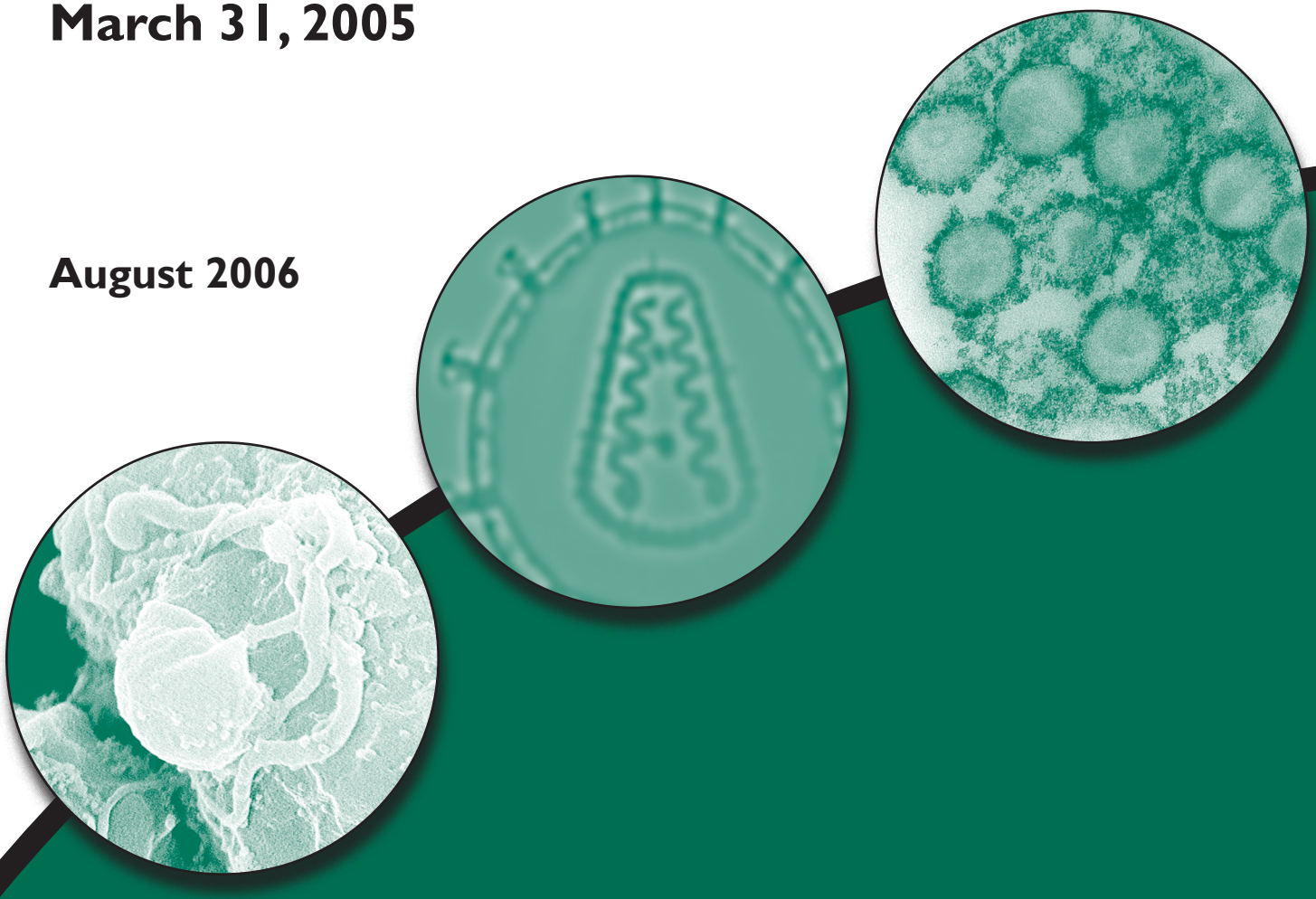
HIV–1 Strain and Primary Drug Resistance in Canada

Surveillance Report to March 31, 2005



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Surveillance and Risk Assessment Division, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada, Tunney's Pasture, AL 0602B, Ottawa, Ontario, Canada K1A 0K9

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Ce rapport est aussi disponible en français. *Les souches VIH-A et la pharmacorésistance primaire au Canada. Rapport de surveillance en date du 31 mars 2005*

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Surveillance and Risk Assessment Division
National HIV and Retrovirology Laboratories
Centre for Infectious Disease Prevention and Control
Public Health Agency of Canada

Centre for Infectious Disease Prevention and Control

Surveillance and Risk Assessment Division Tel: (613) 954-5169

Director	Chris Archibald, MDCM, MHSc, FRCPC
Executive Assistant	Moheenee Soondrum

HIV Drug Resistance and Field Surveillance Section

Manager	Gayatri Jayaraman, PhD, MPH
Research Analyst	Neil Goedhuis, BSc
Senior Field Surveillance Officer	A.M. Tig Shafto, PhD

Field Surveillance Officers

British Columbia and Yukon	Wazi Dlamini-Kapenda, MPH, BSc (Acting)
	Elsie Wong, MBA, BSN
Alberta and Northwest Territories	Sabrina Plitt, PhD
Saskatchewan	Erin Laing, BSc
Manitoba	Souradet Shaw, BA (Acting)
	Michelyn Wood, MSc, BSc
Ontario	Lena Shah, BSc, BA
Nova Scotia and PEI	Tracey MacDonald, BN, MN, CMHN

HIV/AIDS Surveillance Section

Acting Manager	Jennifer Pennock, MSc
Surveillance Officer	Stéphane Racette

National HIV and Retrovirology Laboratories Tel: (613) 957-8060

Director	Paul Sandstrom, PhD
Executive Assistant	Celina Brennan
Biologist	Richard Pilon, BSc

National Laboratory for HIV Genetics

Chief	James Brooks, MD, FRCPC
Technician	Harriet Merks, BSc

National Laboratory for HIV Reference Services

Chief	John Kim, PhD
Technician	Laurie Malloch, BSc

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Surveillance and Risk Assessment Division
National HIV and Retrovirology Laboratories
Public Health Agency of Canada
Tunney's Pasture, PL 0602B
Ottawa, Ontario, K1A 0K9
Tel: (613) 954-5169
Fax: (613) 946-8695

Information to the readers of HIV-1 Strain and Primary Drug Resistance in Canada

On behalf of the Surveillance and Risk Assessment Division and the National HIV and Retrovirology Laboratories, we are pleased to provide you with the *HIV-1 Strain and Primary Drug Resistance in Canada: Surveillance Report to March 31, 2005.* This report is part of an annual series, providing a review of the genetic diversity of HIV in Canada.

The major findings of the surveillance data are outlined in the section entitled *Results at a Glance.* This is followed by a series of tables summarizing the HIV-1 strain and primary drug resistance data. Each table provides specific explanatory details, as appropriate. A further description of HIV-1 strain and primary drug resistance in Canada is available in the *HIV/AIDS Epi Updates* reports available on our web site at http://www.phac-aspc.gc.ca/hast-vsmt/public_e.html#sur. Technical notes, references, and data sources are available in the Appendices.

The first section describes HIV-1 subtypes in Canada as determined by the Canadian HIV Strain and Drug Resistance Surveillance Program and outlines the results from other key studies conducted in Canada, the United States, and Western Europe. The second section describes HIV-1 primary drug resistance in Canada, as determined by the Canadian HIV Strain and Drug Resistance Surveillance Program, and outlines results from other key studies in countries where highly active antiretroviral therapy is widely available. The third section describes data that have been gathered through the Québec program for HIV drug resistance testing.

The Field Surveillance Officers are responsible for coordinating data collection and submission to the HIV Drug Resistance and Field Surveillance Section and the HIV/AIDS Surveillance. The HIV Drug Resistance and Field Surveillance Section is responsible for managing and analyzing data, as well as writing and coordinating the publication of this report. The National Laboratory for HIV Genetics conducts the strain and primary drug resistance genotyping, and phylogenetic analysis. The National Laboratory for HIV Reference Services determines the estimated time of infection, using a combination of two commercially available kits: the bioMérieux Vironostika HIV-1-LS™ and the Abbott 3A11-LS™ assays. This laboratory also serves as a sentinel arm in monitoring the presence of unusual strains of HIV in Canada.

The publication of this report would not be possible without the involvement of the provinces and territories participating in our national HIV strain and drug resistance surveillance program. Key colleagues across Canada provided scientific input and feedback on the program content including helping to develop the infrastructure, information-flow and specimen-transfer processes on which this national surveillance program is based. Their ongoing collaboration and contribution to this surveillance program is gratefully acknowledged in Appendix 7. Thanks also to our colleagues in Québec who shared data from the Québec program for drug resistance testing for inclusion in Section III of this report.

This is the fourth report on HIV strain and primary drug resistance surveillance in Canada. We will be working toward improving this report to reflect changes in the surveillance of HIV strain and primary drug resistance.
We welcome and appreciate your comments and suggestions.

Yours sincerely,

Dr. Gayatri Jayaraman

Dr. James Brooks

Dr. Chris Archibald

Dr. Paul Sandstrom

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SECTION III:

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Results at a Glance

Summary of the Main Findings from the Canadian HIV Strain and Drug Resistance Surveillance Program

- While HIV-1 subtype B continues to predominate, 11.7% of the sampled population (n = 2,759) were infected with non-B subtypes. These non-B subtypes also include various circulating recombinant forms of HIV-1.
- Significantly higher proportions of non-B subtype infections were detected among females (compared with males), among those who were younger at initial diagnosis, among African/Caribbean (compared with Caucasians), and among those reporting heterosexual sex as their primary risk factor (compared with male-to-male sex).
- The data suggest that primary drug resistance among recent infections was higher than that among established infections (9.7% vs. 8.1% respectively).
- There is geographic variation across Canada in the prevalence of non-B HIV-1 subtypes. This variation likely relates to travel and migration from countries where other subtypes predominate.
- The overall prevalence of primary drug resistance to at least one antiretroviral drug has been identified in 8.9% of our sample population of 2,338 newly diagnosed individuals who had never received treatment.
- Multi-drug resistance to $\geq$ 2 classes of antiretroviral drugs has been identified in 1.4% of the sample population.
- Primary drug resistance has been observed in females and males; across different age groups, ethnicities, and exposure categories; in HIV-1 subtypes A, B, and C infections; and among recent and established HIV infections.
- The prevalence of primary drug resistance is similar to the rates observed in other countries, where highly active antiretroviral treatment is widely used.

Public Health Implications

- HIV strain data can be used for research into the development of vaccines and also to assess the usefulness of a potential vaccine in a given setting, because, any vaccine will likely be strain specific.
- HIV isolates from different populations, as well as trends over time in the percentage of non-B HIV and drug-resistant HIV, can be monitored to evaluate diagnostic and screening algorithms, to ensure that all circulating strains are adequately detected.
- Information on the prevalence of primary drug resistance can be used to develop population recommendations for initial therapies (especially for pregnant women and for use in post-exposure prophylaxis).
- The extent to which drug-resistant strains of HIV are being transmitted can serve as an indicator to evaluate to the effectiveness of prevention programs.

SECTION I: HIV-1 Subtypes (1984 - March 31, 2005)

Background:

Since the first reported cases of HIV/AIDS in the mid-1980s, HIV has emerged as one of the most significant infectious agents, with 40 million people infected worldwide. What is key to the pathogenicity of HIV is its genetic heterogeneity, resulting from the error-prone reverse transcriptase, the rapid turnover of HIV-1 *in vivo*, recombination, and the selective immune pressures by the host.

The initial classification of HIV into two main types, HIV-1 and HIV-2, was based on the geographic distribution and the animal source of the human infection: chimpanzee *(Pan troglodytes)* for HIV-1 and sooty mangabey *(Cercocebus atys)* for HIV-2. Expanding access to diverse samples of HIV-1 and the advent of new molecular tools have led to the classification of HIV-1 into three distantly related "groups": M (for main), N (for new, non-M, non-O), and O (for outlier). The vast majority of isolates (> 90%) cluster in the "M" group. Based on partial HIV *gag* and *env* gene sequencing, the circulating genetic forms of this "M" group include nine major "clades" or subtypes (A-D, F-H, J), at least 4 different "sub-clades", and 13 circulating recombinant forms. This classification is not exhaustive; new recombinant HIV strains are arising continually, and this, coupled with the migration of populations, are powerful forces in the spread of HIV worldwide.

Although there has been no systematic surveillance for genetic diversity of HIV subtype in Canada, studies to date on high-risk populations suggest that HIV-1 subtype B is the most common subtype found in the country. Despite the predominance of HIV-1 subtype B, non-B subtypes have also been reported in Canada. With increased international travel and migration, it is inevitable that diverse HIV strains will continue to be introduced into this country. However, little is known about the distribution of HIV subtypes in Canada, how it changes over time, or its effects on particular risk groups in different regions of the country. This information is important to evaluate the utility of potential vaccines in the Canadian setting and to assess any differences in subtype-specific susceptibilities to antiretroviral drugs and in the pathogenicity of the various subtypes. Likewise, conducting the systematic surveillance of HIV genetic diversity would determine whether currently approved assays for HIV in Canada can detect all circulating strains. This includes the ability to control and manage HIV infection through approved viral load test assays and by using other tests that determine the stage and progression of the disease.

Data Tables:

This section highlights the main findings from the Canadian HIV Strain and Drug Resistance Surveillance Program (SDR program) based on specimens from individuals newly diagnosed with HIV infection between 1984 and March 31, 2005. Of note, these results represent individuals who sought testing, who were properly diagnosed, and who reported HIV positive. In addition, results include only those individuals for whom sufficient sera, taken for the purposes of diagnostic testing, was available to send to the Public Health Agency of Canada and of these samples,

the subset for whom RT-PCR amplification and sequencing to identify subtypes were successful (Appendix 4 identifies additional data limitations). A total of 3,723 sera samples, from individuals who were newly diagnosed between 1984 to March 31, 2005 and corresponding non-nominal epidemiological data have been received by the Public Health Agency of Canada from British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Newfoundland, and Nova Scotia for HIV-1 subtype analysis. Discussions are underway to expand the SDR program to the remaining provinces and territories. Viral RNA was successfully amplified from 2,759 (74.1%) of the sera samples. This level of success in amplifying virus from sera specimens will likely improve further by enhancing sample quality and by identifying and using various primer combinations for RT-PCR amplification. Appendix 2 details the laboratory methods used to identify subtypes.

Table 1: Number and percentage distribution of HIV-1 subtypes among newly diagnosed, treatment naïve by year of diagnosis (1984-Mar 31, 2005)

HIV-1 Subtype	Frequency	Percent
B	2437	88.3
C	180	6.5
A	47	1.7
AG	28	1.0
AE[1]	24	0.9
AD	13	0.5
D	12	0.4
BD	4	0.14
G	3	0.11
BC	2	0.07
AB	2	0.07
B/AG	1	0.04
AC	1	0.04
F	1	0.04
H	1	0.04
K	1	0.04
K/AE	1	0.04
K/AG	1	0.04
Total	**2759**	**100**

[1] The circulating recombinant form (CRF) AE has also been referred to as subtype E.

Table 1 illustrates the distribution of HIV-1 subtypes in our sample population. Of note, between July 1998 and December 2000, the C2-V5 region (233 amino acids) of the envelope protein was used to assess HIV subtype. Between January 2001 and June 2004, the sequence analysis of the pol gene (entire protease and the first 253 amino acids of reverse transcriptase) was used for subtype analysis. Since June 2004, an additional 68 amino acids within the reverse transcriptase are also being analysed. While most samples (88.3%) are of HIV-1 subtype B, other subtypes and circulating recombinant strains of HIV-1 have been identified. In decreasing order of prevalence, these include: subtype C (6.5%); A (1.7%); AG (1.0%); AE (0.9); AD (0.5%); D (0.4%); BD (0.14%); G (.11%); AB and BC (0.07% each); and AC, B/AG, F, H, K, K/AE, and K/AG (0.04% each).

While existing studies on high-risk populations also suggest the predominance of HIV-1 subtype B in Canada, subtype A was reported in Canada in 1995 (Montpetit M, AIDS Res Hum Retroviruses 1995, 11(11):1421-22). The vast majority of seroconverters from the POLARIS cohort (comprising men who have sex with men [MSM]) in Ontario are of subtype B (Paul Sandstrom co-investigator, POLARIS cohort, National HIV and Retrovirology Laboratories). The British Columbia Centre for Excellence in HIV/AIDS has identified subtypes A, C, and D in at least 4% of individuals linked to cohort studies and to the B.C. HIV drug treatment program (Alexander C et al. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA, Feb 2000, # 174). All HIV-1 sequences analysed among injecting drug users (n = 17) and MSM (n = 5) residing in Montreal were of subtype B (Bernier L et al. 8th Conference on Canadian HIV/AIDS Research, Vancouver, B.C., May 1999, #104).

Table 2: Number and distribution of HIV-1 subtypes by year of diagnosis

	HIV-1 Subtype								
	B[1]	C[2]	A[3]	AG	AE[4]	AD[5]	D	Others[6]	**Total**
Year of diagnosis	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
≤1996	143 (87.7)	14 (8.6)	5 (3.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)	**163 (100)**
1997	101 (91)	2 (1.8)	7 (6.3)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	**111 (100)**
1998	157 (92.3)	9 (5.3)	2 (1.2)	0 (0)	0 (0)	0 (0)	1 (0.6)	1 (0.6)	**170 (100)**
1999	330 (91.4)	20 (5.5)	4 (1.1)	0 (0)	3 (0.8)	2 (0.6)	2 (0.6)	0 (0)	**361 (100)**
2000	442 (95.0)	12 (2.6)	2 (0.4)	3 (0.7)	1 (0.2)	4 (0.9)	0 (0)	1 (0.2)	**465 (100)**
2001	333 (95.4)	11 (3.2)	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	4 (1.1)	**349 (100)**
2002	135 (84.4)	11(6.9)	0 (0)	3 (1.9)	6 (3.8)	2 (1.2)	2 (1.2)	1 (0.6)	**160 (100)**
2003	186 (75.9)	33 (13.5)	3 (1.2)	9 (3.7)	7 (2.9)	3 (1.2)	1 (0.4)	3 (1.2)	**245 (100)**
2004	517 (83.8)	56 (9.1)	18 (2.9)	10 (1.6)	5 (0.8)	1 (0.2)	5 (0.8)	5 (0.8)	**617 (100)**
2005(Jan-Mar)	30 (60.0)	9 (18.0)	5 (10.0)	2 (4.0)	1 (2.0)	0 (0)	1 (2.0)	2 (4.0)	**50 (100)**
Total	**2374 (88.2)**	**177 (6.5)**	**46 (1.7)**	**28 (1.0)**	**24 (0.9)**	**12 (0.5)**	**12 (0.5)**	**18 (0.7)**	**2691 (100)**

[1] Year of diagnosis was unknown for 63 individuals with HIV-1 subtype B infection.
[2] Year of diagnosis was unknown for three individuals with HIV-1 subtype C infection.
[3] Year of diagnosis was unknown for one individual with HIV-1 subtype A infection.
[4] The circulating recombinant form (CRF) AE has also been referred to as HIV-1 subtype E.
[5] Year of diagnosis was unknown for one individual infected with the CRF AD.
[6] Others refers to the following HIV-1 subtypes and CRFs: AB, AC, BC, BD, B/AG, F, G, H, K, K/AE, K/AG.

Table 2 shows the number and distribution of HIV-1 subtypes by year of diagnosis with HIV infection. Although the samples sizes in certain years are small and the data are not representative of all newly diagnosed cases of HIV in Canada, the results suggest an increase in the prevalence of non-B HIV-1 subtypes from 12.3% prior to 1996 to 16.2% during 2004 ($p<0.05$). The limitations are being addressed in our effort to ensure that the SDR program represents all newly diagnosed cases across Canada.

Table 3: Number and distrubution of HIV-1 subtypes by province

	HIV-1 Subtype								
	B	C	A	AG	AE[1]	AD	D	Other[2]	**Total**
Province	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
Alberta	435 (91.2)	26 (5.4)	2 (0.4)	3 (0.6)	6 (1.3)	0 (0)	0 (0)	5 (1.1)	**477 (100)**
British Columbia	1235 (93.6)	50 (3.8)	16 (1.2)	4 (0.3)	4 (0.3)	0 (0)	5 (0.4)	5 (0.4)	**1319 (100)**
Manitoba	314 (75.8)	58 (14.0)	14 (3.4)	7 (1.7)	4 (1.0)	12 (2.9)	4 (1.0)	1 (0.2)	**414 (100)**
NL	42 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**42 (100)**
Nova Scotia	2 (50.0)	2 (50.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**4 (100)**
Ontario	144 (74.2)	22 (11.3)	5 (2.6)	12 (6.2)	5 (2.6)	0 (0)	0 (0)	6 (3.1)	**194 (100)**
Saskatchewan	265 (85.8)	22 (7.1)	10 (3.2)	2 (0.7)	5 (1.6)	1 (0.3)	3 (1.0)	1 (0.3)	**309 (100)**
Total	**2437 (88.3)**	**180 (6.5)**	**47 (1.7)**	**28 (1.0)**	**24 (0.9)**	**13 (0.5)**	**12 (0.4)**	**18 (0.7)**	**2759 (100)**

[1] The circulating recombinant form (CRF) AE has also been referred to as HIV-1 subtype E.
[2] Others refers to the following HIV-1 subtypes and CRFs: AB, AC, BC, BD, B/AG, F, G, H, K, K/AE, K/AG.

Table 3 presents the number and percentage distribution of HIV-1 subtypes by province of diagnosis. The data indicate geographic variation in the distribution of non-B HIV-1 subtypes. All 42 samples from Newfoundland were identified as subtype B, but 8.8, 6.4, 24.2, 50, 25.8, and 14.2% of analyzed samples from Alberta, British Columbia, Manitoba, Nova Scotia, Ontario and Saskatchewan belonged to non-B HIV-1 subtypes.

Table 4: Number and distribution of HIV-1 subtype by age group

	HIV-1 Subtype								
	B[1]	C[2]	A[3]	AG	AE[4]	AD[5]	D	Others[6]	**Total**
Age Group	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
<15	8 (47.0)	6 (35.3)	2 (11.8)	0 (0)	0 (0)	0 (0)	1 (5.9)	0 (0)	**17 (100)**
15-19	37 (90.2)	2 (4.9)	0 (0)	1 (2.4)	1 (2.4)	0 (0)	0 (0)	0 (0)	**41 (100)**
20-29	479 (84.0)	54 (9.5)	18 (3.1)	5 (0.9)	5 (0.9)	1 (0.2)	3 (0.5)	5 (0.9)	**570 (100)**
30-39	887 (87.3)	78 (7.6)	11 (1.1)	14 (1.4)	13 (1.3)	1 (0.1)	6 (0.6)	6 (0.6)	**1016 (100)**
40-49	669 (92.9)	25 (3.5)	9 (1.2)	3 (0.4)	4 (0. 6)	5 (0.7)	2 (0.3)	3 (0.4)	**720 (100)**
50-59	206 (90.0)	9 (3.9)	4 (1.7)	4 (1.7)	1 (0.4)	3 (1.3)	0 (0)	2 (0.9)	**229 (100)**
60+	79 (89.8)	3 (3.4)	1 (1.1)	1 (1.1)	0 (0)	2 (2.3)	0 (0)	2 (2.3)	**88 (100)**
Total	**2365 (88.2)**	**177 (6.6)**	**45 (1.6)**	**28 (1.0)**	**24 (0.9)**	**12 (0.5)**	**12 (0.5)**	**18 (0.7)**	**2681 (100)**

[1] Age at diagnosis was unknown for 72 individuals with HIV-1 subtype B infection.
[2] Age at diagnosis was unknown for three individuals with HIV-1 subtype C infection.
[3] Age at diagnosis was unknown for two individuals with HIV-1 subtype A infection.
[4] The circulating recombinant form (CRF) AE has also been referred to as HIV-1 subtype E.
[5] Age at diagnosis was unknown for one individual infected with CRF AD.
[6] Others refers to the following HIV-1 subtypes and CRFs: AB, AC, BC, BD, B/AG, F, G, H, K, K/AE, K/AG.

Table 4 shows the number and distribution of HIV-1 subtypes at age of diagnosis. The results identified non-B subtypes in all age groups but the majority were identified in those between 20 to 59 years of age at diagnosis. Of note, in Ontario, only specimens from individuals who were over age 18 years at the time of first diagnosis with HIV infection are eligible for inclusion under the SDR program.

Table 5: Number and distribution of HIV-1 subtypes by gender

	HIV-1 Subtype								
	B[1]	C[2]	A[3]	AG	AE[4]	AD[5]	D	Others[6]	**Total**
Gender	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
Male	1860 (92.0)	90 (4.5)	21 (1.0)	13 (0.6)	14 (0.7)	7 (0.4)	4 (0.2)	12 (0.6)	**2021 (100)**
Female	549 (77.8)	88 (12.5)	25 (3.5)	15 (2.1)	10 (1.4)	5 (0.7)	8 (1.1)	6 (0.9)	**706 (100)**
Total	**2409 (88.3)**	**178 (6.5)**	**46 (1.7)**	**28 (1.0)**	**24 (0.9)**	**12 (0.4)**	**12 (0.4)**	**18 (0.7)**	**2727 (100)**

[1] Gender was unknown for 28 individuals with HIV-1 subtype B infection.
[2] Gender was unknown for two individuals with HIV-1 subtype C infection.
[3] Gender was unknown for one individual with HIV-1 subtype A infection.
[4] The circulating recombinant form (CRF) AE has also been referred to as HIV-1 subtype E.
[5] Gender was unknown for one individual infected with CRF AD.
[6] Others refers to the following HIV-1 subtypes and CRFs: AB, AC, BC, BD, B/AG, F, G, H, K, K/AE, K/AG.

Table 5 identifies the number and percentage distribution of HIV-1 subtypes by gender. The results indicated that the prevalence of non-B subtypes is higher among females than among males (22.2% vs. 8.0%, respectively, $p<0.05$). A greater percentage of females have heterosexual exposure as their primary exposure category, and this exposure category is associated with a higher proportion of non-B HIV-1 subtypes

Table 6: Number and distribution of HIV-1 subtypes by exposure category

	HIV-1 Subtype								
	B[1]	C[3]	A[2]	AG[7]	AE[6]	AD[5]	D[4]	Other[8]	**Total**
Exposure Category	n	n	n	n	n	n	n	n	**n**
MSM[9]	785 (97.7)	7 (0.9)	3 (0.4)	0(0)	3 (0.4)	0(0)	0(0)	5 (0.6)	**803 (100)**
MSM/IDU[10]	84 (92.3)	4 (4.4)	1 (1.1)	0 (0)	2 (2.2)	0 (0)	0 (0)	0 (0)	**91 (100)**
IDU	725 (96.8)	13 (1.7)	4 (0.5)	0 (0)	2 (0.3)	1 (0.1)	1 (0.1)	3 (0.4)	**749 (100)**
Blood/blood products									
Recipient of clotting factors	5 (71.4)	2 (28.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**7 (100)**
Recipient of blood	7 (63.6)	2 (18.2)	1 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (9.1)	**11 (100)**
Recipient of blood or blood products	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**
Heterosexual Contact/Endemic									
Origin in an endemic country	25 (17.2)	78 (53.8)	8 (5.5)	14 (9.7)	7 (4.8)	1 (0.7)	7 (4.8)	5 (3.5)	**145 (100)**
Sexual contact with a person at risk	381 (85.0)	33 (7.4)	14 (3.1)	4 (0.9)	8 (1.8)	4 (0.9)	2 (0.4)	2 (0.4)	**448 (100)**
NIR-Het[11]	148 (79.1)	21 (11.2)	7 (3.7)	4 (2.1)	1 (0.5)	5 (2.7)	0 (0)	1 (0.5)	**187 (100)**
Occupational	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**
Perinatal	2 (40.0)	2 (40.0)	1 (20.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**5 (100)**
Other	5 (71.4)	0 (0)	1 (14.3)	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	**7 (100)**
NIR[12]	2 (66.7)	0 (0)	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	**3 (100)**
Total	**2171 (88.3)**	**162 (6.6)**	**40 (1.6)**	**22 (0.9)**	**24 (1.0)**	**11 (0.4)**	**11 (0.4)**	**17 (0.7)**	**2458 (100)**

[1] Risk exposure was not identified in 266 individuals infected with HIV-1 subtype B infection.
[2] Risk exposure was not identified in 18 individuals infected with HIV-1 subtype C infection.
[3] Risk exposure was not identified in seven individuals infected with HIV-1 subtype A infection.
[4] The circulating recombinant form (CRF) AE has also been referred to as HIV-1 subtype E.
[5] Risk exposure was not identified in two individuals infected with the CRF AD infection.
[6] Risk exposure was not identified in one individual infected with HIV-1 subtype D infection.
[7] Risk exposure was not identified in six individuals infected with CRF AG.
[8] Others refers to the following HIV-1 subtypes and CRFs: AB, AC, BC, BD, B/AG, F, G, H, K, K/AE, and K/AG. Risk exposure was not identified for one individual in this group.
[9] MSM refers to men who have sex with men.
[10] IDU refers to injecting drug use.
[11] NIR-HET refers to non-identified risk related to heterosexual exposure.
[12] NIR - refers to non-identified risk exposures, i.e., when no risk exposures were identified.

Table 6 illustrates the number and percentage distribution of HIV-1 subtypes by exposure category. The results suggest that a higher proportion of individuals infected through heterosexual contact (particularly with individuals from other countries where non-B strains of HIV-1 prevail) have non-B HIV-1 subtypes, compared with individuals who are infected through male-to-male sex or through injecting drug use.

Table 7: Number and distribution of HIV-1 subtypes by ethnicity

	HIV-1 Subtype								
	B[1]	C[2]	A[3]	AG[4]	AE[5]	AD[6]	D	Other[7]	**Total**
Ethnicity	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
Caucasian	1410 (96.1)	26 (1.8)	11 (0.8)	4 (0.3)	8 (0.5)	2 (0.1)	0 (0)	6 (0.4)	**1467 (100)**
African/ Caribbean	59 (25.5)	108 (46.8)	19 (8.2)	19 (8.2)	7 (3.0)	1 (0.4)	11 (4.8)	7 (3.0)	**231 (100)**
Asian/Arabic	68 (88.3)	3 (3.9)	2 (2.6)	0 (0)	2 (2.6)	1 (1.3)	0 (0)	1 (1.3)	**77 (100)**
Aboriginal									
First Nations	355 (96.2)	8 (2.2)	3 (0.8)	0 (0)	1 (0.3)	1 (0.3)	0 (0)	1 (0.3)	**369 (100)**
Inuit	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**3 (100)**
Métis	58 (90.6)	3 (4.7)	1 (1.6)	0 (0)	2 (3.1)	0 (0)	0 (0)	0 (0)	**64 (100)**
Unspecified	134 (88.2)	6 (3.9)	6 (3.9)	0 (0)	0 (0)	5 (3.3)	1 (0.7)	0 (0)	**152 (100)**
South Asian	26 (66.7)	11 (28.2)	0 (0)	0 (0)	1 (2.5)	0 (0)	0 (0)	1 (2.6)	**39 (100)**
Latin American	50 (94.3)	0 (0)	0 (0)	0 (0)	1 (1.9)	0 (0)	0 (0)	2 (3.8)	**53 (100)**
Other/mixed	14 (82.4)	3 (17.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**17 (100)**
Total	**2177 (88.1)**	**168 (6.8)**	**42 (1.7)**	**23 (0.9)**	**22 (0.9)**	**10 (0.4)**	**12 (0.5)**	**18 (0.7)**	**2472 (100)**

[1] Ethnicity was unknown for 260 individuals with HIV-1 subtype B infection.
[2] Ethnicity was unknown for 12 individuals with HIV-1 subtype C infection.
[3] Ethnicity was unknown for five individuals with HIV-1 subtype A infection.
[4] Ethnicity was unknown for five individuals with the CRF AG.
[5] The CRF AE has also been referred to as HIV-1 subtype E. Ethnicity was unknown for two individuals infected with the CRF AE.
[6] Ethnicity was unknown for three individuals infected with the circulating recombinant form (CRF) AD.
[7] Other refers to the following HIV-1 subtypes and CRFs: AB, AC, BC, BD, B/AG, F, G, H, K, K/AE, and K/AG.

Table 7 highlights the number and percentage distribution of HIV-1 subtypes by ethnicity. The results suggest that a higher proportion of African/Caribbean (74.5%), South Asian (33.3%) and Asian/Arabic (11.7%) are infected with non-B HIV-1 subtypes when compared with the Caucasian population (3.9%). These results are likely due to travel and migration from countries where non-B strains of HIV-1 prevail.

Table 8: Number and distribution of HIV-1 subtypes by recently acquired vs. established HIV-1 infections

HIV-1 Subtype

	B[1]	C[2]	A[3]	AG[4]	AE[5]	AD[6]	D[7]	Others[8]	**Total**
Time of infection[9]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
Recent infection	474 (91.6)	23 (4.4)	2 (0.4)	6 (1.2)	6 (1.2)	1 (0.2)	0 (0)	5 (1.0)	**517 (100)**
Established infection	1271 (87.3)	108 (7.4)	19 (1.3)	17 (1.2)	13 (0.9)	9 (0.6)	7 (0.5)	11 (0.8)	**1455 (100)**
Total	**1745 (88.4)**	**131 (6.6)**	**21 (1.1)**	**23 (1.2)**	**19 (1.0)**	**10 (0.5)**	**7 (0.4)**	**16 (0.8)**	**1972 (100)**

[1] Time of infection could not be determined for 692 individuals with HIV-1 subtype B infection.
[2] Time of infection could not be determined for 49 individuals with HIV-1 subtype C infection.
[3] Time of infection could not be determined for 26 individuals with HIV-1 subtype A infection.
[4] Time of infection could not be determined for five individuals infected with CRF AG.
[5] The CRF AE has also been referred to as HIV-1 subtype E. Time of infection could not be determined for five individuals infected with the CRF AE.
[6] Time of infection could not be determined for three individuals infected with the circulating recombinant form (CRF) AD.
[7] Time of infection could not be determined for five individuals with HIV-1 subtype D infection.
[8] Others refers to the following HIV-1 subtypes and CRFs: AB, AC, BC, BD, B/AG, F, G, H, K, K/AE, K/AG. Time of infection could not be determined for three individuals in this group.
[9] Due to kit availability, a combination of two assays (bioMérieux Vironostika™ and Abbott™) were used to determine recent infections. These assays were only used on specimens diagnosed since 2000.

Table 8 identifies the number and percentage distribution of HIV-1 subtypes among recently acquired (within about 170 days of diagnostic specimen collection) versus established infections. Two commercially available kits were used to assess the time of infection: the bioMérieux Vironostika HIV-1-LS™ and the Abbott 3A11-LS™ assays. The availability of test kits aimed at determining incident infections affected the extent to which these data could be generated. Hence, the sample size does not reflect all newly diagnosed cases of HIV-1 infection of samples for which HIV-1 subtyping had been completed. For this reason, significant associations between time of infection and HIV-1 subtype could not be determined. However, 8.4% of recent infections and 12.7% of established infections were non-B HIV-1 subtype infections. Of note, serological assays, developed to detect recently acquired infections, have been based on subtype B-derived antigens and have been shown to occasionally misdiagnose incident non-B infections as established infections. To accurately detect recent acquired infections among other non-B subtypes of HIV-1, further investigation is required to determine the sensitivity of the commercially available assays.

Table 9: Number and distribution of HIV-1 subtypes by primary drug resistance category

	HIV-1 Subtype								
	B[1]	C[2]	A[3]	AG	AE[4]	AD	D[5]	Other[6]	**Total**
Drug resistance mutations[7]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
Wild type/minor mutations[8]	1862 (87.5)	154 (7.2)	29 (1.4)	26 (1.2)	22 (1.0)	9 (0.4)	10 (0.5)	15 (0.7)	**2127 (100)**
NRTI[9]	81 (91.0)	2 (2.3)	3 (3.4)	1 (1.1)	0	0	1 (1.1)	1 (1.1)	**89 (100)**
NNRTI[10]	36 (94.7)	0	0	0	0	2 (5.3)	0	0	**38 (100)**
PI[11]	42 (87.5)	2 (4.2)	1 (2.1)	1 (2.1)	0	2 (4.2)	0	0	**48 (100)**
MDR[12]	32 (97.0)	1 (3.0)	0	0	0	0	0	0	**33 (100)**
Total	**2053 (87.9)**	**159 (6.8)**	**33 (1.4)**	**28 (1.2)**	**22 (0.9)**	**13 (0.6)**	**11 (0.5)**	**16 (0.7)**	**2335 (100)**

[1] Primary drug resistance testing results were not available for 384 individuals infected with HIV-1 subtype B infection.
[2] Primary drug resistance testing results were not available for 21 individuals infected with HIV-1 subtype C infection.
[3] Primary drug resistance testing results were not available for 14 individuals infected with HIV-1 subtype A infection.
[4] The circulating recombinant form (CRF) AE has also been referred to as HIV-1 subtype E. Primary drug resistance testing results were not available for two individuals infected with the (CRF) AE.
[5] Primary drug resistance testing results were not available for one individual infected with HIV-1 subtype D infection.
[6] Others includes the following HIV-1 subtypes and CRFs: AB, AC, BC, BD, B/AG, F, G, H, K, K/AE, K/AG. Primary drug resistance testing results were not available for two individuals infected with CRF AB.
[7] Drug resistance testing was initiated in 2001 and has been conducted on specimens largely derived from individuals diagnosed since 1999.
[8] Wild type indicates no major mutations associated with drug resistance were identified. Minor mutations refers to genetic variables not associated with drug resistance.
[9] NRTI refers to nucleoside reverse transcriptase inhibitor.
[10] NNRTI refers to non-nucleoside reverse transcriptase inhibitor.
[11] PI refers to protease inhibitor.
[12] MDR refers to multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to any two of the three classes of antiretroviral drugs (NRTIs, NNRTIs, or protease inhibitors).

Table 9 provides the number and percentage distribution of primary drug resistance among HIV-1 subtypes. Since drug resistance genotyping began in 1999, almost one year after subtype testing was initiated, not all subtyped samples have been tested for drug resistance. This implies that samples received prior to the initiation of drug resistance testing have not yet been tested for drug resistance. The results, however, indicate that multidrug resistance was identified in an individual infected with HIV-1 subtype C. Single class resistance against NRTIs, NNRTIs or PIs has also been identified among HIV-1 subtype C, as well as HIV-1 subtypes A, and D, and the recombinant HIV-1 subtypes AD, AG, and BC.

SECTION II: HIV-1 Primary Drug Resistance (1996 - March 31, 2005)

Background:

Drug resistance is often cited as a contributing factor to treatment failure. Drug resistance that is associated with individuals who are already on treatment and that is described in the context of treatment failure is commonly referred to as "secondary" drug resistance. A phenomenon that has received considerable attention recently is the transmission of drug-resistant HIV-1. This type of drug resistance, also called "primary" drug resistance, has been reported among individuals who have had no previous treatment for HIV infection and so presumably, these individuals have been infected with drug-resistant HIV. A glossary of terms used in this report is presented in Appendix 5.

Primary drug resistance is becoming more widespread in most countries where antiretroviral therapy is used. Persons infected with drug-resistant variants of HIV may be at an increased risk of drug failure, despite never having been treated. However, the prevalence of primary drug resistance and the variation of this prevalence over time, the geographic area, and the population risk group are not well understood.

Data Tables:

This section highlights the main findings related to the number and distribution of primary drug resistance from specimens submitted through the Canadian HIV Strain and Drug Resistance Surveillance Program (SDR program), based on cases newly diagnosed between 1996 and March 31, 2005. Note that these results represent individuals who sought testing, who were properly diagnosed, and who reported HIV positive. Further, the results include only those individuals for whom sufficient sera, taken for the purposes of diagnostic testing, was available to send to the Public Health Agency of Canada for genotyping, and of these samples, the subset for whom reverse transcriptase PCR amplification and sequencing to identify mutations associated with drug resistance were successful. (See Appendix 4 for additional data limitations.)

As of March 31, 2005, 2,946 sera samples from individuals who were newly diagnosed since 1996 and March 31, 2005 and their corresponding non-nominal epidemiologic data have been received from British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, and Nova Scotia for drug resistance. Discussions are also underway to expand the program to the remaining provinces and territories. Although the goal of the SDR program is to collect sera samples from all newly diagnosed cases, the data presented in this report are a result of convenience sampling methods and may not be representative. Viral RNA had been successfully amplified from 2,338 (79.4%) of the sera samples. This level of success in amplifying virus from sera specimens will likely improve by enhancing sample quality and by identifying and using various primer combinations for RT-PCR amplification. Appendix 2 outlines the laboratory methods used for drug resistance genotyping.

For this report, major mutations identified in the protease gene and mutations identified in the reverse transcriptase genes of HIV were defined by a consensus of listings reported by the International AIDS Society - USA Drug Resistance Mutations Group (Topics in Medicine, October/November 2005; 13(4): 125-131). Appendix 6 provides a complete list of mutations associated with clinical resistance.

Table 10: Number and distribution of primary drug resistance among newly diagnosed, treatment naïve individuals (1996-March 31, 2005)

Primary Drug Resistance	Frequency	Percent
Wild type[1]	2129	91.1
NRTI[2]	90	3.8
NNRTI[3]	38	1.6
PI[4]	48	2.1
NNRTI/NRTI	18	0.8
PI/NNRTI	4	0.2
PI/NRTI	8	0.3
PI/NNRTI/NRTI	3	0.1
Total	**2338**	**100.0**

[1] Wild type includes polymorphisms and minor mutations in the protease gene.
[2] NRTI refers to nucleoside reverse transcriptase inhibitors.
[3] NNRTI refers to non-nucleoside reverse transcriptase inhibitors.
[4] PI refers to protease inhibitors.

Table 10 displays the number and percentage distribution of primary drug resistance among the sample of individuals who were newly diagnosed between 1996 and March 31, 2005, from jurisdictions participating in the SDR program. Mutations associated with drug resistance were present in 8.9% of the sample population of 2,338 newly diagnosed, treatment-naïve individuals. Note that since these individuals have not previously been on treatment, they likely have been infected with a drug-resistant strain of HIV-1. Mutations associated with NRTIs and NNRTIs, and major mutations associated with PIs were identified among 90 (3.8%), 38 (1.6%), and 48 (2.1%) of individuals in the sample population respectively. Of the sample, 33 (1.4%) were infected with multidrug resistant HIV-1, harbouring major mutations to ≥ 2 classes of antiretroviral drugs.

Table 11: Mutations in reverse transcriptase and major mutations in protease

Anti-retroviral drug	Number of individuals *	Major Mutation(s)[1]
NRTI[2] total	90	
	67	M41L[3]
	2	A62V
	2	K65R
	7	D67N
	8	T69D
	1	V75I
	2	F77L
	1	Y115F
	1	F116Y
	15	V118I
	2	Q151M
	16	M184V
	1	M184I
	26	L210W
	11	T215Y
	54	T215C/D/E/S/I/L[4]
	5	K219Q
NNRTI[5] total	38	
	1	L100I
	32	K103N
	11	V108I
	4	Y181C
	1	Y181I
	2	Y188L
	2	G190S
	11	G190A
	2	P225H
	1	M230L
	1	P236L
PI[6] total	48	
	4	D30N
	19	M46I
	12	M46L
	1	G48V
	2	I50V
	1	V82A
	2	V82F
	1	I84V
	22	L90M

* Does not include individuals with resistance-conferring mutations to >1 drug class (n=33). However, certain individuals have >1 resistance-conferring mutation in any given drug class.

[1] Major mutations were identified by sequencing the entire protease enzyme and the first 253 amino acids of reverse transcriptase.

[2] NRTI refers to nucleoside reverse transcriptase inhibitor.

[3] M41L refers to the substitution of amino acid methionine (M) by leucine (L) at position 41 of the reverse transcriptase enzyme. Other mutation nomenclature refers to substitutions as indicated; amino acid abbreviations transcriptase enzyme. Other mutation nomenclature refer to substitutions as indicated; amino acid abbreviations are as follows: K, lysine; R, arginine; T, threonine, D, aspartic acid; N, asparagine; E, glutamic acid; H, histidine; Y, tyrosine; V, valine; I, isoleucine; A, alanine; S, serine; C, cysteine.

[4] These 'transition' mutations have been shown to confer increased risk of virologic failure to certain NRTIs.

[5] NNRTI refers to non-nucleoside reverse transcriptase inhibitor.

[6] PI refers to protease inhibitor.

Table 11 shows the mutations in the reverse transcriptase gene and major mutations in the protease genes of HIV-1 that are associated with resistance to NRTIs, NNRTIs, and PIs. Of the 90 individuals harbouring HIV-1 with mutations associated with resistance to NRTIs, the majority (67, 74.4%) carried virus with an M41L mutation in reverse transcriptase associated with reduced susceptibility to zidovudine and stavudine. M41L refers to the replacement of the amino acid methionine (M) with leucine (L) at position 41 of the reverse transcriptase enzyme. A total of 38 individuals harboured virus resistant to NNRTIs. Of these individuals, the majority (32, 84.2%) carried virus with a K103N mutation associated with reduced susceptibility to delavirdine, efavirenz, and nelfinavir. K103N refers to the replacement of the amino acid lysine (K) with asparagines (N) in position 103 of the reverse transcriptase enzyme. Of 48 individuals harbouring major mutations associated with resistance to PIs, the majority (22, 45.8%) carried virus with an L90M mutation associated with resistance to nelfinavir and saquinivir. L90M refers to the replacement of leucine (L) with methionine (M) at position 90 of the protease enzyme.

Appendix 6 contains a list of mutations associated with drug resistance that were used in the generation of this report.

Table 12: Number and distribution of primary drug resistance in sample population by year of diagnosis

	Primary drug resistance					
	Wild type[1]	NRTI[2]	NNRTI[3]	PI[4]	MDR[5]	**Total**
Year of diagnosis	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
1996	25 (71.4)	3 (8.6)	0 (0)	2 (5.7)	5 (14.3)	**35 (100)**
1997	38 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**38 (100)**
1998	84 (95.5)	3 (3.4)	0 (0)	1 (1.1)	0 (0)	**88 (100)**
1999	280 (91.2)	18 (5.9)	1 (0.3)	5 (1.6)	3 (1.0)	**307 (100)**
2000	411 (93.4)	17 (3.9)	2 (0.5)	5 (1.1)	5 (1.1)	**440 (100)**
2001	315 (90.3)	16 (4.6)	8 (2.3)	6 (1.7)	4 (1.1)	**349 (100)**
2002	145 (90.6)	2 (1.2)	3 (1.9)	7 (4.4)	3 (1.9)	**160 (100)**
2003	215 (89.2)	8 (3.3)	5 (2.1)	11 (4.6)	2 (0.8)	**241 (100)**
2004	556 (91.0)	20 (3.3)	17 (2.8)	10 (1.6)	8 (1.3)	**611 (100)**
2005 (Jan - Mar 31)	41 (83.7)	3 (6.1)	1 (2.0)	1 (2.0)	3 (6.1)	**49 (100)**
Total	**2110 (91.0)**	**90 (3.9)**	**37 (1.6)**	**48 (2.1)**	**33 (1.4)**	**2318 (100)**

[1] Wild type includes polymorphisms and minor mutations in the protease gene. Year of diagnosis was unknown for 19 individuals infected with wild type virus or HIV-1 with minor mutations.
[2] NRTI refers to nucleoside reverse transcriptase inhibitor.
[3] NNRTI refers to non-nucleoside reverse transcriptase inhibitor. Year of diagnosis was unknown for one individual infected with HIV-1 harbouring a major mutation to an NNRTI.
[4] PI refers to protease inhibitors.
[5] MDR refers to multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to any two of the three classes of antiretroviral drugs (NRTIs, NNRTIs, PIs).

Table 12 displays the number and percentage distribution of primary drug resistance in the sample population by year of diagnosis with the HIV-1 infection. However, the following observations should be made cautiously: Among newly diagnosed, treatment naïve persons, resistance to PIs, NRTIs was observed as early as 1996, as was multi-drug resistance. Resistance to NNRTIs was noted as early as 1999. Larger and more representative sample sizes are required to conduct trend analyses and to determine significant associations between time of diagnosis and primary drug resistance. Accordingly, more representative data from additional years are required before any clear temporal trend in drug resistance can occur.

Table 13: Number and distribution of primary drug resistance in sample population by Province

	Primary drug resistance					
	Wild type[1]	NRTI[2]	NNRTI[3]	PI[4]	MDR[5]	**Total**
Province	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
British Columbia	1044 (92.3)	37 (3.3)	20 (1.8)	14 (1.2)	16 (1.4)	**1131 (100)**
Alberta	427 (94.5)	5 (1.1)	4 (0.9)	11 (2.4)	5 (1.1)	**452 (100)**
Saskatchewan	180 (91.8)	6 (3.1)	6 (3.1)	4 (2.0)	0 (0)	**196 (100)**
Manitoba	299 (82.4)	35 (9.6)	5 (1.4)	19 (5.2)	5 (1.4)	**363 (100)**
Ontario	175 (91.1)	7 (3.6)	3 (1.6)	0 (0)	7 (3.7)	**192 (100)**
Nova Scotia	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**4 (100)**
Total	**2129 (91.1)**	**90 (3.8)**	**38 (1.6)**	**48 (2.1)**	**33 (1.4)**	**2338 (100)**

[1] Wild type includes polymorphisms and minor mutations in the protease gene.
[2] NRTI refers to nucleoside reverse transcriptase inhibitor.
[3] NNRTI refers to non-nucleoside reverse transcriptase inhibitor.
[4] PI refers to protease inhibitor.
[5] MDR refers to multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to any two of the three classes of antiretroviral drugs (NRTIs, NNRTIs, PIs).

Table 13 displays the number and percentage distribution of primary drug resistance in the sample population by reporting province at the time of diagnosis with HIV infection. The observations are as follows: Primary drug resistance was identified in British Columbia, Alberta, Saskatchewan, Manitoba, and Ontario; multi-drug resistance was noted among treatment naïve individuals who were newly diagnosed in British Columbia, Alberta, Manitoba, and Ontario.

Table 14: Number and distribution of primary drug resistance in sample population by age group

	Primary drug resistance					
	Wild type[1]	NRTI[2]	NNRTI[3]	PI[4]	MDR[5]	**Total**
Age Group	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
<15	13 (92.9)	1 (7.1)	0 (0)	0 (0)	0 (0)	**14 (100)**
15-19	28 (87.5)	0 (0)	2 (6.3)	1 (3.1)	1 (3.1)	**32 (100)**
20-29	426 (91.4)	21 (4.5)	3 (0.6)	11 (2.4)	5 (1.1)	**466 (100)**
30-39	775 (89.8)	39 (4.5)	16 (1.9)	16 (1.9)	17 (2.0)	**863 (100)**
40-49	595 (92.0)	18 (2.8)	10 (1.5)	15 (2.3)	9 (1.4)	**647 (100)**
50-59	190 (92.2)	6 (2.9)	6 (2.9)	3 (1.5)	1 (0.5)	**206 (100)**
60+	75 (92.6)	4 (4.9)	0 (0)	2 (2.5)	0 (0)	**81 (100)**
Total	**2102 (91.0)**	**89 (3.9)**	**37 (1.6)**	**48 (2.1)**	**33 (1.4)**	**2309 (100)**

[1] Wild type includes polymorphisms and minor mutations in the protease gene. Age at diagnosis was unknown for 27 individuals infected with wild type virus or HIV-1 with minor mutations.

[2] NRTI refers to nucleoside reverse transcriptase inhibitor. Age at diagnosis was unknown for one individual infected with HIV-1 harbouring a major mutation to an NRTI.

[3] NNRTI refers to non-nucleoside reverse transcriptase inhibitor. Age at diagnosis was unknown for one individual infected with HIV-1 harbouring a major mutation to an NNRTI.

[4] PI refers to protease inhibitor.

[5] MDR refers to multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to any two of the three classes of antiretroviral drugs (NRTIs, NNRTIs, PIs).

Table 14 shows the number and distribution of primary drug resistance in the sample population by age at diagnosis with HIV infection. The results demonstrate that primary drug resistance has been identified among individuals within a wide age range. Of note in Ontario, only specimens from individuals who were over 18 years at the time of first diagnosis with HIV infection are eligible for inclusion under the SDR program.

Table 15: Number and distribution of primary drug resistance in the sample population by gender

	Primary drug resistance					
	Wild type[1]	NRTI[2]	NNRTI[3]	PI[4]	MDR[5]	**Total**
Gender	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
Male	1570 (91.4)	72 (4.2)	24 (1.4)	31 (1.8)	21 (1.2)	**1718 (100)**
Female	533 (89.9)	18 (3.0)	13 (2.2)	17 (2.9)	12 (2.0)	**593 (100)**
Total	**2103 (91.0)**	**90 (3.9)**	**37 (1.6)**	**48 (2.1)**	**33 (1.4)**	**2311 (100)**

[1] Wild type includes polymorphisms and minor mutations in the protease gene. Gender was unknown for 26 individuals infected with wild type virus or HIV-1 with minor mutations.
[2] NRTI refers to nucleoside reverse transcriptase inhibitor.
[3] NNRTI refers to non-nucleoside reverse transcriptase inhibitor. Gender was unknown for one individual infected with HIV-1 harbouring a major mutation to an NNRTI.
[4] PI refers to protease inhibitor.
[5] MDR refers to multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to any two of the three classes of antiretroviral drugs (NRTIs, NNRTIs, PIs).

Table 15 presents the number and percentage distribution of primary drug resistance cases in the sample population by gender. The data demonstrate that primary drug resistance has been found among individuals of both genders. While the proportion of cases diagnosed with primary drug resistance is similar among both genders (8.6% among males and 10.1% among females, $p>0.05$), the absolute number of cases with primary drug resistance is greater among males (148 cases) compared with females (60 cases).

Table 16: Number and distribution of primary drug resistance by exposure category

	Primary drug resistance					
	Wild type[1]	NRTI[2]	NNRTI[3]	PI[4]	MDR[5]	**Total**
Exposure Category	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
MSM[6]	629 (90.8)	35 (5.0)	9 (1.3)	6 (0.9)	14 (2.0)	**693 (100)**
MSM/IDU	64 (91.4)	4 (5.7)	2 (2.9)	0 (0)	0 (0)	**70 (100)**
IDU[7]	581 (91.8)	12 (1.9)	15 (2.4)	18 (2.8)	7 (1.1)	**633 (100)**
Blood or Blood Products						
Recipient of clotting factors	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**4 (100)**
Recipient of blood	9 (81.8)	2 (18.2)	0 (0)	0 (0)	0 (0)	**11 (100)**
Recipient of blood or blood products	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**2 (100)**
Heterosexual contact/Endemic						
Origin in an endemic country	130 (92.2)	5 (3.6)	0 (0)	4 (2.8)	2 (1.4)	**141 (100)**
Sexual contact with a person at risk	343 (91.2)	9 (2.4)	4 (1.0)	13 (3.5)	7 (1.9)	**376 (100)**
NIR-Het[8]	134 (86.5)	11 (7.1)	4 (2.6)	5 (3.2)	1 (0.6)	**155 (100)**
Perinatal	5 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**5 (100)**
Other	6 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**6 (100)**
NIR[9]	87 (89.7)	6 (6.2)	2 (2.1)	1 (1.0)	1 (1.0)	**97 (100)**
Total	**1994 (90.9)**	**84 (3.8)**	**36 (1.6)**	**47 (2.1)**	**32 (1.5)**	**2193 (100)**

[1] Wild type includes polymorphisms and minor mutations in the protease gene. Risk exposure was unknown for 135 individuals infected with wild type virus or HIV-1 with minor mutations.
[2] NRTI refers to nucleoside reverse transcriptase inhibitor. Risk exposure was unknown for six individuals infected with HIV-1 harbouring a major mutation to an NRTI.
[3] NNRTI refers to non-nucleoside reverse transcriptase inhibitor. Risk exposure was unknown for two individuals infected with HIV-1 harbouring a major mutation to an NNRTI.
[4] PI refers to protease inhibitor. Risk exposure was unknown for one individual infected with HIV-1 harbouring a major mutation to a PI.
[5] MDR refers to multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to any two of the three classes of antiretroviral drugs (NRTIs, NNRTIs, PIs). Risk exposure was unknown for one individual harbouring multi-drug resistant HIV-1.
[6] MSM refers to men who have sex with men.
[7] IDU refers to injecting drug use.
[8] NIR-HET refers to non-identified risk related to heterosexual exposure.
[9] NIR - refers to non-identified risk exposures, i.e., when no risk exposures were identified.

Table 16 displays the number and distribution of primary drug resistance by exposure category. While a large proportion of individuals had unknown risk factors and there were small sample sizes in certain cells, the data indicate primary drug resistance has been found among the following main exposure categories: male-to-male sex, injecting drug use, and heterosexual contact.

Table 17: Number and distribution of primary drug resistance by ethnicity

	Primary drug resistance					
	Wild type[1]	NRTI[2]	NNRTI[3]	PI[4]	MDR[5]	**Total**
Ethnicity	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
Caucasian	1146 (91.7)	45 (3.6)	21 (1.7)	17 (1.3)	21 (1.7)	**1250 (100)**
African/Caribbean	206 (94.9)	7 (3.2)	0 (0)	3 (1.4)	1 (0.5)	**217 (100)**
Asian/Arabic[6]	60 (92.3)	3 (4.6)	0 (0)	2 (3.1)	0 (0)	**65 (100)**
Aboriginal						
First Nations	276 (90.2)	6 (2.0)	8 (2.6)	11 (3.6)	5 (1.6)	**306 (100)**
Inuit	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**3 (100)**
Métis	52 (91.2)	0 (0)	0 (0)	3 (5.3)	2 (3.5)	**57 (100)**
Unspecified	129 (86.0)	9 (6.0)	2 (1.3)	10 (6.7)	0 (0)	**150 (100)**
South Asian	26 (96.3)	1 (3.7)	0 (0)	0 (0)	0 (0)	**27 (100)**
Latin American	39 (86.7)	3 (6.7)	2 (4.4)	0 (0)	1 (2.2)	**45 (100)**
Other/Mixed	15 (88.2)	2 (11.8)	0 (0)	0 (0)	0 (0)	**17 (100)**
Total	**1952 (91.3)**	**76 (3.6)**	**33 (1.5)**	**46 (2.2)**	**30 (1.4)**	**2137 (100)**

[1] Wild type includes polymorphisms and minor mutations in the protease gene. Ethnicity was unknown for 177 individuals infected with wild type virus or HIV-1 with minor mutations.
[2] NRTI refers to nucleoside reverse transcriptase inhibitor. Ethnicity was unknown for 14 individuals infected with HIV-1 harbouring a major mutation to an NRTI.
[3] NNRTI refers to non-nucleoside reverse transcriptase inhibitor. Ethnicity was unknown for five individuals infected with HIV-1 harbouring a major mutation to an NNRTI.
[4] PI refers to protease inhibitor. Ethnicity was unknown for two individuals infected with HIV-1 harbouring a major mutation to a PI.
[5] MDR refers to multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to any two of the three classes of antiretroviral drugs (NRTIs, NNRTIs, PIs). Ethnicity was unknown for three individuals infected with HIV-1 harbouring multi-drug resistant mutations.
[6] Includes West Asian

Table 17 provides the number and percentage distribution of primary drug resistance in the sample population by ethnicity. The data suggest that while most primary drug resistance cases with known ethnicity were identified among the Caucasian population (56.2%), primary drug resistance has also been noted among Aboriginal, Asian, South Asian, African/Caribbean, and Latin American groups.

Table 18: Number and distribution of primary drug resistance in sample population by HIV-1 subtype

	Primary drug resistance					
	Wild type[1]	NRTI[2]	NNRTI[3]	PI[4]	MDR[5]	**Total**
Subtype	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
B	1862 (90.7)	81 (3.9)	36 (1.8)	42 (2.0)	32 (1.6)	**2053 (100)**
C	154 (96.8)	2 (1.3)	0 (0)	2 (1.3)	1 (0.6)	**159 (100)**
A	29 (87.9)	3 (9.1)	0 (0)	1 (3.0)	0 (0)	**33 (100)**
AG	26 (92.8)	1 (3.6)	0 (0)	1 (3.6)	0 (0)	**28 (100)**
AE	22 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**22 (100)**
AD	9 (69.2)	0 (0)	2 (15.4)	2 (15.4)	0 (0)	**13 (100)**
D	10 (90.9)	1 (9.1)	0 (0)	0 (0)	0 (0)	**11 (100)**
BD	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**4 (100)**
G	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**3 (100)**
BC	1 (50.0)	1 (50.0)	0 (0)	0 (0)	0 (0)	**2 (100)**
B/AG	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**
F	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**
AC	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**
H	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**
K	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**
K/AE	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**
K/AG	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	**1 (100)**
Total	**2127 (91.1)**	**89 (3.8)**	**38 (1.6)**	**48 (2.1)**	**33 (1.4)**	**2335 (100)**

[1] Wild type includes polymorphisms and minor mutations in the protease gene. Subtype was unknown for two individuals infected with wild type virus or HIV-1 with minor mutations.
[2] NRTI refers to nucleoside reverse transcriptase inhibitor. Subtype was unknown for one individual infected with HIV-1 harbouring a major mutation to an NRTI.
[3] NNRTI refers to non-nucleoside reverse transcriptase inhibitor.
[4] PI refers to protease inhibitor.
[5] MDR refers to multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to any two of the three classes of antiretroviral drugs (NRTIs, NNRTIs, PIs).

Table 18 illustrates the number and percentage distribution of primary drug resistance in the sample population by HIV-1 subtype. The data suggest that while most primary drug resistance cases with known subtypes have been identified among HIV-1 subtype B (191 out of 208, 91.8%), primary drug resistance has also been identified among individuals infected with HIV-1 subtypes A, C, D, and the recombinant subtypes AD, AG, and BC.

Table 19: Number and distribution of primary drug resistance in sample population by recent vs. established HIV-1 infection.

	Primary drug resistance					
	Wild type[1]	NRTI[2]	NNRTI[3]	PI[4]	MDR[5]	**Total**
Time of infection[6]	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
Recent infection	458 (90.3)	18 (3.5)	9 (1.8)	11 (2.2)	11 (2.2)	**507 (100)**
Established infection	1302 (91.9)	45 (3.2)	24 (1.7)	30 (2.1)	16 (1.1)	**1417 (100)**
Total	**1760 (91.5)**	**63 (3.3)**	**33 (1.7)**	**41 (2.1)**	**27 (1.4)**	**1924 (100)**

[1] Wild type includes polymorphisms and minor mutations in the protease gene. Time of HIV-1 infection was unknown for 369 individuals infected with wild type virus or HIV-1 with minor mutations.

[2] NRTI refers to nucleoside reverse transcriptase inhibitor. Time of infection was unknown for 27 individuals infected with HIV-1 harbouring a major mutation to an NRTI.

[3] NNRTI refers to non-nucleoside reverse transcriptase inhibitor. Time of infection was unknown for five individuals infected with HIV-1 harbouring a major mutation to an NNRTI.

[4] PI refers to protease inhibitor. Time of infection was unknown for seven individuals with HIV-1 harbouring a major mutation to a PI.

[5] MDR refers to multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to any two of the three classes of antiretroviral drugs (NRTIs, NNRTIs, PIs). Time of infection was unknown for six individuals infected with HIV-1 harbouring multi-drug resistant mutations.

[6] Due to kit availability, a combination of two assays (bioMérieux Vironostika™ and Abbott™) was used to determine recent infections. These assays were only used on specimens diagnosed since 2000.

Table 19 displays the number and percentage distribution of primary drug resistance in the sample population by time of infection. Time of infection was defined as recently acquired (within approximately 170 days before collection of the diagnostic specimen) versus established infections. A combination of two commercially available kits was used to assess the time of infection: The bioMérieux Vironostika HIV-1-LS™ and the Abbott 3A11-LS™ assays. The availability of these test kits aimed at determining incident infections has affected the extent to which these data could be generated. The sample size therefore does not reflect all cases newly diagnosed between 1996 and March 31, 2005. However, the data suggest that primary drug resistance among recent infections was higher that that among established infections (9.7% vs. 8.1% respectively). These data also support results from other studies that suggest that certain mutations may persist over time and may contribute to drug resistance.

Table 20: Summary of key studies on drug resistance among newly diagnosed, treatment naïve individuals in Canada

Province*	Year of diagnosis	Risk exposures**	Sample size	RTIs[§] (%)	PIs[♪] (%)	MDR[#] (%)	**Total (%)**
BC[1]	1996-1998	Mixed	423	1.9	1.9	0.2	**3.5**
QC[2]	1997-1999	IDU (26%), Sexual (69%)	81	20	6	9.9	**-**
QC[3]	1997	Mixed	50	12 (NRTI) 0 (NNRTI)	5	~5	**-**
	1998		42	0 (NRTI) 6 (NNRTI)	0	0	**-**
	1999		17	~18 (NRTI) ~13 (NNRTI)	~18	~12	**-**
	2000		18	~12 (NRTI) ~6 (NNRTI)	~6	~5	**-**
	2001		18	0 (NRTI) 0 (NNRTI)	~6	0	**-**
	2002		18	0 (NRTI) ~6 (NNRTI)	~6	0	**-**
	2003		17	0	0	0	**-**
ON[4]	1997-1999	MSM	23	13	-	-	**-**
BC, AB, SK, MB, ON, NS[5]	1997	Mixed	38	0	0	0	
	1998		84	3.4 (NRTI) 0 (NNRTI)	1.1	0	**4.5**
	1999		280	5.9 (NRTI) 0.3 (NNRTI)	1.6	1.0	**8.8**
	2000		411	3.9 (NRTI) 0.5 (NNRTI)	1.1	1.1	**6.6**
	2001		315	4.6 (NRTI) 2.3 (NNRTI)	1.7	1.1	**9.7**
	2002		145	1.2 (NRTI) 1.9 (NNRTI)	4.4	1.9	**9.3**
	2003		215	3.3 (NRTI) 2.1 (NNRTI)	4.6	0.8	**10.8**
	2004		556	3.3 (NRTI) 2.8 (NNRTI)	1.6	1.3	**9.0**

* BC=British Columbia, QC=Québec, ON=Ontario, AB=Alberta, SK=Saskatchewan, MB=Manitoba, NS=Nova Scotia.

** Reported proportions may not add to 100% since risk exposure category may not be mutually exclusive. IDU=injecting drug use, MSM=men who have sex with men.

§ RTI=reverse transcriptase inhibitor, NRTI=nucleoside reverse transcriptase inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor. Information on NRTI and NNRTI provided where available.

♪ PI=protease inhibitor.

MDR=multi-drug resistance.

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Table 20 summarizes the primary drug resistance results from the SDR program and other cohort and cross-sectional studies in Canada. This table, however, is not meant for inter-study comparisons. It is difficult to make such comparisons and arrive at firm conclusions because of differences in study design. For example, prevalence rates depend on the population being studied (high risk vs. general population); the types of laboratory tests used (genotypic and/or phenotypic testing); and differences in mutations studied and reported. The results suggest that the prevalence of mutations associated with drug resistance in Canada is similar to those described in the United States and in Western Europe (Table 21).

Table 21: Summary of key studies on drug resistance among newly diagnosed, treatment naïve individuals in the United States and in Western Europe

Country	Year of diagnosis	Risk exposures**	Sample size	RTIs§ (%)	PIs‡ (%)	MDR# (%)	**Total (%)**
United States[1]	1989-1998	MSM (80%)	141	3.5 (NRTI) 17 (NNRTI)	10	-	**27.6**
United States[2]	1995-1999	MSM (94%)	80	12.5 (NRTI) 7.5 (NNRTI)	2.4	3.8	**16.3**
United States[3]	1997-2001	Mixed	1082	6.4 (NRTI) 1.7 (NNRTI)	1.9	1.3	**8.3**
United States[4]	1998	Mixed	238	3.4 (NRTI) 0.4 (NNRTI)	0	0	**3.8**
	1999		240	8.3 (NRTI) 2.1 (NNRTI)	1.7	1.7	**10**
	2000		245	6.9 (NRTI) 1.2 (NNRTI)	2	1.2	**9**
United States[5]	2003-2004	Mixed	539	7.1 (NRTI) 9.1 (NNRTI)	3.2	3.2	**15.2**
United States (with samples from Canada)[6]	1995-1998	MSM	377	8.5 (NRTI, n=176) 1.7 (NNRTI, n=176)	0.9 (n=213)	3.8 (n=213)	**8.0 (n=213)**
	1999-2000			5.9 (NRTI, n=82) 7.3 (NNRTI, n=82)	9.1 (n=88)	10.2 (n=88)	**22.7 (n=88)**
United States[7]	1996-2001	Mixed	40	25 (NRTI) 0 (NNRTI)	2.5	2.5	**25**
United States[8]	-	Youth	55	4.0 (NRTI) 15 (NNRTI)	5.5	2	**18**
Germany[9]	1996-1999	Mixed	64	6.3 (NRTI) 3.1 (NNRTI)	1.6	1.6	**12.5**
France[10]	1995-1998	Mixed	48	16.7	2.1	-	**-**
France[11]	1999-2000	Mixed	251	7.6 (NRTI) 4.0 (NNRTI)	5.2	4.8	**10**
France[12]	2001-2002	Mixed	666	2.4 (NRTI) 0.3 (NNRTI)	1.2	7.2	**11.3**
France[13]	1999-2000	Male (82%)	249	8 (NRTI) 4 (NNRTI)	6	5	**10**
France[14]	1996-2004	Male (80%)	518	5.2 (NRTI) 2.5 (NNRTI)	4.4	3.1	**8.5**
	1998-1999		94	7.4 (NRTI) 6.4 (NNRTI)	5.3	1.1	**18.1**
	2000-2001		91	20.9 (NRTI) 13.2 (NNRTI)	7.7	13.2	**27.4**
Spain[15]	1996-1998	Mixed		16.2	6	4.4	**-**
Spain[16]	1997-1999	Mixed (72% MSM)	31	16.1	9.7	0	**25.8**
	2000-2001		21	0	4.8	0	**4.8**
Spain[17]	2004	Mixed	182	2.2 (NRTI) 1.1 (NNRTI)	0.5	-	**~4**

Table 21: Summary of key studies on drug resistance among newly diagnosed, treatment naïve individuals in the United States and in Western Europe

Country	Year of diagnosis	Risk exposures**	Sample size	RTIs[§] (%)	PIs[♪] (%)	MDR[#] (%)	**Total (%)**
Spain[18]	1997	Mixed	9	33.3 (NRTI) 0 (NNRTI)	0	-	**33.3**
	1998		17	29.4 (NRTI) 5.9 (NNRTI)	5.9	-	**29.4**
	1999		5	20 (NRTI) 0 (NNRTI)	0	-	**20**
	2000		7	0 (NRTI) 0 (NNRTI)	14.3	-	**14.3**
	2001		30	3.3 (NRTI) 0 (NNRTI)	0	-	**3.3**
	2002		28	10.7 (NRTI) 3.6 (NNRTI)	3.6	-	**14.3**
	2003		50	8 (NRTI) 4 (NNRTI)	0	-	**10**
	2004		52	3.8 (NRTI) 7.7 (NNRTI)	2	-	**7.7**
	Total		198	9.6 (NRTI) 4.0 (NNRTI)	2	-	**12.1**
Switzerland[19]	1996	Mixed	193	5.6	3	-	**8.6**
	1997			6.9	7.7	-	**14.6**
	1998			6.8	2	-	**8.8**
	1999			3.1	1.9	-	**5**
Switzerland[20]	1999-2001	Mixed	200	6.5 (NRTI) 0.5 (NNRTI)	1	1.5	**10**
Switzerland[21]	1999-2001	Mixed	220	8.6 (NRTI) 0.9 (NNRTI)	2.3	1.4	**10.5**
Netherlands[22]	1994-2002	MSM/IDU	100	10 (NRTI) 2 (NNRTI)	1	0	**13**
United Kingdom[23]	1996-1997	Mixed	310	~7 (NRTI) ~1 (NNRTI)	~1		**~8.5**
	1998		340	~8 (NRTI) ~2 (NNRTI)	~3		**~10**
	1999		358	~10 (NRTI) ~5 (NNRTI)	~2.5		**~11**
	2000		457	~9 (NRTI) ~5 (NNRTI)	~3.5		**~14**
	2001		516	~9 (NRTI) ~5 (NNRTI)	~4		**~13**
	2002		520	~11.5 (NRTI) ~6.5 (NNRTI)	~5		**~16**
	2003		764	~7.5 (NRTI) ~6 (NNRTI)	~3		**~12.5**
	2004		1185	~4 (NRTI) ~4 (NNRTI)	~2.5		**~9**
United Kingdom[24]	2004-2005	Mixed	180	3.3 (NRTI) 2.8 (NNRTI)	1.7	0.6	**7.2**

Table 21: Summary of key studies on drug resistance among newly diagnosed, treatment naïve individuals in the United States and in Western Europe

Country	Year of diagnosis	Risk exposures**	Sample size	RTIs[§] (%)	PIs[♪] (%)	MDR[#] (%)	Total (%)
Italy[25]	1996-2001	Mixed	112	11.6 (NRTI) 3.6 (NNRTI)	2.7	1.8	16.1
Germany[26]	1999-2003	Mixed	49	12.2 (NRTI) 10.2 (NNRTI)	2	-	20.4
Europe/Canada[27]	1987-1995	Mixed	69	5.8 (NRTI) 0 (NNRTI)1	1.4	-	7.2
	1996-1998		145	11.7 (NRTI) 0.1 (NNRTI)	1.4	-	13.1
	1999-2003		224	11.2 (NRTI) 6.2 (NNRTI)	6.2	-	19.6
Europe[28]	1996-2002	Mixed	2208	7.6 (NRTI) 2.9 (NNRTI)	2.5	-	10.4
Europe[29]	2000-2004	Mixed	698	6.1 (NRTI) 4.0 (NNRTI)	1.8	-	10

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Table 21 shows the results from studies on primary drug resistance that were conducted in the United States and countries in Western Europe. This table is not meant for inter-study comparisons since such interpretations are difficult due to differences in study design.

Section III: Primary HIV infections vs. genotyped chronic infections in the province of Québec

Data from the Québec program for HIV drug resistance testing (Programme québeçois de génotypage du VIH pour la résistance aux antiviraux).

The data in this section were obtained through the Québec HIV drug resistance testing program (Programme québeēois de génotypage du VIH pour la résistance aux antiviraux). This program, initiated in September 2001, provides universal access to HIV-1 genotypic drug resistance testing for HIV infected individuals harboring viral loads of >400 copies/ml. Genotypic testing is conducted at one of three Québec test sites (the Hōpital Notre-Dame du Centre Hospitalier de l'Université de Montréal [CHUM], the Jewish General Hospital, and the l'Institut national de santé publique du Québec [INSPQ]).

The protease and reverse transcriptase regions of viral cDNA from plasma samples were sequenced using either the Bayer TRUGENE HIV-1 Genotyping kits or Virco protocols. Genotypic testing is initiated upon receipt of a laboratory test requisition from treating physicians. The clinical indication on test requests are divided into six categories: (1) first treatment failure, (2) subsequent treatment failure (3) pregnancy (4) newborn infants, (5) primary infection (<6 months following seroconversion), (6) chronic infection (>6 months following seroconversions for baseline genotyping prior to treatment initiation) and (7) other. Viral subtype was designated according to the Los Alamos reference database. Drug resistance mutations are reported on Bayer and Virco genotyping reports.

There are some important distinctions between the data presented in this Section and those presented in the previous two Sections of the Canadian HIV Strain and Drug Resistance Surveillance Program (SDR program). HIV-1 subtype and drug resistance data presented in this Section are based on HIV cases who have already accessed care and for whom genotypic testing has been requested by the treating physician between September 2001 and December 2005. Genotypic test requests are based on clinical indication made at the discretion of treating physicians. Furthermore a viral load of at least 400 copies/ml is required to conduct genotypic testing. Therefore, the numbers presented here do not reflect all HIV cases that were newly diagnosed in Québec between September 2001 and December 2005. However, since universal access to testing is provided for those individuals harboring viral loads of >400 copies/ml, the data include the majority of primary/recent infections, as well as chronic patient populations that are potential transmitters (PT).

Primary infections are identified using clinical indication of primary HIV infection which is defined as diagnosis <6 months following seroconversion. It is therefore valid to infer that data presented for PHI is reflective of primary (transmitted) drug resistance. Chronic PT populations may include untreated patients, patients undergoing treatment failures and/or treatment interruption. Therefore, direct comparisons cannot be made between the data presented in this Section and the previous two Sections, which include results from the SDR program.

Data presented in Tables 1, 2, and 3 represent the distribution of HIV-1 subtypes among those individuals for whom HIV genotypic

testing was conducted between September 2001 and December 2005. Table 4 shows the number and distribution of drug resistance among a representative sample of the genotyped primary and chronic PT population. It should be emphasized that non-nominative patient identifiers were used to identify the first genotypic test per patient.

Table 1: Distribution of HIV-1 subtypes in all genotyped persons in Québec (2001-2005)

HIV-1 Subtype	n	% overall	% among non-B samples
B	3147	89.9	
C	154	4.4	43.7
A/AE	74	2.2	21.1
AG	54	1.5	15.3
D	27	0.8	7.7
G	18	0.5	5.1
F	4	0.1	1.1
Other CRFs[1]	21	0.6	6.0
Total	**3499**	**100**	**100**

[1] CRF refers to circulating recombinant forms.

Table 1 demonstrates that while the majority of HIV infections (89.9%) remain subtype B, diverse non-B types and circulating recombinant forms (CRFs) are being introduced into the province.

Table 2: Number and distribution of HIV-1 subtypes by year of first genotypic test

	HIV-1 Subtype								
	B	C	A/AE	AG	D	G	F	Other CRFs[1]	**Total**
Year of Genotyping	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	**n (%)**
Sept-Dec 2001	193 (91.9)	4 (1.8)	5 (2.4)	3 (1.4)	2 (1)	1 (0.5)	1 (0.5)	1 (0.5)	**210 (100)**
2002	897 (92.6)	28 (2.9)	18 (1.9)	13 (1.3)	5 (0.5)	6 (0.6)	0	2(0.2)	**969 (100)**
2003	695 (89.8)	39 (5)	10 (1.4)	15 (1.9)	6 (0.8)	4 (0.5)	**0**	5 (0.6)	**774 (100)**
2004	647 (86.2)	48 (6.4)	22 (2.9)	12 (1.6)	7 (0.9)	4 (0.5)	2 (0.3)	9 (1.2)	**751 (100)**
2005	715 (89.9)	35 (4.4)	19 (2.4)	11 (1.4)	7 (0.9)	3 (0.4)	1 (0.1)	4 (0.5)	**795 (100)**
Total	**3147 (89.9)**	**154 (4.4)**	**74 (2.1)**	**54 (1.5)**	**27 (0.9)**	**18 (0.5)**	**4 (0.1)**	**21 (0.6)**	**3499 (100)**

[1] CRF refers to circulating recombinant forms

Table 2 shows the number and distribution of HIV-1 subtypes by year of first genotypic testing. Genotypic testing may not have necessarily been conducted during the year of first diagnosis with HIV infection. Thus, it would be incorrect to infer that year of genotypic represents the year of first diagnosis with HIV infection. The data suggest that among the sampled population, the prevalence of HIV-1 non-B subtypes increased from 7.4% during 2002 to 10.1% during 2005.

Table 3: Distribution of HIV-1 subtypes by gender

	HIV-1 Subtype								
Gender	B	C	A/AE	AG	D	G	F	Other CRFs	**Total**
Male	84.1	43.8	40.7	42.5	29.6	47.0	25.0	48.1	**79.7**
Female	15.9	56.2	59.2	57.4	70.3	52.9	75.0	51.9	**20.2**

Table 3 identifies the proportion of HIV-1 subtypes by gender. The results indicate that among the samples population, the prevalence of non-B subtypes may be higher among females than among males. Whereas subtype B infections are predominantly of male gender (84%), 58% of genotyped non-B infections are among females.

Table 4: Frequency of drug resistance among primary and chronic patient populations

Drug Resistance Mutations	Primary HIV infections (n=582)	Chronic HIV infections (n=798)
Wild-type	487 (82.4%)	240 (30%)
Any Resistance	104 (17.6%)	558 (69.9%)
NRTI (only)	26 (4.5%)	95 (12%)
NNRTI (only)	43 (7.3%)	28 (3.5%)
PI (only)	17 (2.9%)	15 (2%)
Multidrug resistant	14 (2.4%)	420 (52.6%)

Table 4 shows the number and distribution of drug resistance to NRTIs, NNRTI, and PIs among a representative sample of chronic and primary patient populations. For this analysis, drug resistance mutations are restricted to major and minor resistance mutations identified using the consensus listing of mutations reported by the International AIDS Society – USA Drug Resistance Mutations Group [Johnson VA, Brun-Vézinet F, Clotet B, et al. www.iasusa.org October/November 2005 update.]. Polymorphisms associated with drug resistance, including NNRTI (codons 98 and 179) and PI (codons 10, 20, 36, 63, 71, 73 and 77) mutations were excluded from analysis since these mutations are found at a high frequency in the drug-naïve patient populations.

Among the primary infections (<6 months post infection based on clinical indicators), mutations associated with drug resistance were present in 17.6% of the sample population of 582 individuals. Note that since these individuals have not previously been on treatment, they likely have been infected with a drug resistant strain of HIV-1. Mutations associated with NRTIs and NNRTIs were identified among 26 (4.5%) and 43 (7.3%) of the primary infections, respectively. A combination of major and/or minor mutations associated with resistance to protease inhibitors were among 17 (2.9%) of primary infections and 14 (2.4%) were infected with multidrug resistant HIV-1. Among the chronic infections (which include both treatment naive and treatment experienced patients) mutations associated with drug resistance were present in 69.9% of the sample population of 798 individuals. Mutations associated with NRTIs, NNRTIs, and PIs were present in 95 (12%), 28 (3.5%) and 15 (2%) of the chronic patient sample population, respectively. Of the sample of chronic patients, 420 (52.6%) harboured multidrug resistant HIV-1. The increased prevalence of wild type among primary infections is likely due to one of more of a variety of factors including the composition of the chronic samples which includes patients failing treatment due to the development of drug resistance, the negative impact that drug resistance has on viral load (and therefore rates of transmission) and/or because a high proportion of new infections may be a result of transmission from treatment naive, primary infections i.e., early in the course of infection.

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Bluma G. Brenner and Mark A. Wainberg, McGill AIDS Centre, Jewish General Hospital

Michel Roger, Département de microbiologie, Hôpital Notre Dame du Centre Hospitalier de l'Université de Montréal.

Appendix 1: Overview of the Canadian HIV Strain and Drug Resistance Surveillance Program

As a result of the Krever Commission's recommendations for strengthening Health Canada's Blood Safety Program, the Division of Surveillance and Risk Assessment has been mandated to enhance blood surveillance activities and is developing an integrated surveillance program that will provide support to provinces and territories to develop and maintain their surveillance systems for HIV and AIDS. This development is integrated with, and supported by, an improved federal infrastructure and national monitoring of HIV subtypes and drug resistance. The Canadian HIV Strain and Drug Resistance Surveillance Program (SDR program) is a key component in a national system for the enhanced surveillance of HIV/AIDS, emerging retroviruses, and other sexually transmitted blood-borne pathogens. Initiated in 1998, the SDR program is designed to characterize and monitor the genetic diversity of the HIV epidemic in Canada. It is a collaborative effort between the provinces and territories in Canada and the Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada. In addition, it was designed to serve as an integrated mechanism for the analysis of HIV genetic characteristics as they relate to the epidemiology of HIV, addressing the concerns of affected communities, public health authorities, primary care physicians, and researchers.

The program's primary goals, established during a 1998 consensus workshop in Vancouver, are as follows:

1) To enhance the safety of the blood supply

To ensure the safety of the blood supply, all HIV tests need to reliably detect the different HIV strains that are circulating in the country. The precedent for this goal was the discovery of HIV-2 and highly divergent group O strains of HIV-1, which required modifying some serologic tests by adding new antigens that would ensure detection. The reference services of the National HIV and Retrovirology Laboratories addressed this goal by testing samples with unusual virologic test results, quality assurance, and the monitoring of diagnostic kits.

2) To inform vaccine development

It is important to know the distribution of the HIV strains and clade variations to target vaccine development and testing; the efficacy and effectiveness of vaccines may be strain and subtype specific.

3) To assess genetic markers of HIV drug resistance.

Although antiretroviral therapies have led to a reduction in HIV-related morbidity and mortality in Canada, there is concern that their widespread use, the increased number of treatment failures, and high HIV infection rates may result in increased transmission of HIV drug-resistant virus. The information provided by the SDR program can be used to develop treatment guidelines at the population level for initial therapeutic regimens and for more effective HIV prevention strategies.

4) To determine rates of HIV transmission, pathogenesis, and progression to HIV-related diseases

Although genetic analyses have been used to assess the spread of HIV globally, there is limited information on whether differences in HIV clades and mutations conferring drug resistance affect the rates of transmission, pathogenesis, or HIV-related disease progression. The public health implications of such findings, including prevention and treatment strategies, are of special interest.

As of December 31, 2005, British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Newfoundland, and Nova Scotia are participating in the SDR program. The results presented in this report represent samples for which HIV subtype analysis and primary drug resistance genotyping were completed successfully as of March 31, 2005. Samples and epidemiologic data continue to flow to the Public Health Agency of Canada from participating provinces, and results from these analyses will be presented in future reports. Discussions are underway to expand the collection of samples and epidemiologic data to the remaining provinces and territories.

Appendix 2: Methodology

Epidemiologic data and laboratory specimen collection and transfer

The provincial partners in the Canadian HIV Strain and Drug Resistance Surveillance Program (SDR program) send sera samples taken for diagnostic testing from treatment-naïve individuals with newly diagnosed HIV infection to the Centre for Infectious Disease Prevention and Control (CIDPC), Public Health Agency of Canada. Subtype analysis and primary drug resistance genotyping is conducted at the National Laboratory for HIV Genetics in the National HIV and Retrovirology Laboratories. The National Laboratory for HIV Reference Services in the National HIV and Retrovirology Laboratories conducts testing for the time of infection.

For each submitted laboratory sample, non-nominal epidemiologic information is also sent to the Public Health Agency of Canada. The data include information routinely collected on the national or provincial HIV case reporting forms and, where available, additional information that helps interpret the laboratory results, including treatment history, CD4 count and viral load at diagnosis, and previous HIV testing history. Epidemiologic analyses are conducted at the Surveillance and Risk Assessment Division.

As of December 31, 2005, British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Newfoundland, and Nova Scotia have participated in the SDR program. The results presented in this report represent samples that the Public Health Agency of Canada has received as of March 31, 2005, on which HIV subtype and drug resistance genotyping have been completed successfully.

Meanwhile, samples and epidemiologic data continue to be sent to the Public Health Agency of Canada from participating provinces, and results from these analyses will be presented in future reports. Discussions are underway to expand the collection of samples and epidemiologic data to the remaining provinces and territories.

Genetic algorithm for HIV subtyping and drug resistance testing

Aliquots of archived HIV diagnostic serum specimens are received on dry ice at the National Laboratory for HIV Genetics (NLHG) where they are coded and stored at -80°C. HIV RNA is extracted from the specimens using semi-automated robotic technology. Purified RNA is reverse transcribed and undergoes nested PCR with pol specific primers encompassing the entire protease gene and the first 321 amino acids of reverse transcriptase. The primers are designed to efficiently amplify all Group M HIV subtypes. Amplified nucleic acid is purified and the DNA sequence is determined using dye terminator methodology on an ABI 3130XL genetic analyzer. Viral nucleic acid sequence is determined for both strands with sets of overlapping primers covering the entire protease and most of the RT genes. Between 1998 and December 2000, the C2-V5 region (233 amino acids) of the envelope protein was used to assess HIV subtype.

Additional analysis is carried out if poor quality DNA sequence information is obtained, or is sequence results are available for only one strand. The algorithm for specimen testing allows for repeated extraction of viral nucleic acid, the choice of alternate primers, and the cloning of PCR products for further analysis.

The technology used in the NLHG has the ability to amplify viral nucleic acids and determine the DNA sequence from as few as 100 copies of the source material. By comparison, once amplified, the viral sequences may be present at 1×10^{10} copies or more. The potential to contaminate incoming specimens with one aliquot of the amplified DNA is always present. The laboratory is designed in order to allow workflow in only one direction. The specimens handled in separate rooms from incoming amplified products and the workflow is unidirectional from low to high copy number areas. All of the viral sequences that are generated within the laboratory are compared with one another to ensure that a previous specimen has not contaminated contemporary specimens. The integrity of results from any HIV drug resistance testing laboratory is maintained by participation in an external quality assurance program.

Consensus of mutations associated with drug resistance

Interpretation of results from genetic algorithms requires knowledge of the association between specific mutations and virologic response to antiretroviral drugs. The associations are often complex and not necessarily additive. Consensus drug resistance mutation lists have been published through database banks (e.g. Stanford University, http://hivdb.stanford.edu/hiv and the Los Alamos HIV Sequence Database, http://resdb.lanl.gov/Resist_DB/) and by expert committees on HIV drug resistance (e.g. International AIDS Society-USA Drug Resistance Mutations Group).

A defined set of drug resistance mutations are identified and tracked in this report. Drug resistance mutations are identified using the online analysis tool provided by the Stanford University HIV Database. The HIV drug resistance mutations captured in the SDR program database are those defined by the International AIDS Society[1]. The major protease and all of the nucleoside, nucleotide and non-nucleoside reverse transcriptase resistance mutations are entered into the database for analysis. Appendix 6 provides the list of mutations associated with drug resistance that are used for this report.

Determining time of infection

Recent infections were defined as those that occurred within the past 170 days of serum collection (95% CI=162-183 days) and were identified using one of two enzyme immunoassays: the Abbott 3A11-LS™ or the bioMérieux Vironostika HIV-1-LS™.

[1] International AIDS society-USA Drug Resistance Mutations Group Drug Resistance Mutations in HIV-1, Topics in HIV Medicine 2005; 13(4): 125-131.

Epidemiologic analyses

Laboratory and epidemiologic data are linked using unique identifiers. Significant associations between primary drug resistance or HIV-1 non-B subtypes and epidemiologic characteristics of individuals in the sample population were assessed using the chi-squared test and, where appropriate, Fisher's exact test using SPSS 8.0TM (SPSS Inc. Chicago, IL). The independent variables that were examined included age at diagnosis of HIV infection, gender, exposure category, ethnicity, and year of diagnosis of HIV infection.

Appendix 3: Technical Notes

Data Collection and Reporting

The results in this report represent individuals who sought testing, who were properly diagnosed, and who were reported as HIV positive. Further, they represent those individuals for whom sufficient serum specimen, taken for the purposes of diagnostic testing, was available to send to the National HIV and Retrovirology Laboratories and, of these, the subset for whom subtype analysis and/or primary drug resistance genotyping was completed as of March 31, 2006. The quality of samples received by the National HIV and Retrovirology Laboratories (NHRL) also determines whether subtype and drug resistance results can be generated. The ability to generate accurate subtype and drug resistance results is limited, to some degree by the integrity of the samples received by the NHRL. Multiple repeat attempts at obtaining high quality results using a variety of methods are made for samples that fail the initial analysis. Overall, the success rate for obtaining useful sequences from all specimens in 2005/2006 was 94%.

The epidemiologic data collected through the SDR program contain information included in the National HIV/AIDS reporting form, along with additional data that allow interpretation of the laboratory results. These additional data include the type of laboratory specimen sent, the date of the last negative HIV test, the history of seroconversion (if any), the antiretroviral treatment history (if any), and the viral load count at diagnosis.

There are several limitations to the epidemiologic data (Appendix 4) and one of the key roles of the federal Field Surveillance Officers is to work with the provincial and territorial health partners to facilitate the collection and timely reporting of these data to the Surveillance and Risk Assessment Division.

Exposure Category Hierarchy

HIV cases were assigned to a single exposure category according to an agreed-upon hierarchy of risk factors. The HIV and AIDS in Canada Surveillance Report details this hierarchy and is available by contacting the Surveillance and Risk Assessment Division or by visiting its Web site at www.phac-aspc.gc.ca/publicat/aids-sida/haic-vsac0604/index.html.

Analysis of Drug Resistance

Although both genotypic and phenotypic testing methods are well established, each has its limitations. Both kinds of test provide information only on the virus that predominated at the time of sampling and cannot identify virus that may be present as a result of past drug exposures. This is particularly important as "minority" species of virus may become predominant under selective drug pressures that do not completely inhibit viral replication. Both assays are technically difficult to perform when the concentration of virus is < 1,000 copies/mL and may require highly specialized laboratory facilities and personnel. The ability of both assays to quantify resistance to certain drugs has not yet been determined. Phenotypic testing is expensive. In genotypic testing, repeat analyses may be required because mutations that strongly associate with drug resistance continue to be "discovered", and their complex interactions are only beginning to be understood.

Interpretation of Drug Resistance

The interpretation of genotypic and phenotypic test results for patient care is still uncertain and under active research. The complexity of this task is compounded by the following factors: genotypic and phenotypic test results may not correlate with one another, clinical relevance varies from drug to drug, the concentrations at which a drug is ineffective has not been determined in vivo, and the extent to which pharmaceutical interactions influence resistance is not well known. Appendix 6 lists the mutations that were included as drug resistance mutations in the results presented in this report. We anticipate that this list will change as new information on drug resistance mutations becomes available over time. International expert review panels have been formed. These panels meet periodically to review the latest laboratory and clinical findings for use in developing guidelines to interpret genotypic and phenotypic drug resistance mutations for clinical management. A similar panel of experts is being assembled to identify and standardize mutations, useful for primary drug resistance surveillance.

Appendix 4: Data Limitations

The data presented in this report must be interpreted with caution for the following reasons:

- The data represent cases of newly diagnosed individuals for whom serum specimen and corresponding epidemiologic information are provided to the Public Health Agency of Canada from provincial partners participating in the Canadian HIV Strain and Drug Resistance Surveillance Program (SDR program). The data are based on convenience sampling and therefore do not include all newly diagnosed cases in a given population for any given year. Although we do not anticipate any biases introduced as a result of the convenience sampling, we need to keep in mind that the data are not representative of all newly diagnosed cases in the population.

- The data from the SDR program do not include Québec and may not be representative of cases newly diagnosed in Ontario. Together, however, these two provinces represent about two-thirds of reported HIV infections in Canada. Work is already underway on mechanisms to include representative data from these provinces. For the first time in this report, we present a separate section (Section III) containing data from the Québec program for HIV drug resistance testing which describes the range of subtypes and primary drug resistance in this province.

- This report deals solely with primary drug resistance (i.e. resistance seen among individuals who have never received treatment); for this reason, analysis was conducted on the laboratory specimens collected from treatment-naïve individuals at the time of initial testing for HIV. However, treatment history cannot always be verified. For example, an analysis conducted in 2004 suggested that at least 5% of laboratory specimens from B.C. are likely to have been collected from individuals who have received treatment.

- Missing or unknown epidemiologic data remain problematic, particularly with respect to information on previous HIV testing, date of first positive HIV test, ethnicity, risk behaviour, CD4 and viral load at diagnosis, and previous antiretroviral treatment.

- Subtype analyses reflect what is observed within a small region of the viral genome.

- The serological assays that have been developed to detect recently acquired infections have been based on subtype B-derived antigens and have been shown to occasionally misdiagnose incident non-B infections as established infections. Further investigation is required to determine the sensitivity of the commercially available assays to accurately detect recently acquired infections among other non-B HIV-1 subtypes.

Appendix 5: Glossary of Terms[1]

Cross-resistance: resistance selected by one drug that, in turn, confers resistance to one or more drugs not included in the current treatment

DNA: deoxyribonucleic acid, the genetic material of a cell

Drug resistance: decreased susceptibility to a drug

Drug resistance mutation: a change in amino acid associated with increased resistance of HIV to an antiretroviral drug

Gene: a segment of DNA coding for a particular protein or protein sub-unit

Genotype: specific sequence of nucleotides that determines the genes of HIV-1

Genotypic resistance: presence of mutations to nucleotides that increase resistance of HIV to one or more antiretroviral drugs

Genotypic tests: conducted to determine the presence of mutations in the nucleotide sequence of the viral genome

HIV: Human immunodeficiency virus

Incidence: the number of new occurrences of a disease in a given population during a specified period of time

Major mutation: mutation in the viral protease sequence that, in and of itself, is strongly associated with conferring increased resistance of HIV to protease inhibitors

Minor mutation: mutation in the viral protease sequence that, in combination with other mutations, confers increased resistance of HIV to protease inhibitors

Multi-drug resistance: increased resistance of HIV to more than one class of drugs

Mutation: genetic change in the viral nucleotide sequence

Nucleotide: a monomeric unit consisting of a sugar, phosphate, and nitrogenous base

PCR: polymerase chain reaction, a molecular technique used to amplify nucleotide sequences

Phenotype: characteristics and growth properties of HIV-1

Phenotypic resistance: when four or more times the amount of drug is required to inhibit viral growth by 50% (inhibitory concentration 50)

Phenotypic tests: used to determine the susceptibility of a virus to drug in a virus culture assay

Polymorphism: A variation in the viral RNA sequence that is too common to be due to a new mutation. Typically a polymorphism must have a frequency of at least 1% in the population.

[1] Some definitions are adapted from the *HIV and AIDS in Canada Surveillance Report* to December 31, 2006 and from the International Consultation on Monitoring the Emergence of Antiretroviral Resistance sponsored by WHO, UNAIDS and ISS (October, 2000).

Prevalence: the number of people with the disease in a given population who are alive during a specified period of time

Primary resistance: increased resistance of HIV to antiretroviral drugs seen in individuals who have never before received treatment and so, presumably, have been infected with drug-resistant virus

Protease: an enzyme that breaks down proteins to their subunits or component peptides

Recombinant: HIV-1 containing a sequence corresponding to a mixture of more than one subtype in the envelope gene

Reverse transcriptase: an enzyme that is unique to all retroviruses. It reads the genetic information of the retrovirus, which is RNA, and makes a DNA copy.

RNA: ribonucleic acid, a polymer of nucleotides involved in protein synthesis

RT-PCR: PCR using the enzyme reverse transcriptase (RT), a molecular technique used to amplify RNA sequence into DNA

Secondary resistance: increased resistance of HIV to drugs seen in individuals who are already receiving treatment (presumably a result of treatment failure)

Subtype: also referred to as clade, a group of related HIV variants classified according to degree of genetic similarity

Wild type virus: the most commonly occurring form of HIV-1

Appendix 6: List of mutations used for this report

Protease

Major mutation	Antiretroviral drug
D30N	Nelfinavir
V32I	Lopinavir/ritonavir
L33F	Tipranavir/ritonavir
M46I/L	Indinivir
I47V/A	Lopinavir/ritonavir
G48V	Saquinavir
I50L	Atazanavir
I50V	Amprenavir
V82A/F/T	Indinavir
V82A/F/S/T	Ritonavir
V82L/T	Tipranavir/ritonavir
I84V	Amprenavir, (Fos) amprenavir, Indinavir, Ritonavir, Tipranavir, ritonavir
N88S	Atazanavir
L90M	Saquinavir, Nelfinavir

* Note: The correlation of drug resistance to genotype in this report is based on scientific consensus of mutations associated with HIV resistance to antiretroviral drugs as of November 2005. These correlations do not necessarily imply phenotypic resistance to a particular antiretroviral drug in a clinical setting.

Reverse transcriptase

Mutation	Antiretroviral drug
M41L[1]	Zidovudine, Stavudine
K65R	Abacavir, Tenofovir, Didanosine, Emtricitabine, Lamivudine, Stavudine
D67N	Zidovudine, Stavudine
T69D	Zidovudine, Stavudine
L74V	Didanosine, Abacavir
L100I	Nevirapine, Efavirenz
K103N	Delavirdine, Nevirapine, Efavirenz
V106A	Nevirapine, Efavirenz, Delavirdine
V106A/M	Nevirapine
V108I	Nevirapine, Efavirenz
Y115F	Abacavir
Y181C	Delavirdine, Nevirapine, Efavirenz
Y181I	Nevirapine, Efavirenz
M184I	Lamivudine, Emtricitabine
M184V	Emtricitabine, Abacavir, Lamivudine
Y188C/H	Nevirapine
Y188L	Delavirdine, Nevirapine, Efavirenz
G190A	Nevirapine, Efavirenz
G190S	Efavirenz
L210W	Zidovudine, Stavudine
T215F/Y	Zidovudine, Stavudine
K219E/Q	Zidovudine, Stavudine
P225H	Efavirenz
M230L	Delavirdine, Nevirapine, Efavirenz
P236L	Delavirdine

[1]M41L refers to the substitution of amino acid methionine (M) by leucine (L) at position 41 of the reverse transcriptase enzyme. Other mutation nomenclature refers to substitutions as indicated; amino acid abbreviations transcriptase enzyme. Other mutation nomenclature refers to substitutions as indicated; amino acid abbreviations are as follows: K, lysine; R, arginine; T, threonine, D, aspartic acid; N, asparagine; E, glutamic acid; H, histidine; Y, tyrosine; V, valine; I, isoleucine; A, alanine

Other commonly used names for the indicated anti-retroviral drugs: Zidovudine (AZT, retrovir); stavudine (d4T, zerit); zalcitabine (ddC, hivid); lamivudine (3Tc, epivir); and abacavir (ABC, 1592, ziagen); delavirdine (rescriptor); efavirenz (sustiva); nevirapine (viramune); saquinavir (invirase, fortovase); ritonavir (norvir); amprenavir (agenarase); nelfinavir (viracept); indinavir (crixivan).

Appendix 7: Data Sources for the SDR program

Dr. Michael Rekart
Dr. Mel Krajden
B.C. Centre for Disease Control
655 West 12th Avenue
Vancouver, British Columbia V5Z 4R4

Dr. Jutta Preiksaitis
Provincial Laboratory of Public Health
(Microbiology)
8440-112 Street
Edmonton, Alberta T6G 2J2

Communicable Disease Control Unit
Public Health Branch
Manitoba Health
4th Floor - 300 Carlton Street
Winnipeg, Manitoba R3B 3M9

Dr. Robert Remis
University of Toronto
Department of Public Health Sciences
McMurrich Building, 4th Floor
12 Queens Park Cr. W.
Toronto, Ontario M5S 1A8

Public Health Services
Department of Health Canada
1690 Hollis Street, PO Box 488
Joseph Howe Building
Halifax, Nova Scotia B3J 2R8

Dr. Sam Ratnam
Newfoundland Public Health Laboratory
Leonard A. Miller Centre for Health Services
100 Forest Road, P.O. Box 8800
St. John's, Newfoundland & Labrador A1B 3T2

Dr. Ameeta Singh
Alberta Health and Wellness
TELUS Plaza North Tower
PO Box 1360, STN Main
Edmonton, Alberta T5J 2N3

Dr. Huiming Yang
Dr. Fred Sidaway
Saskatchewan Health
3475 Albert St.
Regina, Saskatchewan S4S 6X6

Dr. Magdy Dawood
Cadham Laboratories
P.O. Box 8450, 750 William Avenue
Winnipeg, Manitoba R3C 3Y1

Ms. Carole Swantee
HIV Laboratory
Laboratory Services Branch
Ontario Ministry of Health
81 Resources Rd.
Etobicoke, Ontario M9P 3T1

Dr. Todd F. Hatchette
QEII Health Sciences Centre
Division of Microbiology
MacKenzie Building, Room 404
5788 University Avenue
Halifax, Nova Scotia B3H 1V8

Dr. Faith Stratton
Newfoundland Department of Health
Disease Control and Epidemiology
West Block, Confederation Bldg, P.O. Box 8700
St. John's, Newfoundland and Labrador A1B 4J6