Why does HIV harm its host?

Samuel Alizon

Ecological and Molecular Modelling of infections

Lyon, 10-11 Dec 2014
Buchbinder et al. (1994, AIDS)
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CCR5Δ32 deletion confers resistance to HIV infection

Liu et al. (1996, Cell)
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A handful of SNPs explains ~22% of the variance in spVL

Fellay et al. (2007, Science)
CCR5Δ32 deletion confers resistance to HIV infection

Liu et al. (1996, Cell)

KIR copy numbers inversely correlate with viral load

Pelak et al. (2011, PLoS Biol)

A handful of SNPs explains ~22% of the variance in spVL

Fellay et al. (2007, Science)
† within 3 years following infection
† within 3 years following infection
† within 3 years following infection
HIV infection course

viral load
(RNA copies/mL plasma)

CD4
T-cells
(cells/mm$^3$)

0 4 8 12 2 3 4 5 6 7 8
weeks years

†

0 100 500 1000

100 1000

10 10

10 10

10 10

10 10

10 10
HIV infection course

**Viral load**
(RNA copies/mL plasma)

**Acute phase**

**CD4 T-cells**
(cells/mm$^3$)

Time:
- 0 weeks
- 4 weeks
- 8 weeks
- 12 weeks
- 2 years
- 3 years
- 4 years
- 5 years
- 6 years
- 7 years
- 8 years

Viral load:
- $10^2$
- $10^3$
- $10^4$
- $10^5$
- $10^6$

CD4 T-cells:
- 500
- 1000

†
HIV infection course

**Viral load**
(RNA copies/mL plasma)

**Acute phase**

**Asymptomatic phase**

**CD4 T-cells**
(cells/mm$^3$)

<table>
<thead>
<tr>
<th>time (weeks)</th>
<th>viral load (RNA copies/mL plasma)</th>
<th>CD4 T-cells (cells/mm$^3$)</th>
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<tbody>
<tr>
<td>0</td>
<td>$10^6$</td>
<td>1000</td>
</tr>
<tr>
<td>4</td>
<td>$10^5$</td>
<td>500</td>
</tr>
<tr>
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<td>$10^4$</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>$10^3$</td>
<td>50</td>
</tr>
<tr>
<td>16</td>
<td>$10^2$</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>$10^1$</td>
<td>5</td>
</tr>
</tbody>
</table>

† indicates end of life.
HIV infection course

**viral load**
(RNA copies/mL plasma)

**CD4 T-cells**
(cells/mm$^3$)

- **Acute phase**
  - Time: 0-4 weeks
  - Viral load: $10^6-10^5$
  - CD4 T-cells: 0-500 cells/mm$^3$

- **Asymptomatic phase**
  - Time: 4-8 weeks
  - Viral load: $10^5-10^4$
  - CD4 T-cells: 500-200 cells/mm$^3$

- **AIDS phase**
  - Time: 8 years onwards
  - Viral load: $10^3-10^2$
  - CD4 T-cells: 200 cells/mm$^3$ or below
HIV infection course

- **viral load** (RNA copies/mL plasma)
- **time**
- **1/virulence**
- **CD4 T-cells** (cells/mm³)

**Acute phase**
- Viral load increases rapidly.

**Asymptomatic phase**
- Viral load decreases as CD4 T-cells remain relatively stable.

**AIDS phase**
- Viral load increases significantly, leading to immune system deterioration and death.
HIV infection course

**viral load**
(RNA copies/mL plasma)

**CD4 T-cells**
(cells/mm$^3$)

**time**

- **weeks:** 0, 4, 8, 12, 2, 3, 4, 5, 6, 7, 8
- **years:** 0, 1, 2, 3, 4, 5, 6, 7, 8

- **Viral load range:** $10^2$ to $10^6$
- **CD4 T-cells range:** 1000 to 200
HIV infection course

viral load
(RNA copies/mL plasma)

set-point viral load

CD4 T-cells
(cells/mm$^3$)

0 4 8 12 2 3 4 5 6 7 8
weeks years

1000
500
200
HIV infection course

**viral load**
(RNA copies/mL plasma)

**CD4 decline slope**

**set-point viral load**

**time**

- **weeks**
- **years**

**CD4 T-cells**
(cells/mm$^3$)
HIV infection course

viral load
(RNA copies/mL plasma)

predictors of virulence

CD4 T-cells
(cells/mm$^3$)

Mellors et al. (1996, Science)
Virus load variations

Fraser et al. (2014, Science)
Virus load variations

Fraser et al. (2014, Science)
Adjusted (for age and sex) $r = 0.206$, $P = 0.030$.

Adjusted (for age and sex) $r = 0.206, \ p = 0.030$.

$r = 0.196, \ p = 0.036$

Transmission couple data problem

• Very little data on transmission chains!

• Infections outside the couple

• Cannot control for within-host evolution

Hollingsworth et al. (2010, PLoS Path)
Transmission chain & phylogeny

patient 0 ($p_0$)

$\text{sample A}$

$\text{sample B}$
unsampled

$\text{sample C}$
unsampled

$\text{sample D}$
unsampled

2012 2013 2014

Emma Saulnier's PhD
Transmission chain & phylogeny

patient 0 (p₀)

sample A
sample B
unsampled
sample C
unsampled
sample D
unsampled

Emma Saulnier’s PhD
Transmission chain & phylogeny

patient $0$ ($p_0$)

sample A

sample B
unsampled

sample C
unsampled

sample D
unsampled

pathogen A ($p_0$ or $p_1$ or $p_3$ or $p_4$?)

pathogen B ($p_0$ or $p_1$ or $p_3$ or $p_4$?)

pathogen C ($p_0$ or $p_1$ or $p_3$ or $p_4$?)

pathogen D ($p_0$ or $p_1$?)

Emma Saulnier’s PhD
Phylogeny of infections

Alizon et al. (2010, PLoS Path)
Phylogeny of infections

Proximity in the phylogeny reflects proximity in the transmission chain...

Alizon et al. (2010, PLoS Path)
Phylogeny of infections

Alison et al. (2010, PLoS Path)
Phylogeny of infections

Do patients close in the phylogeny have similar trait values?

Alizon et al. (2010, PLoS Path)
Phylogenetic comparative method

Luo (2007, Nature)

Felsenstein (1985, Am. Nat.)
Felsenstein (2002)
Phylogenetic comparative method

Phylogenetic signal estimates how the phylogeny explains variations in a quantitative trait among species

Luo (2007, Nature)

Felsenstein (1985, Am. Nat.)

Felsenstein (2002)
Phylogenetic comparative method

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Felsenstein (1985, Am. Nat.)
Phylogenetic comparative method

\[ \frac{|\text{trait}_2 - \text{trait}_1|}{\sqrt{d_1 + d_2}} = \text{contrast A} \]
Phylogenetic comparative method

Phylogenetic comparative method

Phylogenetic comparative method

Freckleton et al. (2002, Am Nat)
Blomberg et al. (2003, Evolution)
Shirreff et al. (2013, EMPH)
Phylogenetic comparative method

• Low variance in contrasts indicates that infections close in the phylogeny have similar traits

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• Phylogeny explains trait distribution assuming **brownian motion** evolution

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• **Genetic heritability** can be inferred from phylogenetic signal using ABC methods

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Freckleton et al. (2002, Am Nat)
Blomberg et al. (2003, Evolution)
Shirreff et al. (2013, EMPH)
Set-point virus load is partly ‘heritable’
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Up to 56% of the variance in set-point virus load can be explained by virus factors

Alizon et al. (2010, PLoS Path)
Shirreff et al. (2013, EMPH)
Set-point virus load is partly ‘heritable’

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Fraser et al. (2014, *Science*)
Why shouldn’t HIV virulence be ‘heritable’?
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Ebert (1998, *Science*)
Why shouldn’t HIV virulence be ‘heritable’?

Within-host competition often favors more virulent strains

*Salmonella typhimurium* (Bacteria)

Ebert (1998, *Science*)
1) Rugged fitness landscape?

Hinkley et al. (2011, *Nat Genet*)
1) Rugged fitness landscape?

Virulence evolution is slow due to strong (epistatic) constraints

Hinkley et al. (2011, Nat Genet)
2) Virulence as a ‘public goods’

Bonhoeffer et al. (2003, *Trends Microbiol*)
Bartha et al. (2008, *Trends Immunol*)
Hool et al. (2013, *Epidemics*)
2) Virulence as a ‘public goods’

More virulent strains are less competitive

(they pay a cost to activate target cells that benefit to all strains)

Bonhoeffer et al. (2003, *Trends Microbiol*)
Bartha et al. (2008, *Trends Immunol*)
Hool et al. (2013, *Epidemics*)
3) Within-host evolution is a ‘dead-end’
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Measure HIV substitution rates at different levels
3) Within-host evolution is a ‘dead-end’

Pybus & Rambaut (2009, Nat. Rev. Genet.)
Why would evolutionary rates differ?

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Why would evolutionary rates differ?

**Store & retrieve**
‘less evolved’ virions are more transmissible

**Stage specific**
heterogeneity in transmission timing + variable ER

Why would evolutionary rates differ?

Store & retrieve
‘less evolved’ virions are more transmissible

Stage specific
heterogeneity in transmission timing + variable ER

Adapt & revert

Pybus & Rambaut (2009, Nat. Rev. Genet.)
Variation among regions?
Variation among regions?
Variation among regions?
Variation among regions?
Alizon & Fraser (2013, Retrovirology)
BH evolutionary rates are lower than WH rates throughout the HIV genome.

Alizon & Fraser (2013, Retrovirology)
BH evolutionary rates are lower than WH rates throughout the HIV genome. 

Supports the store and retrieve hypothesis.
Virulence is (partly) heritable, it affects infection fitness...

How does it evolve?
1) More virulent strains are more competitive WH

2) More virulent strains are more transmitted
1) More virulent strains are more competitive

2) More virulent strains are more transmitted
Coinfections are the rule rather than the exception
Coinfections are the rule rather than the exception
1) More virulent strains are more competitive WH

2) More virulent strains are more transmitted
Variability of set-point virus load

Fraser et al. (2007, PNAS)
Fraser et al. (2014, Science)
Effect on infection fitness

Fraser et al. (2007, PNAS)
Fraser et al. (2014, Science)
Effect on infection fitness

Cost: virulence decreases infection duration

Fraser et al. (2007, PNAS)
Fraser et al. (2014, Science)
Effect on infection fitness

Fraser et al. (2007, PNAS)
Fraser et al. (2014, Science)
Effect on infection fitness

**Benefit:** virulence increases transmission rate

Infectiousness (per 100 person per year)

Fraser et al. (2007, PNAS) Fraser et al. (2014, Science)
Effect on infection fitness

Fraser et al. (2007, PNAS)
Fraser et al. (2014, Science)
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Fraser et al. (2014, Science)
Effect on infection fitness

Fraser et al. (2007, PNAS)
Fraser et al. (2014, Science)
Why do parasites harm their host?

Anderson & May (1982, Parasitology)
Ewald (1994)
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Anderson & May (1982, *Parasitology*)
Ewald (1994)

Bolker et al. (2010, *J R Soc Interface*)
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Doumayrou et al. (2013, Evolution)

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- Anderson & May (1982, Parasitology)
- Ewald (1994)
- Bolker et al. (2010, J R Soc Interface)
- De Roode et al. (2008, PNAS)
- Doumayrou et al. (2013, Evolution)
- Anderson & May (1982, Parasitology)
- Ewald (1994)
Why do parasites harm their host?

Anderson & May (1982, Parasitology)
Ewald (1994)

Jensen et al. (2006, PLoS Biol)
Bolker et al. (2010, J R Soc Interface)
De Roode et al. (2008, PNAS)

Doumayrou et al. (2013, Evolution)
Anderson & May (1982, Parasitology)
Ewald (1994)
HIV virulence evolution (Switzerland)
HIV virulence evolution (USA)

Herbeck et al. (2008, PLoS ONE)
HIV virulence evolution (Italy)

Müller et al. (2009, PLoS Path)
HIV virulence evolution (meta-analysis)

Herbeck et al. (2012, AIDS)
HIV virulence evolution (meta-analysis)

Summary CD4⁺ T-cell count trends by year

- Slope = 0.044
- \( P = 1.5 \times 10^{-4} \)

Summary plasma viral load trends by year

- Slope = -0.00037
- \( P = 2.4 \times 10^{-4} \)

spVL has increased but is now stabilising

Herbeck et al. (2012, AIDS)
Evolution towards the ESS?

Fraser et al. (2007, PNAS)
HIV virulence evolution (The Netherlands)

Gras et al. (2009, PLoS ONE)
HIV virulence evolution and HAART

spVL increase
described by Gras et al.

Duration of AIDS-free infection (years)

Infectiousness (per 100 person per year)

set-point virus load

spVL increase described by Gras et al.
Évolution et traitements

Transmission potential

set-point virus load

untreated population
Évolution et traitements

Transmission potential vs. set-point virus load

- untreated population
- treated

D
Évolution et traitements

Transmission potential

set-point virus load

Eugene Geidelberg’s MSc
Évolution et traitements

Transmission potential

set-point virus load

D

virus load evolution

see also van Baalen (1998, Proc B)
Thanks!

Sebastian Bonhoeffer (& Tanja Stadler, Roger Kouyos, …)

Christophe Fraser (& George Shirreff)

Tsukushi Kamiya (& Nicole Mideo)
In summary…

- HIV virulence is partly ‘heritable’ from one infection to the next

- 3 explanatory hypotheses: the WH fitness landscape is rugged, virulent strains are less competitive, within-host evolution is a ‘dead-end’

- **Immunosuppression** can favor more virulent strains

- HIV-1 virulence seems **adaptive** for the virus (increased transmission)

- Is the evolution towards the ESS affected by **public health policies**?
Annexes
Coinfection, immunosuppression and virulence

ESS immunosuppression

ESS virulence

host base-line immunity

host background mortality rate

Kamiya, Mideo, Alizon (in prep)
All three together…

Fraser et al. (2014, Science)
\lambda \left( \text{Pagel 1994} \ Proc. B, \text{ Freckleton et al. 2002} \ Am. Nat. \right)

- \( \lambda \) is a weight on the off-diagonal terms of \( V \) (distances between taxa)
- \( \lambda = 0 \): evolution independent of the phylogeny
- \( \lambda = 1 \): Brownian motion prediction on the phylogeny

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- Trait evolution from an ancestral state ($\alpha$) under Brownian model:
  \[ y_i = \alpha + \sum_{j=1}^{T_i} \epsilon_{i,j} t_{i,j} \]

- For $n$ species undergoing independent Brownian motion, $y$ has a multinomial probability density:
  \[
p(y) = \frac{1}{(2\pi\sigma^2 t)^{n/2}} \exp\left[ -\frac{(y - \alpha X)^T (y - \alpha X)}{2\sigma^2 t} \right] \]

- However, species evolution is not independent. If species share a common ancestor at time $t_a$:
  \[
  \text{cov}(y_i, y_j) = \sigma^2 t_a
  \]
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However, species evolution is not independent. If species share a common ancestor at time \(t_a\):

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If \(V\) is the \(n \times n\) variance-covariance matrix that describes the phylogeny

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λ (Freckleton et al. 2002, Am. Nat.)

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\( K \) (Blomberg et al. 2003, Evolution)

- \( K \) is based on the MSE (or on the variance in IC)

- The amount of phylogenetic signal is given by the ratio between MSE from data points (\( \text{MSE}_0 \)) and MSE derived from the phylogeny (\( \text{MSE} \))

- The ratio is a function of \( V \), the variance-covariance matrix

\[
\text{MSE}_0 = \frac{(X - \hat{a})^T (X - \hat{a})}{n - 1}
\]

\[
\text{MSE} = \frac{(U - \hat{a})^T (U - \hat{a})}{n - 1}
\]

\[
\frac{\text{MSE}_0}{\text{MSE}} = \frac{1}{n - 1} \left( \text{tr}(V) - \frac{n}{\sum \sum V^{-1}} \right)
\]
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\[
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\[
U = DX
\]

\[
D V D^T = I
\]

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\]

- The ratio is a function of $V$, the variance-covariance matrix

- To correct for tree structure and tree size, the ratio is corrected by the expected value of $K$:

\[
K = \frac{\text{observed} \frac{\text{MSE}_0}{\text{MSE}}}{\text{expected} \frac{\text{MSE}_0}{\text{MSE}}}
\]
Heritability and phylogenetic signal

\[ h^2 = \frac{\text{VAR}(G)}{\text{VAR}(P)} \]
Heritability and phylogenetic signal

- Heritability is the proportion of the genetic variance in the phenotypic variance in a population.

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- Heritability is the proportion of the genetic variance in the phenotypic variance in a population.
- Phylogenetic signal is usually defined for species (not populations)...
- ... but phylogenies of infections are built over a population of infected patients.
- One can also show the equivalence between the two using Lynch’s phylogenetic mixed model (Housworth et al. 2004, Am. Nat.)
Heritability and phylogenetic signal

• Create phylogenies on which traits evolve with a heritability $h^2$

$$x_n = h^2 x_{n-1} + (1 - h^2) y$$
Heritability and phylogenetic signal

- Create phylogenies on which traits evolve with a heritability $h^2$

$x_n = h^2 x_{n-1} + (1 - h^2) y$

K: slope=0.83*** (R²=0.89)
λ: slope=0.95*** (R²=0.88)
Phylogenetic signal estimators

- **$K$** (Blomberg et al. 2003, Evolution)
  - combines independent contrasts and a randomisation test (p-value)
  - robust
  - limited for large trees
  - estimated on a ML tree

- Pagel’s $\lambda$ (Freckleton et al. 2002, Am. Nat)
  - based on a maximum likelihood approach
  - sensitive to small variations in the phylogeny
  - estimated on a set of trees obtained from a Bayesian inference
Other estimators...

The method can only detect high levels of heritability (at least ~40%)
Other estimators...

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Shirreff et al. (2013, EMPH)
Other estimators...

The method can only detect high levels of heritability (at least ~40%)

Not done for PMM (Housworth et al. 2004) and for $d$ (Blomberg et al. 2003).

Shirreff et al. (2013, EMPH)
Set-point virus load

strict spVL criterion

liberal spVL criterion

Fellay et al. (2007, Science)
Fellay et al. (2009, PLoS Genet.)
Transmission groups

![Bar chart showing the number of patients in different transmission groups.](chart.png)
Transmission groups

Kouyos et al. (2010, JID)
Transmission groups

The phylogeny should be closer to the transmission chain for MSMs
Virus control over spVL

mean = 0.41  median = 0.51

Alizon et al. (2010, PLoS Path)
### Virus control over spVL

<table>
<thead>
<tr>
<th></th>
<th>Pagel’s $\lambda$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median 160 trees</td>
</tr>
<tr>
<td></td>
<td>no branch length</td>
</tr>
<tr>
<td><strong>MSM strict</strong></td>
<td>0.51</td>
</tr>
<tr>
<td>$(n=134)$</td>
<td></td>
</tr>
<tr>
<td><strong>strict</strong></td>
<td>0.17</td>
</tr>
<tr>
<td>$(n=230)$</td>
<td></td>
</tr>
<tr>
<td><strong>MSM all</strong></td>
<td>0.13</td>
</tr>
<tr>
<td>$(n=404)$</td>
<td></td>
</tr>
<tr>
<td><strong>all</strong></td>
<td>—</td>
</tr>
<tr>
<td>$(n=661)$</td>
<td></td>
</tr>
</tbody>
</table>

**Virus control over spVL**

<table>
<thead>
<tr>
<th></th>
<th>Pagel’s $\lambda$</th>
<th>Blomberg’s $K$</th>
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<tbody>
<tr>
<td></td>
<td>median 160 trees</td>
<td>p-val by randomisation</td>
</tr>
<tr>
<td></td>
<td>no branch length</td>
<td>branch length</td>
</tr>
<tr>
<td></td>
<td></td>
<td>brownian motion</td>
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<td><strong>MSM strict</strong></td>
<td>0.51</td>
<td>0.59***</td>
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<td><strong>strict</strong></td>
<td>0.17</td>
<td>0.03</td>
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<td>$(n=230)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MSM all</strong></td>
<td>0.13</td>
<td>0.09*</td>
</tr>
<tr>
<td>$(n=404)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>all</strong></td>
<td>—</td>
<td>0.002</td>
</tr>
<tr>
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</tbody>
</table>

Pagel (1994, *Proc B*)
Blomberg et al. (2003, *Evolution*)
Alizon et al. (2010, *PLoS Path*)

**Table Notes:**
- MSM strict: Median 160 trees, no branch length
- strict: Median 160 trees, branch length brownian motion
- MSM all: Median 160 trees, no branch length
- all: Median 160 trees, no branch length

**P-values:**
- 0.59***: Significant at the 0.001 level
- 0.09*: Significant at the 0.05 level
- 0.002: Significant at the 0.001 level
### Virus control over spVL

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<td>0.59***</td>
<td>0.72***</td>
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<tr>
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<td>0.03</td>
<td>0.25*</td>
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