HIV DRUG RESISTANCE AND CLUSTERING PATTERNS AMONG PREVIOUS PREP USERS WHO SEROCONVERTED

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BACKGROUND

Program evaluation is essential to 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 uncharacterized. To evaluate the BC PrEP program, we tested the hypothesis that phylogenetic clustering and drug resistance would differ between previous PrEP users who seroconverted (PUWS) compared to non-PrEP users who seroconverted (NPUWS).

METHODS

- 38,539 HIV partial pol sequences (collected May 1996 - June 2021) from 10,386 participants in the BC Drug Treatment Program were aligned to the HXB2 reference.
- Surveillance drug resistance mutations (SDRMs), treatment selected mutations (TSMs), and resistance scores were called by Stanford HIVdb[1]. SDRM sites were masked in the alignment
- 100 bootstrap approximate maximum likelihood phylogenetic trees were inferred using FastTree2.1.
- Phylogenetic clusters comprising 5+ members with pairwise patristic distance less than 0.02 substitutions/site in at least 90% of bootstraps were identified.
- Lineage-level viral diversification rates[2] were calculated for each tip i as the reciprocal sum of N_i branch lengths (lj) tip to root: lineage-level diversification rate = $(\sum_{j=1}^{N_i} \frac{l_j}{2^{j-1}})^{-1}$
- First detectable viral load was used as a proxy for diagnosis.
- By 24 June 2021, 7465 persons had ever received PrEP via the BC program, of whom there were 15 (0.20%) PUWS diagnosed between 23 October 2018 and 20 November 2020. There were 314 NPUWS over this diagnosis range.

Table 1. Sociodemographic and clinical characteristics of PrEP users who seroconverted (PUWS) and non-PrEP users who seroconverted (NPUWS).

		PUWS		NPUWS	
	Parameter	**Total**	**n (%) clustered**	**Total**	**n (%) clustered**
	n	15	9 (60.0)	314	142 (45.2)
Sex	Total female	0	0 (0)	46	18 (39.1)
	Total male	15	9 (60.0)	242	114 (47.1)
	Total FM	0	0 (0)	0	0 (0)
	Total MF	0	0 (0)	2	1 (50)
Age	Median age	32.5	34.2	40.7	39.1
	Min age	23.5	27.3	0.9	4.0
	Max age	43.0	43.0	74.8	68.1
Reported risk factors	Total risk rep.	14	8 (57.1)	251	117 (46.6)
	Total MSM	13	8 (61.5)	144	63 (43.8)
	Total HET	1	0 (0)	80	33 (41.3)
	Total PWID	3	3	62	42 (67.7)
	Total HCV	2	2	61	45 (73.8)
	Total HBV	0	0 (0)	24	9 (37.5)
Clinical	Total subtype B	13	9 (69.2)	251	138 (55.0)
	Median baseline log(pVL)	5.2	4.7	4.9	5.0
	Median baseline CD4 count	590	520	400	465

1. Liu TF, Shafer RW (2006). Web Resources for HIV type 1 Genotypic-Resistance Test Interpretation. Clin Infect Dis 42(11):1608-18.
2. 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.

Previous PrEP use was not significantly associated with increased risk of drug resistance among seroconverters, however within one inconsistently adherent PrEP user, M184V was likely strongly selected during acute infection.

RESULTS

CLUSTERING and DIVERSIFICATION RATES

- PUWS were not significantly more likely to cluster than NPUWS (60.0% vs. 45.2%, chi-squared test: p=0.26; Fig. 1A). All clusters joined by PUWS were also joined by at least one NPUWS (Fig. 1C).
- 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).

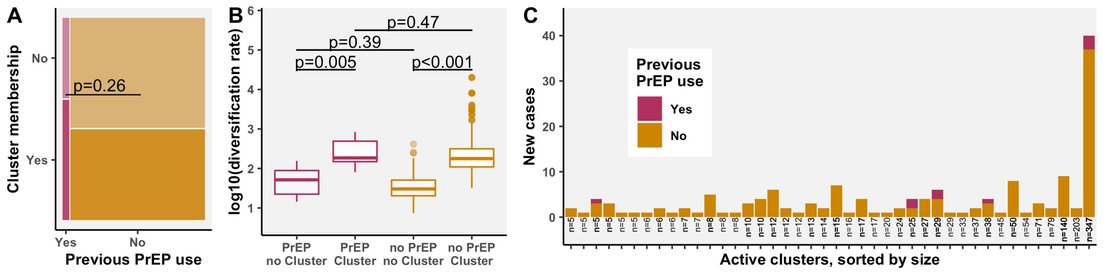


Figure 1. Clustering and diversification among previous PrEP users and non-PrEP users who seroconverted. A) A comparison of the proportion clustering by PrEP use, using a 2-sided chi-squared test. B) Viral lineage-level diversification rates were compared by PrEP use and clustering using a Kruskal-Wallis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

DRUG RESISTANCE

- No significant association between previous PrEP use and any baseline TSMs (chi-squared: p=0.21), SDRMs (p=0.56), NNRTI TSMs (p=0.26), or NRTI TSMs (p=0.95; Fig. 2A). Note: low statistical power.
- K70R was the most common SDRM in the cohort (Fig. 2B) and is increasing in prevalence over time.
- Previous PrEP use was associated with significantly higher baseline FTC and 3TC resistance scores (Fig. 2C); this trend was driven by a single previous PrEP user with M184V resistance, “patient E”.

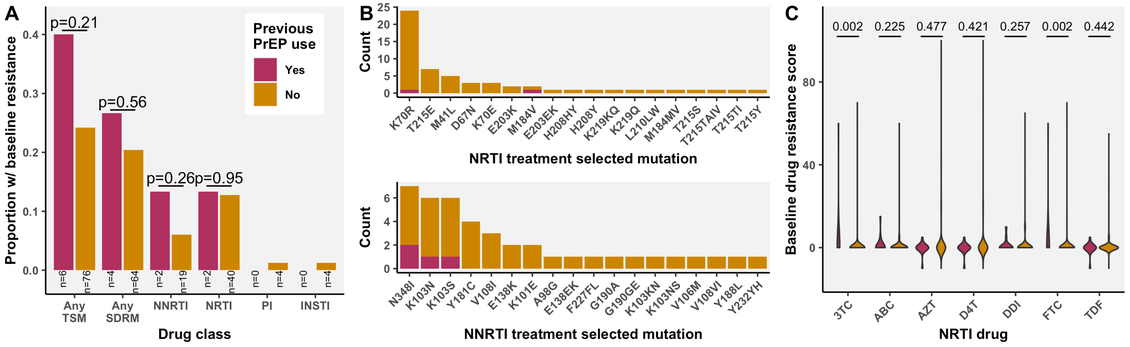
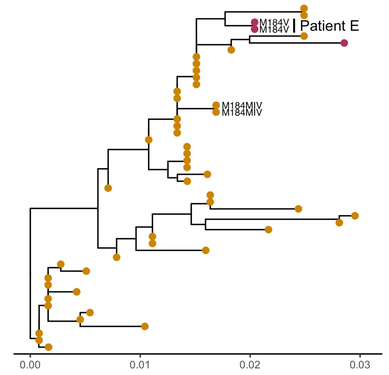


Figure 2. Drug resistance among previous PrEP users and non-PrEP users. A) The proportion of PUWS and NPUWS with any baseline drug resistance mutations each drug class were compared using two-sided chi-squared tests,. B) The occurrence of NRTI and NNRTI TSMs among PrEP users and non-PrEP users. C) Stanford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

NRTI RESISTANCE IN PUWS MAY BE ASSOCIATED WITH INCONSISTENT PREP USE

Among all PUWS, the individual in whom the highest NRTI drug resistance was detected (patient E) had the highest proportion of days not covered by PrEP (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 that incomplete or intermitted PrEP use may have contributed to the selection of M184V



- Nearest viruses to those from patient E do not have M184V, but M184MIV mixture was identified in two isolates within patristic distance of 0.0106 subs/site.
- Next step: Investigate whether M184V was likely acquired anew in patient E or strongly selected from a pre-existing minority variant.

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.

CONCLUSIONS

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 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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