Large NNRTI-Resistant Transmission Cluster in Injection Drug Users from Saskatchewan

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ABSTRACT

Background: Saskatchewan, a Canadian Prairie province, is currently experiencing a unique HIV epidemic characterized by high rates of transmission through injection drug use. Aboriginal peoples are disproportionately affected.

Methods: We reviewed the epidemiologic and clinical characteristics of all HIV-positive individuals who attend the Regina Qu'Appelle Health Region Infectious Diseases Clinic (RQHR IDC), which serves the southern half of Saskatchewan and represents 25% of the province's HIV burden. Molecular phylogenies were inferred from anonymized bulk HIV-1 pol sequences from pre-therapy resistance genotyping of all patients for whom testing was available. Short tip-to-tip distances (patristic distance < 0.02) between sequences from different individuals on the phylogeny were used to define clusters. Resistance data was super-imposed on phylogenetic trees to identify clusters of primary transmitted drug resistance.

Results: 415 individuals were included in the analysis. 227/415 (54.6%) were Aboriginal, 246/415 (59.2%) had injection drug use as their primary risk factor for HIV acquisition, and 243/415 (58.5%) were positive for hepatitis C antibody. Through phylogenetic analysis, a large transmission cluster of 81 individuals (19.5% of clinic) was identified in which 76 individuals were harbouring a G190A mutation in the reverse transcriptase gene, conferring NNRTI resistance. Compared to the overall clinic population, individuals with a G190A mutation in this cluster were more likely to be Aboriginal (58/76 [76.3%], RR 1.5, P < 0.01), have injection drug use as their primary risk for acquisition of HIV (63/76 [82.9%], RR 1.5, P < 0.01), and be co-infected with hepatitis C (64/76 [84.2%], RR 1.6, P < 0.01). 10 other clusters were identified but were of smaller size (≤ 18), and none were associated with transmitted drug resistance.

Conclusions: We describe a cluster of 76 individuals with primary transmitted NNRTI resistance to HIV in southern Saskatchewan, characterized by disproportionate transmission through injection drug use in Aboriginal peoples and high rates of hepatitis C co-infection. This represents a microcosm of the current provincial HIV epidemic. Similar transmission clusters are occurring elsewhere across the province, both in urban and on-reserve settings, where prevalence of injection drug use is high. These transmission dynamics, complicated further by social, cultural and geographic factors, require urgent attention and mobilization of public health and clinical resources.

BACKGROUND

Saskatchewan is a province located in the Canadian Prairies (**Figure 1**) with a population of over 1.1 million. Care for HIV patients is provided primarily in two tertiary referral sites, Regina and Saskatoon. The province currently faces a unique HIV epidemic driven by transmission through injection drug use which disproportionately affects Aboriginal peoples. The all-age HIV diagnosis rate in the province is the highest in Canada (11.4 per 100,000). The Regina Qu'Appelle Health Region Infectious Diseases Clinic (RQHR IDC) is the referral site for HIV care in southern Saskatchewan, serving over 400 HIV-positive individuals, from which this transmission cluster with primary NNRTI resistance is described.

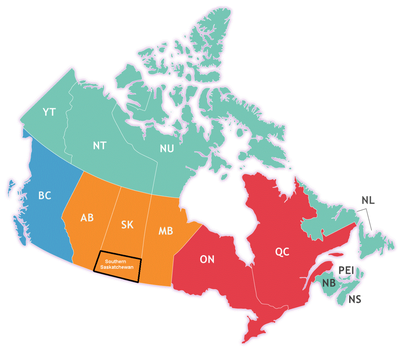


Figure 1: Map of Canada. The Prairie provinces are highlighted in **orange**. Saskatchewan is labelled as **SK**, Southern Saskatchewan labelled within.

RESULTS

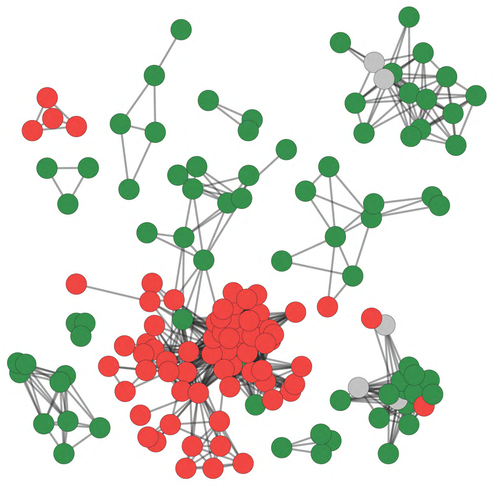


Figure 2: Phylogenetic transmission clusters in southern Saskatchewan. 255 individuals had first-recorded genotyping included, and only clusters containing 3 or more individuals were included. **Red** represents individuals with G190A mutation. **Green** represents individuals without G190A.

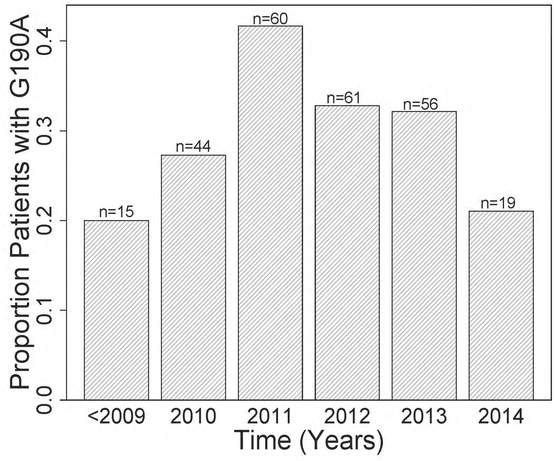


Figure 3: Temporal distribution of individuals with G190A based on first-recorded genotyping. The height of the bars represent the proportion of individuals with a G190A mutation in that time frame. Bars are labelled with the total number of first-recorded genotypes during a given time frame.

	Total (n=415)	With G190A (n=76)	Without G190A (n=339)	Relative Risk (95% CI)	P-Value
Gender					
Male	248 (59.8%)	39 (51.3%)	209 (61.7%)	-	-
Female	167 (40.2%)	37 (48.7%)	130 (38.3%)	1.27 (0.97-1.66)	0.08
Ethnicity					
Aboriginal	**227 (54.7%)**	**58 (76.3%)**	**169 (49.9%)**	**1.53 (1.30-1.80)**	**< 0.0001**
Caucasian	138 (33.3%)	16 (21.1%)	122 (36.0%)	0.59 (0.37-0.92)	0.02
Black	45 (10.8%)	2 (2.6%)	43 (12.7%)	0.21 (0.05-0.84)	0.03
Other (e.g. East Indian, Asian)	5 (1.2%)	0 (0.0%)	5 (1.5%)	-	-
Primary HIV Risk Factor					
Injection Drug Use	**246 (59.3%)**	**63 (82.9%)**	**183 (54.0%)**	**1.54 (1.33-1.77)**	**< 0.0001**
Heterosexual	78 (18.8%)	11 (14.5%)	67 (19.8%)	0.73 (0.41-1.32)	0.30
MSM	49 (11.8%)	2 (2.6%)	47 (13.9%)	0.19 (0.05-0.76)	0.02
Endemic Country	36 (8.7%)	0 (0.0%)	36 (10.6%)	-	-
Other	6 (1.4%)	0 (0.0%)	6 (1.8%)	-	-
Hepatitis C Co-Infection					
Hepatitis C Antibody (+)	**243 (58.6%)**	**64 (84.2%)**	**179 (52.8%)**	**1.59 (1.39-1.83)**	**< 0.0001**
Hepatitis C Antibody (-)	166 (40.0%)	12 (15.8%)	154 (45.4%)	0.35 (0.20-0.59)	0.0001
Unknown	6 (1.4%)	0 (0.0%)	6 (1.8%)	-	-

Table 1: Selected clinical characteristics for those with G190A (n=76) compared to those without G190A (n=339), and relative risk ratios and p-values for selected comparisons of significance. **NB:** 6 individuals with G190A had discrepant sequencing data, hence no clinical information was available for these individuals. They were assumed to be without a G190A mutation for the purposes of this analysis.

DISCUSSION

Figure 2 highlights several large transmission clusters in southern Saskatchewan, the largest containing 81 individuals. Several smaller clusters are present, including one with 18 individuals, one with 16 individuals, and one with 12 individuals. Of 255 individuals with a first-recorded genotype, 82 had a G190A mutation present (32.2%). These reflect the presence of the mutation at the time of testing, and not infection, and are an underestimate of the actual transmission of the mutation as 160 individuals did not have a recorded genotype available. Phylogenetic data was generated from anonymized bulk HIV-1 pol sequences.

Figure 3 demonstrates the remarkable persistence of the mutation over time, as first-recorded genotypes from 2010 through 2014 show ongoing detection of the mutation at a rate of over 20% of first-recorded genotypes. The genotypes containing the mutation have gradually taken hold in the community as a circulating strain of persistent "wild-type" virus.

Table 1 demonstrates the disproportionate rates of representation of Aboriginal peoples, individuals using injection drugs, and individuals with a positive hepatitis C antibody in those possessing the G190A mutation compared to those without. Within the overall clinic population, note the high rates of Aboriginal peoples (54.7%), those with injection drug use as their primary HIV risk factor (59.3%), and those with a positive hepatitis C antibody (58.6%).

This group of 82 individuals with transmitted NNRTI resistance is one of the largest clusters of primary transmitted drug resistance described to date. When recognized in 2010, the presence of the G190A mutation drove the increased use of protease inhibitors in the clinic, likely decreasing rates of secondary drug resistance. The current HIV epidemic in Saskatchewan is complicated further by geography and politics as well as social and cultural stigma, which limit opportunities for HIV testing and access to care. We hypothesize that clustering in southern Saskatchewan is duplicated and perhaps even more extreme in central and northern Saskatchewan. Urgent interventions are required at the provincial and federal government level to mobilize the appropriate public health and clinical resources to curtail and control the HIV epidemic in the province of Saskatchewan, with special attention paid to cultural and social factors relevant to the most vulnerable individuals affected.

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