288 HIV Virulence Has Not Increased in the UK Subtype B Epidemic

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Background: The question of whether HIV is evolving and perhaps becoming more virulent has received considerable attention. Two recent meta-analyses have estimated an increase in set-point viral load (spVL), a predictor of disease progression, of 0.044 log10 copies/mL/year and 0.013 log10 copies/mL/year, interpreted by both studies as an increase in virulence that could be caused by viral factors. This would require that the viral genome exerted substantial influence over the spVL, i.e. spVL having high heritability. Previously we estimated this to be only 5% in the UK subtype B epidemic.

Change in spVL over time could be influenced by selection. Transmission and extinction events, on the lineage down which spVL is evolving, exert between-lineage selection, and within-lineage selection occurs at the individual level, as spVL is correlated with probability of transmission. Here we implemented quantitative genetics methods to estimate change in spVL due to between- and within-lineage selection on the viral genome.

Methodology: 8,483 pre-ART subtype B sequences with corresponding spVL were analysed. A phylogenetic tree was reconstructed from the resistance-site stripped sequences in RAxML. The phylogeny and spVL were fitted in a mixed-model with age, sex, ethnicity, time since diagnosis, and year of diagnosis as fixed effects and year of diagnosis and country of origin as random effects.

Within-lineage change can be estimated from longitudinal data by adding sequence sample date as a covariate in the model. Between-lineage selection can be estimated by looking at the difference in predicted genotypic potential ("breeding value") over time. We used Markov chain Monte Carlo methods to obtain a posterior distribution of evolutionary change by averaging over uncertainty in the estimates. To determine whether any change that has occurred is greater than would be expected by chance (drift), we used posterior predictive tests.

Results: We estimated a small change in spVL due to between-lineage selection of 0.002 log10 copies/mL/year, which this was not significantly different from what could be expected due to drift. Our estimate of the change in spVL due to within-lineage selection and environmental effects was small but significant at -0.05 log10 copies/mL/year.

Conclusions: Our estimate of the change in spVL over time, although small, is significant but negative. This is based on the first direct estimate of the viral contribution to spVL across an epidemic and gives no support to the view that virulence in HIV is increasing. However, we previously showed that most of the phenotypic value of spVL in our model is determined by fixed effects (age, sex, time to diagnosis, etc.) which themselves have changed over the epidemic and propose this is a more probable source of the observed change.