January 18th, 2019

To the Editors of Virus Evolution,

On behalf of my co-authors, I am submitting our manuscript, “Phylogenetic measures of indel rate variation among the HIV-1 group M subtypes” for your consideration.

The extensive diversity and rapid adaptation of the HIV-1 surface envelope glycoprotein (gp120) is the primary obstacle in the treatment and prevention of HIV-1. Because of these attributes, HIV-1 gp120 has also become a model system for understanding molecular evolution. While nucleotide and codon substitution rates have been extensively characterized in HIV-1 gp120, there is surprisingly little known about the rates of insertions and deletions (indels) within the variable regions of this gene, which are known to play significant roles in HIV transmission fitness, resistance to neutralizing antibodies, and viral pathogenesis.

In this study, we develop a phylogenetic method to measure indel rates in the five variable loops of HIV-1 gp120. We used maximum likelihood methods to reconstruct time-scaled phylogenies relating over 6,500 published HIV-1 gp120 sequences from around the world, each representing one of seven major subtypes and circulating recombinant forms in HIV-1 group M. Indel rates were estimated by fitting a binomial-Poisson model to indel events that we mapped to the terminal branches of each phylogeny. Further, we evaluated associations between the indel rate estimates and the nucleotide composition and distribution of N-linked glycosylation sites in the respective variable loops. Our study identifies novel and unexpected patterns in the molecular evolution of HIV-1, including a significant reduction of indel rates in HIV-1 subtype B relative to other clades, and skewed nucleotide frequencies within indels relative to the flanking sequence across HIV-1 clades.

Our manuscript is not submitted or accepted for publication at any other journal. I confirm that all authors have contributed to, seen and approved the final submitted version of this manuscript. Thank you for considering our manuscript for your journal.

Thank you for your time.

Sincerely,

John Palmer (MSc Candidate)