CMV immune monitoring – ready for routine use?

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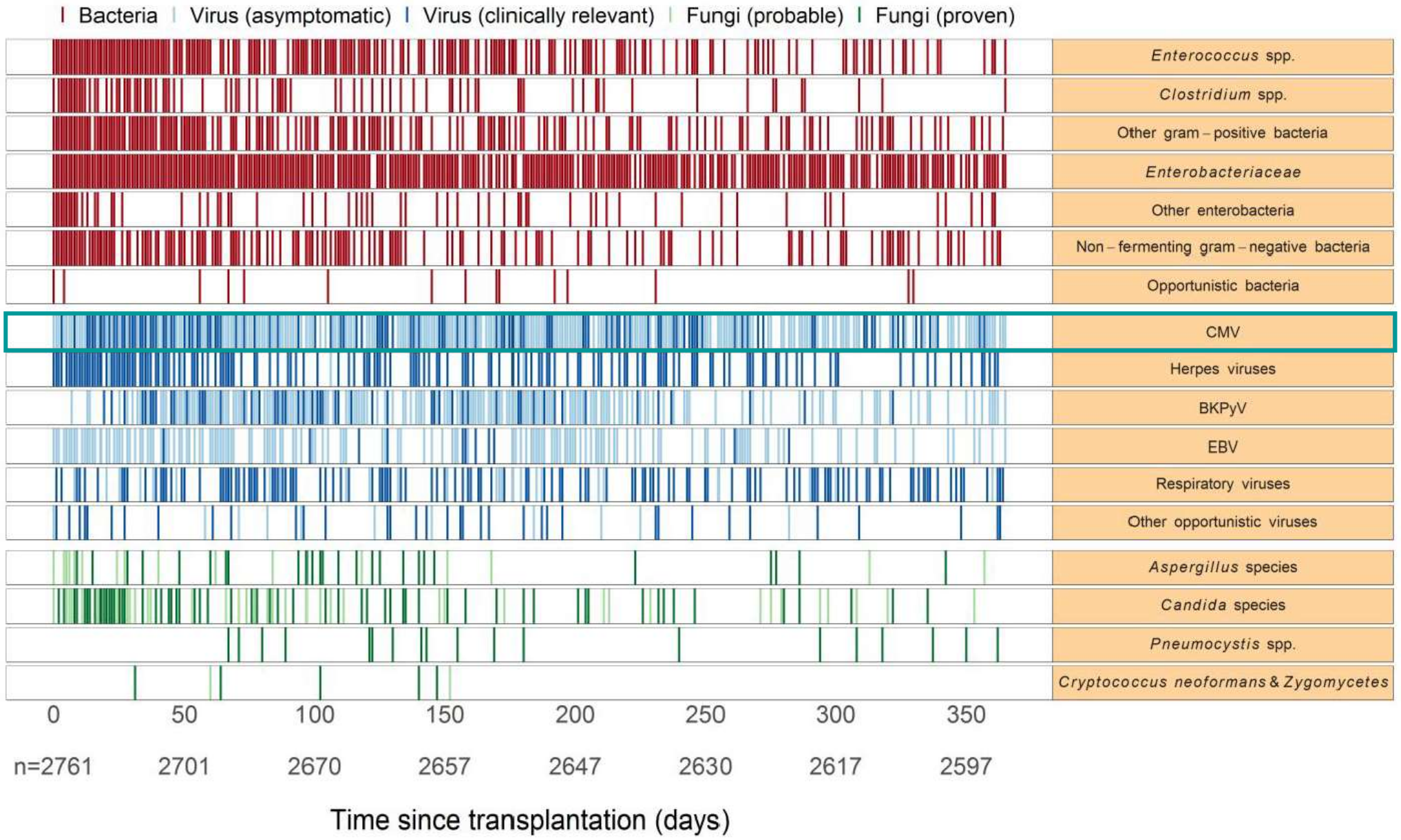
Outline

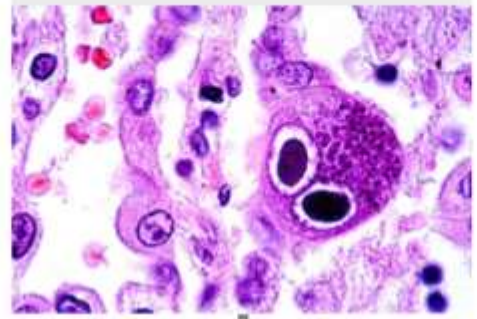
- Rationale for using CMV immune monitoring
- Potential clinical scenarios
- Clinical experience: interventional trials
- Barriers for implementation in the routine clinical setting



SWISS TRANSPLANT COHORT STUDY

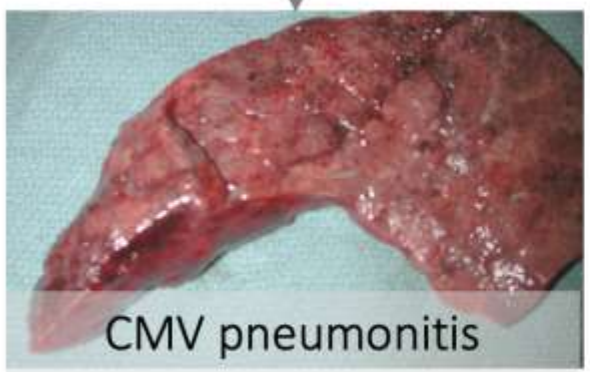
Van Delden C et al. Clin Infect Dis 2020

CMV infection

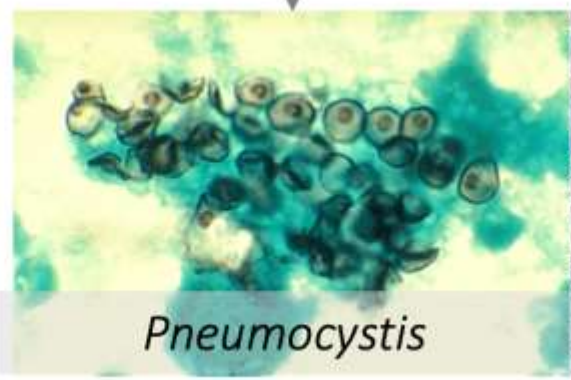


Direct effects

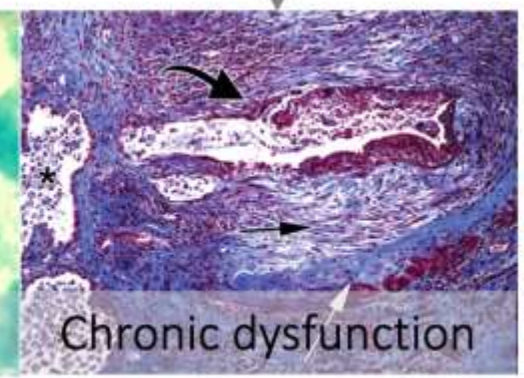
Immunomodulatory effects



CMV pneumonitis



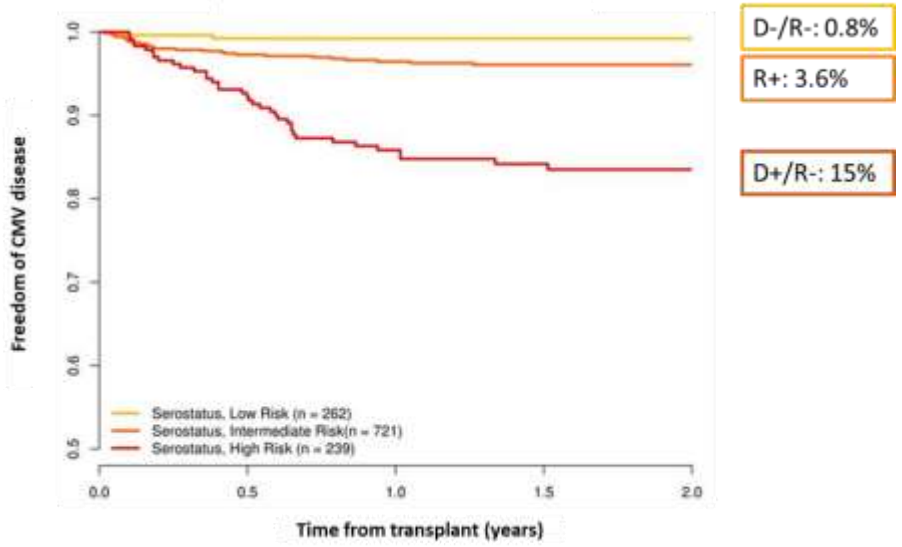
Pneumocystis



Chronic dysfunction

- Current challenges in the prevention of CMV

1

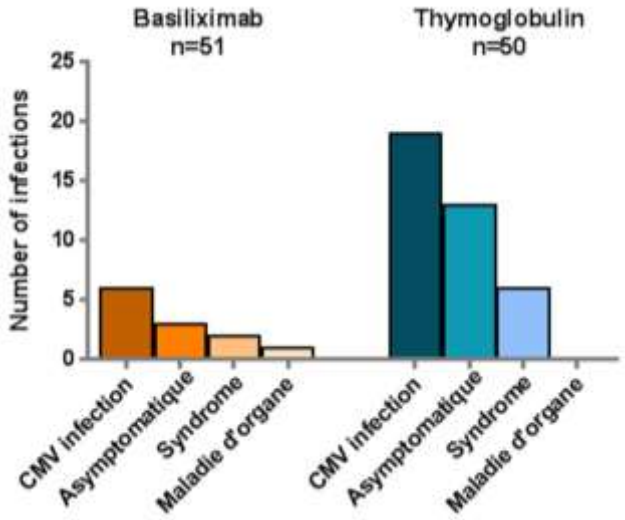


D-/R-: 0.8%

R+: 3.6%

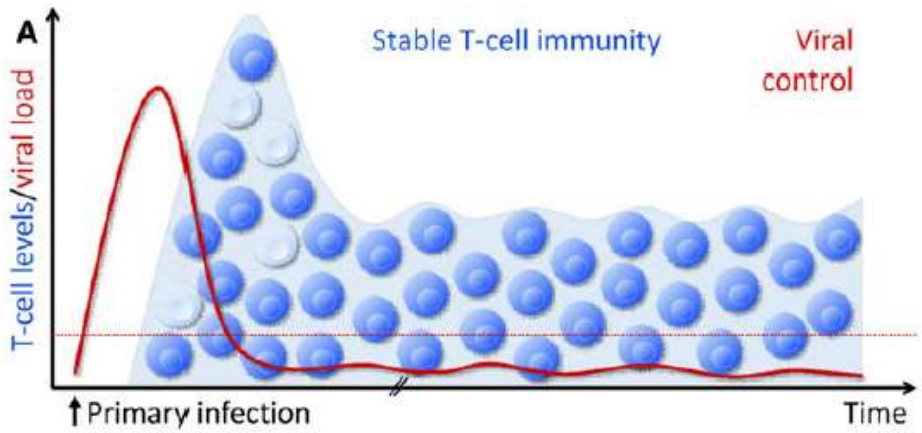
D+/R-: 15%

2

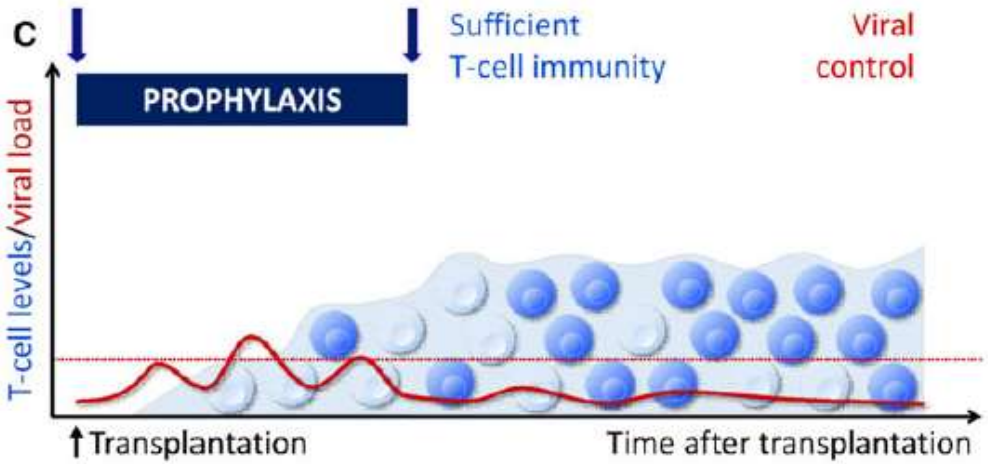


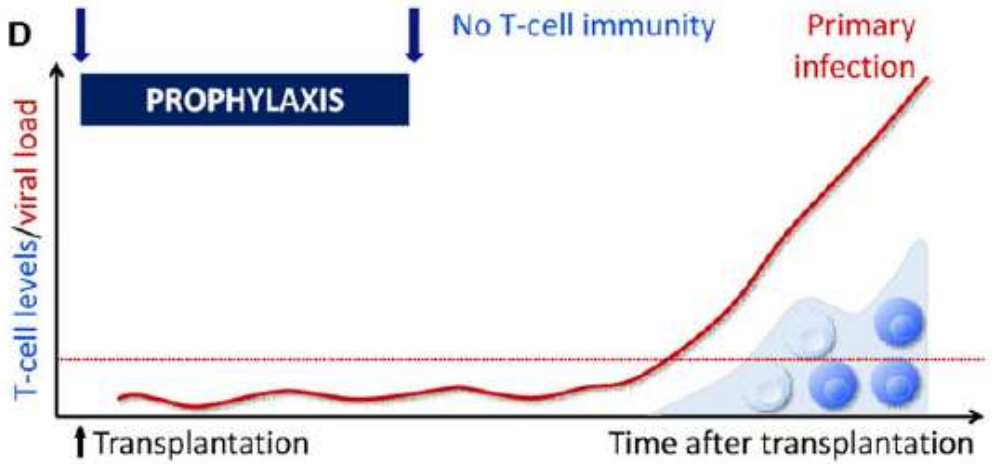
How can we dynamically stratify patients according to the actual risk of developing CMV disease?

Immunocompetent host



Transplant recipient





Sester M et al. Am J Transplant 2016; 16: 1697

• Cell-mediated immunity assays

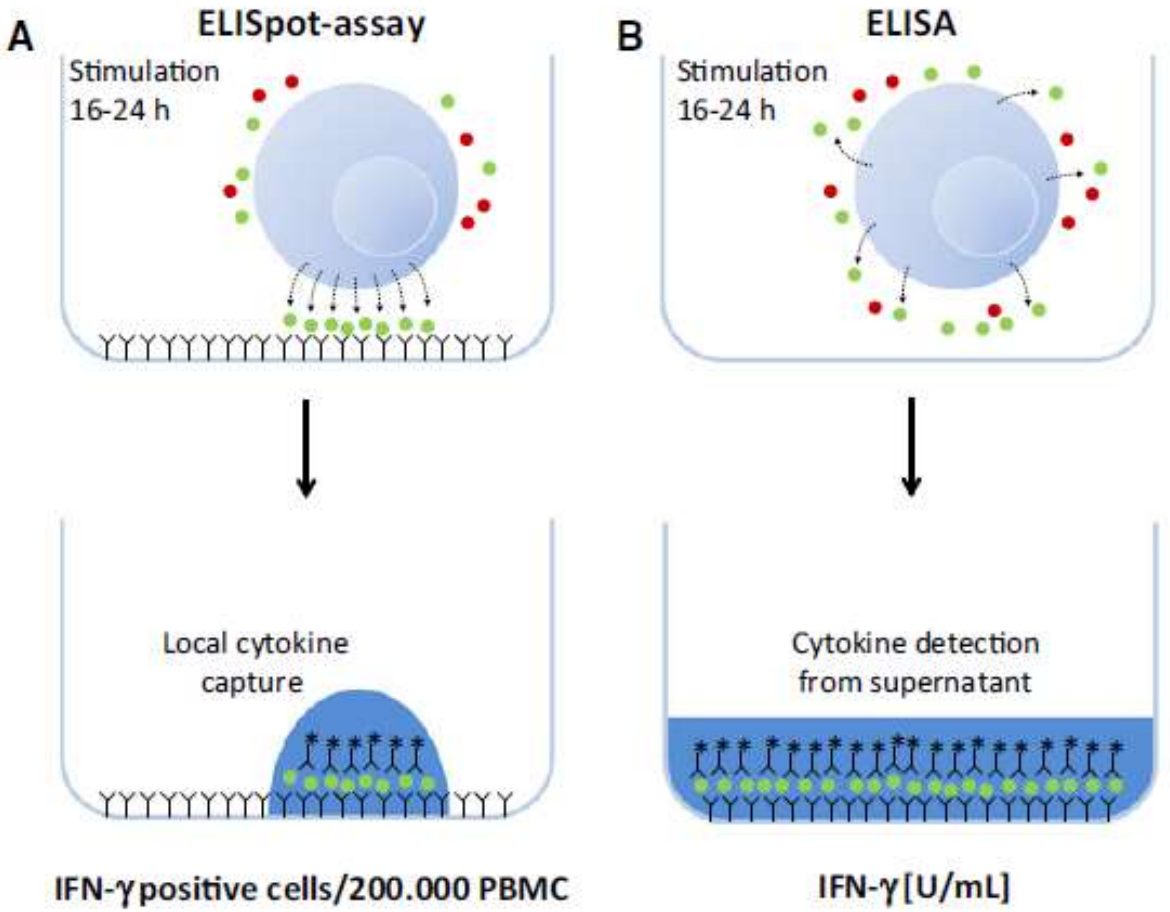
Pros

Low number of indeterminate results

Results by CMV antigen (stratification)

Cons

Need to isolate cells
More cumbersome



Pros

Easy to perform (QF-TB platform)

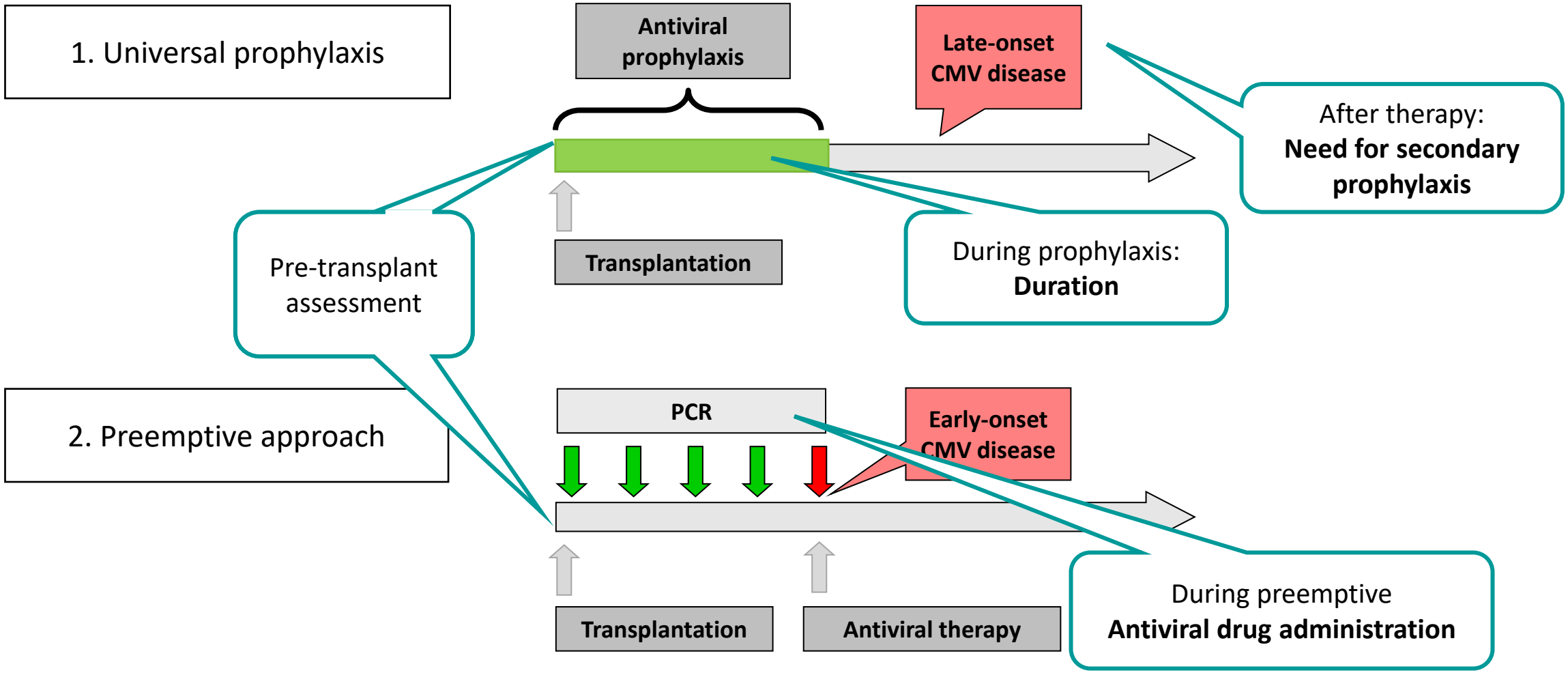
Needs less blood

Cons

Higher number of indeterminates
Less predictive value

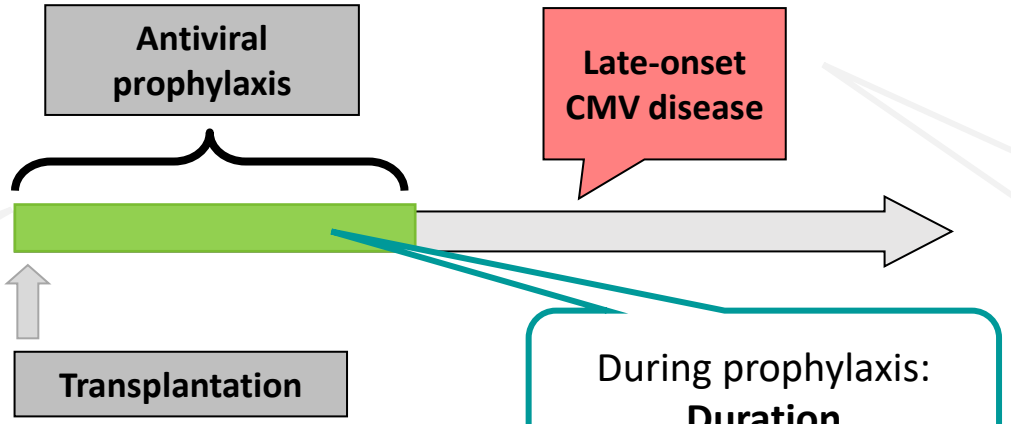
Sester M et al. Am J Transplant 2016; 16: 1697

- # Clinical scenarios



- Clinical scenarios

1. Universal prophylaxis

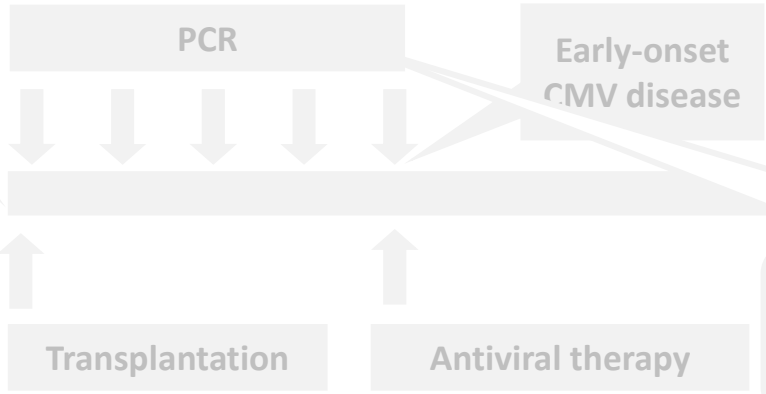


After therapy:
Need for secondary prophylaxis

Pre-transplant assessment

During prophylaxis:
Duration

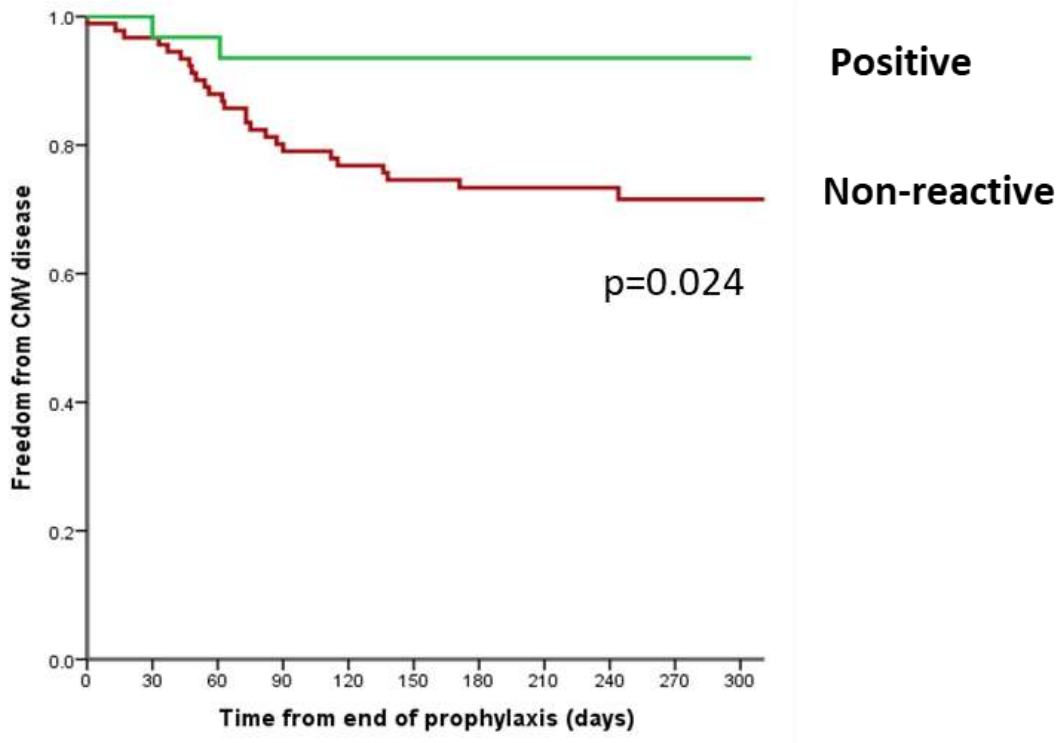
2. Preemptive approach



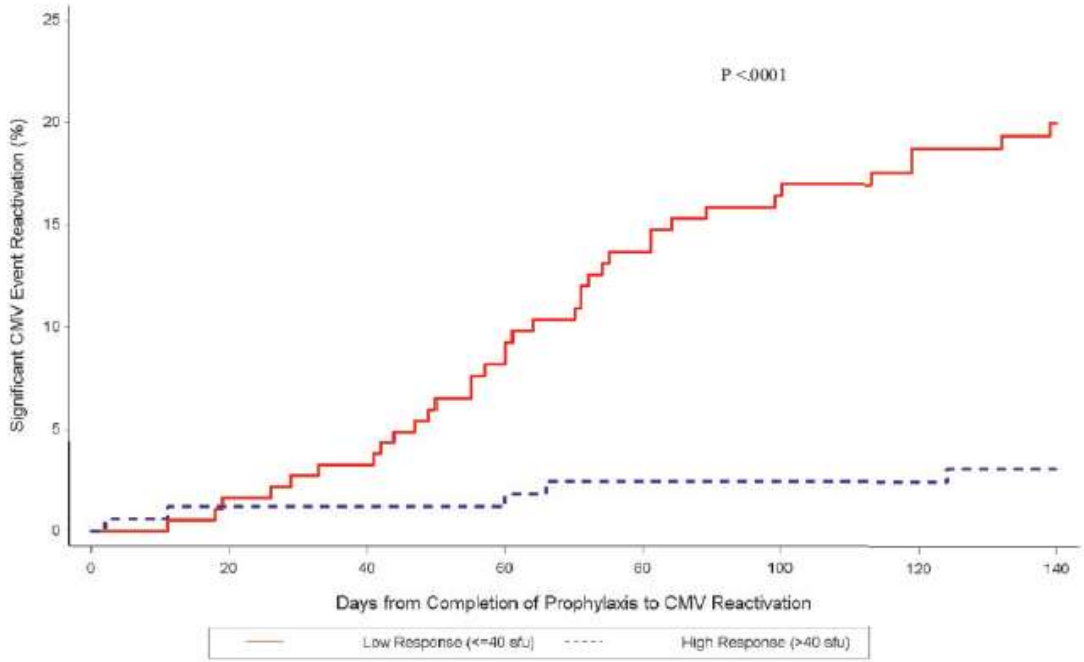
During preemptive
Antiviral drug administration

- # Cell-mediated immunity assays predicts CMV disease after discontinuation of prophylaxis

Quantiferon-CMV



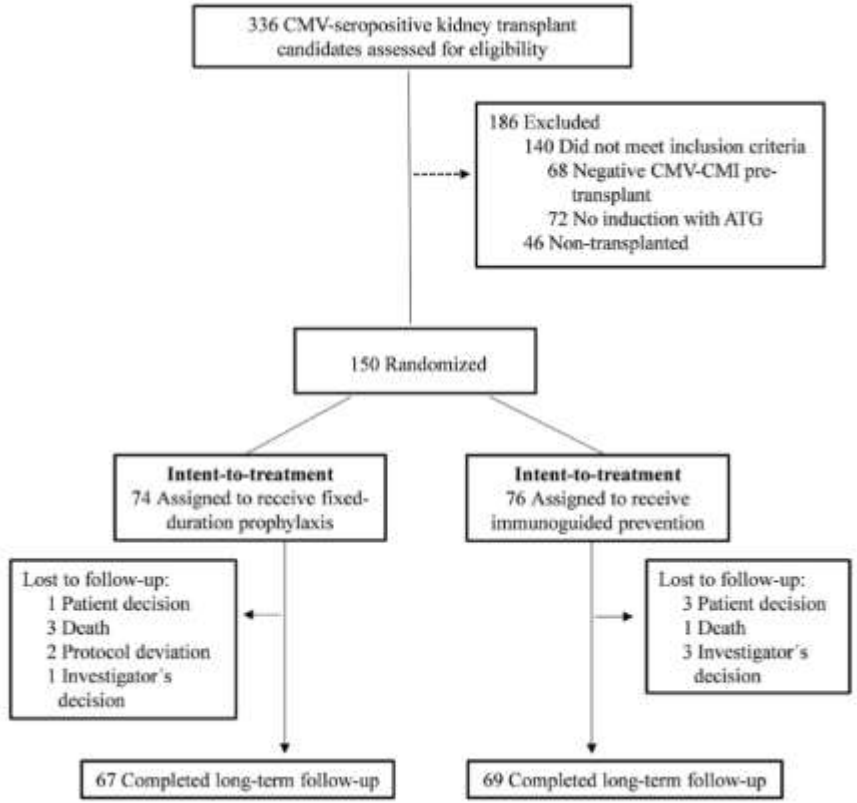
Elispot-CMV



Manuel O et al. Clin Infect Dis 2013; 56: 817
Kumar D et al. Am J Transplant 2019; 19: 2505

Clinical Infectious Diseases
MAJOR ARTICLE

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



R+ ATG	R+ ATG
3 months antiviral prophylaxis	QF-CMV at 30, 45, 60 and 90 days Stop prophylaxis when QF positive

Páez-Vega A et al. Clin infect Dis 2021

	Time Point			
Parameter	**Day 30**	**Day 45**	**Day 60**	**Day 90**
Patients with QuantiFERON-CMV assay results[a]	74 (97.3)	73 (96.1)	72 (94.7)	72 (94.7)
Negative	16 (21.1)	22 (28.9)	23 (30.3)	18 (23.7)
Indeterminate	24 (31.6)	11 (14.5)	4 (5.3)	2 (2.6)
Positive	34 (44.7)	40 (52.6)	45 (59.2)	52 (68.4)
Interferon-gamma, median (interquartile range), IU/mL	2.4 (0.9–9.4)	2.9 (1.0–11.7)	3.6 (1.2–14.0)	8.1 (1.0–16.3)
Discontinuation of prophylaxis[b]	32 (42.1)	7 (9.2)	6 (7.9)	28 (36.8)

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

Páez-Vega A et al. Clin infect Dis 2021

Clinical Infectious Diseases

MAJOR ARTICLE

Immune Monitoring-Guided Versus Fixed Duration of Antiviral Prophylaxis Against Cytomegalovirus in Solid-Organ Transplant Recipients: A Multicenter, Randomized Clinical Trial

Oriol Manuel,[1,2] Mirjam Laager,[3] Cédric Hirzel,[4] Dionysios Neofytos,[5] Laura N. Walti,[4] Gideon Hoenger,[6] Isabelle Binet,[7] Aurelia Schnyder,[7] Susanne Stampf,[8] Michael Koller,[8] Matteo Mombelli,[1,2] Min Jeong Kim,[8,9] Matthias Hoffmann,[10,11] Katrin Koenig,[8,12] Christoph Hess,[6,13] Anne-Valérie Burgener,[6,14] Pietro E. Cippà,[15,16] Kerstin Hübel,[15] Thomas F. Mueller,[15] Daniel Sidler,[17] Suzan Dahdal,[17] Franziska Suter-Riniker,[18] Jean Villard,[19] Andrea Zbinden,[20] Giuseppe Pantaleo,[21] Nasser Semmo,[22] Karine Hadaya,[23,24] Natalia Enríquez,[5] Pascal R. Meylan,[1] Marc Froissart,[25] Dela Golshayan,[2] Thomas Fehr,[14,26] Uyen Huynh-Do,[17] Manuel Pascual,[2] Christian van Delden,[5] Hans H. Hirsch,[27,28] Peter Jüni,[29,a] and Nicolas J. Mueller;[30,a] the Swiss Transplant Cohort Study (STCS)

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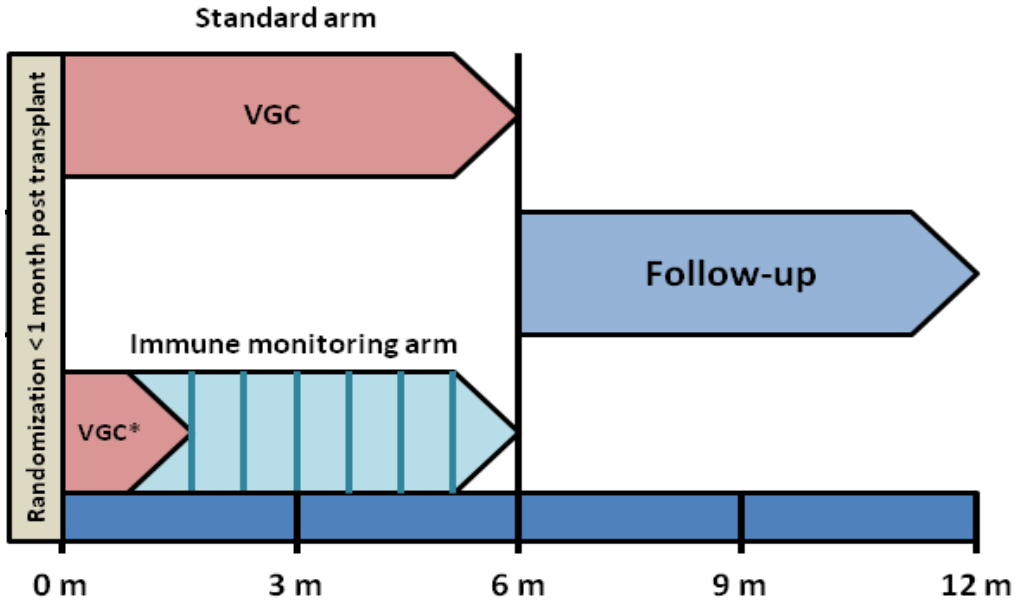
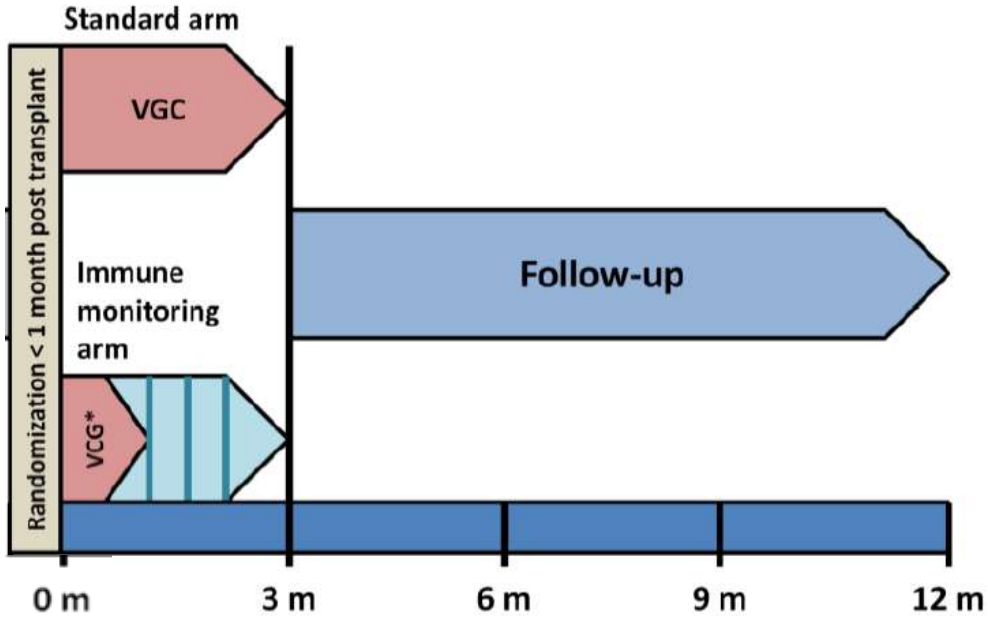
Seronegative (D+/R-) patients



Seropositive (R+) with ATG



* Stop prophylaxis when assay positive

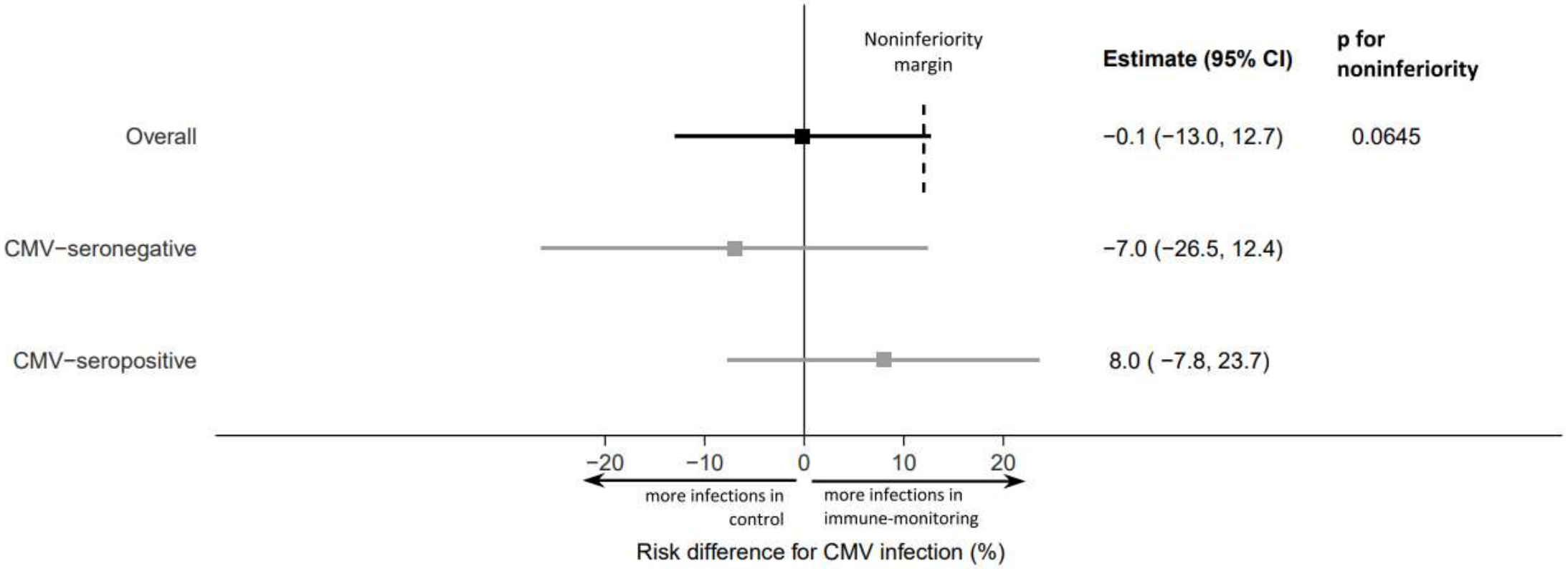
- Baseline characteristics

Baseline Characteristic	Immune Monitoring (N = 87)	Control (N = 98)
Age, median (IQR), y	53.0 (43.5–60.0)	57.5 (45.25–65.0)
Female, no. (%)	29 (33.3)	31 (31.6)
Deceased donor, no. (%)	58 (66.7)	71 (71.6)
Organ		
Kidney	77 (88.5)	87 (88.8)
Liver	10 (11.5)	11 (11.2)
Cytomegalovirus serostatus		
Seropositive	44 (50.6)	40 (40.8)
Seronegative	43 (49.4)	58 (59.2)
Induction therapy		
Antithymocyte globulins	52 (59.8)	51 (52.0)

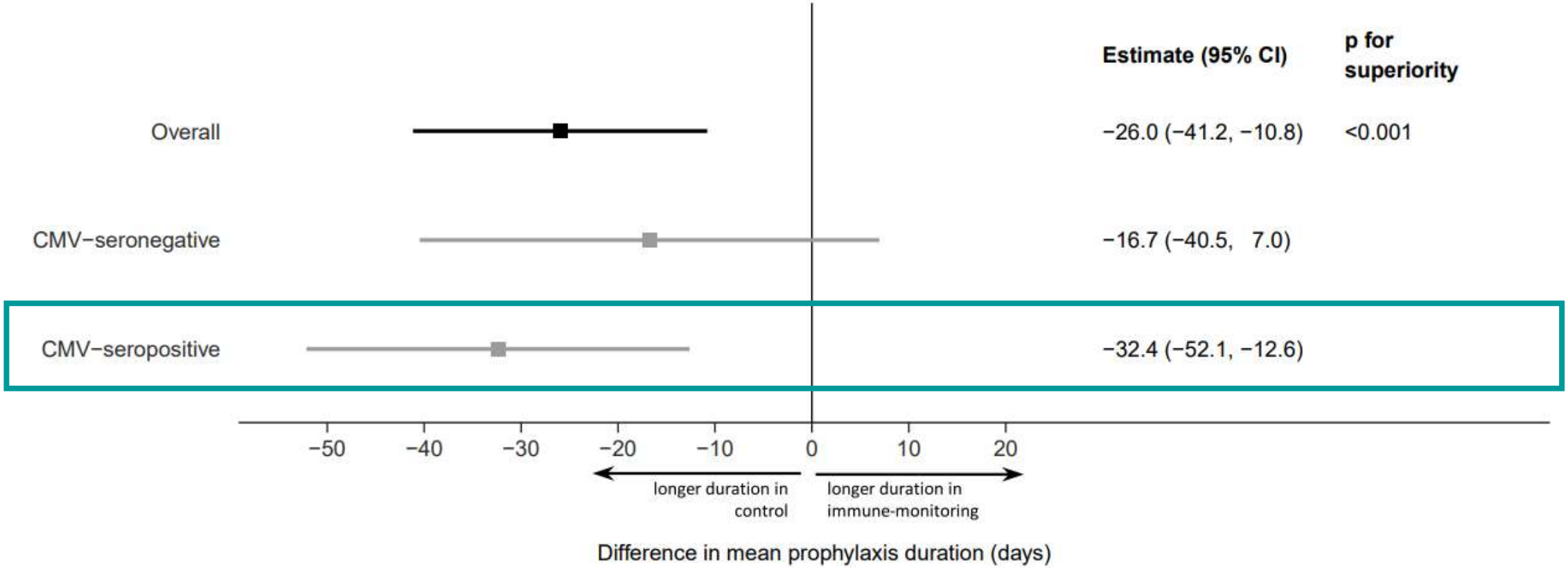
- Co-primary endpoints

Outcome	Immune Monitoring (n = 87)	Control (n = 98)	*P* Value
Clinically significant CMV infection, no. of patients (%)[a]	26 (30.9)	32 (31.1)	.064[b]
Tissue-invasive disease[c]	2 (2.5)	2 (1.9)	…
Viral syndrome[c]	6 (7.6)	8 (7.7)	…
Treated asymptomatic replication[c]	18 (20.7)	22 (21.5)	…
Days of antiviral prophylaxis, mean (standard deviation)[a]	113.7 (47.6)	145.5 (37.9)	<.001

- Subgroup analysis: clinically significant CMV infection



- Subgroup analysis : duration of antiviral prophylaxis



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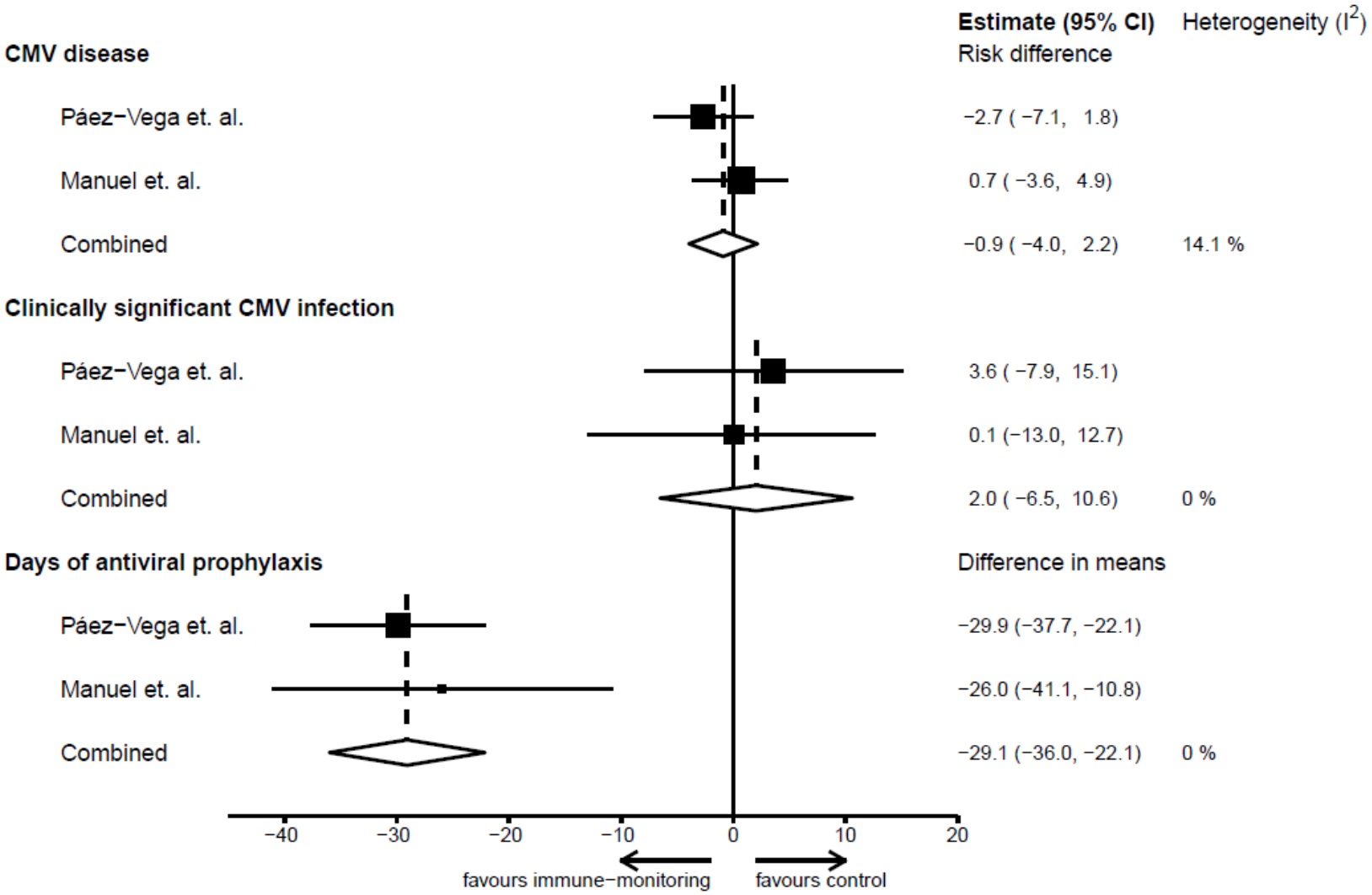
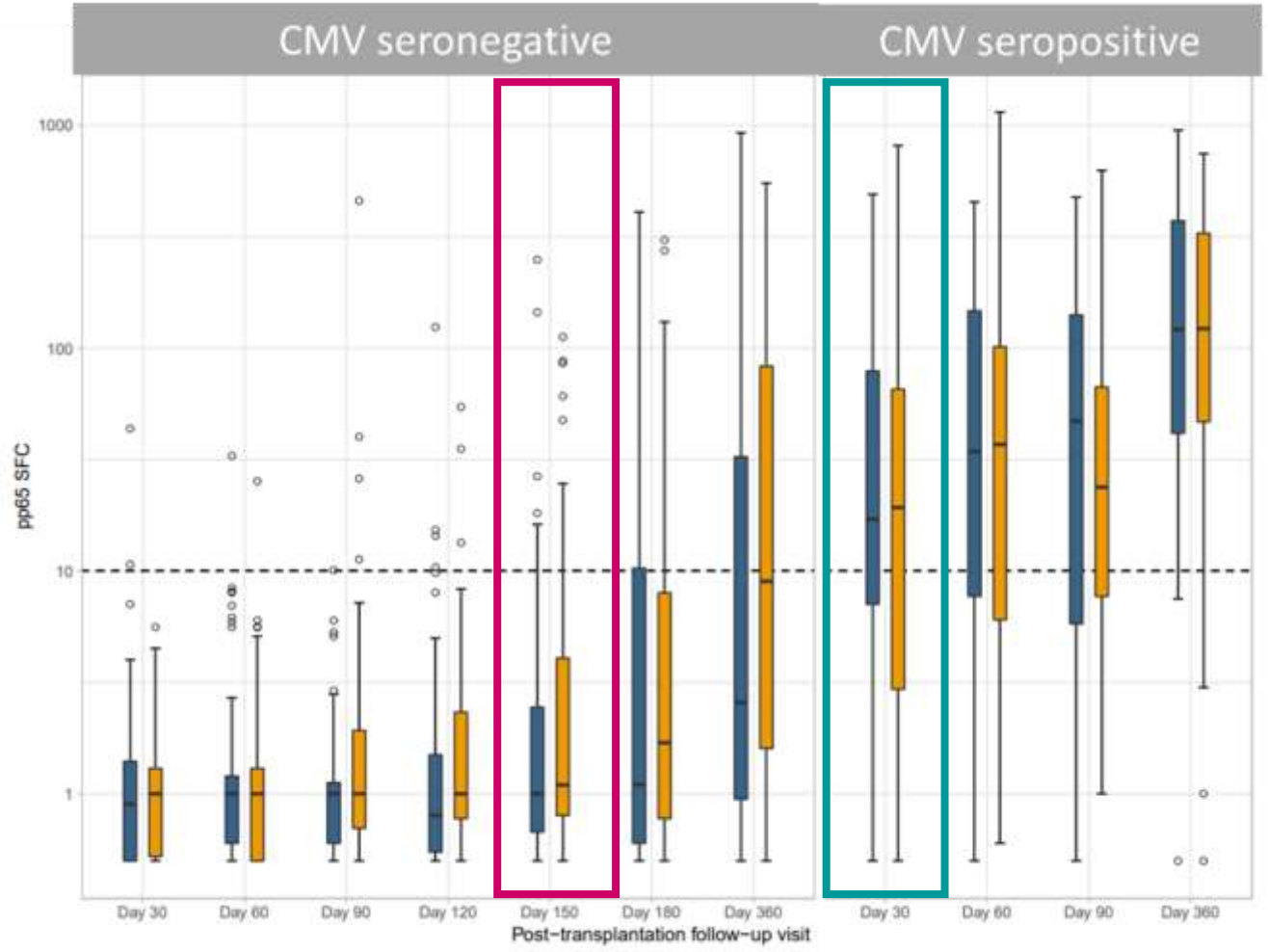


SWISS TRANSPLANT COHORT STUDY

Laager et al. Unpublished data

- Results of the Elispot-CMV according to CMV serostatus

23% of positive assays at 5 months



70% of positive assays at 1 month

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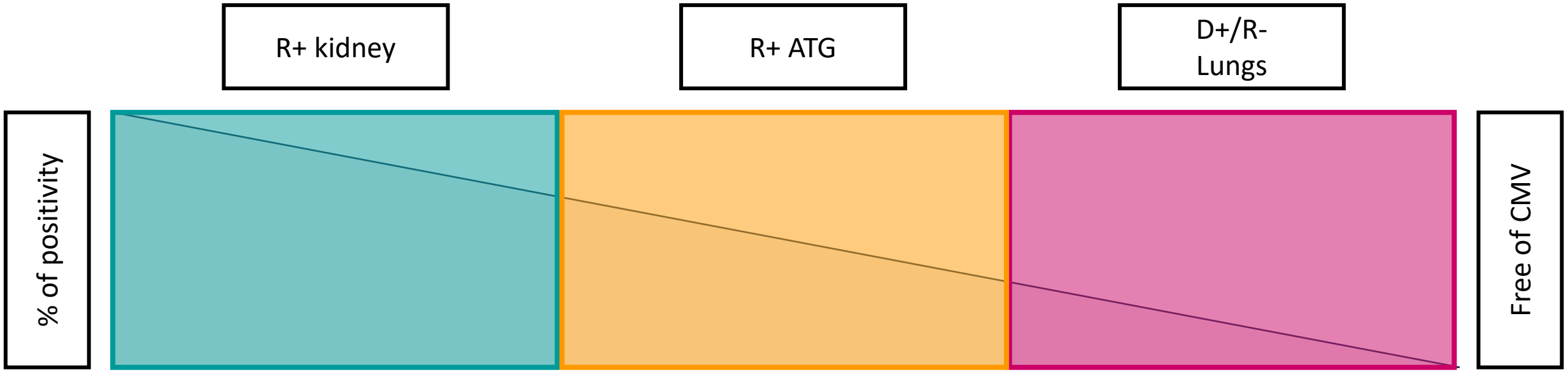
Cell-mediated immune assays

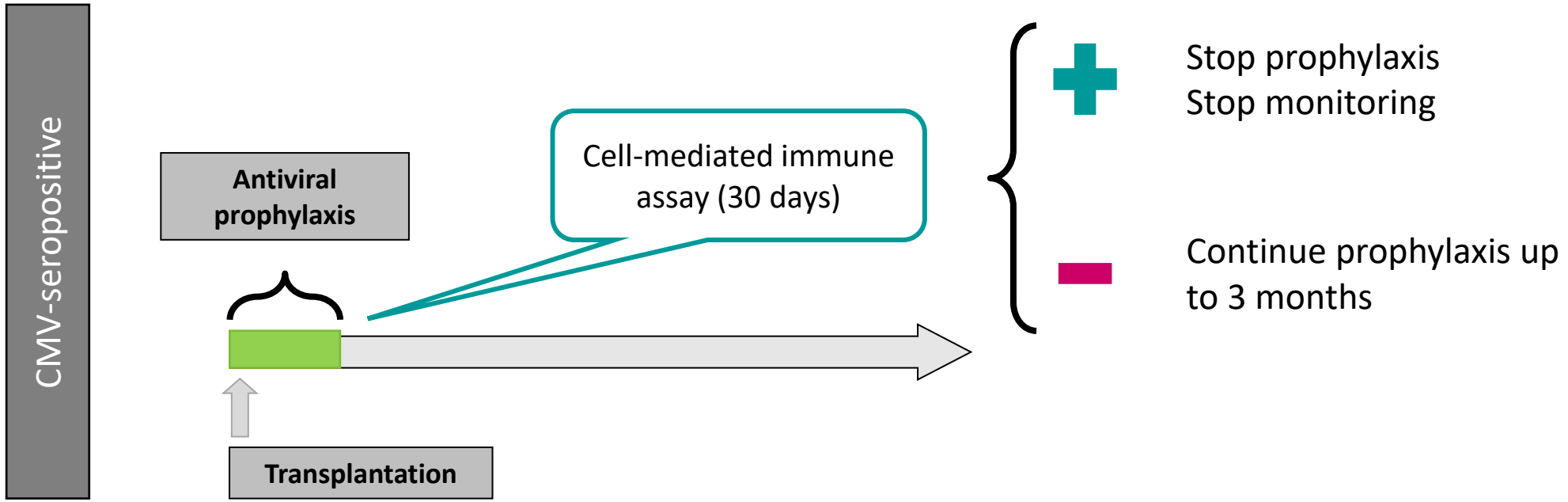
\+ High positive predictive value

\- Low positive predictive value

→ When positive, identify patients at low risk for subsequent CMV events



- Implement-CMV study



Barriers for the implementation in the routine clinical practice

- More intervention data is needed
  - Different clinical scenarios
  - Elispot vs. Quantiferon-CMV
  - Different outcomes (CMV infection/disease)
  - Different transplant populations

Conclusions

- Cell-mediated immune assays predict the risk of CMV replication in different clinical scenarios
  - Good positive predictive value, but positivity decrease in high-risk groups
- Interventional data suggest that the best impact is in R+ patients receiving ATG
- Data on D+/R- patients is inconclusive: large number of patients with a negative result will not develop CMV infection
- More data!

- Acknowledgements

STCS

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