Phylodynamic Analysis of a Regional HIV Epidemic

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BACKGROUND: Understanding the processes shaping epidemics is critical for their prediction and management. Phylogenetic inferences drawn from viral sequence data provide a window into the temporal dynamics of regional epidemics, allowing estimation of rates of incidence, and infection accumulation[1]. Within such 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.

METHODOLOGY: We inferred 1,000 time-scaled phylogenetic trees[2] for 27,296 HIV protease and RT sequences sampled from 7,747 patients annotated with risk factors (Figure 1) in the BC Centre for Excellence in HIV/AIDS database in BC, Canada. All sequences were doubly anonymized to protect patient privacy. Estimates of epidemic age were calculated using the root age of each phylogenetic tree in our distribution. We visualized the accumulation of infections through time using lineage through time plots[3] (LTT). We utilized maximum likelihood approaches for estimating rates of incidence by fitting birth-death models across our distribution of phylogenetic trees for the epidemic as a whole and within risk factors[4]. We calculated a lineage level diversification rate (DR) for each tip[5] in each tree (Figure 2), we compared mean DR among risk factors using t-tests.

RESULTS: Our analysis suggested 1897 (IQR: 1883-1923) as the estimated median time for the origin of the HIV epidemic overall, and 1941 (IQR: 1923-1958) for the subtype B clade. LTT plots (Figure 3) revealed that within and between HIV subtypes, the BC epidemic is composed primarily of variation originating prior to 1990 (the advent of health care intervention). Birth-death models showed the subtype B epidemic has undergone a recent decrease in the estimated rate of incidence (Figure 4). Results are consistent with an epidemic founded by multiple sources and subsequent spread along local networks corresponding to different HIV risk factors, with later declines in spread.

Comparative phylogenetic analyses among risk exposure categories reveals substantial differences in the timing of the HIV epidemic between intravenous drug users (IDU) and men who have sex with men (MSM). IDU experienced a dramatic increase in rate of lineage accumulation and incidence in the mid-1990s whereas the MSM epidemic underwent rapid growth in the 1980's followed by subsequent tapering off. Comparative analysis of DR among risk exposure categories revealed the rate of HIV diversification was significantly higher among IDU 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 5).

CONCLUSIONS: Concordance of our population-level phylogenetic results with epidemiological data[6] validates the use of phylogenetic methods in assessing the past and present dynamics of the HIV epidemic. Further, we show the potential of comparing inferences drawn from phylogenetic trees partitioned by different HIV risk exposure categories.

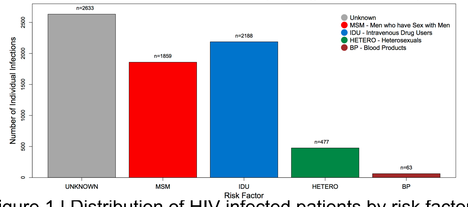

Figure 1 | Distribution of HIV infected patients by risk factor.

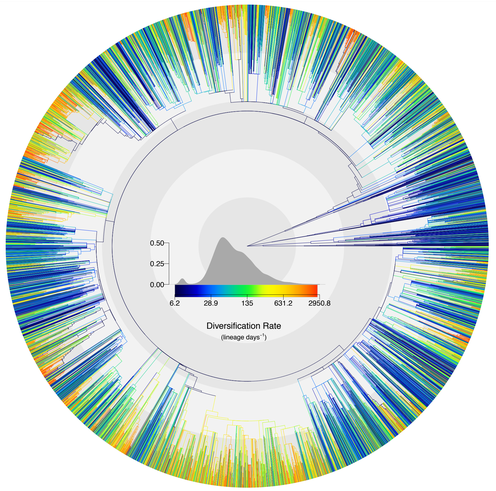

Figure 2 | Inferred maximum likelihood phylogeny and diversification rate of the British Columbia HIV phylogeny. Branches are coloured according to the mean diversification rate of descendent branches. Diversification rate quantifies the splitting rate along branches leading to a tip providing a diversification rate[5], 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.

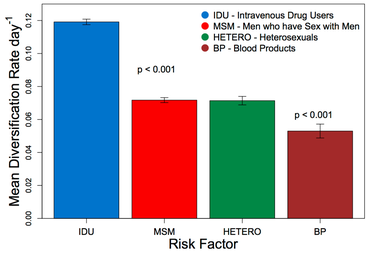

Figure 5 | Comparative analysis of HIV diversification rate (DR), a measure of transmission rate, among risk factors. DR was significantly higher among intravenous drug users relative to men who have sex with men and heterosexuals and significantly lower among infections resulting from infected blood products.

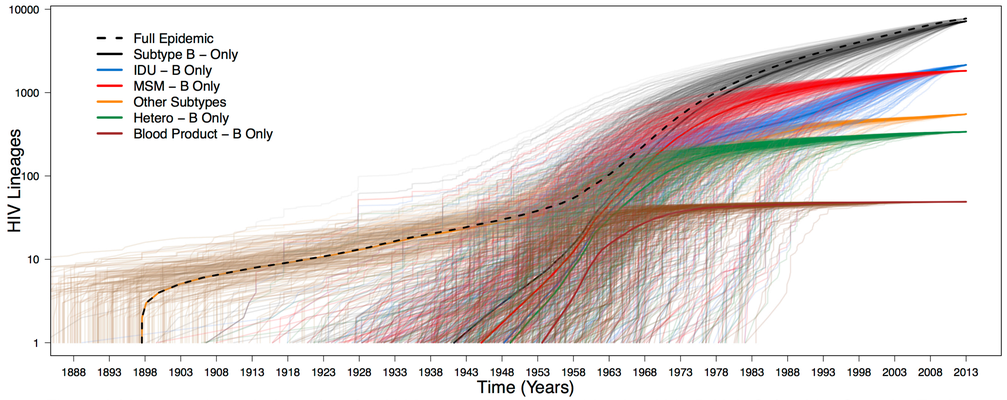

Figure 3 | Lineage through time plots for 1000 trees of the HIV epidemic within British Columbia, Canada. Each tree is plotted as a thin line to encapsulate the variance in the distribution, the mean for each epidemic category istraced in thick solid lines. Results are consistent with epidemiological data[6] showing expansion in IDU in the mid-late 1990's and earlier expansion among MSM followed by subsequent tapering off.

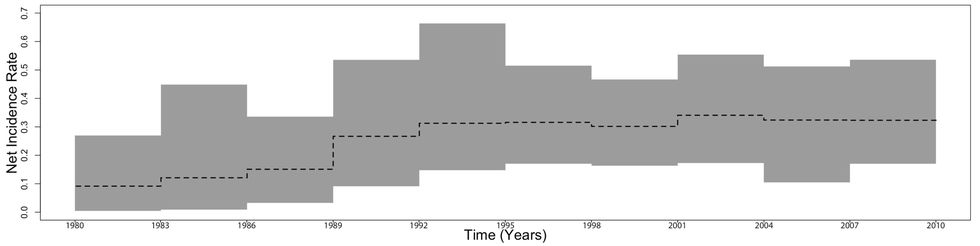

Figure 4 | Epidemic wide incidence rate estimated using birth-death models. Incidence is calculated in intervals of 1095 days (3 years) through time. The shaded region represents the area between the 5th and 95th quantiles for the 1000 assessed trees with the median rate traced as a black dashed line. Intervals before 1983 and after 2010 are not shown due to lack of data (≤ 30 lineages per interval) and the difficulty of accounting for ongoing transmission events, respectively.

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