Regulation and manipulation of virus infection fates

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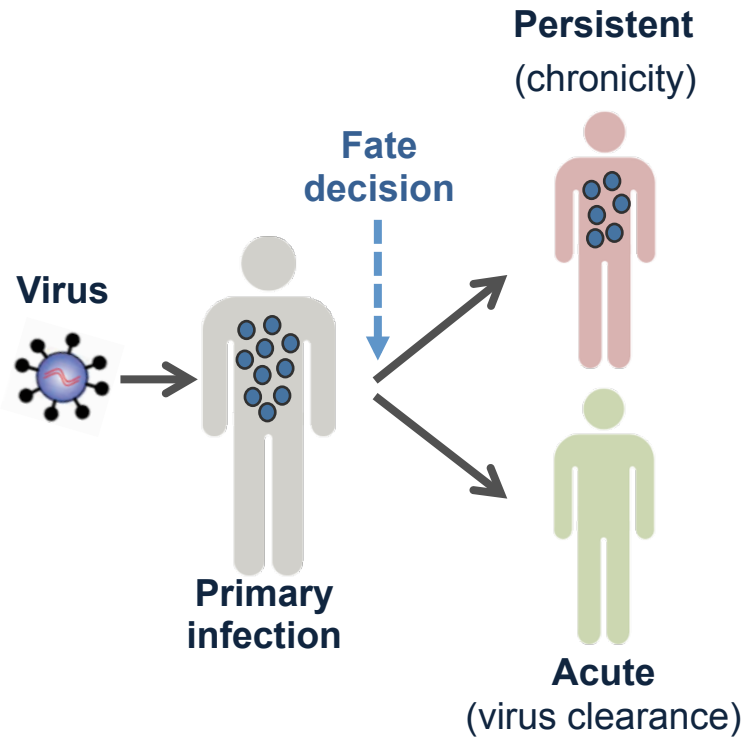
Most common outcomes of "pathogenic" virus infections



our interests:

- **What regulates the outcome?**
- **How can one manipulate it?**

This presentation

- **Concept of a "pathogen"**
- **2 key papers on virus-host interactions that boosted immunotherapy trials in humans**
- **Project on "gain of effector function by anti-exhaustion antibodies" in HIV infection**
- **Future perspectives**

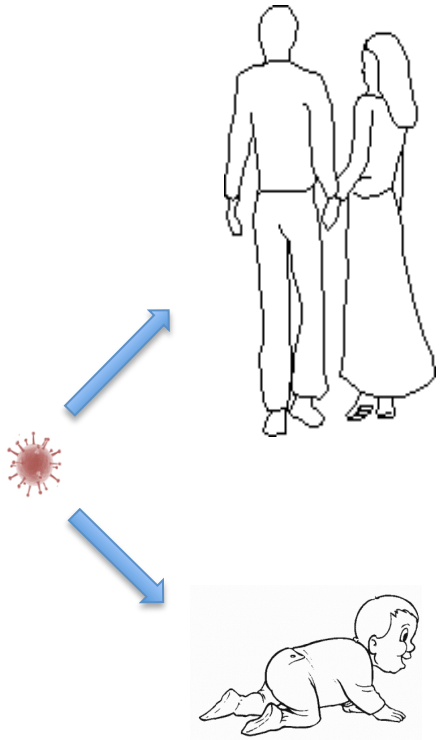
The concept of a pathogen

Postulates of the physician **Robert Koch** (1843 - 1910)

- The organism must be associated regularly with the disease and its characteristic lesions
- The organism must be isolated from the diseased host and grown in culture
- The disease must be reproduced when a pure preparation of the organism is introduced into a healthy, susceptible host
- The same organism must be re-isolated from the experimentally infected host

➔ ***microbe-centred view of pathogenesis***

Acute/chronic infection outcomes in humans



HIV: ≈100% chronic (1% "elite controllers")

HCV: ≈50-80% chronic

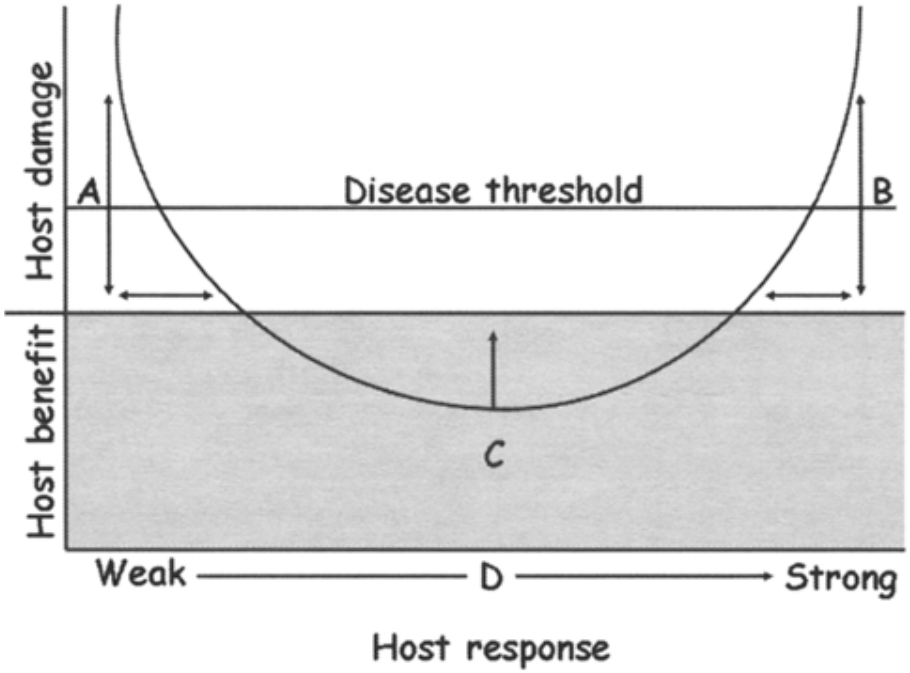
HBV: ≈5% chronic

HIV: ≈100% chronic (rapid progression)

HBV: ≈90% chronic

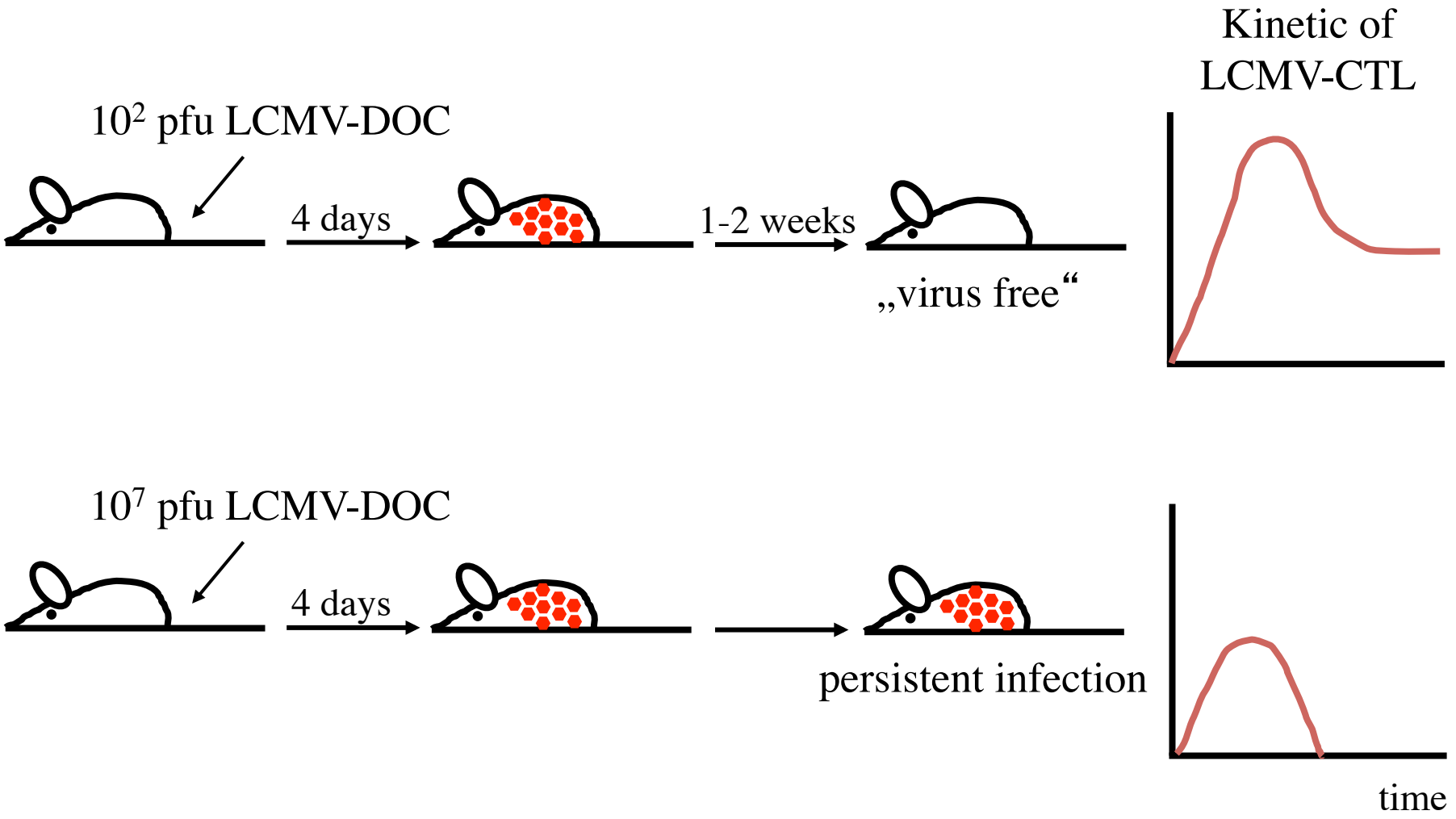
➔ *Koch´s postulates do not cover all aspects of viral pathogenesis*

Damage-response framework (Pirofski & Casadevall 1999)



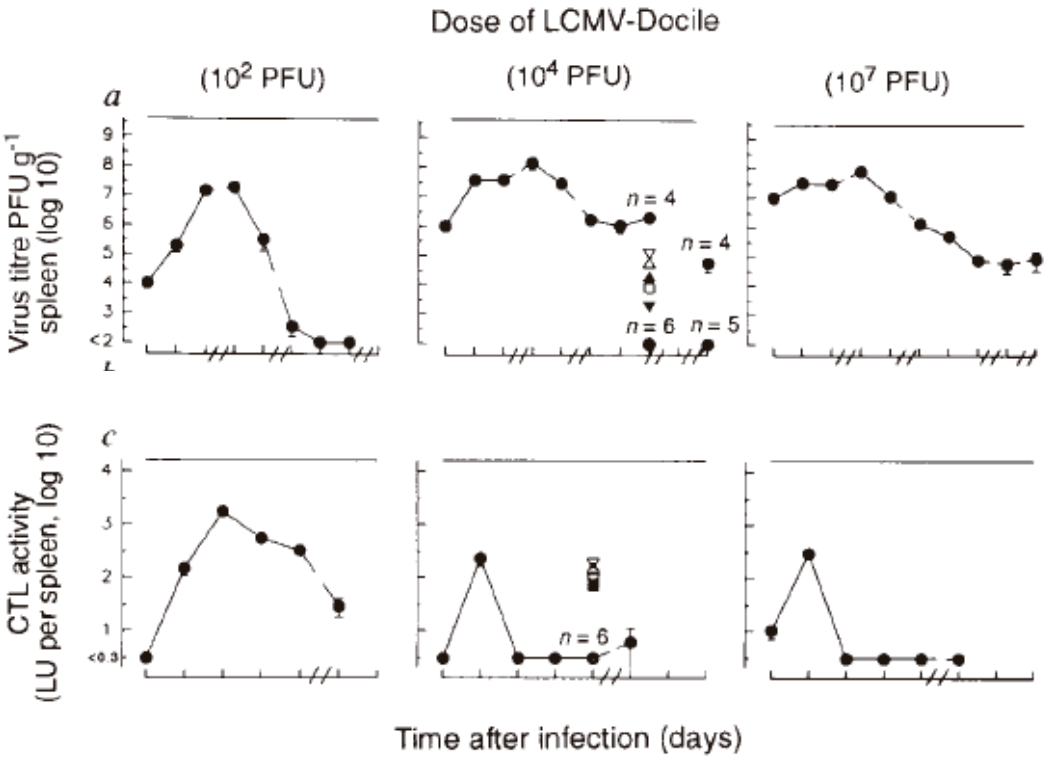
- Microbial pathogenesis requires 2 entities, a host and a microbe
- Host damage can result from microbial factors, host factors, or both

Virus persistence by „exhaustion“ of LCMV-specific CTL (high dose tolerance)



***Rolf Zinkernagel´s group**: Moskophidis et al., Nature 362, 758 (1993)*

Viral persistence due to exhaustion of antiviral cytotoxic T cells

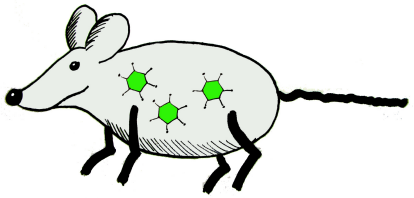


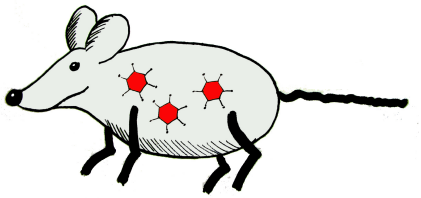
Moskophidis et al., Nature 362, 758 (1993)

Exhaustion of CTL is linked to PD1/PD-L1 interactions

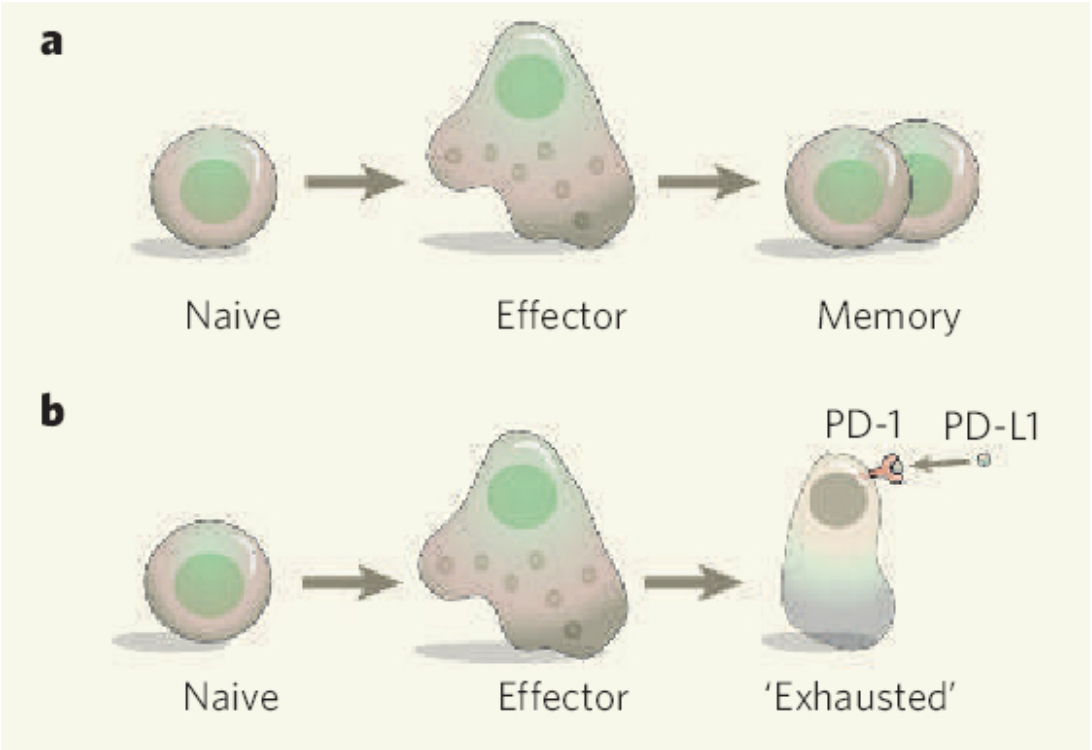
- **Acute infection**
- Virus control after 1 week

LCMV „Armstrong“





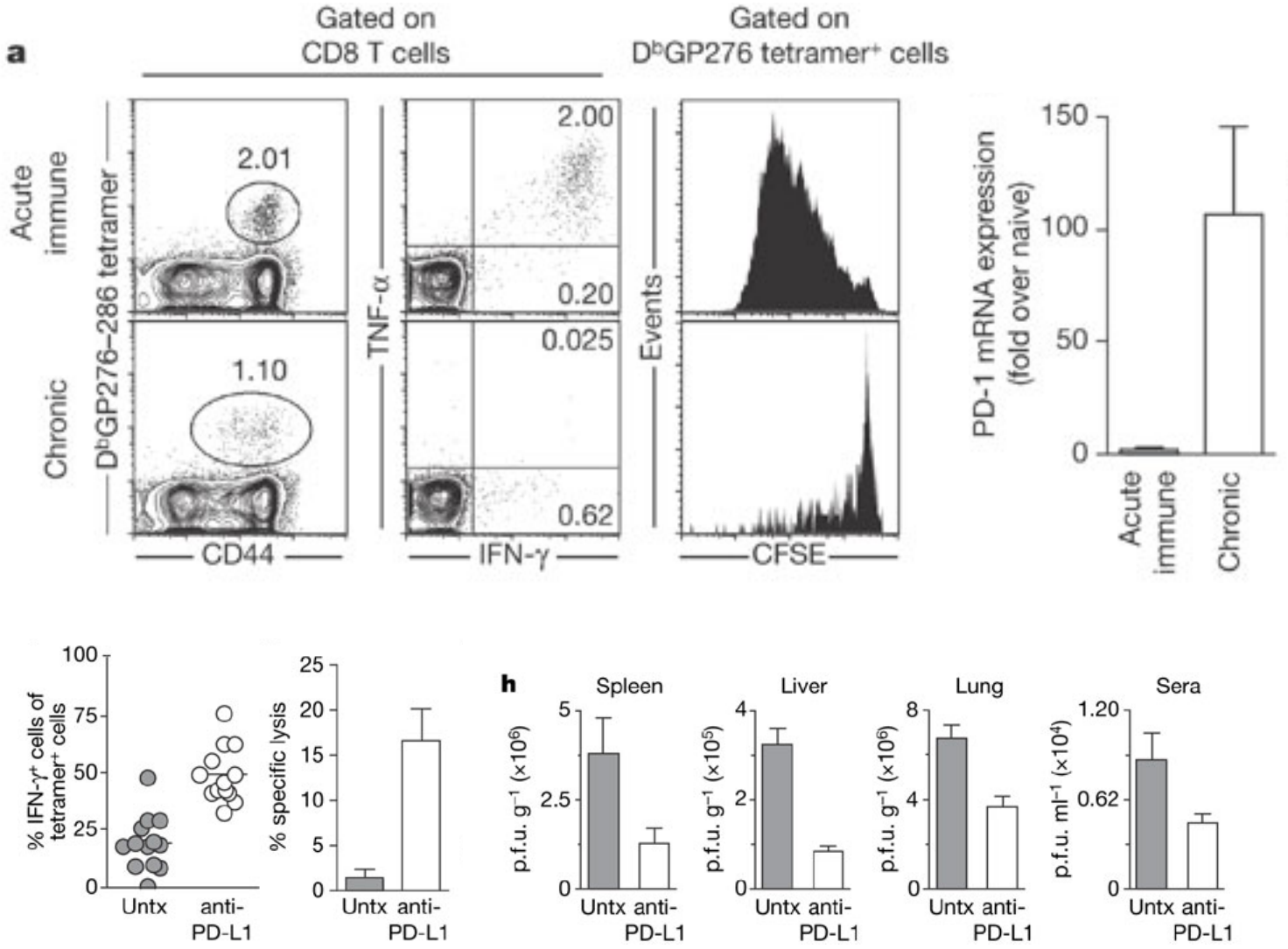
LCMV clone 13
(2 aa changes in Gp and Pol)



- **Chronic infection**
- High virus load
- T cell exhaustion

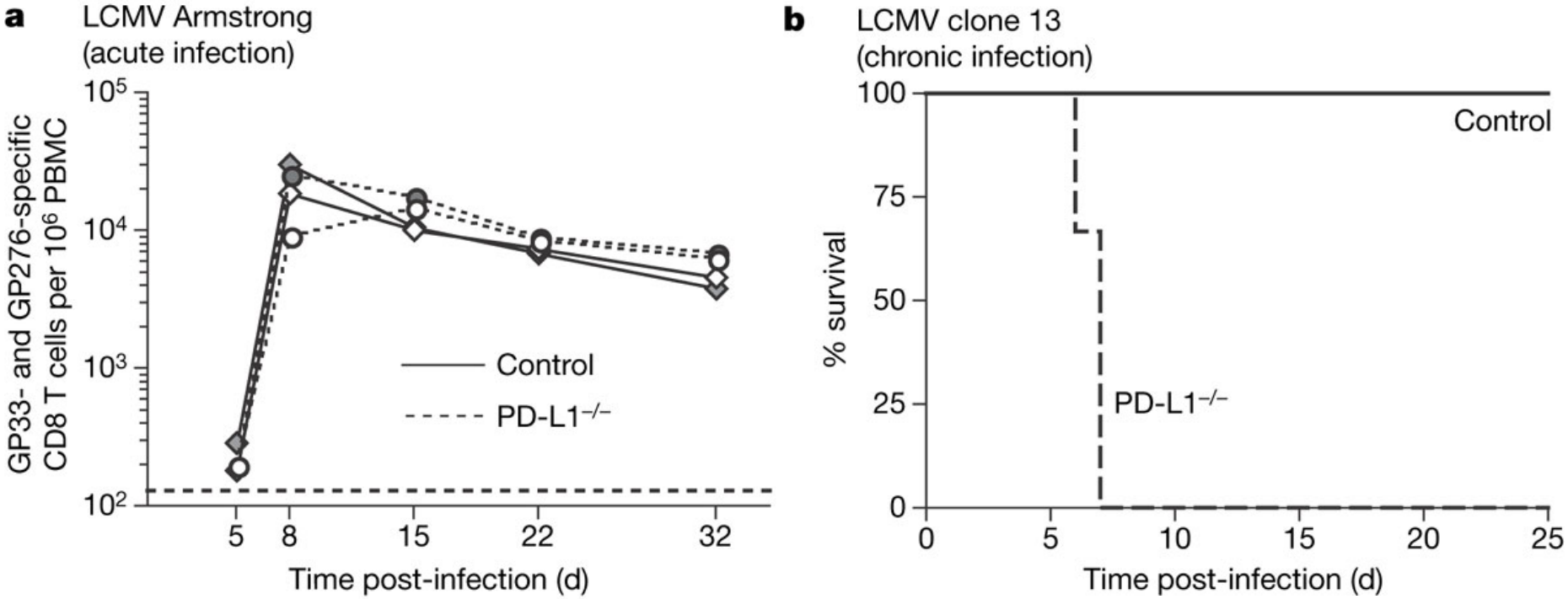
***Rafi Ahmed´s group**: Barber et al., Nature 439, 682 (2006)*

Exhaustion of CTL is linked to PD1/PD-L1 interactions and can be restored by anti-PD-L1 antibodies



Barber et al., Nature 439, 682 (2006)

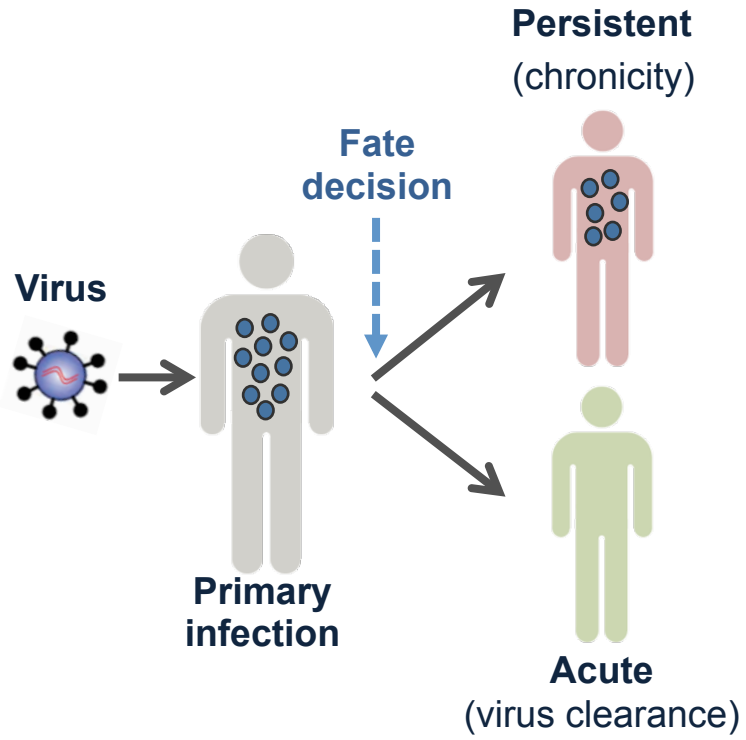
CTL exhaustion avoids immunopathology



➔ *PD1/PD-L1 interaction delivers inhibitory signals that shut down T effector functions and enable host survival*

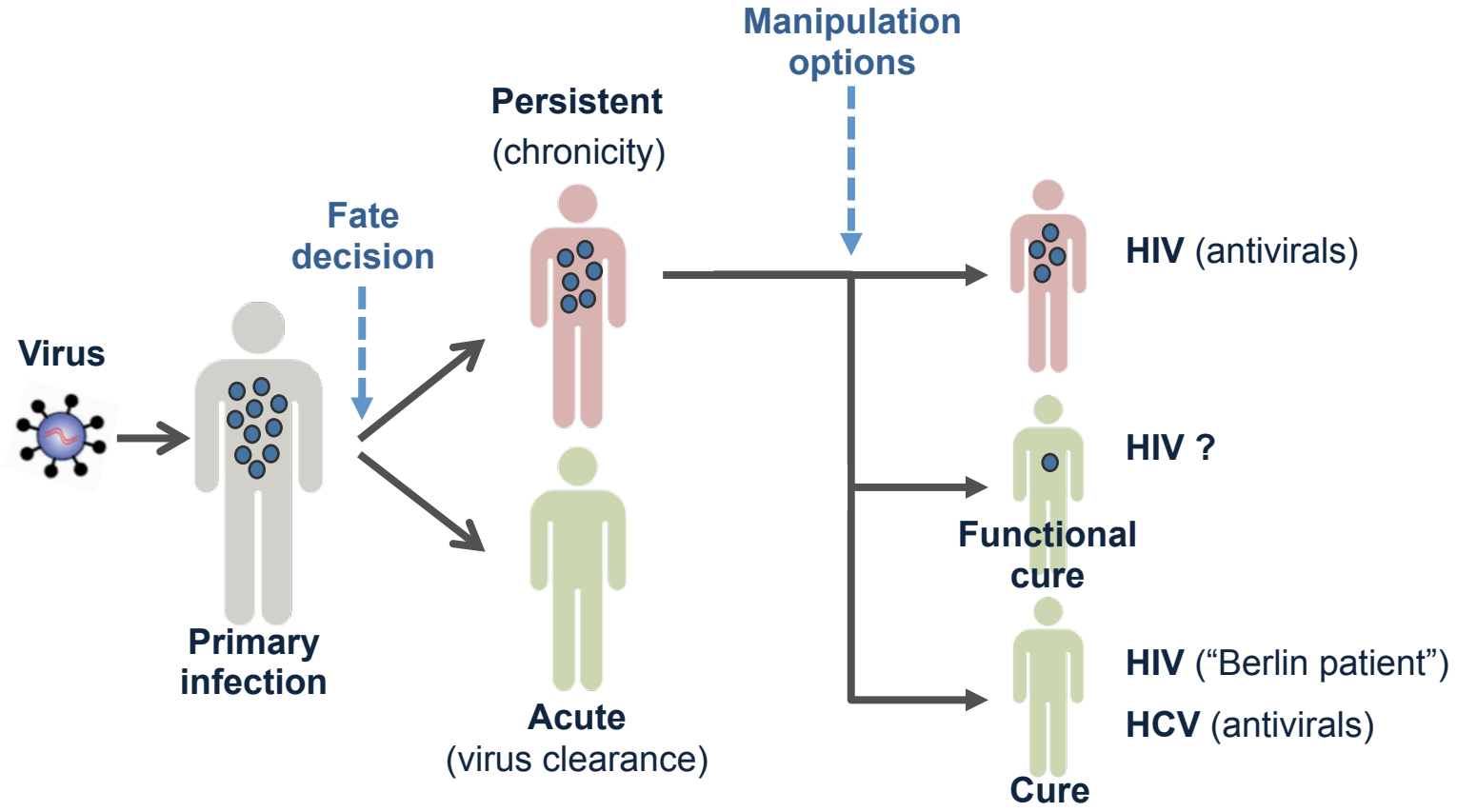
Barber et al., Nature 439, 682 (2006)

PD1/PD-L1-mediated T cell exhaustion in chronic human infections



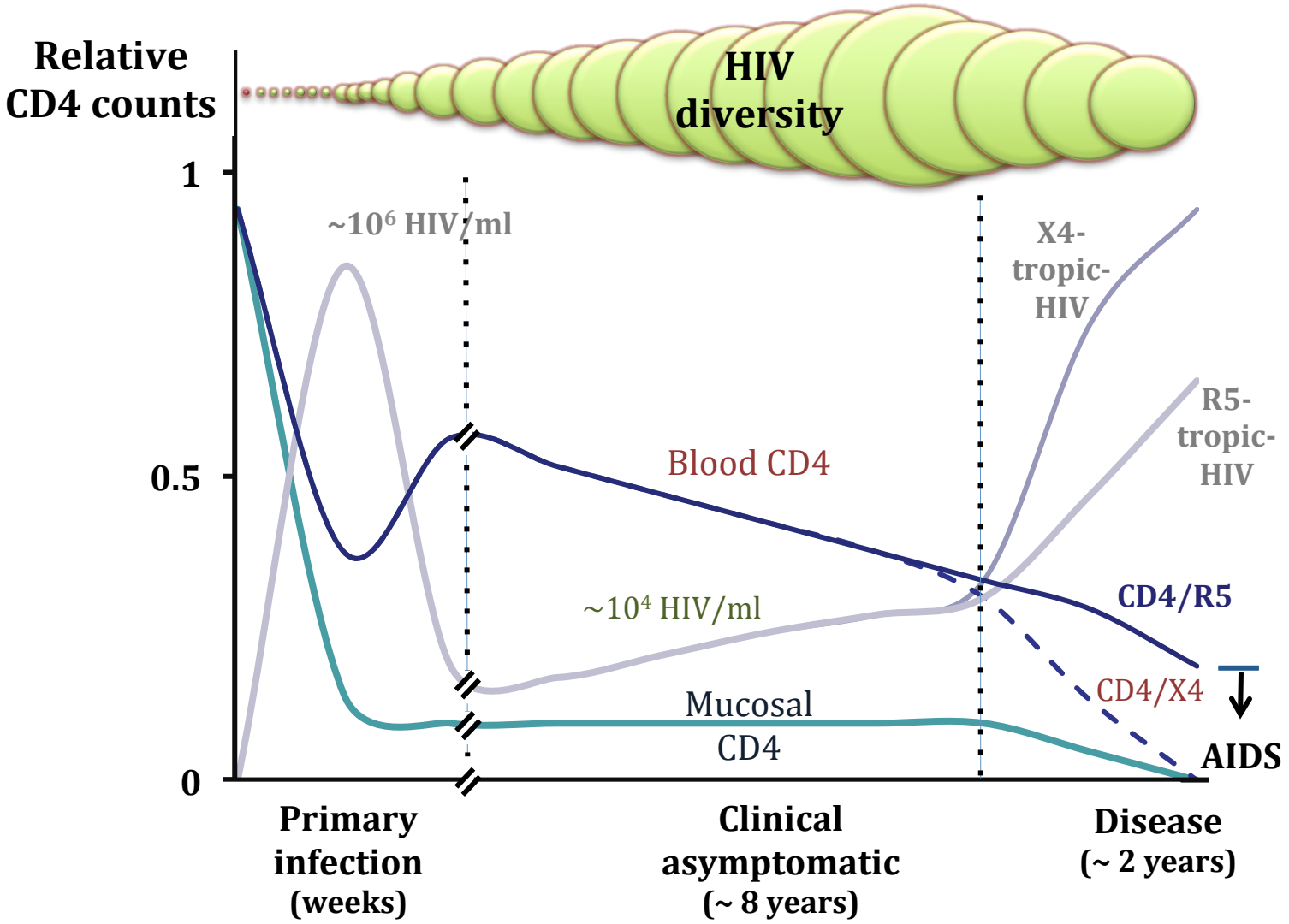
- **HIV**
- **HCV**
- **HBV**
- **CMV (viremic)**

Virus infection fates and manipulation options for persistent HIV and HCV infections

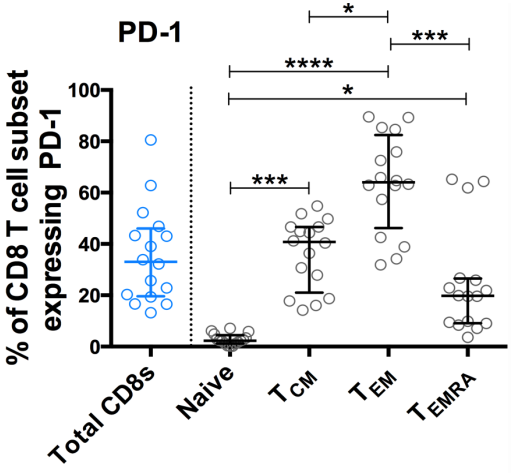


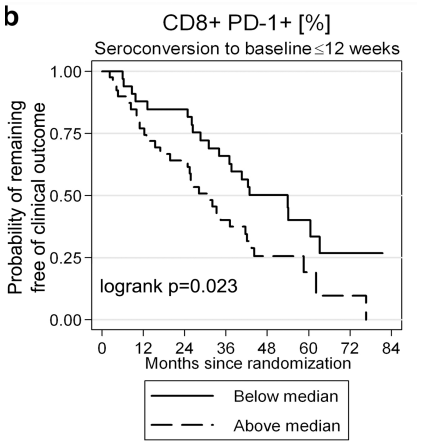
➔ *Inhibition of PD1/PD-L1 interaction may be a therapeutic option for human viral infections*

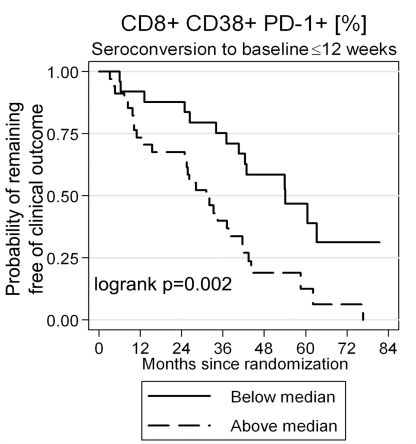
Typical course of an HIV infection

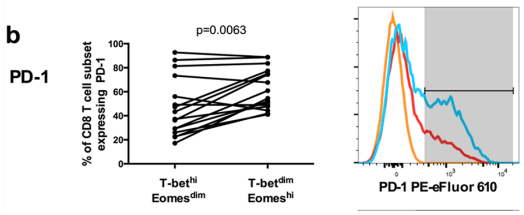


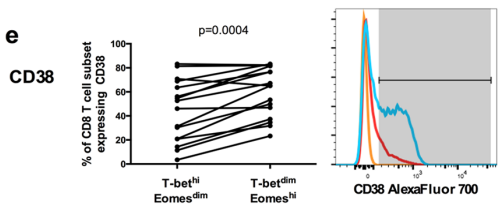
Exhaustion of activated CD8 T cells in early HIV-1 infection predicts disease progression











Hoffmann M, et al. (2016) PLoS Pathogene 12(7): e1005661.

How to regulate infection fates in persistent HIV infection?

Options:

(1) Slow down virus-mediated pathogenesis

- **anti-viral drugs**

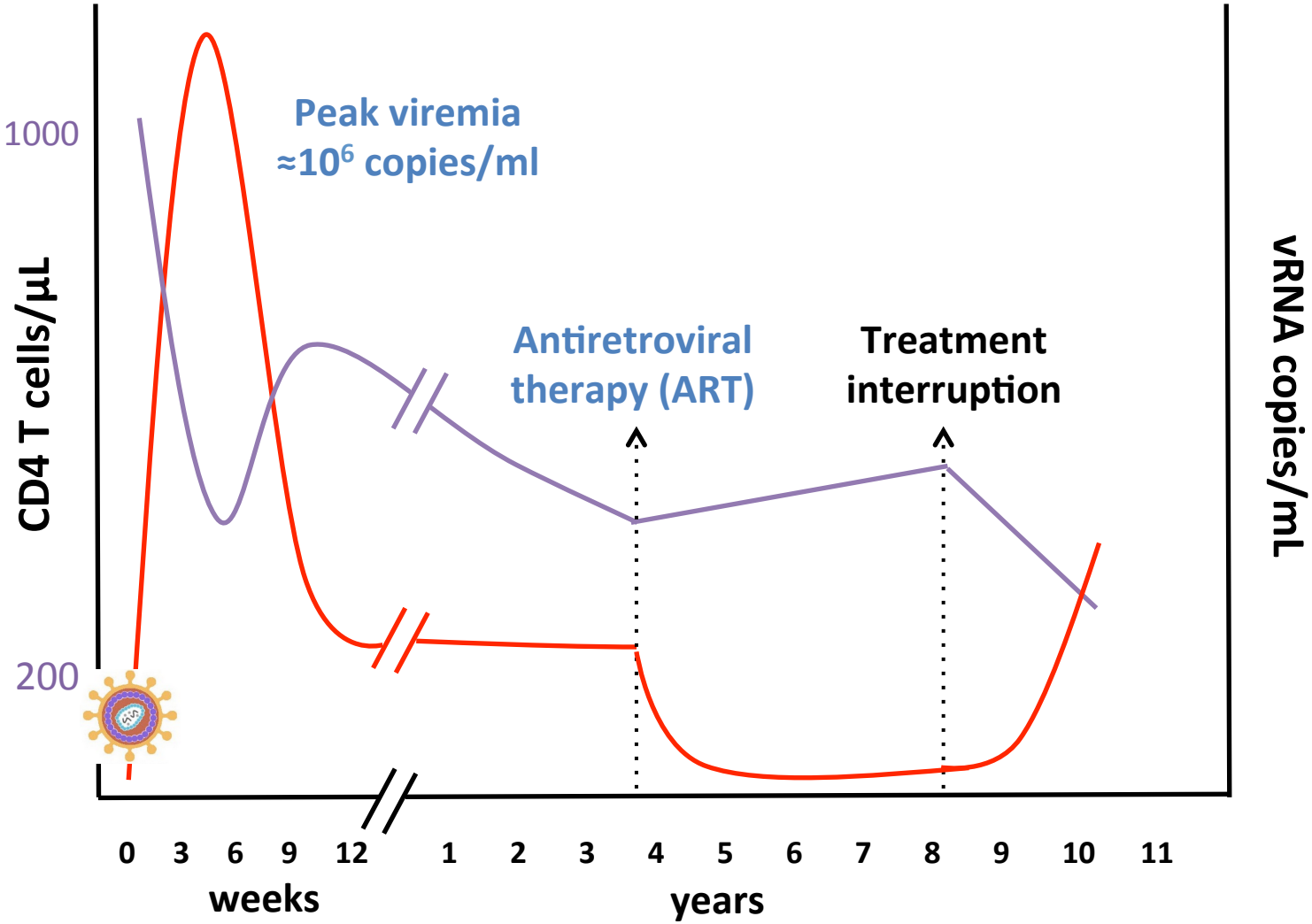
(2) Cure – eliminate HIV & pathogenesis

- **only a single case! … the Berlin patient**

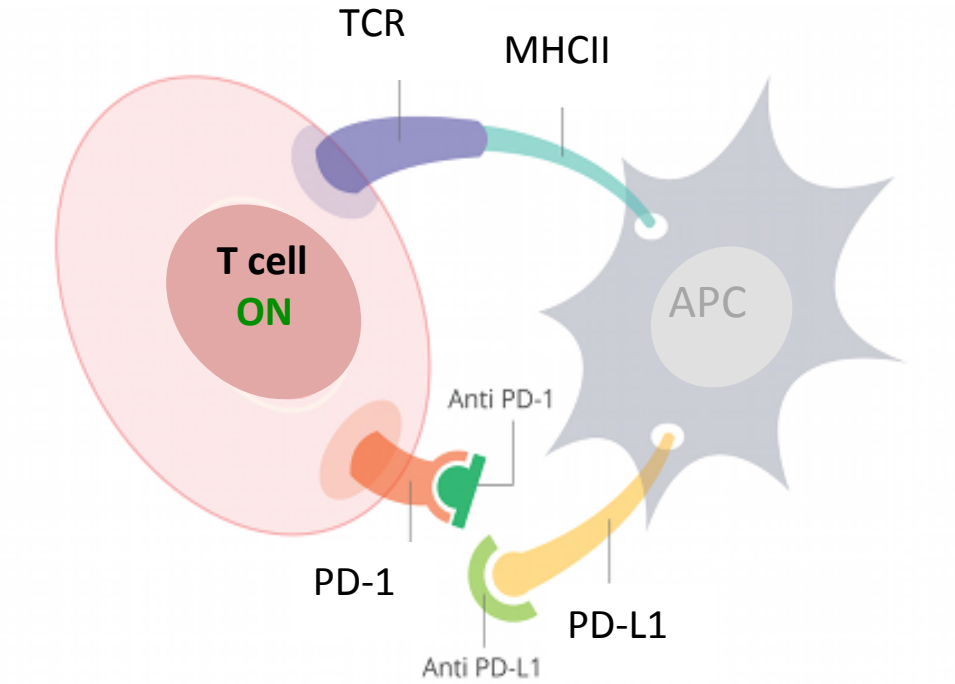
(3) Functional cure – control HIV without drugs

- **changing the virus – immune system balance**

Time course of HIV infection after treatment and treatment interruption



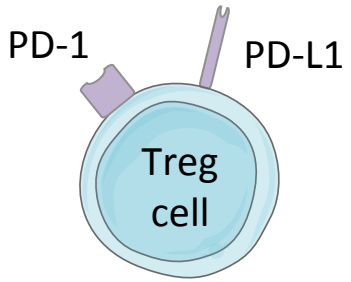
Blocking the PD-1/PD-L1 pathway restores the exhausted phenotype



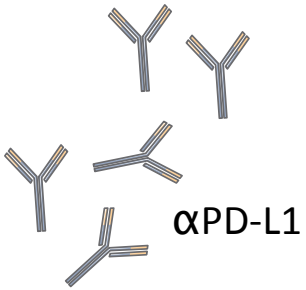
➔ increase of proliferation, cytokine secretion & cytotoxicity

(modified from www.smart patients.com)

OBJECTIVES

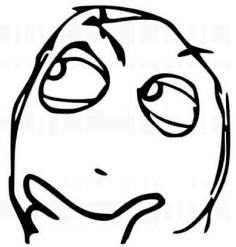


1. To evaluate PD-1 and PD-L1 expression in Teff/Treg cells from HIV-patients.

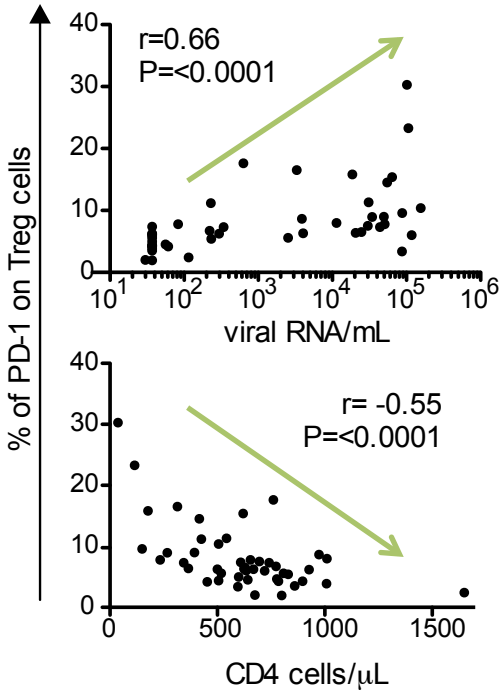


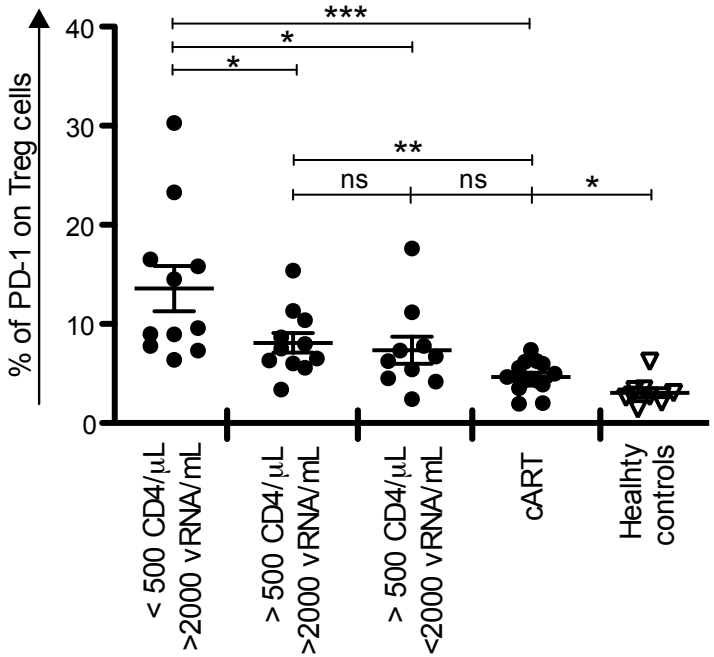
2. To explore the consequences of *ex vivo* PD-L1 blockade for Teff/Treg cells from HIV-patients.

3. To generate hypotheses on patient selection criteria for PD-L1 blockade immunotherapy.



PD-1 expression on Treg cells correlates with disease progression



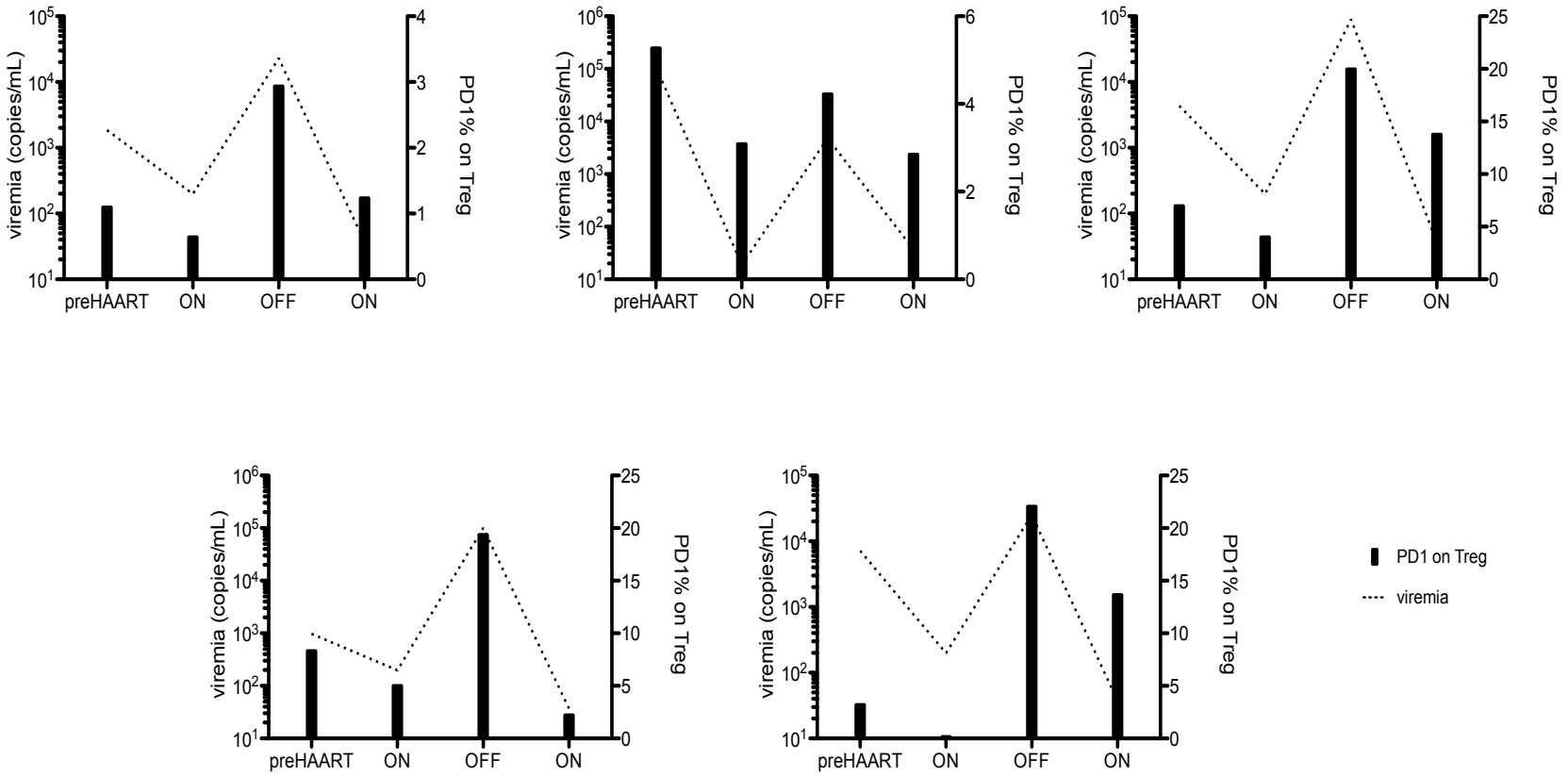


- PD-1 expression on Treg cells correlates:
  - > positively with viral load
  - > negatively with CD4 count

Mean ± SEM shown

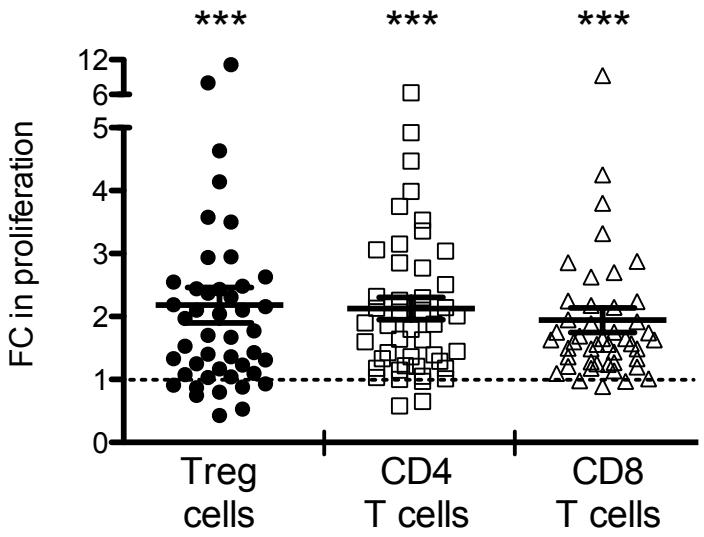
P value: * <0.05; ** <0.01; ***<0.001; ns: non significant

PD-1 expression on Treg cells follows viral load



PD-L1 blockade increases Treg cell proliferation

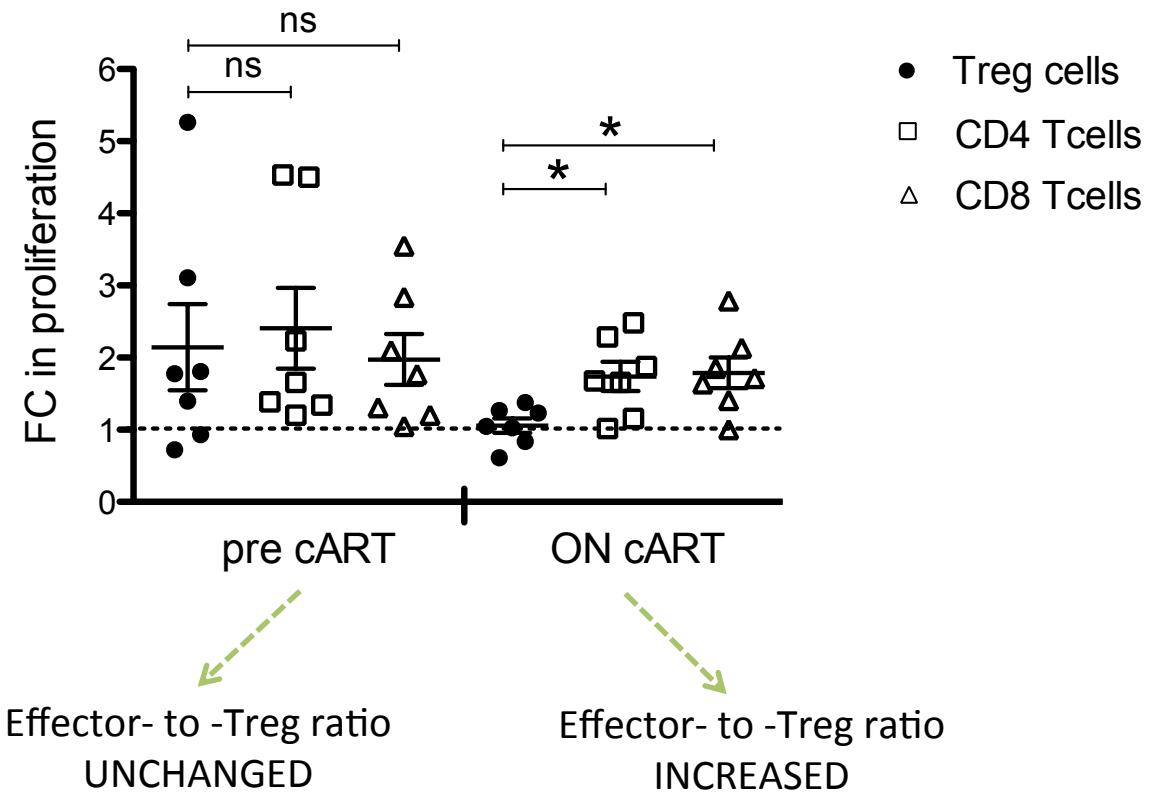
CFSE labelled PBMC + HIV-Gag peptides
+/- PD-L1 blocking antibody → Treg proliferation (day 6)



$$\text{Fold change (FC) in proliferation} = \frac{\text{Proliferation with gag peptides + PD-L1 blocking antibody}}{\text{Proliferation with gag peptides + isotype antibody}}$$

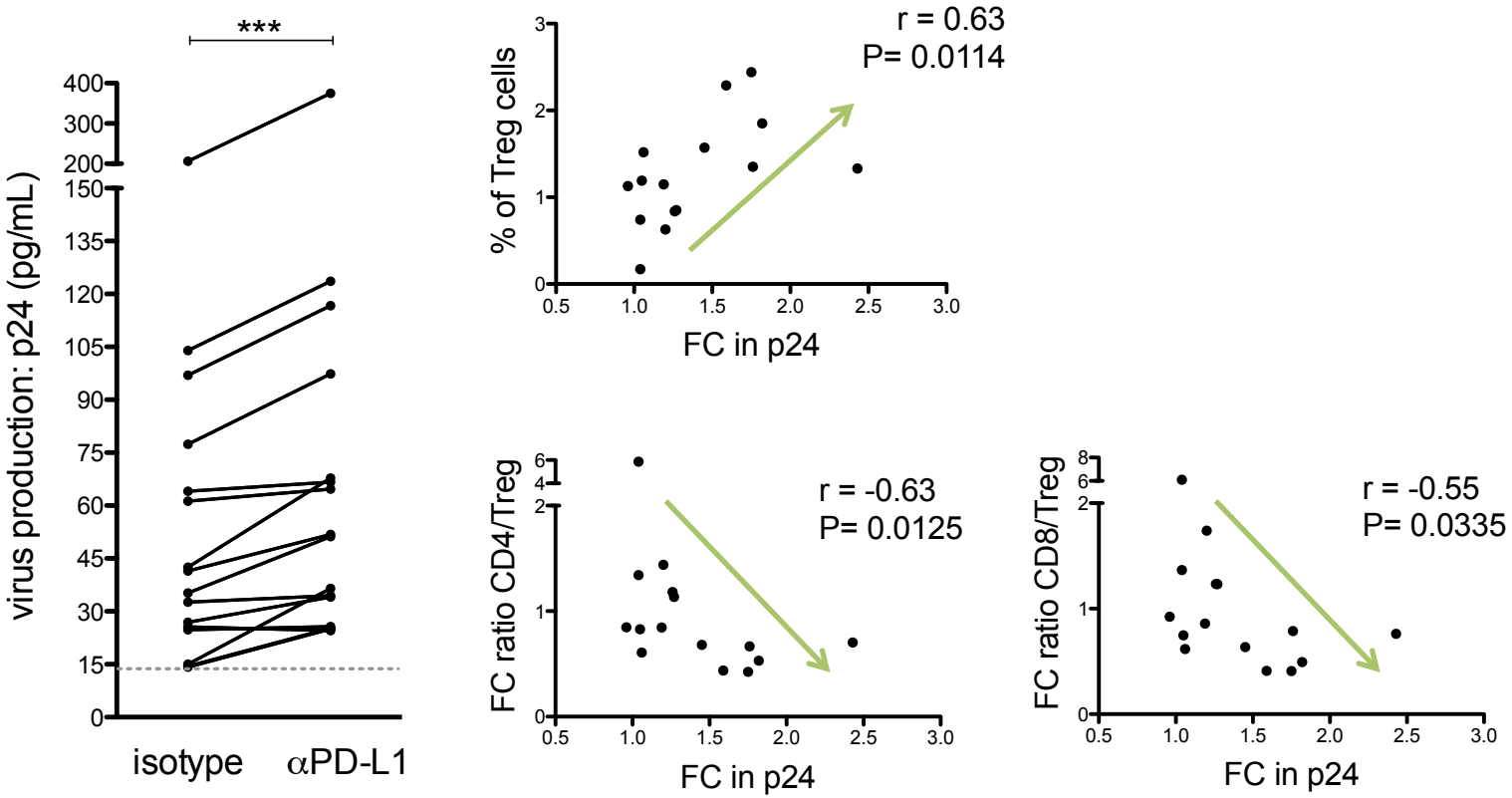
Mean ± SEM shown
P value: ***<0.001

Under cART, PD-L1 blockade increases effector T cell proliferation but not regulatory T cell proliferation



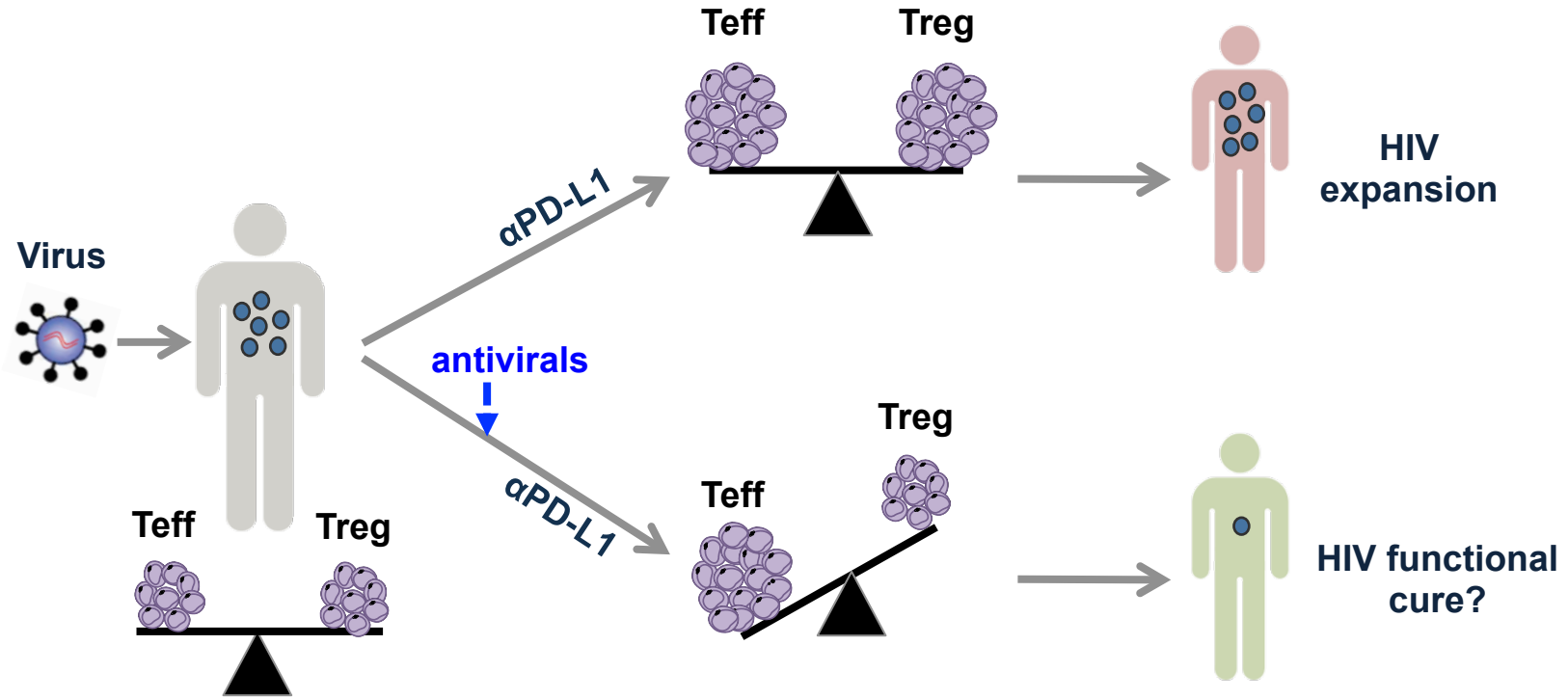
Mean ± SEM shown
P value: * <0.05; ns: non significant

PD-L1 blockade increases virus reactivation in cell cultures from viremic patients



P value: *** <0.001

The net gain of T cell effector function after PD-L1 blockade critically depends on plasma viremia



- Steady state
- High viremia

Conclusions

- There is an increase in PD-1- and PD-L1- expressing Treg cells in HIV-infected individuals.

  Treg cells are likely to be influenced by immunotherapy targeting PD-1/PD-L1 pathway

- *in vitro* PD-L1 blockade differentially impacts Treg cells from HIV-infected individuals depending on the plasma viremia of the host.

  Only HIV-infected individuals under antiretroviral treatment might benefit from PD-L1 blockade immunotherapy

C. Peligero et al., PLOS Pathogens 11(12):e1005270 (2015)

Future perspectives?

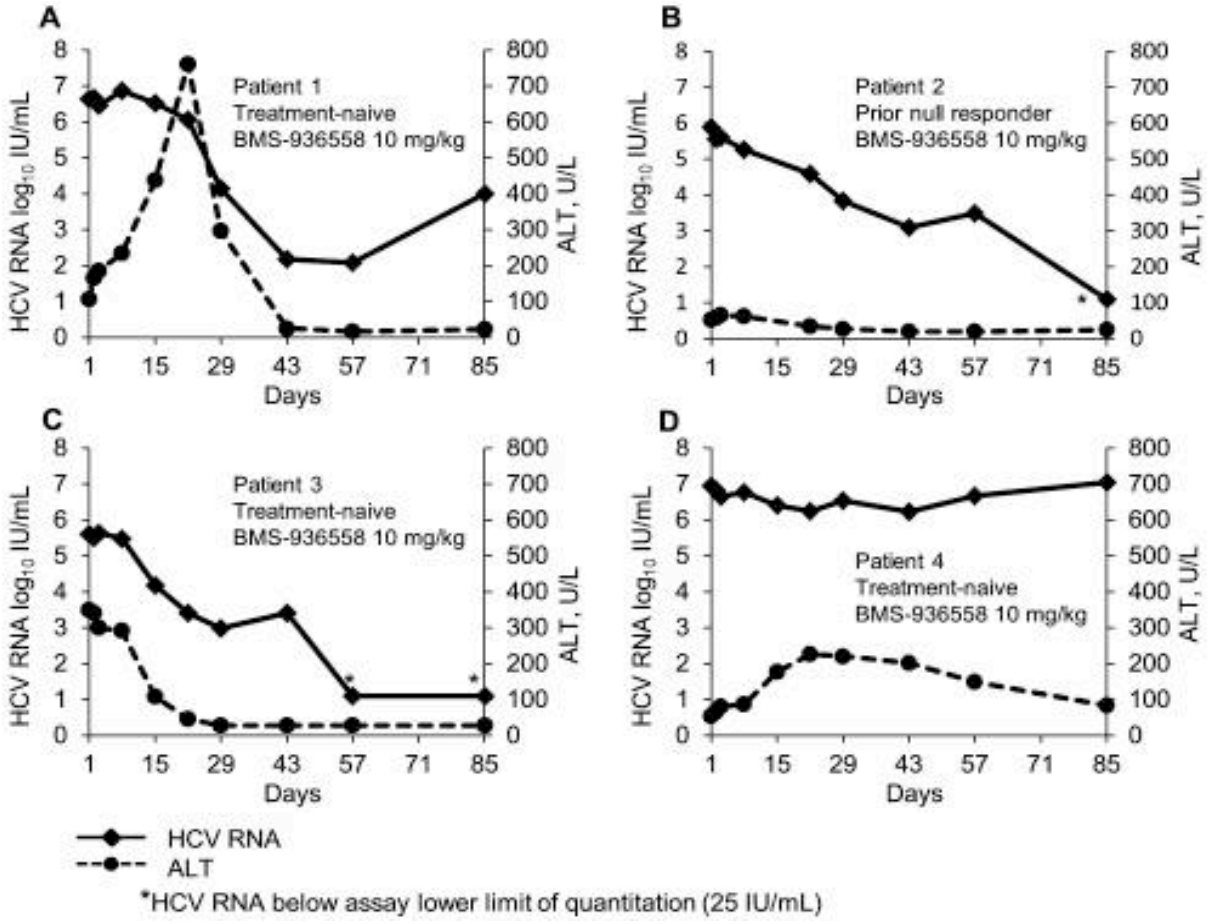
Clinical trials: checkpoint inhibition

- 28 trials (October 2016)
  - Cancer trials against melanoma, pancreatic cancer, glioblastoma, hepatocellular carcinoma etc.

- ***anti- PD1, anti-PD-L1 & anti CTLA-4 and virus***
  - cancers plus/associated to viruses
    HIV, HTLV, HBV, HCV, HPV, EBV, MCPV
  - 1 completed study of HCV infection (2013)

https://clinicaltrials.gov

Significant reduction of HCV in some chronic carriers after anti-PD1 antibody administration



Gardiner D et al., PLoS One. 2013 May 22;8(5):e63818

Perspectives

- **inhibition of T cell exhaustion : a new era of immunotherapy in infectious diseases & cancer**
- **very promising results in influencing infection outcomes**
- **important to understand why some patients respond and others not**
- **important to understand clinical implications**
- **systemic view on exhaustion is needed**

Acknowledgements

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