Within host dynamics of viral infections: bridging immunology & epidemiology

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Immunology brings host heterogeneity to epidemiology

In addition to phenotypic heterogeneity (immunity) the genetic heterogeneity between susceptibles.

MHC is extremely polymorphic:
1. we are all different,
2. almost everyone is heterozygous,
3. most SNP correlations within MHC region.

EHID: Every host is different
Immune systems samples a few peptides and stores contextual information in memory cells.

- naive T cell
- educated T cells

TCR

context

Virus

MHC

protein

peptide

MHC is highly polymorphic

clonal expansion

kill target using the info from 1 peptide
The life history of an acute into chronic infection (SIV)

Immune response after 2 weeks, Tat escapes, Gag wins
Viral contraction coincides with rise of CD8 responses and depletion of target cells (CD4 T cells)
Is the HIV-1 set-point optimized for transmission?

Variation in HIV-1 set-point viral load: Epidemiological analysis and an evolutionary hypothesis

Christophe Fraser†‡, T. Déirdre Hollingsworth†, Ruth Chapman†§, Frank de Wolf†¶, and William P. Hanage†  PNAS 2007

Classical trade-off between virulence and transmission

See also Shireff, Pellis, Laeyendecker & Fraser PCB 2011
Set-point viral load seem to be 20% heritable

Note the huge variation in set-points

Ample heritability to allow for viral evolution

HIV-1 Transmitting Couples Have Similar Viral Load Set-Points in Rakai, Uganda

T. Déirdre Hollingsworth¹, Oliver Laeyendecker²,³, George Shirreff¹, Christl A. Donnelly¹, David Serwadda⁴,⁵, Maria J. Wawer⁵,⁶, Noah Kiwanuka⁴,⁵, Fred Nalugoda⁵, Aleisha Collinson-Streng³, Victor Ssempijja⁵, William P. Hanage⁷, Thomas C. Quinn²,³, Ronald H. Gray⁵,⁶, Christophe Fraser¹

see also Müller et al. Viruses, 2011 for a review
Patients having different set-points and immune responses have very similar loss rate $\delta$ of their infected cells.

$\delta=1$ per day means that virus evolves **hundreds** of generations in one host before infecting the next one.

How can this **one** generation involved in the transmission event overrule the hundreds within every host?

Death rate $\delta$ is estimated from down-slope during therapy:

$$\frac{dI}{dt} = \beta TV - \delta I$$
During early infection virus escapes from several immune responses

5 out of 6 escapes

Early and Dominant response to Nef64-74 is escaped from first

Agent based model: here within host evolution. In each and every host mutations accumulate and revert.

Hosts have on average $k=15$ immune responses.

Escape mutations

$P_{\text{escape}}: e \to e+1$

Deleterious mutations

$P_{\text{revert}}: f \to f-1$

During peak viral load, more mutations.
Virus load in a host is determined by the number of remaining immune responses \((k-e)\), and by the total fitness cost of all mutations \((e+f)\):

\[
V = V_0 - \sigma(k-e) - \phi(e+f)
\]

Virus load can only increase in an individual, which increases the transmission rate and decreases the expected life-span.
Now an epidemic of 300 years with $V_0=10$ and $p_{\text{escape}}=0.01$

Hosts carry and transmit viruses with $k=35$ mutations

Viral load $V<V_0$

Agent based model two time scales
Steady state set-point: sweep with $V_0$ and $p_{\text{escape}}$

Heterogeneous $k=15/300$

Homogeneous $k=15/15$

$V=4.5$ is the “optimal” viral load (heavy line)
Steady state $R_0$: sweep with $V_0$ and $p_{\text{escape}}$

Heterogeneous $k=15/300$

Homogeneous $k=15/15$

Heterogeneity reduces maximal population fitness & allows virus to adapt better in heterogeneous case.
Conclusions part 1.

For realistic mutation rates we do not expect the virus to adapt much on the population level.

Evolution dominated by the hundreds of generations within heterogeneous hosts.

How now to explain that the observed mean viral load of $V=10^{4.5}$ corresponds to an optimized $R_0$?