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HIV Drug Resistance and Phylogenetic Clustering Among Previous Pre-Exposure Prophylaxis Users Who Seroconverted

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Does previous PrEP use affect HIV drug resistance or clustering?

- Program evaluation is essential in public health to identify successes and areas for improvement.
- In British Columbia (BC), Canada, publicly funded pre-exposure prophylaxis (PrEP) has been available since January 2018 at no cost to clients, yet effects on HIV transmission and drug resistance are unclear.
- To evaluate the BC PrEP program, we tested the **hypotheses that phylogenetic clustering and drug resistance would differ based on previous PrEP use.**

APPROACH

- By 24 June 2021, 7465 persons had ever received PrEP via the BC program, of whom there were 15 (0.20%) **PrEP users who seroconverted (PUWS)** diagnosed between 23 October 2018 and 20 November 2020.
- **A retrospective case-control cohort:** all 15 PUWS and 314 **non-PrEP users who seroconverted (NPUWS)** over this diagnosis range, using first detectable viral load was used as a proxy for diagnosis.
- Re-analyzed HIV partial pol and integrase sequences generated through clinical drug resistance testing
  - Compared baseline and longitudinal drug resistance mutations, called by the Stanford HIVdb algorithm[1]
  - Compared phylogenetic clustering and branching rates estimated from HIV trees for all of BC

1. Shafer RW (2006). Web Resources for HIV type 1 Genotypic-Resistance Test Interpretation. Clin Infect Dis 42(11):1608-18.

Phylogenetic clustering by PrEP use

- 38,539 HIV partial pol sequences collected 1996 - 2021 from 10,386 participants in BC Drug Treatment Program: aligned to reference, trimmed codons of known surveillance drug resistance mutations
- Inferred 100 bootstrap approximate maximum likelihood phylogenetic trees using FastTree2.1 with a GTR substitution model
- Identified phylogenetic clusters comprising 5+ members with tree distance less than 0.02 subs/site in >90% of bootstraps
- Lineage-level viral diversification rates (approximate historical transmission rates) were calculated for each tip[2]

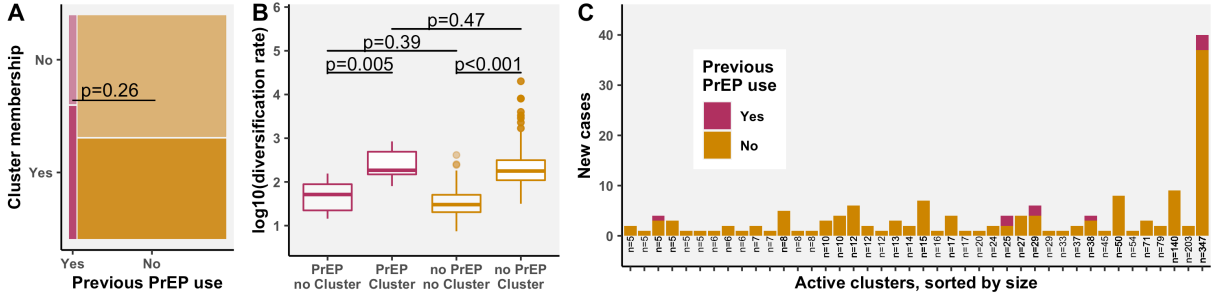


Figure 1. Clustering and diversification among previous PrEP users and non-PrEP users who seroconverted. A) A comparison of the proportion clustering by PrEP use, using a 2-sided chi-squared test. B) Viral lineage-level diversification rates were compared by PrEP use and clustering using a Kruskal-Wallis test, followed by pairwise Mann-Whitney tests. C) The distribution of new cases by PrEP use among active clusters, with new cases between 2018-10-23 and 2020-11-20.

- **PUWS were not significantly more likely to cluster than NPUWS** (60.0% vs. 45.2%, chi-squared test: p=0.26; Table 1; Fig. 1A), although underpowered to detect small differences.
- All clusters joined by PUWS were also joined by at least one NPUWS (Fig. 1C; Table 2).
- **Viral lineage-level diversification rates were not significantly different between PUWS and NPUWS** who clustered (Mann-Whitney test: p=0.47) or did not cluster (p=0.39; Fig. 1B).

2. Liu TF Jetz, W., Thomas, G. H., Joy, J. B., Hartmann, K. & Mooers, A. O. (2012). The global diversity of birds in space and time. Nature 491, 444–448.

Drug resistance by PrEP use

- Surveillance drug resistance mutations (SDRMs), treatment selected mutations (TSMs), and resistance scores called by Stanford HIVdb[1]
- **No significant differences between proportion of PUWS or NPUWS with any baseline TSMs (chi-squared: p=0.21), SDRMs (p=0.56), or NRTI TSMs (p=0.95; Fig. 2A).** PUWS had significantly higher baseline FTC and 3TC resistance scores (p=0.002, Fig. 2C)
- Highest NRTI drug resistance scores were from a PUWS with M184V (patient E) who had the highest proportion of days not covered by PrEP among PUWS (0.4 vs. median 0.056), the longest gap with no refill (155 days vs. median 22), and 64 days between last prescription and diagnosis date (median 200). This **suggests low level PrEP exposure during acute infection selected for M184V**

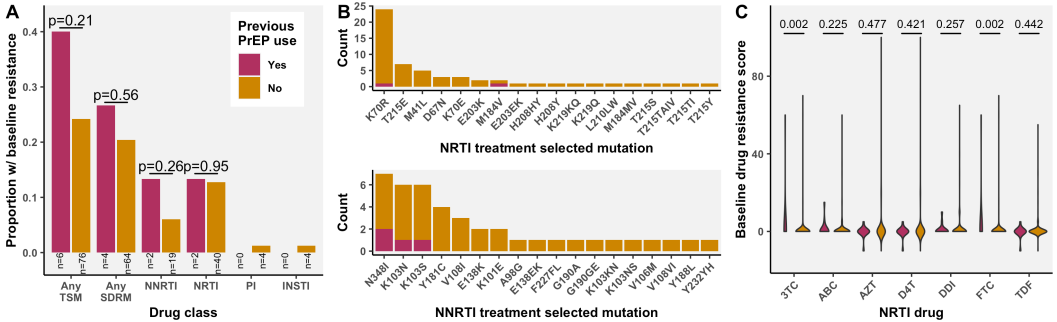
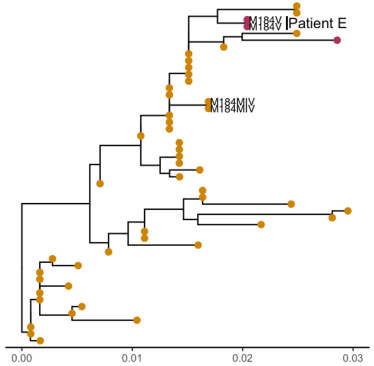


Figure 2. Drug resistance among previous PrEP users and non-PrEP users. A) The proportion of PUWS and NPUWS with any baseline drug resistance mutations each drug class were compared using two-sided chi-squared tests. B) The occurrence of NRTI and NNRTI TSMs among PrEP users and non-PrEP users. C) Stanford drug resistance scores towards NRTI drugs were compared with Kruskal-Wallis tests.



- Nearest phylogenetic neighbours of viruses from patient E do not have M184V, but an M184MIV mixture was detected within cluster.

Figure 3. Phylogeny of viruses within 0.03 substitutions per site to two isolates from patient E, a previous PrEP user who seroconverted with high baseline NRTI resistance.

1. Shafer RW (2006). Web Resources for HIV type 1 Genotypic-Resistance Test Interpretation. Clin Infect Dis 42(11):1608-18.

Conclusion

- Previous PrEP use among HIV seroconversions in BC was not significantly associated with phylogenetic clustering, viral diversification rates, or baseline drug resistance at a population level.
- However, one individual with an unusual PrEP refill pattern had baseline M184V conferring NRTI resistance that was not present in nearby phylogenetic neighbours, suggesting strong selection and/or acquisition of M184V during acute infection in presence of low level of PrEP.
- These results strongly highlight the success of the PrEP program in BC, while highlighting the importance of high PrEP adherence and early diagnosis.

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