Added clinical value of CMV-IGRA in Solid Organ Transplant (SOT) patients

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Cytomegalovirus

Herpesvirus familie

dsDNA

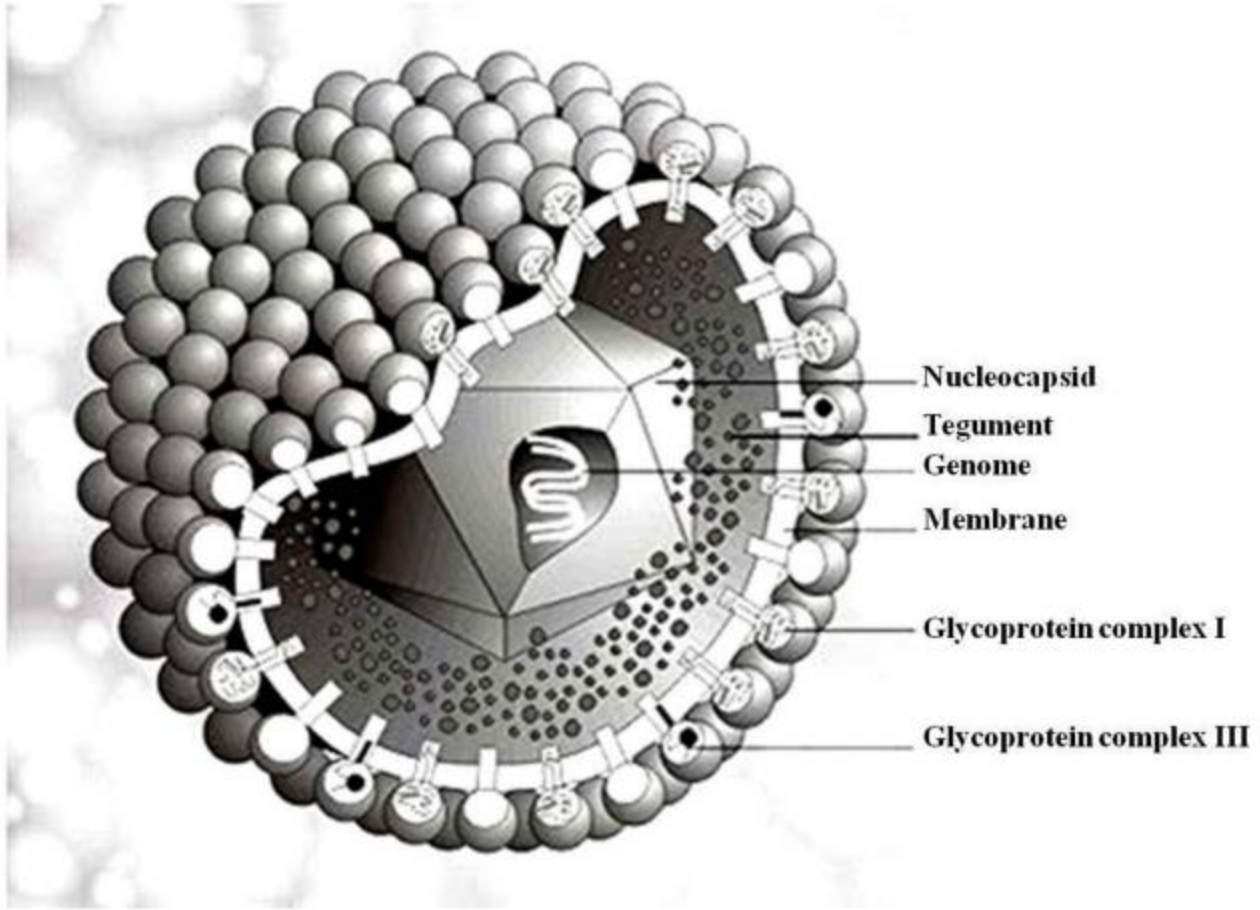


Figure 1 A cartoon depicting the structure of the HCMV virion. (Image obtained from (http://www.virology.net/big_virology/bvdnaherpes.html) courtesy of Dr. Marko Reschke in Marburg, Germany).

(Tomtishen III, J.P., 2012)

Epidemiologie

- Wereldwijd
  - Hoogste seroprevalentie in Zuid-Amerika, Afrika en Azië
  - Lager in West-Europa en VSA
- 40%-100% seroprevalentie

(CMV-Infectie | LCI-Richtlijn, 2015)

Transmissie

- Contact met lichaamsvloeistoffen
- Seksueel contact
- Overdracht via transplantaties en bloedtransfusies

CDC (2024)

Immuuncompetente host

- Meestal asymptomatisch (of atypisch)
- Soms mononucleose-achtig beeld
- Zeldzaam hepatitis of Guillain-Barré
- Levenslange latente infectie

(CMV-Infectie | LCI-Richtlijn, 2015)

Immuungecompromiteerde host

- Reactivatie van latente infectie
- Immunosuppresie ikv transplantatie
- HIV-geïnfecteerden met lage CD4-count

- Ernstige gedisseminеerde infectie
- CMV-weefsel invasieve ziekte (enteritis, colitis, hepatitis, nefritis, pneumonitis, mengitis, encefalitis, retinitis)

Congenitale infecties: zeer divers klinisch beeld, variërend van een asymptomatische infectie tot ernstige neurologische complicaties.

(Santos et al., 2026)
(CMV-Infectie | LCI-Richtlijn, 2015)

Transplantpatiënten

- Significante morbiditeit en mortaliteit
- Profylaxe/pre-emptieve therapie op basis van risico

(Santos et al., 2026)

Overzicht diagnostiek CMV

- Serologie
- PCR
- pp65 antigen
- Cultuur
- Histopathologisch

(Santos et al., 2026)

Risicostratificatie CMV reactivatie

- Belangrijkste huidige risicostratificatie momenteel serostatus donor (D) en receptor (R) en getransplanteerd orgaan
  - Laag risico bij D-/R-
  - Hoog risico bij D+/R-
  - Intermediair risico bij R+

Profylaxe/pre-emptieve therapie richtlijn

TABLE 3.

Recommended approaches for CMV prevention in different organs for adult solid organ transplant recipients

Organ	Serostatus	Risk level	Recommended[a]	Alternate
All	D⁻/R⁻	Low	Monitoring for clinical symptoms; consider antiviral prophylaxis against other herpes infections	Preemptive therapy (if higher risk, ie, significant transfusions)
Kidney	D⁺/R⁻	High	6 mo of (V)GCV or 6 mo of LET or preemptive therapy	High-dose VALACY
	R⁺	Intermediate	3 mo of VGCV or preemptive therapy	High-dose VALACY. If on mTOR-based immunosuppression, preemptive therapy or close clinical monitoring recommended
Liver	D⁺/R⁻	High	3–6 mo of VGCV or preemptive therapy	
	R⁺	Intermediate	3 mo of VGCV or preemptive therapy	
Pancreas	D⁺/R⁻	High	3–6 mo of VGCV	Preemptive therapy
	R⁺	Intermediate	3 mo of VGCV or preemptive therapy	
Islet	D⁺/R⁻	Intermediate	3 mo of VGCV	Preemptive therapy
	R⁺	Intermediate	3 mo of VGCV or preemptive therapy	
Heart	D⁺/R⁻	High	3–6 mo of (V)GCV	-Preemptive therapy -Some experts add CMVIG to prophylaxis
	R⁺	Intermediate	3 mo of (V)GCV or preemptive therapy	
Lung	D⁺/R⁻	High	12 mo of (V)GCV	-Preemptive therapy
	R⁺	Intermediate	6–12 mo of (V)GCV	-Some experts add CMVIG to prophylaxis
Intestinal, composite tissue	D⁺/R⁻	High	Minimum 6 mo (V)GCV	-Preemptive therapy
	R⁺	High	3–6 mo (V)GCV	-Some experts add CMVIG to prophylaxis

[a]When a range is given, the duration of prophylaxis may depend on the degree of immunosuppression, including the use of lymphocyte-depleting antibodies for induction. Surveillance after prophylaxis can be used in at-risk patients. LET can be considered in cases of VGCV intolerance where prophylaxis is used. VGCV is approved by the EMA but not the FDA in liver transplants.

CMV, cytomegalovirus; D, donor; EMA, European Medicines Agency; FDA, Food and Drug Administration; GCV, intravenous ganciclovir; LET, letermovir; mTOR, mammalian target of rapamycin; R, recipient; VALACY, valacyclovir; VGCV, valganciclovir; (V)GCV, ganciclovir or valganciclovir.

Koton CN et al., 2025

In UZ Leuven

Bij SOT R+ of D+/R- standaard profylaxe met valganciclovir gedurende 3 maanden

Bij hematologische stamceltransplantie:
Profylaxe bij R+ dmv letermovir tot D100 post op

Nadien minstens wekelijkse screening dmv CMV PCR op bloed en pre-emptieve strategie.

Problemen

- Langdurige profylaxe nodig
- Moeilijk te voorspellen wie na profylaxe toch opnieuw CMV-reactivatie zal hebben

-> oplossing CMV-CMI?

Vraagstelling CAT

1. Welke commercieel beschikbare testen bestaan er en wat zijn de verschillen?
2. Wat is de klinische meerwaarde van CMV-IGRA?

Testmethodes voor CMV-CMI

Advantages and limitations of various assays for immune monitoring of CMV

Assay	Advantages	Limitations	Comments
ELISA	Whole blood assay with low blood volume (3 mL) is simple to perform, and results are available after 30–40 h. Knowledge of HLA is not necessarily required, can be done in any center, and stimulated plasma can be sent to a reference laboratory	$CD8^+$ responses only. Sensitive to lymphopenia. Rare patients whose HLA types are not covered in assay	Commercial availability (approved in Europe QuantiFERON-CMV (Qiagen, Germany)
ELISpot	Identifies both $CD4^+$/$CD8^+$ T cells. Knowledge of HLA is not necessarily required. Results available after 30–40 h	Need for purified PBMC from 10 mL blood (approximately 1×10^6 PBMC). Cannot differentiate $CD4^+$ and $CD8^+$ T cells	Potential to freeze PBMCs and ship to reference laboratory for testing. Commercial availability (T-SPOT.CMV and T-TRACK CMV CE marketed in Europe; T-SPOT.CMV is LDT in the United States)
ICS	Whole blood assay with low blood volume (1 mL) or PBMC, short incubation time, and results available after 8 h. Identifies $CD4^+$ and $CD8^+$ T cells. Knowledge of HLA is not necessarily required. Provides quantitative and qualitative characterization	Needs access to a flow cytometer. Not standardized	Most data are available with this technique. Potential to freeze PBMCs and ship to reference laboratory for testing. Commercial availability (VIRACOR Insight in the United States)
MHC-multimer staining	Fast assay (1–2 h). Whole blood assay with low blood volume (0.5–1.0 mL) or PBMC	$CD8^+$ responses only. Needs access to a flow cytometer. HLA and epitope specific. No information about the function is available unless combined with ICS. Not standardized	Unlikely to be used on a widespread basis in clinical diagnostics

CMV, cytomegalovirus; ELISpot, enzyme-linked immunosorbent spot; ICS, intracellular cytokine staining; LDT, laboratory-developed test; MHC, major histocompatibility complex; PBMC, peripheral blood mononuclear cell.

UZ LEUVEN

Koton CN et al., 2025

CMV-interferon gamma release assay (IGRA) met enzyme-linked immunosorbent assay (ELISA)

QuantiFERON-CMV (QIAGEN)

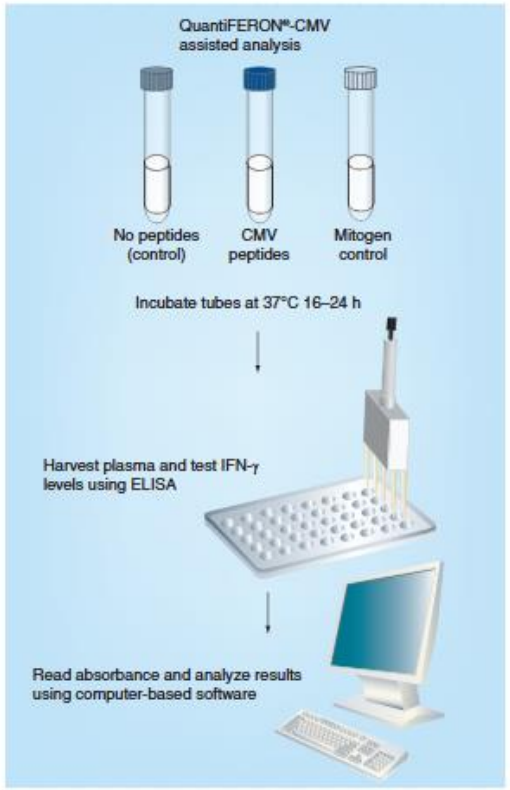


Figure 1. Overview of the QuantiFERON®-CMV methodology.
CMV: Cytomegalovirus.
Reproduced with permission from [32].

Table 1. List of the peptides, cytomegalovirus proteins and HLA class I alleles included in the QuantiFERON®-CMV assay.

Peptide	Sequence	CMV protein	HLA restriction
1	VTEHDTLLY	pp50	A1
2	VLEETSVML	IE-1	A2
3	NLVPMVATV	pp65	A2
4	IMREFNSYK	gB	A3
5	AYAQKIFKIL	IE-1	A23 and A24
6	QYDPVAALF	pp65	A24
7	DIYRIFAEL	pp65	A26
8	TPRVTGGGAM	pp65	B7
9	QIKVRVDMV	IE-1	B8
10	ARVYEIKCR	pp28	B27
11	CPSQEPMSIYVY	pp65	B35
12	ELRRKMMYM	IE-1	B8
13	FEQPTETPP	IE-2	B41
14	QEFFWDANDI	pp65	B44
15	QAIRETVEL	pp65	B57 and B58
16	QMWQARLTV	pp65	B52
17	PTFTSQYRIQGKL	pp65	A24
18	GPISGHVLK	pp65	A11
19	DALPGPCI	pp65	B51
20	KMQVIGDQY	pp65	B40/B60
21	CEDVPSGKL	pp65	B40/B60
22	TRATKMQVI	pp65	Cw6 (A30/B13)

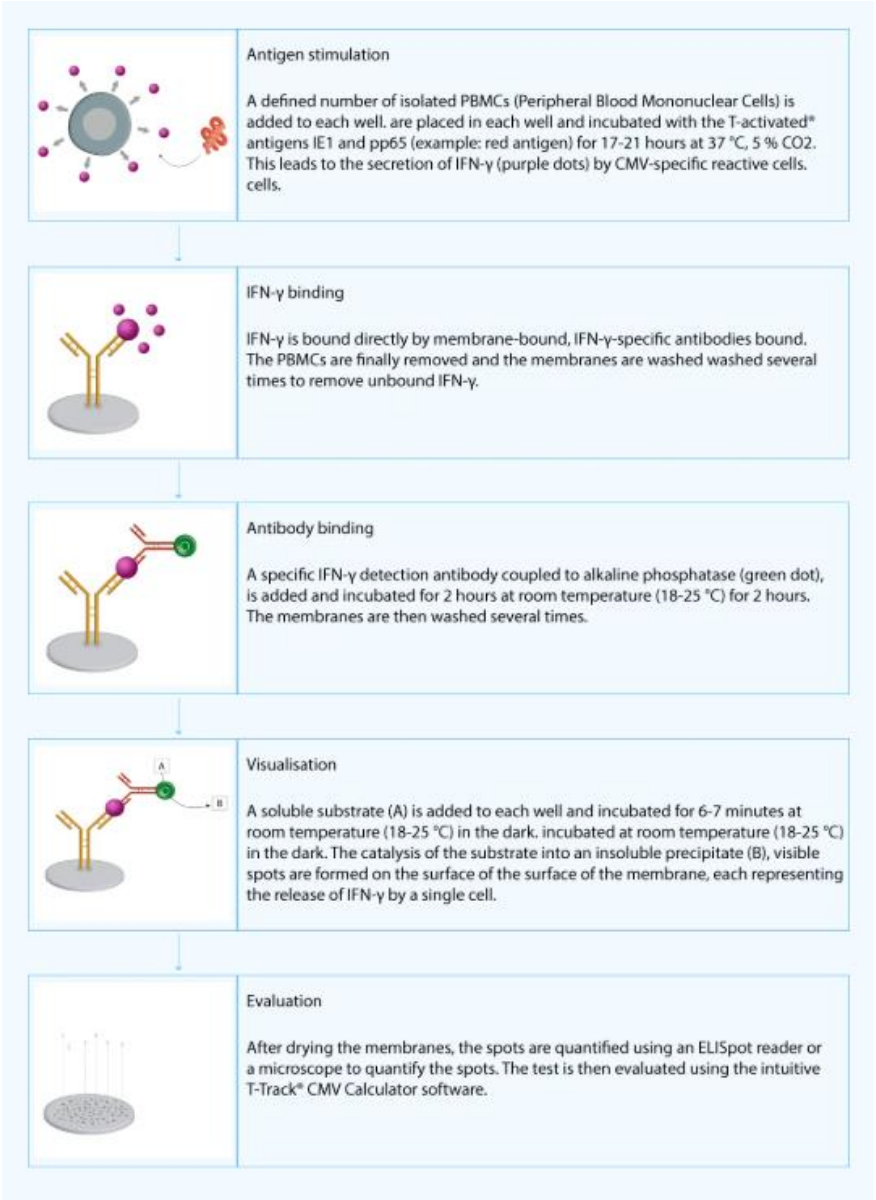
CMV: Cytomegalovirus.

(Giulieri S et al., 2011)

Enzyme-linked immunospot assay (ELISpot)

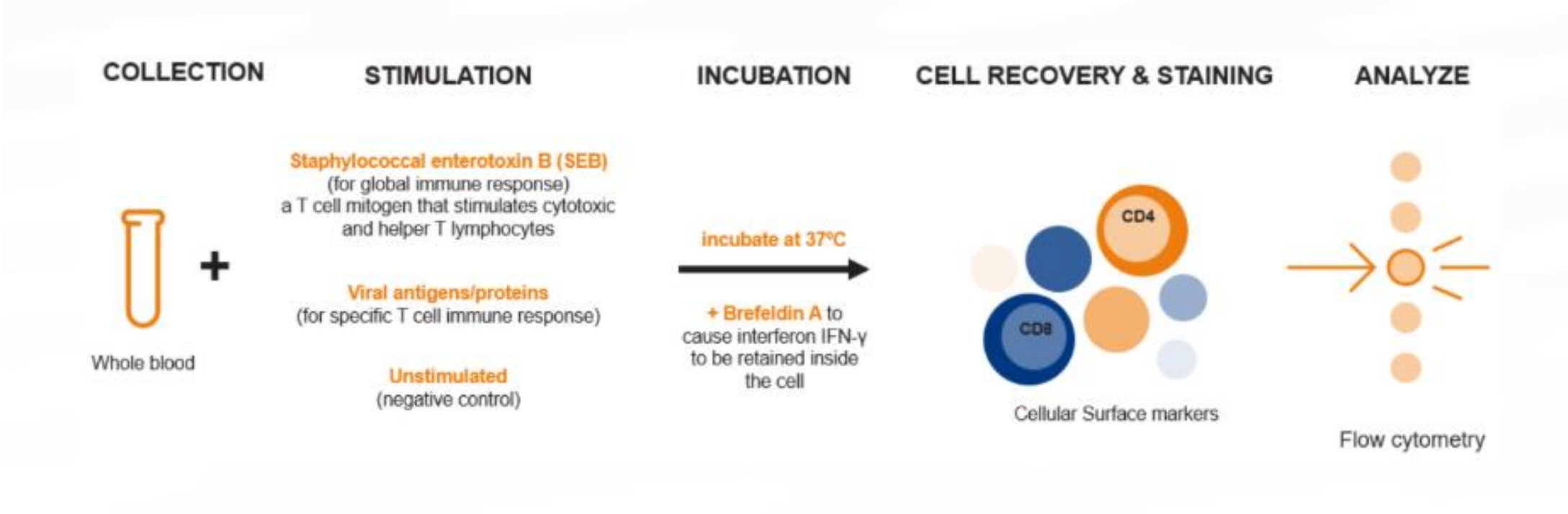
T-SPOT.CMV (Oxford Immunotec)

T-TRACK CMV (Mikrogen)



Mikrogen GmbH (z.d.).

ICS flowcytometrie



Eurofins Viracor. (z.d.)

MHC-multimer staining

- MHC-molecolen met CMV-peptide en fluorescent gelabeld
- Flowcytometrie

- Niet commercieel beschikbaar in Europa

Mayo Clinic Laboratories. (z.d.).

Theoretische klinische meerwaarde

TABLE 7.

Potential clinical uses and management based on CMV-specific immune monitoring

Clinical setting	Viral load	CMI result	Action	Interpretation
Pretransplant				
Pretransplant R+	NA	Negative	Prophylaxis or surveillance	Indicates low-level protection
		Positive	Low accuracy for predicting immune protection. New posttransplant CMV-CMI test recommended.	Induction immunosuppression may hamper a positive pretransplant CMV-CMI and induce a negative CMV-CMI result
R+ 14 d posttransplantation	NA	Negative	Prophylaxis or surveillance	Indicates low-level protection
		Positive	Stop prophylaxis/reduce intensity of monitoring	Indicates protection
Pretransplant seropositive patients with potential passive antibodies	NA	Negative	Assign CMV infection status	Passive immunity (T cells are not transferred)
		Positive		True Infection
Posttransplant prophylaxis				
End of prophylaxis	NA	Positive	Stop prophylaxis	Indicates protection
		Negative	Continue prophylaxis or stop prophylaxis and do surveillance	Indicates lack of protection
R+ on lymphocyte-depleting antibodies during prophylaxis	NA	Positive	Stop prophylaxis	Indicates protection
		Negative	Continue prophylaxis or stop prophylaxis and do surveillance	Indicates lack of protection
Posttransplant preemptive therapy				
Asymptomatic R+ patients (>1 mo posttransplant)	Negative	Positive	Continue surveillance	Low risk; indicates protection
	Negative	Negative	Close surveillance	Increased risk; indicates lack of protection
	Positive	Positive	No treatment; close monitoring	Low risk; indicates sufficient immunity
	Positive	Negative	Treatment	Indicates lack of protection
End of treatment	Negative	Positive	Stop treatment	Low risk of relapse, sufficient immunity
	Negative	Negative	Secondary prophylaxis	High risk of relapse, lack of protection

CMI, cell-mediated immunity; CMV, cytomegalovirus; R+, CMV seropositive.

Koton CN et al., 2025

Evidence SOT

2 prospectieve, interventionele studies

Kumar et al., 2017

Solera et al., 2025

Kumar et al., 2017

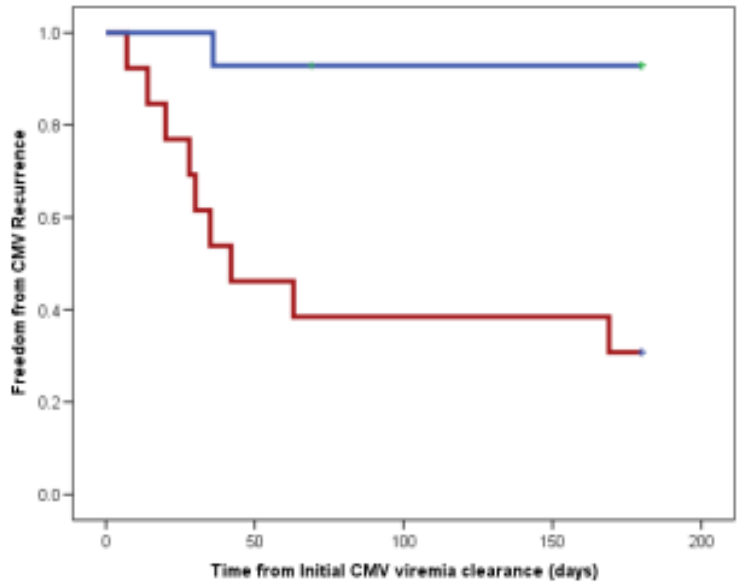


Figure 3: Kaplan–Meier curve of cytomegalovirus (CMV) recurrence ≥500 International Units/mL after initial viral load clearance, in patients with either a positive CMV-cell-mediated immunity (CMI) (blue line-online version or gray line-print version) or negative CMI (red line-online version or black line-print version). Log-rank p-value = 0.001. Of the nine patients who were CMV-CMI negative and had CMV recurrence, two had breakthrough viremia while on prophylaxis, and five had premature discontinuation of prophylaxis due to neutropenia. [Color figure can be viewed at wileyonlinelibrary.com]

Solera et al., 2025

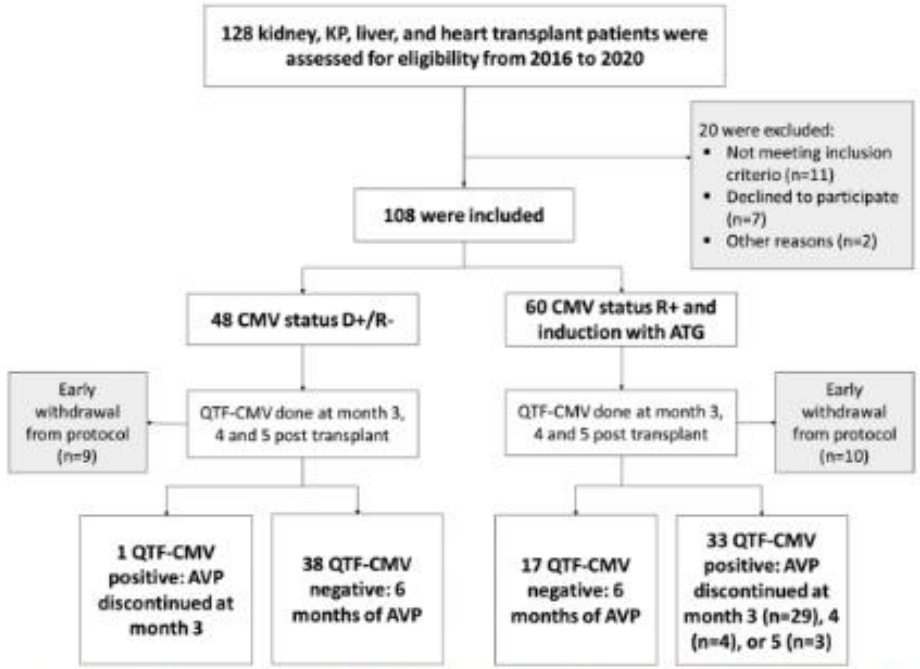


FIGURE 1. Flow diagram of the study. ATG, antithymocyte globulin; AVP, antiviral prophylaxis; CMV, cytomegalovirus; D+, donor CMV-seropositive; KP, kidney-pancreas; QTF, QuantiFERON; R+, recipient-seropositive; R-, recipient-seronegative.

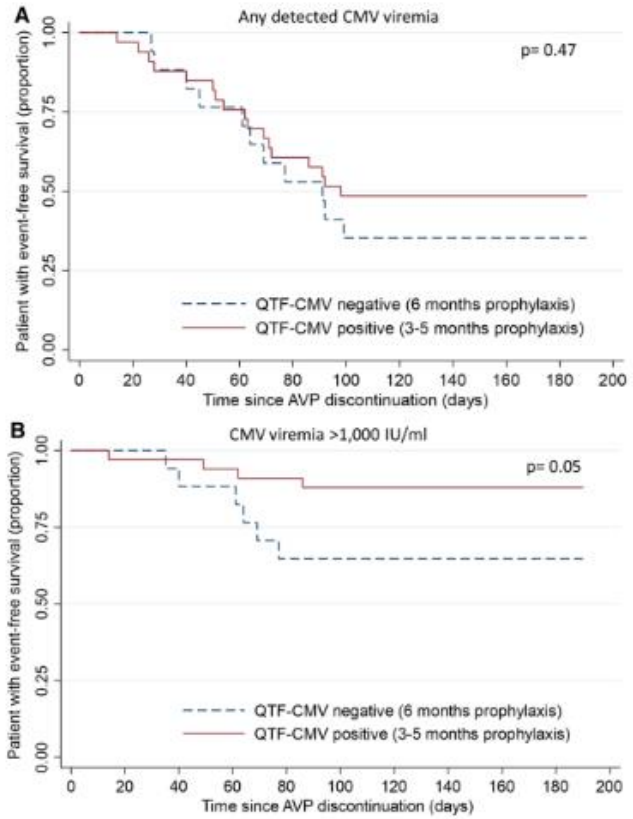


FIGURE 3. Survival analysis of the rate of CMV viremia in R+ patients with ATG induction by the QTF-CMV result and the time of prophylaxis (per-protocol R+ population; n = 50): any detected CMV viremia (A) and CMV viremia >1000 IU/mL (B). ATG, antithymocyte globulin; AVP, antiviral prophylaxis; CMV, cytomegalovirus; QTF, QuantiFERON; R+, recipient-seropositive.

Niertransplantatie

- ELISpot-methoden systematisch beter dan QuantiFERON-CMV voor het voorspellen van CMV-ziekte (Ruan et al., 2019)
- TIMOVAL-trial (Paez-Vega et al., 2022)

Table 3. Outcome of Selected End Points for DOOR Analysis (Intent-to-Treat Population)

End points	Immunoguided Prevention (n = 76)	Fixed-Duration Prophylaxis (n = 74)	*P* Value
Primary outcome			
Incidence of CMV disease	0 (0.0)	2 (2.7)	.243
Secondary outcome			
Incidence of CMV replication	13 (17.1)	10 (13.5)	.542
DOOR at 12 months			
No CMV disease/replication without neutropenia	57 (75.0)	39 (52.7)	<.001
No CMV disease/replication with neutropenia	6 (7.9)	25 (33.8)	<.001
CMV disease/replication without neutropenia	12 (15.8)	7 (9.5)	.248
CMV disease/replication with neutropenia	1 (1.3)	3 (4.1)	.323
DOOR components at 12 months			
CMV disease/replication	13 (17.1)	10 (13.5)	.542
Neutropenia	7 (9.2)	28 (37.8)	<.001

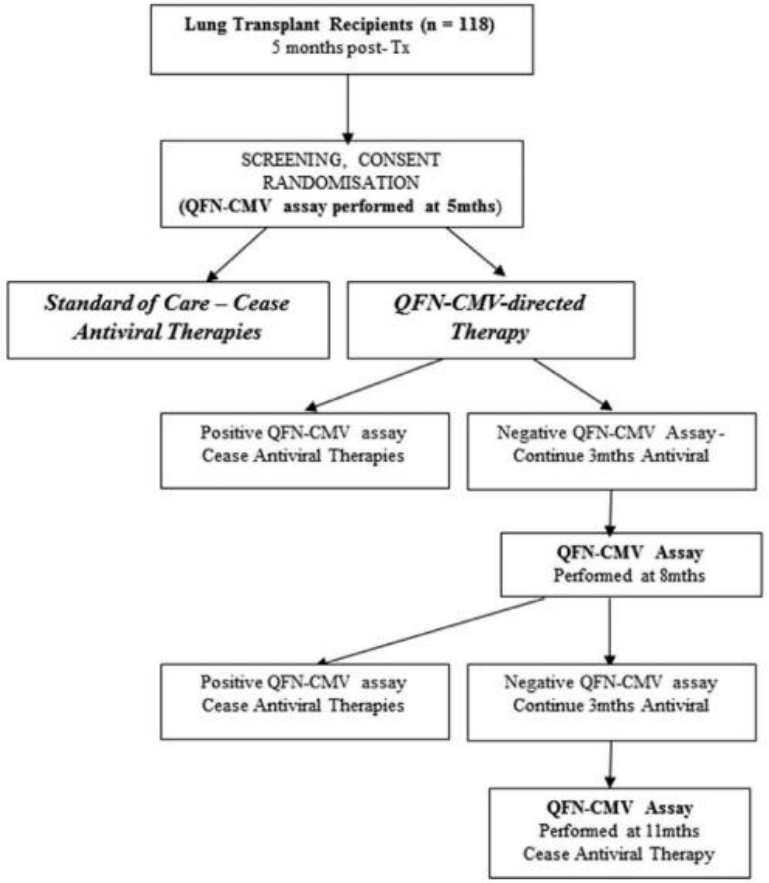
Data are presented as no. (%) unless otherwise indicated. DOOR analysis was performed. For this analysis, the composite variable of incidence of CMV disease or replication was considered. Given that the 2 patients with CMV disease also had CMV replication, only 1 event was considered in these patients. Neutropenia: <1500 neutrophils/mm^3.

Abbreviations: CMV, cytomegalovirus; DOOR, desirability of outcome ranking.

Longtranplantatie

- Westall et al., 2019
- Gardiner et al., 2022
- Páez-Vega et al., 2025

Westall et al., 2019



All LTx patients followed up until 18 months post-LTx

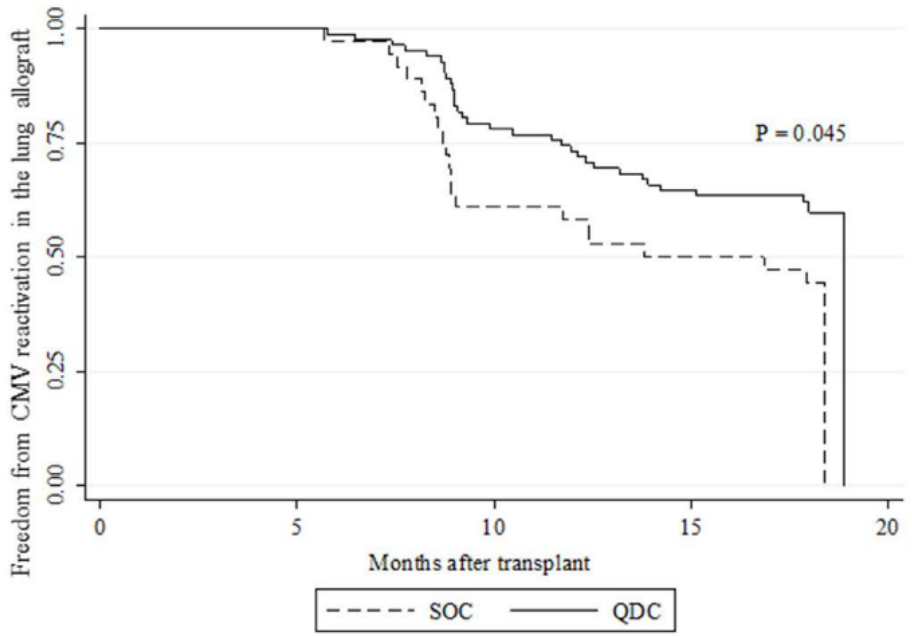
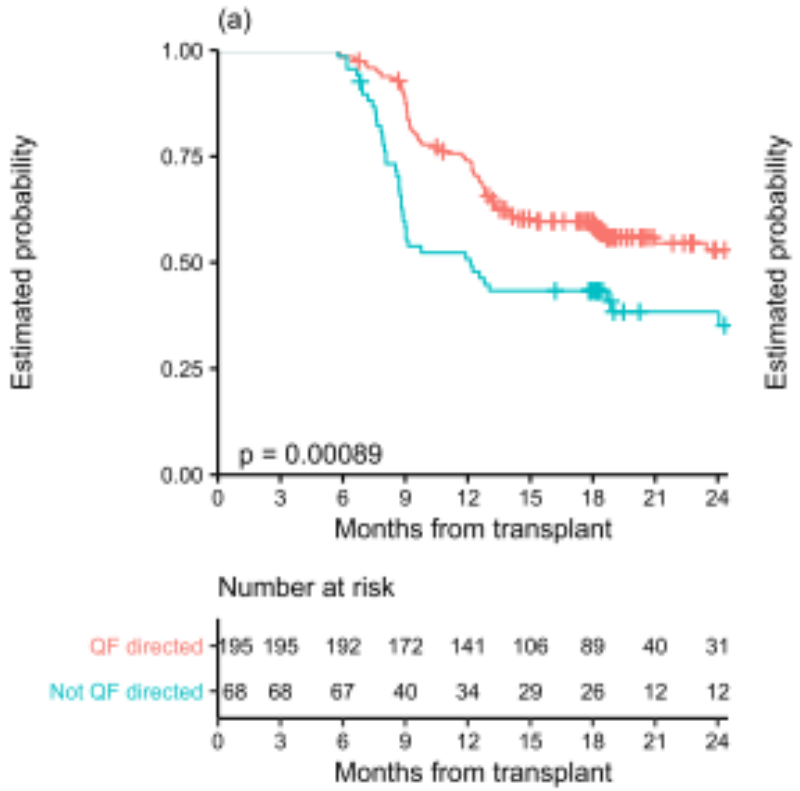
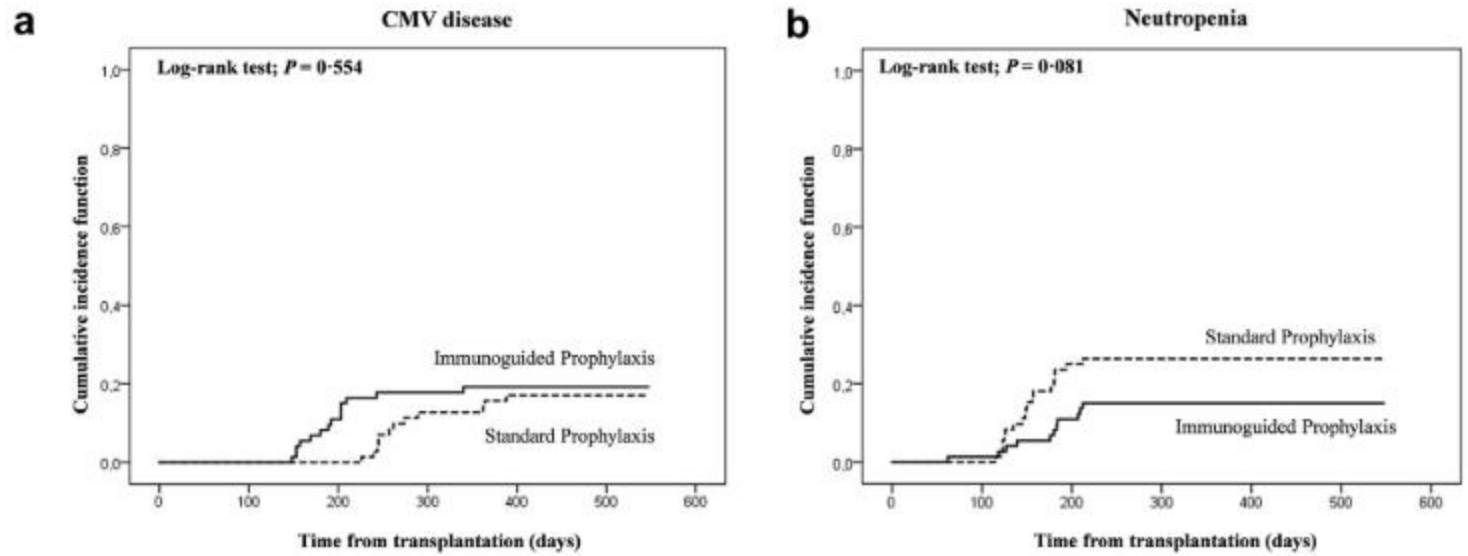


FIGURE 2. Kaplan-Meier curve showing CMV infection in the lung allograft in the treatment arms. CMV, cytomegalovirus; SOC, standard of care.

Gardiner et al., 2022



Páez-Vega et al., 2025



Number at risk

Immunoguided Prophylaxis	75	74	65	58	55	53
Standard Prophylaxis	75	73	72	61	57	56

	75	73	65	60	58	57
	75	73	54	51	50	48

Fig. 2: Event probability of CMV disease (a) and neutropenia (<1500 cells/µL) (b) according to the strategy followed by the patients.

Hematologische stamceltransplantatie

- Meerdere studies tonen prognostische waarde aan, maar geen prospectieve, interventionele data beschikbaar.

- Methode vergelijking tussen T-SPOT.CMV en QuaniFERON-CMV toont moderate agreement op D100 post transplant

(Souan, L. et al., 2025)
(Callens, R et al, 2023)

Kosteneffectiviteit

- Bewezen kosteneffectiviteit bij immunoguided pre-emptieve therapie vergeleken met standaard pre-emptieve therapie bij R+ niertransplant patiënten voor QuantiFERON-CMV in Brazilië.
- Verder weinig literatuur beschikbaar
- In België geen nomenclatuur beschikbaar

(Reusing JO et al., 2024)

Conclusie

- CMV-IGRA als aanvullende risicostratificatie bij transplantpatiënten
- Risico ook nog afhankelijk van subpopulatie
- Nog verder prospectief, interventioneel onderzoek nodig

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