Phylodynamic Analysis of the British Columbia HIV and HCV Epidemics

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BACKGROUND: Understanding the processes shaping epidemics is critical for their prediction and management. RNA viruses evolve measurably on time-scales of transmission among individuals, allowing reconstruction of past epidemic dynamics from the genetic divergence among observable infections over time[1]. Within regional epidemics, different risk factors and associated differences in levels of health care engagement predict both different transmission dynamics and corresponding different viral evolutionary dynamics measureable from the shape of phylogenetic trees. We carried out phylogenetic analysis of the genetic diversification of HIV and HCV in British Columbia (BC) to quantify historical dynamics and to compare these to previous estimates in relation to known periods of epidemic change.

METHODOLOGY: We reconstructed distributions of 1,000 time-scaled phylogenetic trees from 27,296 HIV protease and RT sequences sampled from 7,747 patients in BC (Figure 1 and 2) and from 1,393 HCV NS5B sequences sampled from ~800 HCV RNA reactive patients also in BC (Figure 5 and 6) using Fasttree2[2]. All sequences were doubly anonymized to protect patient privacy. Lineage through time (LTT) plots[3] were used to examine the history of epidemic expansion generally and as a function of clinical, demographic and risk factors (e.g. gender, age, intravenous drug use). We calculated a lineage level transmission rate (diversification rate[2]) for each lineage in each HIV tree (Figure 2), and we compared mean transmission rate among HIV risk factors using t-tests.

RESULTS: Comparative phylogenetic analyses among risk exposure categories revealed differences in timing of the HIV epidemic between IDU and MSM. IDU experienced increases in rates of HIV lineage accumulation in the mid-1990s, whereas the MSM epidemic grew rapidly in the 1980's followed by a reduction in incidence (Figure 3). Comparative analysis of HIV transmission rates among risk exposure categories revealed the rate of HIV transmission was significantly higher among IDU lineages relative to MSM and heterosexuals ($t=15.77$, $p < 0.001$) and significantly lower among infections resulting from infected blood products ($t=3.81$, $p < 0.001$, Figure 4).

LTT plots of HCV reveal rapid diversification of the epidemic 60 years ago (earlier than expected, Figure 7). LTT plots also show that most female and male "baby boomers" currently contribute little to onward HCV transmission (Figure 8) and that most HCV transmission is occurring amongst younger individuals (Figure 8).

Timing of phylogenetically estimated declines in lineage accumulation, and HIV transmisison, are concordant with estimates based on the numbers of new HIV diagnoses, providing independent evidence that reductions in HIV incidence are associated with periods of expanded access to HAART.

CONCLUSIONS: Concordance of our population-level phylogenetic results with epidemiological data[5] validates the use of phylogenetic methods in assessing the past and present dynamics of the HIV and HCV epidemics. Further, we show the potential of comparing inferences drawn from phylogenetic trees partitioned by different HIV and HCV risk exposure categories.

HIV

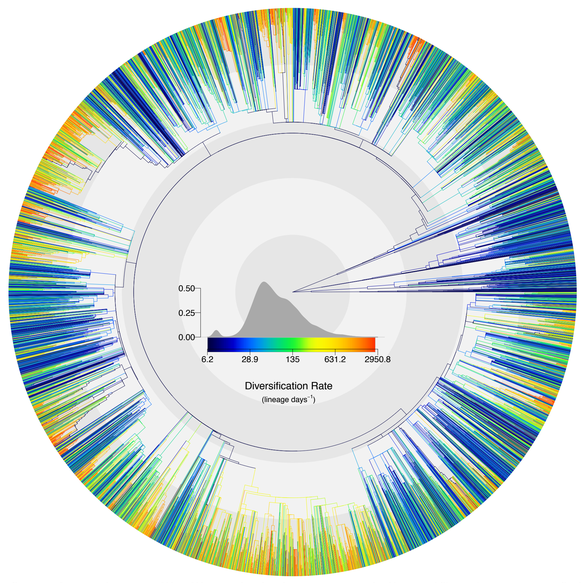

Figure 2 | Inferred maximum likelihood phylogeny and diversification rate of the British Columbia HIV epidemic. Branches are coloured according to the mean diversification rate of descendent branches. Diversification rate quantifies the splitting rate along branches leading to a tip providing a diversification rate[4], a measure of transmission rate, for each tip averaged across 1000 trees. Inset shows the scale and frequency distribution of diversification rate and concentric grey circles correspond to time in intervals of 7000 days.

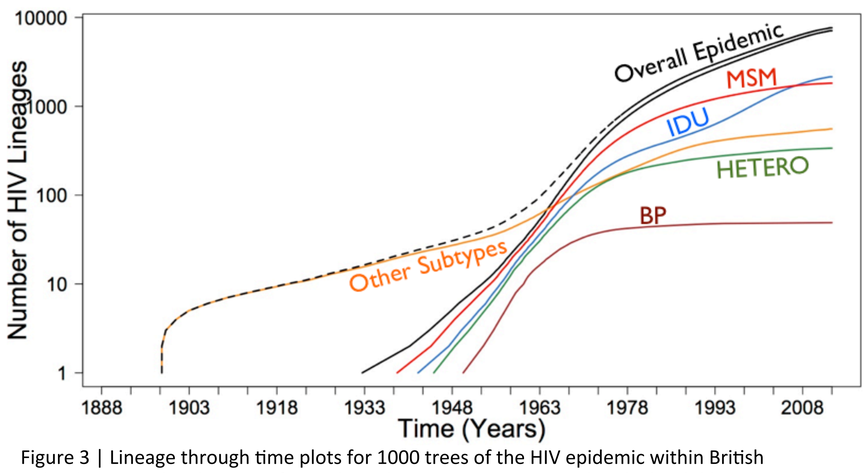

Figure 3 | Lineage through time plots for 1000 trees of the HIV epidemic within British Columbia, Canada. The mean for each epidemic category is traced in thick solid lines. Results are consistent with epidemiological data[5] showing expansion in IDU in the mid-late 1990's and earlier expansion among MSM followed by subsequent tapering off. MSM refers to men having sex with men, IDU to intravenous drug users, HETERO to heterosexuals, BP to blood product infections.

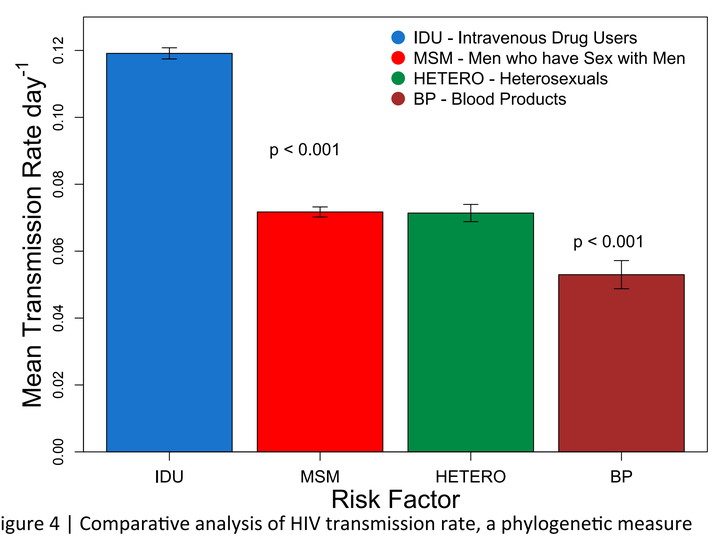

Figure 4 | Comparative analysis of HIV transmission rate, a phylogenetic measure of transmission rate, among risk factors. HIV transmission rate was significantly higher among intravenous drug users relative to men who have sex with men and heterosexuals and significantly lower among infections resulting from infected blood products.

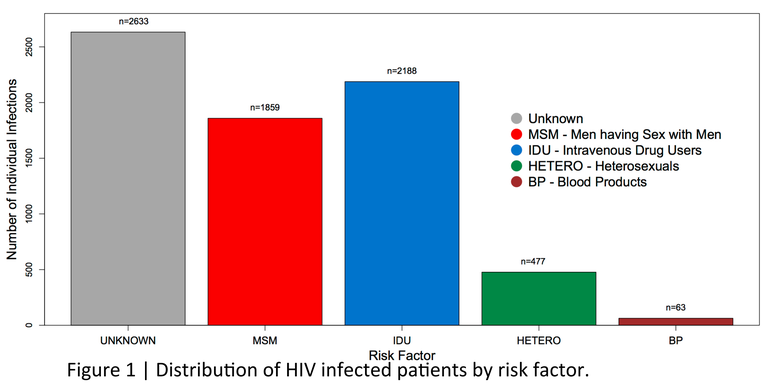

Figure 1 | Distribution of HIV infected patients by risk factor.

HCV

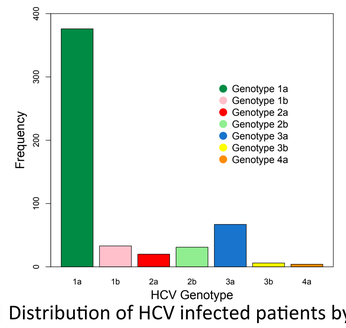

Figure 5 | Distribution of HCV infected patients by genotype, genotypes with only 1 representative not shown (2m, 3g, 4d, 6a).

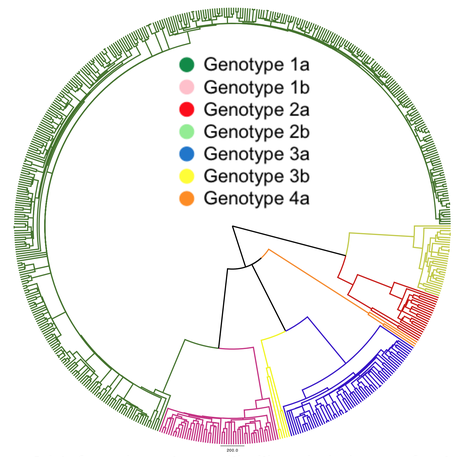

Figure 6 | Inferred maximum likelihood phylogeny for 1,393 HCV NS5B sequences drawn from 800 HCV RNA reactive patients in the British Columbia HCV epidemic. Branches are coloured according to HCV genotype.

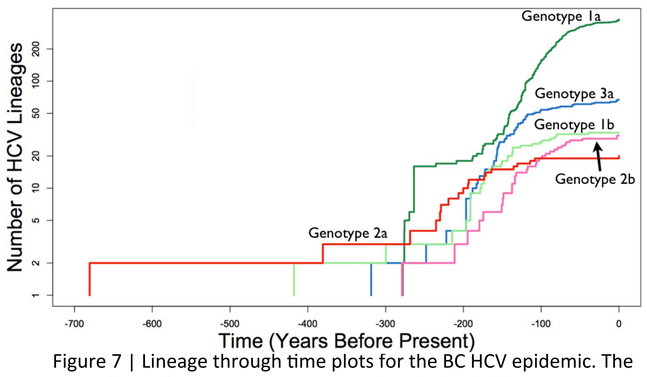

Figure 7 | Lineage through time plots for the BC HCV epidemic. The mean for each HCV genotype is traced in thick solid lines.

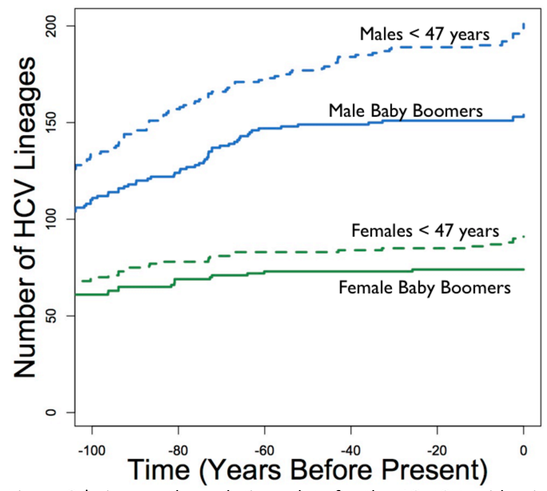

Figure 8 | Lineage through time plots for the BC HCV epidemic by gender and age. Most female and male "baby boomers" currently contribute little to onward HCV transmission. Most HCV transmission is occurring amongst younger individuals .

ACKNOWLEDGMENTS: This work was supported by an operating grant from the Canadian Institutes of Health Research (CIHR, HOP-111406). AFYP is supported by a New Investigator Award from CIHR (Canadian HIV Vaccine Initiative for Vaccine Discovery and Social Research) and a Career Investigator Scholar Award from the Michael Smith Foundation for Health Research / St. Paul's Hospital Foundation - Providence Health Care Research Institute partnership. PRH is supported by a CIHR/GSK Research Chair in Clinical Virology.

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