# PHYLODYNAMIC FEATURES OF ACTIVE LARGE CLUSTERS FUELING THE MSM HIV EPIDEMIC IN QUEBEC

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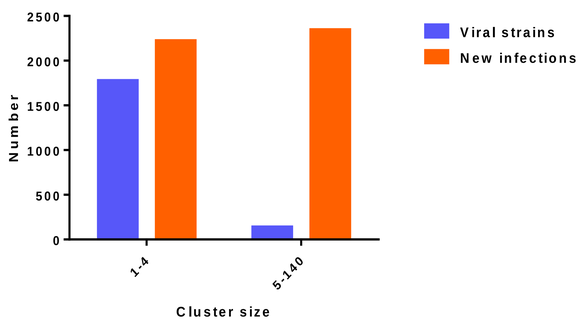
## Background

An understanding of the dynamics of onward spread of HIV is essential to the design and optimization of long-term prevention strategies to control epidemics among Men having Sex with Men (MSM). Our studies used Pol sequence datasets from the Quebec genotyping program and phylogenetic modelling strategies to map transmission networks and deduce factors implicated in the expansion of HIV among MSM in Quebec.

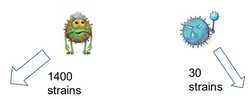
## Methods

Our data comprise 4051 time-stamped HIV Pol sequences taken from the male subtype B infections excluding mixed gender and IDU/HET clusters. Expanding on previous work, 34 large clusters having 20+ distinct members were identified, having high bootstrap support (>90) and sufficient genetic similarity (<0.05 maximum pairwise patristic distance). We applied a birth-death SIR (BDSIR) model available in the phylodynamic add-on for BEAST2 version 2.4.3 and Richard's five parameter asymmetric dose response curves to model growth trajectories. Genotyping across the viral integrase and V3 loop was performed on representative infections within clusters. Epidemiological and demographic data from the genotyping and Montreal primary HIV cohort deduced risk correlates implicated in clustering.

## Two patterns of growth fuel the epidemic amongst MSM in Quebec




## An evolutionary shift towards large cluster outbreaks has offset declines in singleton/small cluster transmissions




## Results

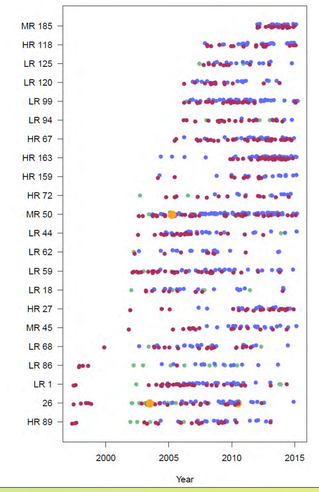
Phylogenetics revealed two patterns of HIV-1 spread among MSM. While half of the HIV epidemic was ascribed to small self-limiting clusters (size 1-4), thirty-two viral strains contributed to micro-epidemics (cluster size 20-145) disproportionately rising from 13%, 25%, and 42% of new diagnoses in 2004-2007, 2008-2011, and 2012-2015, respectively. BDSIR plots deduced early, active and dying phases of expansion for individual clusters. Ten to twelve 20+ clusters fueled spread of HIV in each quadrennial period. Epidemiological and virological data deduced factors contributing to the expansion of the ten active strains from 2012-2016. Clusters were concentrated in the Montreal area with cluster 67B reflecting a second-wave epidemic in Quebec City. Belonging to 20+ clusters was associated with primary/recent infection and being under 30 years of age (odds ratio 3.7 and 3.3, respectively). Clusters over the 2012-2015 quadrennial period arose in significantly younger populations. The heightened transmissibility of strains belonging to distinct 20+ clusters were related to increased viral replicative fitness and/or dual tropism.

### Risk factors associated with transmission clustering

| | Cluster group (transmissions per cluster) | | | | | Test statistic |
|---|---|---|---|---|---|---|
| | 0 (n=1359) | 2-4 (n=652) | 5-9 (n=336) | 10-19 (n=362) | 20-145 (n=1192) | |
| **Age** | | | | | | |
| Median (IQ) | 43 (36-40) | 40 (32-48) | 40 (31-45) | 41 (33-49) | 34 (28-43) | KW=380*** |
| % group under 30 | 14.2 | 21.0 | 22.4 | 2.91 | 35.1 | $X^2$=161*** |
| Odds ratio | 1 | 1.6 | 1.8 | 1.6 | 3.3 | |
| **Clinical indication of primary infection (0-6 months) at first genotyping** | | | | | | |
| % cluster group | 25.0 | 37.8 | 44.6 | 47.0 | 48.3 | |
| Odds-ratio | 1 | 1.9 | 2.4 | 2.7 | 2.8 | $X^2$=159*** |
| **Recent infection (0-0.44% mixed base calls)** | | | | | | |
| % cluster group | 26.9 | 44.7 | 48.0 | 52.5 | 57.4 | KW=354*** |
| Odds ratio | 1 | 2.2 | 2.5 | 2.7 | 3.7 | $X^2$=263*** |
| **Sexual contacts in 3 months prior to primary infection** | | | | | | |
| 5+ partners | 20.7 | 21.7 | 23.0 | 20.0 | 26.4 | $X^2$=14.66 |
| % cluster group | | | | | 1.4 | p= 0.006 |

## Episodic introduction, expansion and persistence of large 20+ clusters

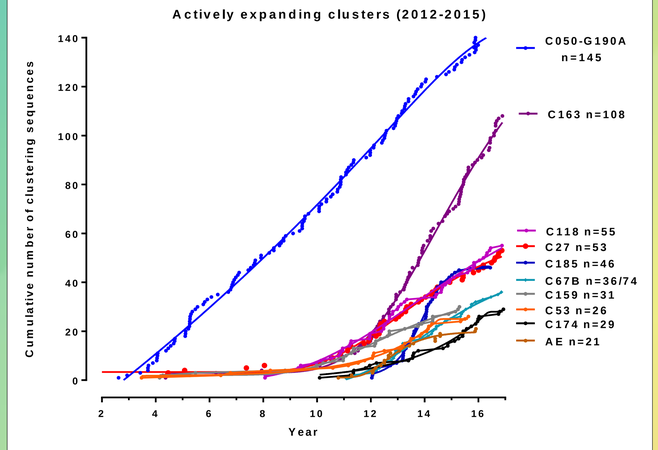
Lines depict median year [25th-50th IQ] for each cluster.
Large cluster 20+ outbreaks persist for median 3.7 year intervals [2.8-4.2 IQ]




**Clinical stage at first genotype**

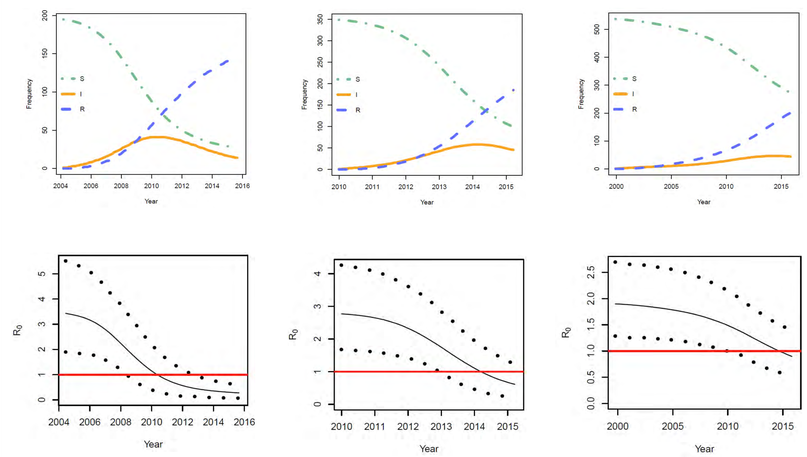
- PHI : 0-6 months
- Chronic ART-naïve, 6+ months

Large cluster outbreaks are fueled by forward transmission of primary infections (0-6 months) and untimely diagnosis and treatment of early chronic stage infections




## A birth-death SIR, Susceptible (green dot dash), Infected (orange) and Removed (blue dash) model reveals varying levels of risk among large clusters

Cluster 94 Low risk | Cluster 185 Moderate risk | Cluster 27 High risk




### Table 1. Bayesian parameter estimates and 95% HPD intervals (in parentheses) from the BDSIR analysis on the 16 well supported MSM clusters within the infected HIV-1 type B population in Quebec.

| ID | $R_0$ | $R_e(t_{100})$ | $s$ | $n_S(0)$ | $\gamma$ | Risk |
|---|---|---|---|---|---|---|
| 27* | 1.90 (1.29, 2.70) | 0.90 (0.49, 1.38) | 0.76 (0.39, 1.00) | 445 (139, 1304) | 0.39 (0.22, 0.62) | high |
| 42 | 2.46 (1.28, 4.25) | 1.12 (0.30, 2.26) | 0.74 (0.45, 0.99) | 147 (33, 516) | 0.1 (0.04, 0.17) | high |
| 51 | 2.49 (1.37, 4.20) | 1.29 (0.47, 2.30) | 0.74 (0.41, 0.98) | 227 (59, 653) | 0.1 (0.04, 0.19) | high |
| 174 | 2.35 (1.29, 3.96) | 0.96 (0.3, 1.79) | 0.79 (0.53, 0.99) | 190 (41, 642) | 0.51 (0.23, 0.83) | high |
| 62 | 3.20 (1.54, 5.62) | 0.51 (0.08, 1.24) | 0.72 (0.40, 0.98) | 136 (41, 404) | 0.14 (0.06, 0.26) | mod |
| 79 | 4.08 (1.49, 8.03) | 0.56 (0.04, 1.90) | 0.72 (0.39, 0.98) | 107 (26, 377) | 0.13 (0.03, 0.3) | mod |
| 83 | 3.78 (1.71, 6.72) | 0.44 (0.05, 1.25) | 0.70 (0.38, 0.98) | 122 (36, 332) | 0.09 (0.03, 0.16) | mod |
| 156 | 3.05 (1.39, 5.55) | 0.47 (0.09, 1.14) | 0.75 (0.45, 0.98) | 116 (36, 347) | 0.30 (0.12, 0.54) | mod |
| 160 | 5.91 (3.01, 9.68) | 0.34 (0.04, 1.27) | 0.71 (0.40, 0.97) | 81 (21, 238) | 0.26 (0.08, 0.53) | mod |
| 185 | 2.77 (1.68, 4.26) | 0.61 (0.18, 1.22) | 0.78 (0.50, 0.99) | 225 (76, 613) | 0.71 (0.37, 1.14) | mod |
| 68 | 3.63 (2.02, 5.7) | 0.35 (0.07, 0.75) | 0.73 (0.40, 0.98) | 170 (57, 433) | 0.16 (0.07, 0.27) | low |
| 94 | 3.43 (1.90, 5.51) | 0.28 (0.07, 0.60) | 0.78 (0.51, 0.99) | 116 (37, 296) | 0.36 (0.18, 0.55) | low |
| 103 | 3.20 (1.36, 5.77) | 0.30 (0.06, 0.78) | 0.79 (0.52, 0.99) | 97 (20, 293) | 0.40 (0.2, 0.64) | low |
| 120 | 3.52 (1.80, 6.03) | 0.27 (0.05, 0.63) | 0.76 (0.48, 0.98) | 108 (36, 303) | 0.40 (0.21, 0.63) | low |
| 125 | 4.15 (2.25, 6.75) | 0.18 (0.03, 0.44) | 0.76 (0.48, 0.98) | 105 (38, 305) | 0.34 (0.17, 0.51) | low |
| 149 | 4.21 (1.87, 7.67) | 0.27 (0.04, 0.74) | 0.72 (0.41, 0.97) | 85 (29, 259) | 0.14 (0.06, 0.25) | low |

*uniform prior

## Conclusion

HIV-1 continues to spread among MSM with an alarming shift towards large cluster outbreaks, emphasizing the need for improved prevention paradigms.

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