HIV Virulence has not Increased in the UK Subtype B Epidemic

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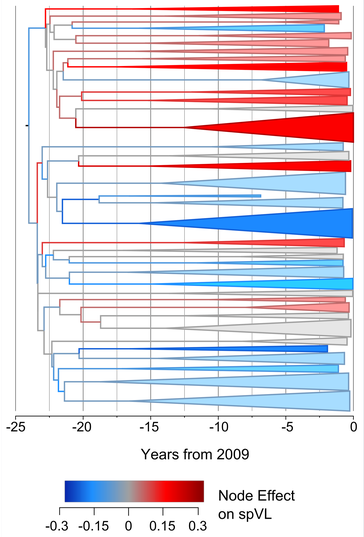
summary

- Significant increases in HIV set-point viral load (spVL) over time have been reported[1,2]
  - Interpreted as a possible increase in virulence
- We have now directly estimated the change in spVL over time that is due to selection on the viral genome
  - The change in the virally-determined component of spVL was -0.05 $\log_{10}$ copies/mL/year
- We therefore found no evidence of an increase in spVL due to viral genotype
- Observed increases in spVL are probably due to changes in host or other factors, which have a much larger effect on spVL

introduction

- The virulence of a pathogen is its ability to cause disease and transmit to other hosts
- Set-point viral load (spVL) predicts HIV disease progression and transmission risk[3]
  - But we have directly estimated the viral genome contributes only 6% of the variation in spVL in the UK subtype B epidemic[4,5]
- Host and environmental factors are therefore more important for determining spVL
  - spVL measures themselves do not reflect the viral genotype well
- Two recent meta-analyses estimated an increase in spVL of 0.044 $\log_{10}$ copies/mL/year[1] and 0.013 $\log_{10}$ copies/mL/year[2], which has been interpreted as an increase in virulence
- Working on a related dataset to ours, a clinical study has also found an increase in spVL over time (see poster 1015, Parsons *et al.*)
- To clarify the contribution of the viral genotype, we have explicitly estimated the change in spVL from this source
- Previously we showed that distinct phylogenetic lineages of HIV differ in respect to their genotypic contribution to spVL (Fig 1): some are defined by a higher than average value, and some lower
- This difference extends over many years of the viral phylogeny; the property is inherited and provides an opportunity for selection to act
- Because our method utilizes the viral phylogeny, our analysis includes the whole time period covered by the phylogeny (Fig 1; 25 yrs) rather than the time period over which our samples were collected

Fig 1 - Genetic Effect on spVL over the Phylogeny



methods

- In order to see if there has been an increase in virulence over time, evidence for a change in the portion of spVL controlled by the viral genome was explicitly analysed for the first time
- This could be due to between-lineage selection, which could lead to fewer or more lineages (Fig 2 a.), or within-host selection, whereby some members of a lineage expand at the expense of others (Fig 2 b.)
- 8,483 subtype B sequences with corresponding spVL and clinical data were available from the UK HIV Drug Resistance Database and UK CHIC[6]

results

- The change in spVL due to between-lineage selection was **not significant** at 0.002 $\log_{10}$ copies/mL/year (p=0.27) (Fig 3 a.)
- The change in spVL due to within-host selection was significant ($p<2.2\times10^{-16}$) but **negative**, estimated at -0.05 $\log_{10}$ copies/mL/year (Fig 3 b.)
- Currently, we cannot distinguish the change due to within-host selection from environmental effects not controlled for in our model

conclusions

- Our analysis directly examined changes in spVL due to the viral genotype
- We found **no evidence** for an increase in virulence in the UK subtype B epidemic
- Our estimates for the change in the viral component of spVL suggest that selection has favoured a slightly lower spVL over time
- In this population viral genotype only determines 6% of the variance in spVL, so other factors affecting spVL, many of which have changed over time, could be responsible for the increase observed

Fig 2 a) Between-lineage selection

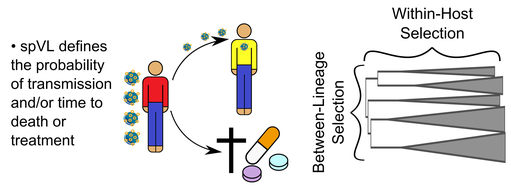
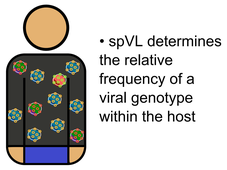
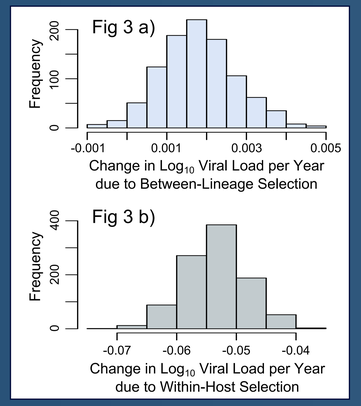


Fig 2 b) Within-host selection





additional methods

- Phylogenies were reconstructed in RAxML[7]
- The phylogeny and spVL were fitted in a mixed model with age, sex, ethnicity, time from diagnosis to spVL date, year of diagnosis, and country of origin using MCMCglmm[8] with 1000 thinned iterations
- Sequence sample date was added as a covariate in the model to estimate the change due to within-host selection in the component of spVL determined by the virus
- To estimate change due to between-lineage selection, the genetic effect of each node was regressed on the root-to-tip distance for each iteration and compared against a null distribution where the genetic effects were randomly generated for each tip
- Simulation analysis shows that our method may underestimate the effect of between-lineage selection, as lineages that do not transmit, or that result in death, may not be sampled

references

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