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Current Trends in HIV Molecular Epidemiology in Canada: Results of the National Surveillance Program

Richard Pilon, James Brooks, Neil Goedhuis, Chris Archibald and Paul Sandstrom

Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada

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Corresponding Author

Richard Pilon
National HIV & Retrovirology Laboratories
Public Health Agency of Canada
0603A1, Tunney's Pasture
Ottawa, Ontario, Canada, K1A 0L2

Phone: (613) 954-1278 **Fax:** (613) 957-1163
E-mail: richard_pilon@phac-aspc.gc.ca

Abstract

Background: Approximately 2,500 new HIV diagnoses are reported annually in Canada. The Canadian HIV Strain & Drug Resistance Surveillance Program monitors HIV drug resistance (DR) in these newly diagnosed, ART-naïve individuals. Here, we present data on the regional distribution of HIV subtypes and DR, as well as results of molecular analyses giving an indication of transmission patterns within and between provinces.

Methods: Diagnostic sera from newly diagnosed HIV positive individuals from provincial partners were analyzed for HIV subtype and genotypic DR. Population-based sequencing was performed on PCR products and DR interpreted using the Stanford HIV Database and IAS guidelines. Phylogenetic analysis was performed by neighbor-joining analysis (K-2-P) as implemented in MEGA 3.1.

Results: Sequence data was available from 537 specimens collected between January and December, 2004 representing approximately 20% of newly diagnosed HIV infections. Within the cohort, 9.7% had at least one primary DR mutation. The prevalence of DR varied from 5.6% to 18.4% among provinces. 1.2% of the samples contained HIV resistant to drugs from 2 or more classes.

The distribution of non-B strains also varied widely among provinces with prevalence as low as 8.7% and as high as 35.6%. The overall rate of non-B infection was 16% with the following breakdown: 8.8%C, 3.1%A, 2.2% A recombinant (AE, AD, AG) and 0.1% each of D, G and H.

Forty-five percent of first-time positive individuals were located in 58 provincial infection clusters consisting of up to 11 individuals. An additional eleven clusters spanned two provinces, and one cluster involved individuals from 3 provinces. Two subtype A clusters were also found within one province.

Conclusions:
1. The prevalence of DR in Canada has remained between 6.5% and 11.5% since 2000. DR prevalence was highest (18.4%) in the province that has historically had the highest DR rates.

2. Overall, non-B strains represented 16% of newly diagnosed HIV infections. However, 36% of new infections in one province were non-B strains. This province concomitantly had the highest rates of DR.

3. The identification of numerous transmission clusters may indicate that individuals who are unaware of their HIV status are the source of new infections.

Tracking changes in the pattern of the Canadian HIV epidemic, through the use of integrated surveillance, can lead to improved patient care and the ability to target prevention strategies.

Introduction

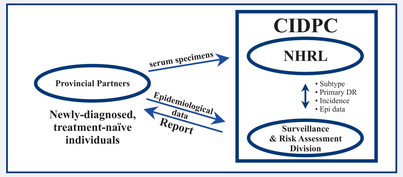
The Canadian HIV Strain and Drug Resistance Surveillance Program (SDR)

SDR was developed as a collaboration between provinces, territories, the National HIV & Retrovirology Laboratories and the Surveillance and Risk Assessment Division to characterize and monitor genetic diversity of the HIV epidemic in Canada, and to identify changes in the epidemic by:

1. Assessing genetic markers of HIV drug resistance.
   - Prevalence of primary drug resistance and changes over time.
   - Contribute to the development of population-level guidelines for initial treatment regimens.
2. Evaluating transmission patterns.
   - Targeted prevention strategies.
3. Determining prevalent subtypes.
   - Inform vaccine development.
   - Enhance the safety of the blood supply, by ensuring HIV tests reliably detect all strains.

HIV testing in Canada is performed at centralized provincial public health laboratories and is a notifiable disease in Canada facilitating development of a national surveillance program.

In this study, we present our analysis showing geographical variations in drug resistance and non-B subtype prevalence for the 2004 calendar year and phylogenetic analysis showing clusters of infections.



Leftover diagnostic specimens along with linked epidemiological data from newly-diagnosed, treatment-naïve individuals are sent to NHRL and SRAD respectively.

Results

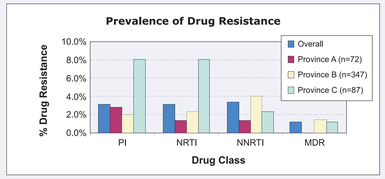
HIV Drug Resistance

For the 2004 calendar year, 568 serum specimens from newly diagnosed HIV infections were submitted to the program.

PCR product was obtained from 95.2% of the specimens of which 99.2% generated useful DNA sequence resulting in 537 interpretations of subtype and drug resistance.

HIV resistance to any drug class, among new HIV diagnoses in 2004 was 9.7%, a value that has remained relatively constant in the past several years.

- the prevalence varies tremendously by region, ranging from 5.6% in province B, to 18.4 % in province C.
- Similar regional variation is seen in the classes of DR and the mutation patterns observed.



Mutations Observed

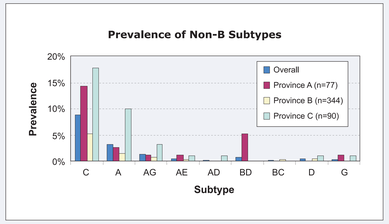
Only the most prevalent are shown

Province	Drug Class						
	PI		NRTI		NNRTI		
	M46I	L90M	M41L	M184V	K103N	V108I	G190A
Prov A	1.4%	0.0%	0.0%	1.4%	1.4%	1.4%	0.0%
Prov B	0.0%	1.2%	1.2%	0.3%	2.6%	0.6%	0.6%
Prov C	6.9%	1.1%	6.9%	1.1%	2.3%	0.0%	1.1%

HIV Subtype Distribution

Until 2001, the Canadian HIV epidemic was between 90-95% subtype B. Since then, there has been a gradual increase in the prevalence of non-B subtypes. For 2004, we observed 84% subtype B.

The overall prevalence of 16% non-B masks the regional distribution of subtypes, which ranged from 8.7% in province B to 35.6% in province C.



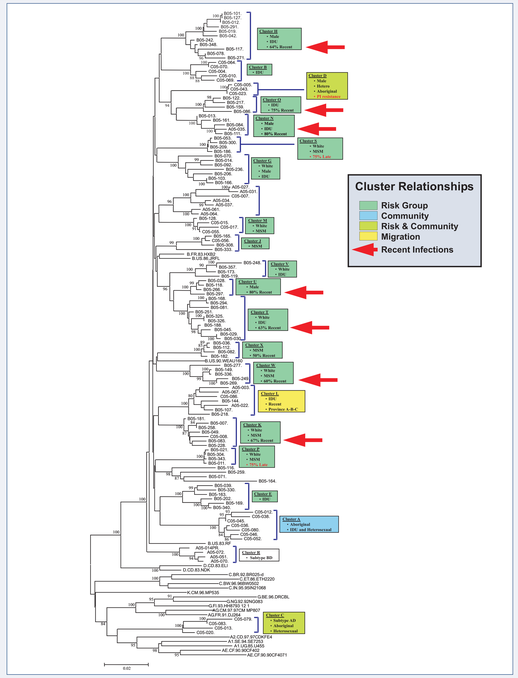
Relationship Between DR and Subtype

- 4/82 Drug Resistant Non-B (4.9%)
- 49/429 Drug Resistant Subtype B (11.32%)

DR appears to be 2-3 times more prevalent in subtype B than in non-B even when even when controlling for the regional variation of subtypes.

(22.4% DR subtype B vs. 9.4% non-B for province C and 9.2% DR subtype B vs. 3.3% non-B for province B)

Infection Clusters



Phylogenetic Analysis

- 45.3% of newly diagnosed infections were related to at least one other new infection in 69 infection clusters consisting of up to 11 individuals. Only clusters of 4 or more sequences are shown.
- 11 Clusters spanned provincial borders with one spanning all 3 participating provinces.
- The mean of within-cluster distances was 1.47% vs. 5.62% between unrelated subtype B sequences.
- The majority of the larger clusters were associated with risk behaviours (Green), although 3 appear to be community associated.
- Based on clustered specimens for which detuned data was available, the majority of these clusters represent incident infections, with the exception of 2 MSM clusters that were predominantly detuned negative.

Methods

Interpretation of Drug Resistance Genotypes

- Genotypes were determined from the Stanford University HIV Drug Resistance Database using HIVdb Program[1] (http://hivdb.stanford.edu/).
- Mutant sites were confirmed from sequence electropherograms.
- Only major mutations, conferring resistance, were included in this analysis.

Phylogenetic Analysis

- Study and reference sequences were aligned using Clustalx[2].
- Tree and distance analyses were performed on gap-deleted alignments using the Neighbour-Joining method of Saitou and Nei with Kimura 2-Parameter model as implemented in MEGA3.0[3].
- Subtypes were determined from the Stanford output and phylogenetic analysis, and recombinants were further analyzed with REGA[4] (http://www.bioafrica.net/subtypetool/html) and RIP[5] (http://www.hiv.lanl.gov)

Conclusions

Among first time diagnosed, ART-naïve individuals in Canada:

- Drug Resistance Prevalence
  - Current estimates for prevalence of drug resistance of 9.7% remain consistent with historical rates[6] which have varied from 6.5% to 11.5%.
  - DR prevalence varies considerably with a 3-fold interprovincial difference in DR rates.
  - DR prevalence remains the highest (13.2%) in the province that has historically had the highest DR rates[7].
- Prevalence of Non-B Subtypes
  - Overall, non-B strains represented 18% of newly diagnosed HIV infections in 2004.
  - However, 36% of new infections in one province were non-B strains. This province concomitantly had the highest rates of DR although his was not associated with non-B subtypes.
  - Drug resistance was more commonly (2-3 times) associated with subtype B than with non-Bs.
- Infection Clusters
  - The finding that almost half of newly diagnosed cases of HIV infection are related to at least one other from the same calendar year may indicate:
    1. Areas of attention for public health intervention where HIV transmission is ongoing.
    2. Areas where public health has already identified a series of HIV transmissions and referred a risk group for testing.
  - The linking of epidemiological information with clusters can help to guide public health policy and activities to those populations/groups most at risk at risk of infection.

Tracking changes in the pattern of the Canadian HIV epidemic through the use of integrated surveillance can lead to improved patient care and the ability to target prevention strategies.

References

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