

Herpes virus reactivation in brain-injured patients : role and mechanisms of CD4 T cell defects. The IBIS virus study

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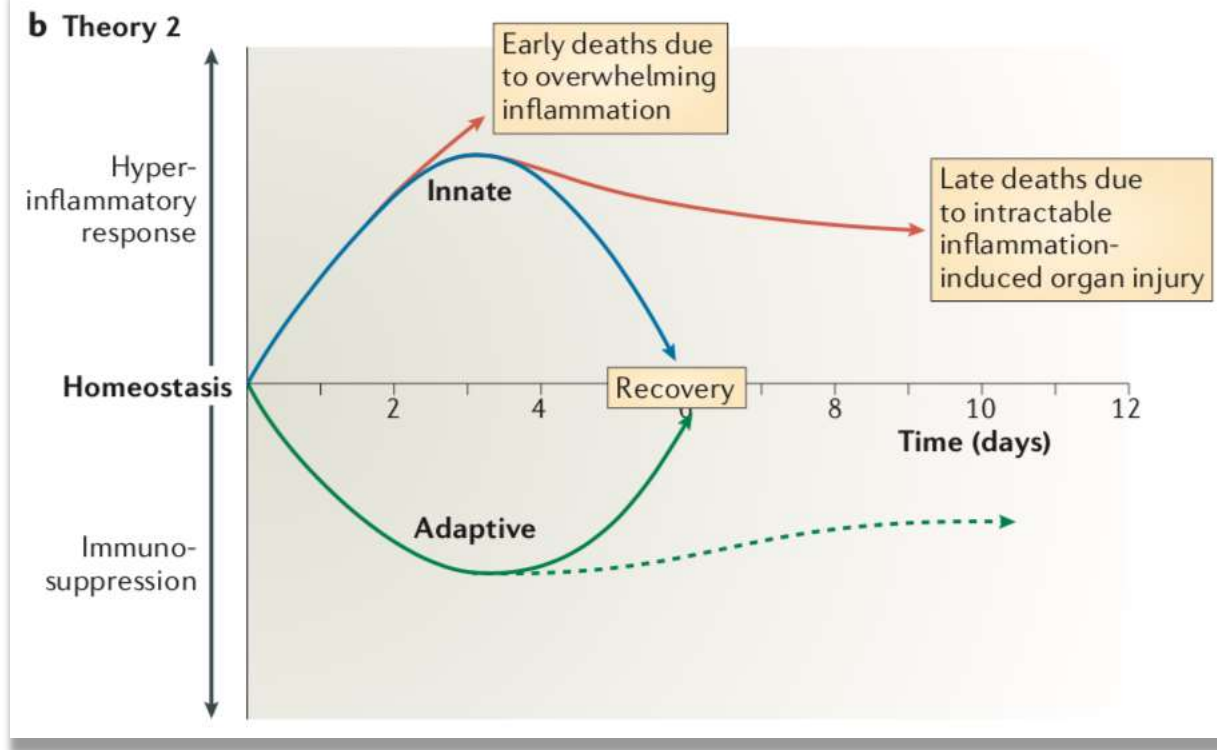




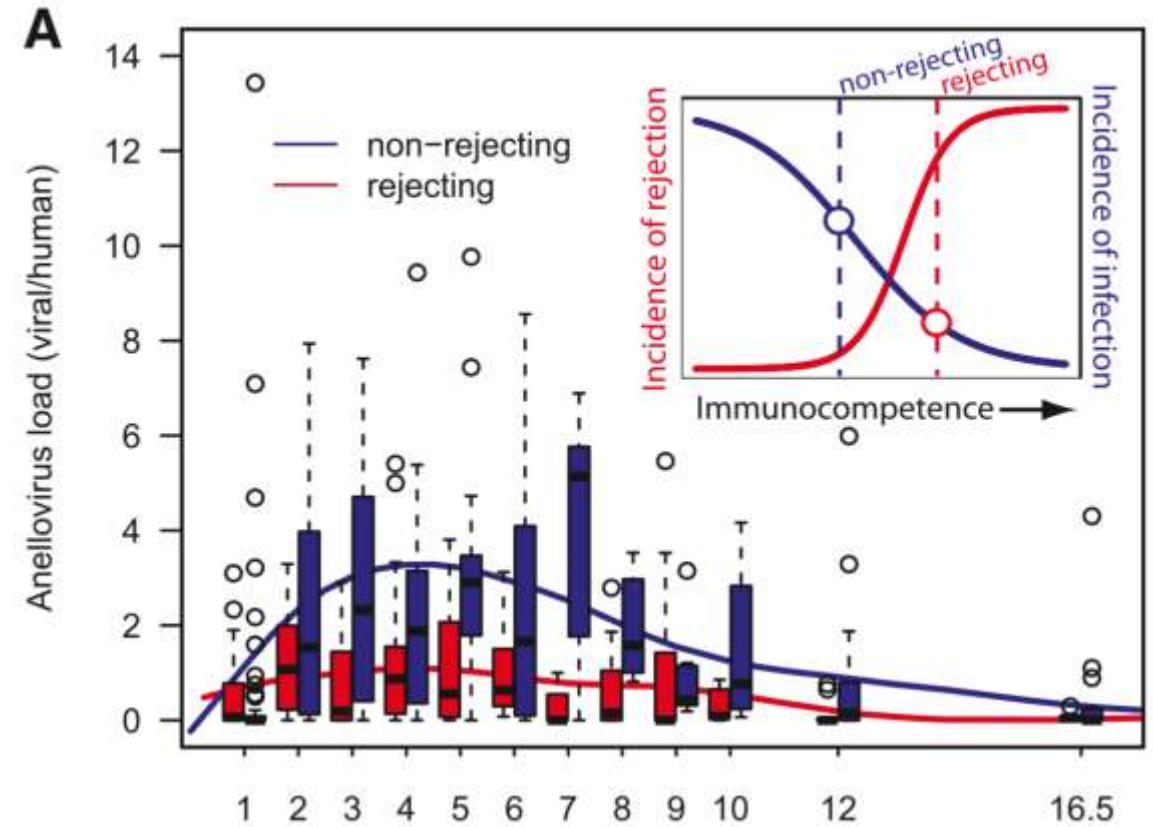
Déclaration d'intérêts de 2014 à 2017

- **Intérêts financiers : néant**
- **Liens durables ou permanents : néant**
- **Interventions ponctuelles : néant**
- **Intérêts indirects : MSD**

Critical-illness related immunosuppression / Virome

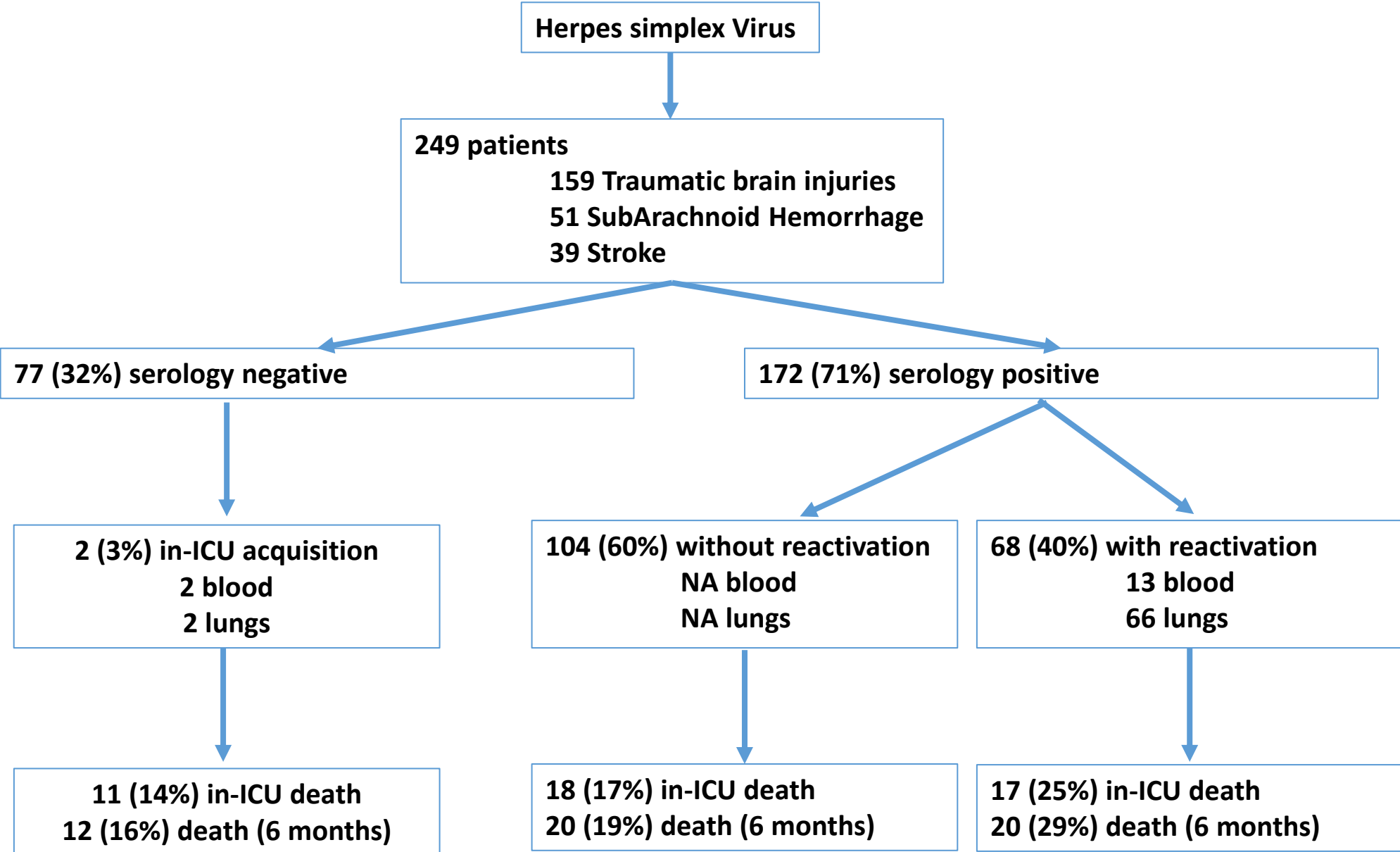


Hotchkiss et al. Nature Immunol 2013

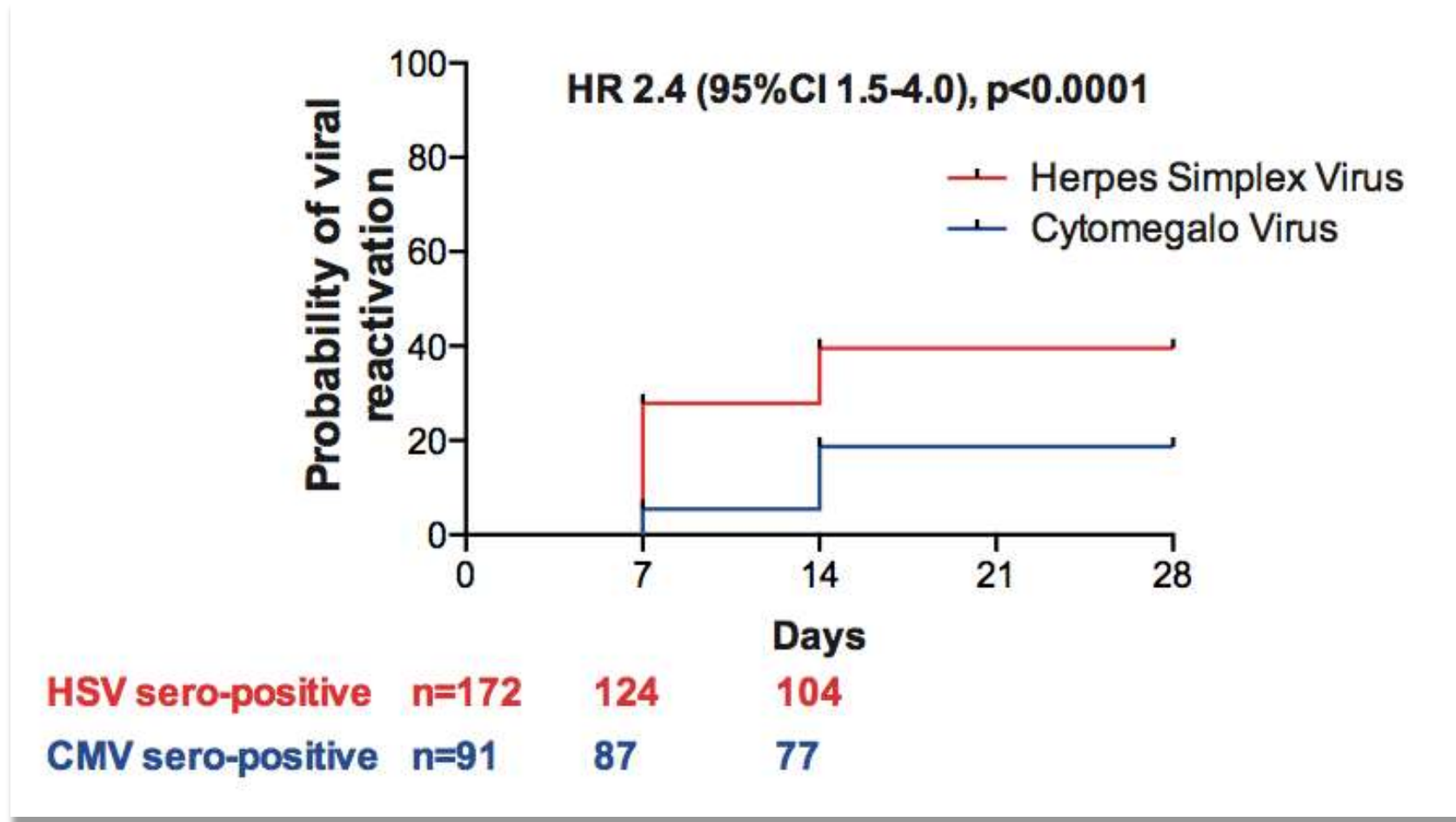


De Vlamincx et al. Cell 2013

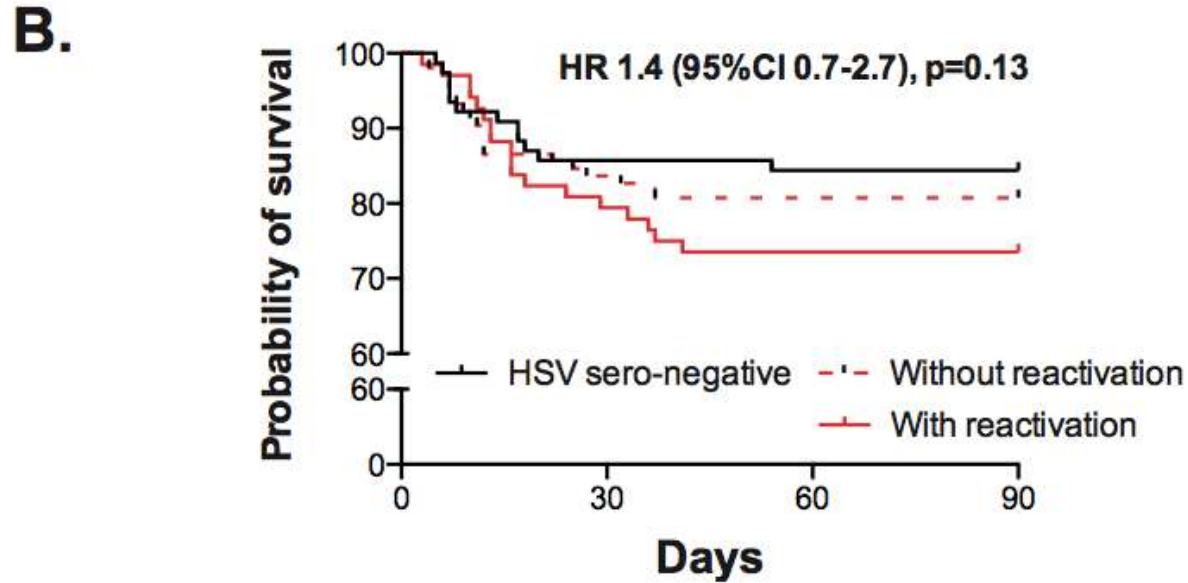
The IBIS Virus project



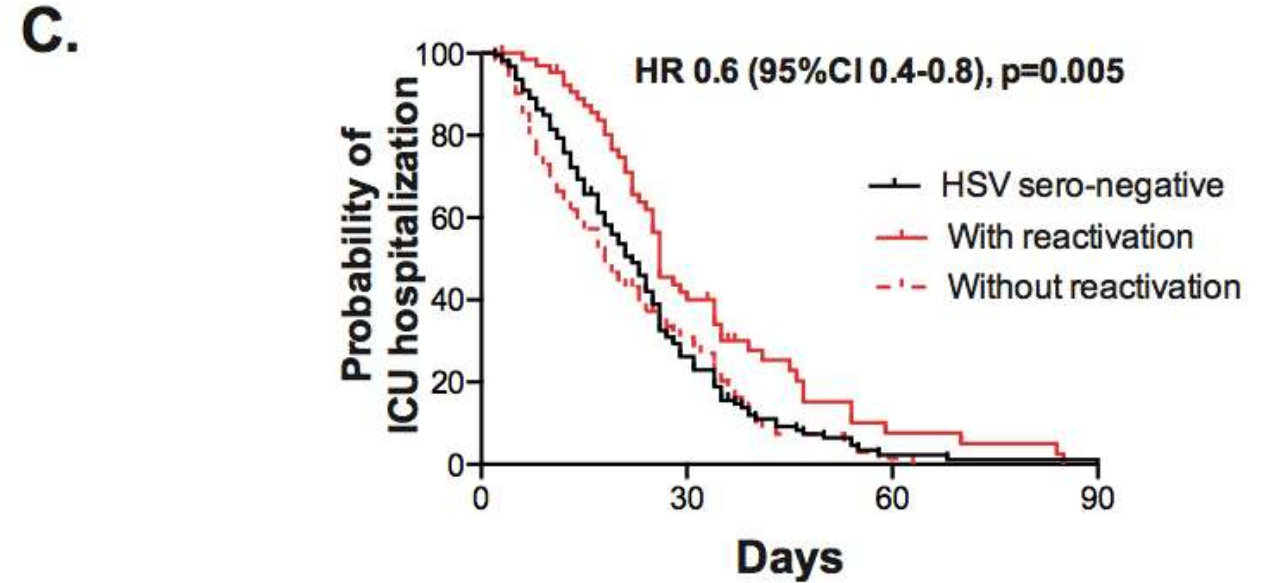
Risk of HSV and CMV reactivations in 249 brain-injured patients



Association of HSV reactivation with poor in-ICU outcomes



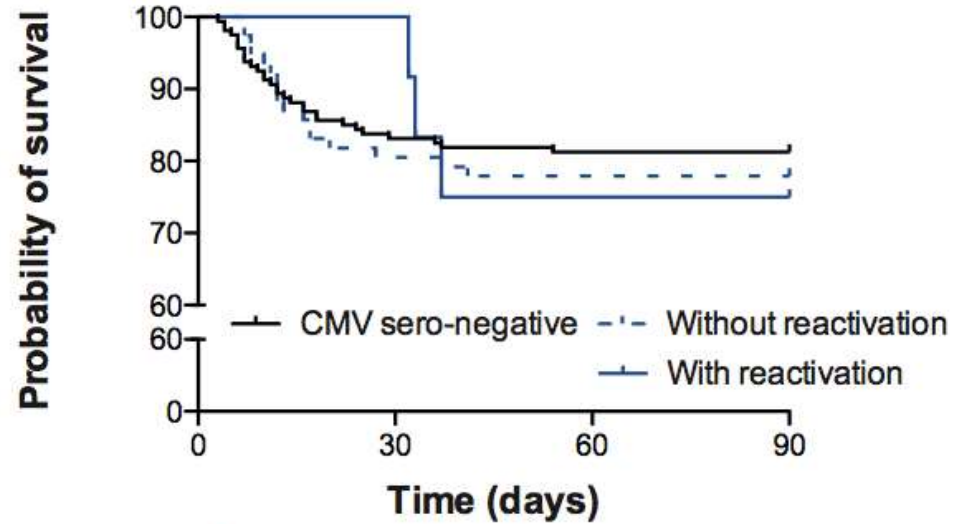
HSV sero-negative	n=77	67	65
Without reactivation	n=104	88	84
With reactivation	n=68	55	50



HSV sero-negative	n=77	18
Without reactivation	n=104	24
With reactivation	n=68	22

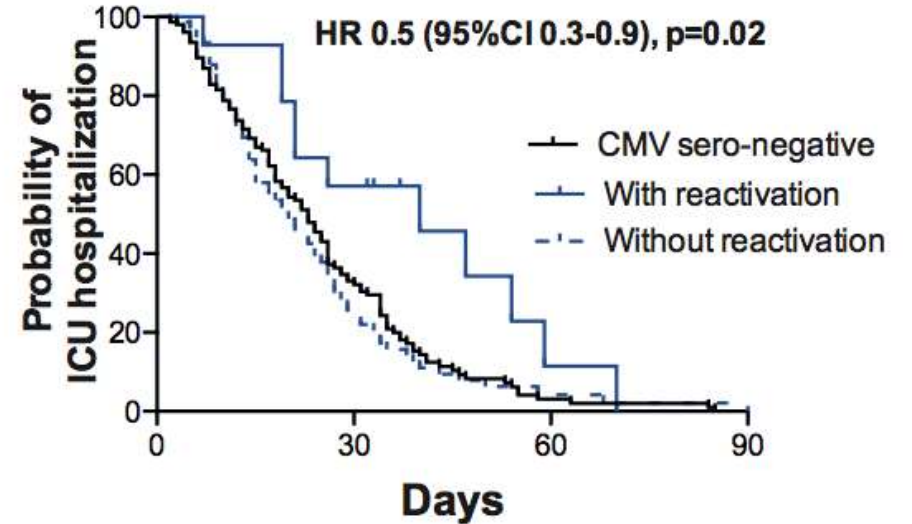
Association of CMV reactivation with outcomes

D.



CMV sero-negative	n=160	134	130
Without reactivation	n=77	63	60
With reactivation	n=12	12	9

E.



CMV sero-negative	n=160	38
Without reactivation	n=77	18
With reactivation	n=12	9

HSV reactivations are associated with poor neurological outcome

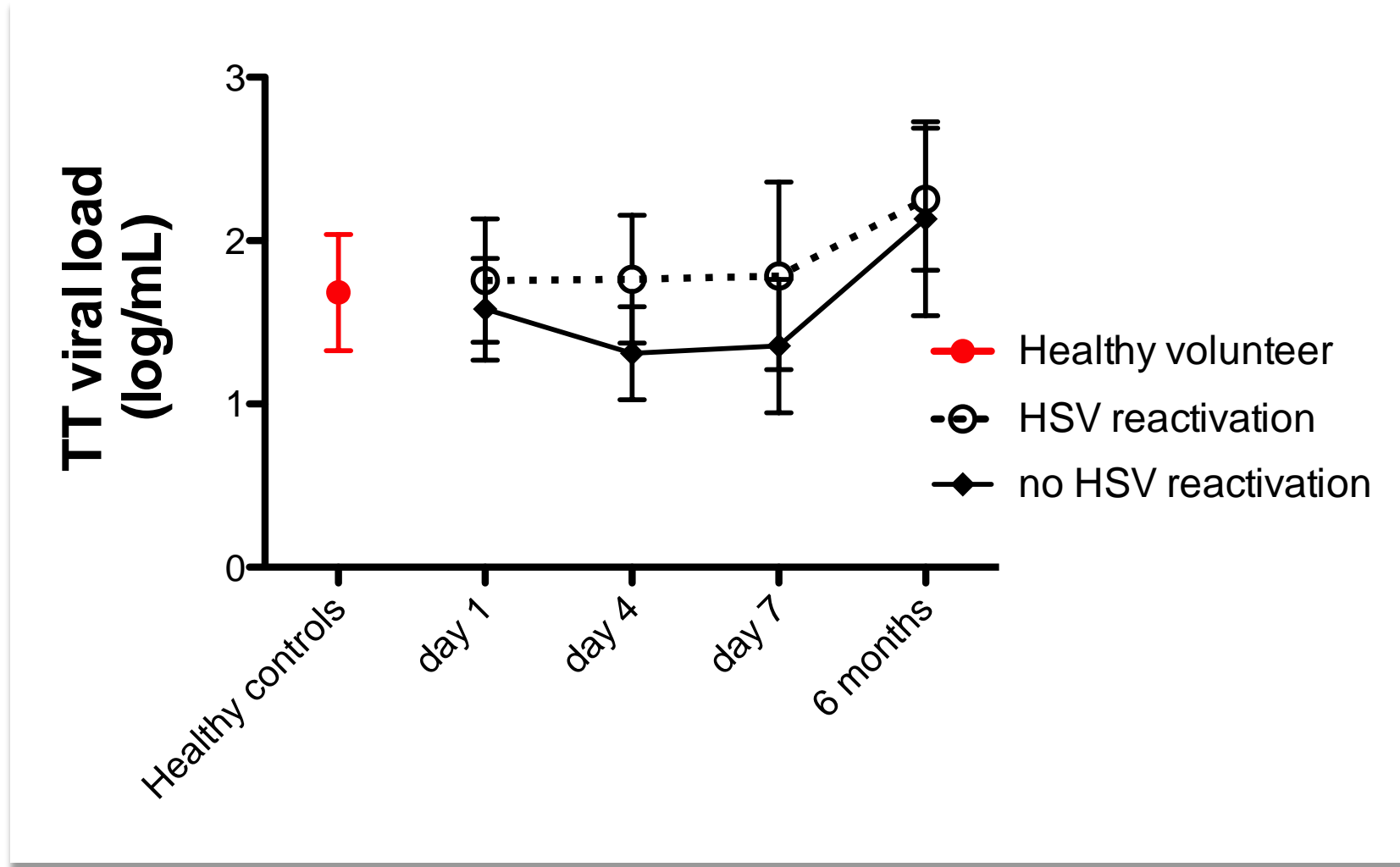
	Bad neurological recovery (GOS-E 1-5)	Good neurological recovery (GOS-E 6-8)	P-values
Number of patients	163	86	
Age, years	53 (34-64)	42 (27-56)	0.002
Male, yes	125 (77)	54 (63)	0.02
Pathology			
Trauma	101 (62)	58 (67)	0.61
Subarachnoid hemorrhage	34 (21)	17 (20)	
Stroke	28 (17)	11 (13)	
Glasgow Coma Scale	5 (3-8)	8 (5-10)	0.0004
<i>Herpes simplex virus</i> reactivation, yes	57 (35)	13 (15)	0.0009
HSV sero-positive	55 (34)	13 (15)	0.002
Lung reactivation, yes	55 (34)	13 (15)	0.002
Blood reactivation, yes	12 (7)	2 (2)	0.10
HSV sero-positive	55 (34)	13 (15)	0.002
Lung reactivation, yes	55 (34)	13 (15)	0.002
Blood reactivation, yes	12 (7)	2 (2)	0.10
<i>Cytomegalovirus</i> reactivation, yes	13	2	0.07
CMV sero-positive	10	2	0.18
Lung reactivation, yes	9	2	0.24
Blood reactivation, yes	6	1	0.25
<i>Virus</i> reactivation (<i>Herpes simplex virus</i> OR <i>Cytomegalovirus</i>), yes	61 (37)	15 (17)	0.01

Working hypothesis :

BI-induced immunosuppression is responsible
for Herpes Simplex Virus reactivation

WP 1 : Increased viral replication or loss of
immune control ?

Decreased circulating viral load of Torque Teno Virus in BI patients without HSV reactivation

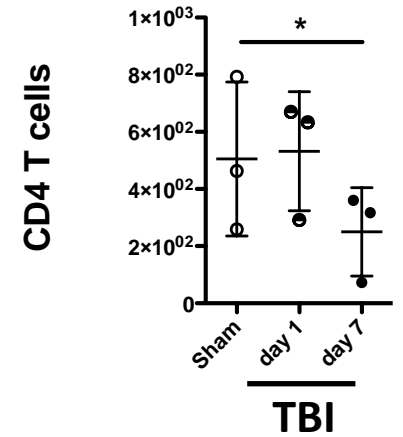
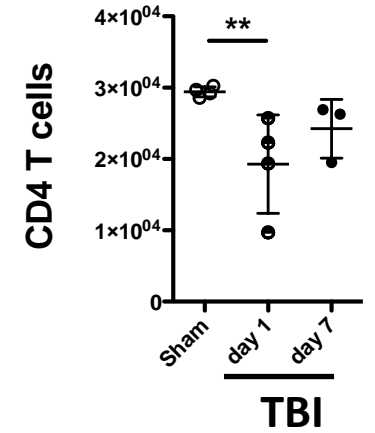
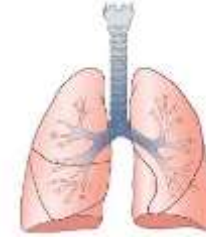
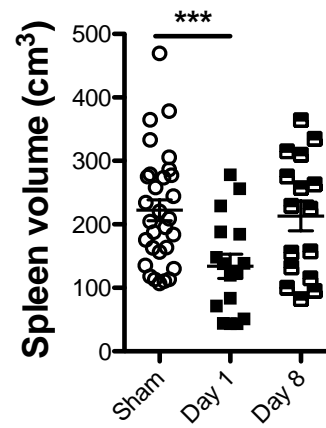
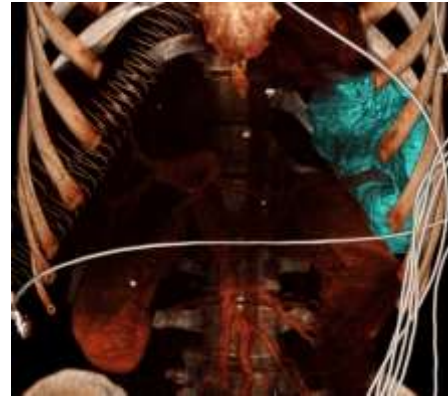
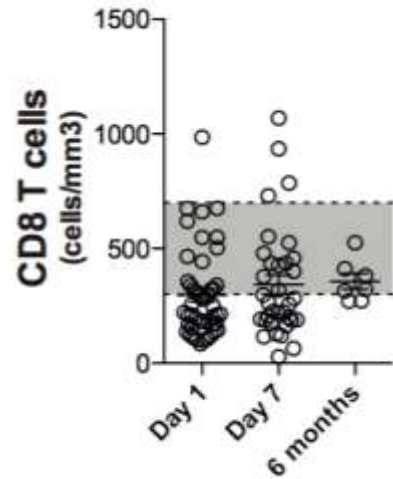
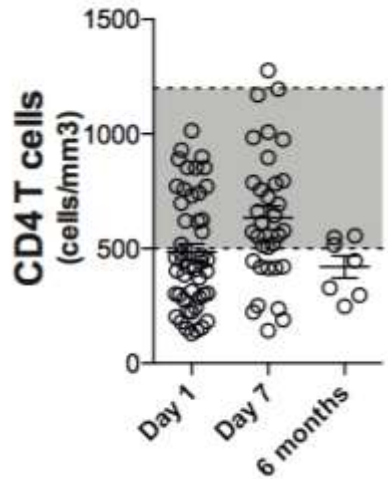
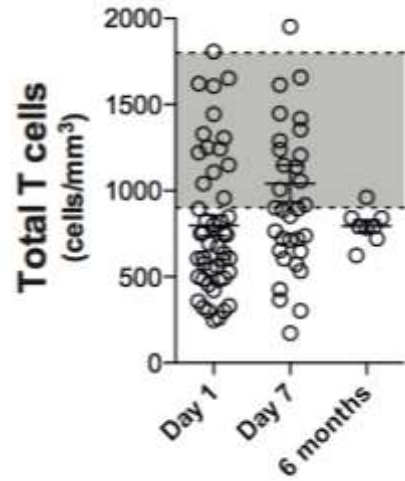


Working hypothesis :

BI-induced **T cell defects** are responsible for
Herpes Simplex Virus reactivation

WP 2 : Does the number of T cells matter ?

Lymphopenia after brain injury

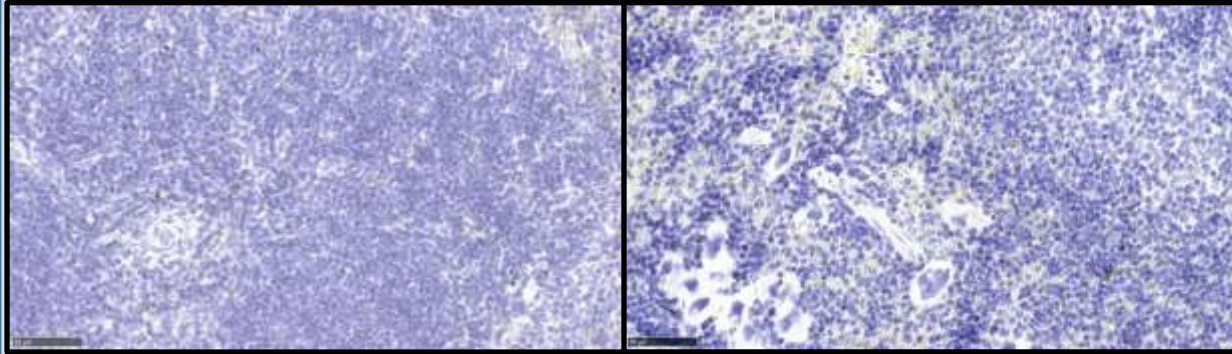


No proof of apoptosis / necrosis of lymphocytes in Spleen Tissue after brain-injury

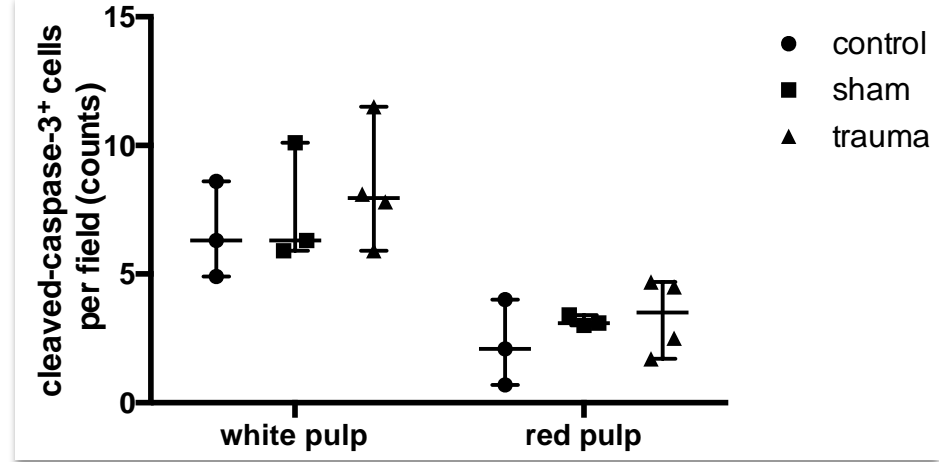
Sham



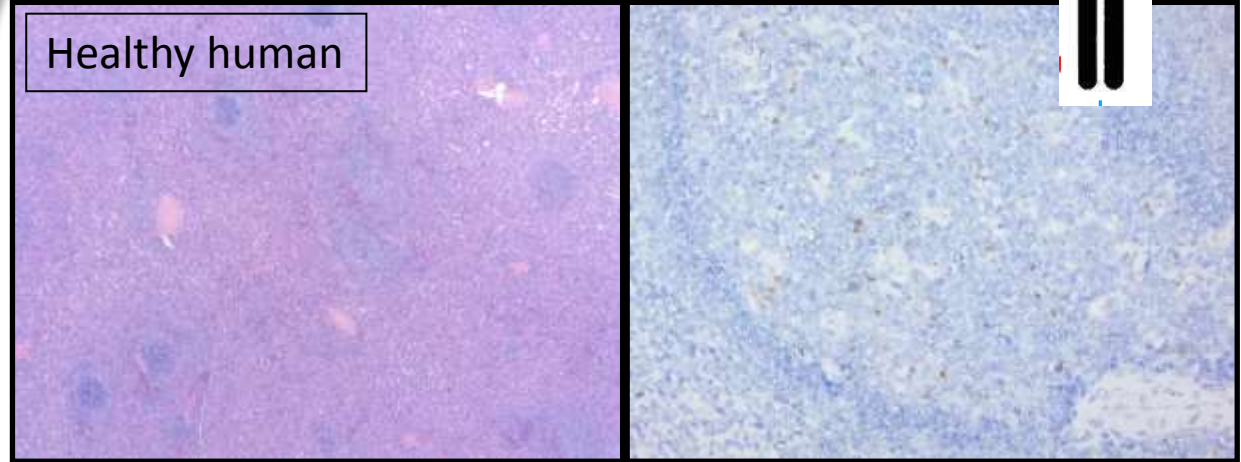
Brain injury



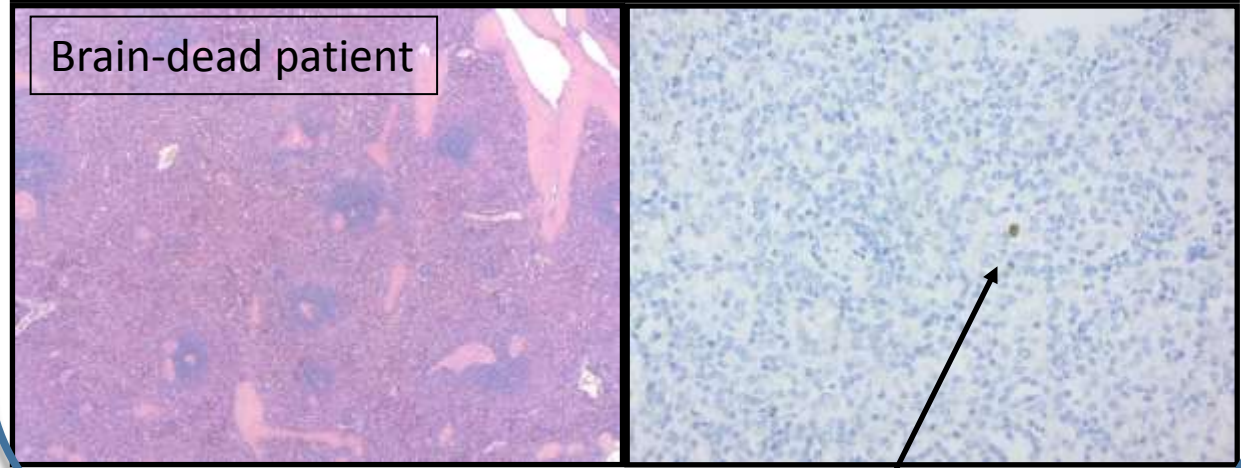
Activated Caspase 3



Healthy human



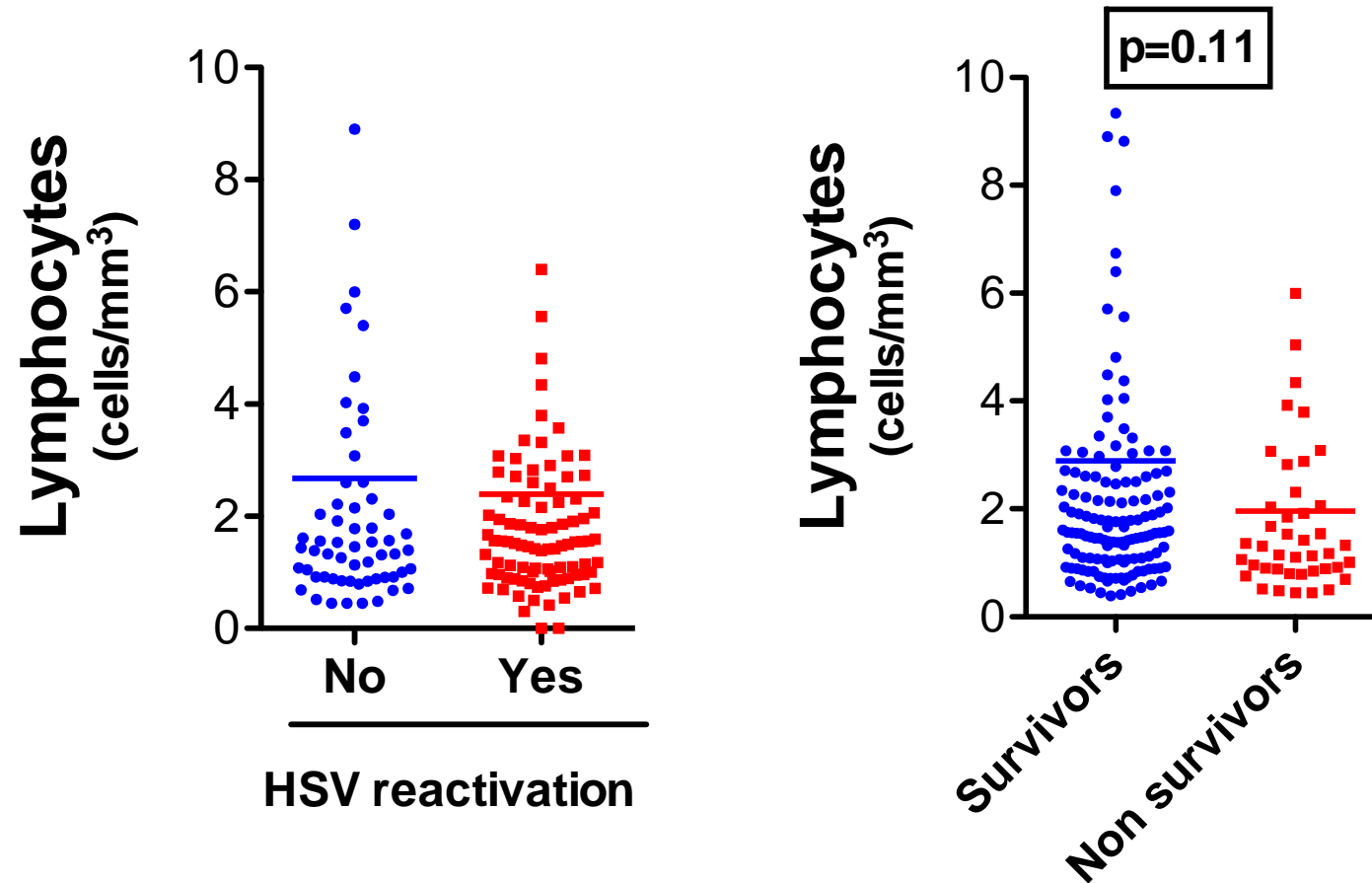
Brain-dead patient



Classical histology

Activated Caspase 3

Lymphopenia is not associated with HSV reactivation, just a marker of severity ?

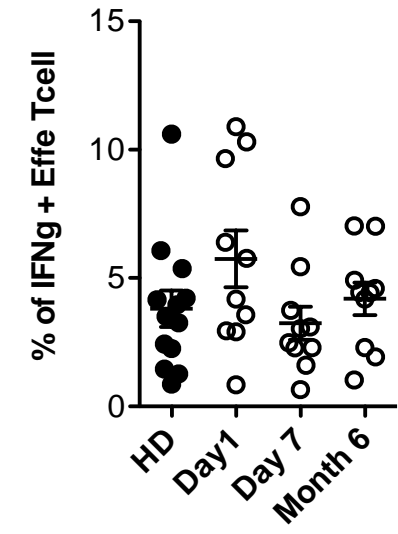
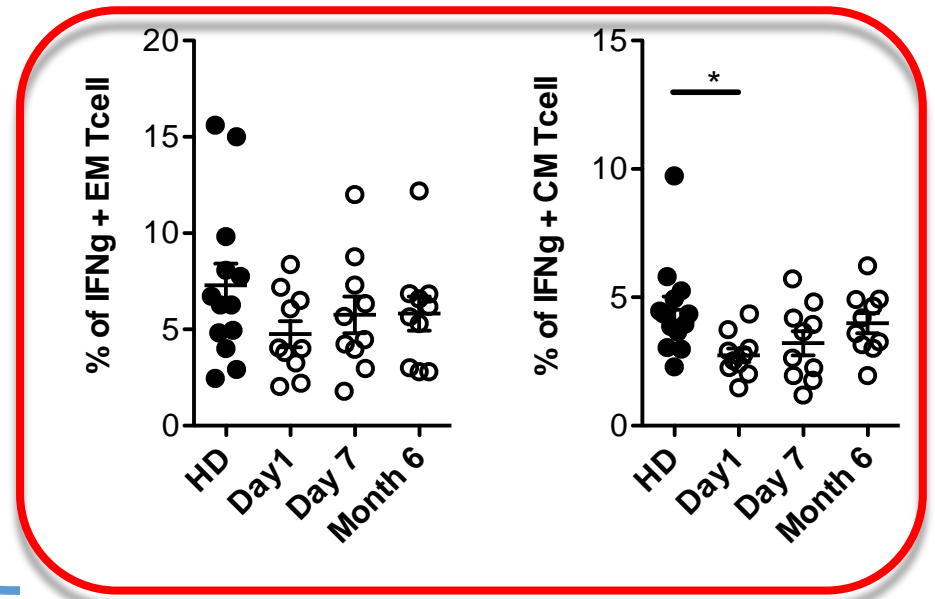
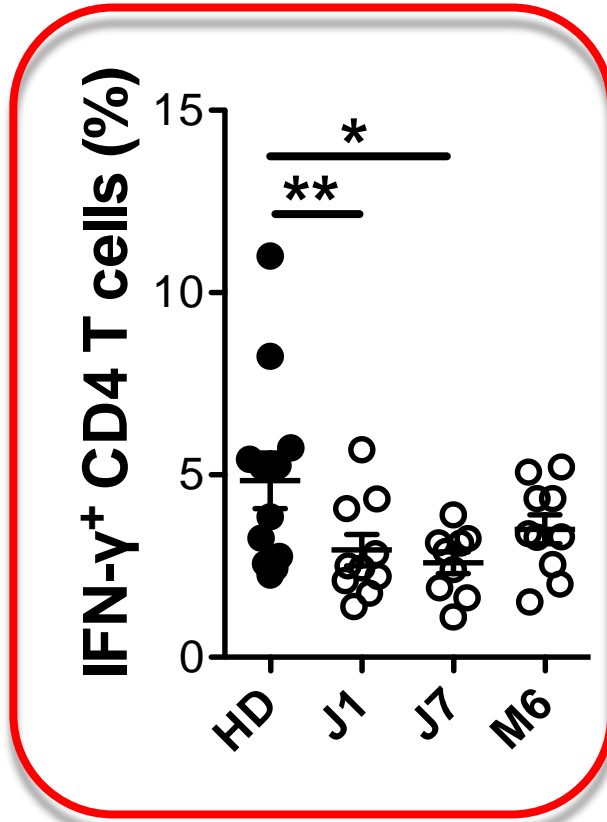
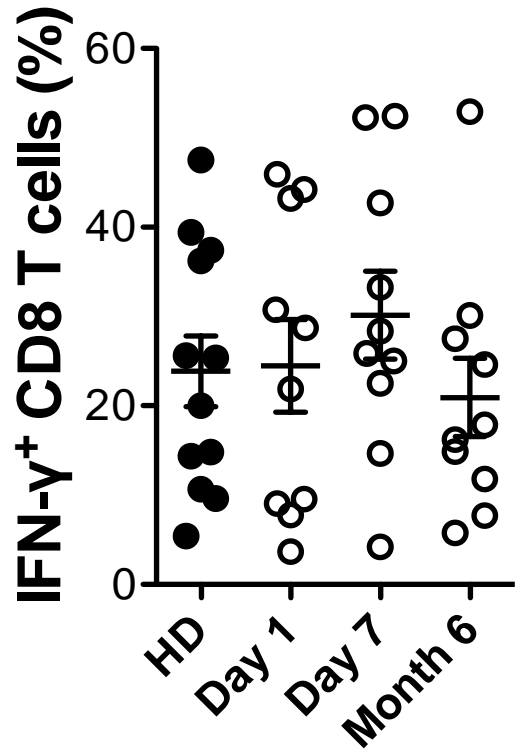


Working hypothesis :

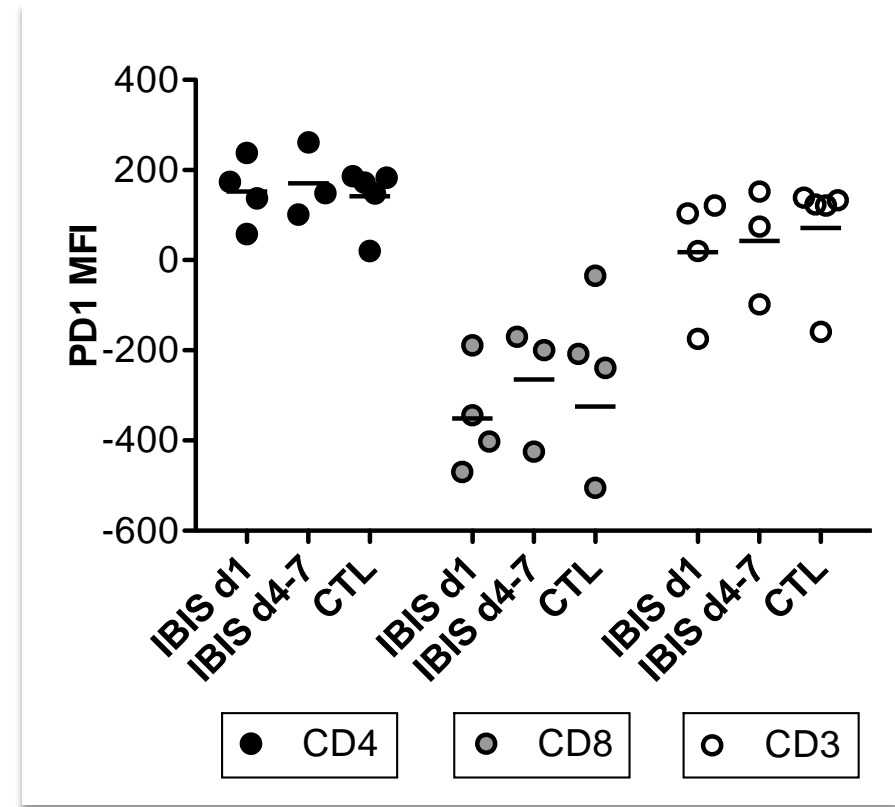
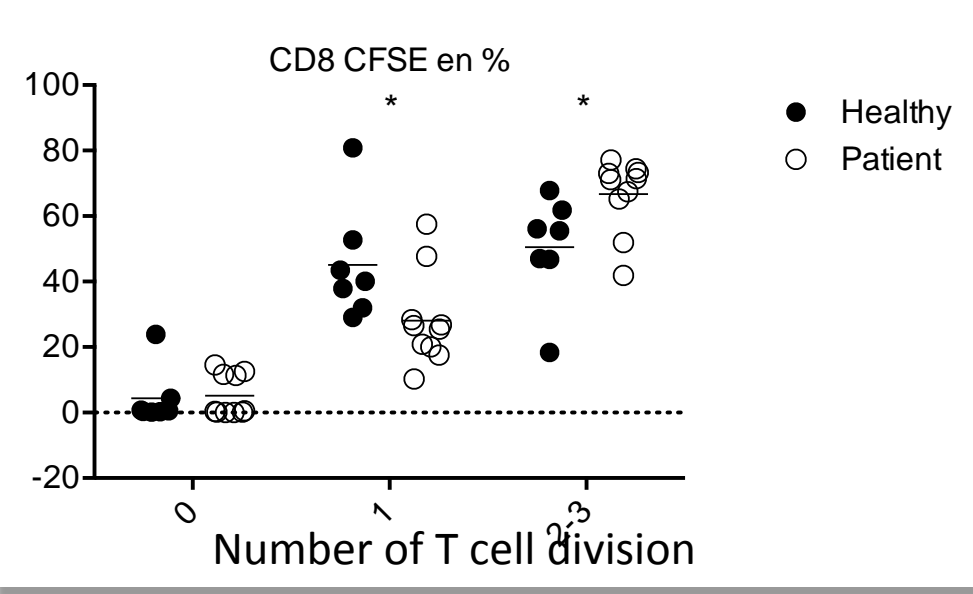
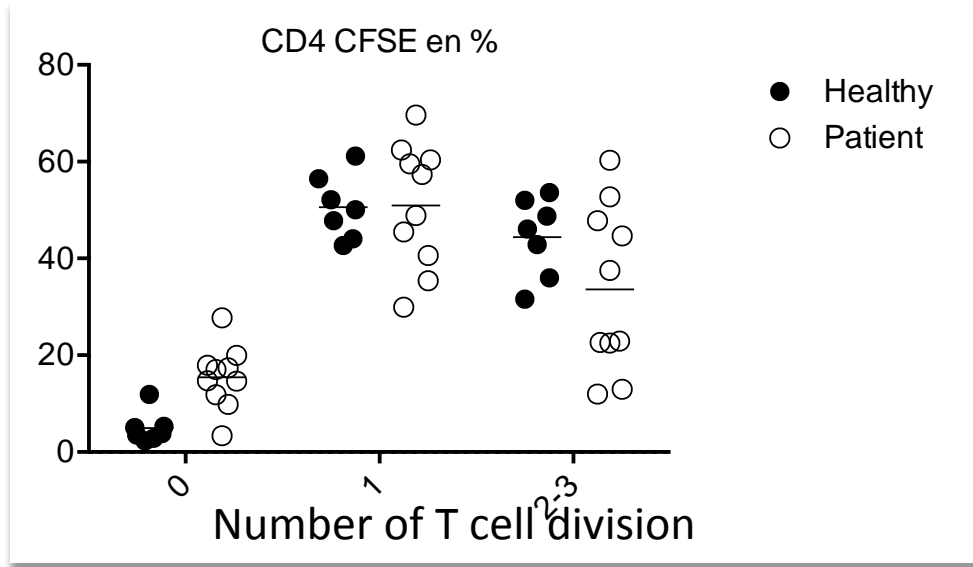
BI-induced T cell defects are responsible for
the severity of HSV reactivation

WP 3 : Do functions of T cells matter ?

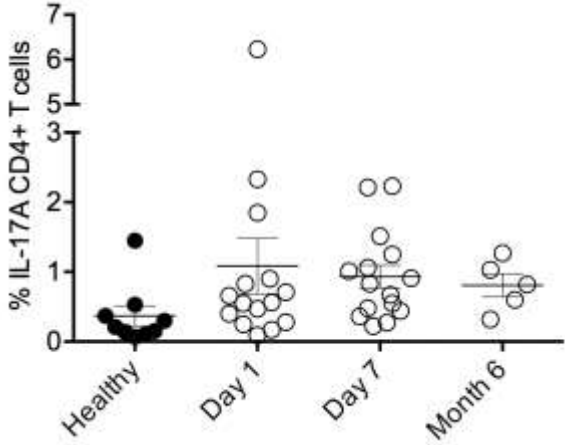
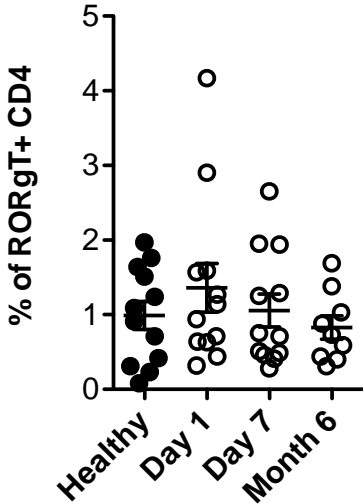
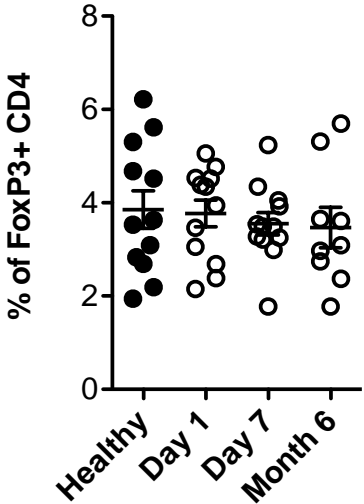
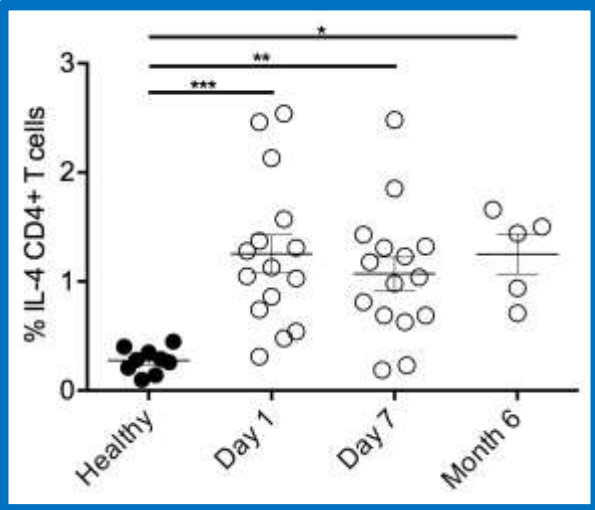
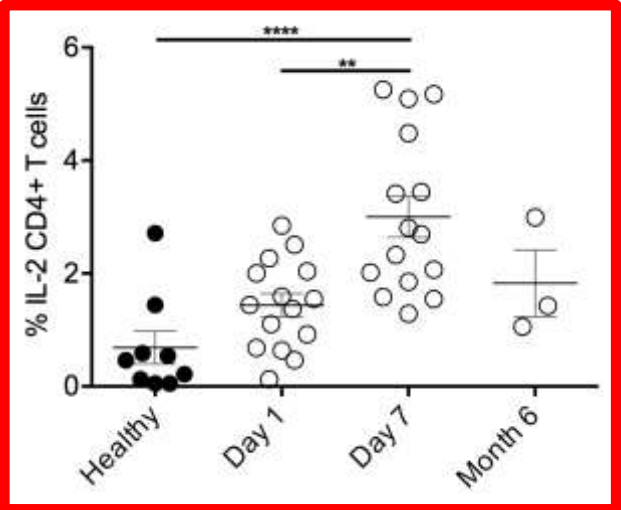
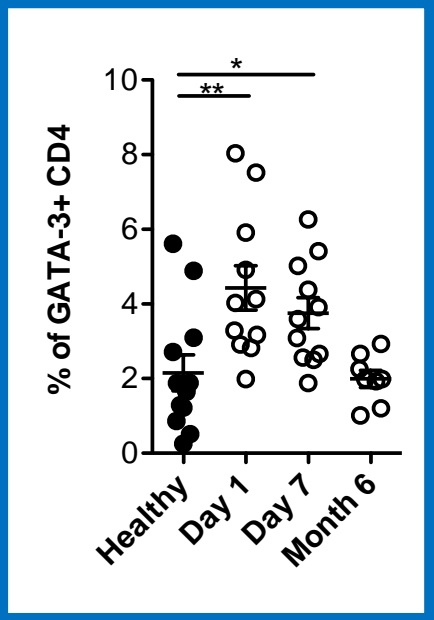
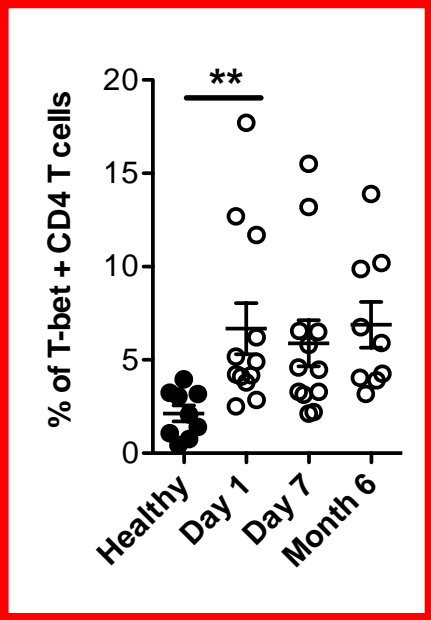
Defective production of IFN- γ by memory CD4 T cells



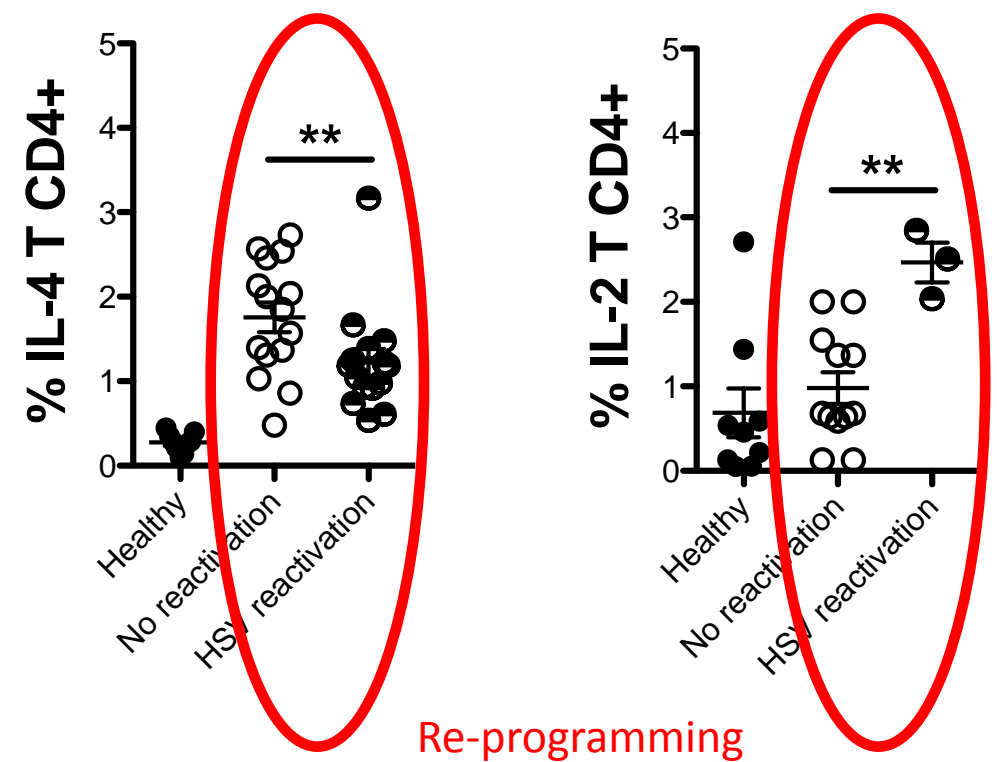
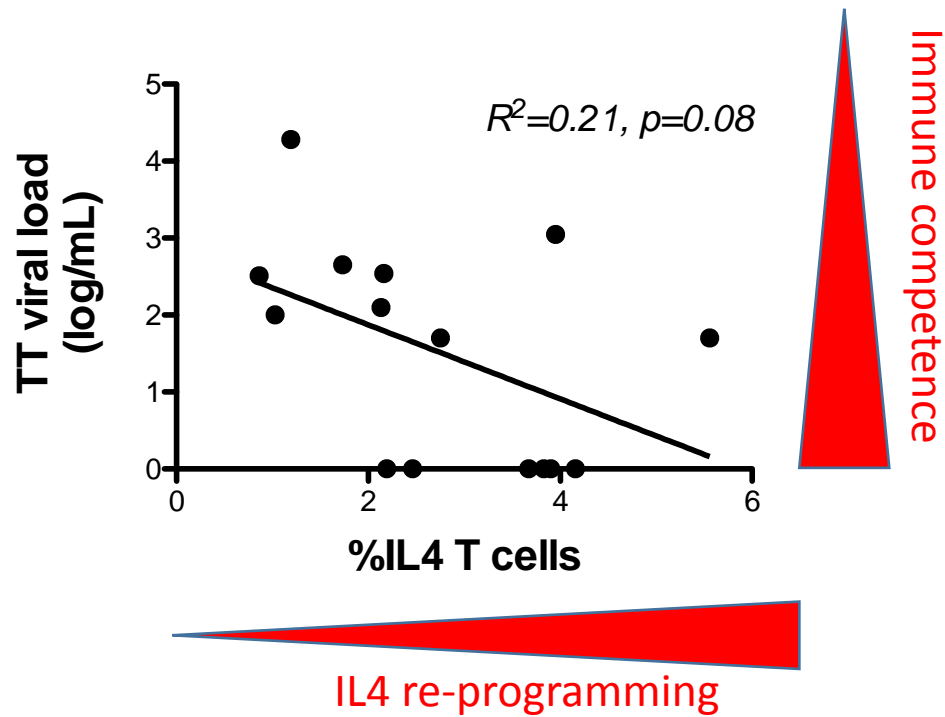
Altered T cells are not exhausted



Brain injury alters the transcriptional factor program of CD4 T



CD4 T cells re-programming is associated with immunosuppression and HSV reactivation

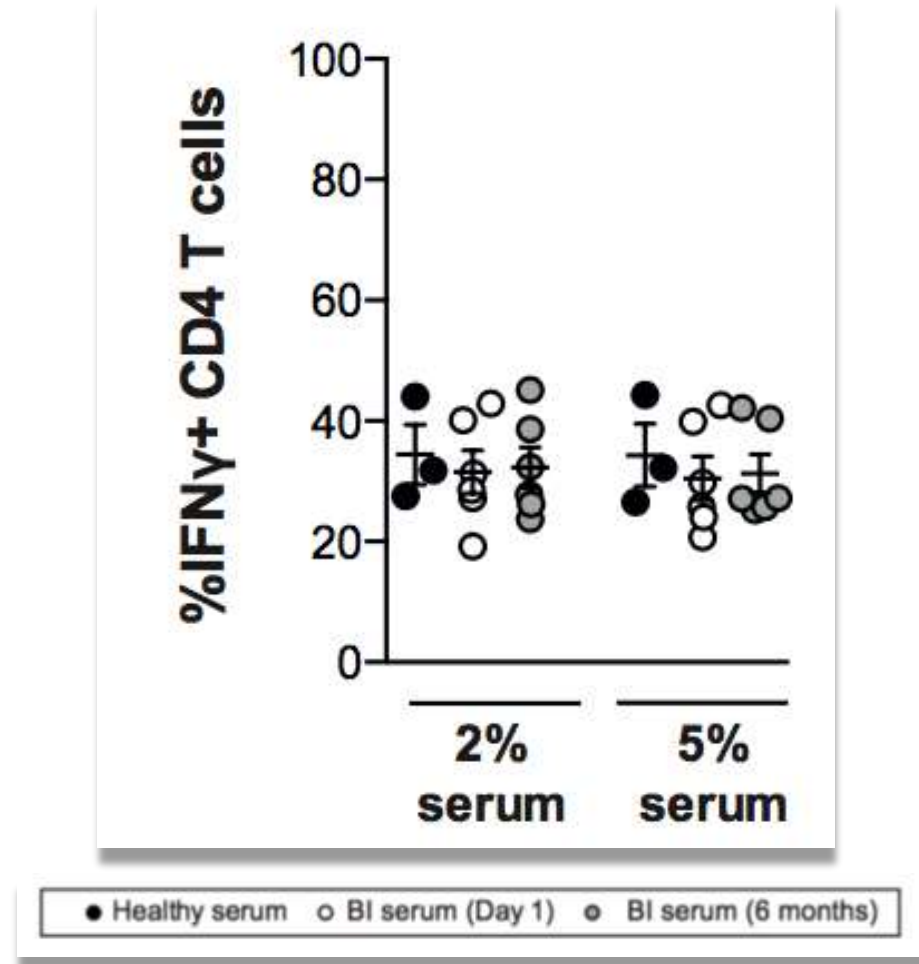
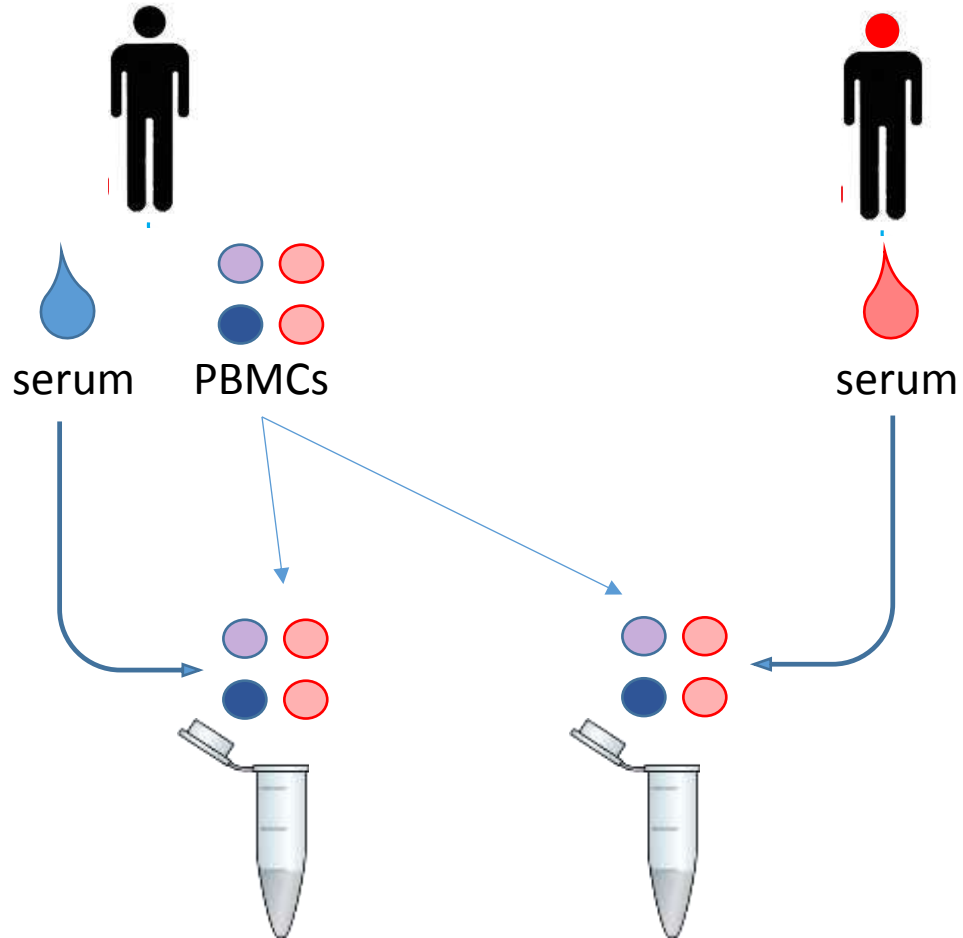


Working hypothesis :

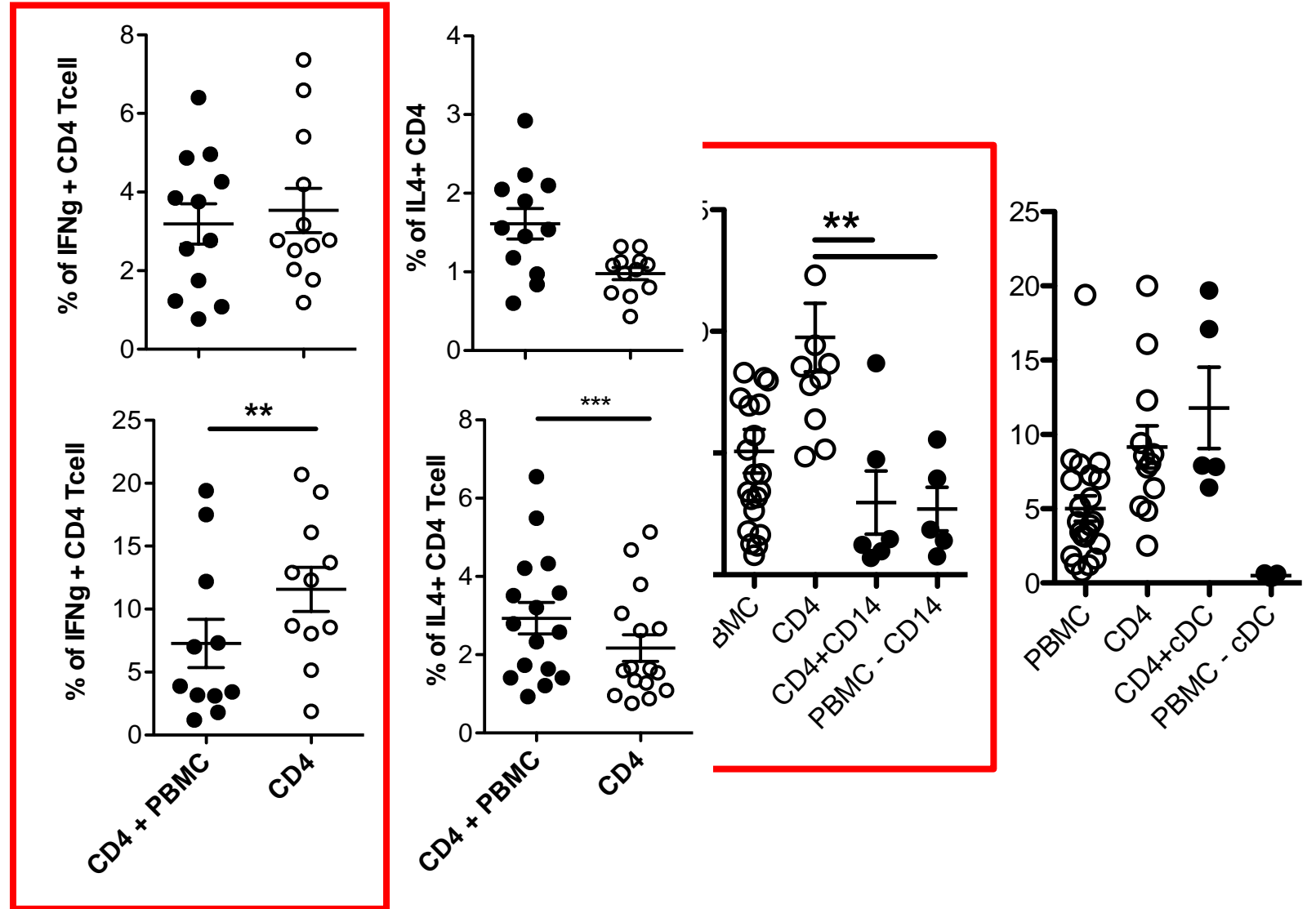
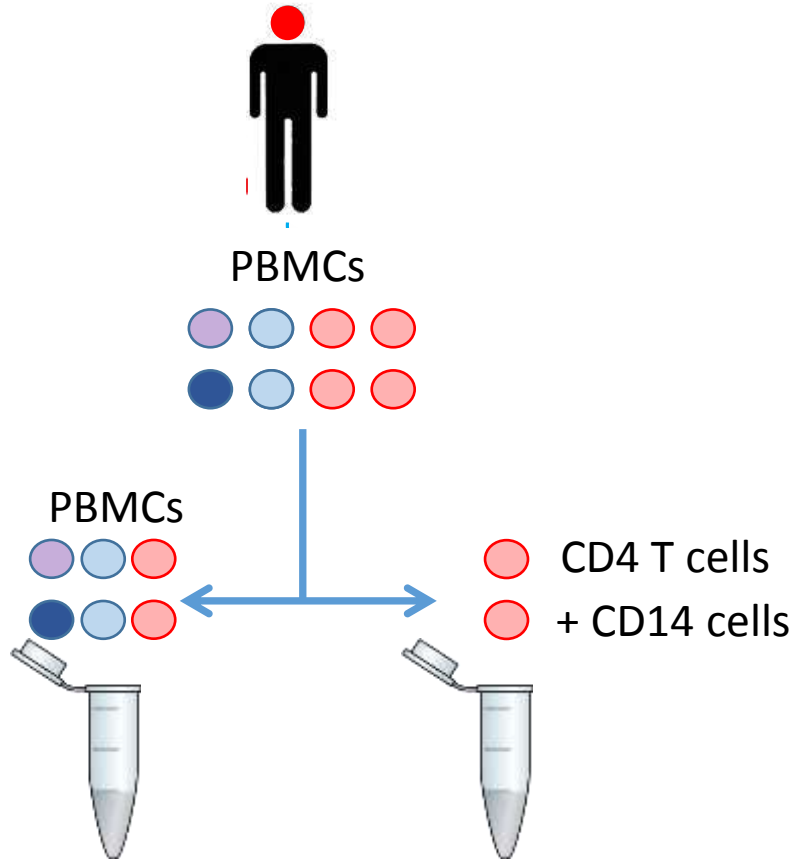
BI-induced T cell defects are responsible for
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WP 4 : Several mechanisms the CD4 T cells re-
programming ?

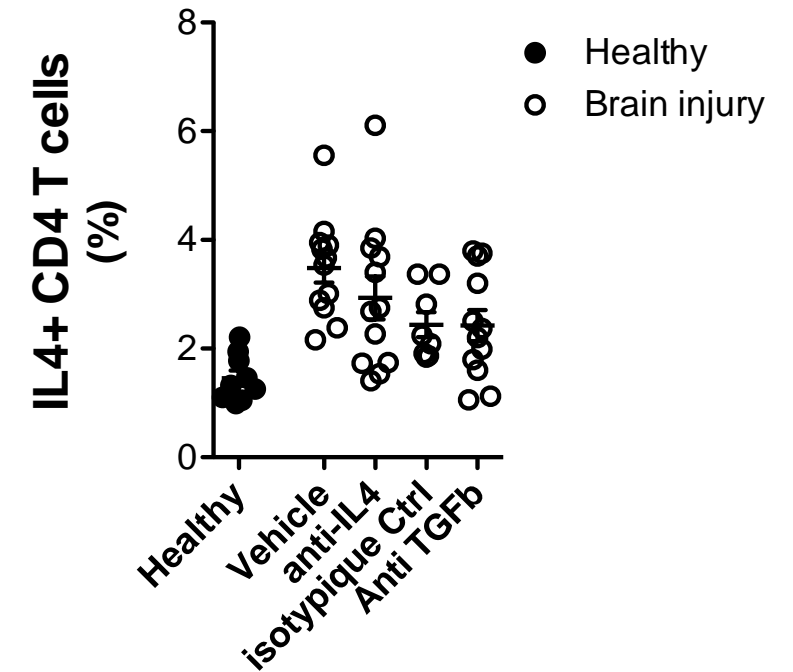
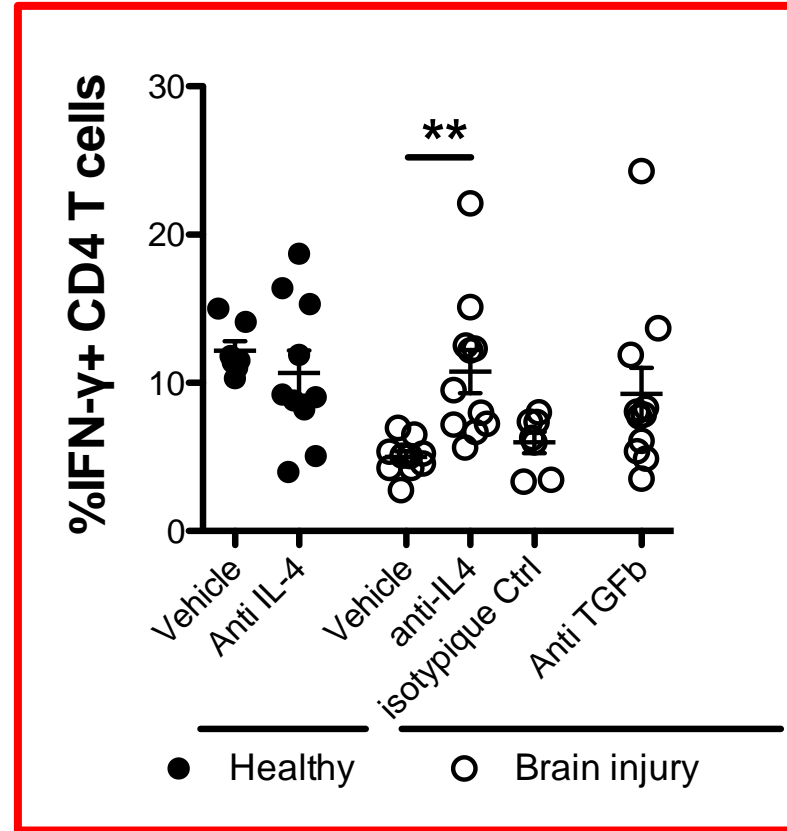
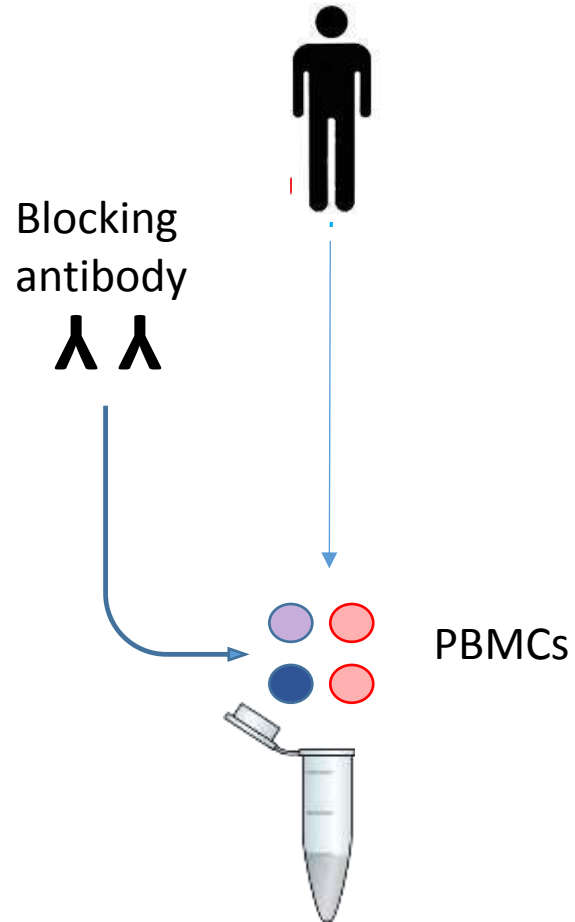
CD4 T cells reprogramming and soluble circulating mediators ?



CD4 T cells reprogramming is continuously maintained by CD14+ cells, and other mediators are involved



CD4 T cells reprogramming is partially IL-4 dependent, but not TGF- β dependent



Conclusions

- **HSV reactivations are common** in brain injured patients, associated with **poor outcome**
- Long-lasting **lymphopenia**
 - No apoptosis (caspase ko mice ?)
 - Not associated with HSV reactivation
- **Long lasting TF reprogramming of CD4 T cells after BI**
 - No exhaustion
- **Altered TF reprogramming of CD4 T cells is associated with HSV reactivation**
 - **Microenvironment : CD14, IL-4.**
 - **Other mechanisms under the scope : epigenetic modifications ? CD14 cells ?**
 - **Role of direct activation by brain-released DAMPs ?**



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