Bridging epidemiology with population genetics to understand the dynamics of HIV-1 transmission of a low incidence MSM-driven subtype B epidemic in Central Europe

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Objective: The HIV-1 epidemic in Slovenia, a small Central European country, has unique characteristics that make it an ideal model to study HIV-1 transmission: slow growth rate, affecting less than 1/1000 individuals, affecting predominantly men who have sex with men, and being dominated by a single subtype (89% of all patients infected with subtype B). The aim of the present study was to analyze in detail the evolutionary history and the determinants of transmission of this unique, slowly growing epidemic.

Methods: A total of 223 partial pol gene sequences from therapy naïve individuals were included, representing 52% of all patients newly diagnosed in 13 years (2000-2012) and analyzed together with genetically similar worldwide sequences, selected in a BLAST search.

Results: Combined analysis (maximum likelihood and Bayesian) of HIV-1 transmission chains revealed 8 major clusters (n≥10 patients), 1 group of 4 patients, 2 trios and 12 transmission pairs, thus leaving only 43 (19.3%) Slovenian patients infected with subtype B without a local epidemiological link, indicating a predominance of local transmission of HIV-1 infection (Figure 1). Bayesian analysis performed on a complete set of sequences estimated several introductions of HIV-1 into Slovenia, with the most recent common ancestor (tMRCA) of the earliest Slovenian cluster dated to the late 1980s, although tMRCAs obtained from separate independent analysis of each cluster showed considerably more recent estimates (Table 1). These findings indicate inconsistencies in molecular clock estimation, which we further explored. We hypothesize that these inconsistent dating estimates across the tree could be caused by an evolutionary rate acceleration of HIV-1 after entering the Slovenia epidemic that is not taken into account by the molecular clock model. It could be caused by a lower transmission rate in this setting, as demonstrated by the low epidemic growth rate estimated by Bayesian skyline plot analysis.

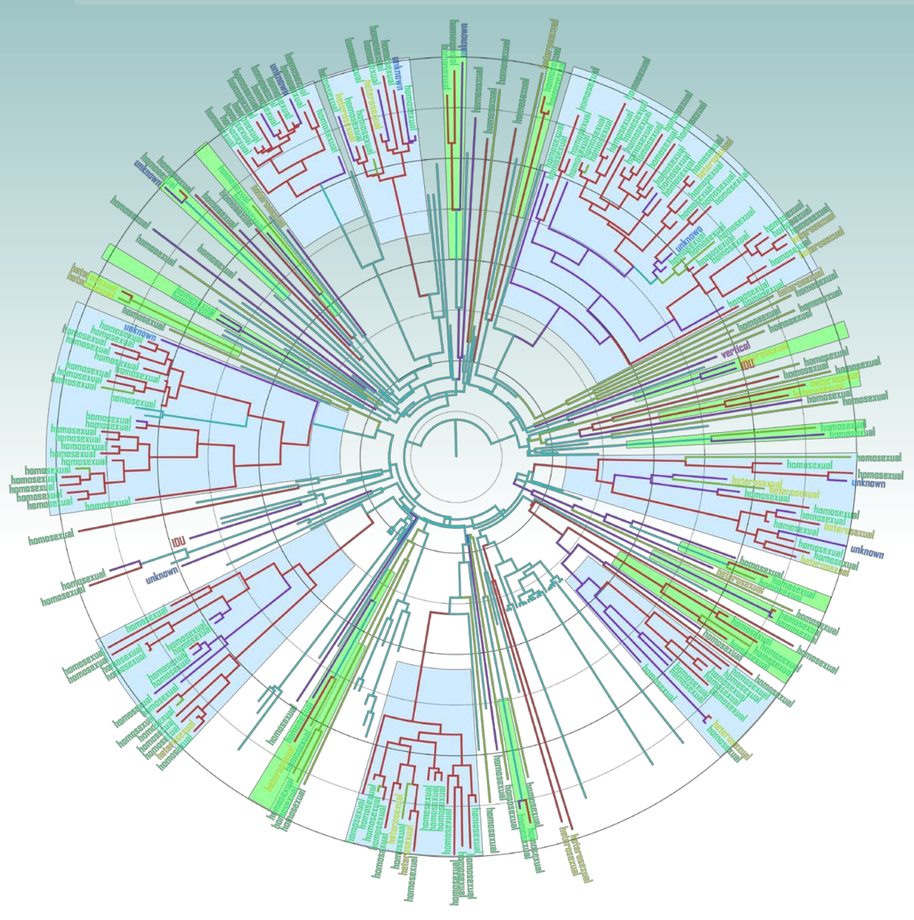

Figure 1. Bayesian maximum clade-credibility trees of the Slovenian subtype B epidemic with defined clusters (n≥10 patients) highlighted in blue and transmission group of 4 patients/trios/pairs in green. The branches of the Slovenian sequences are coloured according to the patients' country of infection: red=Slovenia, green=abroad, purple=unknown; Mode of HIV-1 acquisition is depicted at nodes and colored accordingly: green=homosexual contact, yellow=heterosexual contact, red=intravenous drug use, purple=vertical transmission, blue=unknown. The branches of the control sequences are depicted in light blue. The rings are set at 5-year intervals with the outer circle starting at the sampling time of the latest sequence (2012.97).

Table 1. Times to the most recent common ancestor (tMRCAs) of 8 major clusters of Slovenian sequences obtained by employing Bayesian analysis on two different sets of sequences; set comprised of all Slovenian subtype B sequences and separate sets of only clustered sequences.

	Full analysis			Analysis based on cluster strains				
	mean	median	95% HPD	mean	median	95% HPD	Sampling dates	Time depths[2]
Cluster 1	1990.6	1991.4	1987.1 - 1996.1	1998.0	1998.3	1995.2 - 2000.4	2001.42 - 2012.73	22.13
Cluster 2	1986.9	1988.1	1983.1 - 1992.9	1990.0	1990.8	1980.1 - 1998.1	2003.06 - 2012.68	25.78
Cluster 3	1999.1	1999.9	1995.4 - 2002.9				2005.46 - 2012.74	13.64
Cluster 4	1991.4	1992.2	1987.0 - 1998.1				2002.40 - 2012.64	21.24
Cluster 5[1]	1990.6	1991.1	1987.1 – 1995.6				2000.68 - 2009.47	18.87
Cluster 6	1986.1	1987.4	1981.4 - 1990.5				2000.25 - 2012.92	26.82
Cluster 7	2003.0	2003.6	2000.8 - 2005.3				2005.32 - 2012.45	9.45
Cluster 8	2001.2	2001.7	1999.0 - 2003.4				2004.01 - 2011.77	10.57

Conclusions: HIV subtype B was introduced into Slovenia at several time points from the late 80s onward. The majority of patients had a local transmission link, indicating a closed HIV community. The observed slower epidemic rate suggests that individuals with a long-lasting infection are the driving force of the epidemic in this region.

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