Determinants of viral persistence and clearance during HIV and HCV infections

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Human immunodeficiency virus (HIV) and hepatitis C virus (HCV)

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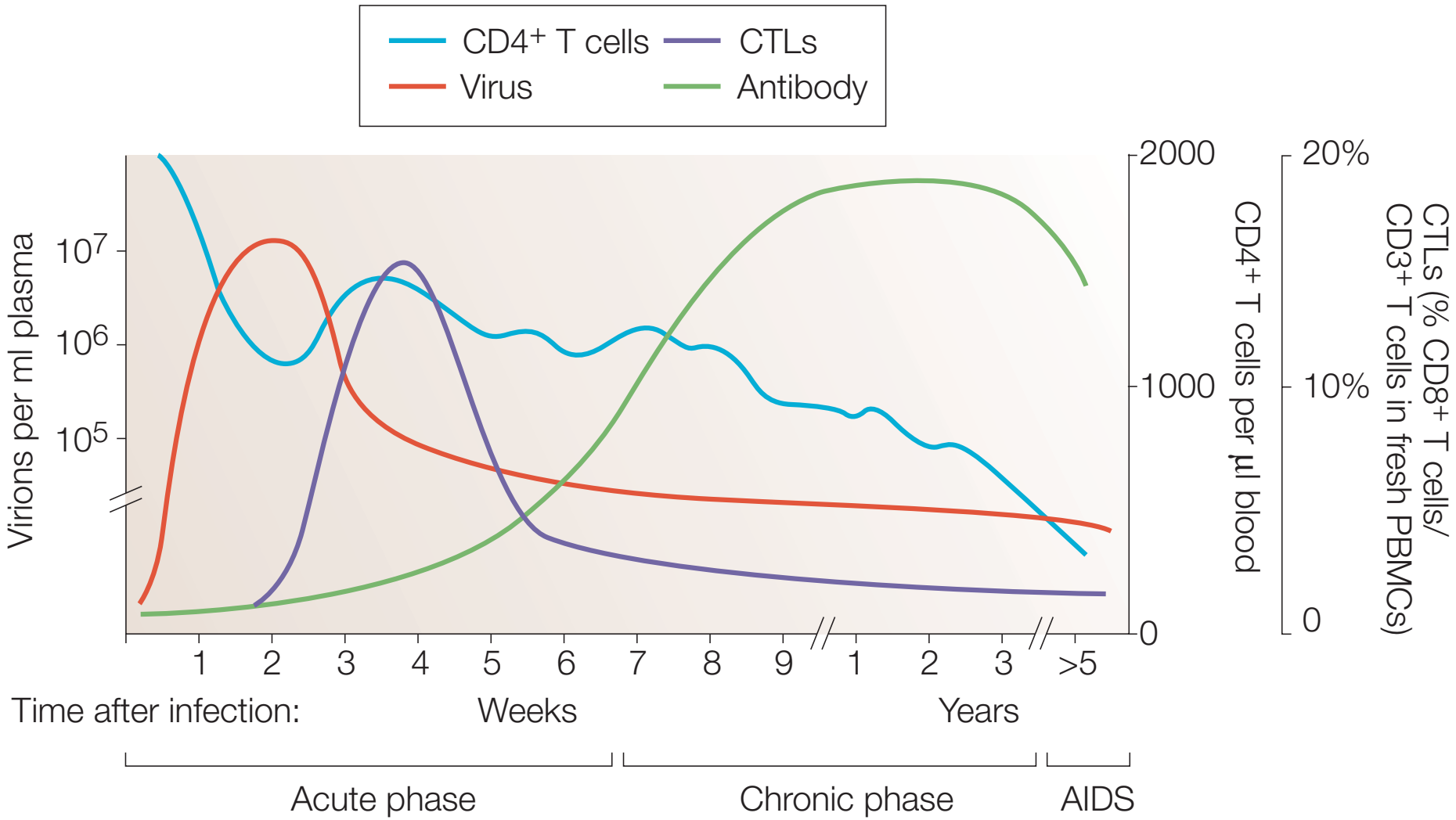
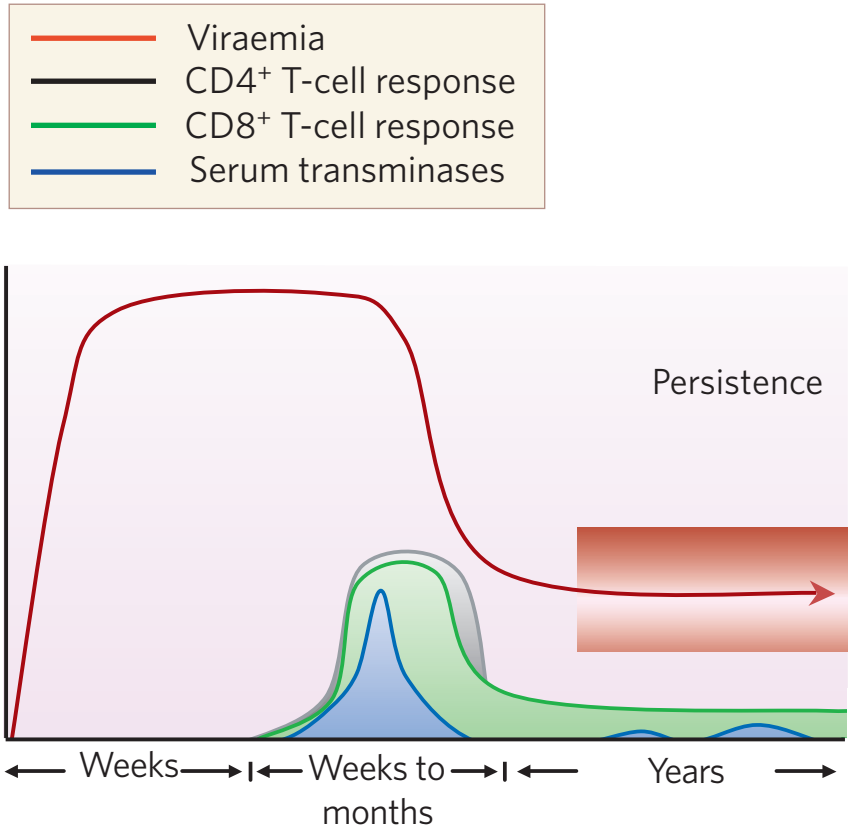
- RNA viruses that can cause **chronic infection** with potentially fatal outcomes (AIDS in HIV and liver disease for HCV infection)
- Distinct acute and chronic phase of infection showing **different outcomes** (spontaneous clearance in HCV and persistence in HIV)
- **Set-point (baseline) viral load** level is an important predictor for disease progression
- Role of immune responses (**antibodies** and **$CD8^+$ T cells**) remains unclear for both infections

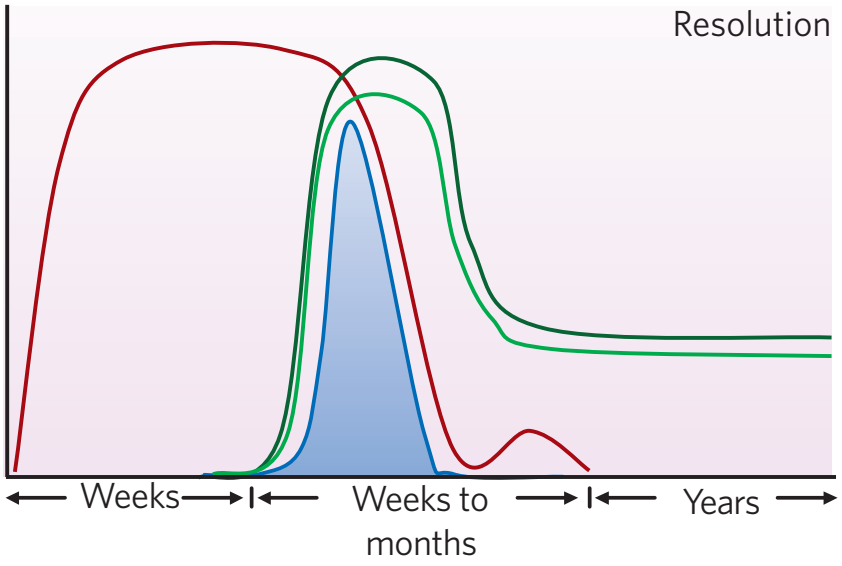
Dynamics of acute and chronic HIV infection



Goulder & Watkins (2004) Nat Rev Immunol

Dynamics of acute and chronic HCV infection





About 26% of individuals clear the infection within the first months.[1]

Bowen & Walker (2005) Nature
[1] Micallef et al. (2006) J Viral Hepat

Distribution of set-point (baseline) viral load for HIV and HCV

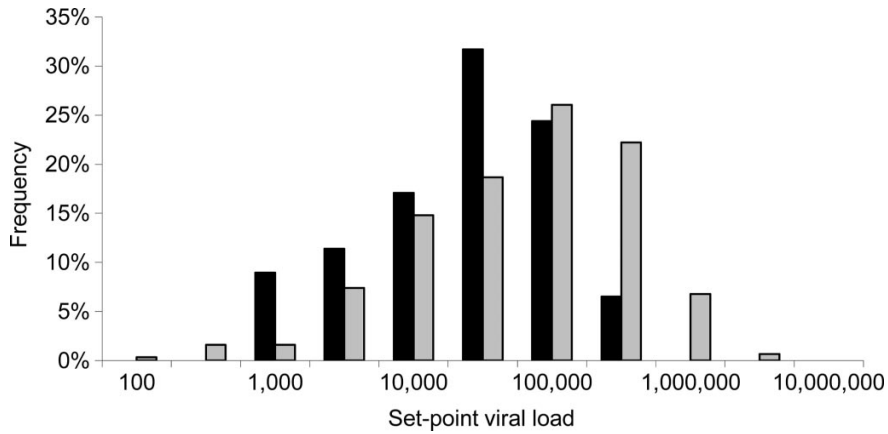


Fig. 1. The distribution of set-point viral loads. The distribution of viral loads (copies per milliliter of peripheral blood) is plotted for untreated individuals in the Amsterdam Seroconverters Cohort (black bars) and the Zambian Transmission Study (7) (gray bars). The bars represent bins 0.5 $\log_{10}$ wide and are labeled by their midpoint viral load.

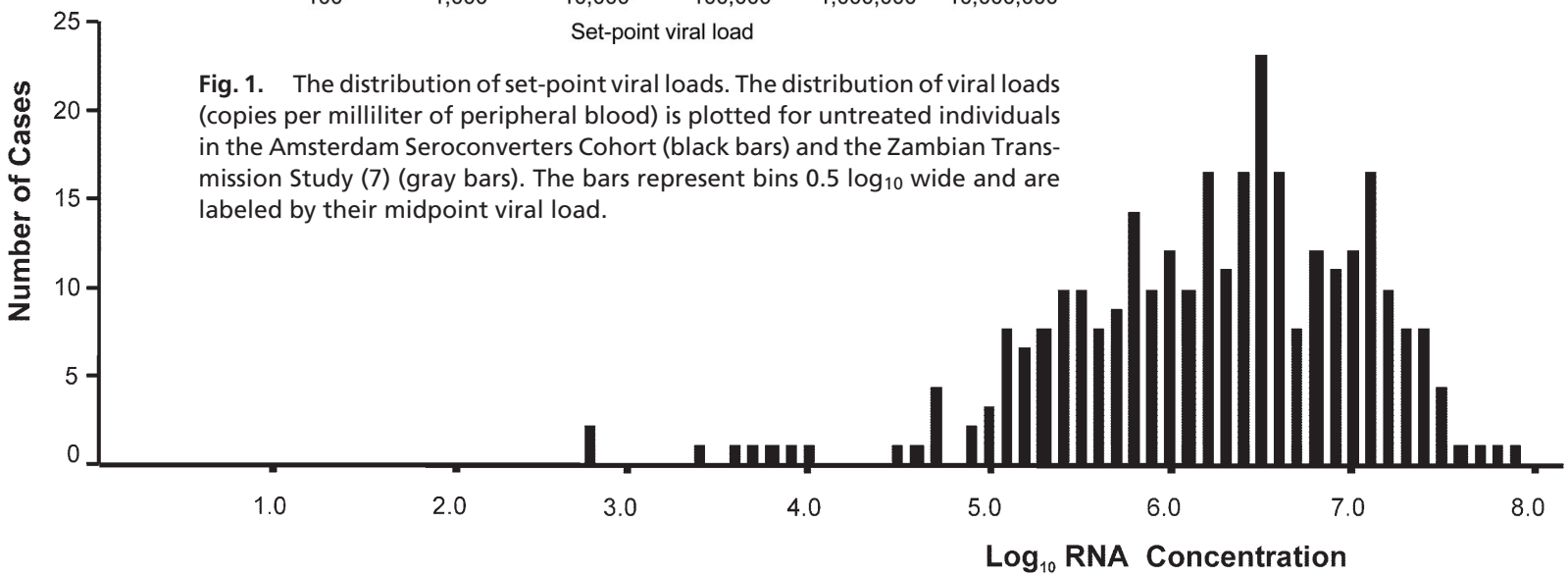


Figure 1. Distribution of hepatitis C virus RNA concentrations among persons with chronic infection.

HIV: Fraser et al. (2007) PNAS
HCV: Nainan et al. (2006) Gastroenterology

Open questions

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- What are the **determinants** of set-point (baseline) viral load levels?
- What type of **immune responses** (antibodies, CD8+ T cells, cytolytic, non-cytolytic) play a major role?
- Why can HCV, but not HIV, **clear** spontaneously?
- Can we learn something for **drug therapy** or **vaccine development**?

Mathematical model

Generic virus dynamics model to describe the dynamics of HIV and HCV within a host[1,2]:

$$\frac{dT}{dt} = \lambda - \beta VT + r_T(1 - \frac{T+I}{T_{\max}}) - dT,$$
$$\frac{dI}{dt} = \beta VT + r_I(1 - \frac{T+I}{T_{\max}}) - \delta I,$$
$$\frac{dV}{dt} = pI - cV,$$

HIV: Target cells *T* represent CD4$^+$ T cells; no proliferation ($r_T = r_I = 0$).
HCV: Target cells *T* represent hepatocytes in the liver.

[1] *Perelson (2002) Nat Rev Immunol*
[2] *Dahari et al. (2009) Gastroenterology*

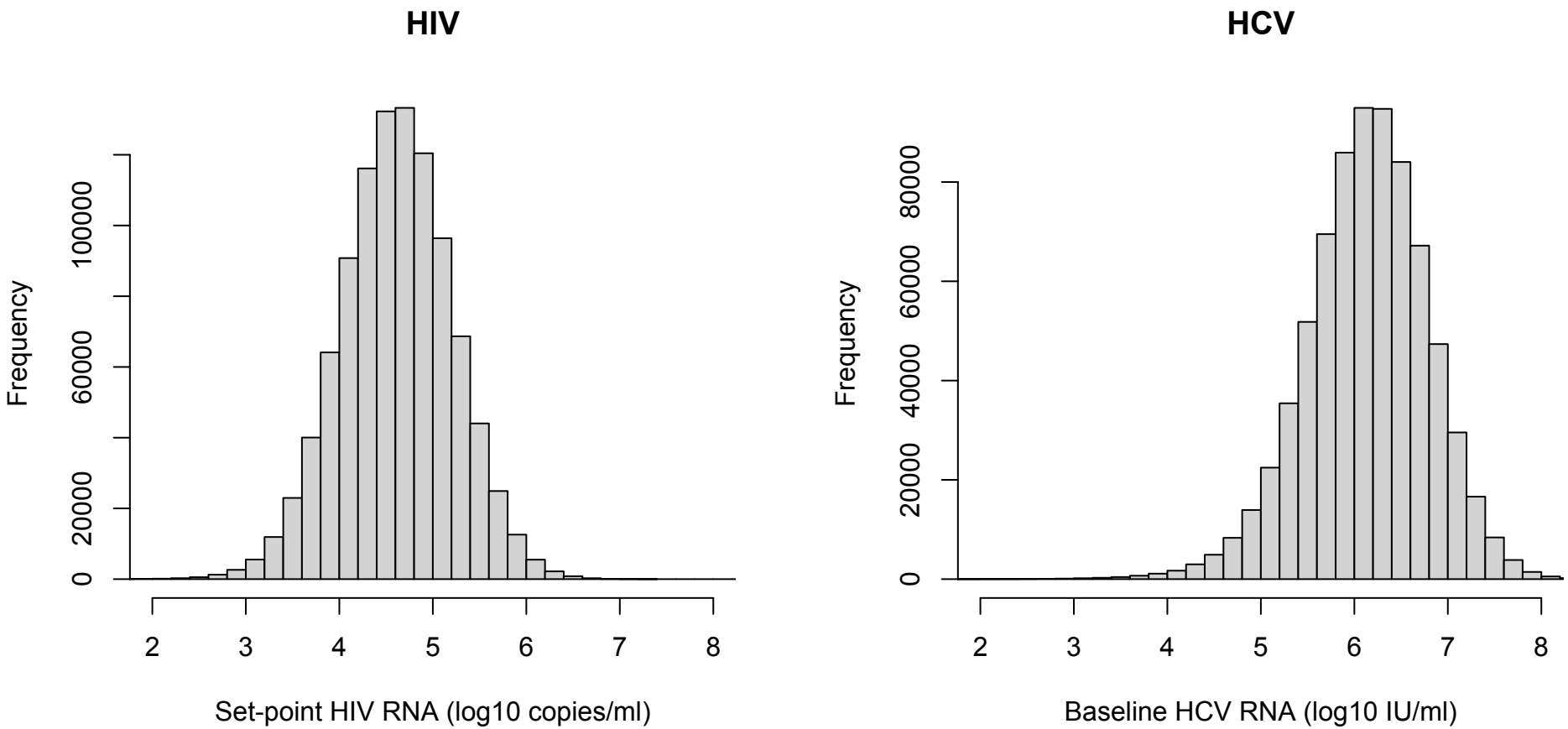
Parameter ranges of virus dynamics

Parameter	Definition	Unit	HIV	HCV
$T_{\max}$	Total number of target cells	10^7 cells ml^{-1}	–	0.4 - 1.3
d	Death rate of target cells	d^{-1}	$0.002 - 0.087$	$0.001 - 0.014$
λ	Production rate of target cells	cells ml^{-1} d^{-1}	$22.1 - 191.5$	$1.0 - dT_{\max}$
β	Infection rate	ml^{-1} virion^{-1} d^{-1}	$10^{-5} - 10^{-3}$	$10^{-9} - 10^{-3}$
δ	Death rate of infected cells	d^{-1}	$0.5 - 1.5$	$d - 0.5$
p	Virus production rate	virions^{-1} cell $^{-1}$ d^{-1}	$10^3 - 10^5$	$0.1 - 6.0$
c	Clerance rate of free virus particels	d^{-1}	$9.1 - 36$	$0.8 - 22.0$
r_T	Max. proliferation rate of target cells	d^{-1}	–	$1.0 - 3.0$
r_I	Max. proliferation rate of infected cells	d^{-1}	–	$0.1 \times r_T - r_T$

- Random assignment of parameters to a cohort of 10^6 hypothetical patients
- Sampling from log-normal distributions
- Range reflects 95% of probability distribution

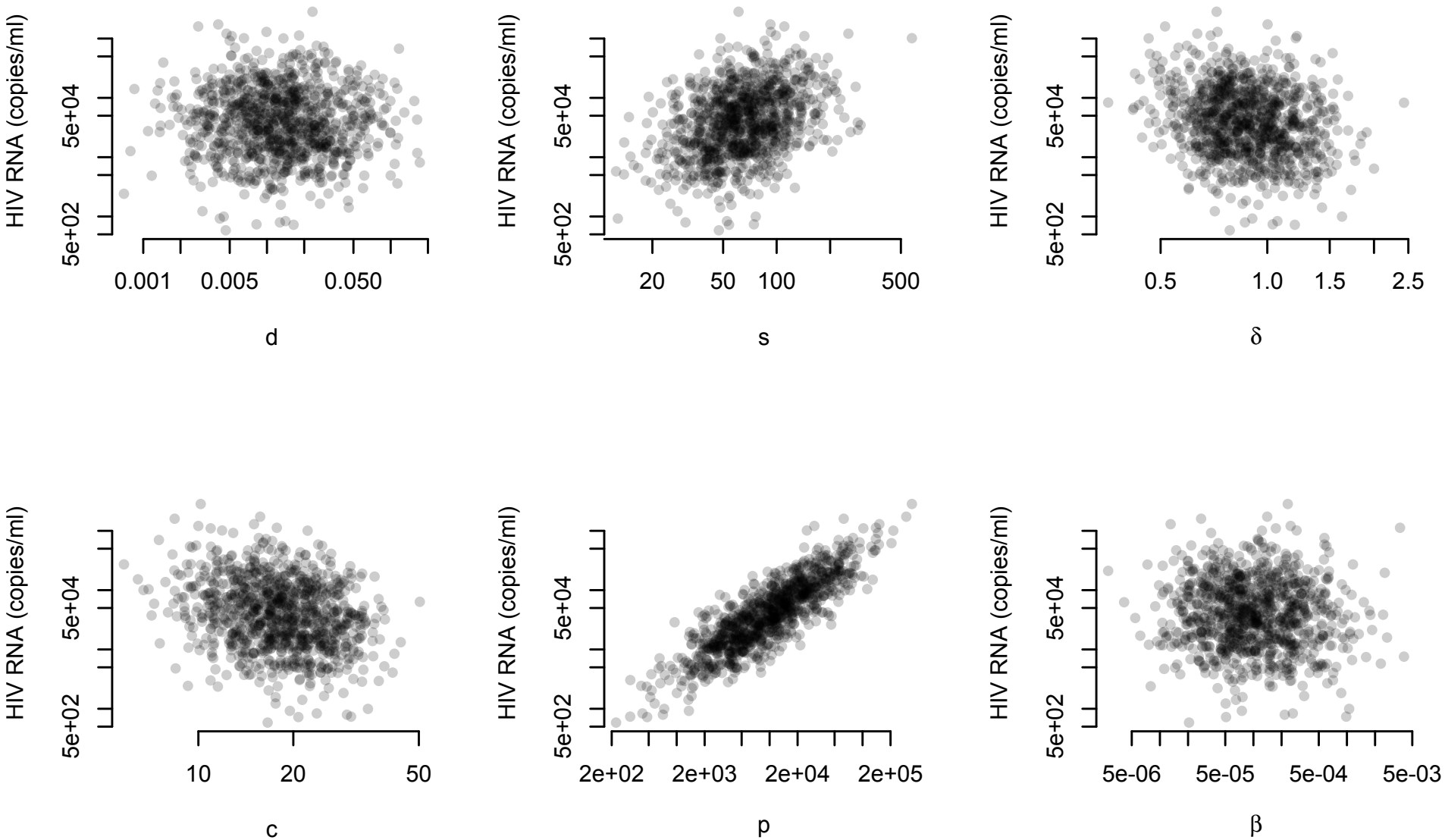
Althaus et al. (manuscript in preparation)
Ramratnam et al. (1999) Lancet
Markowitz et al. (2003) J Virol
Chen et al. (2007) PNAS
Dahari et al. (2009) Gastroenterology

Distribution of set-point (baseline) viral load for HIV and HCV

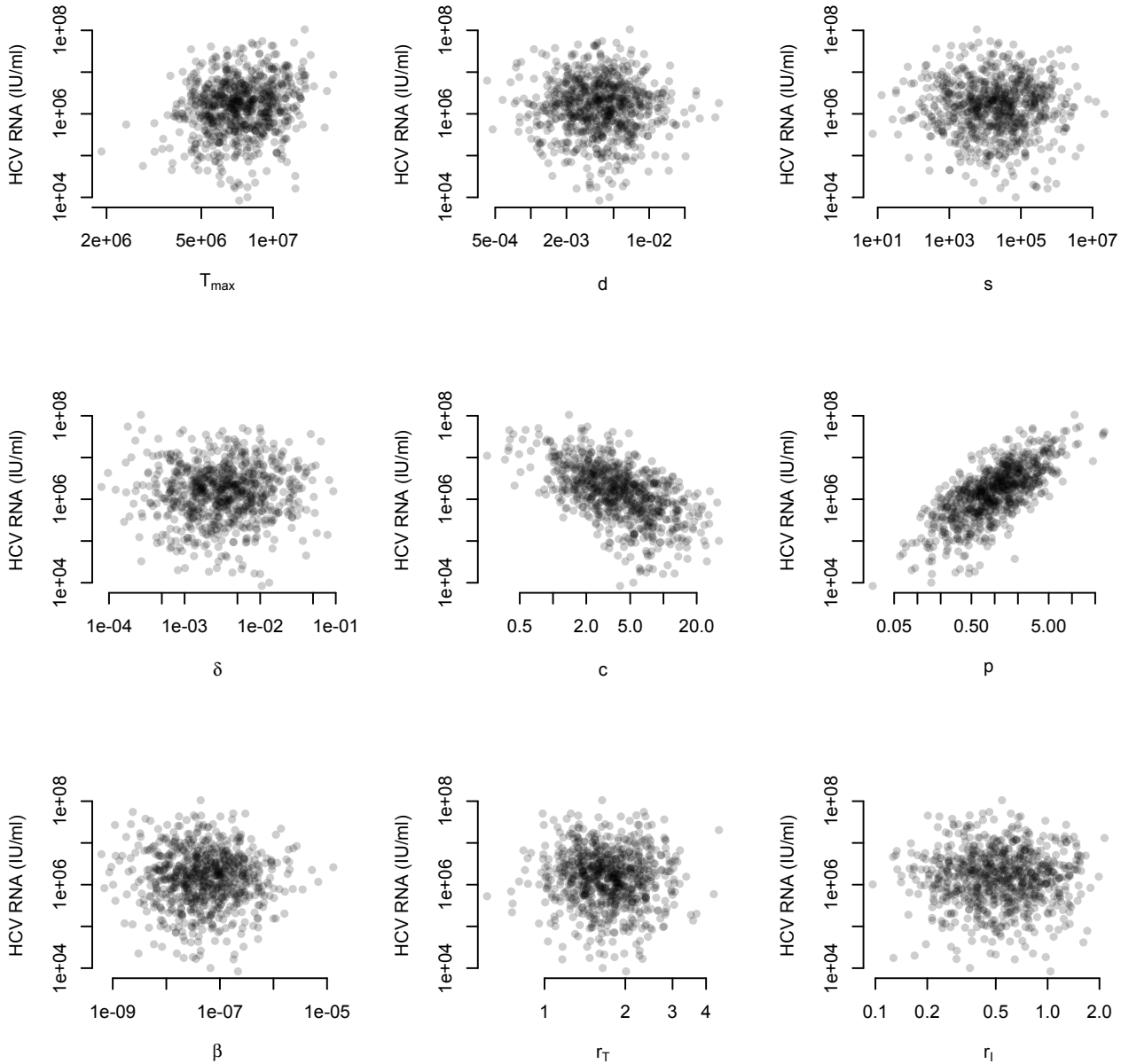


- Models can account for wide variation in HIV set-point and HCV baseline viral load
- Clearance in 25% of HCV infections and 0.2% of HIV infections

Relationship between set-point HIV RNA and individual parameters



Relationship between baseline HCV RNA and individual parameters



Sensitivity of HIV and HCV viral load levels on changes of individual parameters

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Calculating partial rank correlation coefficients (PRCC)[1]:

Parameter	Definition	HIV	HCV
$T_{\max}$	Total number of target cells	–	0.56
d	Death rate of target cells	-0.04	0.03
λ	Production rate of target cells	**0.88**	-0.29
β	Infection rate	0.05	0.35
δ	Death rate of infected cells	-0.69	-0.14
p	Virus production rate	**0.97**	**0.91**
c	Clearance rate of free virus particles	**-0.77**	**-0.87**
r_T	Max. proliferation rate of target cells	–	-0.01
r_I	Max. proliferation rate of infected cells	–	0.01

[1] *Blower & Dowlatabadi (1994) International Statistical Review*

Interpretation of PRCC

- **Production of target cells** has been previously suggested to cause most of the variation in HIV set-point viral load levels[1]

- Virus production rate *p*: **Viral trait** or modulated by **non-cytolytic** immune responses

- Clearance rate of virus particles *c*: Influenced by **antibody response**

[1] *Bonhoeffer et al. (2003) Trends Microbiol*

Sensitivity of HCV clearance on changes of individual parameters

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1. Simulated patient with infected steady-state (chronic infection)
2. Set individual parameter to lower or upper limit of range
3. Calculate the probability of clearance of infection

Parameter	**Definition**	***P***
δ	Death rate of infected cells	83%
β	Infection rate	65%
p	Virus production rate	35%
c	Clerance rate of free virus particels	28%
$T_{\max}$	Total number of target cells	14%
r_T	Max. proliferation rate of target cells	10%
r_I	Max. proliferation rate of infected cells	7%
d	Death rate of target cells	3%
λ	Production rate of target cells	2%

Interpretation of probability of clearance

- Death rate of infected cells δ: Influenced by **cytolytic** $CD8^+$ T cell responses (range much larger than in HIV!)

- Infection rate β: Antiviral **drugs** (ribavirin)

- Virus production rate p: Antiviral **drugs** (telaprevir)

Conclusions

- Mathematical models account for large variation in HIV set-point and HCV baseline levels

- Models consistent with the expected proportion of HCV infections that clear spontaneously

- **Cytolytic** immune responses ($CD8^+$ T cells) likely to play major role in HCV **clearance**[1]

- **Non-cytolytic** immune responses could play the primary role in determining the **chronic outcome** of HIV and HCV infections

[1] *Bowen & Walker (2005) Nature*