

Les prises en charges de demain du CMV : immunomonitoring et immunothérapie

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CMV infections in Solid-organ Transplant recipients (SOTR)

10-20% of SOTR

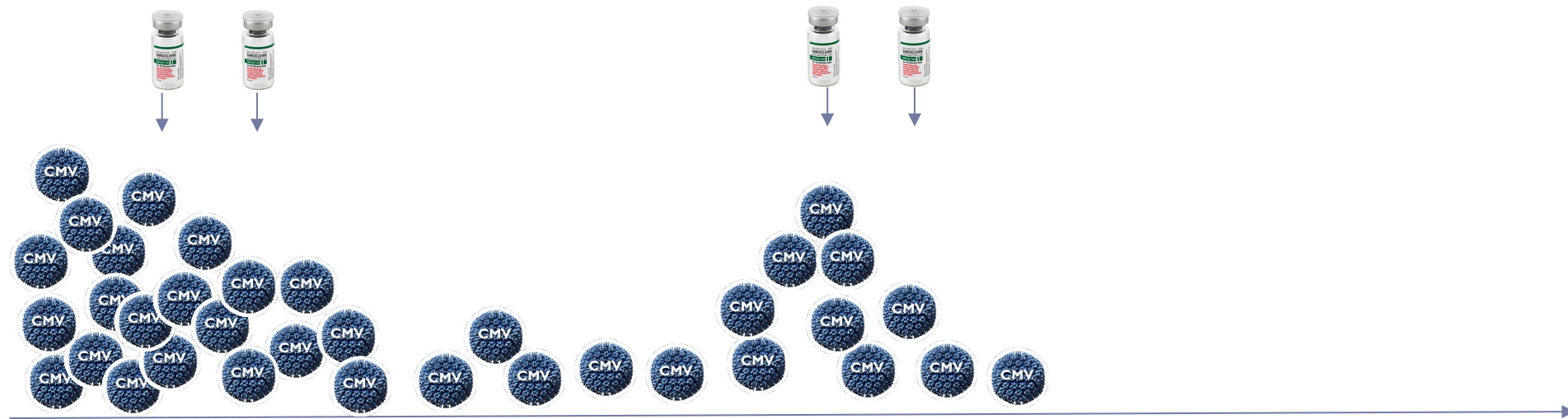


Difficult-to-treat CMV infections



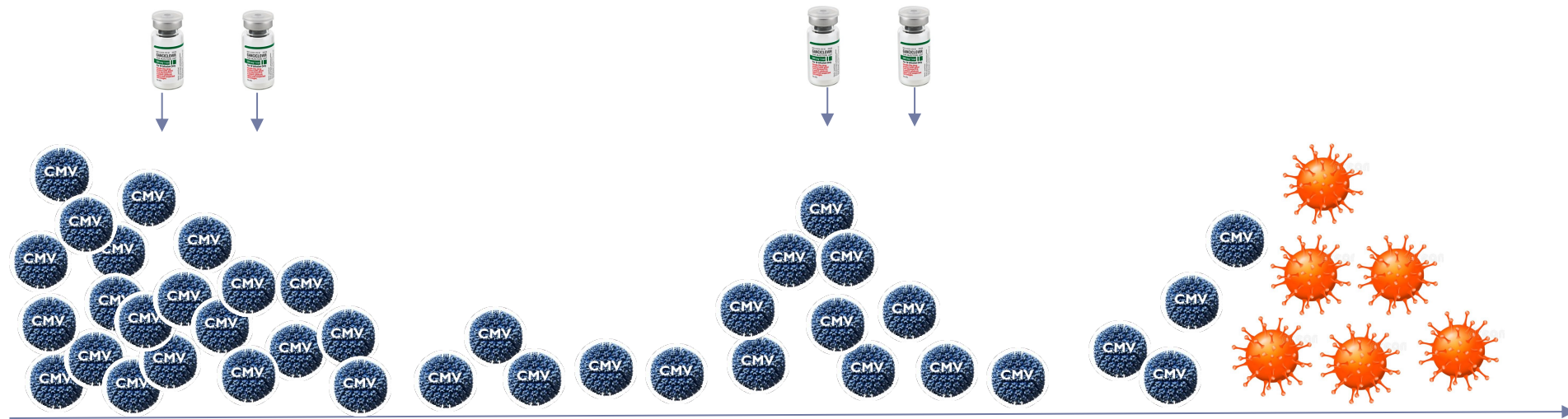
**Persistent CMV infections
(20%)**

Difficult-to-treat CMV infections



**Recurrent CMV infections
(15%)**

Difficult-to-treat CMV infections



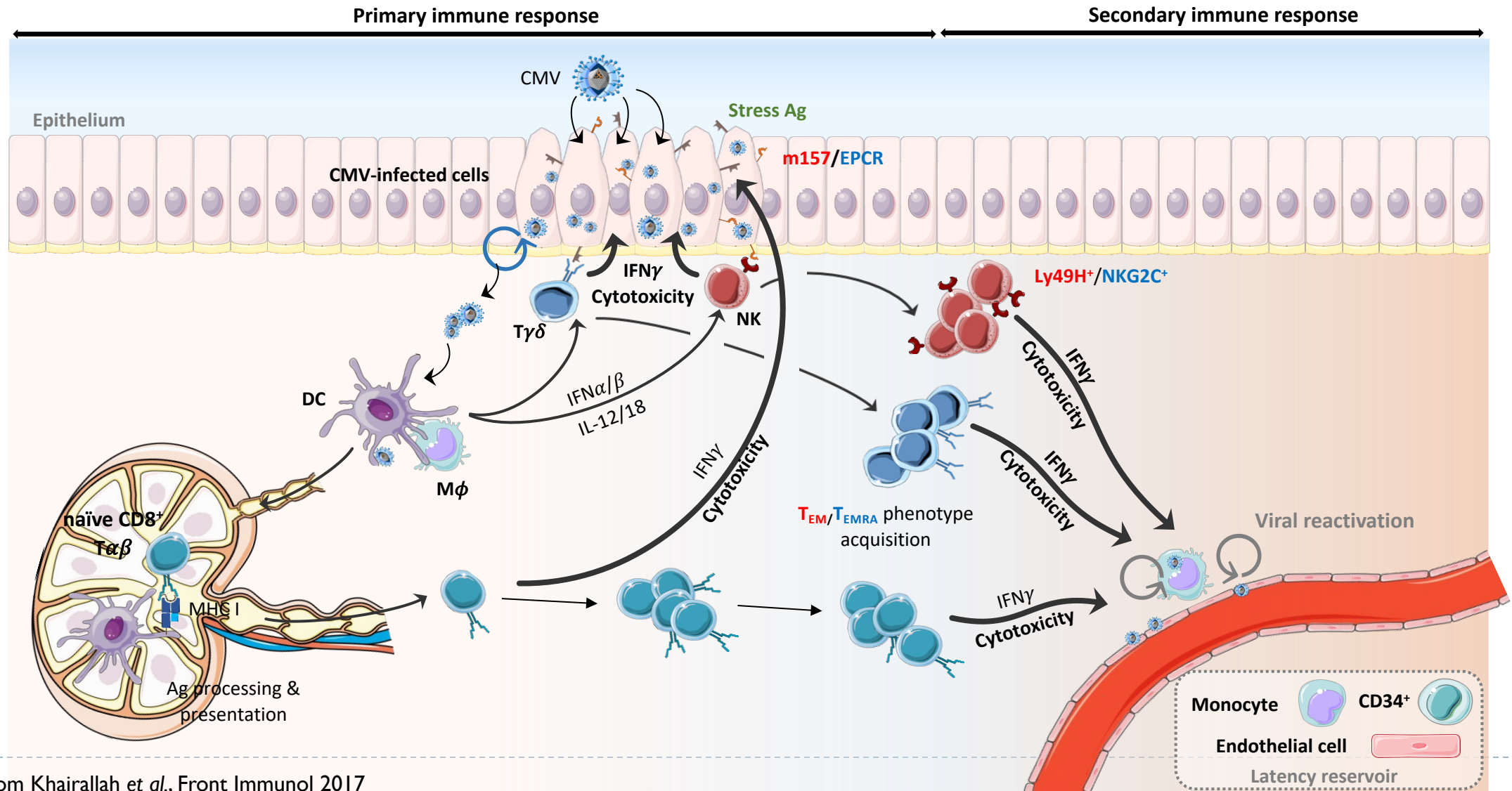
**Antiviral drug resistant
CMV infections
(5%)**

Unmet needs in the field of CMV infection

- Better **prevention strategies**
- Better **safety of treatments**
- Better **second-line therapies** for persistent or recurrent CMV infection

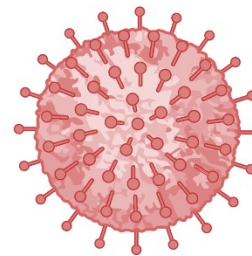
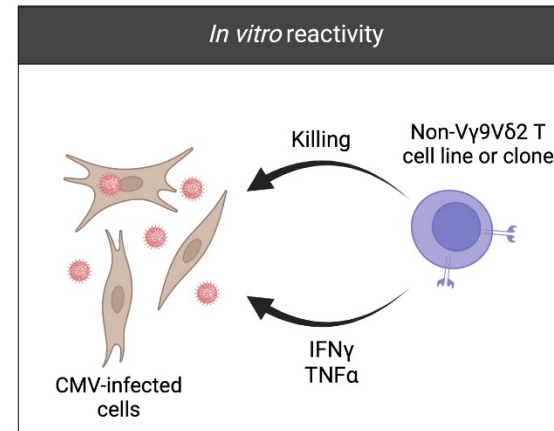
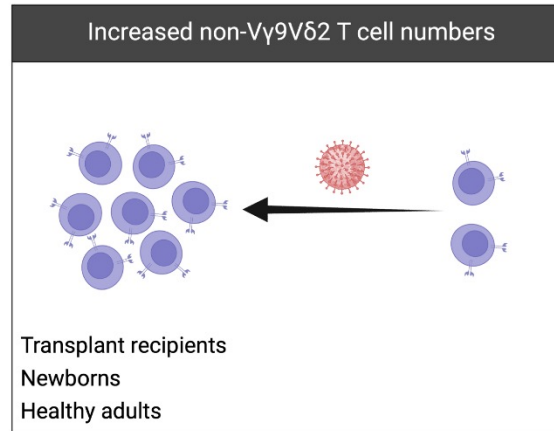


Anti-CMV cellular immune response

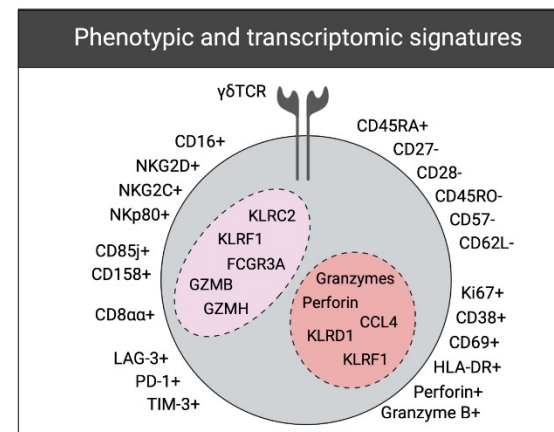
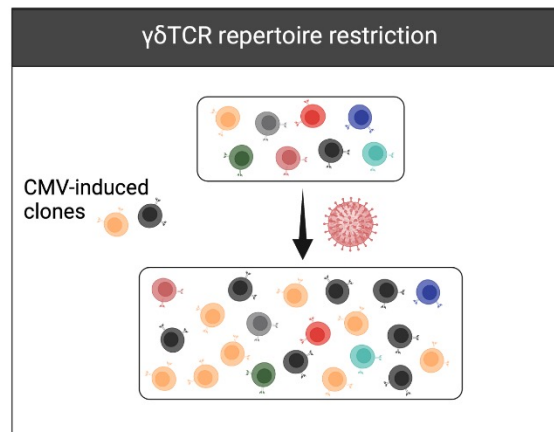




$\gamma\delta$ T cells involvement in the anti-CMV immune response



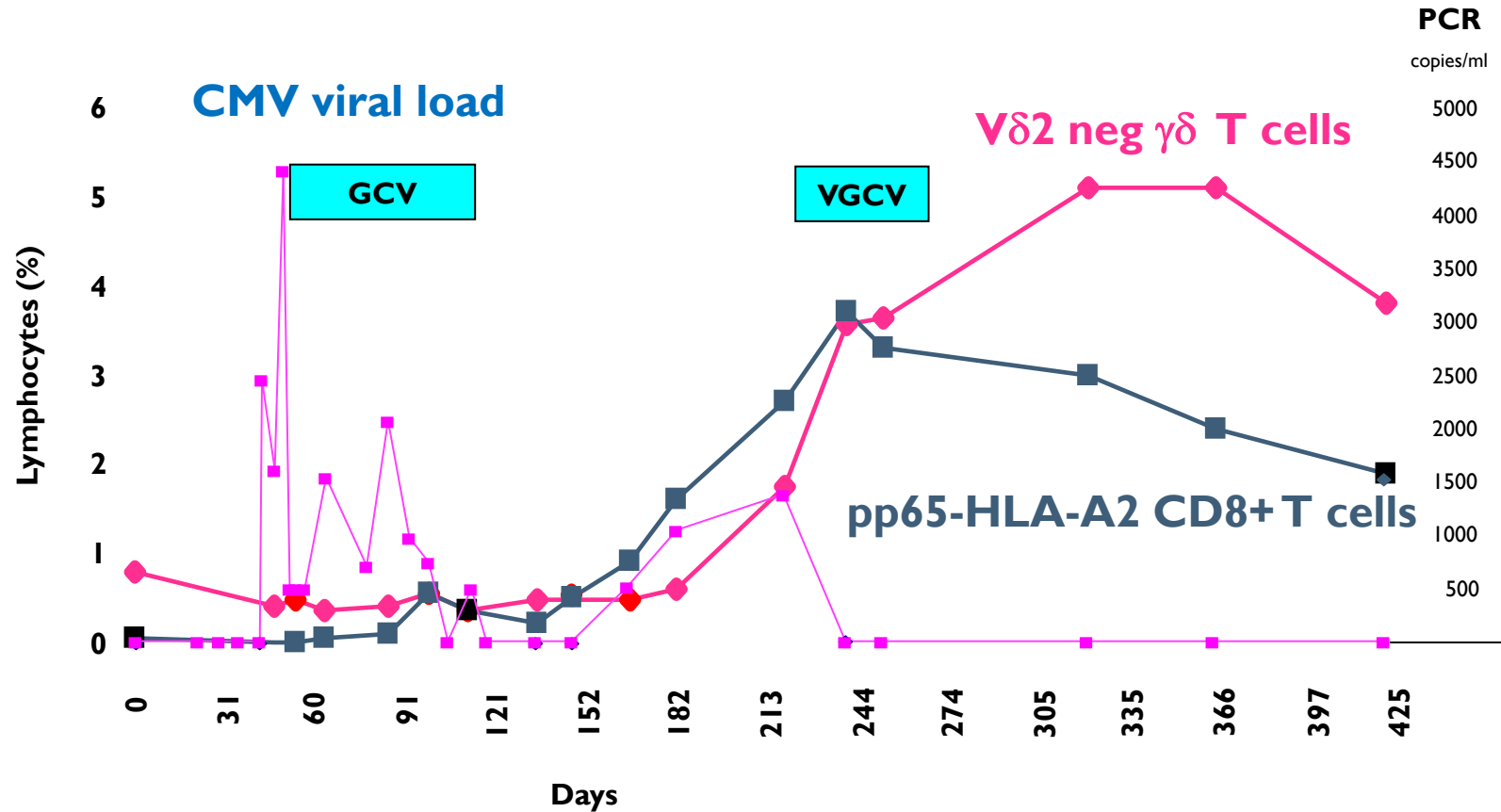
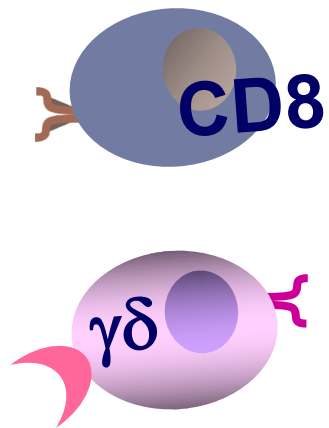
CMV infection



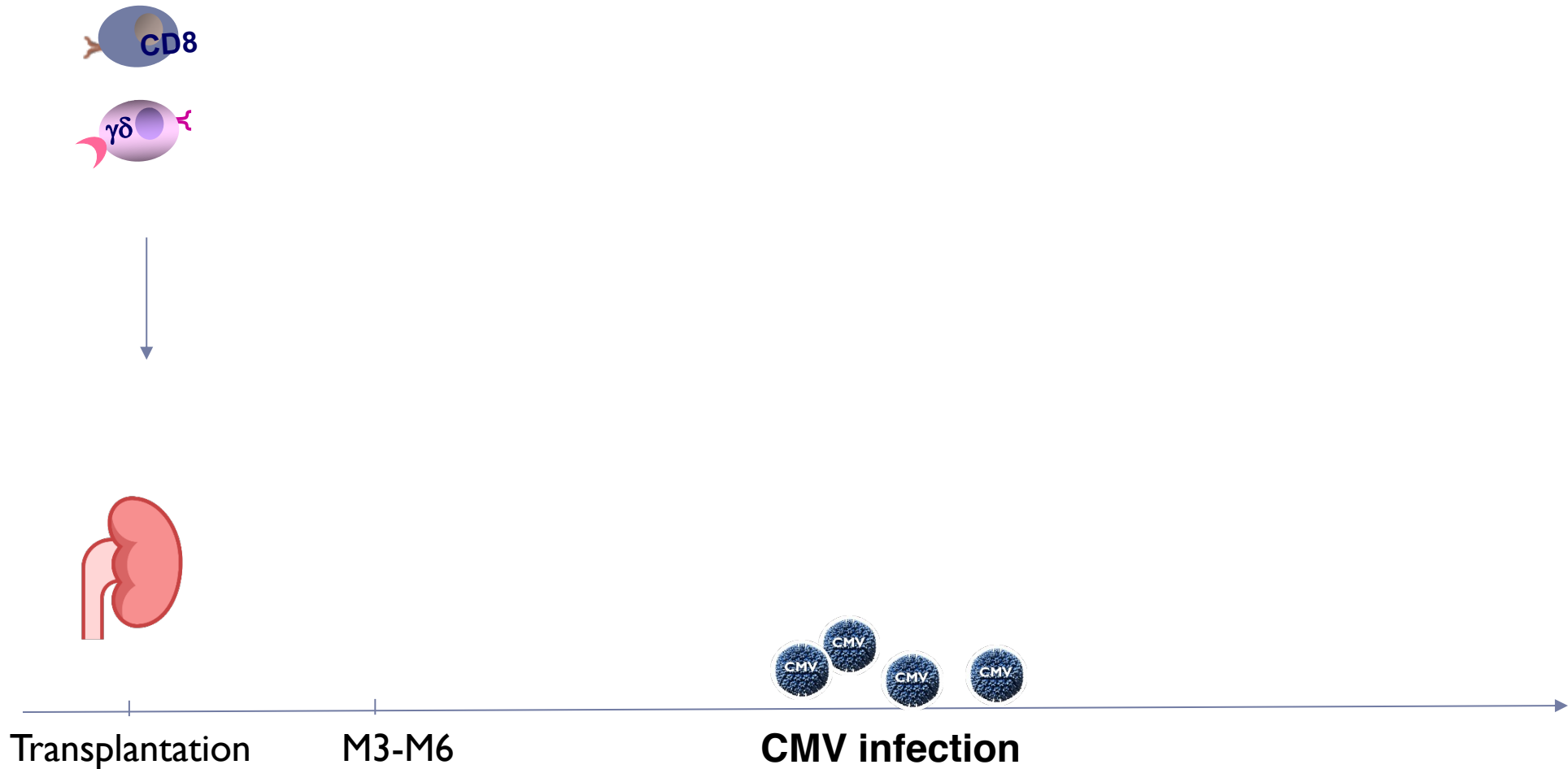
- Upregulated on non-V γ 9V δ 2 cells compared to V γ 9V δ 2 cells
- Upregulated on TEMRA versus naive non-V γ 9V δ 2 cells (CMV+ individual)



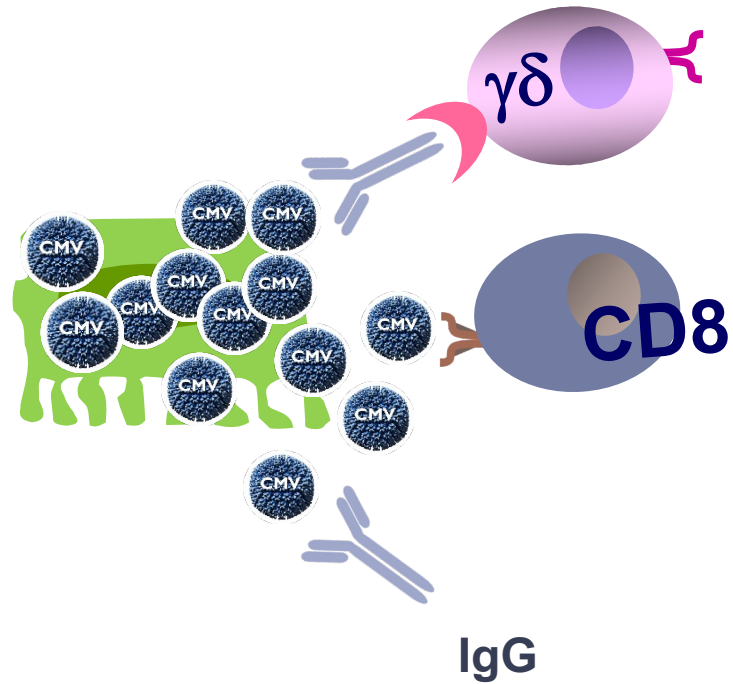
Kinetic of CMV-specific $\gamma\delta$ T cells after a resolutive infection



Anti-CMV immune response and prediction of CMV



CMV immune response: How to use it in the management of SOTR ?

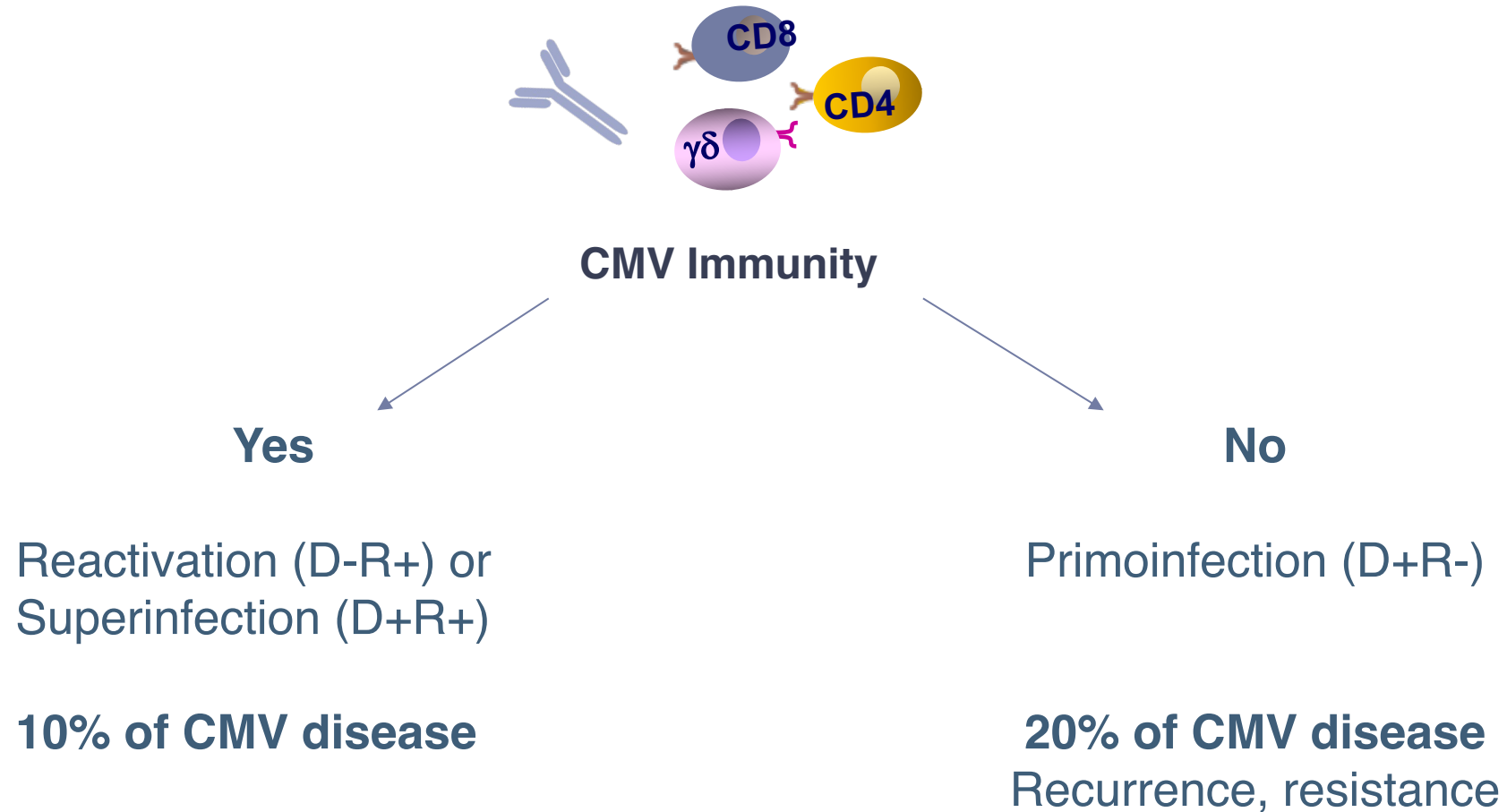


No CMV disease

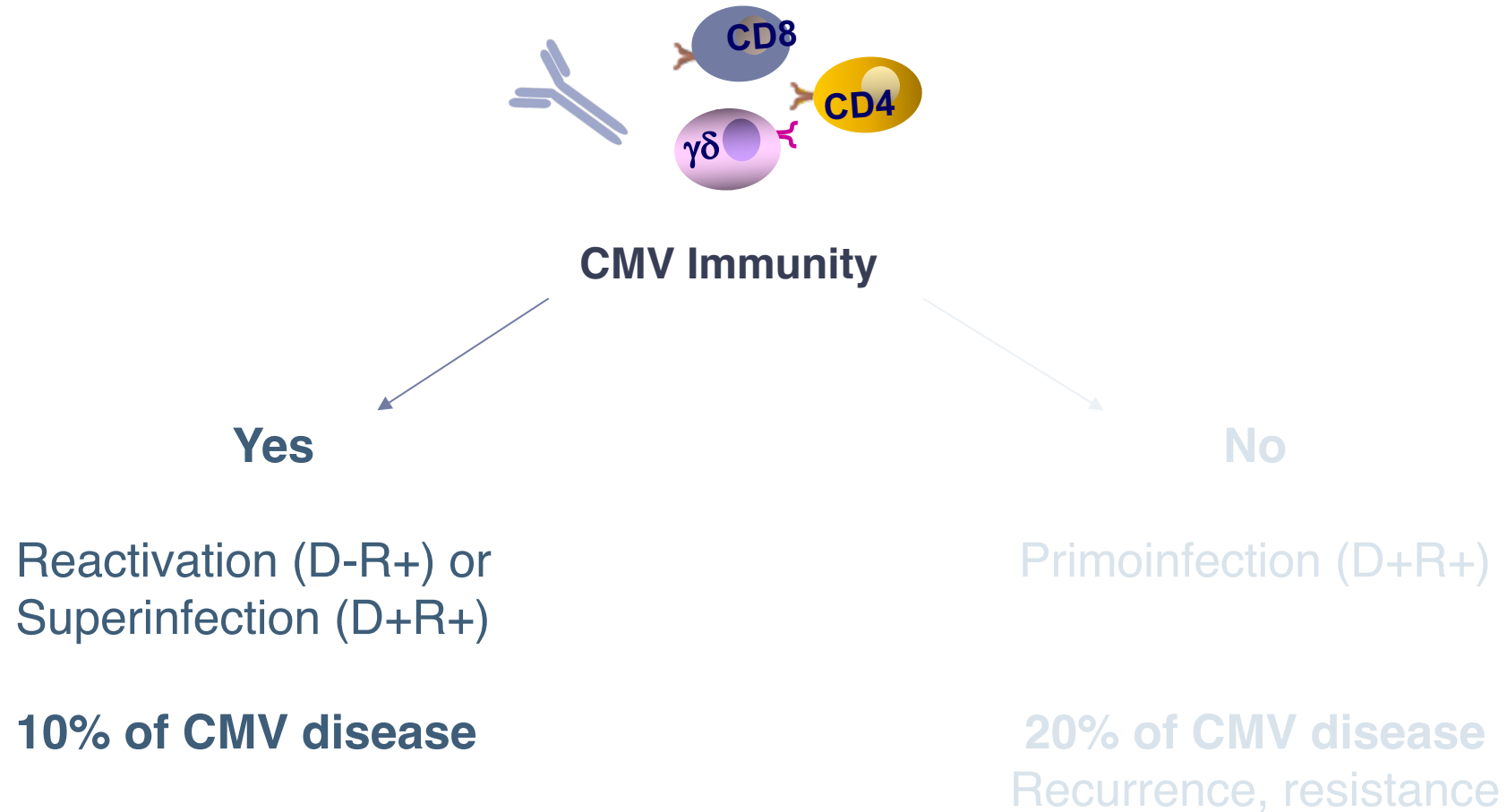


Dissemination and CMV disease

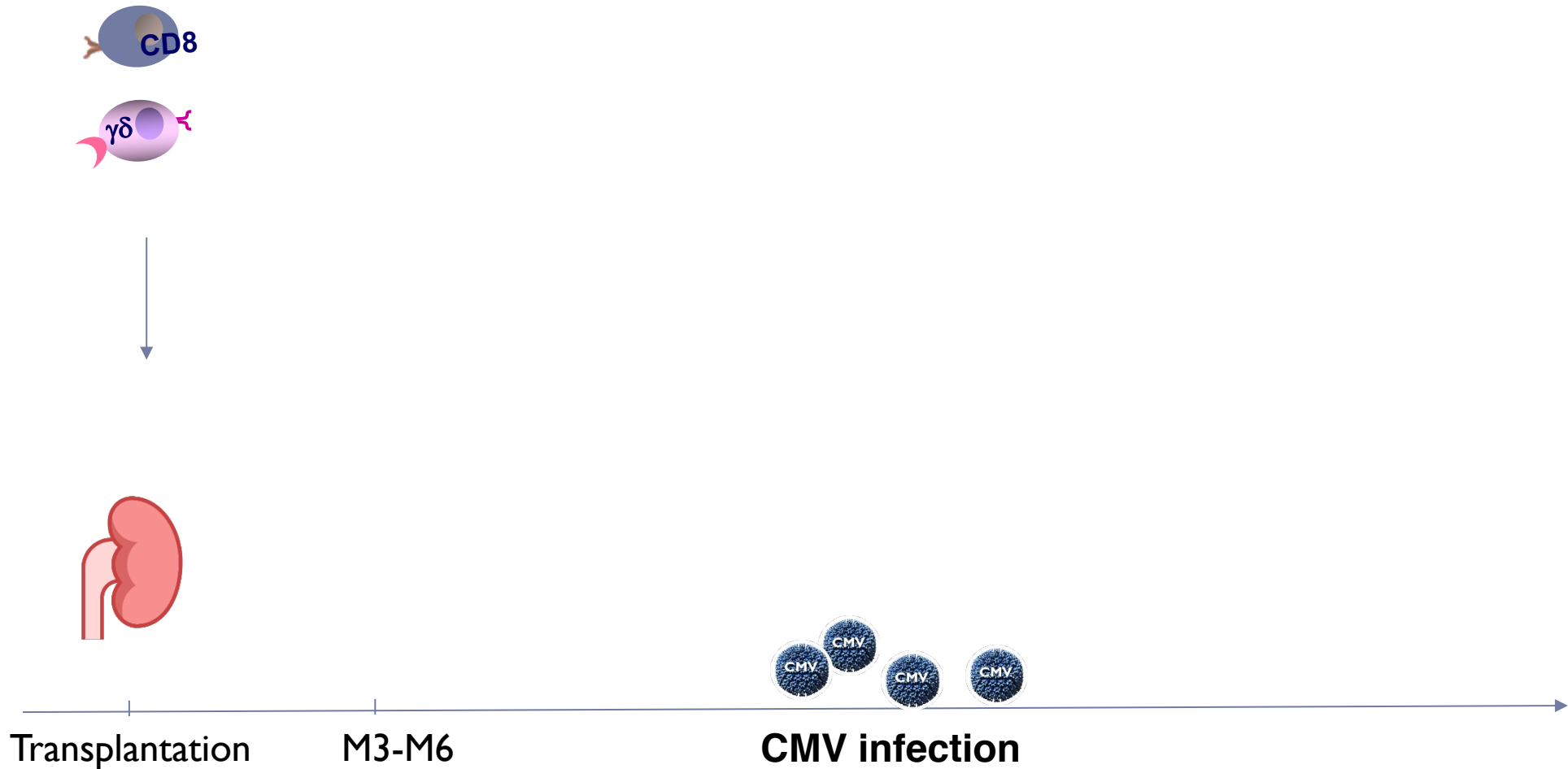
Risk of CMV in SOTR according to CMV immune response



Risk of CMV in SOTR according to CMV immune response

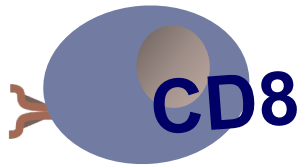


Anti-CMV immune response and prediction of CMV



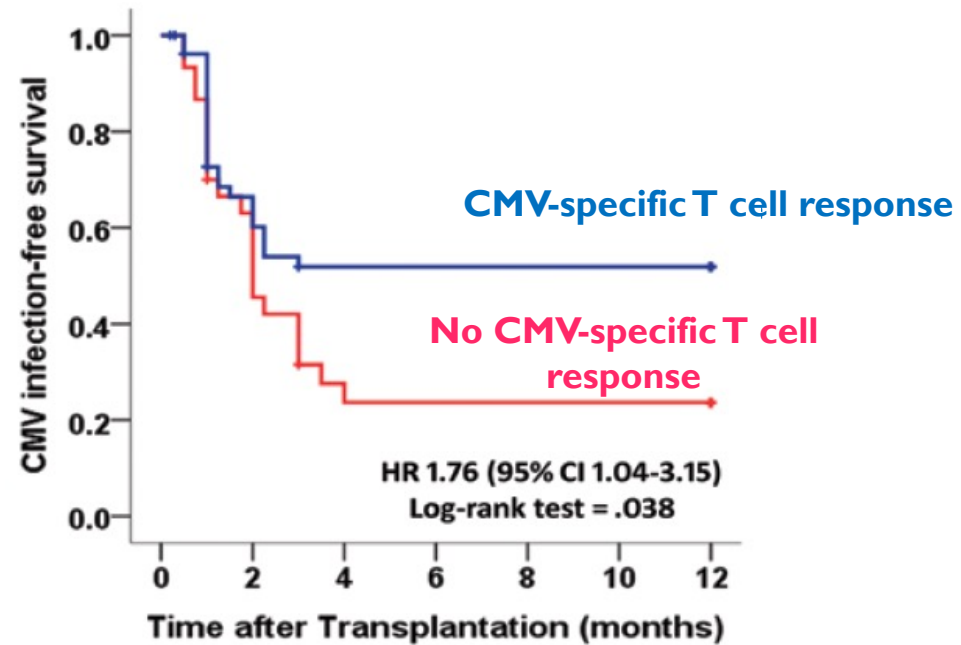
Cellular Immunity to Predict the Risk of CMV Infection in R+ Kidney Transplantation

Pretransplant



ELISPOT IE-I

Preemptive strategy



High-Risk (n)	30	13	6	6	6	6	6
Event-Free (n)	30	14	8	8	8	8	8
Low-Risk (n)	54	29	24	24	24	24	24
Event-Free (n)	54	34	30	30	30	30	30

Basiliximab-treated patient

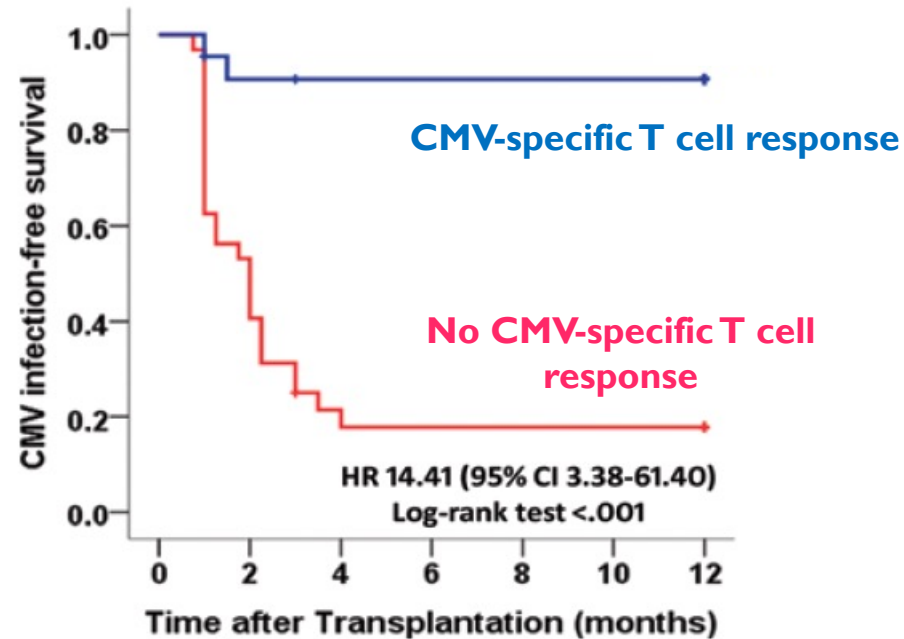
Cellular Immunity to Predict the Risk of CMV Infection in R+ Kidney Transplantation

15 days post-transplant



ELISPOT IE-I

Preemptive strategy



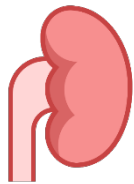
High-Risk (n)	32	13	5	5	5	5	5
Event-Free (n)	32	13	6	6	6	6	6
Low-Risk (n)	22	19	18	18	18	18	18
Event-Free (n)	22	20	20	20	20	20	20

Basiliximab-treated patient

Anti-CMV immune response and prediction of CMV



Valganciclovir prophylaxis



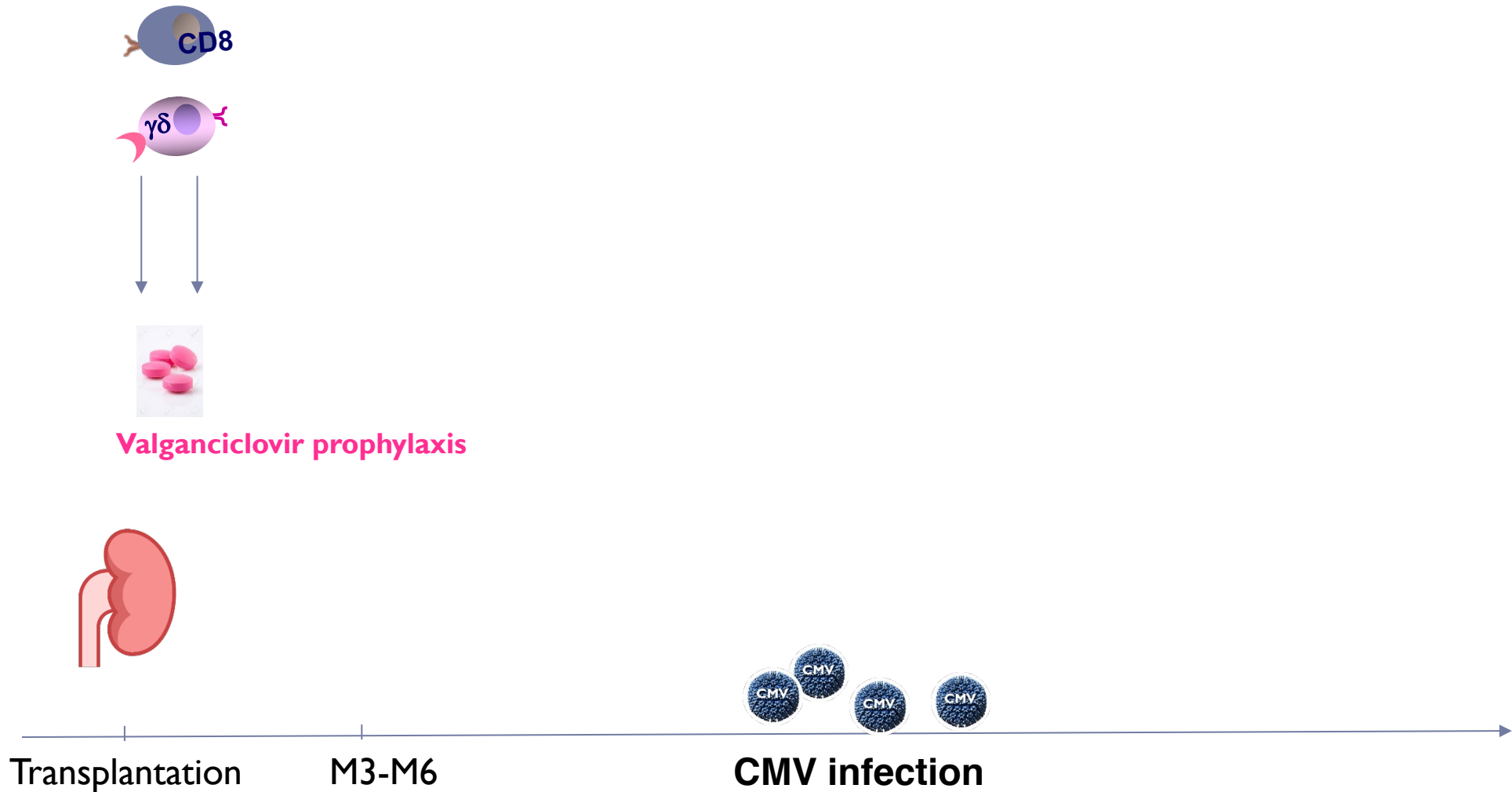
Transplantation

M3-M6

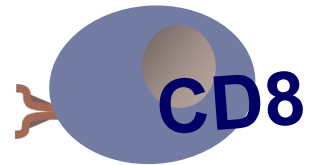
CMV infection



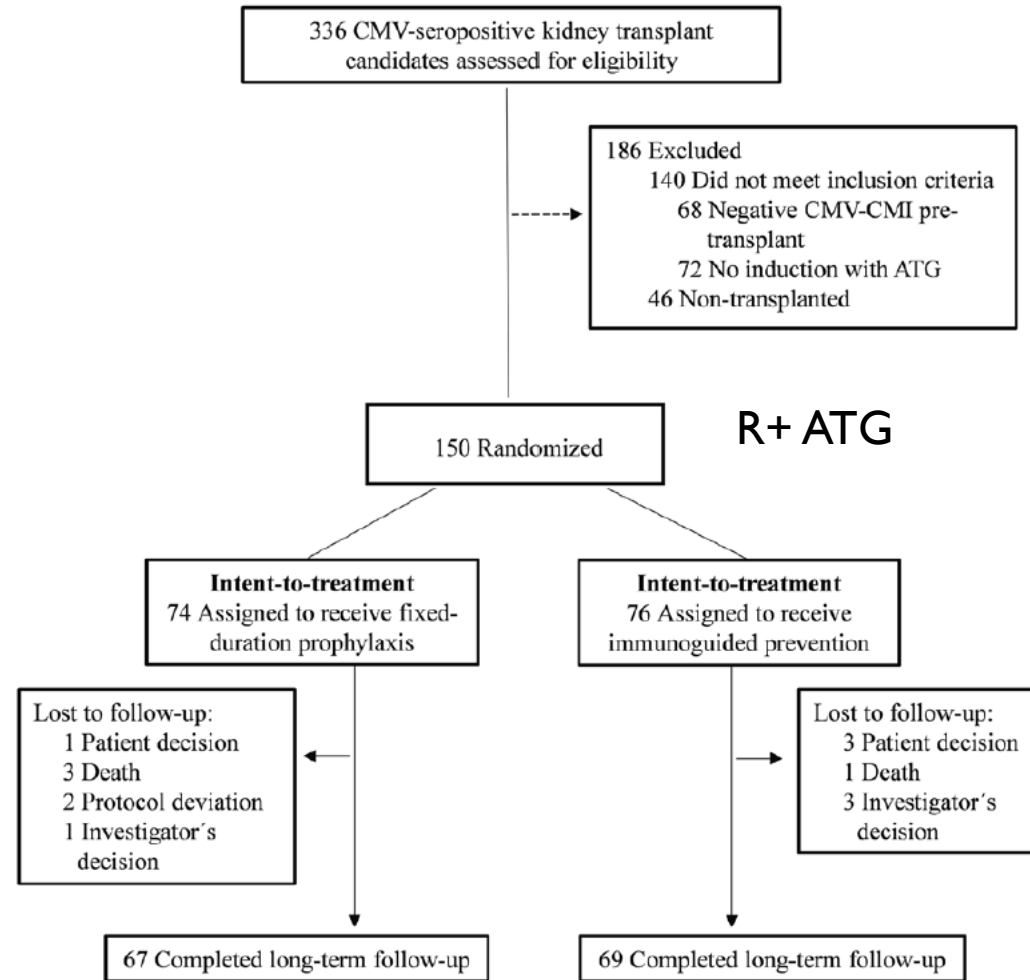
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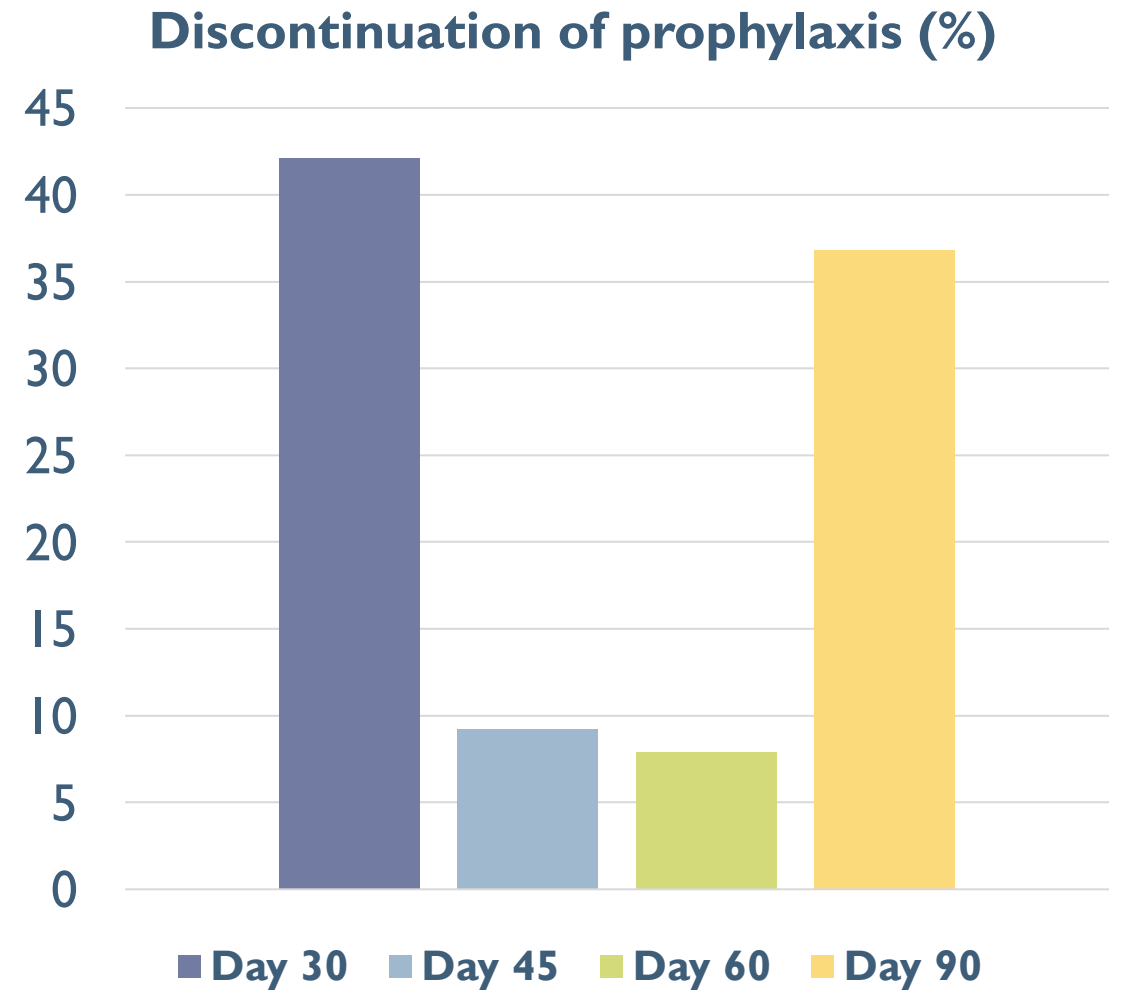
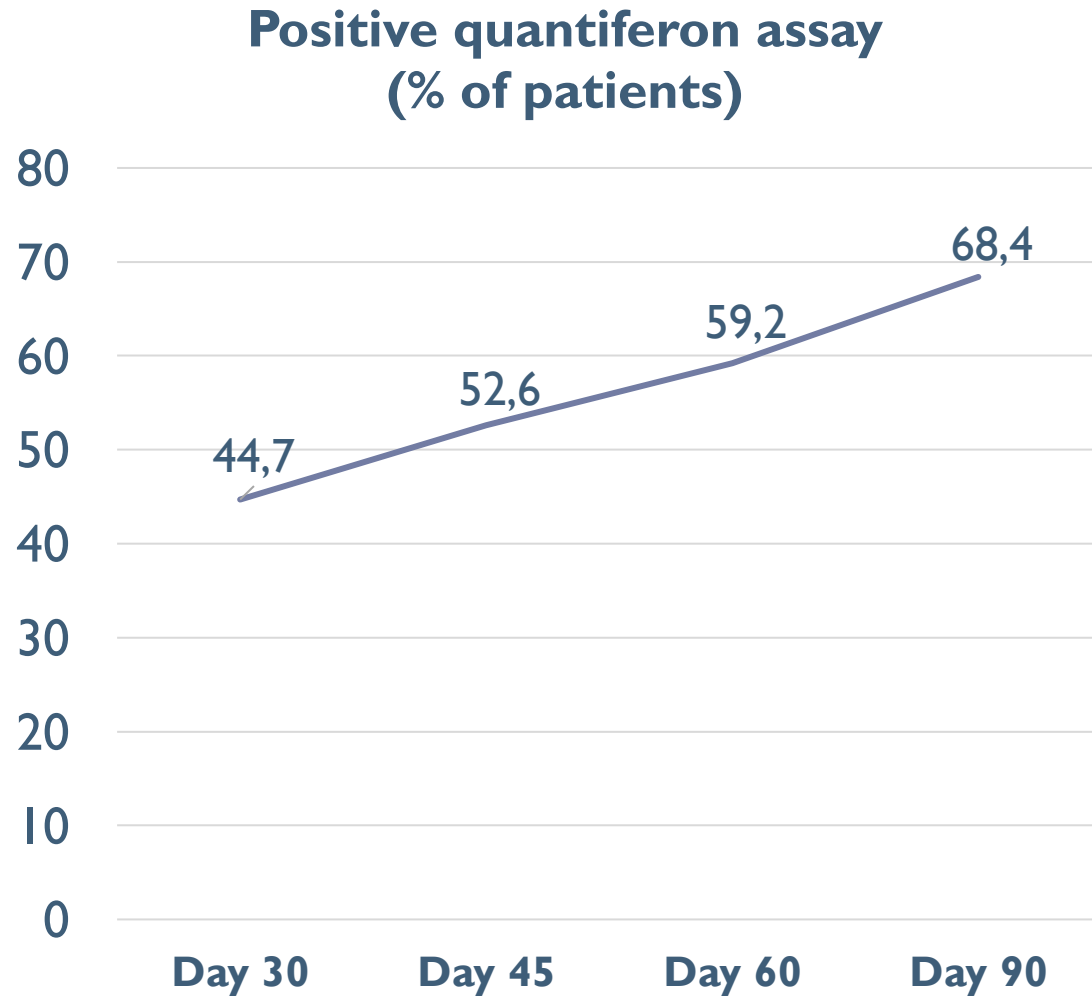
Immunoguided Discontinuation of Prophylaxis



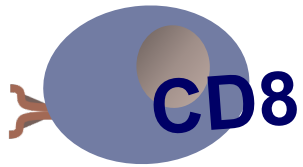
Quantiferon CMV



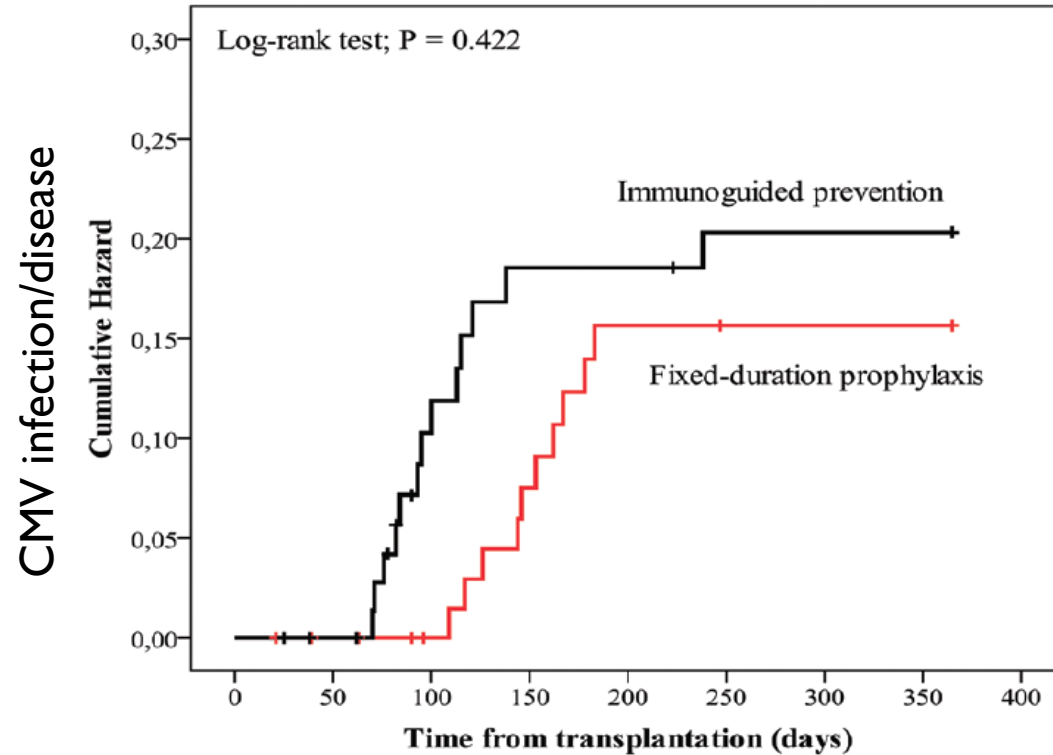
Immunoguided Discontinuation of Prophylaxis



Immunoguided Discontinuation of Prophylaxis



Quantiferon CMV



Number at risk

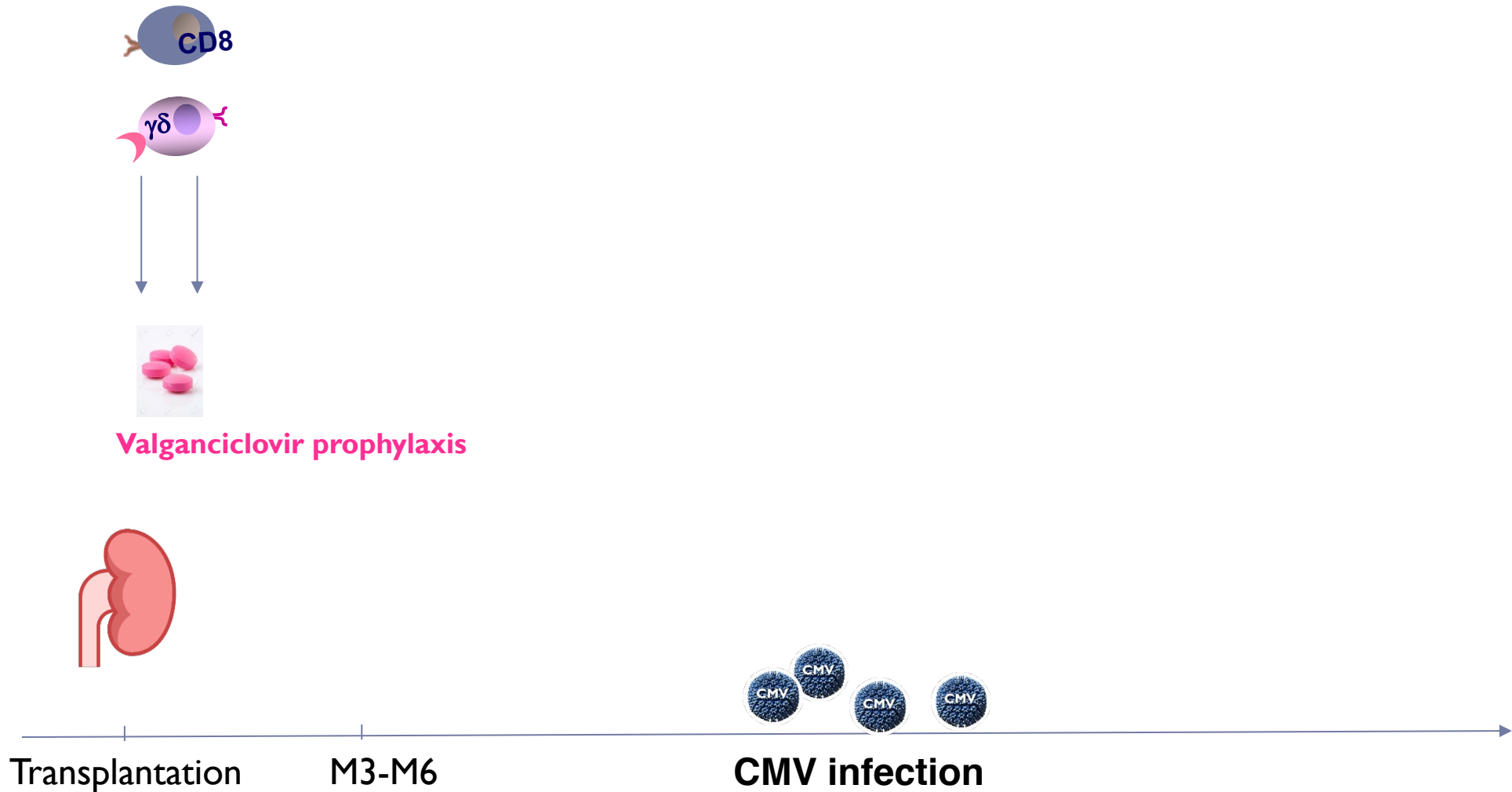
Immunoguided prevention	76	74	62	58	58	56	56	56
Fixed-duration prophylaxis	74	72	69	64	59	58	58	58

Immunoguided Discontinuation of Prophylaxis

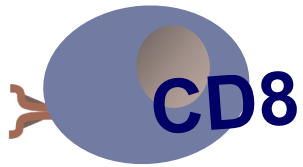
Adverse events	Immunoguided Prevention (n = 76)	Fixed-Duration Prophylaxis (n = 74)	PValue ^a
Overview of safety			
Patients with any adverse event	44 (57.9)	51 (68.9)	.161
Patients with serious adverse events	14 (18.4)	18 (24.3)	.378
All-cause mortality at 12 months	1 (1.3)	3 (4.1)	.363
Common adverse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



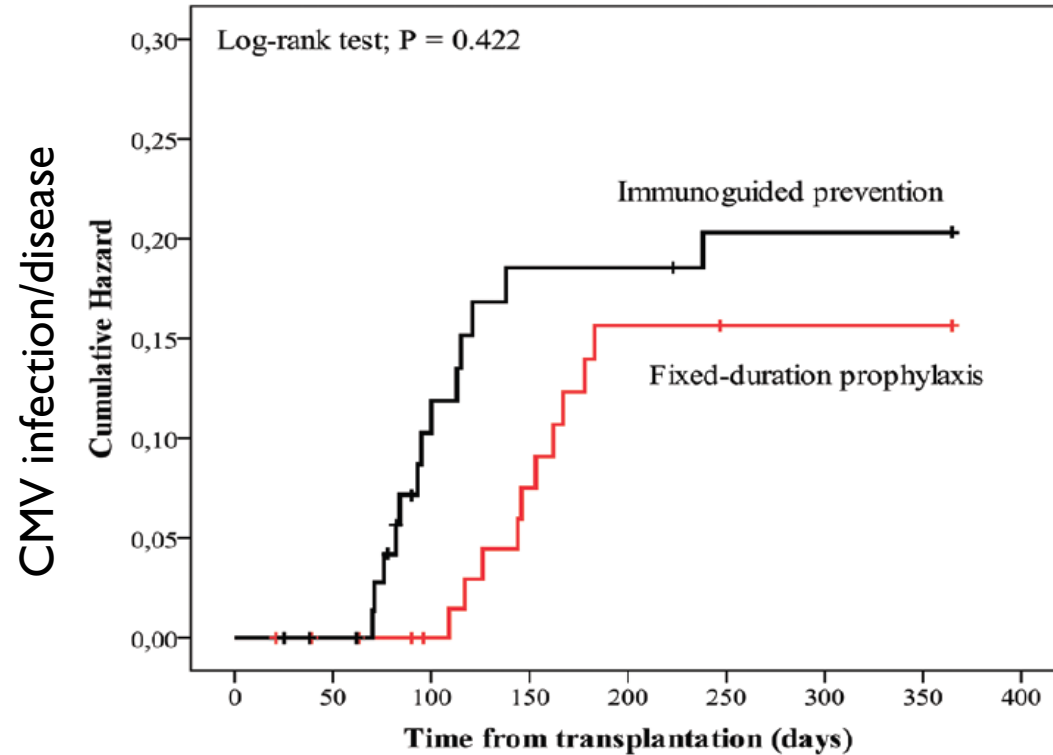
Anti-CMV immune response and prediction of CMV



Immunoguided Discontinuation of Prophylaxis



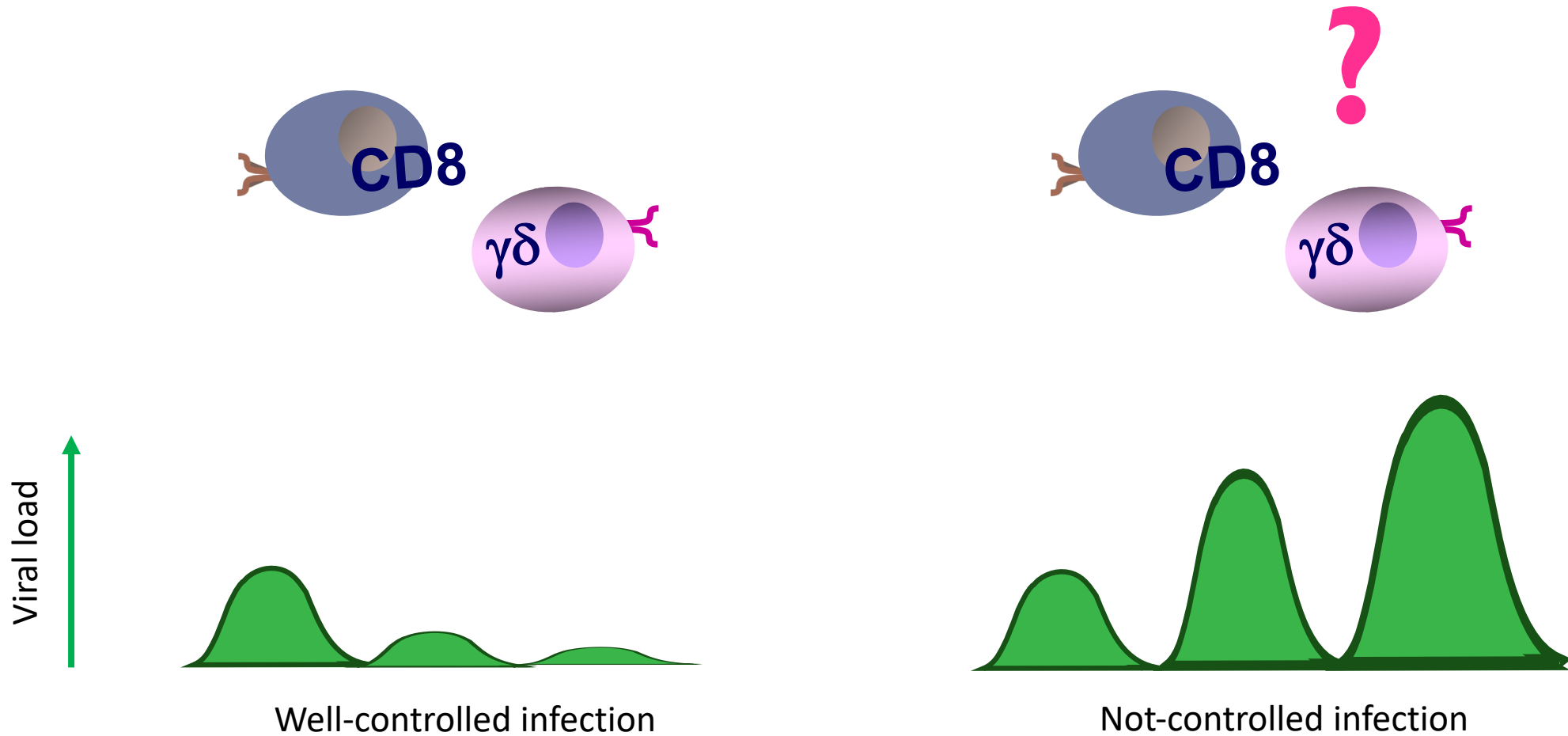
Quantiferon CMV



Number at risk

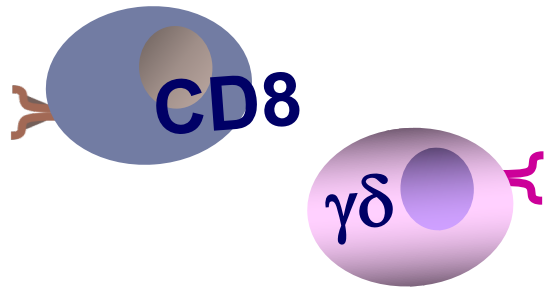
Immunoguided prevention	76	74	62	58	58	56	56	56
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Two functional situations of TEMRA cells in immunocompromised CMV-seropositive hosts

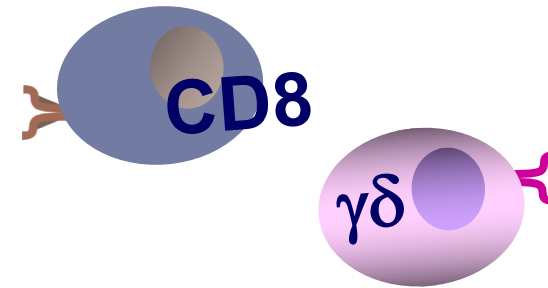


Two functional situations of TEMRA cells in immunocompromised CMV-seropositive hosts

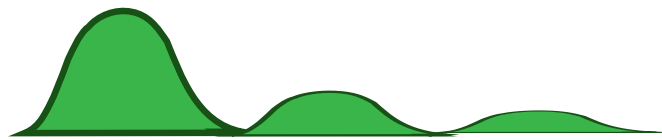
Functional T cells



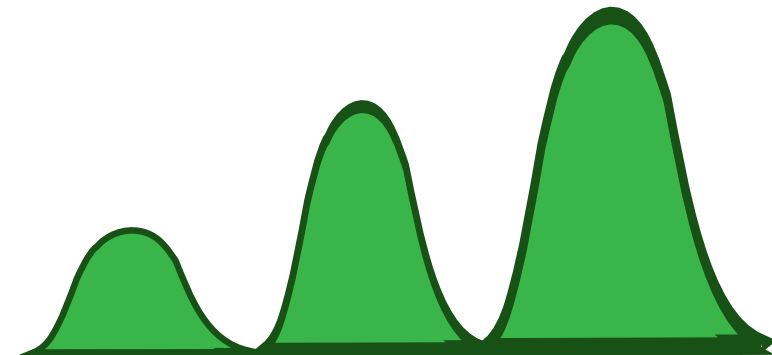
Dysfunctional T cells



Viral load ↑

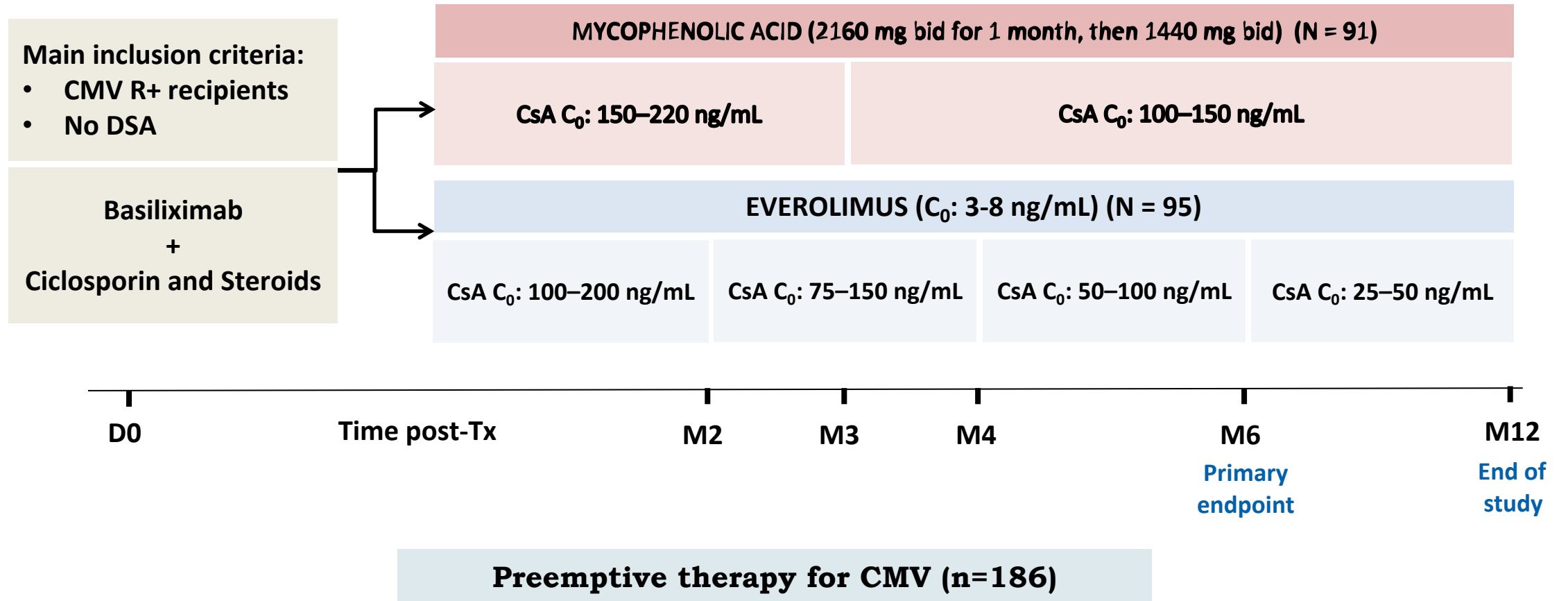


Well-controlled infection



Not-controlled infection

EVERCMV Study

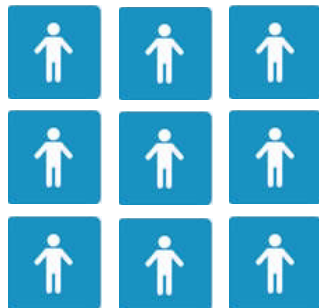


EVERCMV: Ancillary study

MPA



EVR

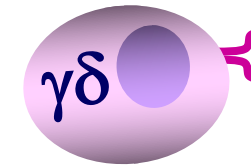
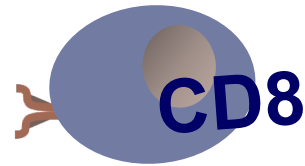


Transplantation

Follow-up

EVERCMV: Ancillary study

MPA



Dysfunctional T cells ?

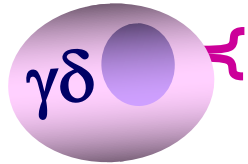
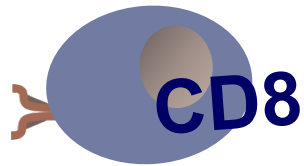


Transplantation

Follow-up

Phenotype of dysfunctional T cells

Dysfunctional T cells



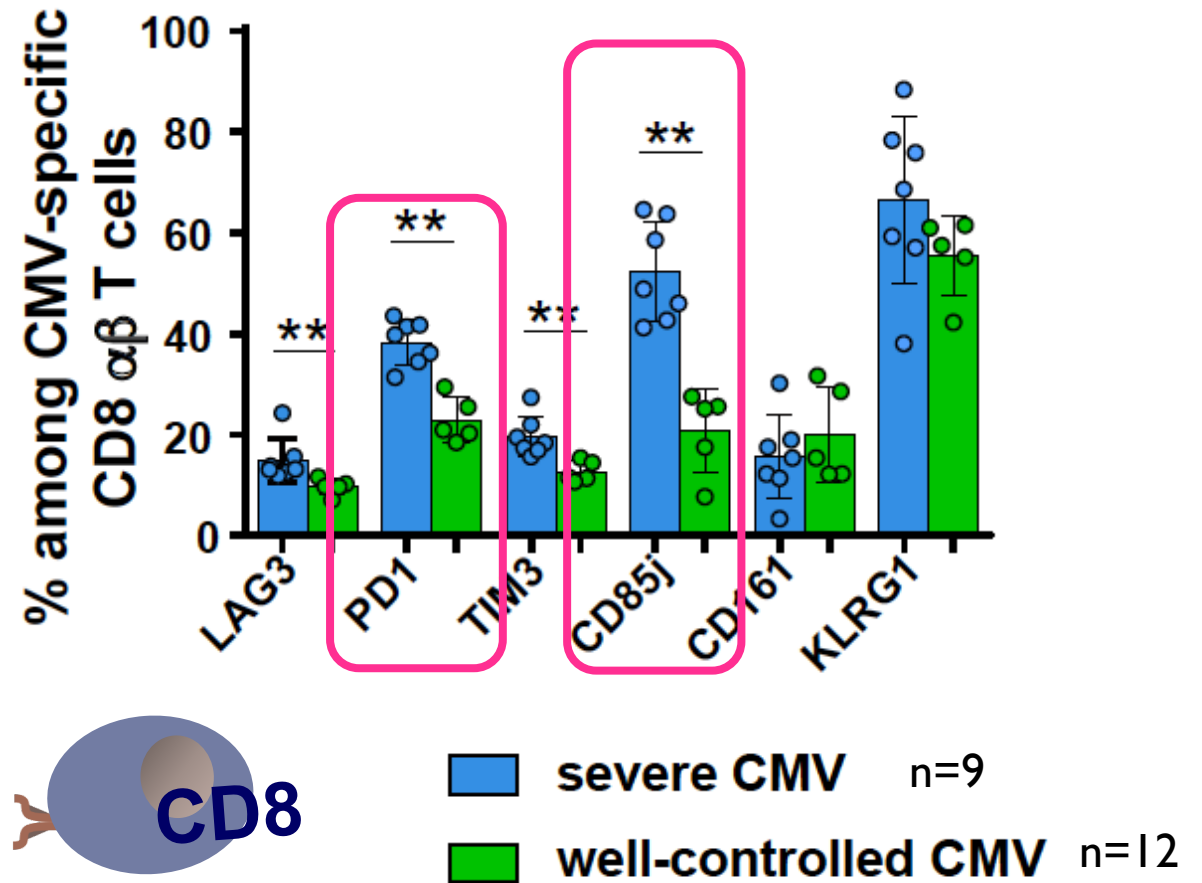
Molecules related to T cell dysfunction or displaying an immune checkpoint function :

- PD-1
- CD85j (ILT-2 or LILRB1)
- LAG-3
- TIM3
- KLRG1

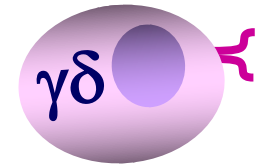
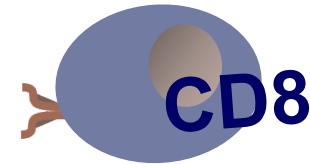


Molecules related to T cell dysfunction before Transplant

MPA



EVERCMV: Ancillary study

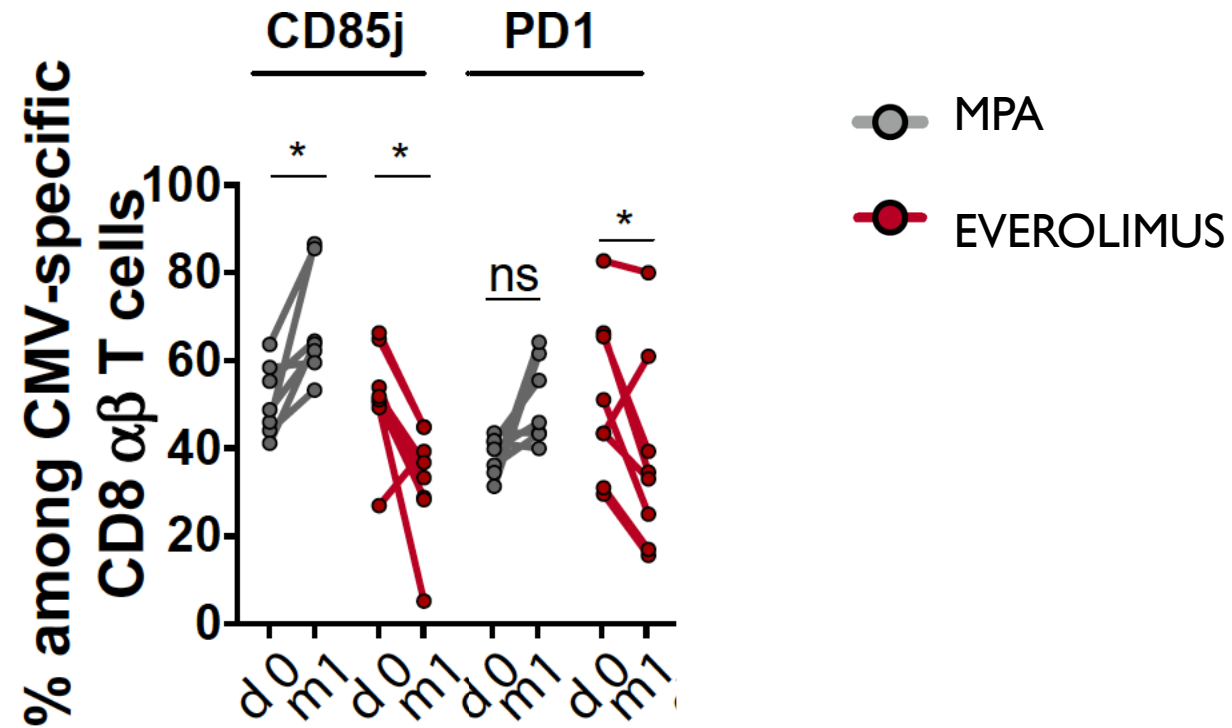
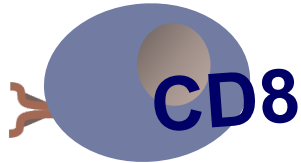


Dysfunctional T cells ?

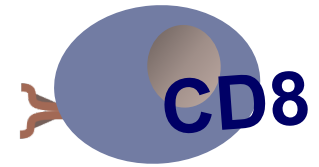
Transplantation

Follow-up

Everolimus decreases the proportion of CD85j+ and PD1+ T cells *in vivo*



EVERCMV: Ancillary study

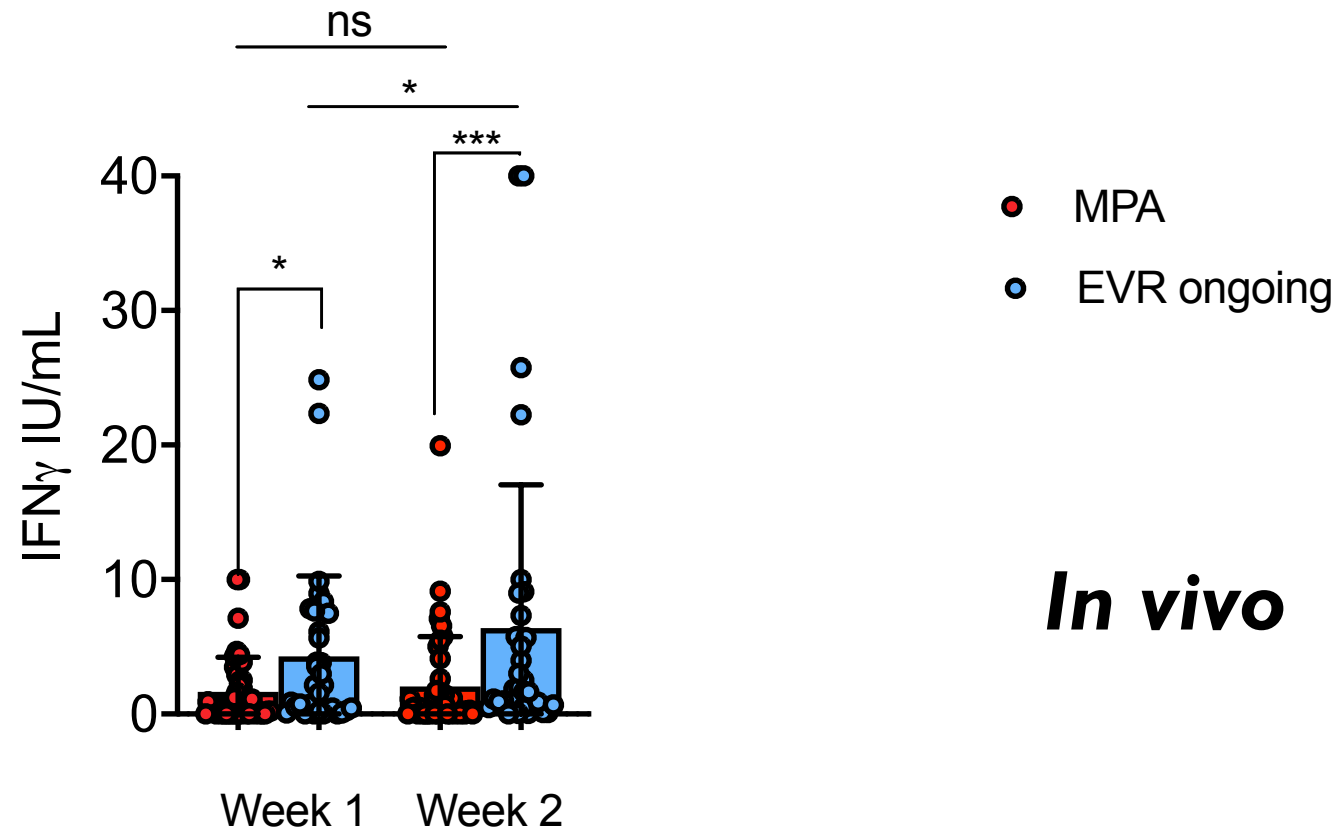
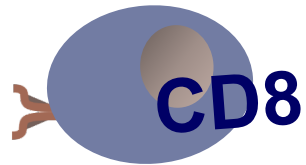


Gamma-interferon in
response to CMV

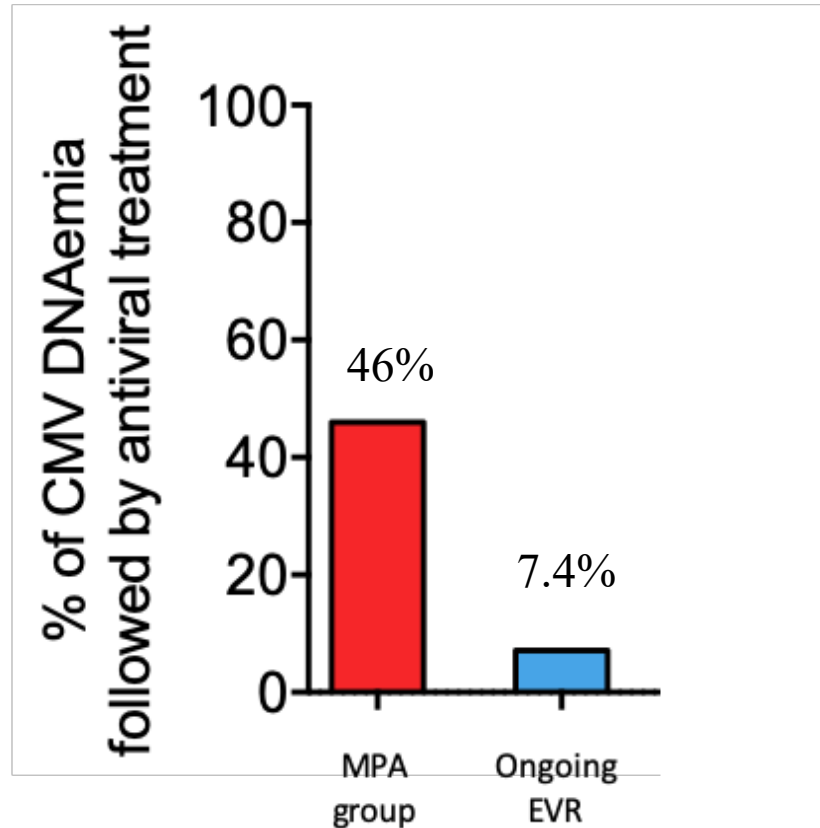
Transplantation

Follow-up

Gamma-interferon production by CMV-specific T cells increases rapidly after the initiation of Everolimus



CMV DNAemia requiring antiviral drug

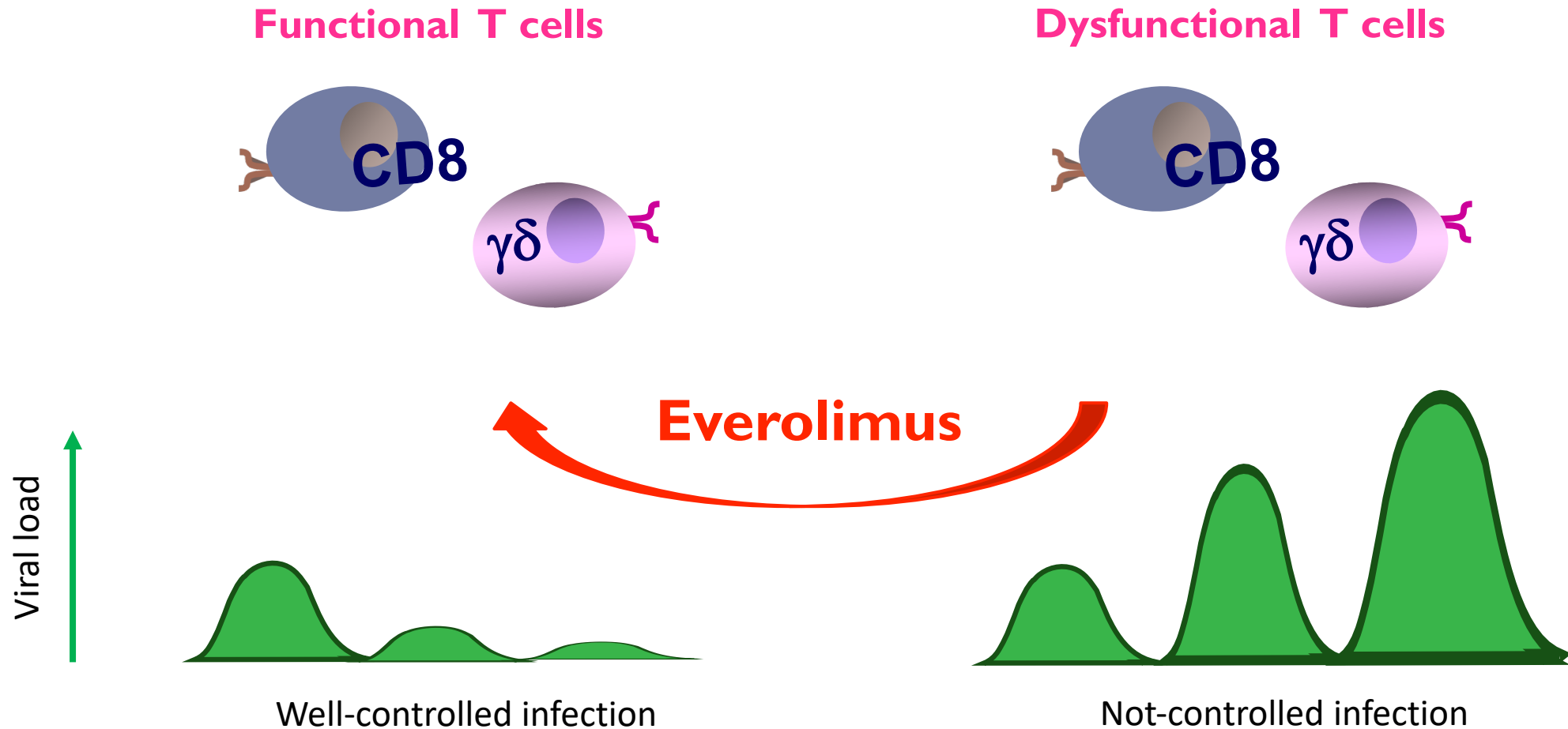


Patients with ongoing EVR treatment

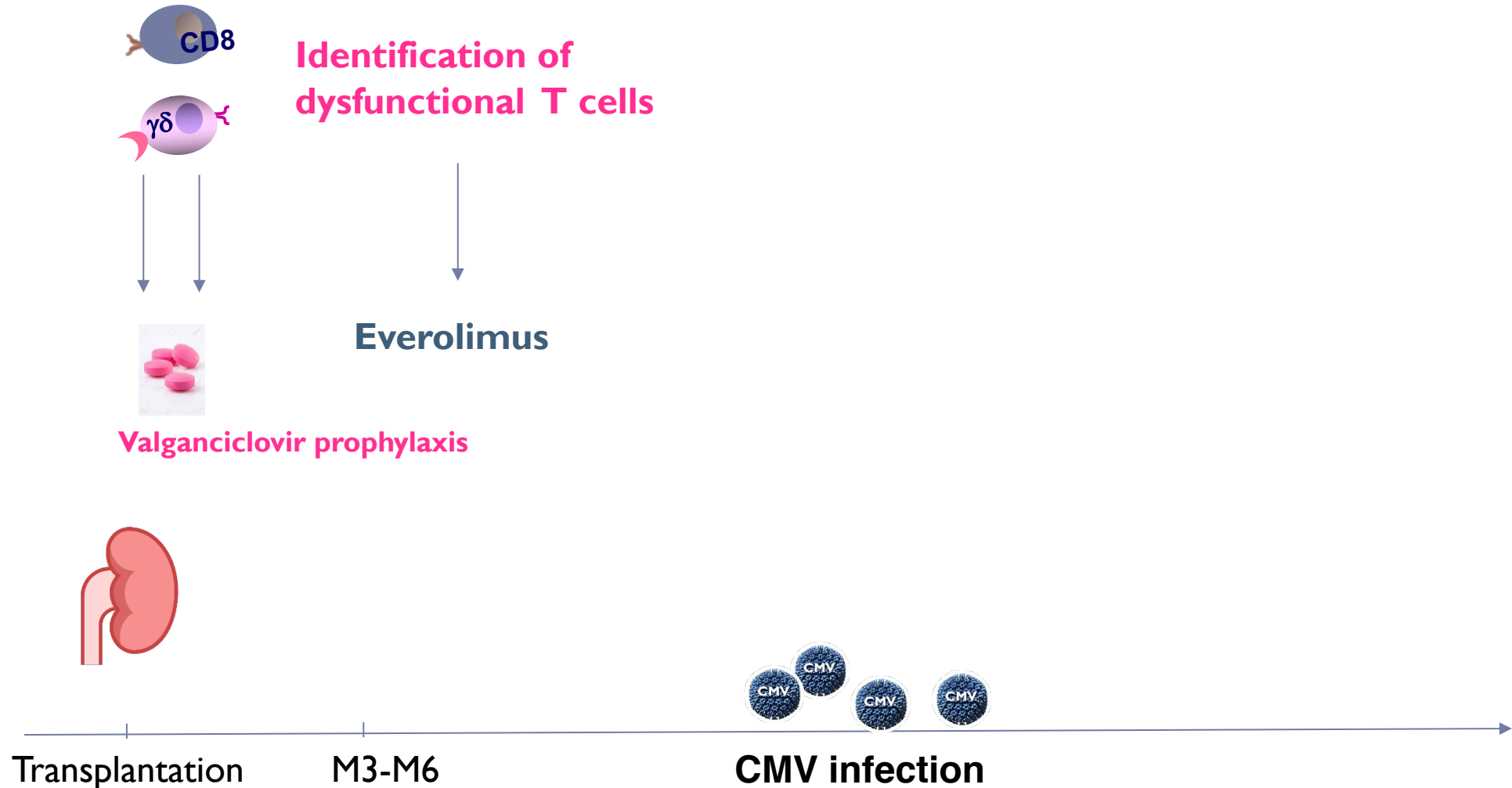
Very low risk of CMV DNAemia requiring antiviral drug

HR 0.08, CI95% 0.03-0.2, p<0.001

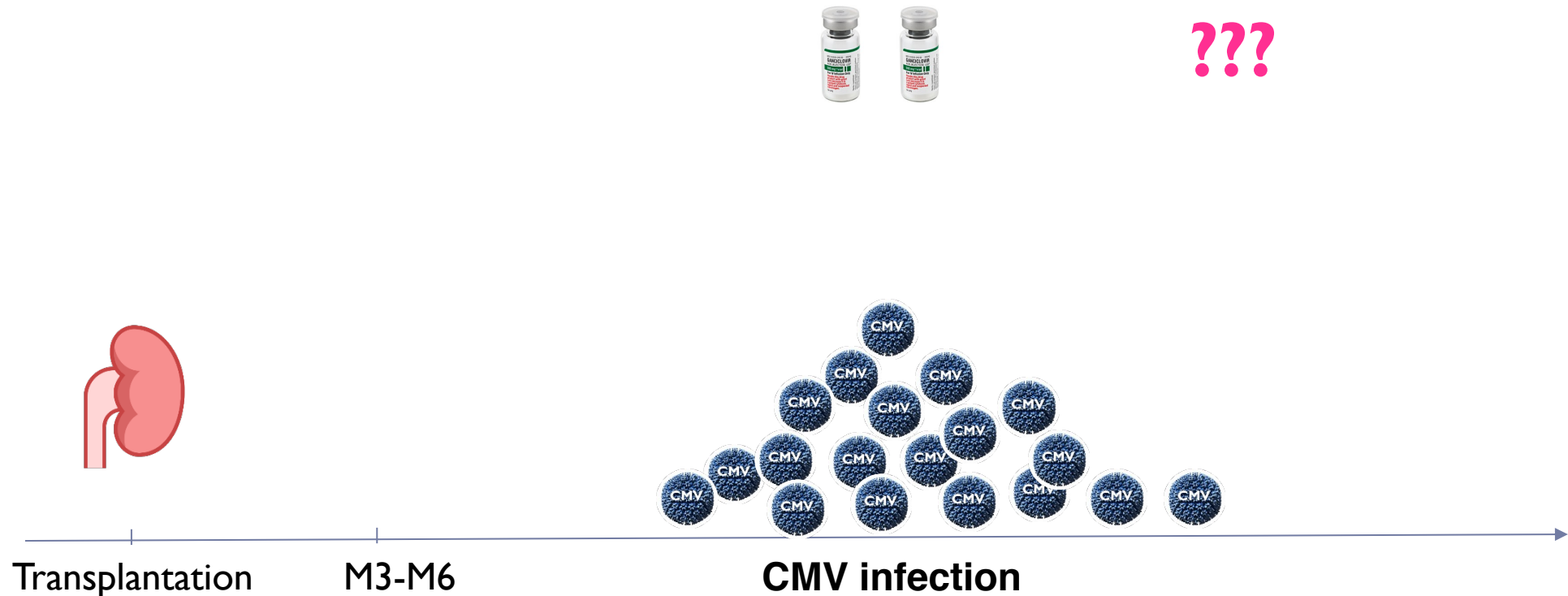
Two functional situations of TEMRA cells in immunocompromised CMV-seropositive hosts



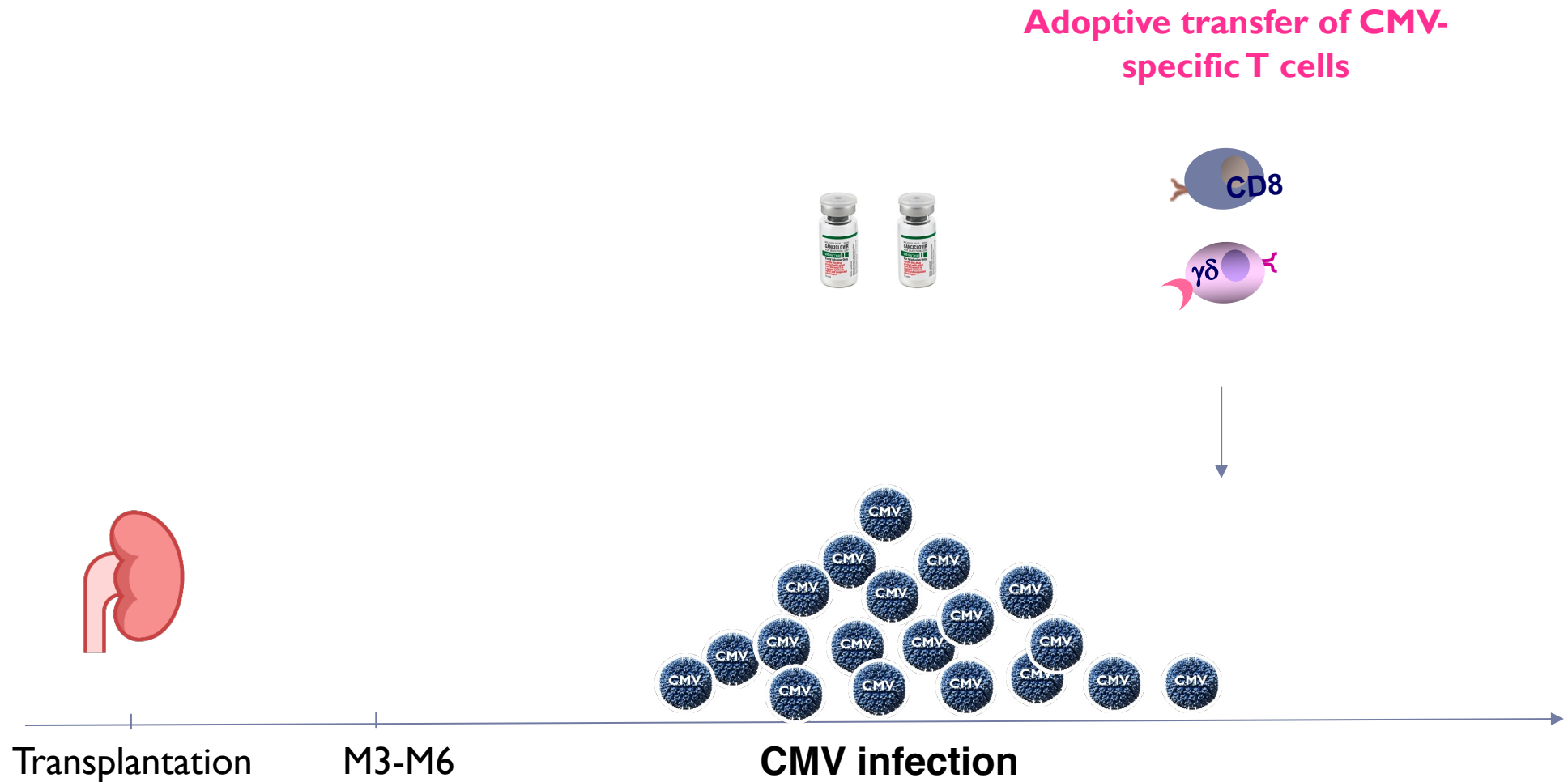
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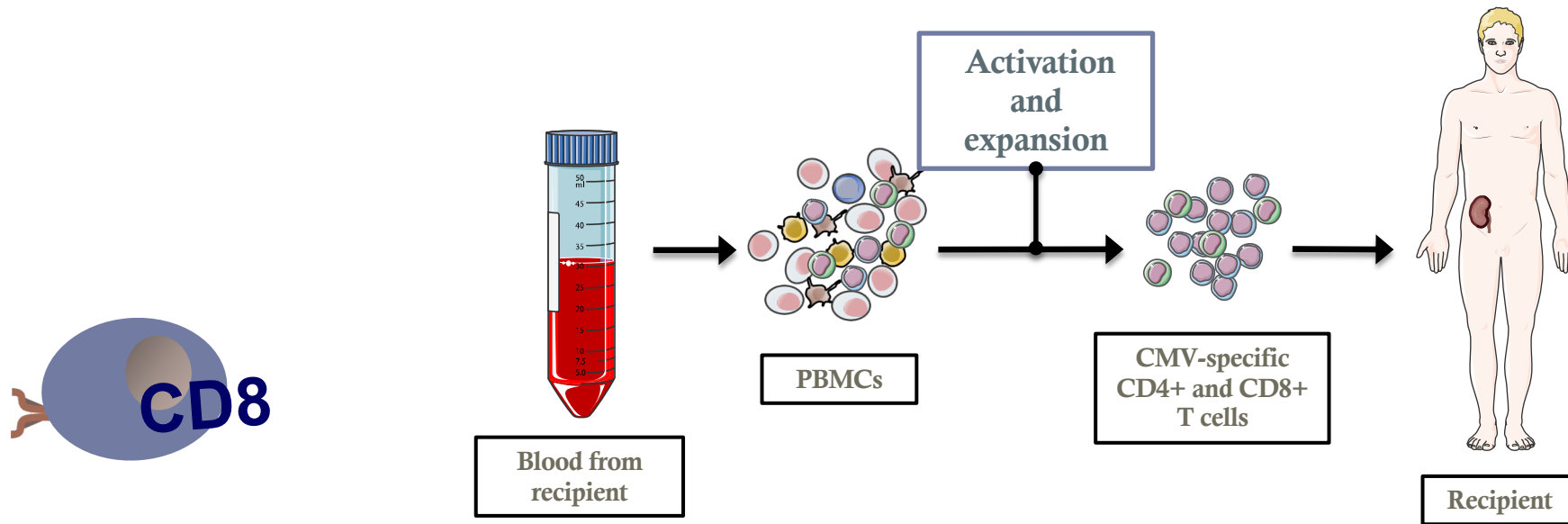
Current issue in the management of CMV infection in SOTR: How to induce a long-lasting CMV-specific T cell response ?



Targeting CMV infection with CD8+ T cell therapies



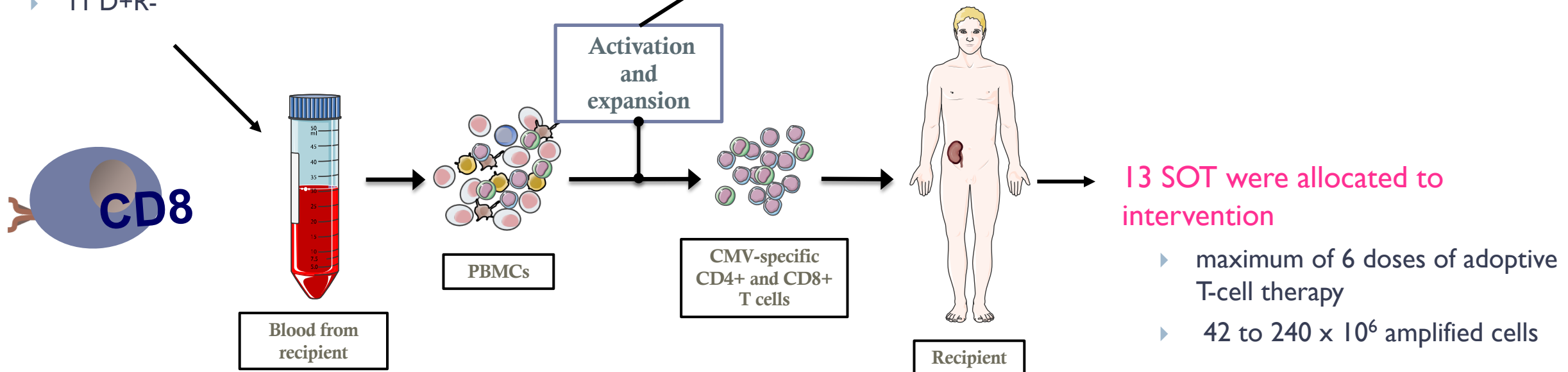
Adoptive CD8 and CD4 T cell therapy: First experience in HSCT recipients



Adoptive CD8 and CD4 T cell therapy in SOT

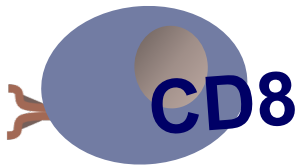
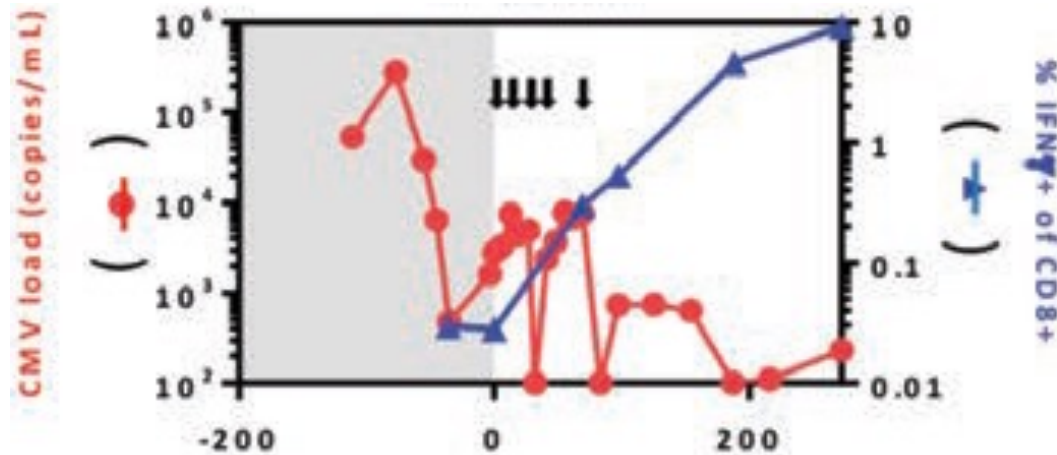
- ▶ Persistent CMV infection or disease or CMV reactivation
- ▶ 21 SOT recipients (13 renal, 8 lung, and 1 heart transplant recipient) were included
 - ▶ 11 D+R-

- PBMCs were stimulated with a peptide pool which includes peptide from pp65, pp50, IE-1, gH, and gB
- IL21 and IL2
- 14 days of culture



Adoptive CD8 and CD4 T cell therapy in SOT

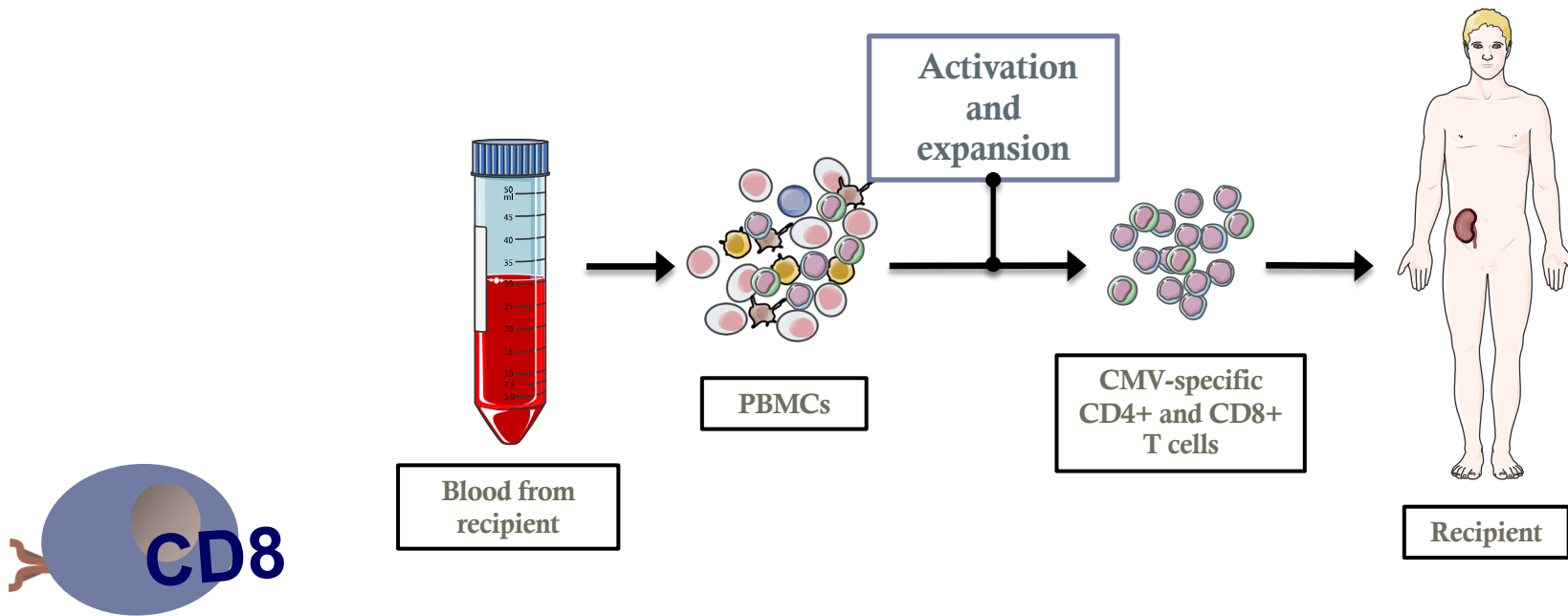
6 doses of adoptive T-cell therapy



Immune reconstitution despite the continuation of immunosuppressive therapies



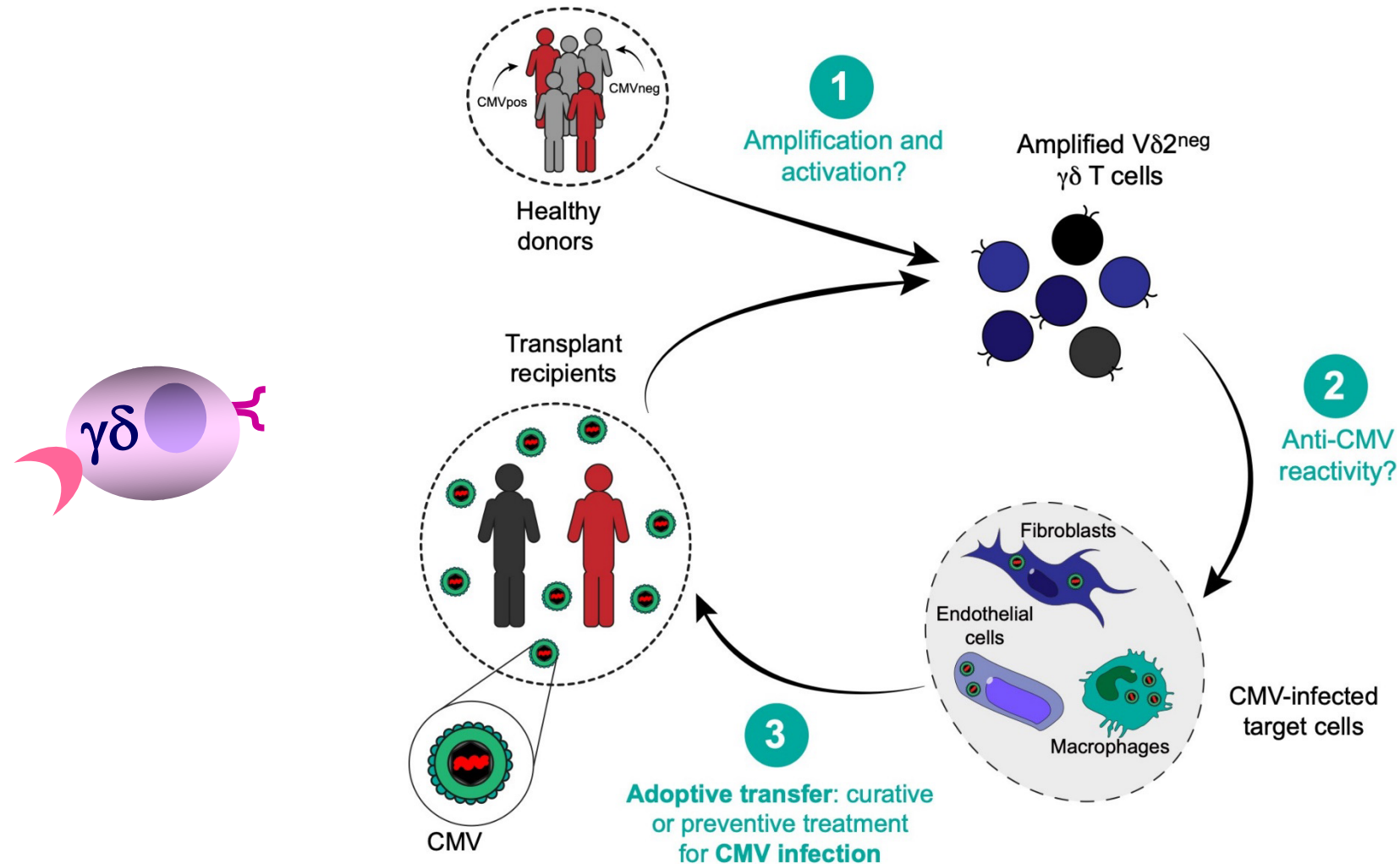
Limits of adoptive CD8 and CD4 T cell therapy in SOTR



Limits associated to $\alpha\beta$ T cell adoptive transfer strategies:

- *Ex vivo* expansion from a patient/donor with pre-existing CMV immunity
- Issues of HLA mismatches and HLA sensitization

Aim: develop a $\gamma\delta$ T cell based therapy to treat CMV infection

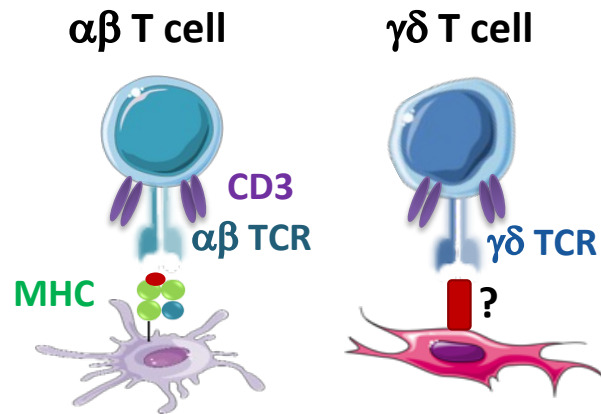


$\gamma\delta$ T cells features of interest for adoptive transfer strategies

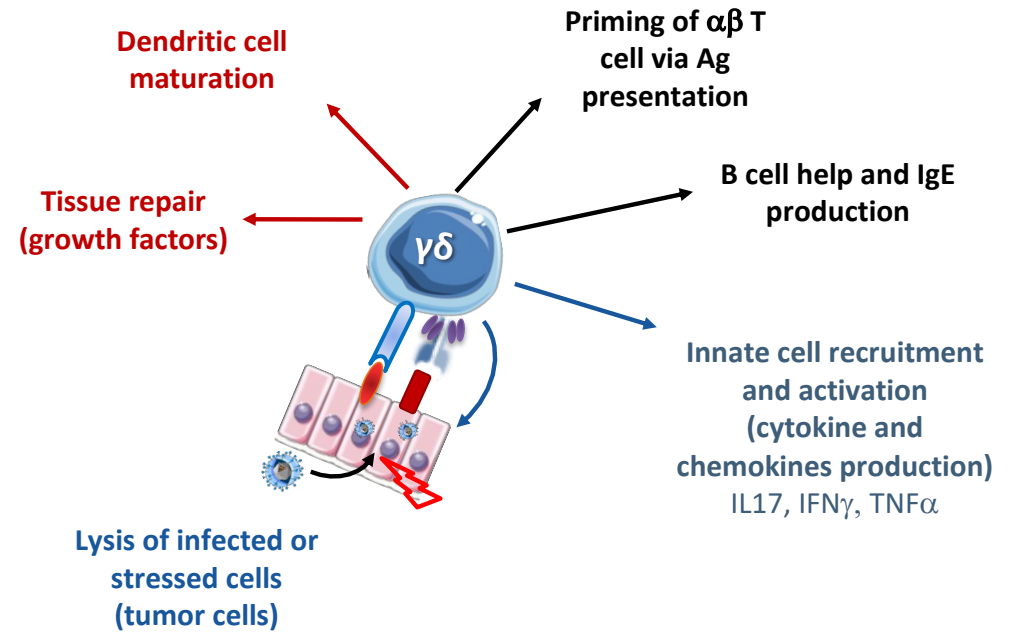
Rational for $\gamma\delta$ T cell-based therapies



$\gamma\delta$ T cells: Tissue resident
30% of T cells in epithelia

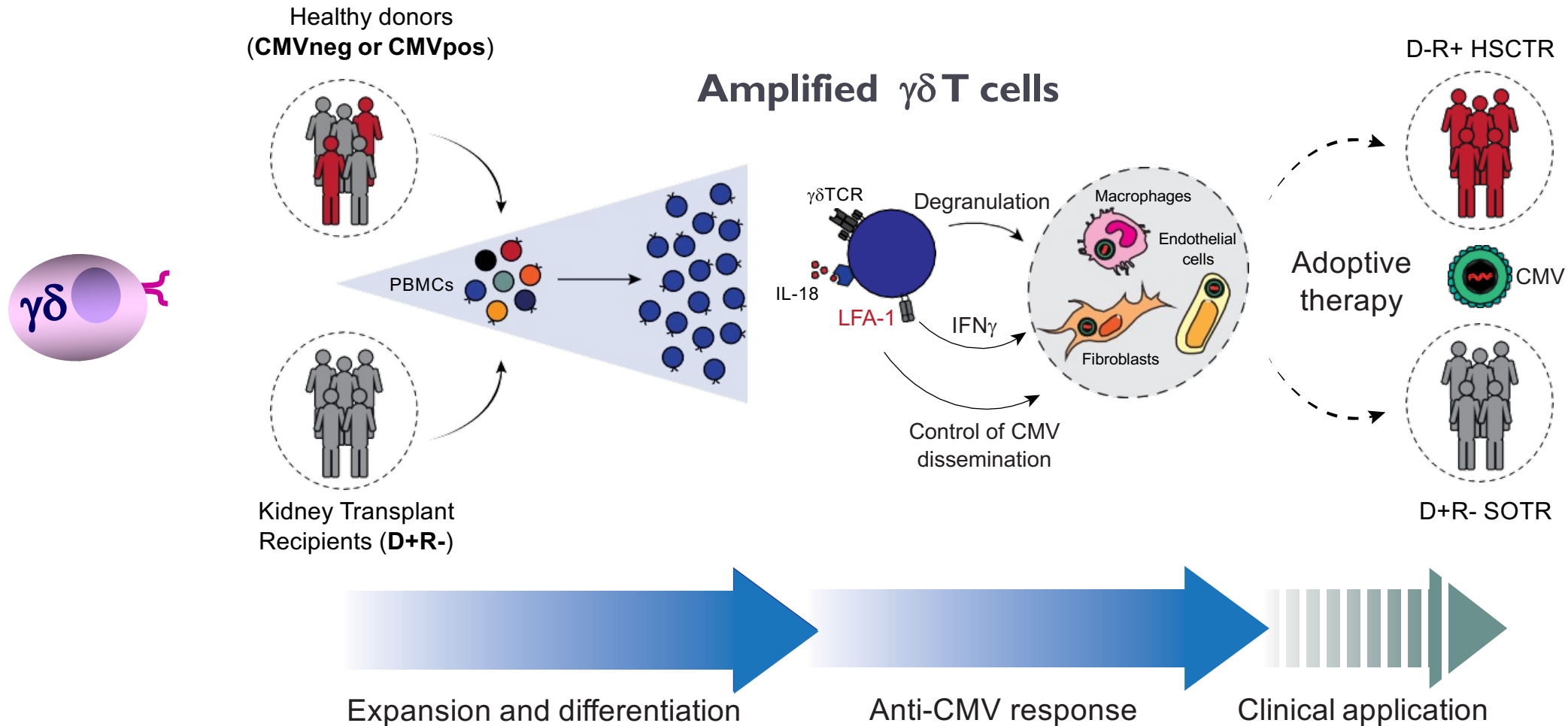


Ligand recognition is not restricted by HLA presentation

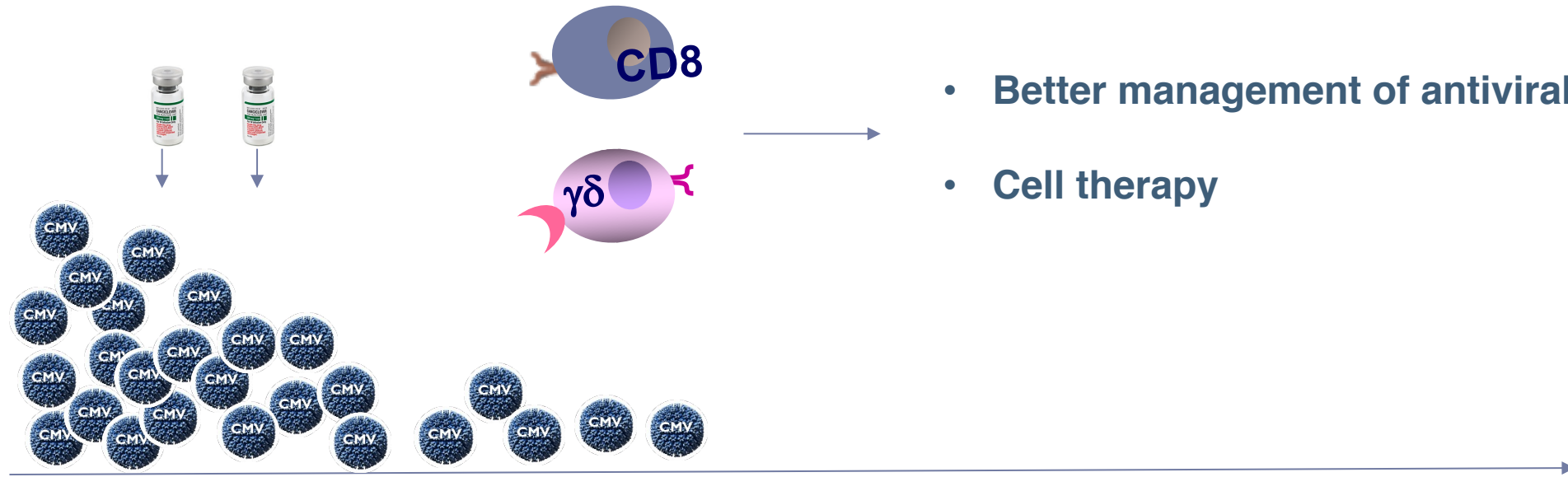


Polyfunctional cells

Adoptive $\gamma\delta$ T cell therapy: a preclinical study



Immune cell response: implications for tomorrow



- Better management of antiviral drugs
- Cell therapy

Acknowledgments



▶ Bordeaux Hospital

- ▶ **Pierre Merville**
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- ▶ Isabelle Garrigue
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- ▶ Mathieu Acquier

▶ Lab

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- ▶ **Gabriel Marseres**
- ▶ **Hannah Kaminski**
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- ▶ Maxime Courant
- ▶ Victor Bigot
- ▶ Claire Tinevez
- ▶ Anais Cosentino



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- Sophie Caillard (Strasbourg)
- Dany Anglicheau (Necker)
- Jean-Philippe Rérolle (Limoges)
- Yann Lemeur (Brest)
- Antoine Durrbach (Kremlin-Bicetre)

Methodology and biostatistics

Rodolphe Thiebaut

