-transplantation

IE1 et pp65 donnent le même résultat mais avec des cut offs différents redéfinis ici pour prégreffe et J15

Cellular Immunity to Predict the Risk of Cytomegalovirus Infection in Kidney Transplantation: A Prospective, Interventional, Multicenter Clinical Trial

Marta Jarque,¹ Elena Crespo,¹ Edoardo Melilli,^{2,3} Alex Gutiérrez,² Francesc Moreso,⁴ Lluís Guirado,⁵ Ignacio Revuelta,⁶ Nuria Montero,² Joan Torras,^{1,2} Lluís Riera,⁷ Maria Meneghini,^{1,2} Omar Taco,² Anna Manonelles,² Javier Paul,² Daniel Seron,² Carme Facundo,⁸ Josep M. Cruzado,^{1,2} Salvador Gil Vernet,² Josep M. Grinyó,^{1,2} and Oriol Bestard^{1,2}

¹Experimental Nephrology Laboratory, Bellvitge Biomedical Research Institute, IDIBELL, Hospital de Llobregat, Spain, ²Kidney Transplant Unit, Nephrology Department, Bellvitge University Hospital, Barcelona, Spain, ³Kidney Transplant Unit, Nephrology Department, Hospital Miguel Servet, Zaragoza, Spain, ⁴Kidney Transplant Unit, Nephrology Department, Vall d'Hebron University Hospital, Barcelona, Spain, ⁵Kidney Transplant Unit, Nephrology Department, Fundació Puigvert, Barcelona, Spain, ⁶Kidney Transplant Unit, Nephrology Department, Hospital Clínic de Barcelona, Barcelona, Spain, and ⁷Urology Department, Bellvitge University Hospital, Barcelona, Spain

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

Le bénéfice de la prophylaxie est maximal pour les patients non réactifs à J15 post transplant permettant de mieux prédire l'infection à CMV (81,3 % contre 9,1 % ; OR : 43,33 [IC à 95 % : 7,89–237,96]).

Une prolongation de la prophylaxie pourrait être proposée aux patients qui restent ELISpot négatifs.

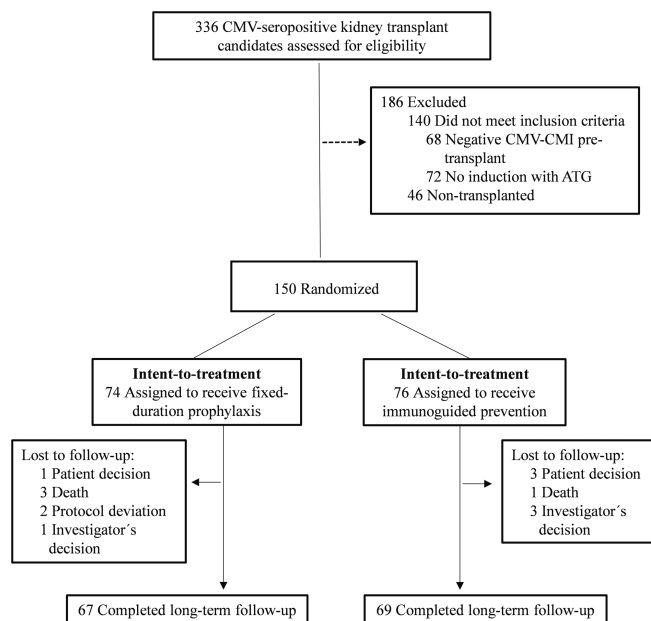
Essai randomisé TIMOVAL immunoguidage de la prophylaxie par le QuantiFERON-CMV chez les receveurs de greffe rénale R+ sous ATG

Clinical Infectious Diseases
MAJOR ARTICLE

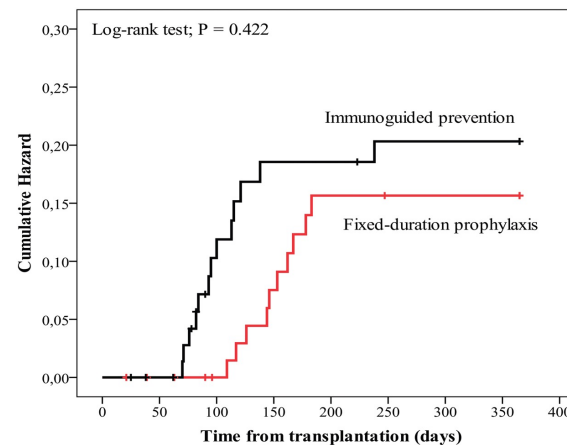


Immunoguided Discontinuation of Prophylaxis for Cytomegalovirus Disease in Kidney Transplant Recipients Treated With Antithymocyte Globulin: A Randomized Clinical Trial

Aurora Pérez-Vega,^{1,2} Belén Gutiérrez-Gutiérrez,^{2,3} María L. Agüero,^{1,4} Carme Facundo,⁵ Dolores Redondo-Pachón,⁶ Marta Suller,⁷ María O. López-Oliva,⁸ Jose R. Yuste,⁹ Miguel Montejo,¹⁰ Cristina Galeano-Alvarez,¹¹ Juan C. Ruiz-San Millán,¹² Ibai Los-Arcos,¹³ Domingo Hernández,¹⁴ María Fernández-Ruiz,¹⁵ Patricia Muñoz,¹⁶ Jorge Valle-Arroyo,¹⁷ Angela Cano,¹⁸ Alberto Rodríguez-Benot,¹⁴ Marta Crespo,¹⁹ Cristian Redondo-Haad,¹⁴ María A. Lobo-Acosta,¹¹ Jose C. Garrido-Gracia,¹⁸ Elisa Vidal,^{12,19} Luis Guirado,⁵ Sara Cantisán,¹² and Julian Torre-Cisneros^{12,19}, on behalf of the TIMOVAL Study Group



Seuil utilisé : seuil du fabricant



Number at risk

Immunoguided prevention	76	74	62	58	58	56	56	56
Fixed-duration prophylaxis	74	72	69	64	59	58	58	58

Non infériorité en terme de réduction :

-des infections (17.1% vs 13.5%; log-rank test, P = .422)

Et

- des maladies à CMV(0% vs 2.7%; P = .149)

mais

bénéfice en terme de neutropénies (9.2% vs 37.8%; odds ratio, 6.0; P < .001) et d'évolution clinique

QuantiFERON® CMV to guide the duration of post-lung transplant prophylaxis



The Journal of
Heart and Lung
Transplantation
<http://www.jhltonline.org>

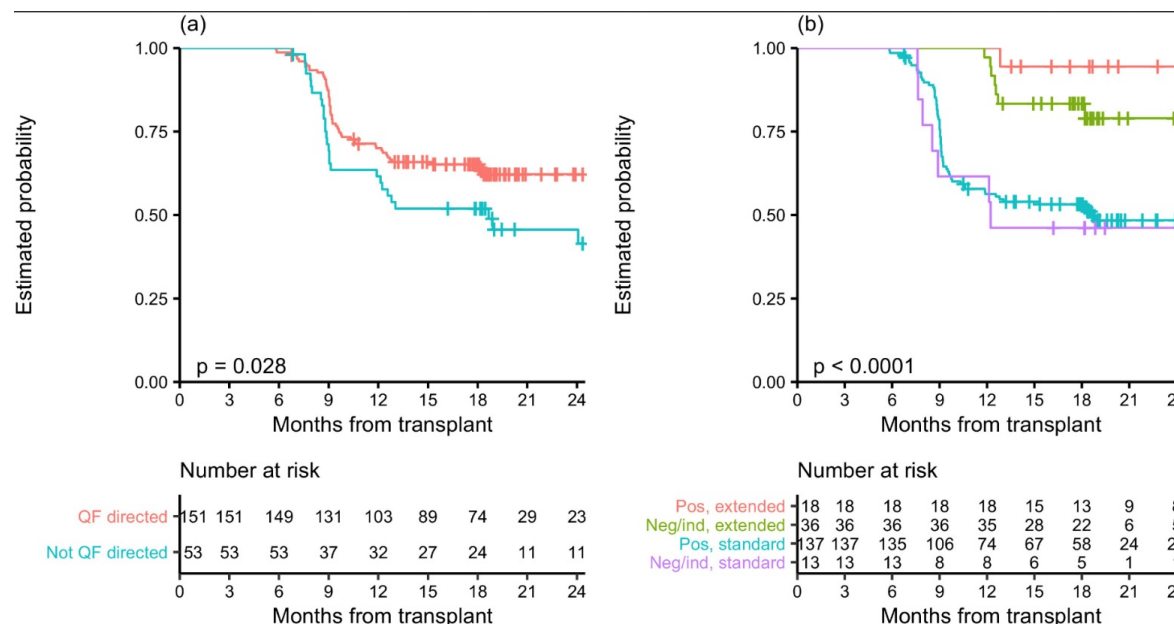
Real-world experience of Quantiferon-CMV directed prophylaxis in lung transplant recipients

Bradley J. Gardiner, MBBS, PhD,^a Sue J. Lee, PhD,^a Allisa N. Robertson, MD,^a
Yvonne Cristiano, BN,^b Gregory I. Snell, MBBS, MD,^b
C. Orla Morrissey, MB, BCh, PhD,^a Anton Y. Peleg, MBBS, PhD,^{*,a,c} and
Glen P. Westall, MBBS, PhD^{*,b}



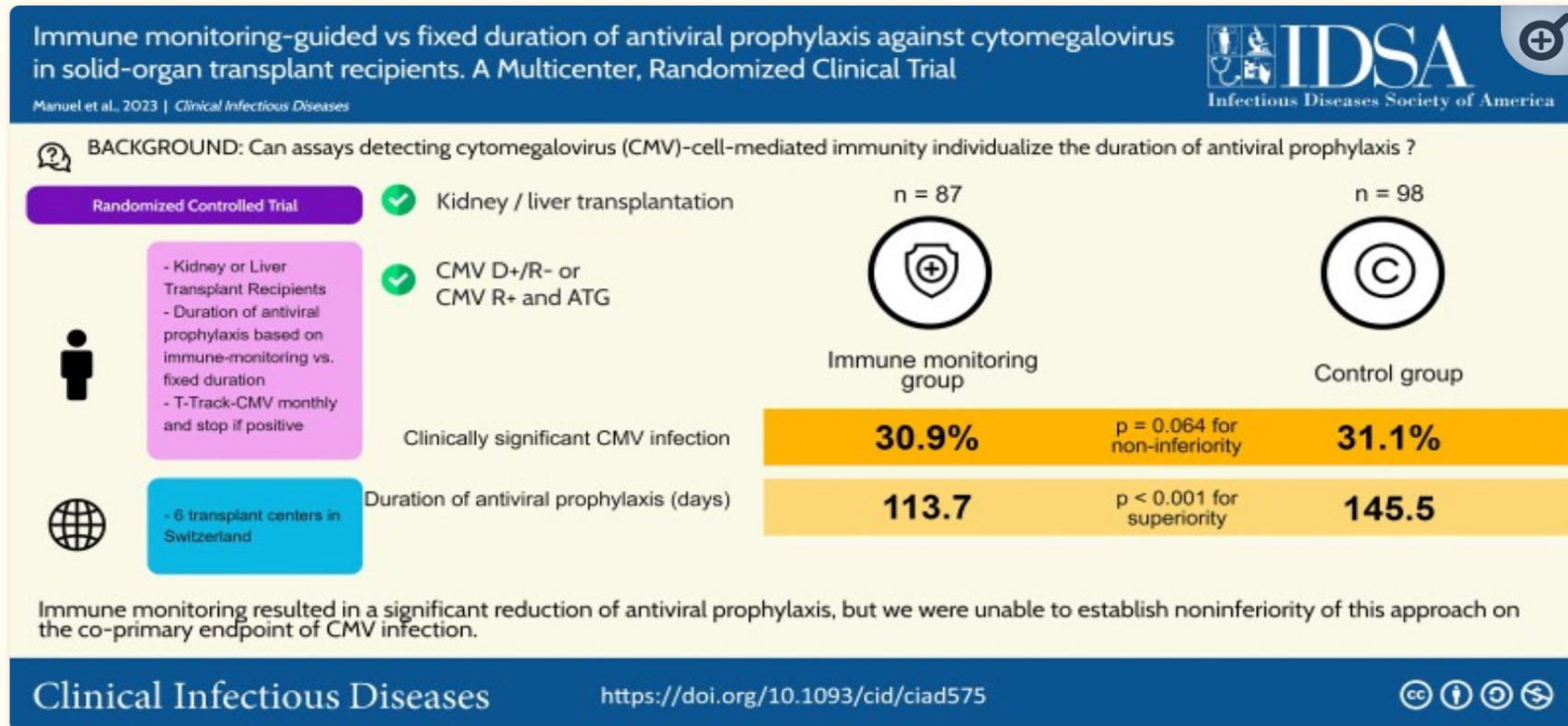
263 patients D+/R- et R+
Arret de la prophylaxie lorsque le test QF
est positif

Resultats corrélés au statut sérologique
plus qu'au résultat du QuantiFERON
NB : QF négatif pendant toute la
prophylaxie chez les R- => Utilisation
potentielle avec seuils plus élevés chez les
R+? À étudier



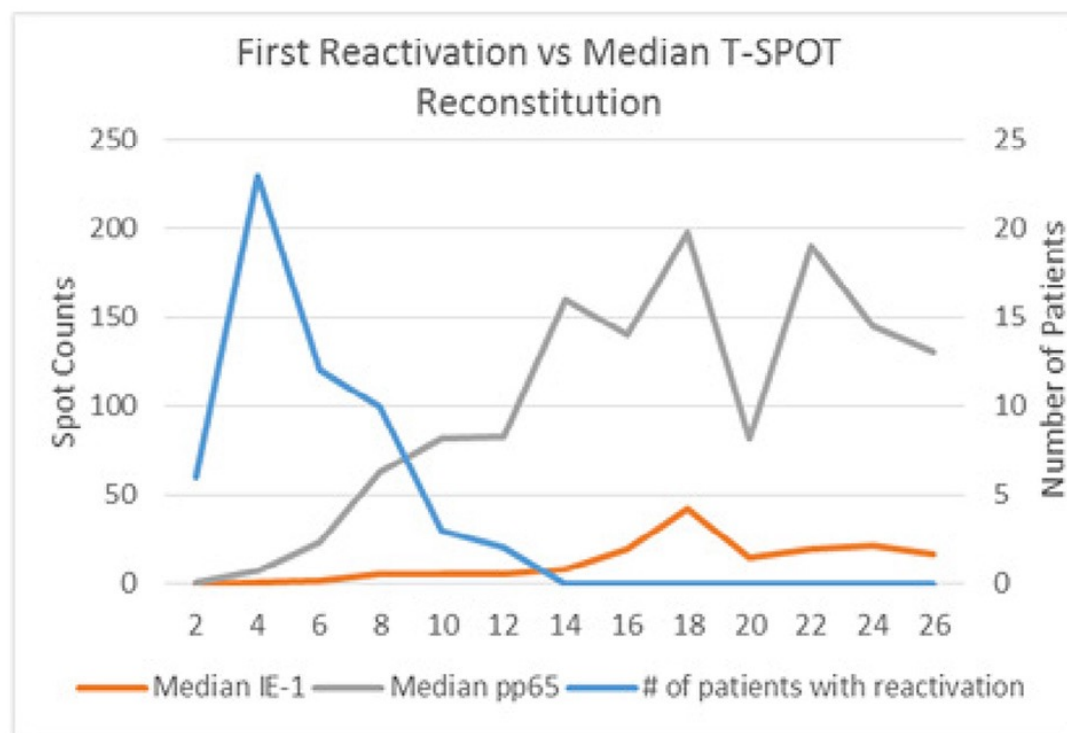
Graphical Abstract

Essai randomisé de prophylaxie immunoguidée par ELISpot



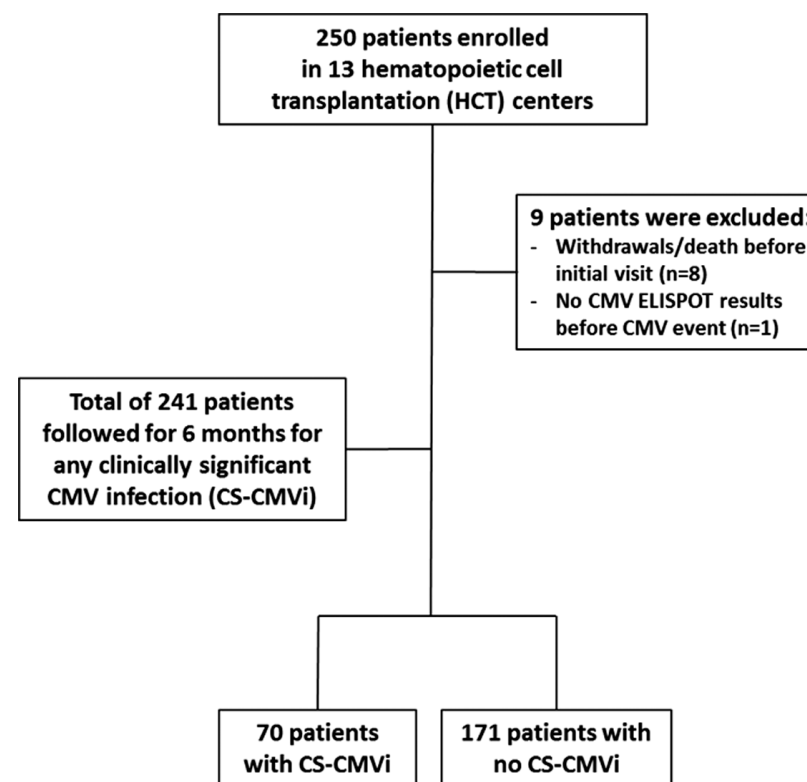
This graphical abstract is also available at Tidbit: <https://tidbitapp.io/tidbits/immune-monitoring-guided-vs-fixed-duration-of-antiviral-prophylaxis-against-cytomegalovirus-in-solid-organ-transplant-recipients-a-multicenter-randomized-clinical-trial-1cd729ef-d7a6-4dca-a470-d73a1f6a3b41>

Evaluation du T-Spot en allo-greffe de CSH étude multicentrique observationnelle REACT

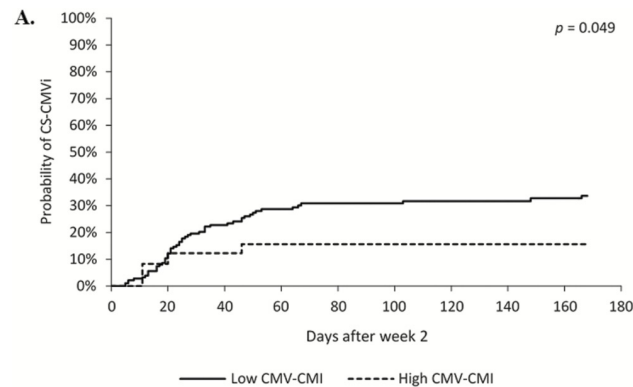


Cytomegalovirus (CMV) Cell-Mediated Immunity and CMV Infection After Allogeneic Hematopoietic Cell Transplantation: The REACT Study

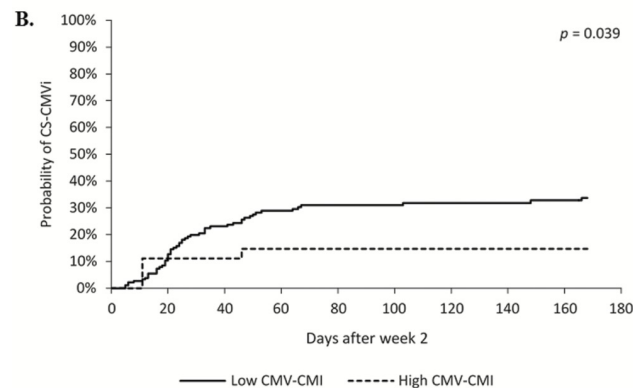
Roy F. Chemaly,¹ Lynn El Haddad,¹ Drew J. Winston,² Scott D. Rowley,³ Kathleen M. Mulane,⁴ Pranatharthy Chandrasekar,⁵ Robin K. Avery,⁶ Parameswaran Hari,⁷ Karl S. Peggs,⁸ Deepali Kumar,⁹ Rajneesh Nath,¹⁰ Per Ljungman,¹¹ Sherif B. Mossad,¹² Sanjeet S. Dadwal,¹³ Ted Blanchard,¹⁴ Dimpy P. Shah,¹⁵ Ying Jiang,¹ and Ella Ariza-Heredia¹



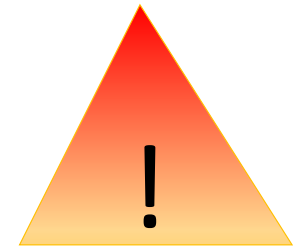
L'ELISpot permet d'identifier les patients à risque d'infection à CMV



Cut-off IE >100

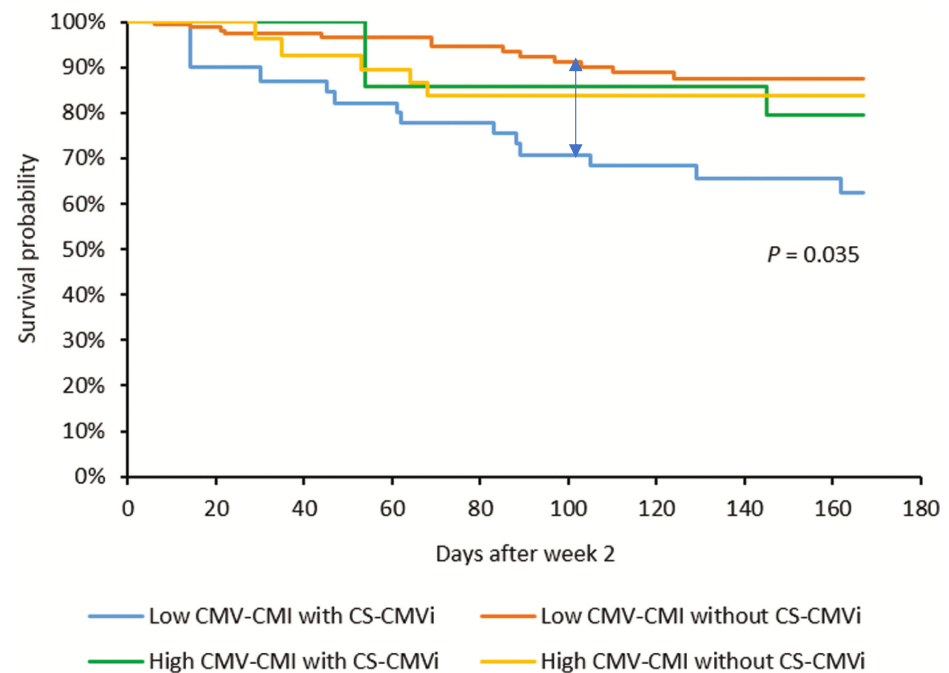
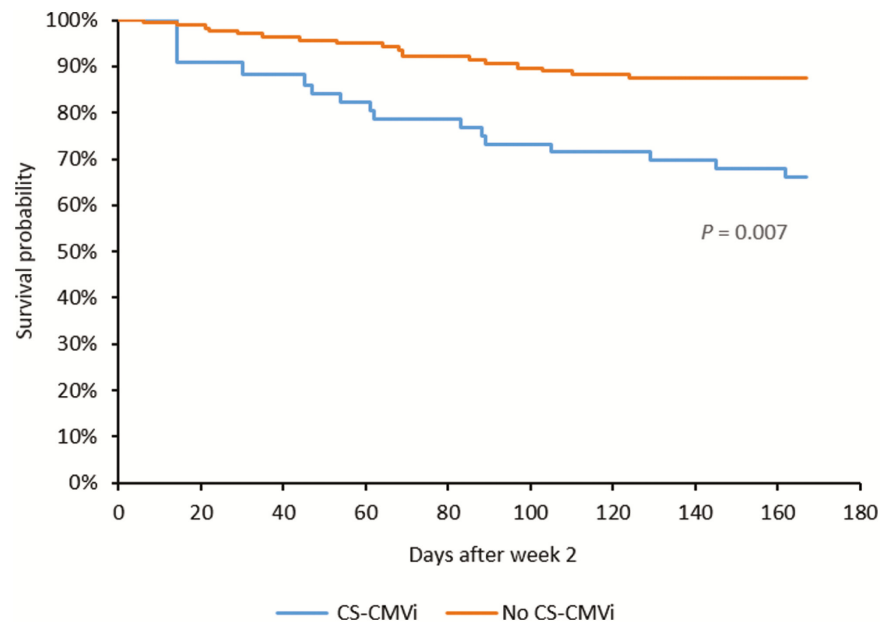


Cut-off IE >100
et PP65>100



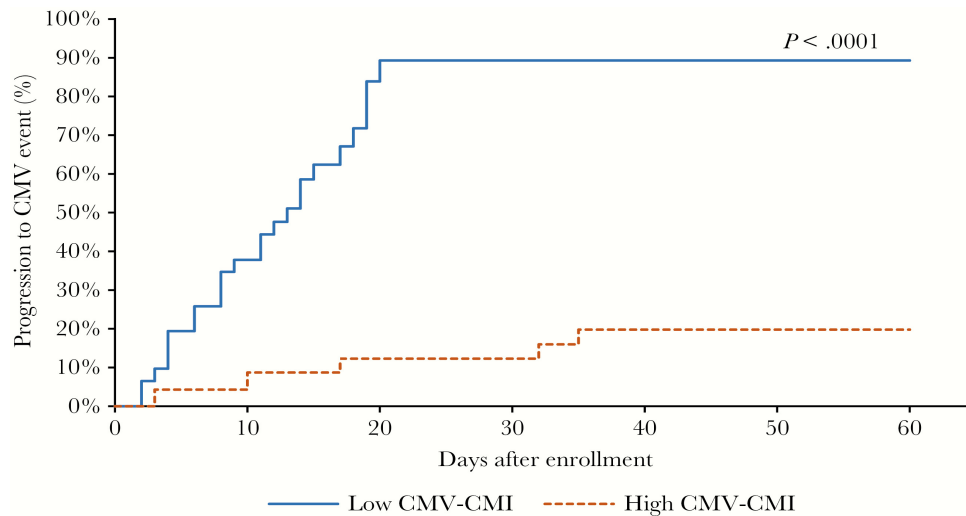
Cut-off à définir par test
et par antigène

Impact significatif sur la survie des patients d'une faible réponse cellulaire associée à une infection à CMV cliniquement significative (augmentation de CV justifiant un traitement CS-CMV))

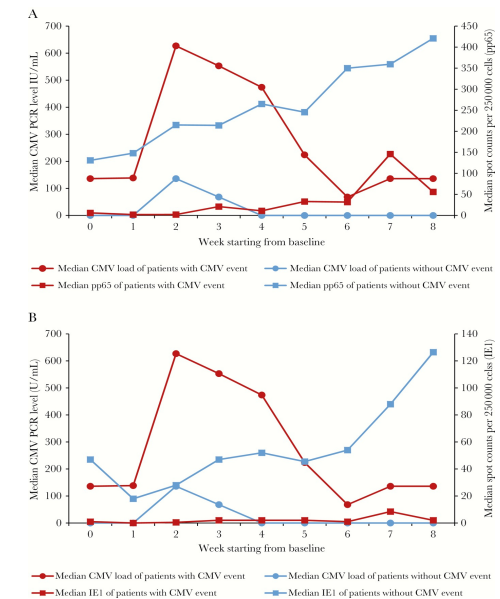


CUT-OFF : IE <100 spots=Low

L'Elispot permet de prédire l'évolution d'une charge virale faible vers une charge virale élevée chez les patients à bas risque d'infection CMV



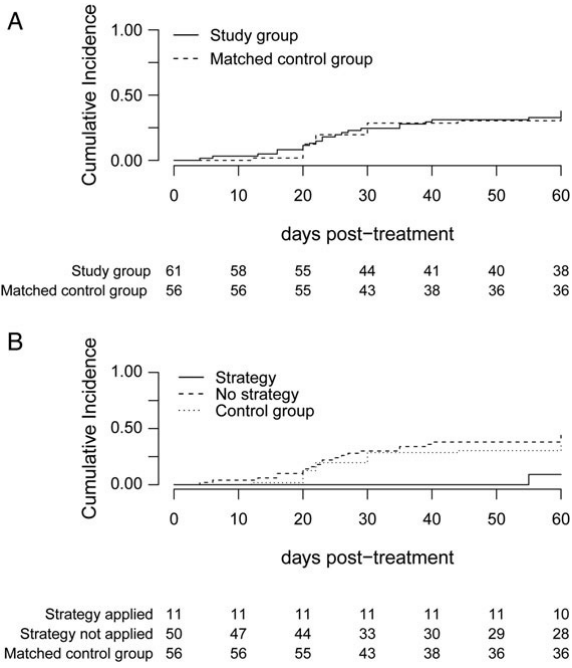
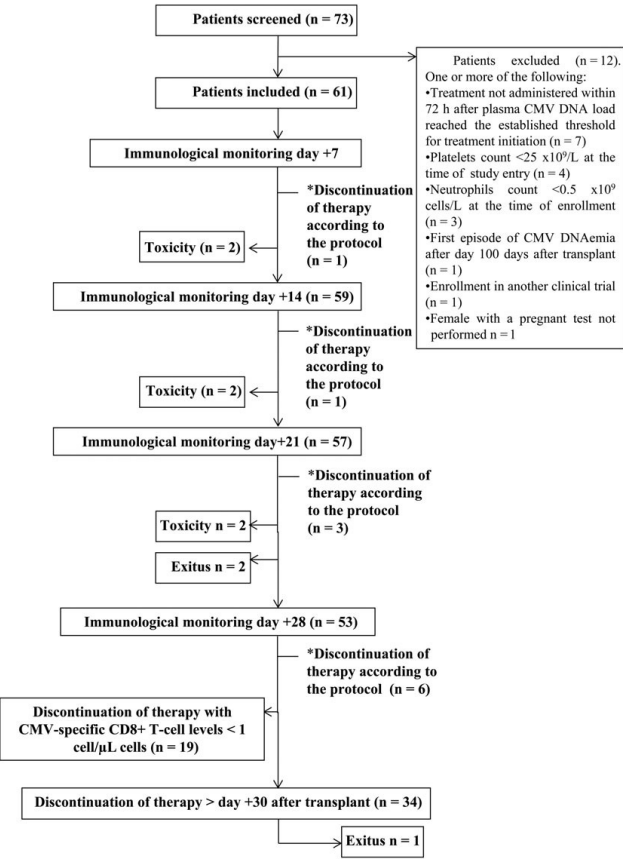
- **55 Patients greffés de CSH suivis en T Spot (Oxford technologies)**
- **Endpoint :** CMV >1000 IU/ml si bas risque; CMV>500 IU/mL si haut risque (GVHD, TT par corticostéroïdes pendant la durée de l'étude (60 j))
- Pas de différences significatives entre pp65 et IEI mais seuils différents : pp65 SPC: 100/250 000 cells et IEI ≤ 50 SPC/250 000 cells.



pp65

IE

L'ELISpot pourrait permettre de guider l'arrêt du traitement préemptif en cas d'infection à CMV et donc diminuer les neutropénies



Récurrence de l'ADNémie à CMV?
Impact de la stratégie ELISpot-guidée
sur l'incidence des infections à CMV dans les deux mois suivant l'arrêt
du traitement par valganciclovir

L'immunomonitoring est donc recommandé pour préciser la durée de la prophylaxie avec des restrictions

SOT

- If available, we recommend performing a CMV-CMI test **in R+ kidney transplant recipients** with (strong, moderate) or without (weak, very low) lymphocyte-depleting antibodies **and discontinuing antiviral prophylaxis in case of a positive test.**
- Although a precise timepoint for performing the CMV-CMI test cannot be recommended, we suggest a single timepoint at 1-month post-transplant or once a month during prophylaxis. A preemptive approach after stopping prophylaxis is suggested (weak, moderate).
- **We suggest not routinely using CMV-CMI tests in D+/R- for any organ type.** Immune monitoring appears to be less predictive given the large number of patients in whom CMV-CMI remains undetectable or who have indeterminate responses (weak, low).

HCT

- Sequential monitoring of IFN- γ -producing CMV-specific T cells may provide potentially useful information for the management of CMV infection after allo-HCT, that may be used to personalize PET (CII).
- The main applications of these assays may include **extending or shortening the duration of primary LMV prophylaxis (II), withholding therapy for low level viral loads (CII), and to identify patients that may benefit from secondary LMV prophylaxis (CII).**
- For future non-interventional or randomized studies assessing the clinical value of monitoring IFN- γ -producing CMV-specific T-cell responses in the management of CMV infection, the **use of commercially-available CMV IGRA** that were investigated in clinical settings are preferable over laboratory-developed flow cytometry-based immunoassays (CII).

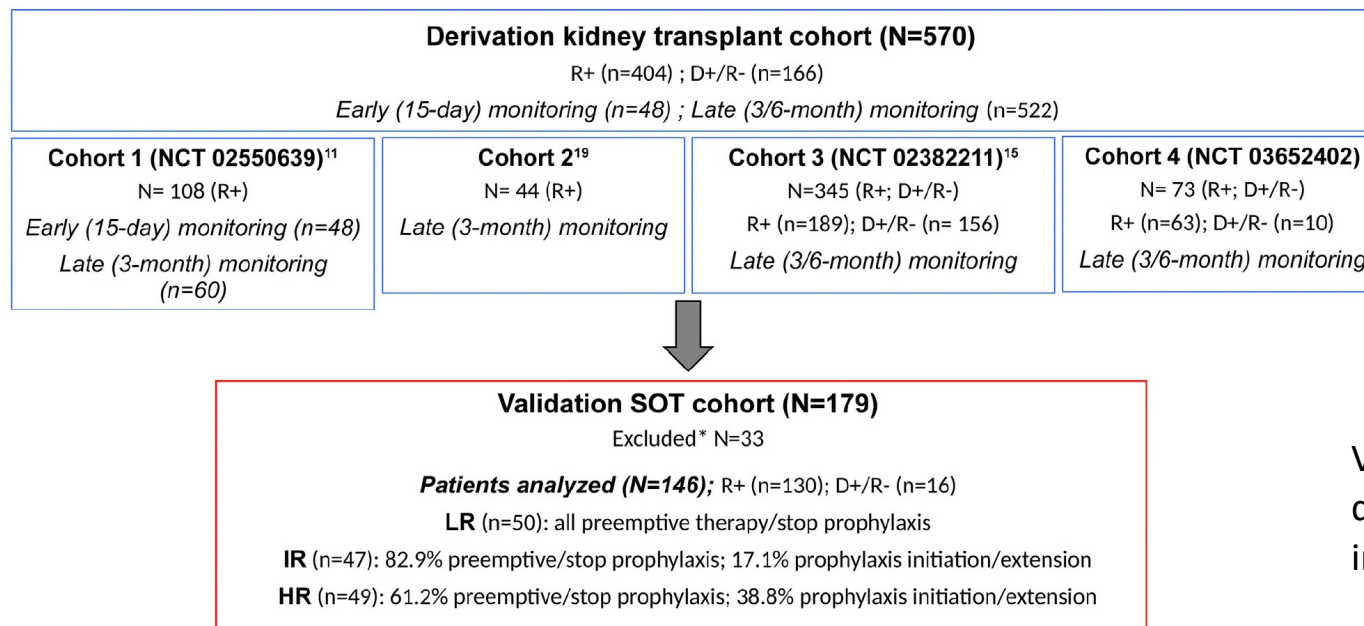
- Kotton C et al., Fourth Intl consensus guidelines on the management of cytomegalovirus in solid organ transplantation. Transplantation 2025
- Ljungman P. et al., Recommendations from the 10th European Conference on Infections in Leukaemia for the management of cytomegalovirus in patients after allogeneic haematopoietic cell transplantation and other T-cell-engaging therapies . Lancet ID 2025

Peut-on affiner les résultats ?

Analyse poolée des patients de 4 études utilisant le même ELISpot en transplantation rénale (T Spot)

A New Prognostic Score Based on Cell-Mediated Immunity for Cytomegalovirus Infection After Transplantation

Delphine Kervella^{1,2,3}, Franc Casanova-Ferrer^{2,3}, Camille N. Kotton⁴, Laura Donadeu^{2,3}, Deepali Kumar⁵, Silvia Pineda⁶, Elena Crespo^{2,3}, Maria Meneghini^{1,2,3}, José González-Costelo⁷, Elena García-Romero⁷, Laura Lladó⁸, Alba Cachero⁸, Edoardo Melilli⁹, Irina B. Torres^{1,2,3}, Anna Martínez-Lacalle^{2,3}, Zaira Castañeda^{1,2,3}, Mónica Martínez-Gallo^{10,3}, Oscar Len^{11,3}, Ibai Los-Arcos^{11,3}, Enric Trilla-Herrera^{12,3}, Enric Miret^{12,3}, Magali Giral¹³, Sophie Brouard³, François R. Girardin¹⁴, Jean Villard¹⁵, Klemens Budde¹⁶, Carmen Lefaucheur¹⁷, Alexandre Loupy^{18,19}, Francesc Moreso^{1,2,3} and Oriol Bestard^{1,2,3}



Définition des seuils

Validation des paramètres prédictifs dans une nouvelle cohorte prospective immunoguidée

Figure 1. Flow-chart of the study. D+, CMV IgG seropositive donor; HR, high-risk CMI; IR, intermediate-risk CMI; LR, low-risk CMI; R-, CMV IgG seronegative recipient; R+, CMV IgG seropositive-recipient; SOT, solid organ transplants. *Patients excluded from validation cohort because of loss of follow-up (n = 13), use of antirejection therapy (n = 7), unavailable blood samples (n = 7), and prophylaxis initiation before the CMV-CMI test (n = 6).

A New Prognostic Score Based on Cell-Mediated Immunity for Cytomegalovirus Infection After Transplantation

Delphine Karvella^{1,2,3,4}, Franc Casanova-Ferrer^{1,2,3}, Camille N. Kottan¹, Laura Donadeu^{1,2,3}, Despat Kumar¹, Silvia Pinola¹, Elena Crespo¹, Maria Moragheg^{1,2,3}, Joa González-Castell¹, Elena García-Romero¹, Laura Lado¹, Alba Cacho¹, Eduardo Melillo¹, Irina B. Torres^{1,2,3}, Anna Martínez-Lacort^{1,2,3}, Zaira Castañeda^{1,2,3}, Monica Martínez-Gallardo^{1,2,3}, Oscar Lee^{1,2,3}, Bae Lu-Aroa^{1,2,3}, Eric Trilla-Hernández^{1,2,3}, Enric Miró^{1,2,3}, Magali Girat¹, Sophie Brouard¹, François R. Girardin¹, Jean Villard¹, Klarmene Budde^{1,2,3}, Carmen Lefebvre^{1,2,3}, Alexandre Loozy^{1,2,3}, Francesc Moreau^{1,2,3} and Oriol Bestard^{1,2,3}

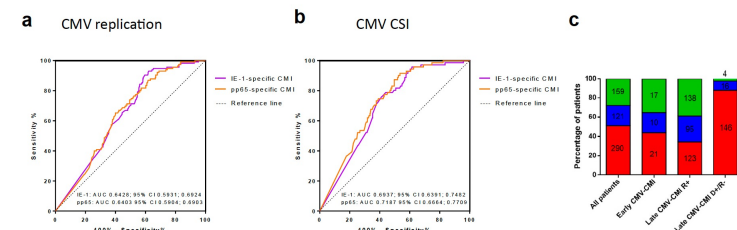
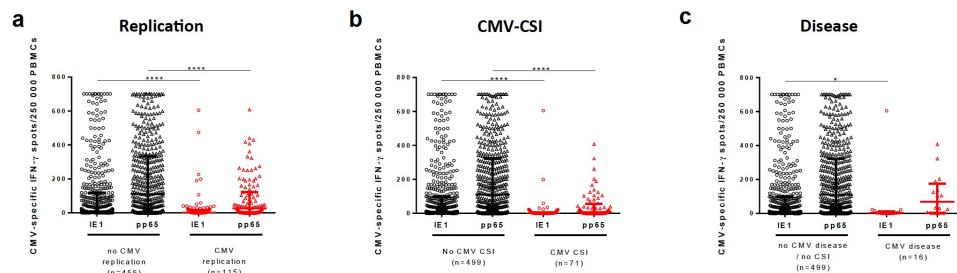


Figure 3. Risk-score classification with IE-1 and pp65-specific CMV-CMI. (a) ROC curves for the risk of CMV replication. (b) ROC curves for the risk of CMV-CSI. (c) Classification of patients in 3 distinct risk categories considering the combination of both IE-1 and pp65-specific CMI (CMV-CMI risk-score): low-risk (LR), intermediate-risk (IR), and high-risk (HR). CMI, cell-mediated immunity; CMV, cytomegalovirus; CSI, clinically significant infection; IE-1, immediate-early protein 1; pp65, 65 kDa phosphoprotein; ROC, receiver operating characteristics.

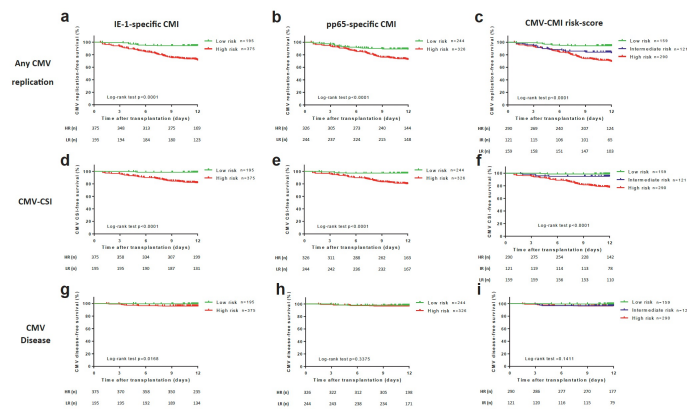


Figure 4. CMV infection rates according to CMV-CMI risk stratification in the derivation cohort. Kaplan-Meier CMV infection-free survival

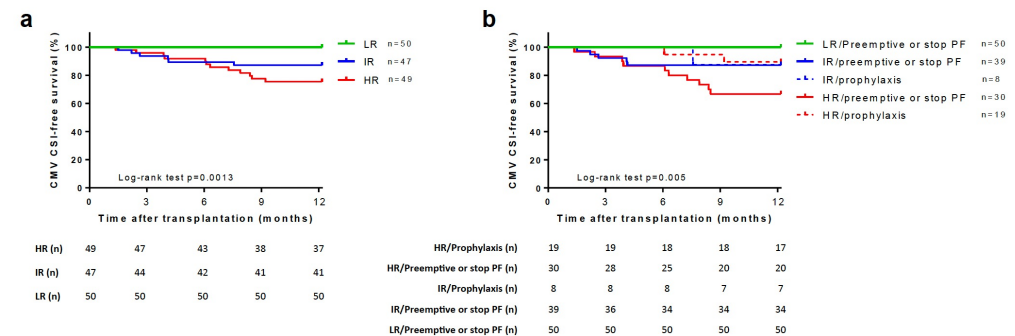


Figure 5. Kaplan-Meier CMV CSI-free survival curves in the validation cohort. (a) KM CMV-CSI-free survival curves between different CMI-CMV risk-scores and (b) when stratified according to the prevention strategies used. CMI, cell-mediated immunity; CMV, cytomegalovirus; CSI, clinically significant infection; HR, high-risk CMI; IR, intermediate-risk CMI; LR, low-risk CMI.

Derivation cohort: impact uniquement sur l'infection

Validation des seuils pour identifier le risque dans la cohorte de validation

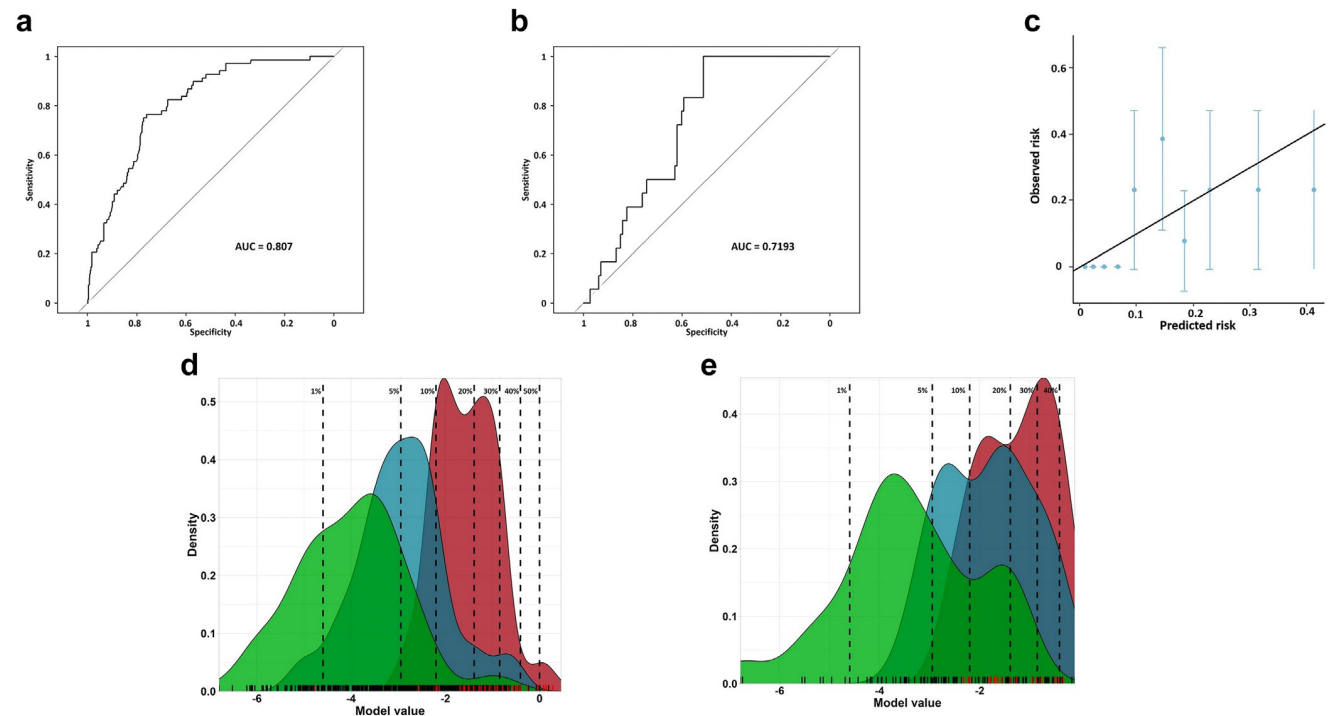
A New Prognostic Score Based on Cell-Mediated Immunity for Cytomegalovirus Infection After Transplantation

Delphine Kervella^{1,2,3}, Franc Casanova-Ferre^{4,5}, Camille N. Kotton⁶, Laura Donadeu^{7,8}, Deepali Kumar⁹, Silvia Pinada⁹, Elena Crespo¹⁰, Maria Monoghis^{11,12}, José González-Críos¹³, Elena García-Romero¹⁴, Laura Lladó¹⁵, Alba Cechero¹⁶, Eduardo Mellini¹⁷, Irina B. Torres^{18,19}, Anna Martínez-Lacort²⁰, Zaira Castañeda^{21,22}, Mónica Martínez-Gallo^{23,24}, Oscar Lam²⁵, Kai-Lin Axtell²⁶, Enrico Tilla-Nenna^{27,28}, Eric Mire²⁹, Magali Girard³⁰, Sophie Brouard³¹, François R. Girardin³², Jean Villard³³, Karmen Budde³⁴, Carmen Lefaucheur³⁵, Alexandre Loupy^{36,37}, Francesco Morens^{38,39} and Oriol Bastard⁴⁰

Table 4. Univariate and multivariate logistic regression analysis of main clinical, demographic and immunological variables predicting CMV-CSI

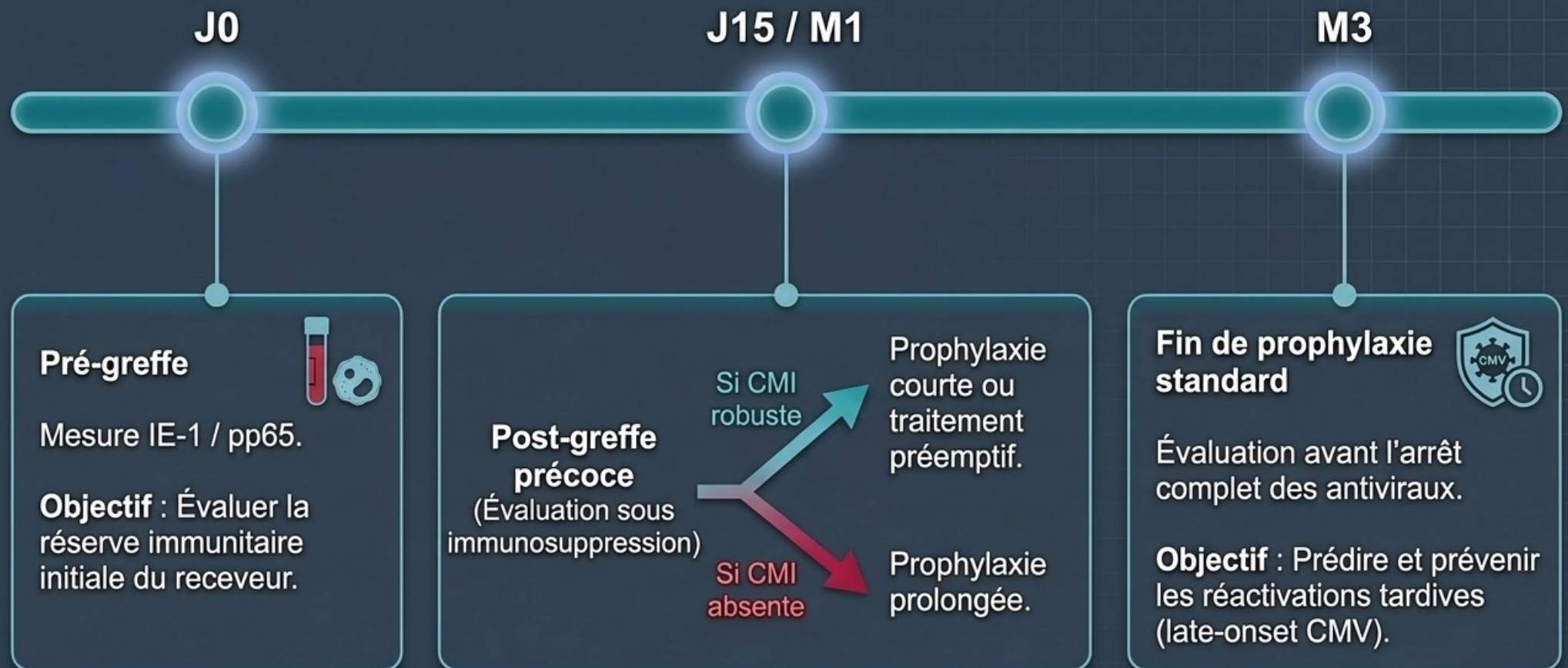
Variables predicting CMV-CSI	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Type of CMV preventive therapy (Prophylaxis vs. preemptive)	0.264	0.135–0.517	< 0.0001	0.171	0.064–0.456	< 0.0001
Sex (Male)	1.058	0.626–1.788	0.834			
Age (yrs)	1.030	1.009–1.052	0.004	1.034	1.011–1.058	0.004
Induction (T-cell depletion)	0.603	0.366–0.993	0.047	1.215	0.646–2.282	0.546
Serological risk (D+/R– vs R+)	2.920	1.760–4.844	< 0.0001	2.222	1.173–4.210	0.014
IE-1 HR vs. LR	14.176	4.399–45.686	< 0.0001	5.721	1.565–20.913	0.008
Pp65 HR vs. LR	8.270	3.717–18.402	< 0.0001	4.198	1.635–10.780	0.003
Absolute lymphocyte counts (Giga/L)	1.204	0.858–1.691	0.283			

CI, confidence interval; CMI, cell-mediated immunity; CMV, cytomegalovirus; CSI, clinically significant infection; D+, CMV IgG seropositive donor; HR, high-risk CMI; IE-1, immediate-early protein 1; LR, low-risk CMI; OR, odds ratio; pp65, 65 kDa phosphoprotein; R–, CMV IgG seronegative recipient; R+, CMV IgG seropositive-recipient.



La Cinétique de Décision : Le Modèle de Stratification d'Oriol Bestard

Essais cliniques RESPECT & ELISPOT-TC (Greffe rénale et cardiaque).



Le Test QuantiFERON® CMV ne permet pas de prédire la maladie à CMV

Clinical Trial > Clin Infect Dis. 2026 Feb 25;82(2):e316–e324. doi: 10.1093/cid/ciaf632.

Cytomegalovirus (CMV)-Specific Cell-Mediated Immunity for Prediction of Postprophylaxis CMV Disease in a Phase 3 Trial of Letermovir Versus Valganciclovir Prophylaxis in Donor CMV-Seropositive/Recipient CMV-Seronegative Kidney Transplant Recipients

Ajit P Limaye¹, Marta Crespo², Nassim Kamar³, Atul Humar⁴, Robert P Carroll⁵, Marcus R Pereira⁶, Natalya Brody⁷, Weiwen Wang⁷, Barbara Haber⁷

Cytomegalovirus-specific cell-mediated immunity for prediction of post-prophylaxis CMV disease in a phase 3 trial of letermovir vs valganciclovir prophylaxis in donor CMV-seropositive recipient CMV-seronegative kidney transplant recipients

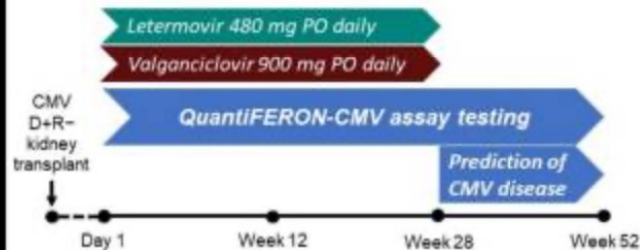
Limaye et al., 2025 | *Clinical Infectious Diseases*

Study objectives

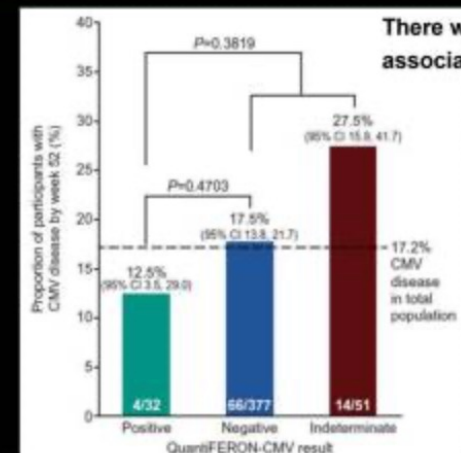
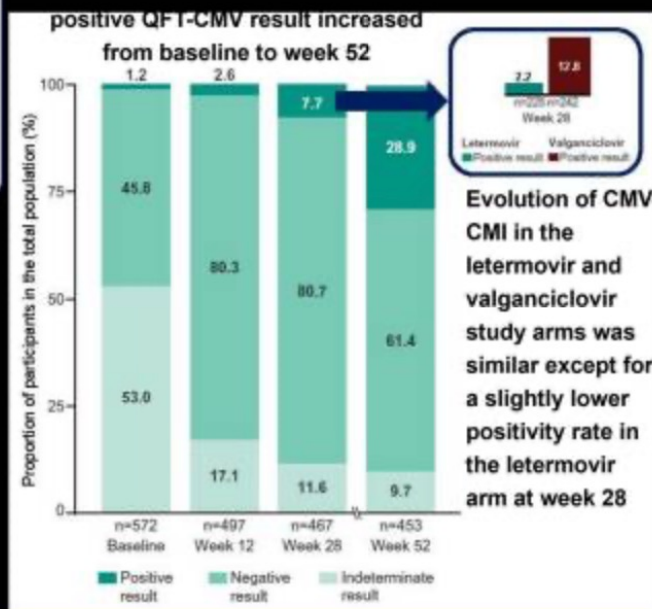
In a large population of CMV D+R- KTRs

- 1.) Characterize the evolution of CMV-specific cell-mediated (CMV-CMI) with letermovir vs valganciclovir
- 2.) Determine the clinical utility of the QuantiFERON-CMV (QFT-CMV) assay for prediction of post-prophylaxis CMV disease

Methods



QFT-CMV assay was performed prospectively in a central laboratory by personnel masked to the study arm. CMV disease reported by the investigators.



Positive versus pooled negative and indeterminate results			
	Total	Letermovir	Valganciclovir
Sensitivity, % (95% CI)	7.4 (4.8, 10.1)	2.2 (0.7, 4.4)	12.2 (7.7, 16.8)
Specificity, % (95% CI)	95.2 (90.7, 99.8)	97.7 (93.3, 100.0)	92.5 (84.3, 100.0)
PPV, % (95% CI)	87.5 (76.0, 99.0)	80.0 (45.0, 100.0)	88.9 (77.0, 100.0)
NPV, % (95% CI)	18.7 (15.0, 22.4)	19.6 (14.4, 24.9)	17.7 (12.5, 22.9)

LOW sensitivity for identifying those who remain CMV disease free after prophylaxis

Based on the results of this study, the QuantiFERON-CMV result at the end of prophylaxis has limited clinical utility to predict post-prophylaxis CMV disease in CMV D+R- KTRs

Peut-on améliorer les scores prédictifs d'infection à CMV du QuantiFERON® CMV en modifiant les seuils, au moins en transplantation rénale ?

population homogène de 73 greffés rénaux R+ suivi sur 12 mois post-greffe dans 9 centres français du groupe SPIESSER et de la FHU SUPORT (Etude QuanticR+) (2)

TABLE 5 Diagnostic performance of the QF-Ag or the QF-Mg at M1 using manufacturer's cut-offs for prediction of CMV reactivation in the R+ KTR cohort.

Cut-off (IU/ml)	Time point	Follow-up	Sensitivity* % [95% CI]	Specificity* % [95% CI]	PPV* % [95% CI]	NPV* % [95% CI]
QF-Ag < 0.2	M1	M1-M4	25.0 [3.2; 65.1]	78.0 [64.0; 88.5]	15.4 [1.9; 45.4]	86.7 [73.2; 95.0]
	M1	M1-M6	27.3 [6.0; 61]	78.7 [64.3; 89.3]	23.1 [5.0; 53.8]	82.2 [68.0; 92.0]
	M1	M1-M12	28.6 [8.4; 58.1]	79.5 [64.7; 90.2]	30.8 [9.1; 61.4]	77.8 [62.9; 88.8]
QF-Mg < 0.5	M1	M1-M4	37.5 [8.5; 75.5]	80.0 [66.3; 90.0]	23.1 [5.0; 53.8]	88.9 [76.0; 96.3]
	M1	M1-M6	45.5 [16.8; 76.6]	83.0 [69.2; 92.4]	38.5 [13.9; 68.4]	86.7 [73.2; 95.0]
	M1	M1-M12	42.9 [17.7; 71.1]	84.1 [69.9; 93.4]	46.1 [19.2; 74.9]	82.2 [67.9; 92.0]

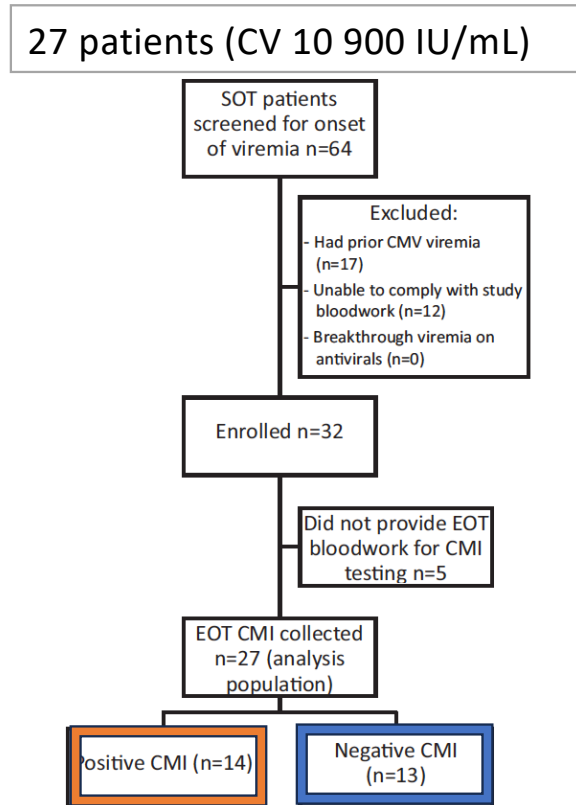
PPV, positive predictive value; NPV, negative predictive value; and CI, confidence interval. *Calculated in patients with data available over the study period.

TABLE 6 Diagnostic performance of the QF-Ag or the QF-Mg at M1 using optimized cut-offs determined by ROC curves for prediction of CMV reactivation in the R+ KTR cohort.

Cut-off (IU/ml)	AUC	Time point	Follow-up	Sensitivity* % [95% CI]	Specificity* % [95% CI]	PPV* % [95% CI]	NPV* % [95% CI]
QF-Ag < 2.23	0.53	M1	M1-M4	62.5 [24.5; 91.5]	52.0 [37.4; 66.3]	17.2 [5.8; 35.8]	89.7 [72.7; 97.8]
QF-Ag < 9.12	0.56	M1	M1-M6	90.9 [58.7; 99.8]	27.7 [15.6; 42.6]	22.7 [11.5; 37.8]	92.9 [66.1; 99.8]
QF-Ag ≤ 2.48	0.61	M1	M1-M12	71.4 [41.9; 91.6]	54.5 [38.8; 69.6]	33.3 [17.3; 52.8]	85.7 [67.3; 95.6]
QF-Mg < 1.29	0.61	M1	M1-M4	62.5 [24.5; 91.5]	68.0 [53.3; 80.5]	23.8 [8.2; 47.2]	91.9 [78.1; 98.3]
QF-Mg < 1.29	0.69	M1	M1-M6	72.7 [39.0; 94.0]	72.3 [57.4; 84.4]	38.1 [18.1; 61.6]	91.9 [78.1; 98.3]
QF-Mg ≤ 1.27	0.68	M1	M1-M12	64.3 [35.1; 87.2]	72.7 [57.2; 85.0]	42.9 [21.8; 66.0]	86.5 [71.2; 95.5]

AUC, Area under the ROC Curve; PPV, positive predictive value; NPV, negative predictive value; and CI, confidence interval. *Calculated in patients with data available over the study period.

QuantiFERON® CMV pour prédire l'utilité d'une prophylaxie secondaire en organe solide :



14/27 (51.9%) => No prophylaxis : 1 recurrent infection

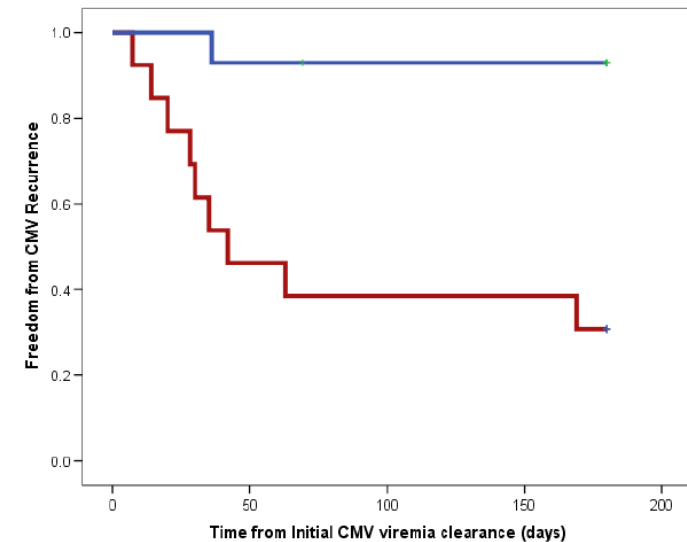
13/27 (48.1%) => 2 Months secondary prophylaxis 62% recurrent infection

Brief Communication

An Interventional Study Using Cell-Mediated Immunity to Personalize Therapy for Cytomegalovirus Infection After Transplantation

D. Kumar*, M. Mian, L. Singer  and A. Humar Introduction

CMV CMI Interventional Study



positive CMV-cell-mediated immunity (CMI) (blue line-online version or gray line-print version) or negative CMI (red line-online version or black line-print version). Log-rank p-value = 0.001.

L'ELISpot prédit l'infection à CMV tardive après l'arrêt du letermovir

Zamorin et al.

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> Bone Marrow Transplant. 2025 Aug;60(8):1137-1145. doi: 10.1038/s41409-025-02611-4. Epub 2025 May 6.

ELISPOT as a predictor of clinically significant cytomegalovirus infection after hematopoietic cell transplantation in letermovir recipients

Daniel Zamorin^{1,2}, Hu Xie³, Elizabeth Wong¹, Clarissa Santiano¹, Andrea Vivas-Jimenez¹, Alicja Sadowska-Klasa^{1,4}, Eleftheria Kampouri^{1,5}, Terry Stevens-Ayers¹, Masumi Ueda⁶, Yoshima^{3,6}, Wendy M Leisenring³, Joshua A Hill^{1,2}, Michael Boeckh^{7,8,9}

Affiliations + expand

PMID: 40328898 PMCID: PMC12818887 DOI: 10.1038/s41409-025-02611-4

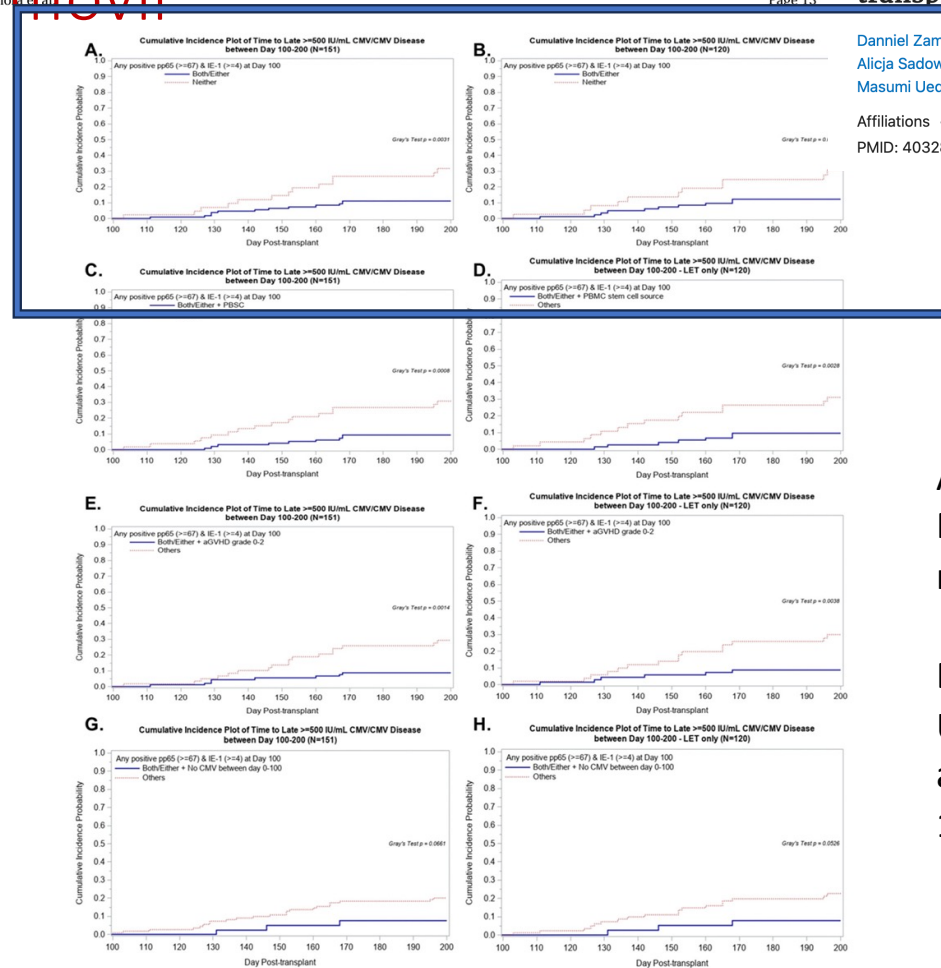


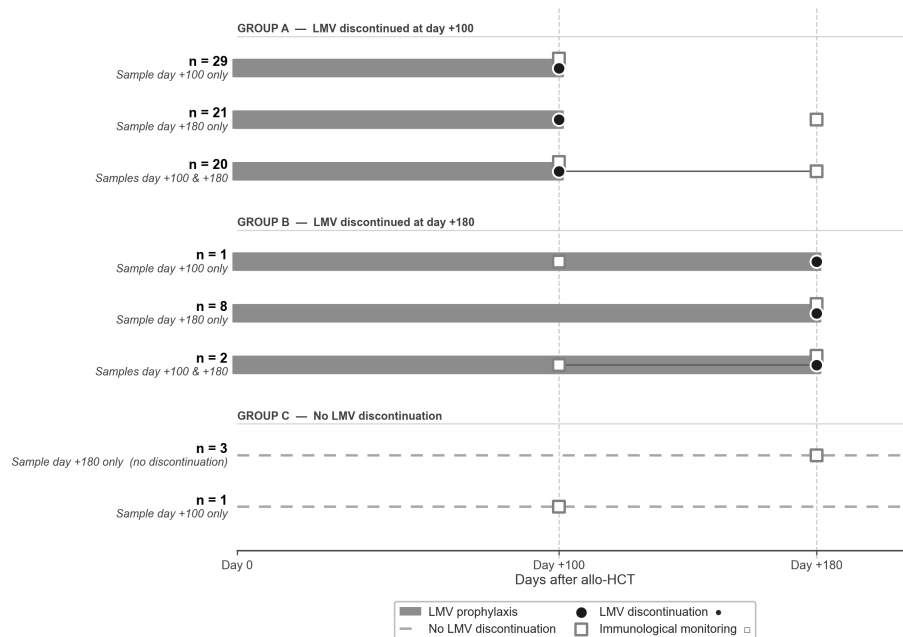
Figure 3. –. Cumulative incidence of late clinically significant CMV (csCMV) infection from 100–200 days post-HCT stratified by CMV cell-mediated immunity (CMV-CMI) and other clinical parameters.

Seuils définis sur cette population : 67 et 4 spots/250,000 cellules pour pp65 et IE-1, pour prédire l'infection à CMV entre 100 et 200 j post greffe justifiant un traitement (CS-CMV).

A,C,E,G : tous
Préemptif n= 48 et LTV
n=160

B,D,F,H
Uniquement les patients
ayant reçu du letermovir
100j

Nouveaux tests IGRA pour mesurer la reconstitution immune sous letermovir après allo-CSH



Pas de prédiction de la virémie
avec le Test IGRA Ag CMV
BioMérieux

Le T Spot est prédictif

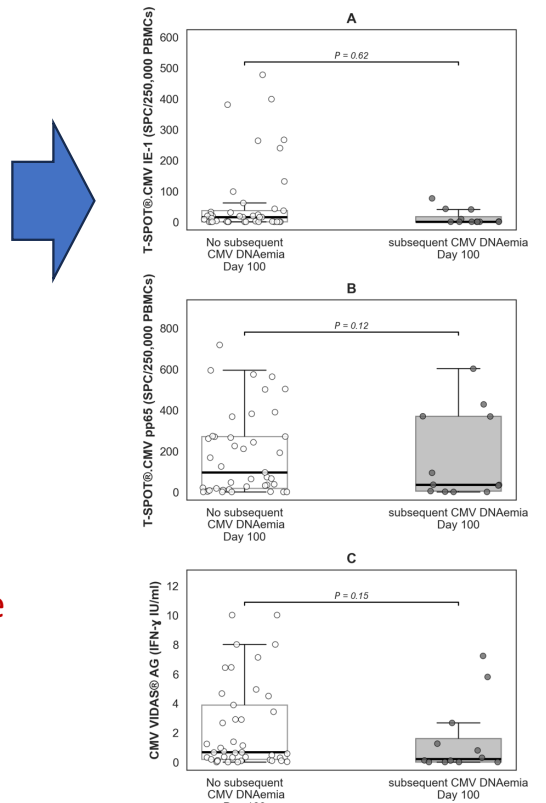
Concordance médiocre
Vidas/ELISPOT

**CONCLUSION : les TESTS IGRA ne
sont pas interchangeables**

A comparative performance evaluation of the VIDAS cytomegalovirus (CMV) interferon-gamma release assay (IGRA) and T-SPOT CMV for measuring CMV-specific T-cell responses in allogeneic hematopoietic stem cell transplant recipients receiving letermovir prophylaxis

Carlos Solano de la Asunción,¹ Ester Colomer,¹ Lourdes Vázquez,² Irene García Cadenas,³ María Jesús Pascual,⁴ Pablo Granados,⁵ Carlos Martín,⁶ Olga Asó,⁷ Soukaina Boutrig,⁸ Eliseo Albert,⁹ Ariadna Pérez,⁹ José Luis Piñana,⁹ Carlos Solano,^{6,7} Estela Giménez,^{1,8} David Navarro^{1,8*}

doi:10.1128/JCM.01151.131



Que retenir?

- L'immunomonitoring des infections à CMV repose sur la mesure des réponses cellulaires contre des antigènes majeurs au minimum **pp65 et IE**
- Les seuls tests validés (marqués CE) sont les tests IGRA **QuantiFERON®CMV ou ELISpot** . Les autres tests (analyse des cytokines intracellulaires ou test IGRA sur lysat BioMérieux Vidas) sont en cours de validation
- Le QuantiFERON®CMV est disponible et automatisable au CNR ou dans de nombreux laboratoires de virologie, L'ELISpot nécessite une entente préalable pour envoi de sang frais au laboratoire concerné dans un délai de 24h00
- Leurs indications selon les recommandations internationales sont
 - Vérification de séroposativité du receveur en cas de doute (IgG équivoques) avant greffe d'organe
 - Minimisation de la durée de prophylaxie primaire après greffe de rein chez les receveurs séropositifs (non validé en greffe pulmonaire, en cours de validation en greffe cardiaque, accepté pour le foie)
 - Extension de la prophylaxie primaire par letermovir après allogreffe de cellules souches hématopoiétiques suggéré mais à évaluer
 - Décision de prophylaxie secondaire post traitement de maladie ou infection à CMV suggéré mais à évaluer
- L'ELISpot a une bonne valeur prédictive négative et positive, sous réserve d'utiliser les seuils adaptés
- Des seuils plus élevés du QuantiFERON®CMV pourraient être nécessaires
- Les indications dans les autres contextes (HIV, MICI, autres immunodépressions ou infection congénitale à CMV) sont à évaluer.



L'avenir? des scores et algorithmes plus étendus
permettant une évaluation de tous les aspects de la réponse immune?

Casting Light on HOst-cytomegalovirus interaction in Solid organ transplantation

Projet Européen HORUS (Horizon Europe 2022-2027) – Grant Agreement 101057651 / Proposal SEP-210765406 : Casting light on HOst-cytomegaloviRUs interaction in Solid organ transplantation. Coord. H. Kaminski (Université/CHU de Bordeaux).

• Objectif & Périmètre : Consortium européen de 25 partenaires dans 8 pays créant la 1ère cohorte prospective multicentrique européenne en SOT.

HORUS

HORUS is organised in 5 scientific work-packages described in Figure 1.

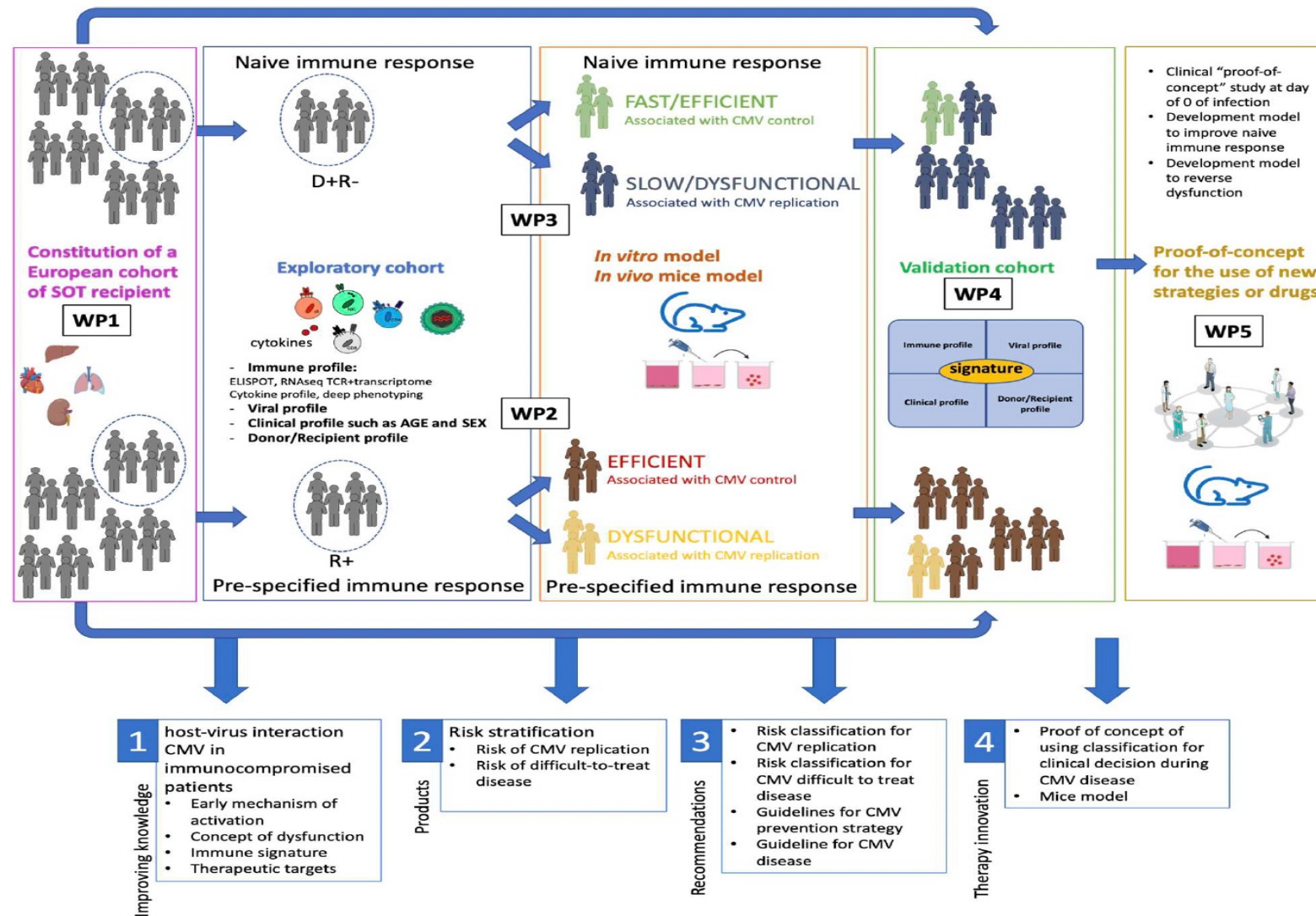


Figure 1. Global overview of scientific WorkPackages 1 to 5 and parallel objectives fulfilled

Merci de votre attention!

