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Metamorphosis of the Montreal MSM Epidemic: Large Cluster Viruses Fuel Transmission

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Abstract

Background

The 25-50% decline in HIV transmissions with antiretroviral therapy has raised optimism that Treatment-as-Prevention (TasP) may control the global pandemic by 2030. Paradoxically, transmissions among MSM have not declined, raising concerns that early-stage infection, frequently undiagnosed, may offset the benefit of TasP. Phylogenetics ascribe the growth of the Montreal MSM epidemic to large cluster outbreaks, averaging 43 linked transmissions/cluster. This study characterized the distinct genotypic and phenotypic features of large cluster viral variants favoring their selection advantage.

Materials & Methods

Phylogenetic analysis was performed on RT/protease sequences from all newly infected MSM (n=4319, 2002-2014), assessing clustering dynamics (frequency, size, periodicity). Nucleotide mixed base calls estimated recency of infection, using a 0.44% cut-off for primary HIV infection (PHI). PHI cohort data evaluated the natural history (viral load, risk behaviour) for subjects belonging to large clusters vs. solitary transmission groups.

Viruses were amplified from representative large clusters (n=7, 20+ linked transmissions/cluster) and solitary transmissions (n=6). Viruses from both groups were compared for tropism, drug susceptibility and emergent resistance to integrase inhibitors. Amplified viruses were serially passaged in CBMCs in the presence of increasing concentrations of (DTG), elvitegravir (EVG), and DTG +3TC dual pressure. Genotyping was performed at select passages to evaluate time to the development of drug resistance.

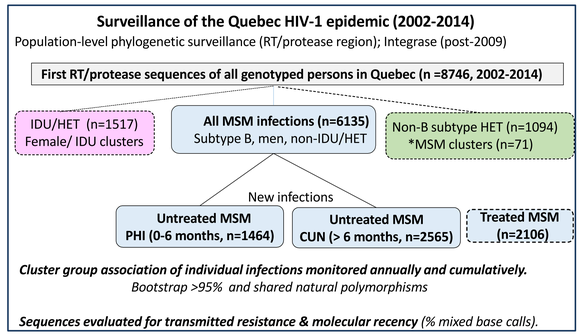
Results

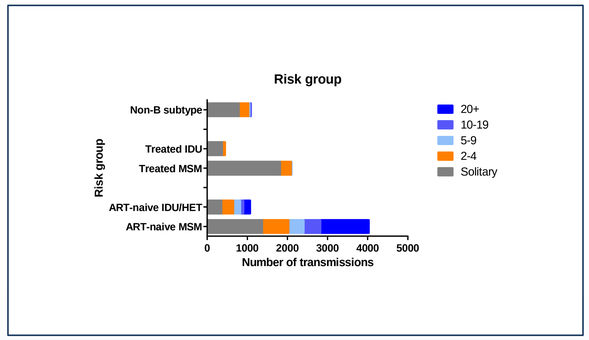
Phylogenetic analysis revealed a significant rise in the relative contribution of large clusters (10+ linked transmissions/cluster) in transmission dynamics, accounted for 29%, 34%, and 46% of new infections over the 2002-2005, 2006-2009 and 2010-2014 periods. Overall, 40 viral lineages contributed to 1235 transmissions as compared to 1375 solitary "dead-end" transmissions. PHI/EHI (0-0.44% genetic diversity) accounted for 57% and 26% of transmissions in large cluster and solitary transmission groups, respectively. Viruses from seven representative large clusters often harbored X4/R5 dual tropic viruses (n=5/7) as compared to dominant R5 tropism in the unique transmission group (0/6). Overall, 10% of transmitted viruses associated with large clusters harbored drug resistance mutations (G190A, K103N, T215 revertants). Tissue culture studies showed accelerated development of resistance under DTG, (R263K, H51Y or S153Y), elvitegravir (EVG), 3TC (M184I/V), and DTG/3TC dual pressure (R263K +M184V). Resistance mutations for DTG arose within 6-8 weeks in large cluster lineages while solitary transmission variants retained wild-type genotype at 26 weeks.

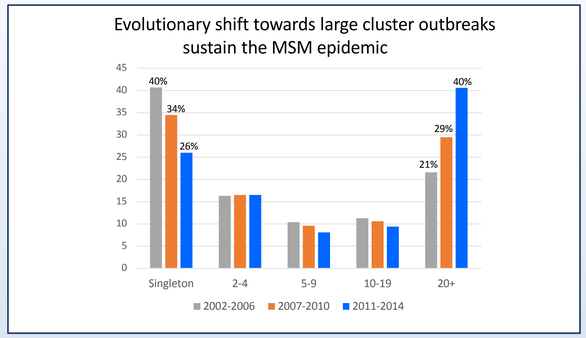
Conclusion

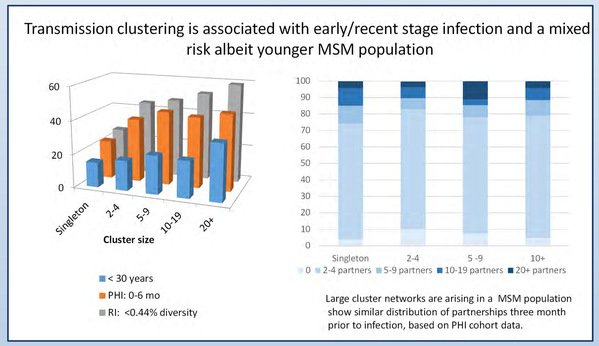
Failure to control early stage transmissions is leading to worrisome trends towards the selection of super-viruses showing prolonged high viremia, dual tropism, rapid tropism shift, and/or facilitated escape from drug pressure.

Phylogenetic surveillance of MSM epidemic

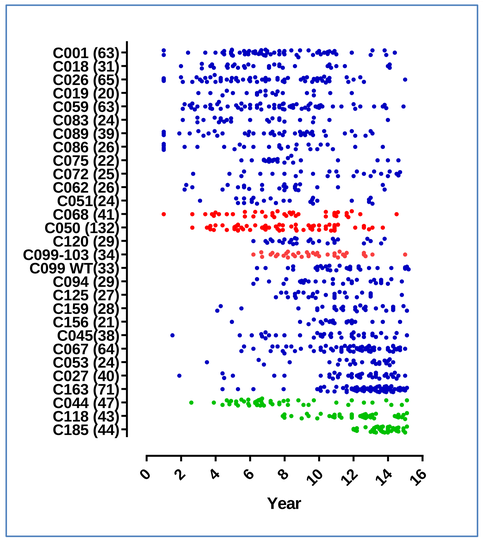


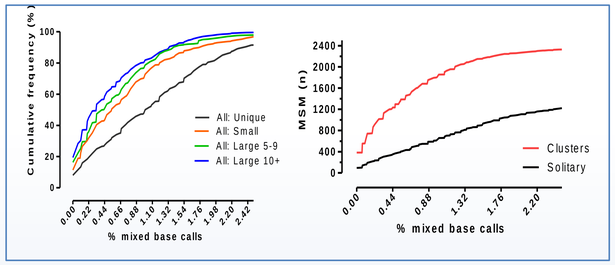


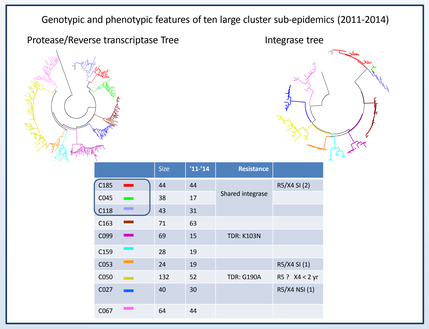


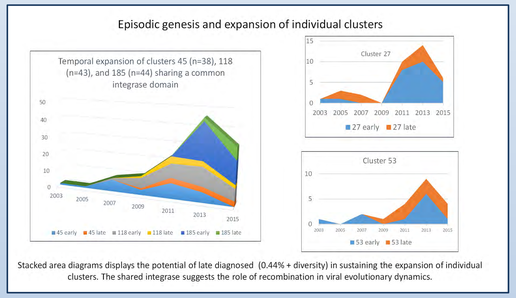


Persistence of large cluster outbreaks related to early stage infection/ untimely diagnosis

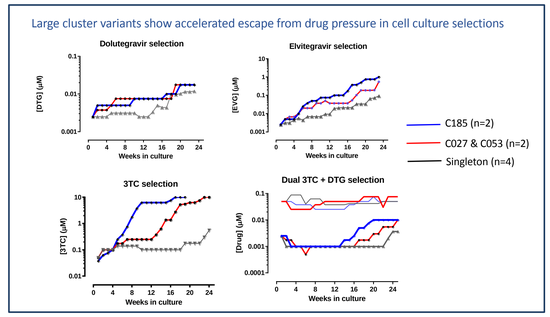








Facilitated escape from integrase inhibitors



Large cluster variants show accelerated selection of resistance

Cluster group (cluster size)	Lab number	Drug	First appearance of drug resistance				Drug resistance Week 36	
			Week		Mutation			
Singletons	4 isolates	DTG			-		WT	
Cluster 185 (44)	14947	DTG	6		R263K		R263K	
Cluster 185 (44)	14637	DTG	8		S153Y		S153Y	
Cluster 27 (40)	14977	DTG	8	12	R263K/R	R263K	R263K	
Cluster 53 (24)	14969	DTG	23		H51Y		H51Y	
Singletons	14514	EVG	23		T66I		T66I	
Singletons	15366	EVG	23		T66I, L74M		T66I, L74M	
Cluster 185	14947	EVG	6	8	T66I	T66I, R263K/R	T66I, R263K, E157Q	
Cluster 185	14637	EVG	12		N155H		N155H, Q95K, S230R	
Cluster 27 (40)	14997	EVG	8		T66IT, E92EG		T66I, E92EG, L74LM, E157Q	
Cluster 53 (24)	14969	EVG	12		S147G		S147G, Q148R	
Singletons	1 isolates	3TC					M184I/V	
Cluster 185 (44)	14947	3TC	6		M184V	M184V	M184V	
Cluster 185 (44)	14637	3TC	8	15	M184I	M184V	M184V	
Cluster 27 (40)	14977	3TC	8		M184I		M184I	
Cluster 53 (24)	14969	3TC	8		M184I		M184I	
Singletons	4 isolates	DTG+3TC					WR	
Cluster 185 (44)	14947	DTG +3TC	8	12	R263K	R263K, M184IM	R263K	M184V

Acknowledgements

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