To the Editors of Molecular Biology and Evolution,

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

The high prevalence and rapid spread of HIV-1 worldwide highlights the importance of elucidating mechanisms that influence HIV-1 transmission. Evolution occurring within the five variable loop regions of the HIV-1 gp120 surface envelope glycoprotein is one such mechanism that modulates HIV-1 pathogenesis and transmission fitness. While nucleotide substitutions have been extensively characterized in the env gene, insertions and deletions (indels) remain studied to a far lesser extent despite their suggested role in HIV-1 mucosal transmission and coreceptor switching.

In our study, we develop and use phylogenetic methods to provide the first estimates of indel rates in the five variable loops of surface envelope gp120. Specifically, we reconstructed phylogenies using over 6,500 patient-derived HIV-1 sequences worldwide and applied a Poisson model to the distribution of indels across pairs of closely related sequences to estimate these rates. Furthermore, our study analyzes indel nucleotide composition and measures the impacts of indels on N-linked glycosylation sites in gp120. Analyzing data from a global HIV-1 database enabled comparisons of these results across five subtypes and two circulating recombinant forms of HIV-1 group M. We provide novel information on indels within key regions of gp120 with the intent to elucidate an understudied mechanism shown to play a role in transmission fitness and coreceptor switching of HIV-1. We note that our analysis can be adapted to within host sequence data to more precisely and accurately measure the process of indel generation.

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