Guidelines on CMV: Best Practice Prevention, Diagnosis, And Treatment

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Disclosures: Camille Nelson Kotton MD

Company	Role	Details
Merck	Consultant, Adjudication committee member	Transplant infections, CMV antiviral trial
QIAGEN	Consultant	Transplant diagnostics (CMV)
Oxford Immunotec	Consultant, research	Novel diagnostics in transplant patients
Shire-Takeda	Consultant, adjudication committee member	CMV management in transplant patients
Hookipa	Consultant, research	CMV vaccine
Hologic	Consultant	CMV diagnostics
Synklino	Consultant	CMV therapeutics
COGEN Therapeutics, Inc.	Consultant	CMV immunology
GSK	Consultant	CMV vaccines

I will discuss off label use and/or investigational use in my presentation

Original Clinical Science—General

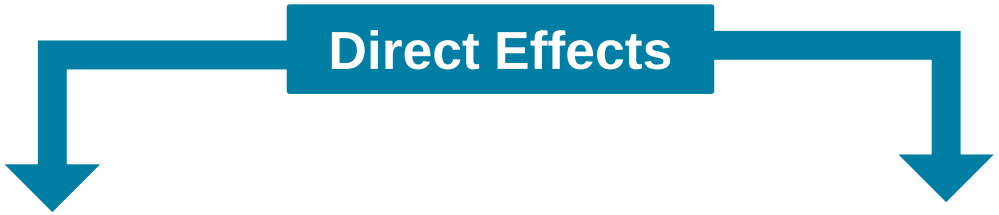
Transplantation ■ June 2018 ■ Volume 102 ■ Number 6

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, MD[7]
on behalf of the The Transplantation Society International CMV Consensus Group

For this talk, emphasis on seropositive recipients & recent literature updates

Direct Effects of CMV Infection



CMV Viral Syndrome

- Flu-like syndrome: fever, malaise, myalgia
- Leukopenia, thrombocytopenia

Tissue-Invasive Disease

- GI diseases: Colitis, Hepatitis
- Pneumonitis
- Carditis
- Myocarditis
- Nephritis
- Encephalitis, retinitis

Torres-Madriz G, Boucher HW. *Clin Infect Dis*. 2008;47(5):702-711;
Kotton CN, CMV: Prevention, Diagnosis and Therapy, AJT 2013

Indirect Effects of CMV Infection

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General Indirect Effects – Elevated Risks

Bacterial, viral, fungal infections

Post transplant lymphoproliferative disorder

Cardiovascular events

New-onset diabetes after transplantation

Immunosenescence

Acute rejection

Mortality***

Transplant-specific Indirect Effects

Chronic allograft nephropathy and/or loss after renal transplant

Accelerated hepatitis C recurrence, hepatic artery thrombosis after liver transplant

Allograft vasculopathy after cardiac transplant

Bronchiolitis obliterans after lung transplant

Optimal CMV management may have a major impact on both individual AND programmatic outcomes.

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Kotton CN, CMV: Prevention, Diagnosis and Therapy, AJT 2013 HW.; Rubin RH. *Curr Opin Infect Dis.* 2007;20(4):399-407; Pescovitz MD. *Transplantation.* 2006; 82(2 suppl):S4-S8.

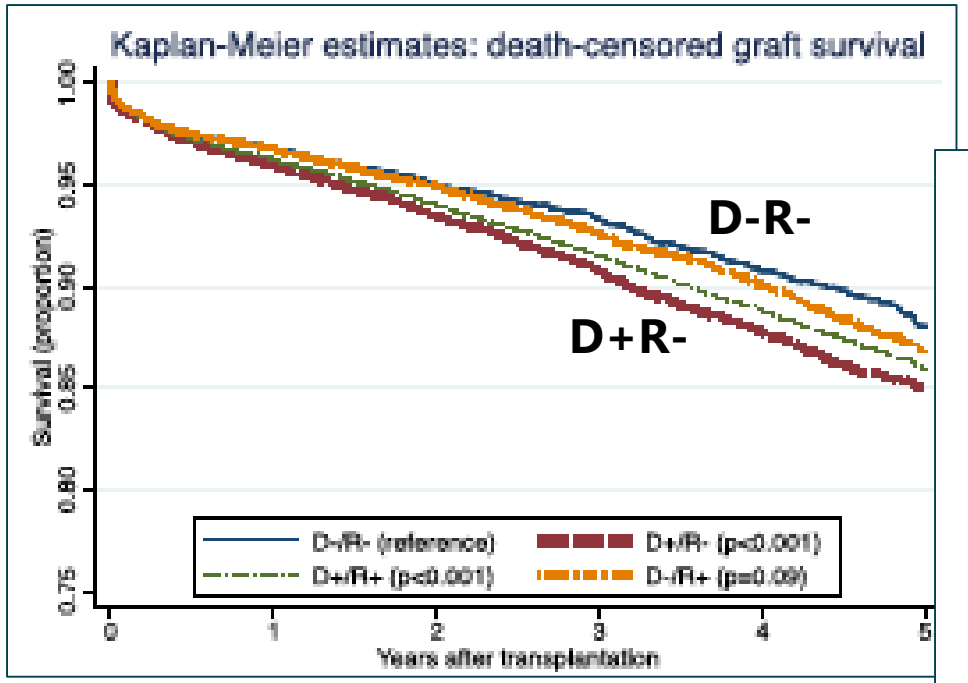
Received: 11 June 2018 | Revised: 1 November 2018 | Accepted: 2 November 2018
DOI: 10.1111/ajt.15183

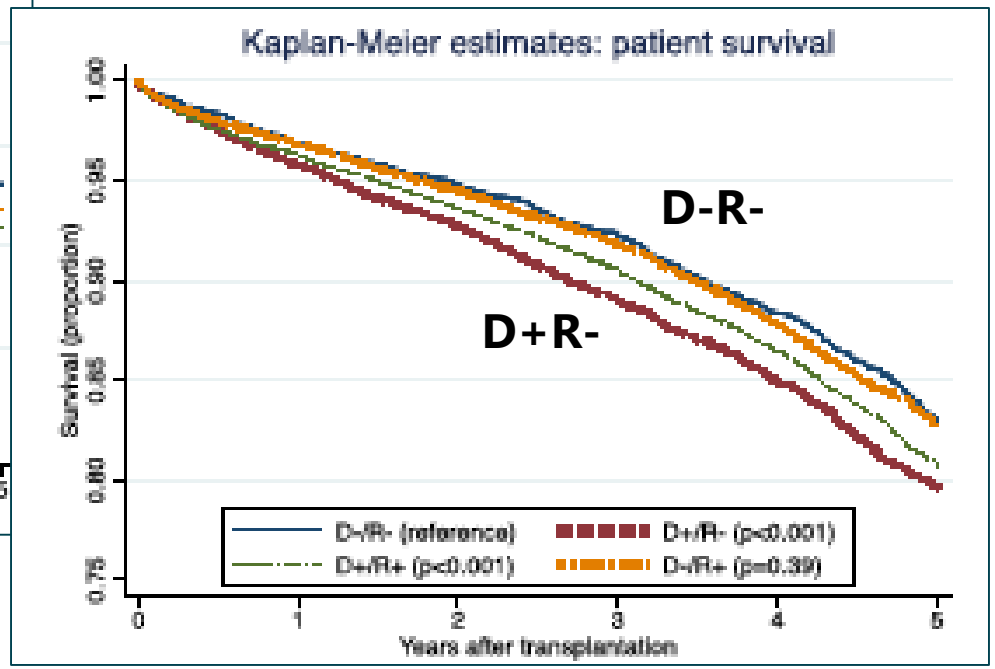
BRIEF COMMUNICATION

AJT

Cytomegalovirus mismatch still negatively affects patient and graft survival in the era of routine prophylactic and preemptive therapy: A paired kidney analysis

Napat Leeaphorn[1] | Neetika Garg[2] | Natanong Thamcharoen[1] | Eliyahu V. Khankin[1] | Francesca Cardarelli[1] | Martha Pavlakis[1]





Scientific Registry of Transplant Recipients (SRTR) data

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Risk Factors for CMV in SOT Transplant Recipients

- **Primary infection in recipient without prior immunity**
  - **CMV D+/R-** >> CMV D+/R+ > D-/R+
  - CMV D-/R- lowest risk (using filtered/seronegative blood products)
  - Lung, small bowel, composite tissue > heart, liver, kidney transplant
- **"Net state of immunosuppression"/Intensity of immunosuppression**
  - SOT: Induction/rejection: Lymphocyte-depleting agents
  - Maintenance immunosuppression
    - mTor lower CMV risk*/might obviate need for prophylaxis in low risk**
    - belatacept may impact D+R- risk***
- **Host factors that increase risk**
  - Advanced age, comorbidities, prior immunosuppression/conditioning
  - Leukopenia/lymphopenia, genetic immune factors

D=donor
R=recipient
+=CMV IgG seropositive
- =CMV IgG seronegative

*Tedesco-Silva et al, Safety of Everolimus With Reduced Calcineurin Inhibitor Exposure in De Novo Kidney Transplants: An Analysis From the Randomized TRANSFORM Study, Transplantation Feb 2019
**Cristelli et al, Use of mTOR inhibitor as prophylaxis for CMV disease after kidney transplantation: a natural experiment, accepted 2019
***Xu et al, The allo- and viral-specific immunosuppressive effect of belatacept, but not tacrolimus, attenuates with progressive T cell Maturation, AJT 2014

American Journal of Transplantation 2017; 17: 1439–1446
Wiley Periodicals Inc.

doi: 10.1111/ajt.14195

Minireview

Transplant Infectious Diseases: A Review of the Scientific Registry of Transplant Recipients Published Data

C. N. Kotton[1,*], S. Huprikar[2] and D. Kumar[3]

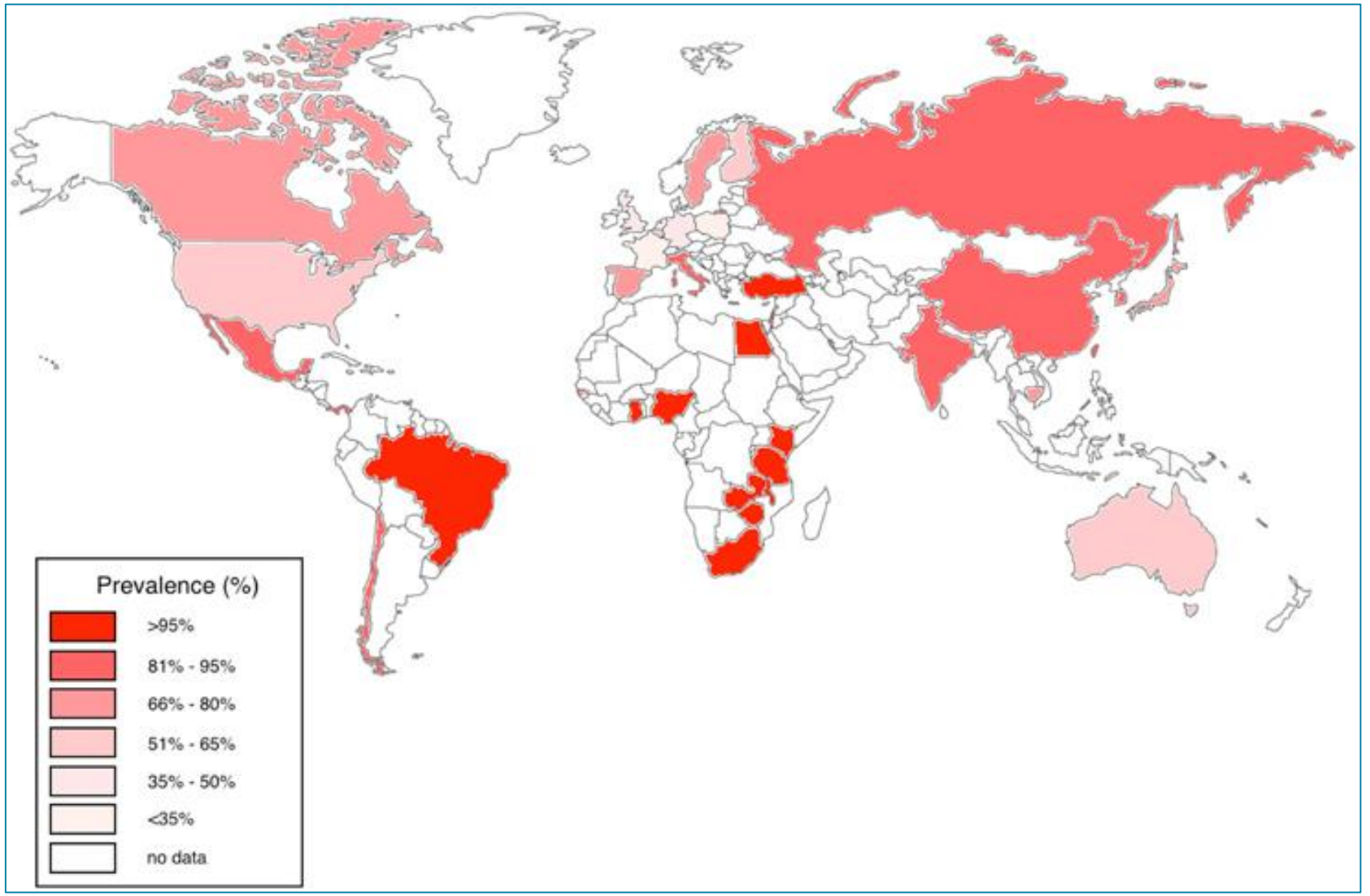
Table 1: Donor–recipient cytomegalovirus serology pairs, 2010–2014 and 2005–2009

		2005–2009				2010–2014			
		Recipient negative		Recipient positive		Recipient negative		Recipient positive	
Adult	Donor type	Donor negative	Donor positive	Donor negative	Donor positive	Donor negative	Donor positive	Donor negative	Donor positive
Kidney	DD	11.4	17.4	23.1	42.8	12.6	18.4	24.8	42.5
	LD	20.9	14.4	18.9	32.6	23.8	16.3	20.7	34.6
Pancreas	DD	18.7	28.0	17.9	29.1	19.0	26.9	20.7	31.5
Liver	DD	10.3	18.6	20.6	40.9	11.5	19.5	23.0	42.9
	LD	NR	NR	NR	NR	27.3	12.8	25.1	25.2
Heart	DD	13.4	21.6	21.3	37.4	15.1	23.2	22.0	36.2
Lung ≥12 years old	DD	15.7	23.4	19.1	35.5	15.7	25.0	19.4	35.4

According to the National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2004, the overall age-adjusted CMV seroprevalence among individuals in the United States aged 6–49 years was **50.4%**. *Bate et al, Clin Infect Dis 2010*

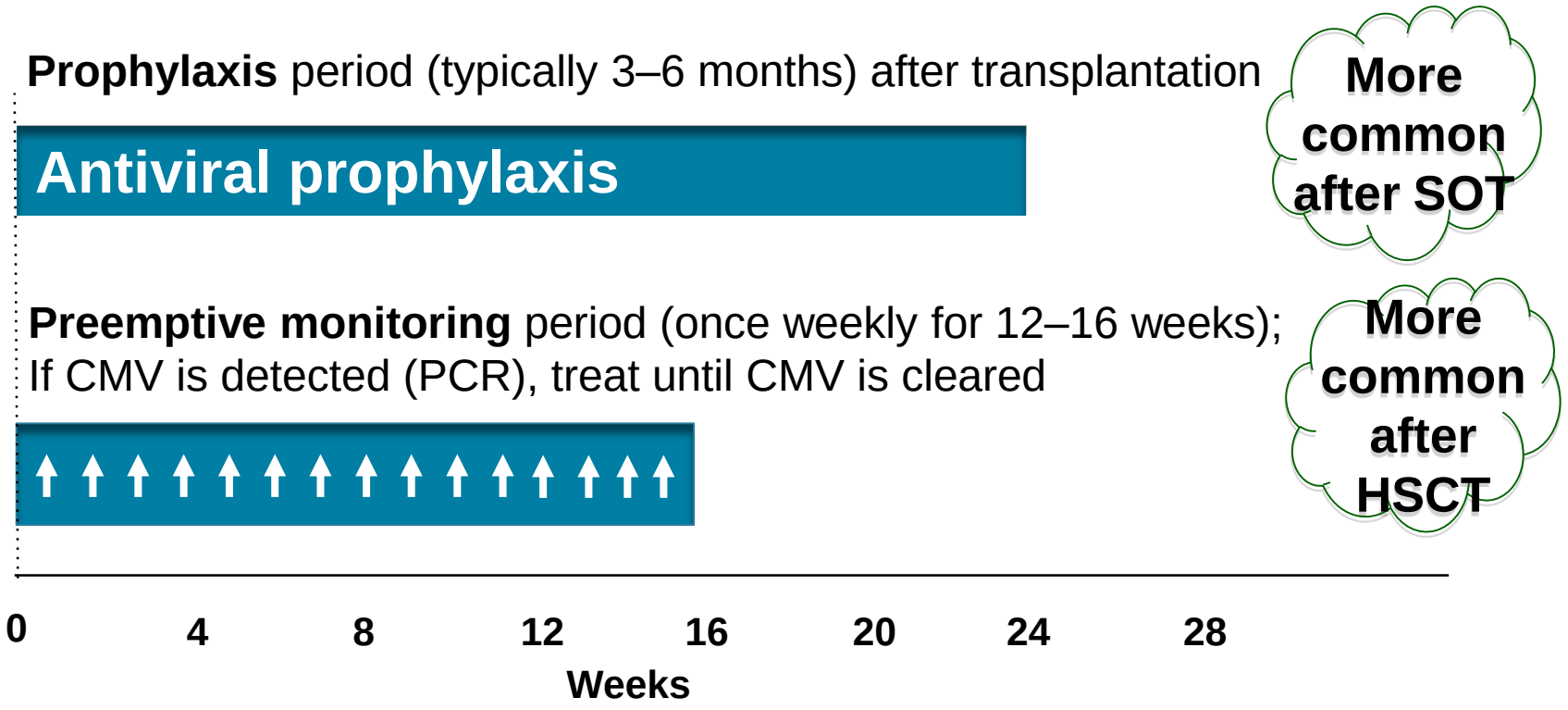
Scientific Registry of Transplant Recipients (SRTR) is managed by U.S. federal contract/funding and with oversight from the Health Resources and Services Administration (HRSA). It evolved from the United Network of Organ Sharing (UNOS) Scientific Renal Transplant Registry.

Worldwide CMV seroprevalence rates in adults



Adland et al, Front. Microbiol. 2015

Prophylaxis vs. Preemptive Therapy

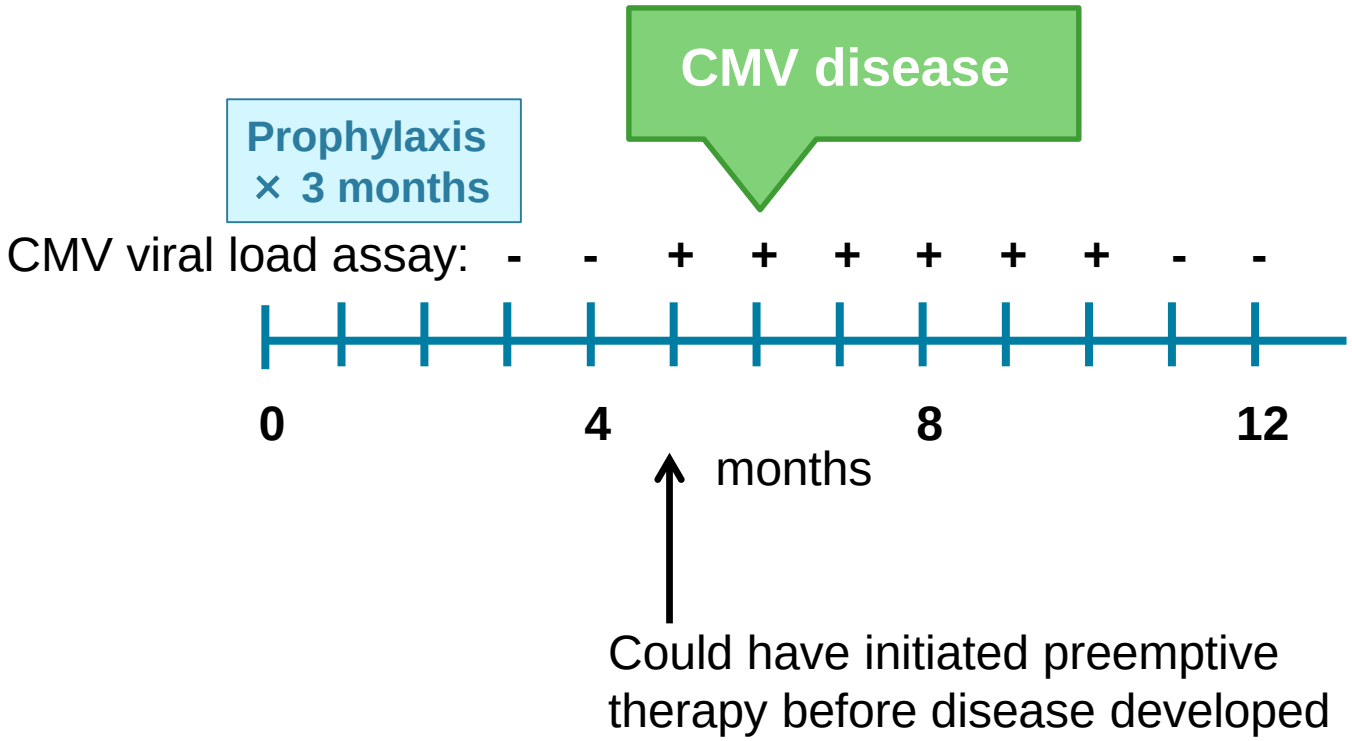


"surveillance after prophylaxis" combines both to prevent late CMV

Modified from Humar A, Snydman D; AST Infectious Diseases Community of Practice. *Am J Transplant*. 2009;9 (Suppl 4):S78-S86.

Hybrid Strategy for SOT: Surveillance After Prophylaxis

- Weekly monitoring after end of prophylaxis, for ~12 weeks
- High risk (D+/R-) may be highest yield population (for late disease)
  - Other high-risk groups (potent immunosuppression, treatment of rejection)
- CMV Guidelines III experts use approach, not strongly evidence-based



Valganciclovir Prophylaxis Versus Preemptive Therapy in Cytomegalovirus-Positive Renal Allograft Recipients: Long-term Results After 7 Years of a Randomized Clinical Trial

Oliver Witzke, MD,[1] Martin Nitschke, MD,[2] Michael Bartels, MD,[3] Heiner Wolters, MD,[4] Gunter Wolf, MD,[5] Petra Reinke, MD,[6] Ingeborg A. Hauser, MD,[7] Ulrich Alshuth, PhD,[8] and Volker Kliem, MD[9]

Transplantation ■ May 2018 ■ Volume 102 ■ Number 5

low-intense surveillance protocol

Incidence of CMV infection, CMV disease, graft loss, death, rejection, as well as renal function at 12 and 84 months

	12 mo		84 mo	
Variables	Prophylaxis (n = 148)	Preemptive (n = 151)	Prophylaxis (n = 148)	Preemptive (n = 151)
CMV infection, n (%)				
All patients	16 (10.8)****	59 (39.1)	17 (11.5)****	60 (39.7)
D+/R+	14 (15.4)****	43 (54.4)	15 (16.5)****	43 (54.4)
D–/R+	2 (3.5)***	16 (22.2)	2 (3.5)**	17 (23.6)
CMV disease[a], n (%)				
All patients	7 (4.7)**	23 (15.2)	7 (4.7)**	24 (15.9)
D+/R+	5 (5.5)**	18 (22.8)	5 (5.5)***	19 (24.1)
D–/R+	2 (3.5)	5 (6.9)	2 (3.5)	5 (6.9)
Graft loss, n (%)				
All patients	2 (1.4)	7 (4.6)	11 (7.4)	13 (8.6)
D+/R+	0 (0.0)	3 (3.8)	6 (6.6)	9 (11.4)
D–/R+	2 (3.5)	4 (5.6)	5 (8.8)	4 (5.6)
Death, n (%)				
All patients	3 (2.0)	2 (1.3)	14 (9.5)	17 (11.3)
D+/R+	3 (3.3)	0 (0.0)	11 (12.1)	9 (11.4)
D–/R+	0 (0.0)	2 (2.8)	3 (5.3)	8 (11.1)
Rejection[b], n (%)				
All patients	27 (18.2)	20 (13.2)	43 (29.1)	43 (28.5)
D+/R+	16 (17.6)	13 (16.5)	28 (30.8)	28 (35.4)
D–/R+	11 (19.3)	7 (9.7)	15 (26.3)	15 (20.8)
eGFR[c], mL/min per 1.73 m^2				
All patients	59.3 ± 23.2	60.7 ± 22.1	58.2 ± 26.3	59.9 ± 25.7
D+/R+	59.9 ± 21.3	56.1 ± 19.6	57.0 ± 27.2	57.6 ± 25.7
D–/R+	58.4 ± 26.0	65.3 ± 23.6	60.6 ± 24.9	61.6 ± 26.0

"Incidences of graft loss (7.4% vs 8.6%), death (9.5% vs 11.3%), rejection (29.1% vs 28.5%), and renal function were not significantly different between prophylaxis and preemptive treatment…
Similarly effective in **preventing graft loss and death** under the conditions of this long-term trial with a threshold of 400 copies/mL for initiation of anti-CMV treatment."

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

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TABLE 4.

Comparison of prophylaxis versus preemptive therapy

	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

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2018 Guidelines: CMV Prevention

For D+/R-, we recommend the use of either prophylaxis or pre-emptive therapy after kidney and liver transplant (strong, high).

For D+/R-, we suggest the use of prophylaxis over pre-emptive therapy after heart and lung transplant, based on the available data suggesting better graft survival and clinical outcomes (weak, low).

For seropositive recipients (R+) after kidney or liver transplant, we recommend either strategy (prophylaxis or pre-emptive therapy)(strong, high). Pre-emptive therapy has not been well studied in some seropositive populations including lung, heart, vascularized composite, pancreas, islet, and intestinal transplant; we suggest prophylaxis may be preferable (weak, low).

For programs or patients unable to meet the stringent logistic requirements required with a pre-emptive therapy strategy, prophylaxis is preferred.

2018 Guidelines: CMV Prevention

Use of surveillance after prophylaxis may be considered in patients considered at increased risk for post-prophylaxis CMV disease (weak, low). The value is probably greatest if done weekly for 8-12 weeks. Bi-weekly or monthly monitoring is insufficient for preemptive interventions (low, weak).

With pre-emptive therapy, we recommend monitoring at least once weekly for 3 - 4 months after transplant; longer monitoring would be indicated if they are perceived to be at ongoing increased risk for CMV disease (strong, moderate).

We recommend that treatment of rejection with antilymphocyte antibodies in at-risk recipients should result in reinitiation of prophylaxis or pre-emptive therapy for 1 to 3 months (weak, moderate) [259-261]; a similar strategy may be considered during treatment of rejection with high dose steroids or plasmapharesis (weak, very low).

Approaches & Duration

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TABLE 6.

Recommended approaches for CMV prevention in different organs for adult SOTR

Organ	Serostatus	Risk level	Recommended	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 months of GCV/VGCV OR Preemptive therapy	
	R+	Intermediate	3 months of VGCV OR Preemptive therapy	
Liver	D+R−	High	3 -6 months of VGCV (VGCV not FDA approved in liver) OR Preemptive therapy	
	R+	Intermediate	3 months of VGCV (VGCV not FDA approved in liver) OR Preemptive therapy	
Pancreas	D+R−	High	3 -6 months of VGCV	Preemptive therapy
	R+	Intermediate	3 months of VGCV OR Preemptive therapy	
Islet	D+R−	Intermediate	3 months of VGCV	Preemptive therapy
	R+	Intermediate	3 months of VGCV OR Preemptive therapy	
Heart	D+/R−	High	3-6 months of GCV/VGCV	-Preemptive therapy -Some experts add CMV Ig to prophylaxis
	R+	Intermediate	3 months of GCV/VGCV OR Preemptive therapy	
Lung	D+/R−	High	6-12 months of GCV/VGCV -Some experts add CMV Ig to prophylaxis	-Preemptive therapy
	R+	Intermediate	Minimum 6 months of GCV/VGCV	
Intestinal, composite tissue	D+/R−	High	Minimum 6 months GCV/VGCV + − surveillance after prophylaxis	-Preemptive therapy -Some experts add CMV Ig
	R+	High	3-6 months GCV/VGCV + − surveillance after prophylaxis	

Transplantation ■ June 2018 ■ Volume 102 ■ Number 6

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

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Dosage recommendations for ganciclovir and valganciclovir and valacyclovir for adult patients with impaired renal function (using Cockcroft-Gault formula)

Intravenous ganciclovir (adapted from[265])

CrCl, mL/min	Treatment dose	Maintenance/prevention dose
≥70	5.0 mg/kg q12 h	5.0 mg/kg q24 h
50-69	2.5 mg/kg q12 h	2.5 mg/kg q24 h
25-49	2.5 mg/kg q24 h	1.25 mg/kg q24 h
10-24	1.25 mg/kg q24 h	0.625 mg/kg q24 h
<10	1.25 mg/kg 3 times a week after hemodialysis	0.625 mg/kg 3 times a week after hemodialysis

Valganciclovir (adapted from[263,264])

CrCl, mL/min	Treatment dose	Maintenance/prevention dose
≥60	900 mg every 12 h	900 mg once daily
40-59	450 mg every 12 h	450 mg once daily
25-39	450 mg once daily	450 mg every 2 d
10-24	450 mg every 2 d	450 mg twice weekly
<10	200 mg 3 times a week after hemodialysis[a]	100 mg 3 times a week after hemodialysis[a]

Valacyclovir (high dose)[167]

CrCr, mL/min	Prevention dose (kidney only)
>75	2000 mg 4 times per day
51-75	1500 mg 4 times per day
26-50	1500 mg 3 times per day
10-25	1500 mg twice daily
<10 or dialysis	1500 mg once daily

Neutropenia Management

Your kidney transplant pt (D+R+) is started on valganciclovir 450mg a day, based on GFR of ~ 50 mL/min/1.73 m^2, intended for 3 months. After two months, he becomes quite leukopenic, with an absolute neutrophil count of 0.4 x 10^3 cells/µL. What is the best method of prevention, moving forward?

A. Reduce the dose of valganciclovir by half to help with the leukopenia

B. Switch to pre-emptive therapy with weekly CMV viral load monitoring for 8-12 weeks and treat if he has a significant CMV viral load, which you decide ~1,500 IU/ml when tested on plasma, based on data from your institution

C. Check a CMV-specific cellular immunity assay and use those results to either continue or stop the valganciclovir

D. Continue the same dose of valganciclovir, lower the dose of MMF, and give a white blood cell stimulating factor (i.e. G-CSF) with plans to give this until you reach you intended 3 month endpoint

Neutropenia Management

Your kidney transplant pt (D+R+) is started on valganciclovir 450mg a day, based on GFR of ~ 50 mL/min/1.73 m^2, intended for 3 months. After two months, he becomes quite leukopenic, with an absolute neutrophil count of 0.4 x 10^3 cells/μL. What is the best method of prevention, moving forward?

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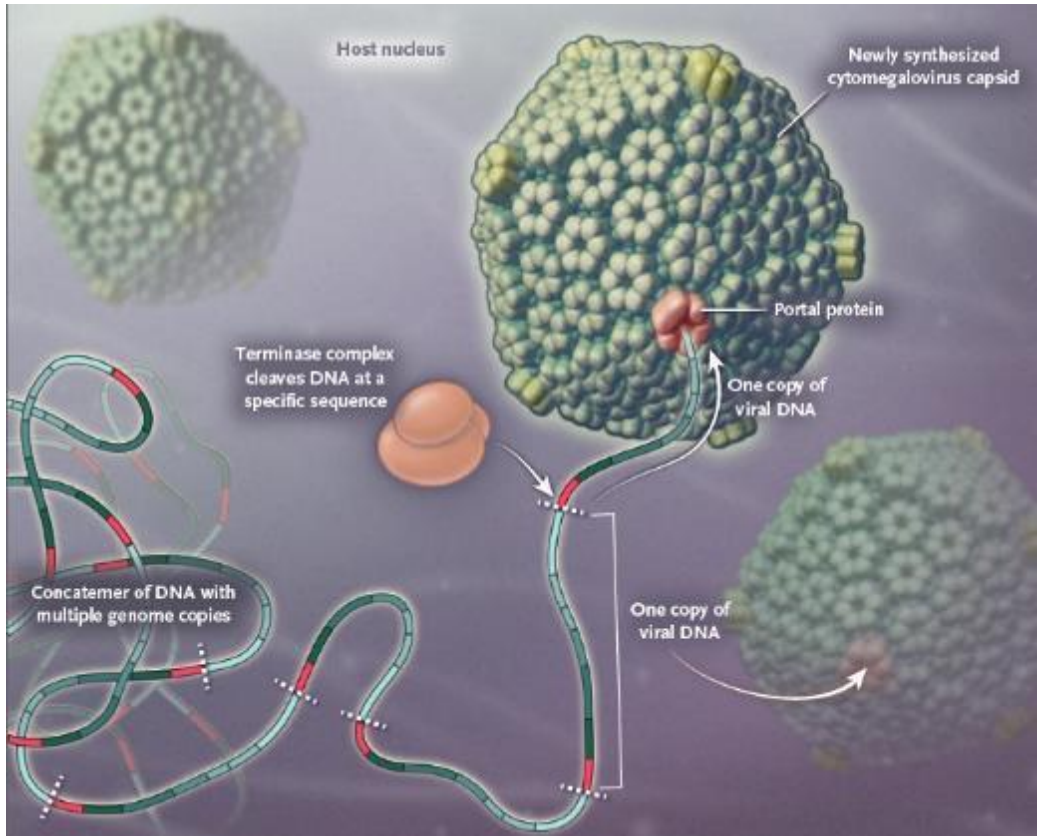
Letermovir

- **Terminase complex inhibitor**
  - Binds at UL56
- **Covers CMV only**
  - Need acyclovir for HSV/VZV prevention
- **Good safety profile in clinical trials, approved for stem cell transplant (phase III, Marty et al NEJM 2017)**
- **Drug interactions with CyA, tacrolimus, voriconazole, others**
- **High-grade resistance mutations in UL56 terminase gene are readily selected *in vitro* under letermovir; clinical correlation needed (not UL97/UL54) (Chou 2015)**
- **Study for prevention in kidney transplant recipients underway**



Griffiths and Emery, "Taming the Transplantation Troll by Targeting Terminase", NEJM 370;19 (2014)

Be aware…

Jung et al. BMC Infectious Diseases (2019) 19:388
https://doi.org/10.1186/s12879-019-4016-1

BMC Infectious Diseases

CASE REPORT Open Access

Fast breakthrough of resistant cytomegalovirus during secondary letermovir prophylaxis in a hematopoietic stem cell transplant recipient

Susanne Jung[1], Manuela Michel[2], Thomas Stamminger[2] and Detlef Michel[2*]

Abstract

Background: The compound letermovir (LMV) has recently been approved for the prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV seropositive recipients of an allogeneic hematopoietic stem cell transplant. LMV inhibits CMV replication by binding to the viral terminase complex. However, first cases of clinical LMV resistance have been occurred. Here we report a fast breakthrough of resistant cytomegalovirus during secondary LMV prophylaxis in a hematopoietic-cell transplant recipient.

Case presentation: A 44-year-old male patient with acute myeloid leukemia (AML) experienced a CMV-reactivation within the first 4 weeks of allogeneic hematopoietic-cell transplantation. Administration of LMV was initiated at day + 34. Due to increasing viral loads, LMV treatment was discontinued after 8 days. The patient was then administered with valganciclovir (valGCV) until viral DNA was undetectable. Due to neutropenia, valGCV treatment was switched to LMV secondary prophylaxis. For 4 weeks, the patient maintain virologic suppression. Then, CMV viral loads increased with a fast kinetic. Genotypic testing of the viral polymerase UL54, the kinase UL97 as well as the viral terminase UL56 and UL89 revealed the mutation C325Y in UL56, which is associated with the high level LMV resistance.

Conclusion: It is known that Letermovir is approved for prophylactic purposes. However, it may be used for some patients with CMV infection who either have failed prior therapies or are unable to tolerate other anti-CMV compounds. Particularly, the administration of LMV should be avoided in patients with detectable viral loads. When this is not possible, viral load must be routinely monitored along with UL56 genotyping. Furthermore, LMV administration at high virus loads may foster the rapid selection of resistant CMV mutants.

Optimal Duration of Prophylaxis: Personalized Medicine

Predictive tools we use:

- **CMV R+ versus D+R-**
- **Organ type**
- **Net state of immunosuppression**
  - Comorbidities, organ failure, diabetes, other factors
  - Immunosuppression: induction plus maintenance
- **Total IgG, lymphocyte & leukocyte count**

Not able to know precise answer in individual patient

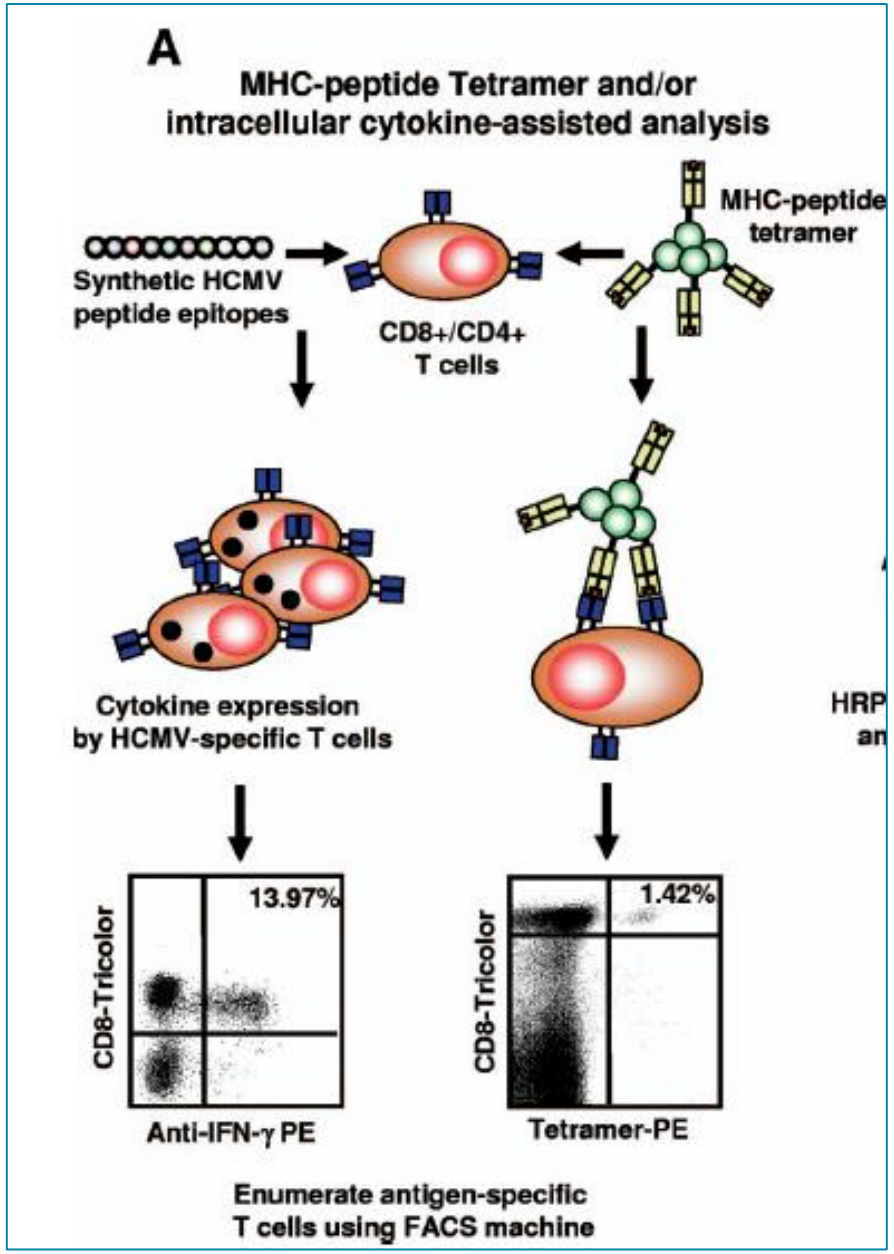
…Don't we need to test the immune system more precisely??

CMV Specific Immunologic Assays

Assay	Specimen	Availability	Advantages/Limitation	Disease prediction?
Intracellular cytokine staining (ICS)	Whole blood or PBMC	Primarily academic; CMV T Cell Immunity Panel, Viracor Eurofins	Short incubation, not HLA dependent, Needs flow cytometer, Not standardized	Yes No published data for Viracor assay
MHC multimer staining	Whole blood	Primarily academic	CD8+ only, need flow cytometer, HLA & epitope specific, Not standardized	Yes
Interferon gamma release assay, ELISA	Whole blood	Some academic labs QuantiFERON®-CMV (QIAGEN)	Rapid results, CD8+ only, HLA dependent	Yes
Interferon gamma release assay, ELISpot	Purified PBMC	Some academic labs T-Track® CMV (Lophius) T-SPOT.CMV (Oxford Immunotec)	CD4+/CD8+ reported together, Not standardized	Yes

Across different methodologies, results not necessarily comparable

Ex vivo monitoring of HCMV-specific T-cell responses: using MHC-peptide tetramers or intracellular cytokine staining



Tania Crough, and Rajiv Khanna Clin. Microbiol. Rev. 2009; doi:10.1128/CMR.00034-08

QuantiFERON-CMV: Measurement by ELISA of interferon-γ production by CMV-specific CD8+ T lymphocytes

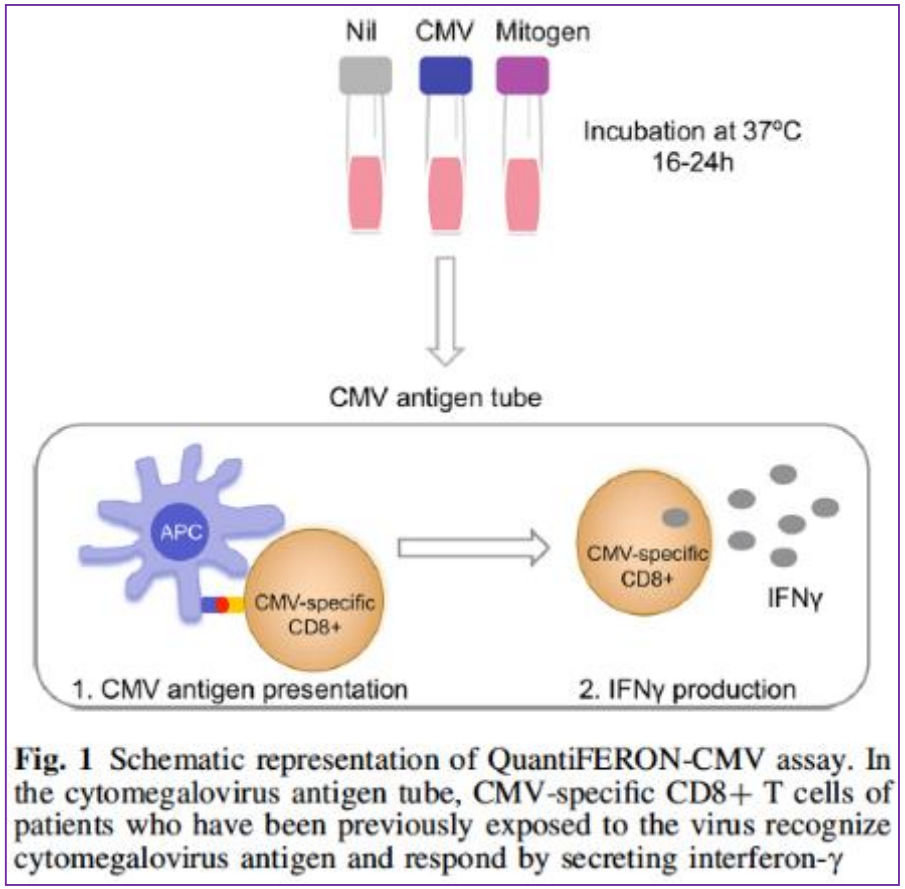


Fig. 1 Schematic representation of QuantiFERON-CMV assay. In the cytomegalovirus antigen tube, CMV-specific CD8+ T cells of patients who have been previously exposed to the virus recognize cytomegalovirus antigen and respond by secreting interferon-γ

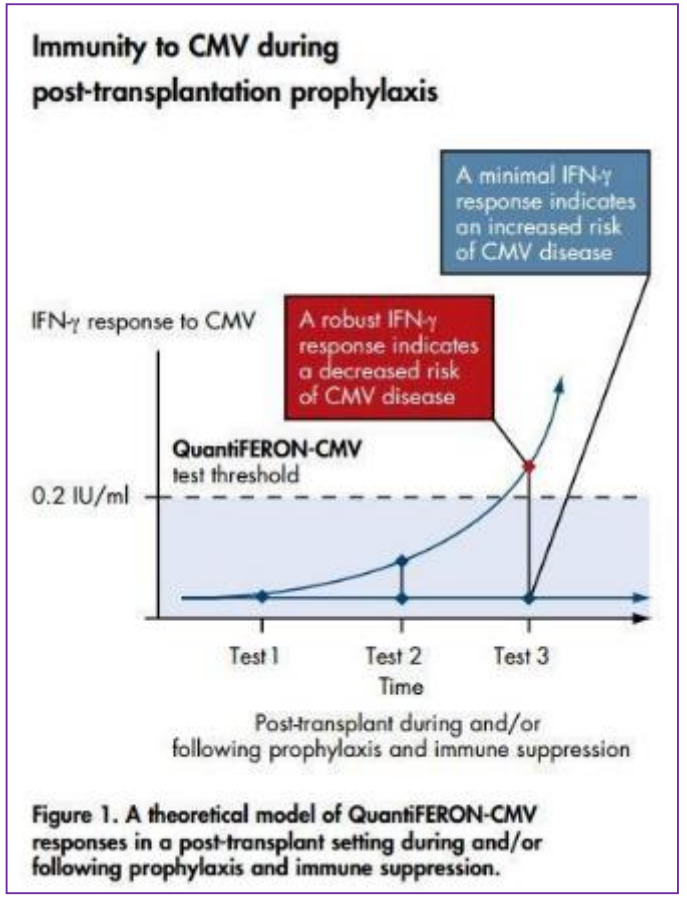


Figure 1. A theoretical model of QuantiFERON-CMV responses in a post-transplant setting during and/or following prophylaxis and immune suppression.

QuantiFERON-CMV is available in RSA

Commercially made by QIAGEN
Caston et al, Intensive Care Med (2016) 42:46–53
https://www.quantiferon.com/wp-content/uploads/2017/01/ShowMedia.aspx.jpeg (package insert)

T-SPOT.*CMV*, T-Track® CMV ELIspots

Lymphocyte-based assay of 2 CMV specific antigens:

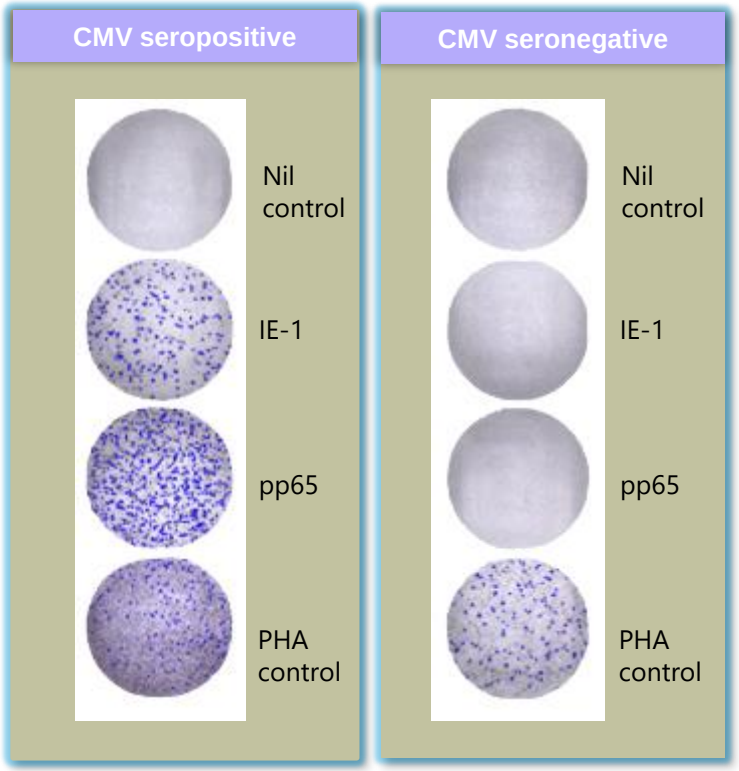
- IE-1
- pp65

The T-SPOT.*CMV* results are interpreted by quantifying the number of spots in each well and subtracting the spot count in the nil control from the IE-1, pp65 and positive control wells.

The number of spots is indicative of the strength of the cellular immune response to the CMV antigens IE-1 and pp65

Commercially, made by Oxford Immunotec

Similar assay T-Track® CMV (Lophius)



Prediction of Late CMV after the End of Prophylaxis?

A prospective multicenter observational study of cell-mediated immunity as a predictor for cytomegalovirus infection in kidney transplant recipients

Am J Transplant. 2019;1–12.

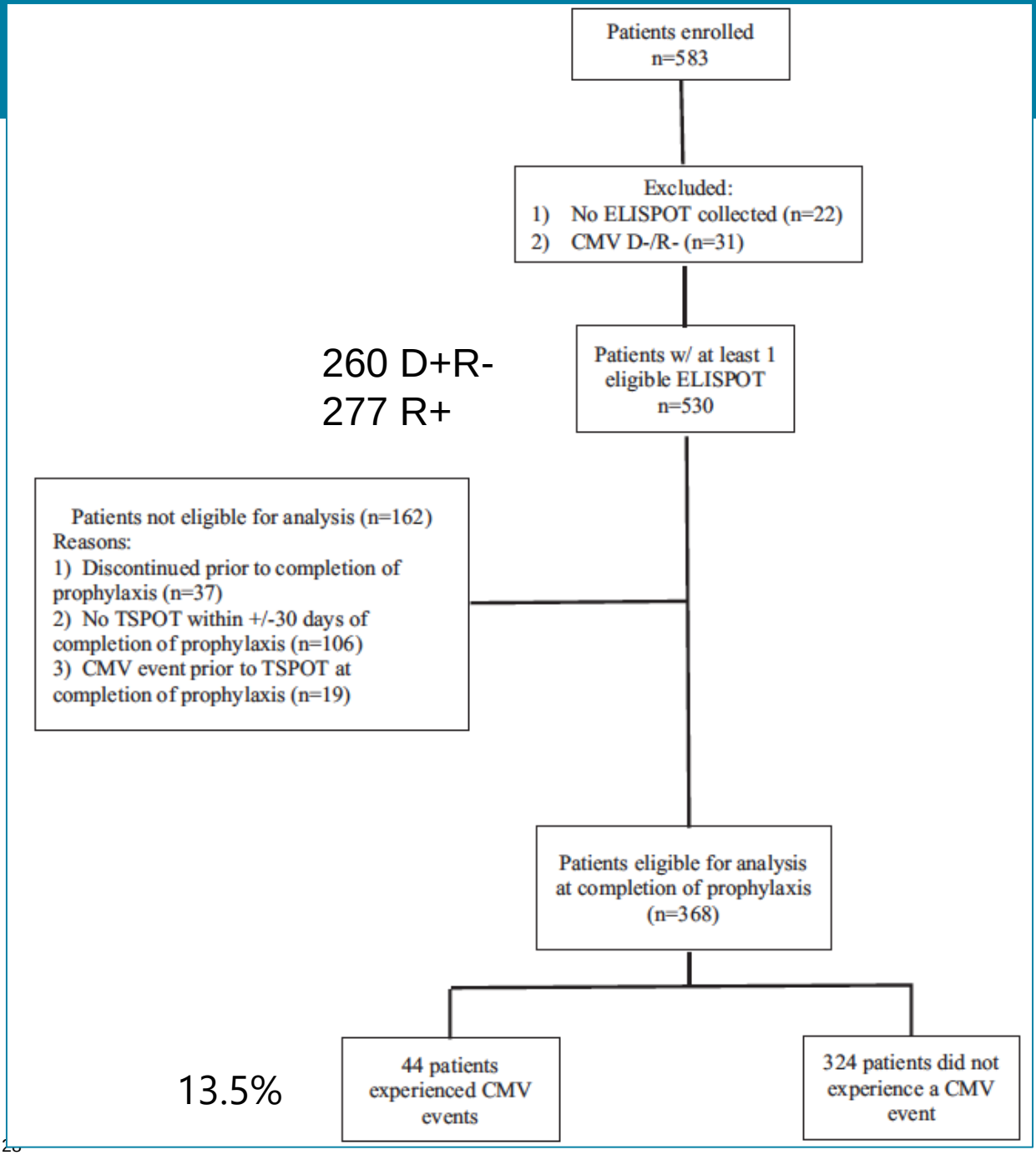
Deepali Kumar[1] | Peter Chin-Hong[2] | Liise Kayler[3] | David Wojciechowski[4] | Ajit P. Limaye[5] | A. Osama Gaber[6] | Simon Ball[7] | Aneesh K. Mehta[8] | Matthew Cooper[9] | Ted Blanchard[10] | James MacDougall[11] | Camille N. Kotton[12]

Patients were enrolled from 43 centers (United States, 36; United Kingdom, 6; and Canada, 1)

Followed for 12 months after transplant

Exclusion criteria:

- Multiple organ transplantation
- Active immunosuppression within 2 months prior to transplant
- Human immunodeficiency virus (HIV) infection



Demographics

	All enrolled pts (n = 530)	Total (n = 368)	CMV event (n = 44)	No CMV event (n = 324)
Age (y), median (range)	51 (20-77)	52 (20-77)	58 (21-73)	52 (20-77)
Sex, n (%)				
Male	339 (64)	231 (63)	29 (66)	202 (62)
Female	191 (36)	137 (37)	15 (34)	122 (38)
Race, n (%)				
White	363 (68)	251 (68)	31 (70)	220 (68)
African American	113 (21)	75 (21)	7 (16)	68 (21)
Asian	32 (6)	23 (6)	3 (7)	20 (6)
Unknown/other	22 (4)	19 (5)	3 (7)	16 (5)
CMV Serostatus, n (%)				
D+/R−	257 (48)	167 (45)	37 (84)	130 (40)
R+	273 (52)	201 (55)	7 (16)	194 (60)
Induction therapy, n (%)				
T cell–depleting therapy	342 (65)	250 (68)	30 (68)	220 (68)
Non-T cell–depleting	188 (35)	118 (32)	14 (32)	104 (32)
[a]CMV prophylaxis duration, n (%)				
3 months	268 (51)	204 (55)	17 (39)	187 (58)
6 months	254 (49)	164 (45)	27 (61)	137 (42)
Immunosuppression at completion of prophylaxis,n (%)				
Prednisone	353 (67)	263 (71)	30 (68)	233 (72)
Mycophenolate	418 (79)	303 (82)	35 (80)	268 (83)
Calcineurin inhibitor	441 (83)	318 (86)	36 (82)	282 (87)
mTOR inhibitor	16 (3)	10 (3)	0 (0)	10 (3)
Other	34 (6)	12 (3)	7 (16)	12 (4)

TABLE 1 Baseline characteristics of all study participants (n = 530), those eligible for analysis at the completion of prophylaxis (n = 368) and those with CMV events after completion of anti-CMV prophylaxis (n = 44) and no CMV event (n = 324)

CMV event
22% D+R-
3.5% R+

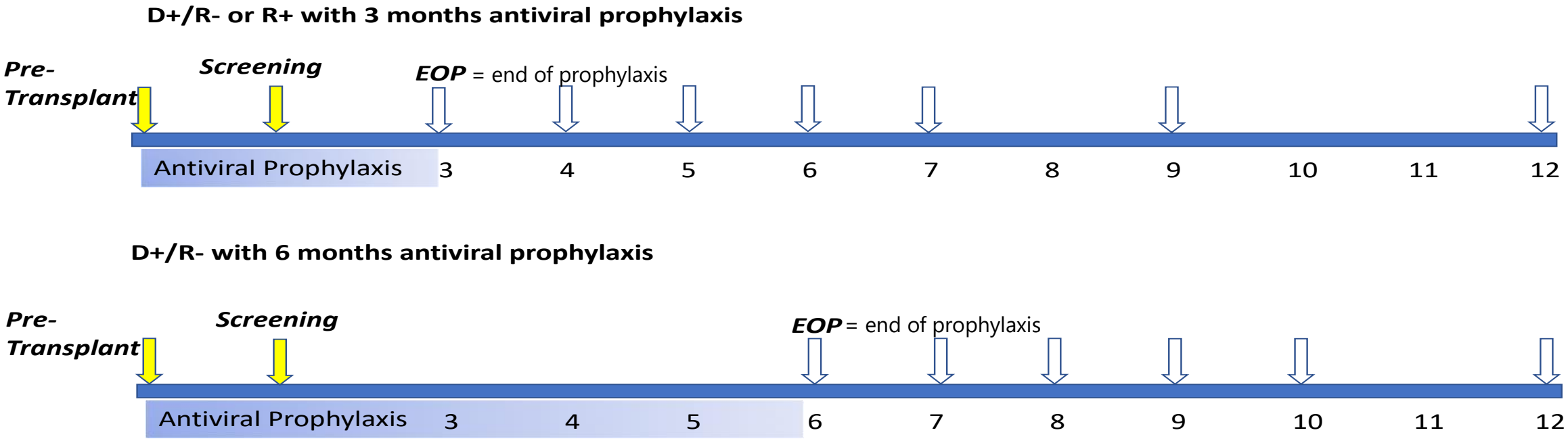


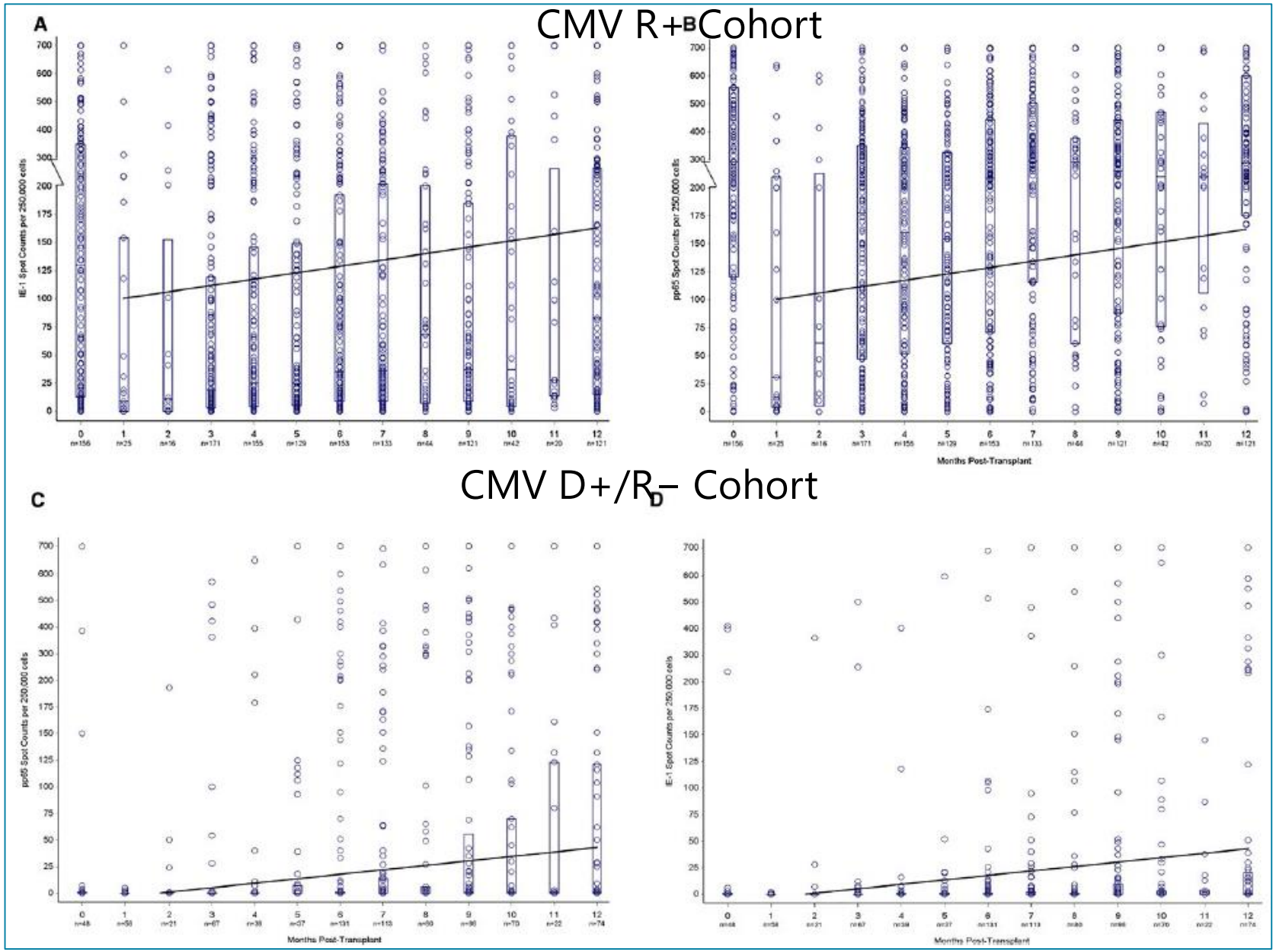
Figure S1: Study Design in D+/R- or R+ subjects who received 3 months of antiviral prophylaxis and D+/R- subjects who received 6 months of antiviral prophylaxis. Yellow arrows represent optional blood collection time-points whereas red arrows represent study blood collection time-points at various months post-transplant.

Primary Endpoint: clinically significant CMV infection

The primary endpoint was the first occurrence of "a clinically significant CMV infection within the first 12 months posttransplant".

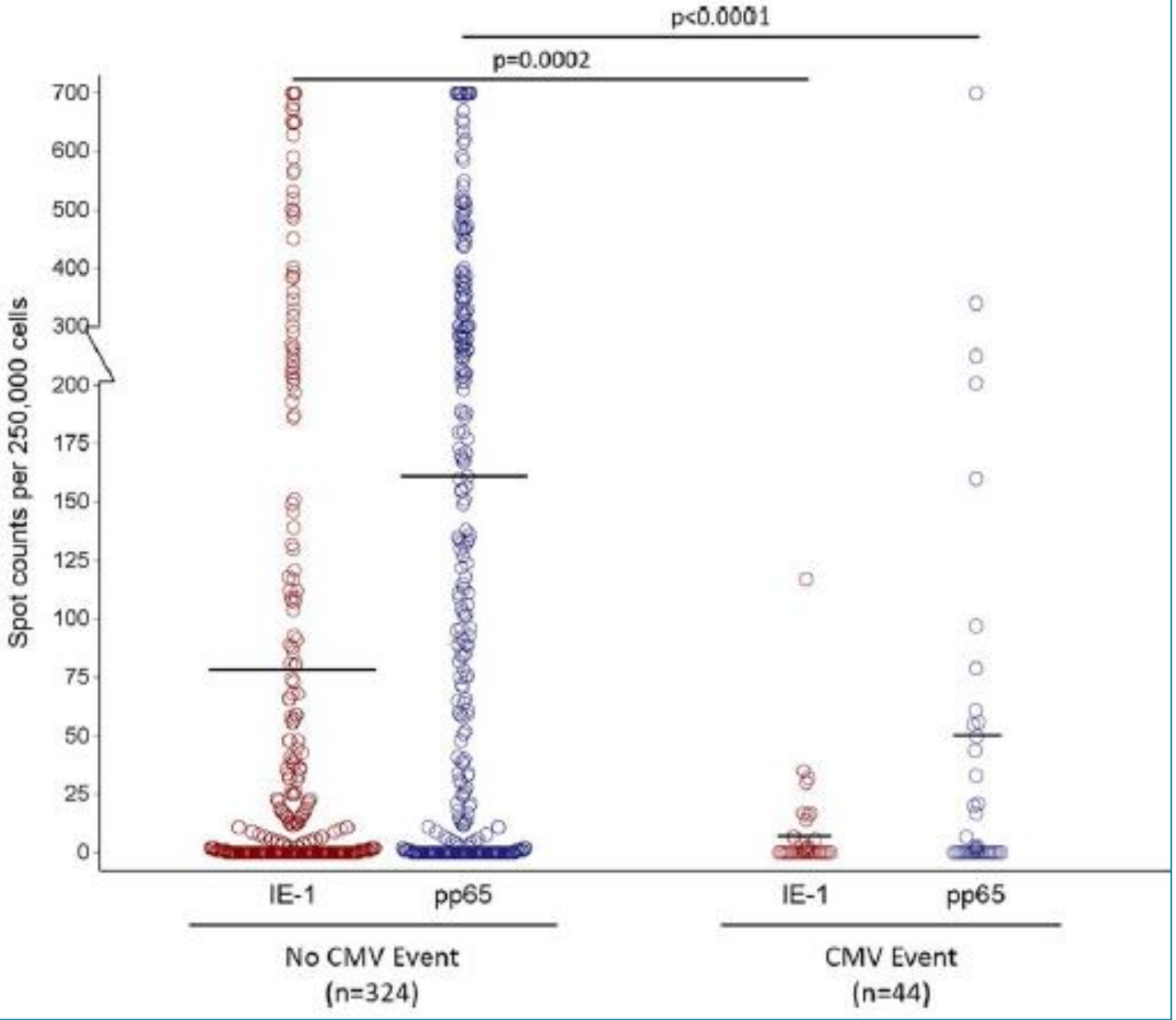
- **Defined as site-determined viremia or disease that necessitated a change in antiviral therapy.**
  - Duration of prophylaxis also site determined
- **Because this was an observational study and viral load testing was not centrally performed, this outcome allowed for evaluation of test performance in the "real-world" setting.**
- **To be included in the analysis, the CMV event had to occur after completion of prophylaxis.**

Scatterplots for number of spots produced in the CMV-specific (pp65/IE-1) ELISPOT assay at various timepoints



- Trend lines join the mean value at each month
- Horizontal lines at each time point represent median values
- Boxes represent interquartile range
- Spot-forming units from patients after first CMV event were excluded from the analysis

FIGURE 2 A, Cytomegalovirus (CMV) R+ Cohort scatterplot for number of spots produced in the CMV-specific enzyme-linked immunosorbent spot (ELISPOT) assay for immediate-early protein-1 (IE1) antigen at various timepoints. The trend lines are based on the longitudinal analysis from the Mixed-Model Repeated Measure (MMRM) applied to IE-1 spot-forming units. The trend lines join the mean value at each month. Horizontal lines at each time point represent median and boxes represent interquartile range. Spot-forming units from patients after first CMV event were excluded from the analysis. B, CMV R+ Cohort scatterplot for number of spots produced in the CMV-specific ELISPOT assay for phosphoprotein 65 (pp65) antigen at various time points. The trend lines are based on the longitudinal analysis from the Mixed-Model Repeated Measure (MMRM) applied to pp65 spot forming units. The trend lines join the mean value at each month. Horizontal lines at each time point represent median and boxes represent interquartile range. Spot-forming units from patients after first CMV event were excluded from analysis. C, CMV D+/R– Cohort scatterplot for number of spots produced in the CMV-specific ELISPOT assay for immediate-early protein-1 (IE-1) antigen at various time points. The trend lines are based on the longitudinal analysis from the MMRM applied to IE-1 spot-forming units. The trend lines join the mean value at each month. Horizontal lines at each time point represent median and boxes represent interquartile range. Spot-forming units from patients after first CMV event were excluded from analysis. D, CMV D+/R– Cohort Scatterplot for number of spots produced in the CMV-specific ELISPOT assay for pp65 antigen at various time points. The trend lines are based on the longitudinal analysis from the MMRM applied to pp65 spot-forming units. The trend lines join the mean value at each month. Horizontal lines at each time point represent median and boxes represent interquartile range. Spot-forming units from patients after first CMV event were excluded from analysis



F I G U R E 3 Cytomegalovirus (CMV)–specific cell-mediated immune response to intermediate-early protein 1 (IE-1) and phosphoprotein 65 (pp65) with or without a clinically significant CMV event.

- Circles = individual patient spot count
- Horizontal line = mean spot count.
- For patients experiencing a CMV event, spot count is the value from the preceding visit.
- For patients who did not experience a CMV event, spot count value is from the *visit closest to the median time from prophylaxis completion to event* (37.5 days; from the 44 patients with events)

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

Predictive value of T-SPOT.CMV assay thresholds at the completion of prophylaxis

B) R+ kidney transplant patients

TABLE 2 (A) T-SPOT.CMV performance results at the completion of prophylaxis for pp65 and IE-1 at various thresholds (all eligible subjects; n = 368); (B) Predictive value of T-SPOT.CMV assay thresholds at the completion of prophylaxis for R+ kidney transplant patients; (C) Predictive value of T-SPOT.CMV assay thresholds at the completion of prophylaxis for D+/R− kidney transplant patients

Antigen	Threshold	PPV	NPV	% Patients above threshold	P-value
pp65	>20	9.4%	97.6%	84.1%	.082
pp65	>40	9.1%	98.6%	72.6%	.0174
pp65	>50	8.1%	98.6%	69.2%	.03
pp65	>100	7.0%	99.1%	57.2%	.0436
pp65	>150	6.9%	100.0%	49.3%	.0141
IE-1	>20	4.7%	97.9%	46.8%	.4519
IE-1	>40	5.8%	100.0%	39.8%	.0434
IE-1	>50	5.6%	100.0%	37.8%	.0462
IE-1	>100	4.8%	100.0%	27.9%	.1937
IE-1 or pp65	>20	6.9%	97.1%	85.6%	.2665
IE-1 or pp65	>40	10.0%	98.7%	75.1%	.0112
IE-1 or pp65	>50	8.9%	98.6%	72.1%	.0189
IE-1 or pp65	>100	7.5%	99.2%	60.2%	.0167
IE-1 or pp65	>150	7.3%	100.0%	52.2%	.005
IE-1 and pp65	>20	5.5%	98.9%	45.3%	.0936
IE-1 and pp65	>40	5.6%	100.0%	37.3%	.0377
IE-1 and pp65	>50	5.3%	100.0%	34.8%	.049
IE-1 and pp65	>100	4.6%	100.0%	24.9%	.1212
IE-1 and pp65	>150	4.3%	100.0%	18.9%	.1935

C) D+R- kidney transplant patients

TABLE 2 (A) T-SPOT.CMV performance results at the completion of prophylaxis for pp65 and IE-1 at various thresholds (all eligible subjects; n = 368); (B) Predictive value of T-SPOT.CMV assay thresholds at the completion of prophylaxis for R+ kidney transplant patients; (C) Predictive value of T-SPOT.CMV assay thresholds at the completion of prophylaxis for D+/R− kidney transplant patients

Antigen	Threshold	PPV	NPV	% Patients above threshold	P-value
pp65	>20	22.9%	81.5%	16.2%	.8013
pp65	>40	23.4%	86.4%	13.2%	.4131
pp65	>50	23.4%	86.4%	13.2%	.4131
pp65	>100	23.1%	85.0%	12.0%	.5697
pp65	>150	22.8%	83.3%	10.8%	.7658
IE-1	>20	22.6%	83.3%	7.2%	1
IE-1	>40	22.0%	75.0%	4.8%	1
IE-1	>50	22.0%	75.0%	4.8%	1
IE-1	>100	21.5%	50.0%	2.4%	.2131
IE-1 or pp65	>20	22.9%	81.5%	16.2%	.8013
IE-1 or pp65	>40	23.6%	87.0%	13.8%	.4164
IE-1 or pp65	>50	23.6%	87.0%	13.8%	.4164
IE-1 or pp65	>100	23.1%	85.0%	12.0%	.5697
IE-1 or pp65	>150	22.8%	83.3%	10.8%	.7658
IE-1 and pp65	>20	22.6%	83.3%	7.2%	.6346
IE-1 and pp65	>40	21.9%	71.4%	4.2%	.6763
IE-1 and pp65	>50	21.9%	71.4%	4.2%	.6763
IE-1 and pp65	>100	21.5%	50.0%	2.4%	.1747
IE-1 and pp65	>150	22.4%	100.0%	1.2%	.4478

"Our goal was to take the most conservative approach in identifying patients who have a high probability of not reactivating (NPV)"

Kaplan-Meier plot: time to clinically significant cytomegalovirus (CMV) infection determined by the T-SPOT.CMV assay at the end of antiviral prophylaxis

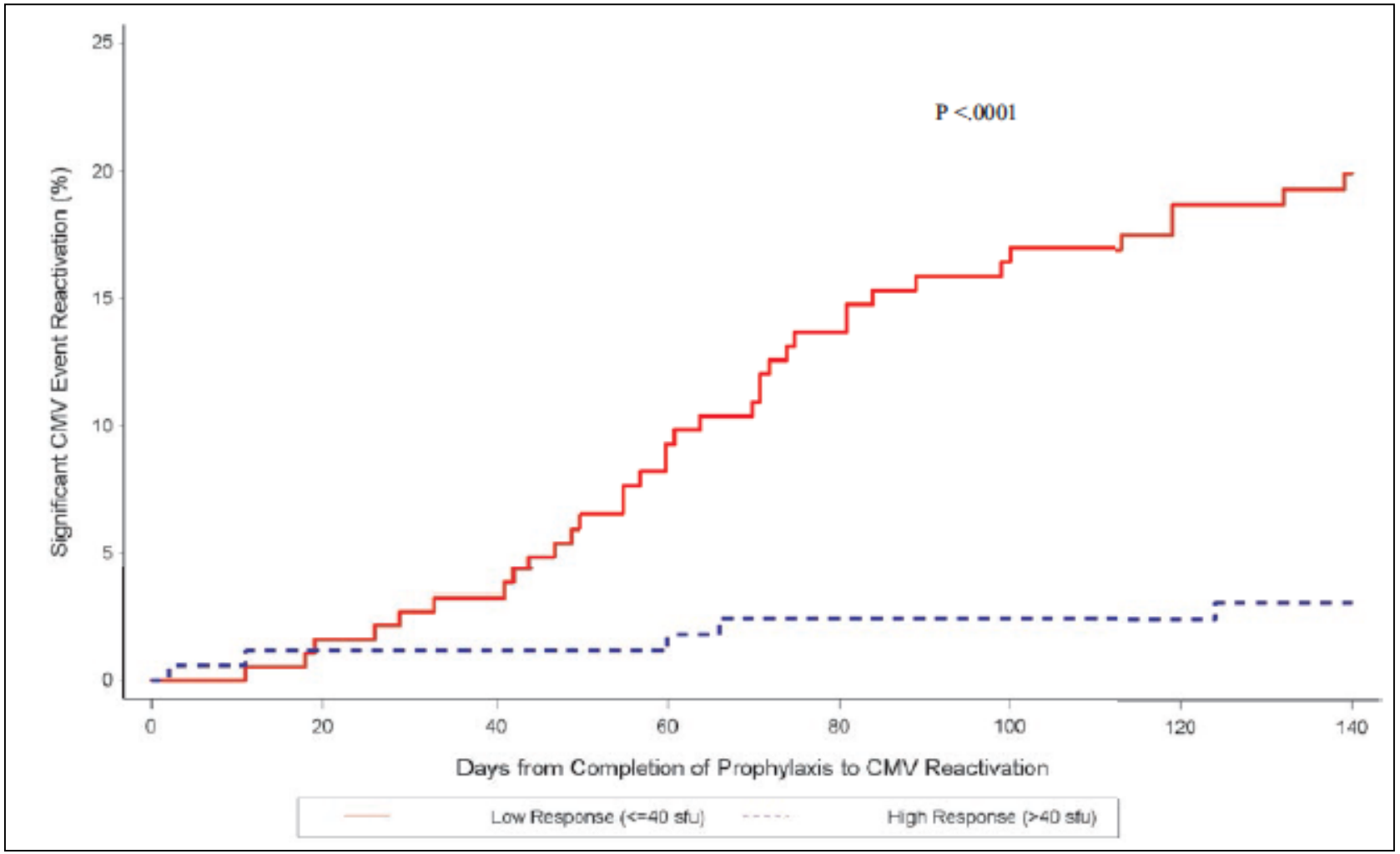
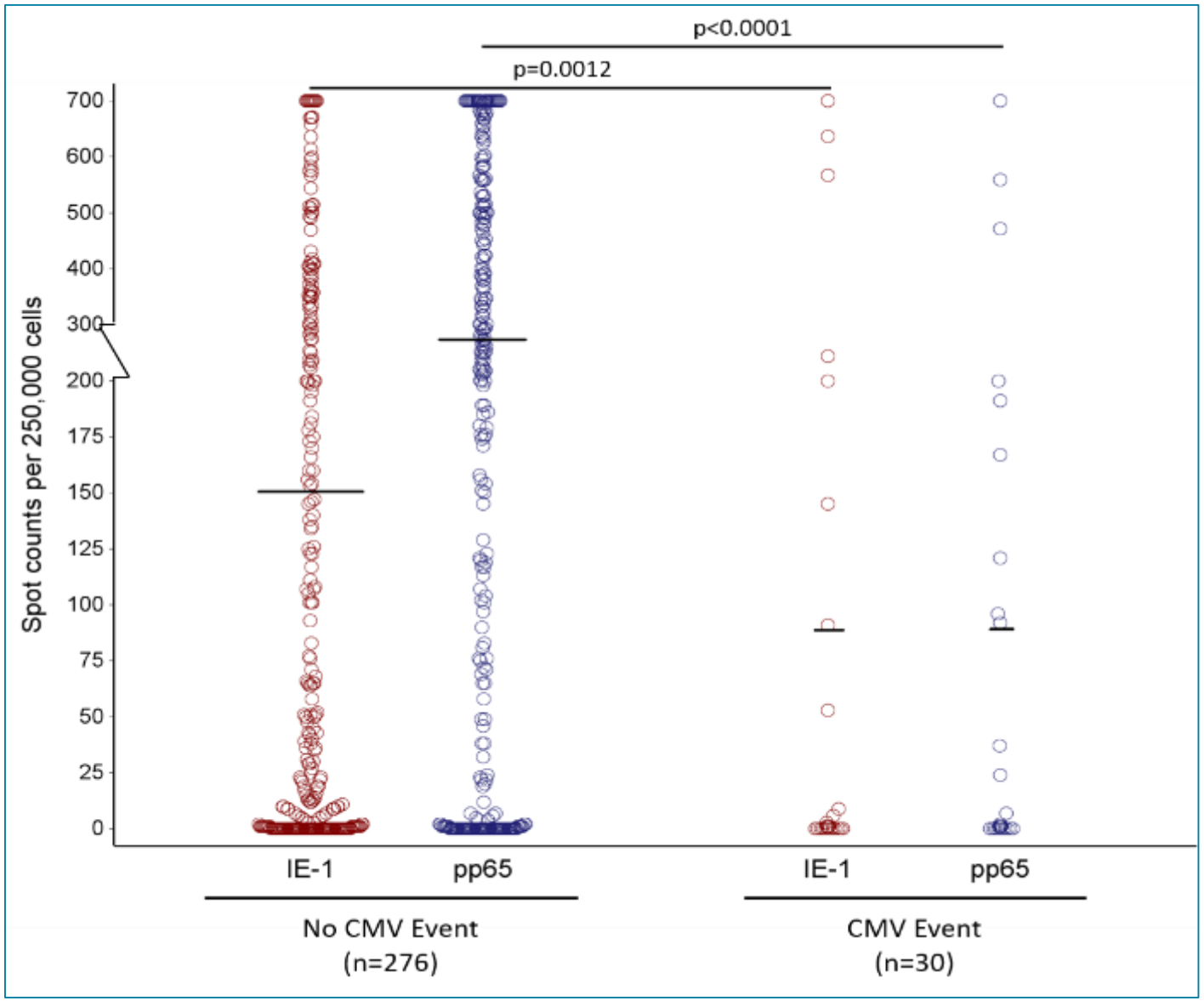


FIGURE 5 Kaplan-Meier plot for time to clinically significant cytomegalovirus (CMV) infection in patients with intermediate-early protein 1 (IE-1) or phosphoprotein 65 (pp65) counts >40 sfu (blue line) or ≤40 sfu (red line) as determined by the T-SPOT.*CMV* assay at the end of antiviral prophylaxis

Kumar AJT 2019

Figure S5: Pre-Transplant CMV-specific Cell Mediated Immune Response to IE-1 and pp65 recipients with or without a clinically significant CMV event.



- "Median IE-1 sfu were **1 vs 23** (range 0-700) in those with and without a CMV event, respectively (P = .0012)
- Median pp65 sfu were **1 vs 179** (range 0-700) in those with and without a CMV event, respectively (P < .0001)
- The NPV using a threshold of IE-1 or pp65 >40 sfu against the occurrence of a posttransplant CMV event was 95%."

A Randomized Study of Quantiferon CMV-directed Versus Fixed-duration Valganciclovir Prophylaxis to Reduce Late CMV After Lung Transplantation

Glen P. Westall, MD,[1] Yvonne Cristiano, RN,[1] Bronwyn J. Levvey, RN,[1] Helen Whitford, MD,[1] Miranda A. Paraskeva, MD,[1] Eldho Paul, PhD,[2] Anton Y. Peleg, MD,[3] and Gregory I. Snell, MD[1]

Transplantation ■ May 2019 ■ Volume 103 ■ Number 5

Interventional Trial*

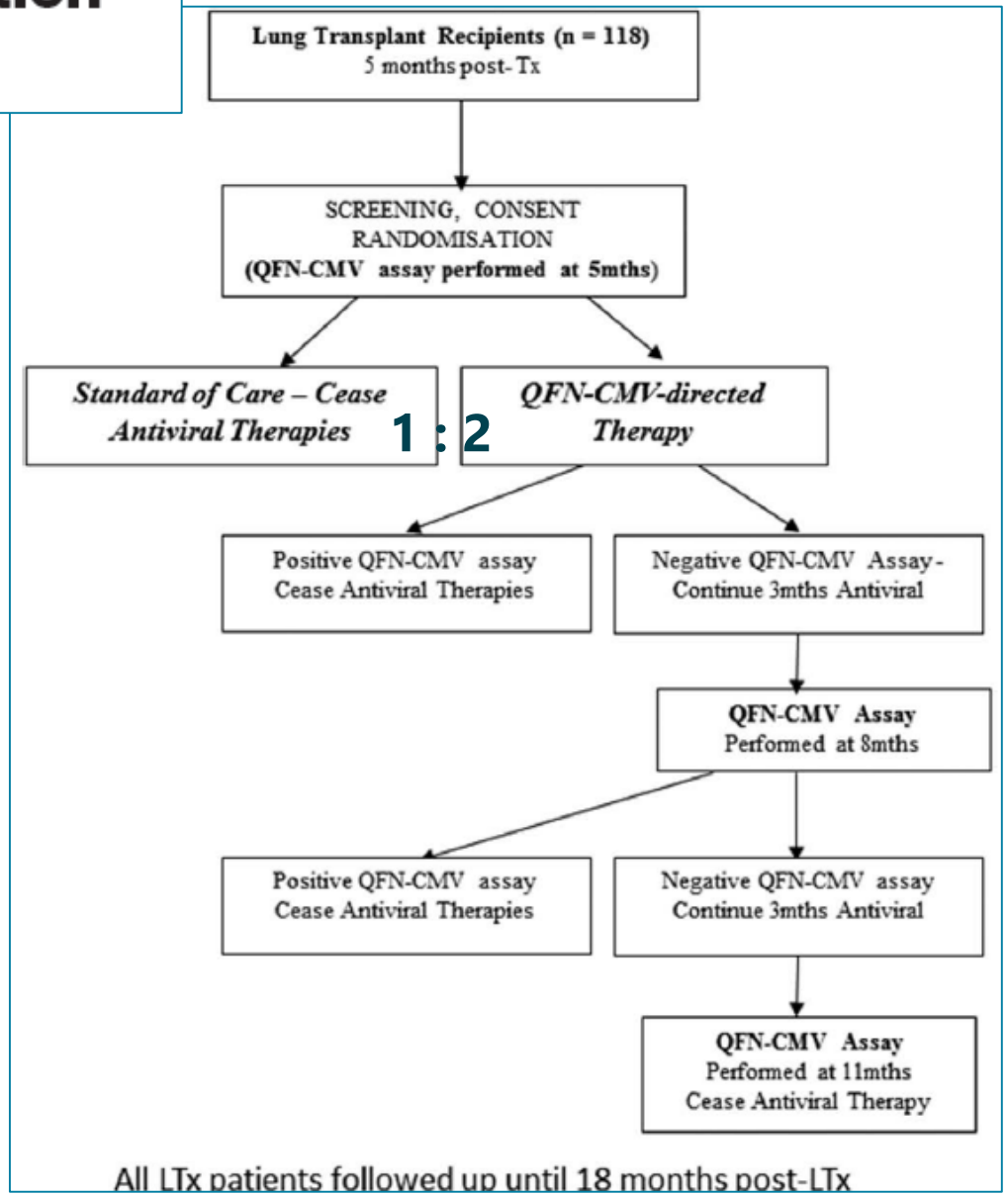


TABLE 1.
Study cohort characteristics

	Standard of care (n = 36)	QFN-CMV directed (n = 82)	*P*
Age: mean (SD), y	56.3 (11.6)	55.5 (10.5)	0.74
Male sex, n (%)	14 (39)	50 (61)	0.03
Chronic obstructive pulmonary disease, n (%)	20 (56)	46 (56)	0.96
Basiliximab induction, n (%)	14 (39)	29 (35)	0.71
CMV D/R serostatus, n (%)			
D+/R-	8 (22)	22 (27)	0.60
D+/R+	13 (36)	30 (37)	0.96
D-/R+	15 (42)	30 (37)	0.60
IgG at 3 mo post-tx, g/dL	6.7 (2.2)	7.4 (2.3)	0.15
QFN-CMV assay, days post-tx	153 (149–158)	153 (145–158)	0.24
Antivirals ceased, days post-tx	160 (155–165)	176 (157–333)	0.001
Antivirals ceased at 5 mo post-tx, n (%)	36 (100)	43 (52)	<0.001

CMV, cytomegalovirus; QFN, QuantiFERON; SD, standard deviation; tx, transplantation.

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Transplantation ■ May 2019 ■ Volume 103 ■ Number 5

-Primary end-point**: incidence of CMV infection in the lung allograft** was significantly reduced in QFN-CMV directed arm (**37% vs 58%**, p = 0.03).
-Acute rejection & chronic lung allograft dysfunction did not differ
-**Incidence of viremia** (> 600 copies/ml) within the blood was significantly reduced in patients with a positive QFN-CMV assay compared to those without protective immunity (**13% vs 67%**, p = 0.0003)
-Incidence of **severe viremia** (>10,000 copies/ml) (**3% vs 50%,** p < 0.001)

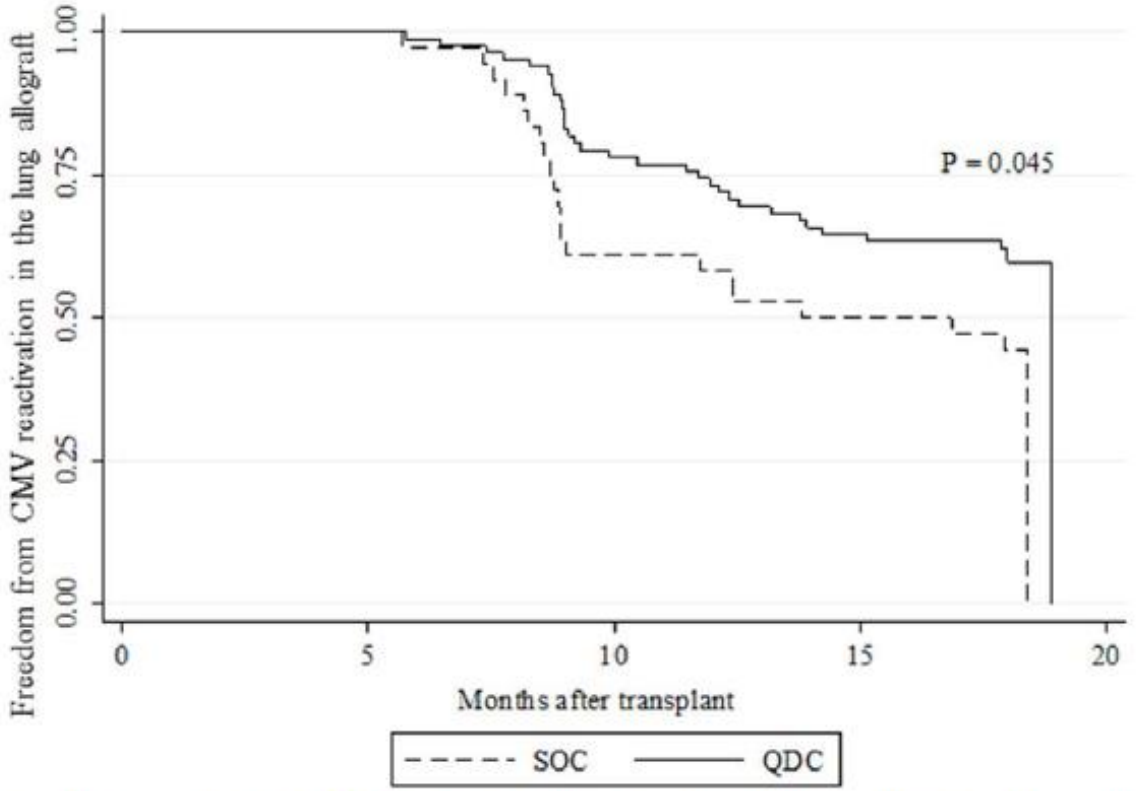

FIGURE 2. Kaplan-Meier curve showing CMV infection in the lung allograft in the treatment arms. CMV, cytomegalovirus; SOC, standard of care.

Guidelines on CMV: Best Practice for Diagnosis

Methods to Detect CMV after Organ Transplant

Molecular assays

- CMV “viral load” or PCR or nucleic acid test (QNAT) or DNAemia
- A **quantitative** assay using international units is preferred over qualitative assay
- Pick **whole blood or plasma**, pick one lab or testing platform, and don’t switch between both
- Viral loads in CMV disease are significantly greater than in asymptomatic viremia, allows for endpoint (Natori et al)
- **Kinetics of viral replication** are strongly associated with progression to disease

Antigenemia

- Largely replaced by CMV viral testing
- Higher sensitivity w/ qPCR test (82.1%) vs antigenemia (59.0%); qPCR more accurate (Franco et al)
- Major inter-lab variation, not standardized, significant human time processing test

Serology (IgG/IgM) – only to stratify risk, not for diagnostics

Histopathology

- Both by routine pathology and special immunohistochemistry stains for CMV; gold standard for invasive CMV infection

Culture

- Best when done on tissue or bronchoscopy fluid, not urine/stool/saliva

Natori et al, Use of Viral Load as a Surrogate Marker in Clinical Studies of Cytomegalovirus in Solid Organ Transplantation: A Systematic Review and Meta-analysis. CMV Consensus Forum. Clin Infect Dis. 2018
Franco et al, Evaluation of diagnostic tests for cytomegalovirus active infection in renal transplant recipients, J Bras Nefrol. 2017 Mar

Nuances on Blood DNAemia

We recommend that only changes in viral load exceeding 0.5 $\log_{10}$ IU/ml (3-fold) are considered to represent clinically significant differences in DNAemia (strong, low).

Although harmonization of QNAT has improved, universal thresholds for therapy or treatment endpoints have not been established and current published thresholds remain assay specific. Accordingly, we recommend that centers establish their own thresholds and audit clinical outcomes to verify the thresholds used (strong, moderate).

With the use of highly sensitive QNAT (lower limit of quantification (LLOQ), <200 IU/ml), we suggest discontinuing therapy after one result is less than the LLOQ. If this approach is used, confirmatory testing should be done one week after discontinuing therapy. If the assay is not highly sensitive, then 2 consecutive undetectable (negative) results are needed to discontinue therapy (weak and moderate).

From *The Third International Consensus Guidelines on the Management of Cytomegalovirus in SOT*

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SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

WILEY Clinical TRANSPLANTATION

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

Raymund R. Razonable[1] | Atul Humar[2,3]

from

Clinical Infectious Diseases
INVITED ARTICLE
CID 2017:64 (1 January)
IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD
IMMUNOCOMPROMISED HOSTS: David R. Snydman, Section Editor

Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials

Per Ljungman,[1,2] Michael Boeckh,[4,5] Hans H. Hirsch,[6] Filip Josephson,[3] Jens Lundgren,[7] Garrett Nichols,[8] Andreas Pikis,[9] Raymund R. Razonable,[10] Veronica Miller,[11] and Paul D. Griffiths[12]; for the Disease Definitions Working Group of the Cytomegalovirus Drug Development Forum[a]

TABLE 1 Consensus definitions of cytomegalovirus infection and disease

	Proven or definite	Probable
CMV syndrome	Not defined	Detection of CMV in the blood by viral isolation, rapid culture, antigenemia, or QNAT Plus, at least two of the following: 1. Fever ≥38°C for at least 2 d 2. New or increased malaise or fatigue 3. Leukopenia or neutropenia on 2 separate measurements 4. 5% atypical lymphocytes 5. Thrombocytopenia 6. Hepatic aminotransferases increase to two times ULN (except non-liver transplant recipients)
Gastrointestinal CMV disease	Presence of upper and/or lower GI symptoms plus macroscopic mucosal lesions plus CMV documented in tissue by histopathology, virus isolation, rapid culture, immunohistochemistry, or DNA hybridization techniques	Presence of upper and/or lower GI symptoms and CMV documented in tissue but without macroscopic mucosal lesions CMV documented in blood by NAT or antigenemia alone is not sufficient for diagnosis of CMV GI disease
CMV pneumonia	Clinical symptoms and/or signs of pneumonia such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea combined with CMV documented in lung tissue by virus isolation, rapid culture, histopathology, immunohistochemistry, or DNA hybridization techniques	Clinical symptoms and/or signs of pneumonia such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea combined with detection of CMV by viral isolation and rapid culture of BALF, or quantitation of CMV DNA in BALF
CMV hepatitis	Abnormal liver tests plus CMV documented in liver tissue by histopathology, immunohistochemistry, virus isolation, rapid culture, or DNA hybridization techniques plus the absence of other documented cause of hepatitis	Not defined
CMV retinitis	Typical ophthalmological signs as assessed by an ophthalmologist experienced with the diagnosis of CMV retinitis If the presentation is atypical or an experienced ophthalmologist is not available, the diagnosis should be supported by CMV documented in vitreous fluid by NAT	Not defined
CMV encephalitis	CNS symptoms plus detection of CMV in CNS tissue by virus isolation, rapid culture, immunohistochemical analysis, in situ hybridization, or quantitative NAT	CNS symptoms plus detection of CMV in CSF without visible contamination of blood ("bloody tap") plus abnormal imaging results
Refractory CMV infection	CMV DNAemia or antigenemia increases (ie, >1 log10 increase in CMV DNA levels in blood between peak viral load within the first week and the peak viral load at 2 wk or more) after at least 2 wk of appropriately dosed antiviral therapy	Viral load persistence (at the same level or higher than the peak viral load within 1 wk but <1 log10 increase in CMV DNA titers) after at least 2 wk of appropriately dosed antiviral therapy
Refractory CMV disease	Worsening in signs and symptoms or progression into end-organ disease after at least 2 wk of appropriately dosed antiviral therapy	Lack of improvement in clinical signs and symptoms after at least 2 wk of appropriately dosed antiviral therapy
Resistant CMV	Presence of viral genetic alteration that confer reduced susceptibility to one or more antiviral drugs	

BALF, bronchoalveolar lavage fluid; CMV, cytomegalovirus; CNS, central nervous system; NAT, nucleic acid amplification test; QNAT, quantitative NAT; ULN, upper limit of normal.
References (Ljungman et al and Chemaly et al).[10,12]

Guidelines on CMV: Best Practice for Treatment

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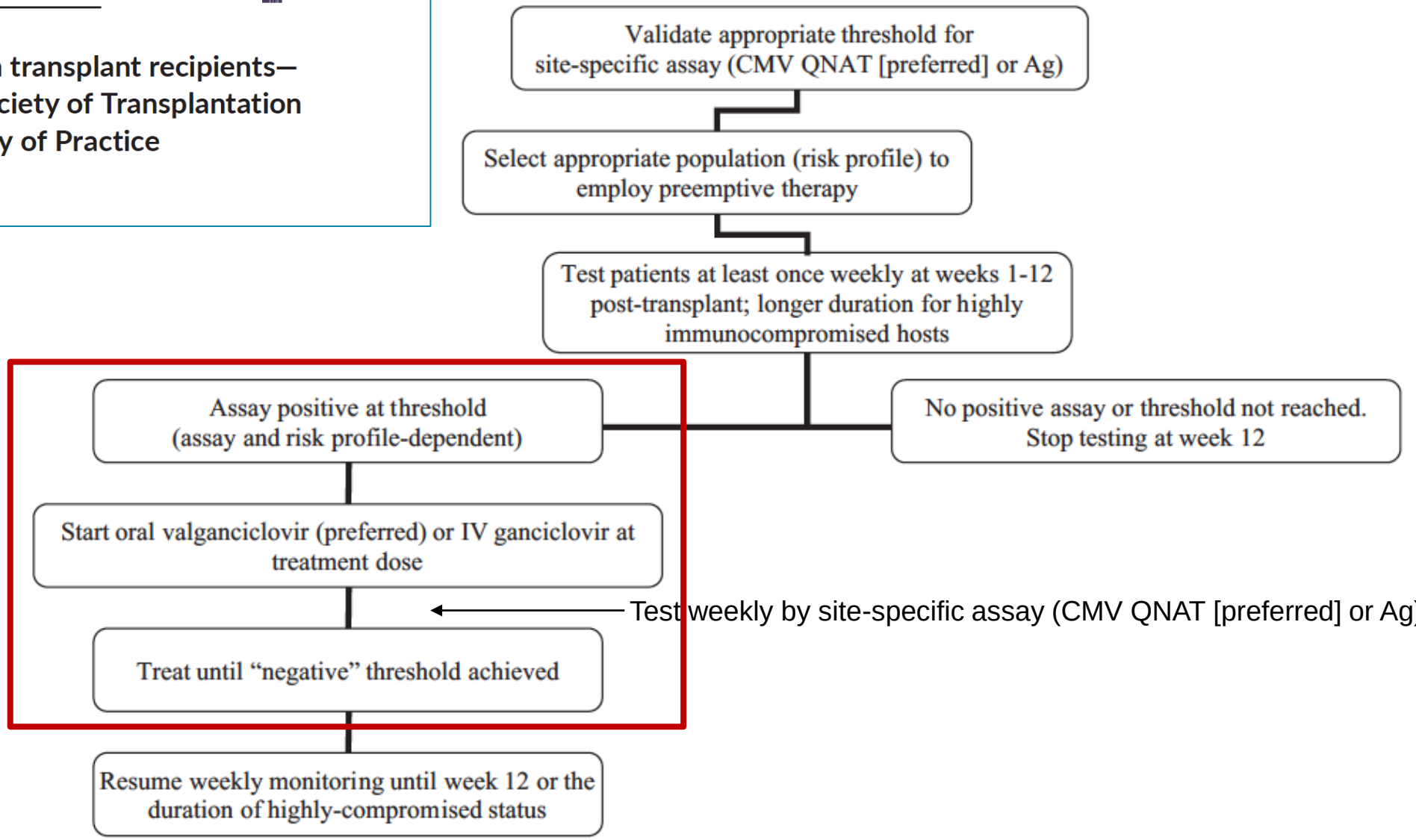
SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

WILEY Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

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

Raymund R. Razonable[1] | Atul Humar[2,3]

Suggested algorithm for preemptive therapy



Consensus Statements and Recommendations

- **For initial and recurrent episodes of CMV disease, VGCV (900 mg every 12 hours) or intravenous GCV (5 mg/kg every 12 hours) are recommended as first-line treatment in adults with normal kidney function (strong, moderate).**
  - Valganciclovir is recommended in patients with mild to moderate CMV disease who can tolerate and adhere to oral medication (strong, moderate).
  - Intravenous GCV is recommended in life-threatening & severe disease (strong, low).
  - After clinical response, intravenous GCV may be transitioned to VGCV

- **In patients without concomitant rejection, reduction of immunosuppression is suggested in the following settings: *severe CMV disease, inadequate clinical response, high viral loads, and cytopenia (weak, very low).***

- **During the treatment phase, weekly plasma CMV DNA testing is recommended using an assay calibrated to the WHO standard to monitor response (strong, high).**

- **During the treatment phase, frequent monitoring of renal function is recommended to guide dosage adjustments (strong, moderate).**

Adjunctive immunoglobulin therapy is not routinely recommended (strong, low).

Consensus Statements and Recommendations

Antiviral treatment dosing should be continued for a minimum of two weeks, until clinical resolution of disease and eradication of CMV DNAemia below a specific threshold (LLOQ < 200 IU/ml) on one or two consecutive weekly samples (strong, moderate).

In the setting of leukopenia, changing (val)ganciclovir to another agent is not recommended before the addition of granulocyte colony stimulating factor and/or discontinuation of other myelosuppressive therapies (strong, low).

In patients who are intolerant to (val)ganciclovir during the treatment phase, foscarnet is the recommended second-line agent (strong, very low).

Drug resistance should be suspected in patients with a prior cumulative (val)ganciclovir exposure that exceeds six weeks and clinical treatment failure despite at least two weeks of antiviral treatment or development of CMV DNAemia during prophylaxis(strong, moderate).

Secondary prophylaxis is not routinely recommended (low, weak).

How to Prevent Recurrent Infection

Secondary Prophylaxis: Does it Work? Not Really

"Given the potential toxicity and cost, we do not recommend the routine use of secondary prophylaxis following treatment of CMV infection or disease (low, weak). We would consider either secondary prophylaxis or pre-emptive therapy in certain higher risk situations, i.e. potent immunosuppression, augmented risk of complications from recurrent CMV, or inability to monitor closely due to extenuating circumstances. (weak, low)"

- Natori et al, Transplantation 2016, mixed population of SOT, "Recurrence occurred in 73/226 (32.3%) of patients that received prolonged antivirals vs. 13/56 (23.2%) in those with no prolonged antivirals (p=0.19)."
- Sullivan et al, Transplantation 2015, kidney/liver recipients, "The use of secondary prophylaxis was not significantly associated with fewer episodes of CMV relapse, graft loss, or death.
- Gardiner et al, CID 2017, 1995-2015 mixed SOT, secondary prophylaxis vs none, 6 weeks after end of tx, risk of relapse did not significantly differ between the 2 groups (HR, 1.18; 95% CI, 0.46–2.99).

Can use monitoring after end of treatment (i.e. weekly CMV DNAemia); hassle, expensive

Lymphopenia (it's at your fingertips)

Multivariate analysis among 276 liver transplant patients - pretransplant lymphopenia was the strongest independent predictor of CMV disease.[1]

Lymphocyte counts also tended to be lower in patients who have recurrent CMV infections.[2]

> Absolute lymphocyte count at CMV clearance (cells/μL): 1.03 (median; range, 0-9.25)

A retrospective cohort study of heart, liver, and kidney transplant recipients treated for an episode of CMV disease[3]:

> Relapse occurred in 33 of 170 participants (19.4%). Mean ALC in relapse-free patients was 1.08 +/- 0.69 vs 0.73 +/- 0.42 x 10^3 cells/μL in those who relapsed

1. Nierenberg NE, Poutsiaka DD, Chow JK, et al. Pretransplant lymphopenia is a novel prognostic factor in cytomegalovirus and noncytomegalovirus invasive infections after liver transplantation. Liver Transpl. 2014;20:1497–1507.
2. Natori Y, Humar A, Husain S, et al. Recurrence of CMV infection and the effect of prolonged antivirals in organ transplant recipients. Transplantation. 2017;101:1449–1454.
3. Gardiner B et al, Absolute Lymphocyte Count: A Predictor of Recurrent Cytomegalovirus Disease in Solid Organ Transplant Recipients, CID 2018; 67: 1395

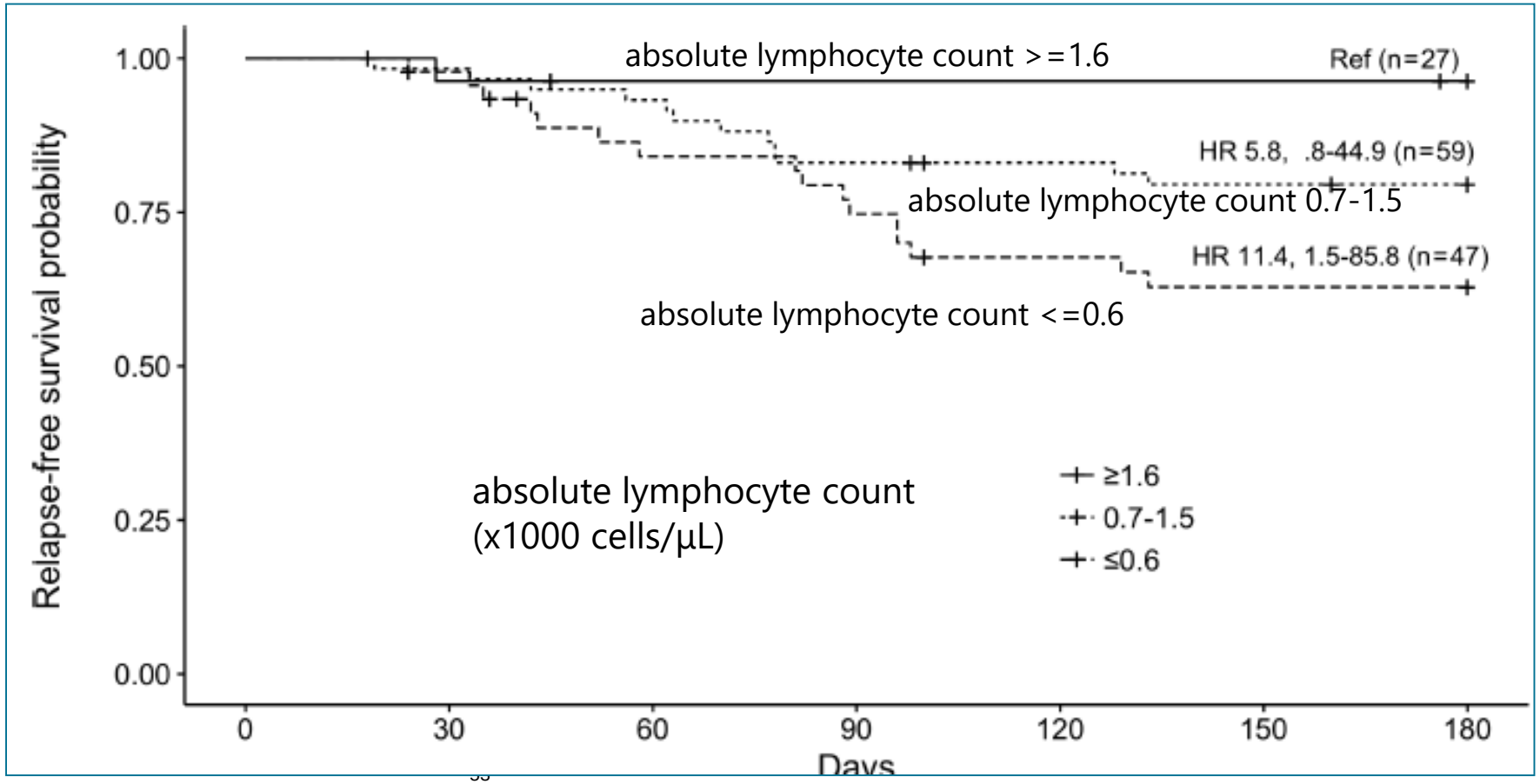
Clinical Infectious Diseases
MAJOR ARTICLE

Absolute Lymphocyte Count: A Predictor of Recurrent Cytomegalovirus Disease in Solid Organ Transplant Recipients

November 2018

Bradley J. Gardiner,[1,2] Natalie E. Nierenberg,[1] Jennifer K. Chow,[1] Robin Ruthazer,[3,4] David M. Kent,[4,5] and David R. Snydman[1,4]

- Retrospective cohort study of heart, liver, and kidney transplant recipients treated for an episode of CMV disease
- Primary outcome was time to relapse of CMV within 6 months



American Journal of Transplantation 2017; XX: 1–6
Wiley Periodicals Inc.

doi: 10.1111/ajt.14347

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

Interventional trial

End of Treatment→ QuantiFERON-CMV

CMV serology	
D+/R-	12 (44.4%)
R+	13 (48.1%)
D-/R-	1 (3.7%)
Unknown	1 (3.7%)

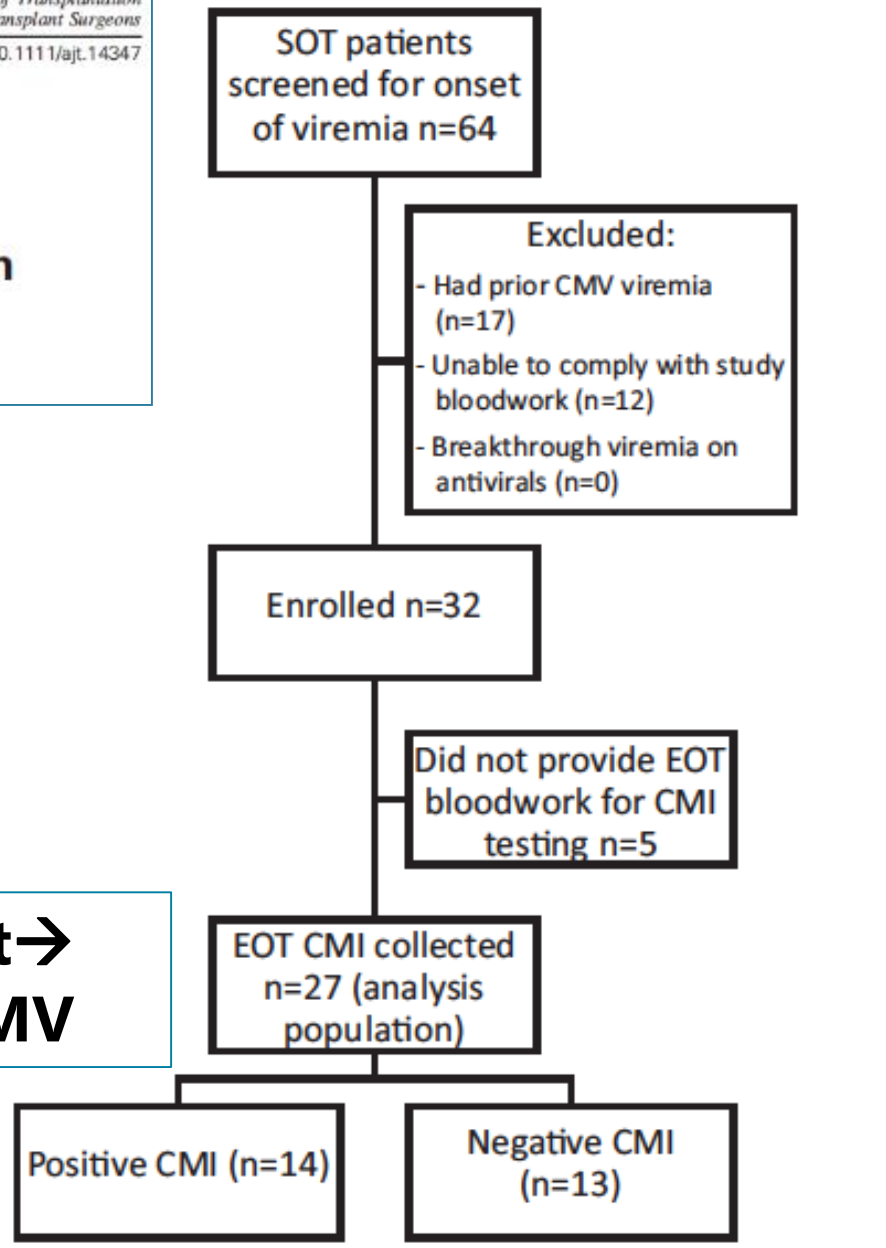


Figure 1: Study flow. CMI, cell-mediated immunity; CMV, cytomegalovirus; EOT, end of treatment; SOT, solid organ transplant.

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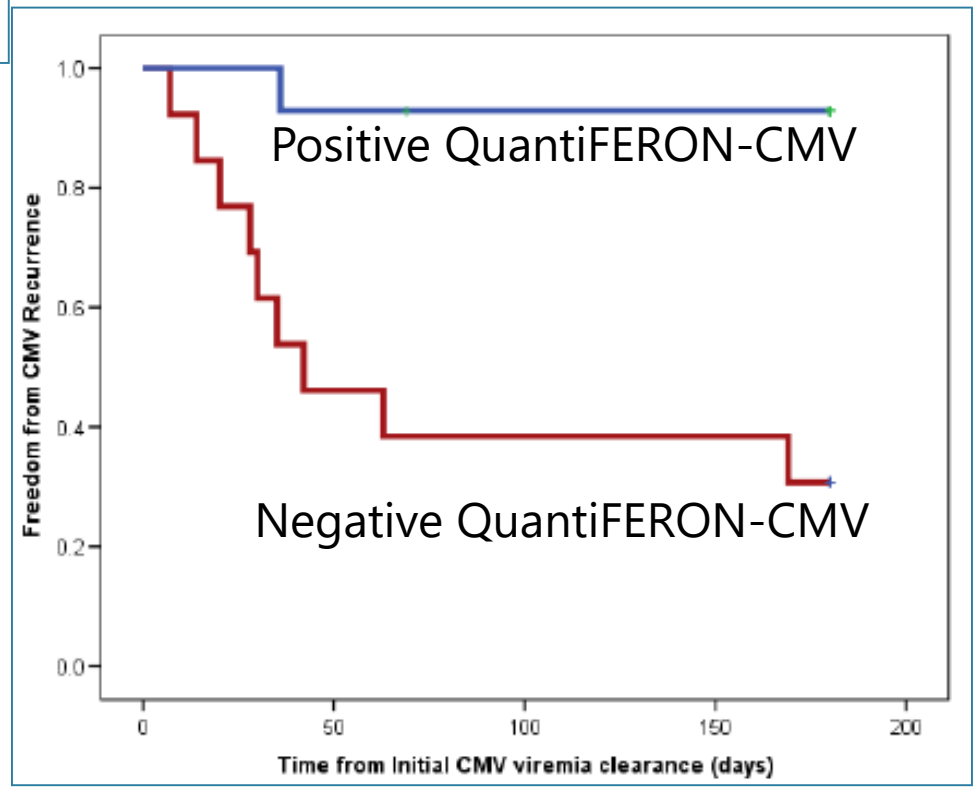
Brief Communication

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

- At end of treatment, 14/27 (51.9%) had a positive CMV-CMI response and had antivirals discontinued→ 1 experienced a low-level asymptomatic recurrence.
- The remaining 13/27 (48.1%) patients had a negative CMV-CMI response and received **2 months of secondary antiviral prophylaxis → recurrence was observed in 69.2% of CMI-negative patients despite more prolonged antivirals** (p = 0.001).



In conclusion, this is the first study to demonstrate the feasibility and safety of real-time CMV-specific CMI assessment to guide changes to the management of CMV infection.

What about (Val)ganciclovir-resistant CMV?

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, MD[7]
on behalf of the The Transplantation Society International CMV Consensus Group

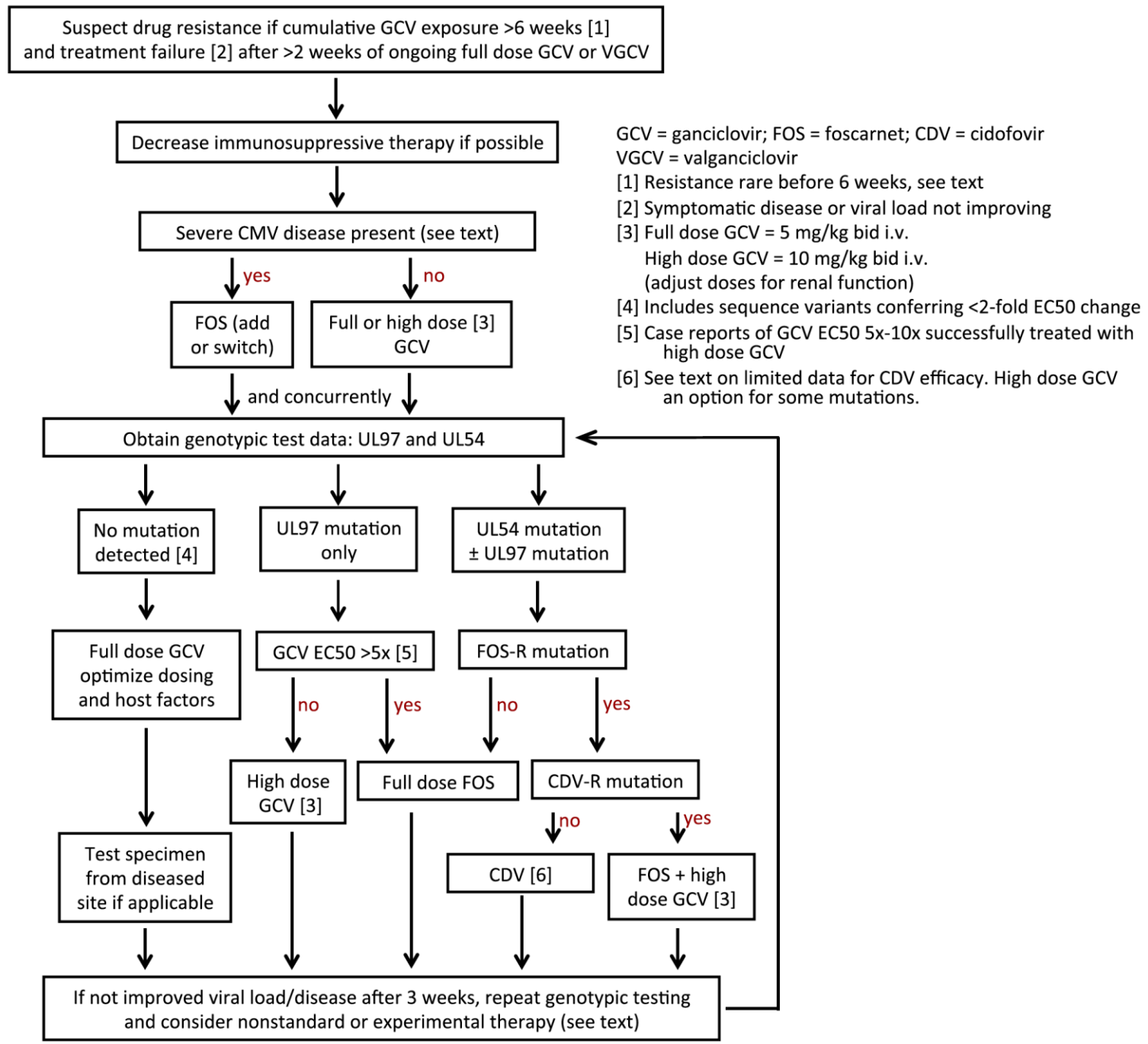


FIGURE 2. Proposed algorithm for management of suspected antiviral drug resistance, based on consensus expert opinion. There are no controlled trials that define clinical outcomes according to genotypic diagnosis and selection of alternative therapy.

Maribavir

UL97 kinase inhibitor

Overlap with ganciclovir-resistant mutations

- Elicits a different set of UL97 mutations, clustered around ATP binding site

Covers CMV, EBV

- need acyclovir for HSV/VZV prevention

May have less impact on lymphoproliferative/CMV-specific cellular immune responses than ganciclovir

Stachel D, et al. *J Clin Virol*. 2016;75:53-59.

Clinical Infectious Diseases
MAJOR ARTICLE

Maribavir for Refractory or Resistant Cytomegalovirus Infections in Hematopoietic-cell or Solid-organ Transplant Recipients: A Randomized, Dose-ranging, Double-blind, Phase 2 Study

CID Oct 2018

Genovefa A. Papanicolaou,[1] Fernanda P. Silveira,[2] Amelia A. Langston,[3] Marcus R. Pereira,[4] Robin K. Avery,[5] Marc Uknis,[6] Anna Wijatyk,[7] Jingyang Wu,[7] Michael Boeckh,[8] Francisco M. Marty,[9,a] and Stephen Villano[6,a]

Hematopoietic-cell or solid-organ transplant recipients with R/R CMV infections & plasma CMV DNA ≥1000 copies/mL were randomized (1:1:1) to twice-daily, dose-blinded maribavir 400, 800, or 1200 mg for up to 24 weeks.

N=40/arm (120 total); 32 died before completing study

The primary efficacy endpoint was the proportion of patients with confirmed undetectable plasma CMV DNA within 6 weeks of treatment.

Clinical Infectious Diseases
MAJOR ARTICLE

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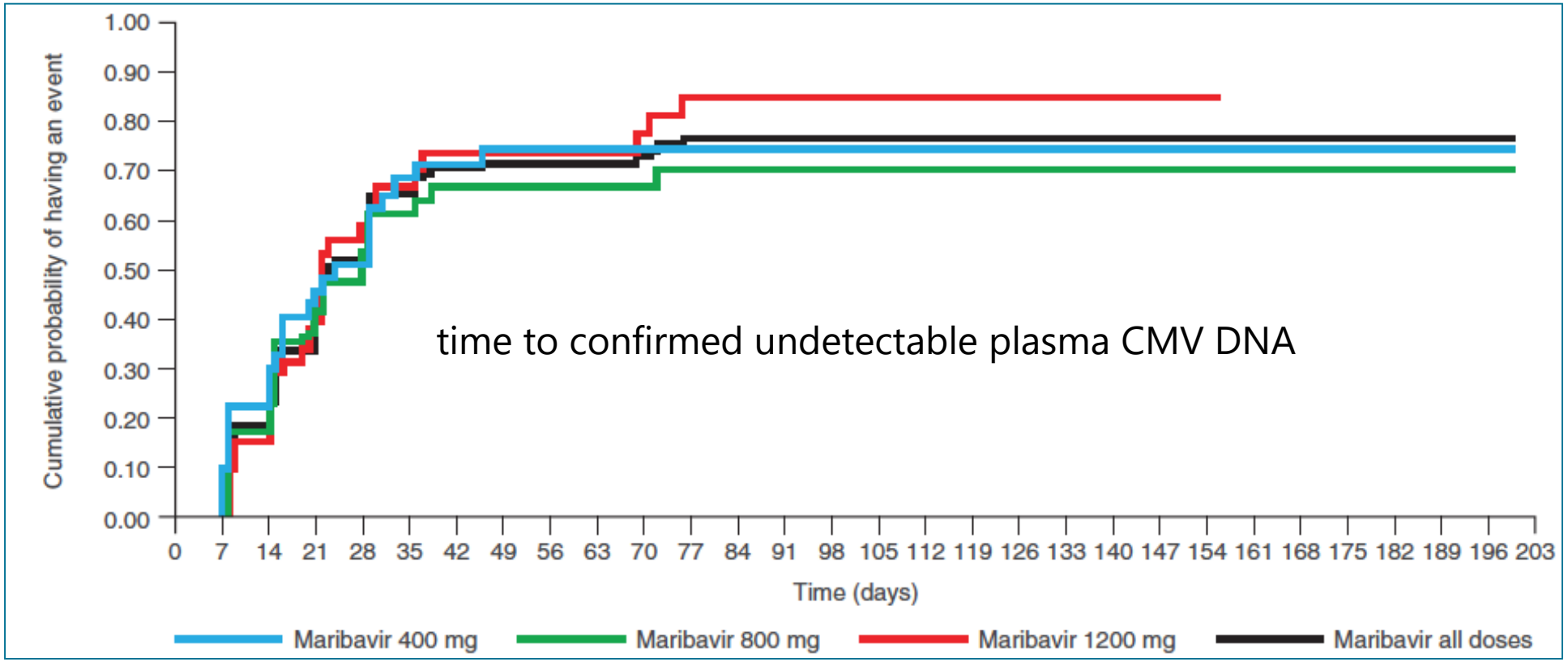

Maribavir: Trials Underway

Phase 3, efficacy and safety of maribavir in transplant recipients with cytomegalovirus (CMV) infections that are refractory or resistant to treatment (ClinicalTrials.gov NCT02931539)

Study for the treatment of cytomegalovirus (CMV) infection in hematopoietic stem cell transplant recipients (ClinicalTrials.gov NCT02927067)

Updates on antiviral drugs for cytomegalovirus prevention and treatment

Curr Opin Organ Transplant 2019, 24:469–475

Camille N. Kotton

Table 1. Antiviral agents with efficacy (at least *in vitro*) against multiple transplant-related viruses

Antiviral agent	CMV	HSV	Varicella	BK	Adeno-virus	EBV
Commercially available						
Ganciclovir/Valganciclovir	X	X	X			
Letermovir	X					
Acyclovir/Valacyclovir/Famciclovir[a]	High dose ±	X	X			
Foscarnet[b]	X	X	X			
Cidofovir[b]	X	X	X	Poor	± (IC50 dependent)	
Novel/Investigational antiviral agents (SOT)						
Brincidofovir	X	X	X	X	X	X
Maribavir	X					X

CURRENT OPINION

Updates on antiviral drugs for cytomegalovirus prevention and treatment

Curr Opin Organ Transplant 2019, 24:469–475

Camille N. Kotton

Table 2. Transplant-related drug versus antiviral drug interactions

	(Val)Ganciclovir	Foscarnet	Cidofovir	Letermovir	Maribavir
Tacrolimus	Concurrent use may result in an increased risk of nephrotoxicity	Potential for enhanced nephrotoxic effect; concurrent use of tacrolimus and cardiac QT interval prolonging drugs may result in increased risk of QT interval prolongation	Potential for enhanced nephrotoxic effect	Letermovir may increase the serum concentration of tacrolimus	Increases tacrolimus exposure by ~50%, presumably caused by inhibition of CYP3A4 and P-glycoprotein [9,10]
Cyclosporine	(Val)Ganciclovir may enhance the nephrotoxic effect of cyclosporine			Letermovir may increase the serum concentration of cyclosporine[a]	
Mycophenolate mofetil	Each may increase the serum concentration of the other				
Sirolimus/Everolimus				Letermovir may increase the serum concentration of everolimus and sirolimus	

Future: development of an equation with multiple factors predictive of CMV infection after SOT?

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- CMV cellular mediated immunity
- CMV serology
- viral load
- type of induction
- maintenace: mTor, mycophenolate mofetil and tacrolimus dosing
- numbers of transplants, immunological risk
- type of donor
- biopsy-proven acute rejection
- delayed or current graft function

Guidelines on CMV: Best Practice Prevention, Diagnosis, And Treatment

- Prophylaxis with 3 months if R+ (6 months for D+R-) of valganciclovir, properly dosed OR pre-emptive therapy, weekly monitoring x 12-16 weeks
- Immunologic monitoring (when available)
- mTor inhibitors may help decrease CMV risk
- Careful diagnostics and treatment
- Decrease in CMV replication → better longterm outcomes
- Pretransplant vaccine (when available)

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TRANSPLANT CENTER

Cytomegalovirus: the troll of transplantation

Balfour HH, Jr. Arch Intern Med. 1979;139(3):279-80

Remember the tale of "The Three Billy Goats Gruff?" The transplant patient, like the billy goats, initially is on rocky ground and wants to cross the bridge over the rushing river to greener pastures on the other side. Cytomegalovirus is the troll under the bridge, hidden in shadows and often undetectable even by the most sophisticated diagnostic techniques. As we immunosuppress patients to help them cross the bridge, the troll comes out and threatens to devour them. Like the two smaller billy goats in the story, we clinicians are passing the buck to stall for time, hopeful that in the near future our patients, armed with either a vaccine or an effective antiviral agent, will be strong enough to throw the voracious CMV troll off the bridge and back into obscurity.