Epidemiological Correlates of HIV Lineage-Level Diversification Rate

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Poster #0862
CROI 2019
Seattle, Washington
March 4-7, 2019
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Background

- Identifying HIV transmission risk factors can inform the prioritization of health care services.
- While projections suggested that British Columbia (BC) is on track to meet the UNAIDS 2020 Target, particular groups remain disproportionately affected by HIV/AIDS.
- Conducting phylogenetic analyses of viral genetic sequences from PLHIV helps us to infer the transmission network and identify subpopulations at high risk.
- Although phylogenetic clustering of HIV sequences is routinely performed to evaluate characteristics associated with transmission, clusters membership over-simplifies the range of transmission activity across a population.
- **Since transmission of HIV to a new host is equivalent to the formation of a new lineage, viral lineage-level diversification rates inferred from phylogenetic trees can serve as estimates of between-host transmission rates to evaluate risk factors associated with transmission.**

Methods

- A total of 36,271 HIV-1 resistance genotype tests - sequencing the HIV *protease* and partial *reverse transcriptase* genes (partial *pol*) – were run for 9,630 participants enrolled in the Drug Treatment Program (DTP) at the BC Centre for Excellence in HIV/AIDS (BCCfE), based out of St. Paul's Hospital in Vancouver, BC between May 1996 and March 2018,
- Additional anonymized data for this analysis included sample collection date; date of first viral load; plasma viral load (HIV RNA copies/mL); HIV subtype classifications; ethnicity; birth year; sex at birth; self-reported risk factors (injection drug user, men who have sex with men, heterosexual contact, any receipt of blood product or exposure to blood risk, other risk exposure); having ever tested positive for hepatitis C infection; having ever had AIDS; if applicable date of mortality and cause of death; health authority (HA) of requested test.
- All sequences were aligned to HXB2 reference genome using MAFFT version 7.310[1]. Insertions and deletions relative to HXB2, as well as amino acids corresponding to WHO recognized drug resistance mutation sites[3] were removed from the alignment prior to tree inference. A set of shuffled bootstrap alignments were generated to infer 100 approximate maximum likelihood phylogenetic trees in FastTree2.1[4]. Trees were pruned to include each patient's oldest sample and then rooted using root-to-tip regression in ape version 5.0[5].
- For each tip on each bootstrap tree, the viral lineage-level diversification rate was calculated and the mean diversification rate across 100 bootstrap trees for each patient was carried forward.
- The adjusted relative risks of patient attributes in relation to their viral diversification rate in 2018 were investigated using a gamma generalized linear model with a log-link. The significant associations were compared to those obtained from a phylogenetic cluster analysis conducted with an older version of the dataset, wherein Poon *et al.* defined clusters as having pairwise patristic distances <0.02 subs/site, corresponding to the 95th percentile of within-host patristic distances[7].

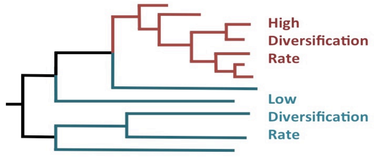

Figure 1. Viruses with a high diversification rate (red) are characterized by short branches and high splitting frequency, whereas viruses with a low diversification rate (blue) are characterized by long branches and infrequent splitting.

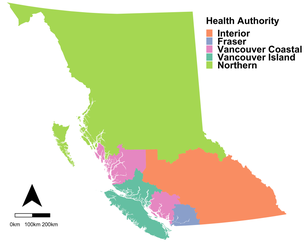

Figure 2. The five regional health authorities in British Columbia

Results

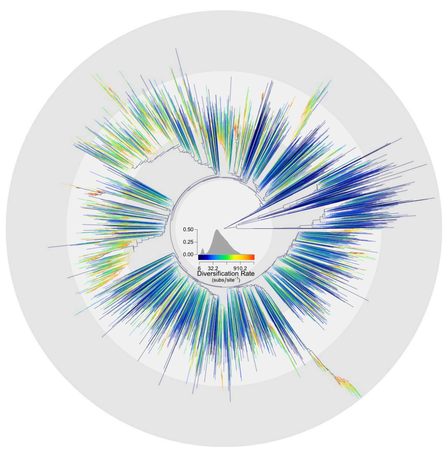

Figure 3. A representative bootstrap approximate maximum likelihood HIV phylogenetic tree colored by lineage-level diversification rates in 2018.

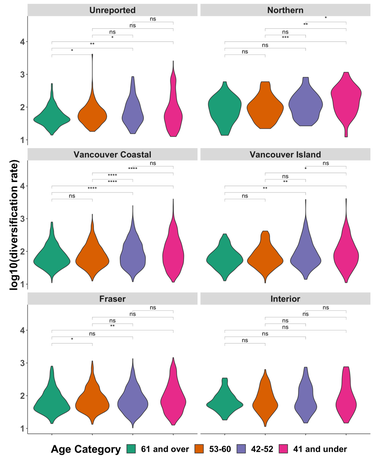

Figure 4. Distribution of lineage-level diversification rate by health authority and age group. Wilcoxon tests were used to compare mean ranks, where $p \leq 0.05$ (*), $p \leq 0.01$ (**) , $p \leq 0.001$ (***), $p \leq 0.0001$ (****).

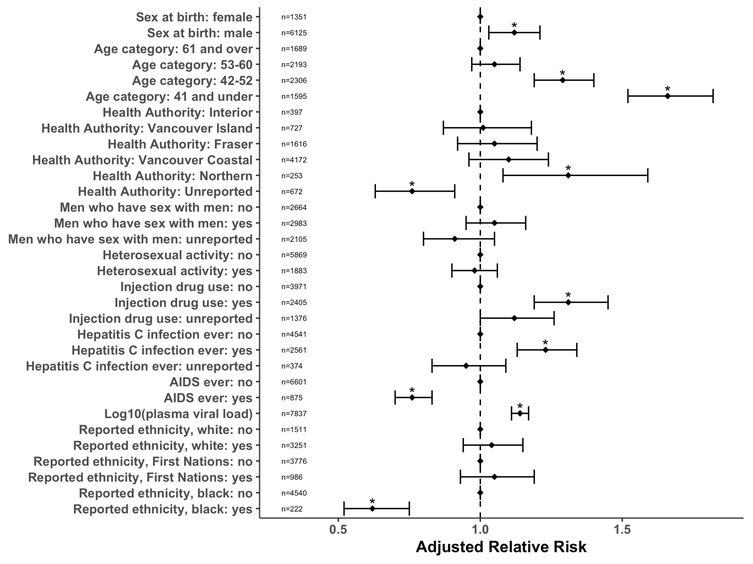

Figure 5. A summary of the adjusted relative risks for patient attributes associated with HIV lineage-level diversification rate. Risks were estimated using a multiple gamma regression with a log-link.

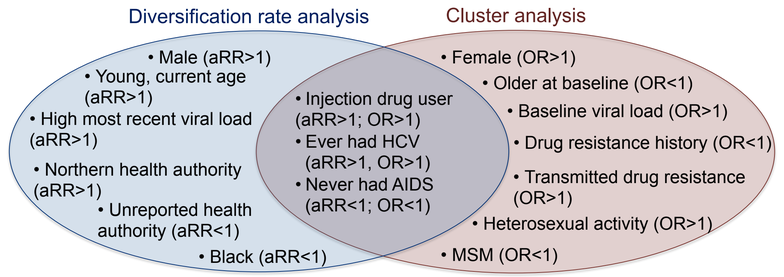

Figure 6. A comparison of significant correlates of HIV transmission activity estimated by viral lineage-level diversification rates (adjusted relative risks, aRR) or phylogenetic cluster membership (odds ratios, OR), as evaluated by Poon *et al.* with an earlier version of the dataset[7].

Conclusions

- The effect of age on lineage-level diversification rate varied by health authority.
- **The risk of having an elevated HIV lineage-level diversification rate among PLHIV in BC was significantly higher for those who were male, young, injection drug users, ever had HCV, lived in the Northern health authority, and had a high most recent viral load. Identifying as black and ever having had AIDS were significantly associated with lower diversification rates.**
- **Our findings illuminated previously unknown correlates and were complementary to previous models evaluating risk factors associated with phylogenetic cluster membership.**
- Lineage-level diversification rate is a useful approximation of pathogen transmission rate that could be used to supplement existing tools for prioritizing groups for HIV treatment and prevention services, and could be applied to other rapidly evolving pathogens, as well.

References

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Acknowledgments

Thank you to the BC Centre for Excellence in HIV/AIDS at St. Paul's Hospital (Providence Health Care) for coordinating the Drug Treatment Program, the laboratory for running >36,000 resistance genotype tests, and to the PLHIV in the DTP for participating in HIV research in British Columbia.

Financial Disclosure

Angela McLaughlin has received funding through the BC Centre for Excellence in HIV/AIDS, Canadian Institute of Health Research, and the British Columbia Health Officers Council. Jeffrey Joy is funded by a Genome Canada and Genome BC Bioinformatics and Computational Biology grant - 287PHY and the Public Health Agency of Canada.

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