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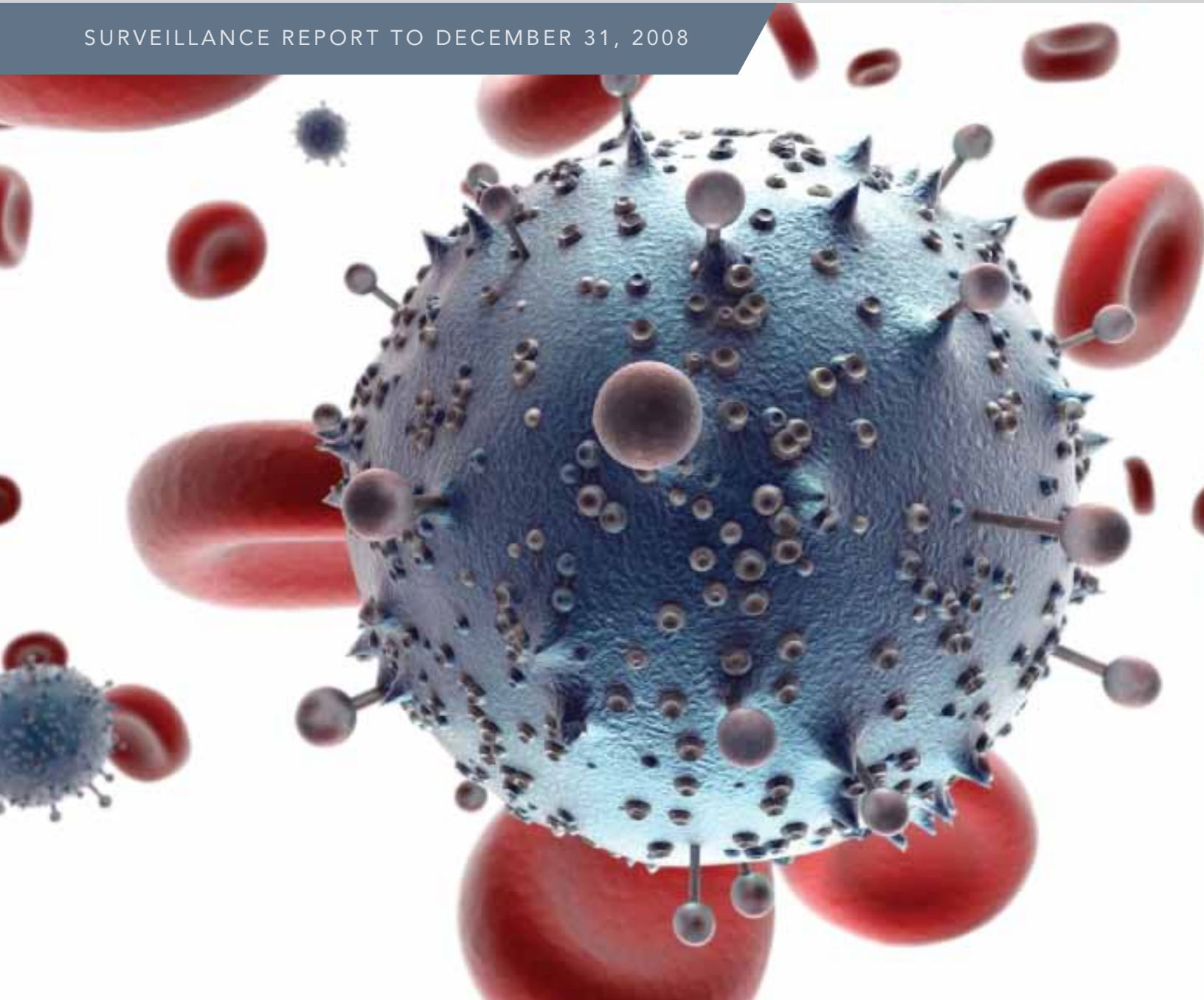
Canada

# HIV–1 STRAIN AND TRANSMITTED DRUG RESISTANCE IN CANADA

SURVEILLANCE REPORT TO DECEMBER 31, 2008



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# HIV-1 STRAIN AND TRANSMITTED DRUG RESISTANCE IN CANADA

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**Acknowledgements:** We acknowledge the provincial/territorial HIV/AIDS coordinators, laboratories, healthcare providers, and reporting physicians for providing the data required to publish this report. Please refer to Appendix D and section III for a list of these contributors.



**Suggested citation:** Public Health Agency of Canada. *HIV-1 Strain and Transmitted Drug Resistance in Canada: Surveillance Report to December 31, 2008.* Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada, 2012.

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

On behalf of the Centre for Communicable Diseases and Infection Control and the National HIV and Retrovirology Laboratories, we are pleased to provide you with the *HIV-1 Strain and Transmitted Drug Resistance in Canada: Surveillance Report to December 31,2008.* This report is part of an ongoing 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 transmitted drug resistance data. Each table provides specific explanatory details, as appropriate. A further description of HIV-1 strain and transmitted 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/aids-sida/publication/index-eng.php#surveillance. 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 (SDR) Surveillance Program. The second section describes HIV-1 transmitted 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 fourth section outlines results from other key studies conducted in Canada, the United States, and Western Europe.

The Field Surveillance Officers are responsible for coordinating data collection and submission to the SDR program. The SDR program 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 transmitted drug resistance genotyping, and phylogenetic analysis. The National Laboratory for HIV Reference Services determines the estimated time of infection, using one of three commercially available kits: the bioMérieux Vironostika HIV-1- LS™, Abbott 3A11-LS™ or Calypte BED™ assay. 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 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 D. Thanks also to our colleagues in Quebec who shared data from the Quebec program for drug resistance testing for inclusion in Section III of this report.

This is the fifth report on HIV strain and transmitted drug resistance surveillance in Canada. We will be working toward improving this report to reflect changes in the surveillance of HIV strain and transmitted drug resistance.

We welcome and appreciate your comments and suggestions.

Yours sincerely,

Jessica Halverson
Dr. Chris Archibald
Dr. James Brooks
Dr. Paul Sandstrom

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# RESULTS AT A GLANCE

## Summary of main findings from the Canadian HIV Strain and Drug Resistance Surveillance Program

- Among 4,521 newly diagnosed, treatment-naïve individuals from 1999 to 2008, an overall proportion of 9.8% exhibited transmitted drug resistance to either one or more therapies. The majority of drug resistant specimens were resistant to the nucleoside reverse transcriptase inhibitor (NRTI) (38.2%) and the non-nucleoside reverse transcriptase inhibitor (NNRTI) (32.4%) drug classes, while approximately 10.2% exhibited multi-drug resistance (≥2 drugs).

- Overall drug resistance increased during the time period 1999-2008, with resistance to NNRTI drug class experiencing the most significant increase.

- While all participating provinces experienced some fluctuation, most of the increase in overall drug resistance was due to unique patterns observed within the province of Saskatchewan. Increased resistance within the province was observed primarily in the NNRTI drug class. The Saskatchewan provincial HIV strategy, launched in 2010, is based on the four pillars of community engagement and education, prevention and harm reduction, clinical management, and surveillance and research. All of these elements will be used both in responding to and monitoring drug resistance trends.

- HIV-1 subtype B continues to account for the vast majority of new HIV diagnoses in Canada, at 88.3% of specimens analyzed from 1984-2008. However, increasing proportions of non-B subtypes were observed from 2003 onwards. The most common non-B subtypes were subtypes C and A, comprising a combined 3-12% of annual cases analyzed.

- Non-B subtypes were most common in the provinces of Ontario and Manitoba, were more common among females, and were strongly associated with the heterosexual/HIV-endemic exposure category and reported Black ethnicity.

- A higher proportion of drug resistance was observed in recent HIV infections compared to established infections, particularly among subtype B.

# METHODOLOGY

## Epidemiologic data and laboratory specimen collection and transfer

The provincial partners in the Canadian HIV Strain and Drug Resistance Surveillance (SDR) Program send sera samples taken for diagnostic testing from treatment-naïve individuals with newly diagnosed HIV infection to the Centre for Communicable Diseases and Infection Control (CCDIC) within the Public Health Agency of Canada (PHAC). Subtype analysis and primary drug resistance genotyping is conducted at the National Laboratory for HIV Genetics (NLHG) in the National HIV and Retrovirology Laboratories. The National Laboratory for HIV Reference Services in the National HIV and Retrovirology Laboratories conducts testing to determine whether or not each case is a recent infection.

For each submitted laboratory sample, non-nominal epidemiologic information is also sent to PHAC. 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 Centre for Communicable Diseases and Infection Control.

British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Newfoundland and Labrador, and Nova Scotia are current participants in the SDR program. The results presented in this report represent samples from cases diagnosed up to December 31, 2008, on which HIV subtype and drug resistance genotyping have been completed successfully.

## Genetic algorithm for HIV subtyping and drug resistance testing

Aliquots of archived HIV diagnostic serum specimens are received on dry ice at the 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.

Additional analysis is carried out if poor quality DNA sequence information is obtained, or if 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 $1 \times 10^{10}$ copies or more. The potential to contaminate incoming specimens with one aliquot of the amplified DNA is always present. The laboratory is designed to facilitate a unidirectional workflow with pre- and post-amplification products separated in space and time. 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 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 Stanford University HIV Database. The HIV drug resistance mutations captured in the SDR program database are those defined by the World Health Organization's *List of mutations for surveillance of transmitted drug resistant HIV: 2009 update*, which is intended to provide a simple, unambiguous and standardized measure of transmitted drug resistance in HIV-1 (Bennett et al).

## Determining recent infection

A variety of laboratory methods have been used to estimate HIV incidence. Previously, recent infections were identified using one of two enzyme immunoassays: the Abbott 3A11-LS™ or the bioMérieux Vironostika HIV-1-LS™ (often known as STARHS- Serologic Testing Algorithm for Recent HIV-1 Seroconversion). These modified commercial assays defined recent infections as those that occurred within the past 170 days of serum collection (95% CI=162-183 days). These assays were developed with HIV-1 subtype B antigens limiting their usefulness to populations with subtype B infections. They are no longer available and have been replaced by newer technology.

Currently, incidence testing is performed using a 2$^{nd}$ generation assay, the Calypte BED™. This assay defines recent infection as 155 days after seroconversion (95% CI=146-165 days). It is an IgG-capture EIA using a multi-subtype antigen making it suitable for both subtype B and non-subtype B population incidence determination.

## Epidemiologic analyses

Laboratory and epidemiologic data were linked using unique identifiers. Univariate summary statistics were calculated on drug resistance or non-B subtypes. The independent variables examined included age at diagnosis of HIV infection, sex, exposure category, race/ethnicity, and year of diagnosis of HIV infection; all these variables were categorized. The variables were summarized using percentages. Temporal trends were examined by Cochran-Armitage trend test. The tests were two-sided and a $p<0.05$ was considered to be statistically significant. Data analyses were performed with SAS Enterprise Guide 4 (SAS Institute, Cary, NC).

Reference: Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, Kiuchi M, Heneine W, Kantor R, Jordan MR, Schapiro JM, Vandamme AM, Sandstrom P, Boucher CA, van de Vijver D, Rhee SY, Liu TF, Pillay D, Shafer RW. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. PLoS One. 2009;4(3):e4724. Epub 2009 Mar 6.

# SECTION I: HIV-1 SUBTYPES

## Background

During the three decades since the first reported cases of HIV/AIDS in the early 1980s, HIV has emerged as one of the world's most significant infectious diseases. With an estimated 33.3 million people living with the disease worldwide in 2009, and with 2.6 million new infections and 1.8 million deaths that same year, it has proved to be a significant public health challenge. Despite significant advances in our understanding of the virus, patterns of transmission and host responses to infection, control of this infection remains a significant challenge. Part of the pathogenicity of the virus is attributable to the variability in the virus that results from the error-prone mechanism of action of the enzyme reverse transcriptase, the high rate of replication, recombination, and the selective immune pressures by the host.

There are two types of HIV: HIV-1 and HIV-2. Both types are transmitted by sexual contact, through blood, and from mother to child, and both types also appear to cause clinically indistinguishable AIDS. However, it seems that HIV-2 is less easily transmitted, and the period between initial infection and illness is longer in the case of HIV-2. Worldwide, the predominant virus is HIV-1, and generally when people refer to HIV without specifying the type of virus, they are referring to HIV-1. As a result, HIV-1 has been used as the prototype in the majority of studies on HIV epidemiology, pathogenesis and treatment. The relatively uncommon HIV-2 type is concentrated in West Africa and is rarely found in other regions.

HIV-1 is classified into four groups: the 'major" group M, the "outlier" group O and two new groups, N and P. Infections from group M viruses constitute the vast majority of all HIV cases. Within group M viruses, distinct viral lineages are further divided into subtypes or clades. The subtypes are designated with a letter (A to D, F to H, J, and K) and sometimes followed by a number (e.g., A1, A2) if there is sufficient variability within a subtype. As more specimens have been analyzed, it has become apparent that different HIV subtypes have recombined to create new circulating recombinant forms (CRFs) that identify the constituent subtypes (e.g., CRF02_AG) by letters, of which there are approximately 50. The proliferation of recombinant HIV forms presents significant challenges to vaccine design.

HIV-1 subtypes are distributed heterogeneously across the globe and their distribution is dynamic. Many studies have been conducted to estimate the regional and global distribution of HIV-1 subtypes and circulating recombinant forms. Globally, the most prevalent HIV-1 subtypes are C, A and B in descending frequency. In Canada, analysis of specimens from all new HIV diagnoses made available to the National HIV & Retrovirology Laboratories show that HIV-1 subtype B is the most common subtype. Historically, subtype B infections constituted more than 95% of all new diagnoses in Canada; however, with changing patterns of immigration the percent of non-B subtype infections may now represent approximately one third of new diagnoses in some provinces. As a result, the distribution of HIV subtypes in Canada and trends over time is monitored by the Public Health Agency of Canada's (PHAC) Strain and Drug Resistance Surveillance (SDR) Program.

The potential for increasing diversity of HIV-1 subtypes in Canada has implications for HIV diagnosis testing, responses to antiretroviral treatment (including the development of resistance) and vaccine development. HIV-1 subtype surveillance serves as a platform for examining subtype- specific differences in transmissibility, pathogenicity and treatment. To address the challenges posed by these aspects of HIV strain diversity, it is therefore important to continue the systematic collection and analysis of information related to the dynamic evolution of HIV subtypes in Canada.

## Data Tables

This section highlights the main findings related to the number and distribution of HIV subtypes from specimens submitted through the (SDR) Program. The data presented in this report are from individuals who were tested and received their first-time diagnosis of HIV infection. Subtyping results are only available from those individuals for whom sufficient sera were available for sequencing. Subtyping is based upon the genetic sequence of the pol gene including all of protease and the first 321 codons of RT. Classification was based upon result from the Stanford HIV DB and the Rega Subtyping Tool.

Specimens were obtained from 6,186 of 30,607 (20.2%) persons newly diagnosed with HIV in seven provinces during the time period 1984 through 2008, whose cases were reported to PHAC. Among them, 5,082 samples (82.2%) had sufficient specimen volume for sequencing to identify subtypes. The detailed numbers of successful sequencing results for isolates received by the SDR Program, by province and diagnosis year, is listed in Table 1.1.

## Table 1.1: Number of isolates with successful sequencing results, by province and diagnosis year

| Year of diagnosis | Number of isolates with successful sequencing results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | British Columbia | Alberta | Manitoba | Newfoundland | Nova Scotia | Ontario | Saskatchewan | Total |
| ≤1998 | 232 | 39 | 55 | 39 | 0 | 5 | 83 | 453 |
| 1999 | 200 | 58 | 53 | 3 | 9 | 1 | 27 | 351 |
| 2000 | 274 | 113 | 42 | 0 | 1 | 9 | 16 | 455 |
| 2001 | 237 | 45 | 35 | 0 | 3 | 2 | 18 | 340 |
| 2002 | 312 | 97 | 42 | 0 | 12 | 1 | 20 | 484 |
| 2003 | 201 | 88 | 81 | 0 | 16 | 37 | 34 | 457 |
| 2004 | 331 | 34 | 83 | 0 | 27 | 117 | 49 | 641 |
| 2005 | 203 | 57 | 95 | 0 | 19 | 22 | 80 | 476 |
| 2006 | 253 | 73 | 57 | 0 | 15 | 0 | 60 | 458 |
| 2007 | 300 | 88 | 23 | 0 | 16 | 0 | 100 | 527 |
| 2008 | 215 | 81 | 0 | 0 | 13 | 0 | 131 | 440 |
| Total | 2758 | 773 | 566 | 42 | 131 | 194 | 618 | 5082 |

## Table 1.2: Number and proportion of HIV-1 subtypes in successfully sequenced specimens of newly diagnosed, treatment-naïve cases submitted to the SDR Program, 1984-2008

| HIV-1 Subtype | Frequency | Proportion (%) |
|---|---|---|
| B | 4490 | 88.3 |
| Non-B | 592 | 11.7 |
| C | 317 | 6.2 |
| A | 99 | 2.0 |
| CRF02_AG | 55 | 1.1 |
| CRF01_AE | 50 | 1.0 |
| D | 26 | 0.5 |
| G | 15 | 0.3 |
| AD | 11 | 0.2 |
| BD | 4 | 0.08 |
| CRF06_cpx | 3 | 0.06 |
| F | 2 | 0.04 |
| AB | 2 | 0.04 |
| AC | 1 | 0.02 |
| BC | 1 | 0.02 |
| B/AG | 1 | 0.02 |
| H | 1 | 0.02 |
| J | 1 | 0.02 |
| K | 1 | 0.02 |
| K/AE | 1 | 0.02 |
| K/AG | 1 | 0.02 |
| Total | 5082 | 100.0 |

Table 1.2 illustrates the distribution of HIV-1 subtypes. The majority of specimens were identified as HIV-1 subtype B (88.3%), while non-B subtypes comprised 11.7% of specimens analyzed. The most common non-B subtype was subtype C (6.2%), followed by subtype A (2%), CRF02_AG (1.1%) and CRF01_AE (1.0%), while all other subtypes each comprised less than 1% of the total sample.

## Table 1.3a: Number and proportion of HIV-1 subtypes by year of diagnosis

| | B | Non-B | Total |
|---|---|---|---|
| **Year of diagnosis** | **n (%)** | **n (%)** | **n** |
| ≤1998 | 411 (90.7) | 42 (9.3) | 453 |
| 1999 | 323 (92.0) | 28 (8.0) | 351 |
| 2000 | 433 (95.2) | 22 (4.8) | 455 |
| 2001 | 323 (95.0) | 51 (5.0) | 340 |
| 2002 | 436 (90.1) | 48 (9.9) | 484 |
| 2003 | 379 (82.9) | 78 (17.1) | 457 |
| 2004 | 540 (84.2) | 101 (15.8) | 641 |
| 2005 | 393 (82.6) | 83 (17.4) | 476 |
| 2006 | 388 (84.7) | 70 (15.3) | 458 |
| 2007 | 475 (90.1) | 52 (9.9) | 527 |
| 2008 | 389 (88.4) | 51 (11.6) | 440 |
| Total | 4490 (88.3) | 592 (11.7) | 5082 |

## Table 1.3b: Number and proportion of non-B subtypes among all specimens by year of diagnosis

| | C | A | CRF02_AG* | CRF01_AE* | Others** | Total |
|---|---|---|---|---|---|---|
| **Year of diagnosis** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| ≤1998 | 25 (5.5) | 13 (2.9) | 0 (0.0) | 1 (0.2) | 3 (0.7) | 42 (9.3) |
| 1999 | 18 (5.1) | 3 (0.9) | 0 (0.0) | 3 (0.9) | 4 (1.1) | 28 (8.0) |
| 2000 | 12 (2.6) | 1 (0.2) | 3 (0.7) | 1 (0.2) | 5 (1.1) | 22 (4.8) |
| 2001 | 11 (3.2) | 1 (0.3) | 1 (0.3) | 0 (0.0) | 4 (1.2) | 51 (5.0) |
| 2002 | 19 (3.9) | 5 (1.0) | 8 (1.7) | 10 (2.1) | 9 (1.2) | 48 (9.9) |
| 2003 | 41 (9.0) | 6 (1.3) | 8 (1.8) | 13 (2.8) | 10 (2.2) | 78 (17.1) |
| 2004 | 56 (8.7) | 19 (3.0) | 10 (1.6) | 5 (0.8) | 11 (1.7) | 101 (15.8) |
| 2005 | 42 (8.8) | 16 (3.4) | 10 (2.1) | 3 (0.6) | 12 (2.5) | 83 (17.4) |
| 2006 | 38 (8.3) | 14 (3.1) | 4 (0.9) | 5 (1.1) | 9 (1.9) | 70 (15.3) |
| 2007 | 23 (4.4) | 10 (1.9) | 5 (1.0) | 8 (1.5) | 6 (1.1) | 52 (9.9) |
| 2008 | 32 (7.3) | 11 (2.5) | 6 (1.4) | 1 (0.2) | 1 (0.2) | 51 (11.6) |
| Total | 317 (6.2) | 99 (2.0) | 55 (1.1) | 50 (1.0) | 71 (1.4) | 592 (11.7) |

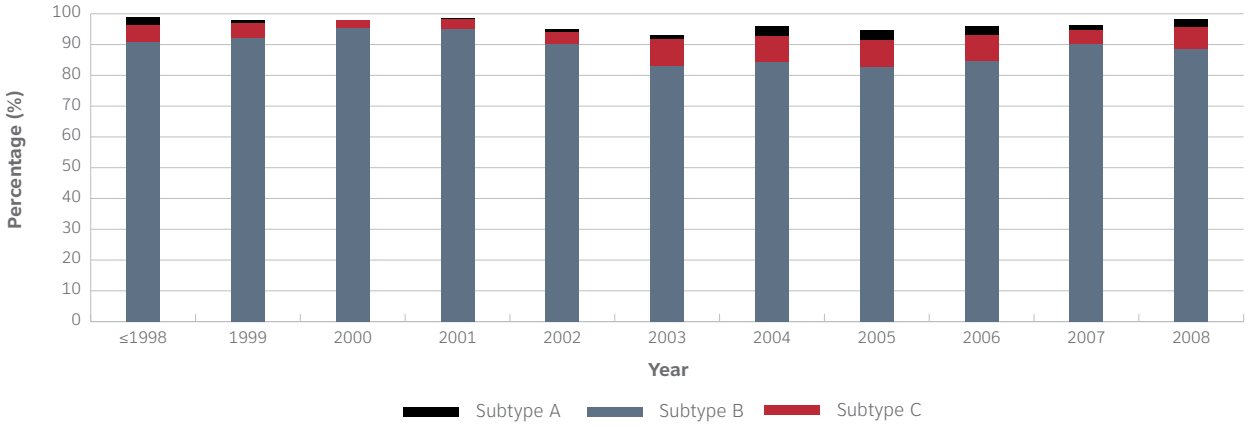
*CRF = circulating recombinant form

**Others refer to the following HIV-1 subtypes and CRFs: D, G, AB, AC, AD, B/AG, BC, BD, F, H, J, K, K/AE, K/AG and CRF06_cpx.

Tables 1.3a and 1.3b show the number and distribution of HIV-1 subtypes by year of HIV diagnosis. The proportion of subtype B increased from 1998 to 2001, decreased from 2001 to 2003, stabilized from 2003 to 2006, increased slightly in 2007 and decreased slightly in 2008. However, the overall trend indicated a decrease for the full time period of 1984-2008 (p value <0.0001) (Figure 1.1).

There was variation in the proportion of subtypes C and A during the time period 1984-2008; however, the overall trend was an increase in these subtypes (p value 0.002 for subtype C and 0.009 for subtype A).

## Figure 1.1: Proportion of HIV-1 subtypes B, C and A by year of HIV diagnosis




## Table 1.4a: Number and proportion of HIV-1 subtypes by province, 1984-2008

| | B | Non-B | Total |
|---|---|---|---|
| **Province** | **n (%)** | **n (%)** | **n** |
| Alberta | 656 (84.9) | 117 (15.1) | 773 |
| British Columbia | 2574 (93.3) | 184 (6.7) | 2758 |
| Manitoba | 418 (73.9) | 148 (26.1) | 566 |
| Newfoundland | 42 (100.0) | 0 (0.0) | 42 |
| Nova Scotia | 113 (86.3) | 18 (13.7) | 131 |
| Ontario | 144 (74.2) | 50 (25.8) | 194 |
| Saskatchewan | 543 (87.9) | 75 (12.1) | 618 |
| Total | 4490 (88.3) | 592 (11.7) | 5082 |

## Table 1.4b: Number and proportion of non-B subtypes among all specimens by province, 1984-2008

| | C | A | CRF02_AG* | CRF01_AE* | Others** | Total |
|---|---|---|---|---|---|---|
| **Province** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Alberta | 76 (9.8) | 8 (1.0) | 12 (1.6) | 8 (1.0) | 13 (1.7) | 117 (15.1) |
| British Columbia | 99 (3.6) | 30 (1.1) | 11 (0.4) | 28 (0.9) | 19 (0.7) | 184 (6.7) |
| Manitoba | 84 (14.8) | 23 (4.0) | 14 (2.5) | 5 (0.9) | 22 (3.9) | 148 (26.1) |
| Newfoundland | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Nova Scotia | 7 (5.3) | 6 (4.6) | 2 (1.5) | 1 (0.8) | 2 (1.5) | 18 (13.7) |
| Ontario | 22 (11.3) | 5 (2.6) | 12 (6.2) | 5 (2.6) | 6 (3.1) | 50 (25.8) |
| Saskatchewan | 29 (4.7) | 27 (4.4) | 4 (0.6) | 6 (1.0) | 9 (1.4) | 75 (12.1) |
| Total | 317 (6.2) | 99 (2.0) | 55 (1.1) | 50 (1.0) | 71 (1.4) | 592 (11.7) |

*CRF= circulating recombinant form.

**Others refer to the following HIV-1 subtypes and CRFs: D, G, AB, AC, AD, B/AG, BC, BD, F, H, J, K, K/AE, K/AG and CRF06_cpx.

Tables 1.4a and 1.4b outline the number and distribution of HIV-1 subtypes by province of diagnosis for years 1984 through 2008. The data indicate geographic variation in the distribution of non-B subtypes. Notably, all 42 samples from Newfoundland and Labrador were identified as subtype B, while 15.1%, 6.7%, 26.1%, 13.7%, 25.8%, and 12.1% of subtypes diagnosed in Alberta, British Columbia, Manitoba, Nova Scotia, Ontario and Saskatchewan respectively were non-B subtypes. Due to small numbers of specimens or incomplete study years in some provinces, the trend analysis was limited to the provinces in Figure 1.2, namely, Alberta, British Columbia, Manitoba and Saskatchewan. The proportion of non-B subtypes increased significantly since 1984 in Alberta ($p < 0.0001$) and Manitoba ($p < 0.0001$), while no change was found during 1984-2008 either in British Columbia (p value 0.83) or Saskatchewan (p value 0.12) (Figure 1.2).

Figure 1.2: Proportion of non-B subtypes by year of HIV diagnosis in selected provinces

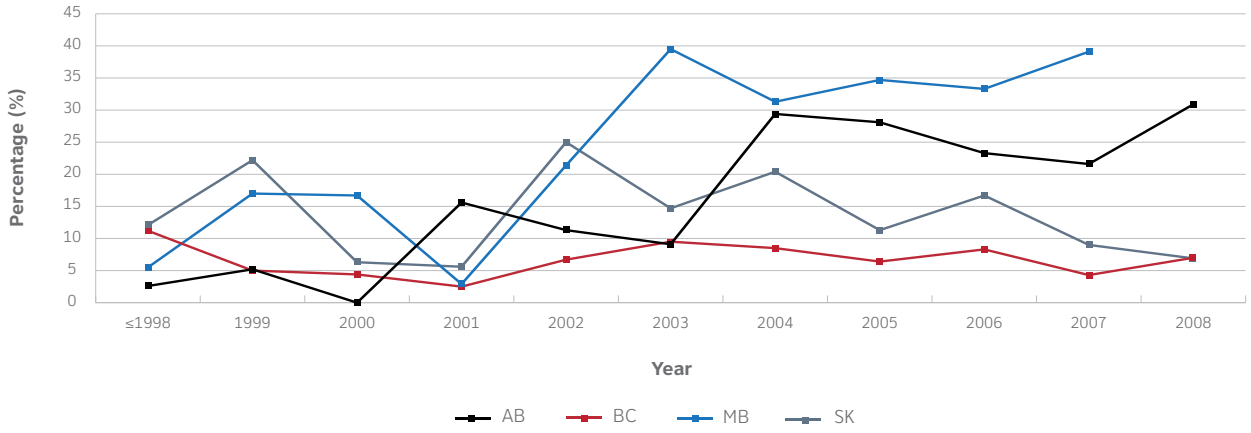



Table 1.5a: Number and proportion of subtypes by age group, 1984-2008

| Age group (years) | B | Non-B | Total |
|---|---|---|---|
| | n (%) | n (%) | n |
| <15 | 10 (32.3) | 21 (67.7) | 31 |
| 15-19 | 88 (90.7) | 9 (9.3) | 97 |
| 20-29 | 926 (85.1) | 162 (14.9) | 1088 |
| 30-39 | 1557 (86.6) | 241 (13.4) | 1798 |
| 40-49 | 1280 (93.3) | 92 (6.7) | 1372 |
| 50+ | 624 (90.6) | 65 (9.4) | 689 |
| Total | 4485 (88.4) | 590 (11.6) | 5075 |

Table 1.5b: Number and proportion of non-B subtypes among all specimens by age group, 1984-2008

| Age group (years) | C | A | CRF02_AG* | CRF01_AE* | Others** | Total |
|---|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| <15 | 12 (38.7) | 5 (16.1) | 0 (0.0) | 0 (0.0) | 4 (12.9) | 21 (67.7) |
| 15-19 | 5 (5.2) | 1 (1.0) | 1 (1.0) | 1 (1.0) | 1 (1.0) | 9 (9.3) |
| 20-29 | 86 (7.9) | 35 (3.2) | 10 (0.9) | 11 (1.0) | 20 (1.8) | 162 (14.9) |
| 30-39 | 141 (7.8) | 31 (1.7) | 26 (1.5) | 22 (1.2) | 21 (1.2) | 241 (13.4) |
| 40-49 | 48 (3.5) | 18 (1.3) | 5 (0.4) | 7 (0.5) | 14 (1.0) | 92 (6.7) |
| 50+ | 24 (3.5) | 8 (1.2) | 13 (1.9) | 9 (1.3) | 11 (1.6) | 65 (9.4) |
| Total | 316 (6.2) | 98 (1.9) | 55 (1.1) | 50 (1.0) | 71 (1.4) | 590 (11.6) |

*CRF= circulating recombinant form.

**Others refer to the following HIV-1 subtypes and CRFs: D, G, AB, AC, AD, B/AG, BC, BD, F, H, J, K, K/AE, K/AG and CRF06_cpx.

Tables 1.5a and 1.5b show the number and distribution of HIV-1 subtypes by age groups at the time of diagnosis. The results identified non-B subtypes in all age groups, but the highest proportion was observed in those aged less than 15 years old at time of diagnosis.

## Table 1.6a: Number and proportion of subtypes by sex, 1984-2008

| | B | Non-B | Total |
|---|---|---|---|
| **Sex** | **n (%)** | **n (%)** | **n** |
| Male | 3483 (92.5) | 283 (7.5) | 3766 |
| Female | 997 (76.3) | 309 (23.7) | 1306 |
| Total | 4490 (88.3) | 592 (11.7) | 5082 |

## Table 1.6b: Number and proportion of non-B subtypes among all specimens by sex, 1984-2008

| | C | A | CRF02_AG* | CRF01_AE* | Others** | Total |
|---|---|---|---|---|---|---|
| **Sex** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Male | 152 (4.0) | 42 (1.1) | 23 (0.6) | 33 (0.9) | 33 (0.9) | 283 (7.5) |
| Female | 165 (12.6) | 57 (4.4) | 32 (2.5) | 17 (1.3) | 38 (2.9) | 309 (23.7) |
| Total | 317 (6.2) | 99 (2.0) | 55 (1.1) | 50 (1.0) | 71 (1.4) | 592 (11.7) |

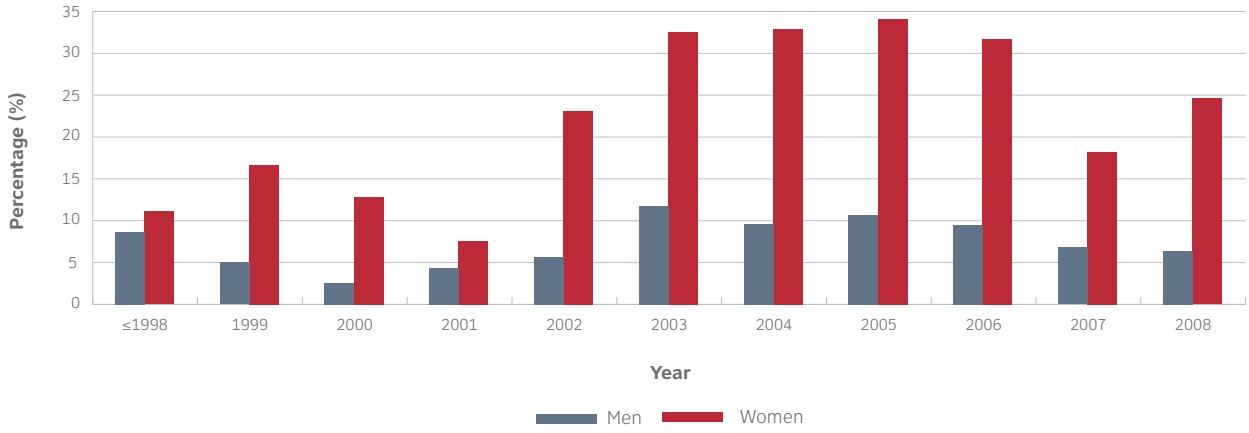
*CRF= circulating recombinant form.

**Others refer to the following HIV-1 subtypes and CRFs: D, G, AB, AC, AD, B/AG, BC, BD, F, H, J, K, K/AE, K/AG and CRF06_cpx.

Tables 1.6a and 1.6b show the number and percentage distribution of HIV-1 subtypes by sex. The results presented in Table 1.6a indicate that the prevalence of non-B subtypes was higher among females than among males (23.7% vs. 7.5%). The explanation for this finding is that a greater percentage of females were reported in the Heterosexual exposure category; this exposure category (especially the Heterosexual/HIV-endemic subcategory) was associated with a higher proportion of non-B HIV-1 subtypes. In contrast, the majority of HIV diagnoses among men in Canada were among men who have sex with men (MSM), which were predominantly associated with B subtype (please refer to Tables 1.7a and 1.7b).

Figure 1.3 illustrates the proportion of non-B subtypes, which was relatively stable among men during 1984-2008, while the corresponding figure for women was variable, with an overall increase ($p < 0.0001$).

## Figure 1.3: Proportion of non-B subtypes by sex and year of diagnosis



## Table 1.7a: Number and proportion of subtypes by reported exposure category, 1984-2008

| | B | Non-B | Total |
|---|---|---|---|
| **Exposure category** | **n (%)** | **n (%)** | **n** |
| MSM[1] | 1593 (97.9) | 35 (2.1) | 1628 |
| MSM/IDU | 159 (95.8) | 7 (4.2) | 166 |
| IDU[2] | 1501 (97.3) | 41 (2.7) | 1542 |
| Heterosexual/Endemic[3] | 21 (8.6) | 223 (91.4) | 244 |
| Heterosexual/Non-Endemic[4] | 945 (80.9) | 223 (19.1) | 1168 |
| Others[5] | 67 (67.7) | 32 (32.3) | 99 |
| Total | 4286 (88.3) | 561 (11.7) | 4847 |

[1] MSM refers to men who have sex with men.

[2] IDU refers to people who use injection drugs.

[3] Heterosexual/Endemic refers to origin in a country where HIV is endemic (where heterosexual sex is the main mode of transmission and HIV prevalence is high, mainly countries in sub-Saharan Africa and the Caribbean).

[4] Heterosexual/Non-Endemic refers to heterosexual contact with a person who is either HIV infected or at risk of HIV or heterosexual contact as the only identified risk.

[5] Others refers to recipients of blood transfusion or clotting factor, perinatal and occupational transmission.

## Table 1.7b: Number and proportion of non-B subtypes among all specimens by reported exposure category, 1984-2008

| | C | A | CRF02_AG* | CRF01_AE* | Others** | Total |
|---|---|---|---|---|---|---|
| **Exposure category** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| MSM[1] | 12 (0.7) | 7 (0.4) | 1 (0.1) | 6 (0.4) | 9 (0.5) | 35 (2.1) |
| MSM/IDU | 4 (2.4) | 1 (0.6) | 0 (0.0) | 2 (1.2) | 0 (0.0) | 7 (4.2) |
| IDU[2] | 16 (1.0) | 14 (0.9) | 1 (0.1) | 5 (0.3) | 20 (1.3) | 41 (2.7) |
| Heterosexual/Endemic[3] | 142 (58.2) | 24 (9.8) | 27 (11.1) | 6 (2.5) | 24 (9.8) | 223 (91.4) |
| Heterosexual/Non-Endemic[4] | 112 (9.6) | 40 (3.4) | 20 (1.7) | 27 (2.3) | 24 (2.1) | 223 (19.1) |
| Others[5] | 18 (18.2) | 6 (6.1) | 1 (1.0) | 2 (2.0) | 5 (5.0) | 32 (32.3) |
| Total | 304 (6.2) | 92 (2.0) | 50 (1.1) | 48 (1.0) | 67 (1.4) | 561 (11.7) |

[1] MSM refers to men who have sex with men.

[2] IDU refers to people who use injection drugs.

[3] Heterosexual/Endemic refers to origin in a country where HIV is endemic (where heterosexual sex is the main mode of transmission and HIV prevalence is high, mainly countries in sub-Saharan Africa and the Caribbean).

[4] Heterosexual/Non-Endemic refers to heterosexual contact with a person who is either HIV infected or at risk of HIV or heterosexual contact as the only identified risk.

[5] Others refers to recipients of blood transfusion or clotting factor, perinatal and occupational transmission.

*CRF= circulating recombinant form.

**Others refer to the following HIV-1 subtypes and CRFs: D, G, AB, AC, AD, B/AG, BC, BD, F, H, J, K, K/AE, K/AG and CRF06_cpx.

Tables 1.7a and 1.7b outline the number and percentage distribution of HIV-1 subtypes by reported exposure category. These results suggest that a higher proportion of HIV infections among persons who reported heterosexual contact were non-B subtypes, with the trend most pronounced in the Heterosexual/HIV-endemic subcategory. In contrast, cases among MSM or IDU had the lowest proportion of non-B subtypes.

## Table 1.8a: Number and proportion of subtypes by reported race/ethnicity, 1984-2008

| | B | Non-B | Total |
|---|---|---|---|
| **Race/Ethnicity** | **n (%)** | **n (%)** | **n** |
| White | 2674 (96.4) | 101 (3.6) | 2775 |
| Black | 86 (20.1) | 342 (79.9) | 428 |
| Asian | 131 (85.6) | 22 (14.4) | 153 |
| Aboriginal total | 1115 (94.7) | 63 (5.3) | 1178 |
| First Nations | 807 (96.3) | 31 (3.7) | 838 |
| Inuit | 4 (100.0) | 0 (0.0) | 4 |
| Métis | 110 (93.2) | 8 (6.8) | 118 |
| Unspecified | 194 (89.0) | 24 (11.0) | 218 |
| Arab/South/West Asian | 77 (70.6) | 32 (29.4) | 109 |
| Latin American | 121 (95.3) | 6 (4.7) | 127 |
| Other | 18 (85.7) | 3 (14.3) | 21 |
| Total | 4222 (88.1) | 569 (11.9) | 4791 |

## Table 1.8b: Number and proportion of non-B subtypes among all specimens by reported race/ethnicity, 1984-2008

| | C | A | CRF02_AG* | CRF01_AE* | Others** | Total |
|---|---|---|---|---|---|---|
| **Race/Ethnicity** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| White | 41 (1.5) | 18 (0.6) | 8 (0.3) | 21 (0.8) | 13 (0.4) | 101 (3.6) |
| Black | 209 (48.8) | 47 (11.0) | 41 (9.6) | 7 (1.6) | 38 (8.9) | 342 (79.9) |
| Asian | 5 (3.3) | 2 (1.3) | 1 (0.7) | 12 (7.8) | 2 (1.3) | 22 (14.4) |
| Aboriginal total | 20 (1.7) | 26 (2.2) | 1 (0.1) | 3 (0.2) | 13 (1.1) | 63 (5.3) |
| First Nations | 10 (1.2) | 13 (1.6) | 1 (0.1) | 1 (0.1) | 6 (0.7) | 31 (3.7) |
| Inuit | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Métis | 3 (2.5) | 3 (2.5) | 0 (0.0) | 2 (1.7) | 0 (0.0) | 8 (6.8) |
| Unspecified | 7 (3.2) | 10 (4.6) | 0 (0.0) | 0 (0.0) | 7 (3.2) | 24 (11.0) |
| Arab/South/West Asian | 25 (23.0) | 2 (1.8) | 0 (0.0) | 4 (3.7) | 1 (0.9) | 32 (29.4) |
| Latin American | 2 (1.6) | 0 (0.0) | 0 (0.0) | 1 (0.8) | 3 (2.4) | 6 (4.7) |
| Other | 2 (9.5) | 1 (4.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (14.3) |
| Total | 304 (6.3) | 96 (2.0) | 51 (1.1) | 48 (1.0) | 70 (1.5) | 569 (11.9) |

*CRF= circulating recombinant form.

**Others refer to the following HIV-1 subtypes and CRFs: D, G, AB, AC, AD, B/AG, BC, BD, F, H, J, K, K/AE, K/AG and CRF06_cpx.

Tables 1.8a and 1.8b outline the number and distribution of HIV-1 subtypes by reported race/ethnicity for the 1984-2008 time period. These results indicate that a higher proportion of cases identified as Black (79.9%) or Arab/South/West Asian (29.4%) were infected with non-B subtypes, when compared with the White population (3.6%). These results are likely due to travel and migration from countries where non-B strains of HIV-1 prevail.

## Table 1.9a: Number and proportion of subtypes by recent versus established infection, 1984-2008

| | B | Non-B | Total |
|---|---|---|---|
| **Time of infection*** | **n (%)** | **n (%)** | **n** |
| Recent infection | 1182 (91.8) | 106 (8.2) | 1288 |
| Established infection | 2577 (87.0) | 385 (13.0) | 2962 |
| Total | 3759 (88.4) | 491 (11.6) | 4250 |

*Samples were tested using a serologic testing algorithm for recent HIV seroconversion and classified as recent infection (within 170 days prior to sample collection) or established infection (greater than 170 days) by one of three modified EIA tests (Abbott 3A11, bioMérieux Vironostika HIV-1-LS or Calypte BED assay).

## Table 1.9b: Number and proportion of non-B subtypes among all specimens by recent versus established HIV-1 infection, 1984-2008

| | C | A | CRF02_AG* | CRF01_AE* | Others** | Total |
|---|---|---|---|---|---|---|
| **Time of infection*** ** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Recent infection | 49 (3.8) | 21 (1.6) | 12 (0.9) | 13 (1.0) | 11 (0.9) | 106 (8.2) |
| Established infection | 216 (7.3) | 51 (1.7) | 39 (1.3) | 32 (1.1) | 47 (1.6) | 385 (13.0) |
| Total | 265 (6.2) | 72 (1.7) | 51 (1.2) | 45 (1.1) | 58 (1.4) | 491 (11.6) |

*CRF= circulating recombinant form.

**Others refer to the following HIV-1 subtypes and CRFs: D, G, AB, AC, AD, B/AG, BC, BD, F, H, J, K, K/AE, K/AG and CRF06_cpx.

***Samples were tested using a serologic testing algorithm for recent HIV seroconversion and classified as recent infection (within 170 days prior to sample collection) or established infection (greater than 170 days) by one of three modified EIA tests (Abbott 3A11, bioMérieux Vironostika HIV-1-LS or Calypte BED assay).

Tables 1.9a and 1.9b outline the number and proportion of HIV-1 subtypes among recently acquired (within about 170 days of diagnostic specimen collection) versus established infections. One of three modified EIA tests (Abbott 3A11, bioMérieux Vironostika HIV-1-LS or Calypte BED assay) were used to determine recent infections. Due to limited availability of these tests, the total specimen count does not reflect all newly diagnosed cases of HIV-1 infection for which HIV-1 subtyping had been completed. As shown in Table 1.9a, 8.2% of recent infections and 13.0% of established infections were non-B subtypes. Alternatively, among non-B subtypes, there were fewer recent infections (21.6%) than established infections (78.4%). In contrast, compared to non-B, cases with subtype B were found to have a higher proportion of recent infections (31.4% of all subtype B cases).

## Table 1.10a: Number and proportion of subtypes by transmitted drug resistance category, 1984-2008

| | B | Non-B | Total |
|---|---|---|---|
| **Drug class** | **n (%)** | **n (%)** | **n** |
| Wild type[1] | 3700 (87.6) | 524 (12.4) | 4224 |
| NRTI[2] | 165 (94.8) | 9 (5.2) | 174 |
| NNRTI[3] | 140 (98.0) | 3 (2.0) | 143 |
| PI[4] | 78 (88.6) | 10 (11.4) | 88 |
| MDR[5] | 44 (88.0) | 6 (12.0) | 50 |
| Total | 4127 (88.2) | 552 (11.8) | 4679 |

[1] No major mutations associated with drug resistance were identified.

[2] Nucleoside reverse transcriptase inhibitor

[3] Non-nucleoside reverse transcriptase inhibitor

[4] Protease inhibitor

[5] Multi-drug resistance; includes mutations in HIV-1 that are associated with resistance to at least two of the three classes of antiretroviral drugs (NRTIs, NNRTIs and protease inhibitors).

## Table 1.10b: Number and proportion of non-B subtypes among all specimens by transmitted drug resistance category, 1984-2008

| | C | A | CRF02_AG* | CRF01_AE* | Others** | Total |
|---|---|---|---|---|---|---|
| **Drug class** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Wild type[1] | 282 (6.7) | 80 (1.9) | 53 (1.3) | 47 (1.1) | 62 (1.4) | 524 (12.4) |
| NRTI[2] | 4 (2.3) | 3 (1.7) | 1 (0.6) | 0 (0.0) | 1 (0.6) | 9 (5.2) |
| NNRTI[3] | 1 (0.7) | 2 (1.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (2.0) |
| PI[4] | 2 (2.3) | 2 (2.3) | 1 (1.1) | 0 (0.0) | 5 (5.7) | 10 (11.4) |
| MDR[5] | 6 (12.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (12.0) |
| Total | 295 (6.3) | 87 (1.9) | 55 (1.2) | 47 (1.0) | 68 (1.4) | 552 (11.8) |

[1] No major mutations associated with drug resistance were identified.

[2] Nucleoside reverse transcriptase inhibitor

[3] Non-nucleoside reverse transcriptase inhibitor

[4] Protease inhibitor

[5] Multi-drug resistance; includes mutations in HIV-1 that are associated with resistance to at least two of the three classes of antiretroviral drugs (NRTIs, NNRTIs and protease inhibitors).

*CRF= circulating recombinant form

**Others refer to the following HIV-1 subtypes and CRFs: D, G, AB, AC, AD, B/AG, BC, BD, F, H, J, K, K/AE, K/AG and CRF06_cpx.

Tables 1.10a and 1.10b show the number and distribution of HIV-1 subtypes by transmitted drug resistance category for years 1984-2008. Historically, drug resistance genotyping began in 1999, and therefore, not all subtyped samples have been tested for drug resistance. Single class resistance to nucleoside reverse transcriptase inhibitors (NRTIs) or protease inhibitors (PIs) was identified among many or most HIV-1 subtypes, while single class resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) was only observed among subtypes B, C and A. Multi-drug resistance was only observed among specimens identified as subtypes B and C.

# SECTION II: HIV-1 TRANSMITTED DRUG RESISTANCE

## Background

The introduction of highly active antiretroviral therapy (HAART) has significantly decreased morbidity and mortality among people with HIV infection. However, these benefits can be adversely affected by the development of drug-resistant forms of the virus (Oette M et al, 2006; Kozal MJ et al, 2007).

Resistance to antiretroviral therapy (ART) is classified as transmitted or secondary based on how it develops. Secondary or acquired drug resistance refers to resistance that develops in individuals secondary to sub-optimal therapy. Transmitted or primary drug resistance is resistance observed in treatment-naïve individuals, in whom resistance is presumably due to the transmission of a drug- resistant variant of HIV-1. Both types of drug resistance limit strategies for ART, have implications for clinical outcome, and may result in increased health care costs. The emergence of drug resistance in treated populations (antiretroviral treatment-experienced patients) and transmission of drug- resistant strains to newly infected individuals are important public health concerns in the prevention and control of HIV.

Transmitted drug resistance has been documented and observed in most countries where ART is used. Overall, studies have shown variation in the reported prevalence of transmitted drug resistance. This variation reflects the heterogeneity of the study design, the demographic characteristics of the population, the geographical location, stages of HIV infection, subtypes of HIV-1 and resistance detection methodology.

Although the interpretation of results is difficult and continues to evolve, people infected with drug- resistant variants of HIV may be at increased risk of drug failure despite being therapy-naïve. The standard of care, as recommended by a number of guidelines, is to perform pre-treatment drug resistance testing. However, there may be cases when the results of these tests would not be available before treatment needs to be started. Situations where this may occur would be in the cases of needle-stick injuries or sexual exposure, where post-exposure prophylaxis is being considered, and also in cases of peri-partum diagnosis of HIV infection when therapy is needed to prevent mother-to-child transmission of HIV. Continued surveillance of transmitted drug resistance is needed to help develop guidelines for this empiric therapy and also to better understand, monitor, and prevent the transmission of resistant HIV. This surveillance report is intended to provide evidence and data that can help inform treatment guidelines and simultaneously illustrate national trends in transmitted drug resistance over time.

## Data Tables

This section highlights the main findings related to the number and distribution of transmitted drug resistance from specimens submitted through the Canadian HIV Strain and Drug Resistance Surveillance (SDR) Program. The data presented in this report are derived from specimens collected from ART-naïve individuals who received their first time diagnosis of HIV infection. In addition, these results reflect only those individuals for whom sufficient sera were available for testing and for whom successive genotyping was successful.

Specimens were obtained from 5,646 of 14,839 (38.0%) persons newly diagnosed with HIV and reported in 6 provinces during the time period of 1999 to 2008. Among them, 4,521 samples (80.2%) had sufficient specimen volume to successfully complete the analysis of genotypic drug resistance (Table 2.1). Of these, 442 (9.8%) were found to have one or more drug resistance mutations (as per the updated mutation list published by Bennett et al[1]).

[1] Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, et al. Drug Resistance Mutations for Surveillance of Transmitted HIV-Drug Resistance: 2009 Update. *PLos ONE* 4(3): e4724. doi:101371/journal.pone.0004724.

## Table 2.1: Number of specimens with successful genotyping results, by year of diagnosis and province

| Year of diagnosis | Number of specimens with successful genotyping results | | | | | | |
|---|---|---|---|---|---|---|---|
| | British Columbia | Alberta | Manitoba | Nova Scotia | Ontario | Saskatchewan | Total |
| 1999 | 158 | 55 | 49 | 9 | 1 | 26 | 298 |
| 2000 | 262 | 107 | 42 | 1 | 8 | 11 | 431 |
| 2001 | 237 | 45 | 35 | 2 | 2 | 18 | 339 |
| 2002 | 294 | 97 | 42 | 12 | 1 | 20 | 466 |
| 2003 | 199 | 84 | 81 | 16 | 37 | 34 | 451 |
| 2004 | 330 | 33 | 81 | 27 | 116 | 49 | 636 |
| 2005 | 203 | 57 | 97 | 19 | 22 | 79 | 477 |
| 2006 | 253 | 73 | 58 | 14 | 0 | 61 | 459 |
| 2007 | 300 | 88 | 23 | 14 | 0 | 100 | 525 |
| 2008 | 215 | 81 | 0 | 12 | 0 | 131 | 439 |
| Total | 2451 | 720 | 508 | 126 | 187 | 529 | 4521 |

## Table 2.2: Number and percentage of samples with transmitted drug resistance among 4521 newly diagnosed, treatment-naïve individuals, 1999-2008

| Drug class | Frequency | Percent (%) |
|---|---|---|
| NRTI [1] only | 169 | 3.7 |
| NNRTI[2] only | 143 | 3.2 |
| PI[3] only | 85 | 1.9 |
| NNRTI/NRTI | 25 | 0.6 |
| PI/NNRTI | 6 | 0.1 |
| PI/NRTI | 11 | 0.2 |
| PI/NNRTI/NRTI | 3 | 0.1 |
| Overall drug resistance | 442 | 9.8 |

[1] Nucleoside reverse transcriptase inhibitors

[2] Non-nucleoside reverse transcriptase inhibitors

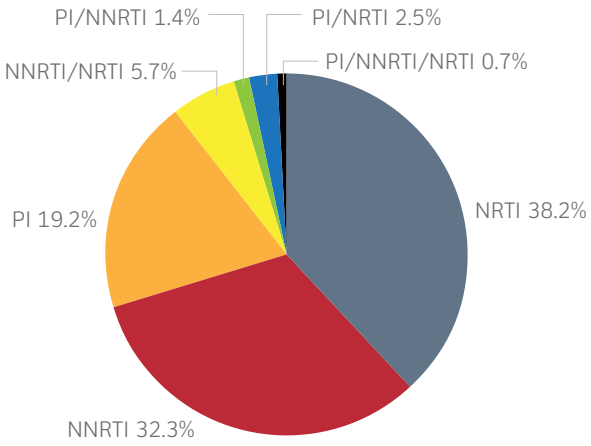
[3] Protease inhibitors

Table 2.2 presents the number and percentage of transmitted drug resistance among newly diagnosed, treatment-naïve individuals from January 1, 1999 to December 31, 2008. 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 drug resistance were present in 9.8% of the population analyzed. Mutations associated with resistance to nucleoside reverse transcriptase inhibitors (NRTIs) alone were identified among 169 (3.7%) of specimens, non-nucleoside reverse transcriptase inhibitors (NNRTIs) resistance alone among 143 (3.2%) of specimens, and protease inhibitors (PIs) resistance alone among 85 (1.9%) of individuals of the specimens analyzed. Of all samples, 45 (1.0%) were infected with multidrug resistant HIV-1. Multidrug resistance (MDR) was defined as mutations associated with resistance to at least two of the three classes of antiretroviral drugs.

Transmitted drug resistance to any of the three evaluated antiretroviral drug classes were as follows: 208 (4.6%) had transmitted drug resistance to any NRTIs, 173 (3.8%) had transmitted drug resistance for any NNRTIs, and 105 (2.3%) had transmitted drug resistance to any PIs.

## Figure 2.1: Distribution of transmitted drug resistance by drug class, 1999-2008




NRTI: Nucleoside reverse transcriptase inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, PI: Protease inhibitors.

Figure 2.1 presents the distribution of transmitted drug resistance among newly diagnosed, treatment-naïve individuals for years 1999 to 2008. As depicted, resistance only to nucleoside reverse transcriptase inhibitors (NRTI) and resistance only to non-nucleoside reverse transcriptase inhibitors (NNRTI) comprised the largest proportion of all specimens with drug resistance, at 38.2% and 32.4%, respectively. MDR comprised 10.3% of resistant specimens (NNRTI/NRTI: 5.7%, PI/NRTI: 2.5%, PI/NNRTI: 1.4% and PI/NNRTI/NRTI: 0.7%).

## Table 2.3: Mutations in sequences with resistance to associated drug class, 1999-2008

| Anti-retroviral drug | Mutation(s) | Number of specimens (% of drug class)* |
|---|---|---|
| NRTI[1] | | 208 |
| | M41L | 116 (55.8%) |
| | K65R | 3 (1.4%) |
| | D67G | 1 (0.5%) |
| | D67N | 11 (5.3%) |
| | T69D | 9 (4.3%) |
| | K70R | 4 (1.9%) |
| | L74I | 1 (0.5%) |
| | V75A | 1 (0.5%) |
| | V75I | 1 (0.5%) |
| | F77L | 1 (0.5%) |
| | Y115F | 1 (0.5%) |
| | F116Y | 2 (1.0%) |
| | K129E | 1 (0.5%) |
| | K129Q | 13 (6.3%) |
| | K129R | 2 (1.0%) |
| | Q151M | 3 (1.4%) |
| | M184I | 4 (1.9%) |
| | M184V | 19 (9.1%) |
| | L201L | 1 (0.5%) |
| | L201W | 37 (17.8%) |
| | T215 revertants | 101 (48.6%) |

| Anti-retroviral drug | Mutation(s) | Number of specimens (% of drug class)* |
|---|---|---|
| NNRTI[2] | | 173 |
| | L100I | 3 (1.7%) |
| | K101E | 9 (5.2%) |
| | K103N | 90 (52.0%) |
| | K103S | 2 (1.2%) |
| | V106A | 1 (0.6%) |
| | Y181C | 12 (6.9%) |
| | Y181I | 1 (0.6%) |
| | Y188H | 1 (0.6%) |
| | Y188L | 4 (2.3%) |
| | G190A | 49 (28.3%) |
| | G190E | 4 (2.3%) |
| | G190S | 9 (5.2%) |
| | P225H | 4 (2.3%) |
| | M230L | 1 (0.6%) |
| PI[3] | | 105 |
| | D30N | 1 (1.0%) |
| | V32I | 2 (1.9%) |
| | M46I | 27 (25.7%) |
| | M46L | 26 (24.8%) |
| | I47V | 1 (1.0%) |
| | G48V | 1 (1.0%) |
| | I50V | 4 (3.8%) |
| | F53L | 1 (1.0%) |
| | F53Y | 1 (1.0%) |
| | I54T | 1 (1.0%) |
| | I54V | 1 (1.0%) |
| | G73S | 1 (1.0%) |
| | V82A | 2 (1.9%) |
| | V82F | 2 (1.9%) |
| | V82T | 1 (1.0%) |
| | I84V | 2 (1.9%) |
| | N88D | 2 (1.9%) |
| | L90M | 31 (29.5%) |

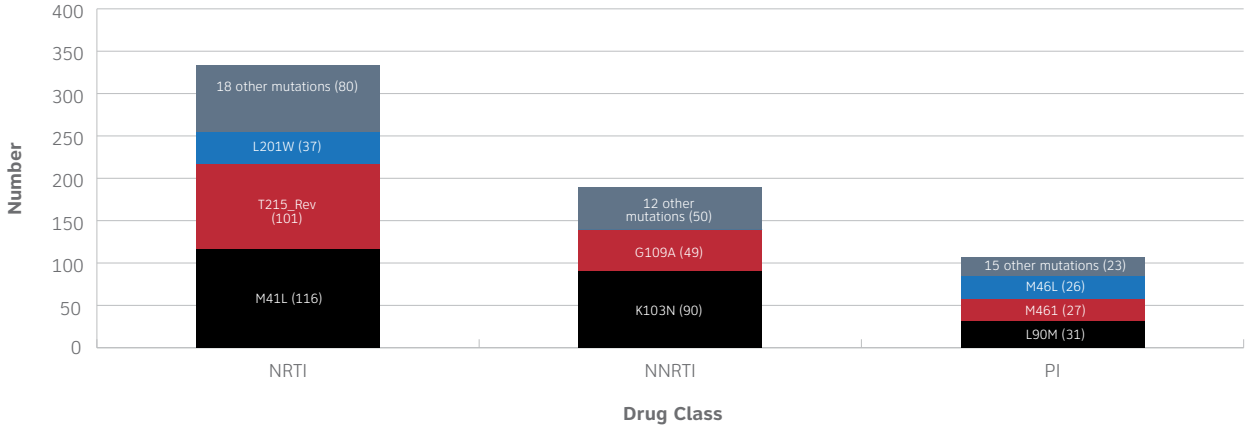
[1] NRTI refers to nucleoside reverse transcriptase inhibitor.

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

[3] PI refers to protease inhibitor.

*Persons with multiple mutations have been counted more than once, as such the total number of mutations presented here will add up to greater than the total of all samples analyzed.

## Figure 2.2: Transmitted drug resistance by drug class, 1999-2008




As shown in Table 2.3, the majority of mutations by drug class were observed in NRTI (208), followed by NNRTI (173), and lastly, PI (105). Within these transcriptase and protease groups, certain mutations were observed in greater proportions, as depicted in Figure 2.2. In particular, the M41L (55.8%) and T215 revertants (48.6%) were most predominant, followed by L201W (17.8%) in NRTI, while K103N (52.0%) and G109A (28.3%) mutations were the most predominant mutations in NNRTI. Lastly, L90M (29.5%), M46L (25.7%) and M46I (24.8%) mutations were the predominant mutations in PI.

## Table 2.4: Distribution of transmitted drug resistance among newly diagnosed, treatment-naïve individuals, by year of diagnosis

| Year of diagnosis | Number of specimens | Transmitted drug resistance | | | | |
|---|---|---|---|---|---|---|
| | | NRTI[1] only | NNRTI[2] only | PI[3] only | MDR[4] | Overall drug resistance |
| | | n (%) | n (%) | n (%) | n (%) | n (%) |
| 1999 | 298 | 16 (5.4) | 0 (0.0) | 5 (1.7) | 3 (1.0) | 24 (8.1) |
| 2000 | 431 | 18 (4.2) | 2 (0.5) | 6 (1.4) | 4 (0.9) | 30 (7.0) |
| 2001 | 339 | 16 (4.7) | 7 (2.1) | 6 (1.8) | 3 (0.9) | 32 (9.5) |
| 2002 | 466 | 10 (2.1) | 13 (2.8) | 10 (2.1) | 6 (1.3) | 39 (8.3) |
| 2003 | 451 | 12 (2.7) | 9 (2.0) | 12 (2.7) | 4 (0.9) | 37 (8.2) |
| 2004 | 636 | 23 (3.6) | 19 (3.0) | 11 (1.7) | 8 (1.3) | 61 (10.0) |
| 2005 | 477 | 14 (2.9) | 20 (4.2) | 7 (1.5) | 7 (1.5) | 48 (10.3) |
| 2006 | 459 | 24 (5.2) | 12 (2.6) | 10 (2.2) | 3 (0.7) | 49 (10.7) |
| 2007 | 525 | 17 (3.2) | 32 (6.1) | 12 (2.3) | 2 (0.4) | 63 (12.0) |
| 2008 | 439 | 19 (4.3) | 29 (6.6) | 6 (1.4) | 5 (1.1) | 59 (13.4) |
| Total | 4521 | 169 (3.7) | 143 (3.2) | 85 (1.9) | 45 (1.0) | 442 (9.8) |

[1] Nucleoside reverse transcriptase inhibitor

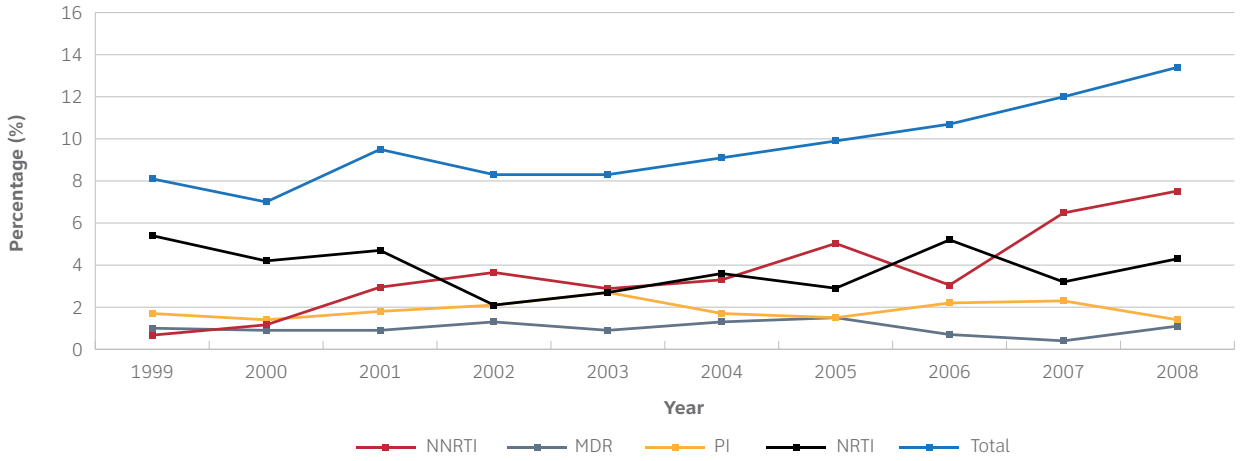
[2] Non-nucleoside reverse transcriptase inhibitor

[3] Protease inhibitors

[4] Multi-drug resistance includes mutations in HIV-1 that are associated with resistance to any two or three of the three classes of antiretroviral drugs (NRTI, NNRTI and PI).

Table 2.4 displays the number and percentage of transmitted drug resistance in the analyzed population, by year of HIV diagnosis. Overall drug resistance increased over the time period, while each drug class exhibited some year-to-year fluctuation. Some of the increase observed for the time period 2004-2008 was likely due to an increase primarily in the province of Saskatchewan during each of those years. Geographical variations are shown below in Figures 2.4-2.7.

## Figure 2.3: Prevalence of transmitted drug resistance, by drug class and year of diagnosis




The proportion of overall transmitted drug resistance increased significantly during the time period 1999-2008 (p value <0.001). Specifically, the proportion of NNRTI increased significantly during 1999-2008 (p value <0.0001); however, the proportion of NRTI, PI and MDR had no overall change during the same time period (p value 0.78, 0.85 and 0.65 respectively, Figure 2.3). The increase over time was primarily due to unique increases observed within the province of Saskatchewan during these years. The geographical variation of resistance trends over time to individual antiretroviral drug classes are shown in Figures 2.4-2.7.

## Table 2.5: Distribution of transmitted drug resistance, by province, 1999-2008

| Province | Number of specimens | Transmitted drug resistance | | | | |
|---|---|---|---|---|---|---|
| | | NRTI[1] only | NNRTI[2] only | PI[3] only | MDR[4] | Overall drug resistance |
| | | n (%) | n (%) | n (%) | n (%) | n (%) |
| British Columbia | 2451 | 71 (2.9) | 75 (3.1) | 37 (1.5) | 15 (0.6) | 198 (8.1) |
| Alberta | 720 | 18 (2.5) | 10 (1.4) | 18 (2.5) | 11 (1.5) | 57 (7.9) |
| Saskatchewan | 529 | 23 (4.3) | 47 (8.9) | 7 (1.3) | 3 (0.6) | 80 (15.1) |
| Manitoba | 508 | 43 (8.5) | 7 (1.4) | 22 (4.3) | 6 (1.2) | 78 (15.4) |
| Ontario | 187 | 7 (3.7) | 3 (1.6) | 0 (0.0) | 7 (3.7) | 17 (9.0) |
| Nova Scotia | 126 | 7 (5.5) | 1 (0.8) | 1 (0.8) | 3 (2.4) | 12 (9.5) |
| Total | 4521 | 169 (3.7) | 143 (3.2) | 85 (1.9) | 45 (1.0) | 442 (9.8) |

[1] Nucleoside reverse transcriptase inhibitor

[2] Non-nucleoside reverse transcriptase inhibitor

[3] Protease inhibitors

[4] Multi-drug resistance includes mutations in HIV-1 that are associated with resistance to any two or three of the three classes of antiretroviral drugs (NRTI, NNRTI and PI).

Table 2.5 presents the number and percentage of overall transmitted drug resistance, as well as as resistance by antiretroviral drug class among newly diagnosed, treatment-naïve cases by province from 1999 to 2008. There was some variation by year and jurisdiction, demonstrated in Figures 2.4-2.7 in this section.

*Secular Trend Analysis by Province*

Due to small specimen numbers or incomplete data from study years in some provinces, the analyses below are limited to the provinces of Alberta, British Columbia, Manitoba, and Saskatchewan.

## Figure 2.4: Percentage of overall drug resistance by year and province

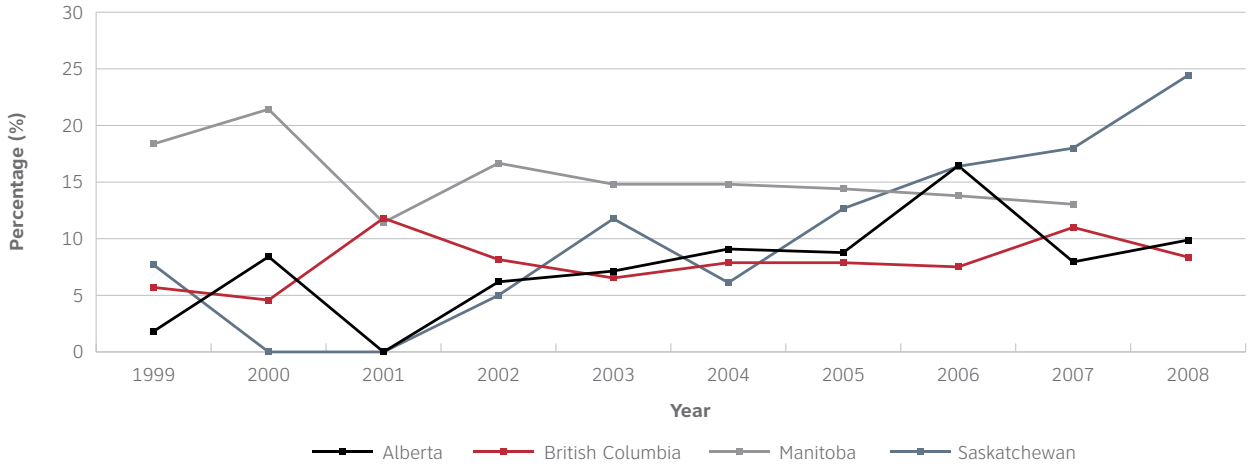
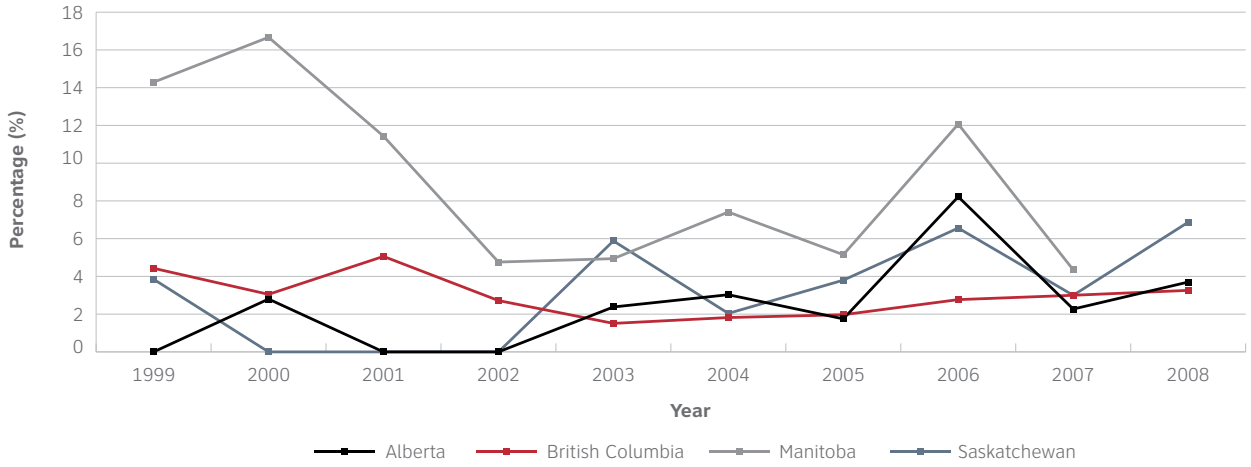


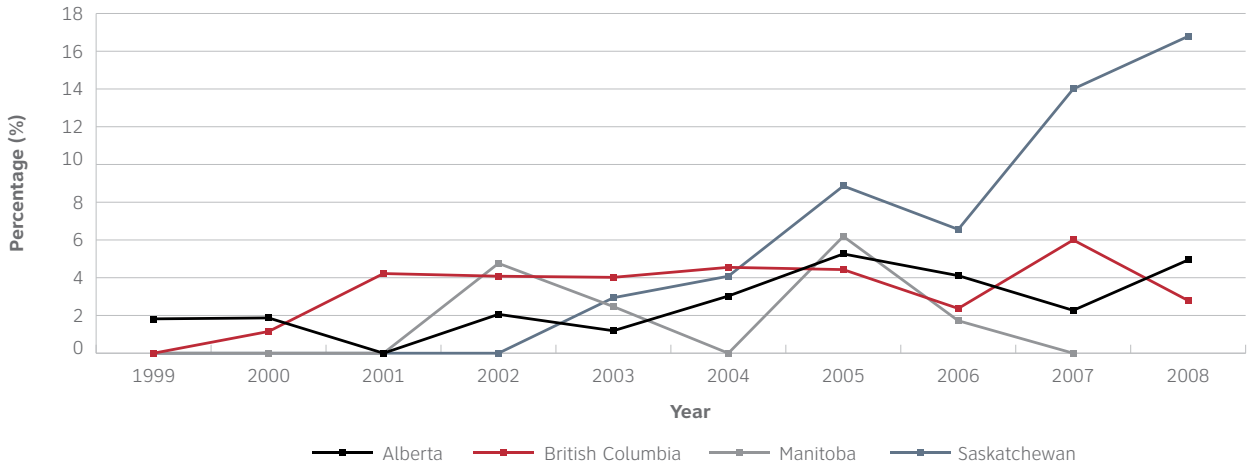

Figure 2.4 illustrates the percentage of overall transmitted drug resistance among newly diagnosed, treatment-naïve individuals by year and province from 1999 to 2008. The proportion of overall transmitted drug resistance increased significantly in Alberta during 1999-2008 (p value 0.02) and Saskatchewan during 1999-2008 (p value <0.0001); however, there was no change in British Columbia during 1999-2008 (p value 0.13) or in Manitoba during 1999-2007 (p value 0.28).

## Figure 2.5: Percentage of NRTI drug resistance by year and province



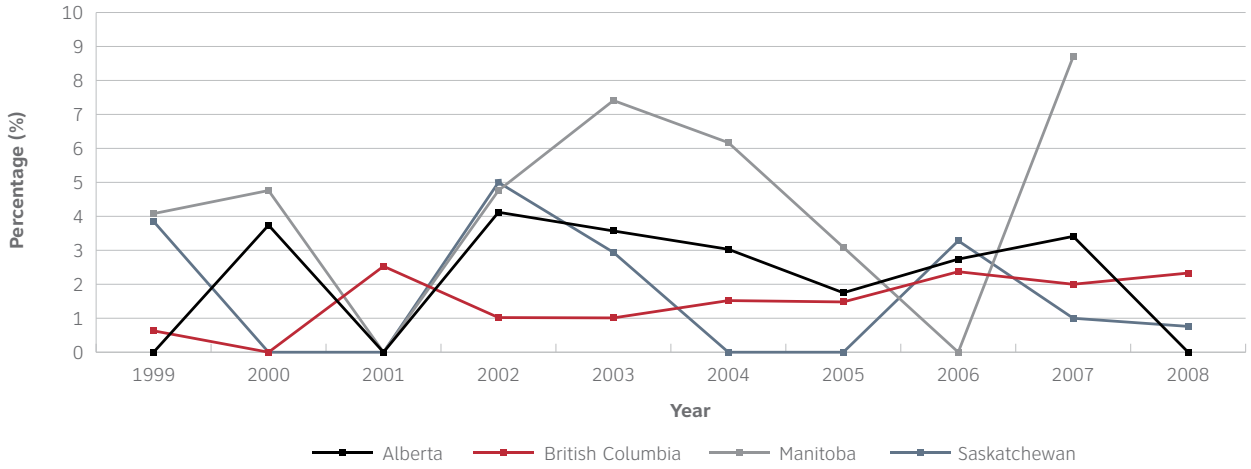

Regarding the percentage of NRTI drug resistance by year and province from 1999 to 2008 (Figure 2.5), the proportion increased significantly in Alberta (p value 0.04), while there was no change in British Columbia (p value 0.30), Manitoba (p value 0.06) or Saskatchewan (p value 0.14).

## Figure 2.6: Percentage of NNRTI drug resistance by year and province




As shown in Figure 2.6, the percentage of NNRTI drug resistance significantly increased over time in Saskatchewan (p value <0.0001) and British Columbia (p value 0.03), while no change was observed in Alberta (p value 0.09) or Manitoba (p value 0.22).

## Figure 2.7: Percentage of PI drug resistance by year and province




As shown in Figure 2.7, the percentage of PI drug resistance significantly increased over time only in British Columbia (p value 0.04); there was no change observed in Alberta (p value 0.69), Manitoba (p value 0.88) or Saskatchewan (p value 0.33).

No change was observed in MDR during 1999-2008 in any of these four provinces (p value 0.26, 0.06, 0.76 and 0.51 for Alberta, British Columbia, Manitoba and Saskatchewan, respectively).

## Table 2.6: Distribution of transmitted drug resistance, by age group, 1999-2008

| Age group (years) | Number of specimens | Transmitted drug resistance | | | | |
|---|---|---|---|---|---|---|
| | | NRTI[1] only | NNRTI[2] only | PI[3] only | MDR[4] | Overall drug resistance |
| | | n (%) | n (%) | n (%) | n (%) | n (%) |
| <15 | 27 | 1 (3.7) | 0 (0.0) | 0 (0.0) | 1 (3.7) | 2 (7.4) |
| 15-19 | 85 | 3 (3.5) | 8 (9.4) | 2 (2.4) | 2 (2.4) | 15 (17.7) |
| 20-29 | 934 | 33 (3.5) | 31 (3.3) | 22 (2.4) | 7 (0.8) | 93 (10.0) |
| 30-39 | 1574 | 67 (4.3) | 44 (2.8) | 21 (1.3) | 19 (1.2) | 151 (9.6) |
| 40-49 | 1250 | 43 (3.4) | 44 (3.5) | 25 (2.0) | 11 (0.9) | 123 (9.8) |
| 50+ | 647 | 21 (3.2) | 16 (2.5) | 15 (2.3) | 5 (0.8) | 57 (8.8) |
| Total | 4517 | 168 (3.7) | 143 (3.2) | 85 (1.9) | 45 (1.0) | 441 (9.8) |

[1] Nucleoside reverse transcriptase inhibitor

[2] Non-nucleoside reverse transcriptase inhibitor

[3] Protease inhibitors

[4] Multi-drug resistance includes mutations in HIV-1 that are associated with resistance to at least two of the three classes of antiretroviral drugs (NRTI, NNRTI and PI).

Table 2.6 presents the number and percentage of overall transmitted drug resistance, as well as resistance by antiretroviral drug class among newly diagnosed, treatment-naïve individuals by age group from 1999 to 2008. Overall, the largest proportion was found in the 15-19 age group (17.7%), while the lowest was observed in the <15 age group (7.4%). The main difference observed among age groups was specific to NNRTI resistance (9.4% of NNRTI resistance occurred in the 15-19 age group, compared to 0% in the <15 age group and 2.5-3.5% in the others). This apparent high rate among young people may be unreliable due to the small number of specimens in younger age groups; in addition the number of specimens among young people was predominantly from Saskatchewan, which further biases the already small sample size.

## Table 2.7: Distribution of transmitted drug resistance by sex, 1999-2008

| Sex | Number of specimens | Transmitted drug resistance | | | | |
|---|---|---|---|---|---|---|
| | | NRTI[1] only | NNRTI[2] only | PI[3] only | MDR[4] | Overall drug resistance |
| | | n (%) | n (%) | n (%) | n (%) | n (%) |
| Male | 3353 | 139 (4.1) | 87 (2.6) | 59 (1.8) | 29 (0.9) | 314 (9.4) |
| Female | 1159 | 30 (2.6) | 56 (4.8) | 26 (2.2) | 16 (1.4) | 128 (11.0) |
| Total | 4512 | 169 (3.7) | 143 (3.2) | 85 (1.9) | 45 (1.0) | 442 (9.8) |

[1] Nucleoside reverse transcriptase inhibitor

[2] Non-nucleoside reverse transcriptase inhibitor

[3] Protease inhibitors

[4] Multi-drug resistance includes mutations in HIV-1 that are associated with resistance at least two of the three classes of antiretroviral drugs (NRTI, NNRTI and PI).

Table 2.7 presents the number and percentage of overall transmitted drug resistance, as well as resistance by antiretroviral drug class by sex, from 1999-2008. Overall, a greater proportion of females had drug resistance (11.0%) compared to males (9.4%). It is important to note that this trend differed for NRTI resistance, where the proportion among males was higher than in females (4.1% vs. 2.6%).

## Table 2.8: Distribution of transmitted drug resistance by exposure category, 1999-2008

| Risk exposure | Number of specimens | Transmitted drug resistance | | | | |
|---|---|---|---|---|---|---|
| | | NRTI[1] only | NNRTI[2] only | PI[3] only | MDR[4] | Overall drug resistance |
| | | n (%) | n (%) | n (%) | n (%) | n (%) |
| MSM[5] | 1474 | 77 (5.2) | 32 (2.2) | 19 (1.3) | 14 (1.0) | 142 (9.6) |
| MSM/IDU | 142 | 7 (4.9) | 3 (2.1) | 2 (1.4) | 0 (0.0) | 12 (8.4) |
| IDU[6] | 1358 | 33 (2.4) | 75 (5.5) | 26 (1.9) | 10 (0.7) | 144 (10.6) |
| Heterosexual/Endemic[7] | 235 | 6 (2.6) | 0 (0.0) | 5 (2.1) | 5 (2.1) | 16 (6.8) |
| Heterosexual/Non-endemic[8] | 1021 | 30 (3.0) | 29 (2.8) | 29 (2.8) | 13 (1.3) | 101 (9.9) |
| Others[9] | 89 | 3 (3.4) | 1 (1.1) | 1 (1.1) | 1 (1.1) | 6 (6.7) |
| Total | 4319 | 156 (3.6) | 140 (3.2) | 82 (1.9) | 43 (1.0) | 421 (9.8) |

[1] Nucleoside reverse transcriptase inhibitor

[2] Non-nucleoside reverse transcriptase inhibitor

[3] Protease inhibitors

[4] Multi-drug resistance includes mutations in HIV-1 that are associated with resistance to at least two of the three classes of antiretroviral drugs (NRTI, NNRTI and PI).

[5] MSM refers to men who have sex with men.

[6] IDU refers to injecting drug use.

[7] Heterosexual/Endemic refers to reported heterosexual contact and origin from a country where HIV is endemic (defined as having an adult prevalence of HIV that is 1.0% or greater and where heterosexual sex is the main mode of transmission).

[8] Heterosexual/Non-Endemic refers to reported heterosexual contact with a person who is either HIV- infected or at increased risk of HIV infection (e.g. person who injects drugs, bisexual male, etc.), or reported heterosexual contact as the only identified risk.

[9] Others refer to recipients of blood transfusion or clotting factor, perinatal and occupational transmission, as well as cases in which the mode of transmission is known but cannot be classified into any of the major exposure categories.

Table 2.8 displays the number and percentage of overall transmitted drug resistance, as well as resistance by antiretroviral drug class by exposure category from 1999 to 2008. In total, the largest proportion was observed in the IDU category (10.6%), while the smallest was found in the Heterosexual/Endemic category (6.8%). Heterosexual/Non-endemic and MSM had the second and third highest proportion of drug resistance (9.9 and 9.6% respectively). The main drug resistance for cases with reported risk exposure category of MSM or MSM/IDU was NRTI (5.2% and 4.9% respectively), while NNRTI resistance was predominant among cases attributed to IDU (5.5%). Among cases in the Heterosexual/Endemic category, there was no resistance to NNRTI and similar proportions of resistance to NRTI (2.6%) and PI (2.1%), while cases in the Heterosexual/Non-endemic category were found to have similar levels of resistance to the three individual drug classes (NRTI: 3.0%, NNRTI: 2.8% and PI: 2.8%).

## Table 2.9: Distribution of transmitted drug resistance by race/ethnicity, 1999-2008

| Race/Ethnicity | Number of specimens | Transmitted drug resistance | | | | |
|---|---|---|---|---|---|---|
| | | NRTI[1] only | NNRTI[2] only | PI[3] only | MDR[4] | Overall drug resistance |
| | | n (%) | n (%) | n (%) | n (%) | n (%) |
| White | 2453 | 103 (4.2) | 65 (2.6) | 36 (1.5) | 26 (1.1) | 230 (9.4) |
| Black | 403 | 8 (2.0) | 4 (1.0) | 7 (1.7) | 6 (1.5) | 25 (6.2) |
| Asian | 140 | 6 (4.3) | 1 (0.7) | 2 (1.4) | 0 (0.0) | 9 (6.4) |
| Aboriginal total | 1068 | 34 (3.2) | 59 (5.5) | 31 (2.9) | 9 (0.8) | 133 (12.5) |
| First Nations | 741 | 22 (3.0) | 48 (6.5) | 16 (2.1) | 6 (0.8) | 92 (12.4) |
| Inuit | 4 | 0 (0.0) | 1 (25.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) |
| Métis | 108 | 2 (1.9) | 3 (2.8) | 3 (2.8) | 2 (1.8) | 10 (9.3) |
| Unspecified | 215 | 10 (4.6) | 7 (3.3) | 12 (5.6) | 1 (0.5) | 30 (14.0) |
| Arab/South/West Asian | 97 | 3 (3.1) | 2 (2.1) | 1 (1.0) | 0 (0.0) | 6 (6.2) |
| Latin American | 116 | 4 (3.4) | 6 (5.2) | 3 (2.6) | 1 (0.9) | 14 (12.1) |
| Other | 21 | 1 (4.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.8) |
| Total | 4298 | 159 (3.7) | 137 (3.2) | 80 (1.9) | 42 (1.0) | 418 (9.7) |

[1] Nucleoside reverse transcriptase inhibitor

[2] Non-nucleoside reverse transcriptase inhibitor

[3] Protease inhibitors

[4] Multi-drug resistance includes mutations in HIV-1 that are associated with resistance to at least two of the three classes of antiretroviral drugs (NRTI, NNRTI and PI).

## Figure 2.8: Percentage of transmitted drug resistance by race/ethnicity, 1999-2008

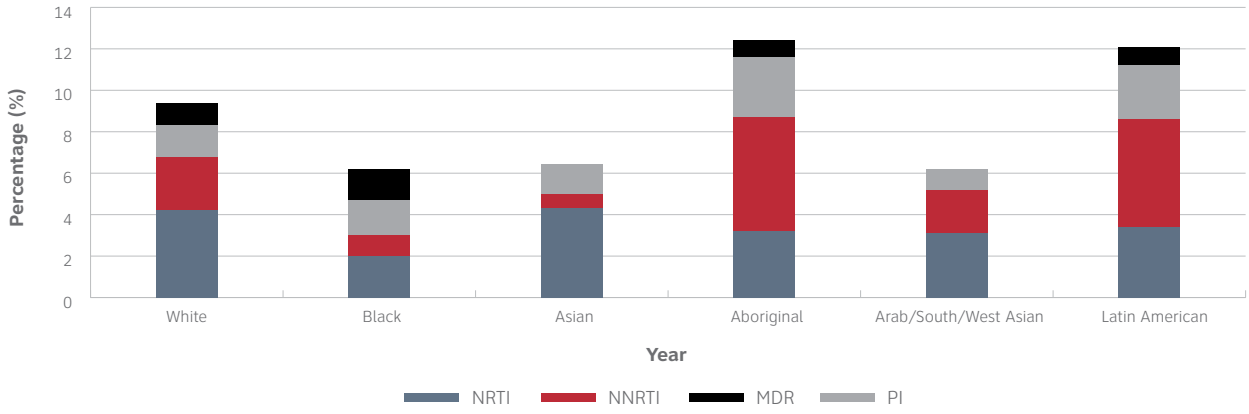



Table 2.9 and Figure 2.8 display transmitted drug resistance by race/ethnicity during 1999-2008. During this time period, the largest proportion was observed in cases identified as Aboriginal (12.5%), the majority of which were attributed to the Aboriginal-Unspecified category. The Latin American category comprised the second highest proportion, at 12.1%, followed by the White category (9.4%). Smaller proportions of cases identified as Asian, Arab or Black had drug resistance (6.4%, 6.2% and 6.2%, respectively).

## Table 2.10: Distribution of transmitted drug resistance by HIV-1 subtype, 1999-2008

| Subtype | Number of specimens | Transmitted drug resistance | | | | |
|---|---|---|---|---|---|---|
| | | NRTI[1] only | NNRTI[2] only | PI[3] only | MDR[4] | Overall drug resistance |
| | | n (%) | n (%) | n (%) | n (%) | n (%) |
| B | 3979 | 159 (4.0) | 140 (3.5) | 75 (1.9) | 39 (1.0) | 413 (10.4) |
| Non-B | 539 | 9 (1.7) | 3 (0.6) | 10 (1.9) | 6 (1.1) | 28 (5.2) |
| C | 286 | 4 (1.4) | 1 (0.4) | 2 (0.7) | 6 (2.1) | 13 (4.6) |
| A | 84 | 3 (3.5) | 2 (2.4) | 2 (2.4) | 0 (0.0) | 7 (8.3) |
| CRF02_AG | 55 | 1 (1.8) | 0 (0.0) | 1 (1.8) | 0 (0.0) | 2 (3.6) |
| CRF01_AE | 47 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| D | 25 | 0 (0.0) | 0 (0.0) | 3 (12.0) | 0 (0.0) | 3 (12.0) |
| G | 16 | 0 (0.0) | 0 (0.0) | 1 (7.1) | 0 (0.0) | 1 (7.1) |
| Others | 32 | 1 (3.1) | 0 (0.0) | 1 (3.1) | 0 (0.0) | 2 (6.2) |
| Total | 4518 | 168 (3.7) | 143 (3.2) | 85 (1.9) | 45 (1.0) | 441 (9.8) |

[1] Nucleoside reverse transcriptase inhibitor

[2] Non-nucleoside reverse transcriptase inhibitor

[3] Protease inhibitors

[4] Multi-drug resistance includes mutations in HIV-1 that are associated with resistance to any two or three of the three classes of antiretroviral drugs (NRTI, NNRTI and PI).

Table 2.10 displays transmitted drug resistance by HIV subtype during 1999-2008. Persons infected with subtype B had a higher proportion of overall drug resistance (10.4%) compared to those with non-B subtypes (5.2%). The most common drug resistance in individuals infected with subtype B was NRTI (4.0%), followed by NNRTI (3.5%) and PI (1.9%). The most common drug resistance in individuals infected with non-B subtypes was PI (1.9%), followed by NRTI (1.7%); very few cases were resistant to NNRTI (0.6%).

## Table 2.11: Distribution of transmitted drug resistance by recent versus established infection, 1999-2008

| Time of infection[5] | Number of specimens | Transmitted drug resistance | | | | |
|---|---|---|---|---|---|---|
| | | NRTI[1] only | NNRTI[2] only | PI[3] only | MDR[4] | Overall drug resistance |
| | | n (%) | n (%) | n (%) | n (%) | n (%) |
| Recent infection | 1261 | 57 (4.5) | 64 (5.1) | 19 (1.5) | 17 (1.4) | 157 (12.5) |
| Established infection | 2886 | 94 (3.3) | 70 (2.4) | 57 (2.0) | 25 (0.9) | 246 (8.5) |
| Total | 4147 | 151 (3.6) | 134 (3.2) | 76 (1.8) | 42 (1.0) | 403 (9.7) |

[1] Nucleoside reverse transcriptase inhibitor.

[2] Non-nucleoside reverse transcriptase inhibitor.

[3] Protease inhibitors.

[4] Multi-drug resistance includes mutations in HIV-1 that are associated with resistance to any two or three of the three classes of antiretroviral drugs (NRTI, NNRTI and PI).

[5] Samples were tested using a serologic testing algorithm for recent HIV seroconversion and classified as recent infection (within 170 days prior to sample collection) or established infection (greater than 170 days) by one of three modified EIA tests (Abbott 3A11, bioMérieux Vironostika HIV-1-LS or Calypte BED assay).

Table 2.11 presents the number and percentage of transmitted drug resistance by time of infection, for samples from 1999-2008. Samples were tested using a serologic testing algorithm for recent HIV seroconversion and classified as recent infection (within 170 days prior to sample collection) or established infection (greater than 170 days) by one of three modified EIA tests (Abbot 3A11, bioMérieux Vironostika HIV-1-LS or Calypte BED assay). Overall, a greater proportion of cases with recent infection exhibited drug resistance (12.5%) compared to cases with established infection (8.5%).

# SECTION III: QUEBEC HIV DRUG RESISTANCE TESTING PROGRAM

## HIV-1 Subtypes and Primary Drug Resistance among treatment-naïve persons newly diagnosed with HIV in the Province of Quebec

## Data from the provincial HIV Drug Resistance Testing Program, 2001-2008

### Introduction

Genotyping is carried out as part of clinical follow-up of HIV-infected patients to determine resistance to antiretrovirals. In the event of therapeutic failure, genotyping serves as a valuable tool to guide clinicians in determining the optimal treatment strategy specific to the patient's HIV-1 resistance profile. In the province of Quebec, antiretroviral therapy is universally available for all HIV-infected persons.

In Quebec, HIV genotyping carried out as part of routine clinical follow-up was initiated in October 2001 via a network of three laboratories located at the Hôpital Notre-Dame (HND) at the CHUM, the McGill AIDS Centre at the Jewish General Hospital (JGH) and the Laboratoire de santé publique du Québec (LSPQ). A clinical advisory committee is in place which determines indications for HIV genotyping and reviews the need to add new analytical tests to this program. Since 2001, clinical indications for HIV genotyping include therapeutic failure, perinatal transmission, pregnant women who test positive for HIV, and primary HIV infection. The latter is defined as a newly diagnosed HIV infection where seroconversion likely occurred in the six months prior to collection of the diagnostic specimen. In 2004, genotyping was initiated for patients with established HIV infection for the purpose of assessing antiretroviral resistance in treatment-naïve individuals who have been seropositive for at least six months.

### Methodology

The three laboratories in the network use standardized gene amplification equipment and sequencing methods. From October 2001 to May 2004 and from September 2006 to December 2008, the Quebec program issued drug resistance reports from virtual phenotyping (VirtualPhenotype or vircoTYPE, Virco) using analytic methods developed by Virco. From June 2004 to August 2006, drug resistance was interpreted using the analytic methods associated with the TRUGENE HIV-1 assay (Bayer HealthCare).

Despite the decentralized nature of testing, genotyping data as well as interpretation of antiretroviral resistance results generated by the three laboratories are compiled in a unique data bank (pgDB). Non-nominal sociodemographic data, clinical information pertaining to the prescribed genotyping test, and measures of HIV viral load are added to the genotyping results. Viral load may be assessed using the same sample submitted for genotyping, or may have been carried out on a previous sample up to two months prior to the genotyping test. Initially, a 1,000 copies/mL cut-off value was set as the minimum required viral load for genotyping; however, this was adjusted to 400 copies/mL in 2004. Provision of clinical and viral load data is not a mandatory requirement for genotyping to be carried out.

During the time period when the Virco assay was used, resistance interpretation reports were accompanied by an analysis of the HIV subtype. However, when the TRUGENE HIV-1 kit was used, the subtype was determined by comparing the sequence of the *Pol* gene to the reference sequences provided in the HIV Sequence Database at the Los Alamos National Laboratory (Los Alamos, NM). This process was centralized. Where no association between a specific sequence (as determined by Virco or LSPQ) and a reference sequence could be made, the result was deemed as "indeterminate".

Overall, the provincial program database serves as a management and internal quality control tool. Analytical data are captured directly from results provided by sequencing assays, while resistance interpretations are obtained from secondary reports. Sociodemographic data are requested by each of the laboratories on a retroactive basis and are integrated into the pgDB according to a predetermined schedule. Each centre uses a unique identifier to track records. As these data are non-nominal, it is not possible to identify patients who are tested more than once. Procedures pertaining to the integrated management of laboratory analyses, such as periodic archiving, also limit the ability to monitor individual patient results over time.

For the above reasons and in an attempt to exclude duplicates, data presented in this report are based on selective extracts from the pgDB. Data have been refined based on comparisons of unique identifiers, date of birth, HIV subtypes, resistance profiles and nucleotide sequences. For example, where nucleotide sequences from patients with the same date of birth had less than a 2.0% difference, only the earlier sequence was included for analysis. Comparison of resistance profiles enabled validation of the cases selected. The same methodology is routinely used to detect and control cross-contamination in laboratories. Although not perfect, this method enables a certain degree of precision in identifying the first genotyping test carried out for a patient by the provincial program. Results presented by year are based on the date of specimen collection.

## Results

### Distribution of HIV Subtypes

The data presented in this section are based on drug resistance reports from the first HIV genotyping test carried out by the Quebec program for each patient registered in the pgDB. All patients who were clinically eligible for HIV genotyping were included.

Table 3.1 shows that a variety of HIV subtypes circulated in the province of Québec during the period studied, but B subtypes predominated (88.4%). Since 2001, there was a slow but steady increase in the proportion of non-B subtypes among persons treated with antiretrovirals and monitored through genotype testing. However, among non-B subtypes, there was no increase in any particular subtype in relation to other subtypes over time (Table 3.2). The proportion of sequenced isolates accounted for by subtype C specimens was 6.6% in 2005, but this decreased in subsequent years. The proportion of A and AE subtypes have increased since 2002, and represented over 5% of samples sequenced in 2008.

Almost 80% of genotyping tests were carried out among men (Table 3.3). This proportion is comparable to the distribution of HIV cases by sex in Quebec during the period studied. The proportion of B subtypes was higher among men (94.0%) compared to women (67.6%). The prevalence of non-B subtypes was five times higher among women than in men.

The distribution of subtypes by age group is presented in Table 3.4. There was a difference in the proportion of non-B subtypes among younger compared to older persons. The proportion of non-B subtypes decreased with age, from 35.0% in children under 15 to 5.2% among persons aged 60 years or older. There was a decrease in the prevalence of the non-B subtypes in each age group among persons under 50 years of age.

### Primary HIV-1 drug resistance

Transmission of antiretroviral resistant HIV is concerning from a clinical point of view because it is associated with reduced treatment options for patients. Transmission of drug resistant strains also complicates the selection of appropriate medication for postexposure prophylaxis. The distribution of transmitted drug resistance is presented in Table 3.5. Results in this section are based on samples from patients who have never been on antiretroviral treatment. Only patients for whom HIV genotyping was indicated as a result of a new HIV diagnosis (recent or established) or perinatal transmission were included in order to exclude patients who were not treatment-naïve. Resistance to antiretrovirals was assessed by the presence of primary mutations as per the World Health Organization's *List of mutations for surveillance of transmitted drug resistant HIV: 2009 update* (Bennett et al). These mutations are considered to be induced specifically by antiretroviral treatment. Mutations associated with HIV-1 subtype polymorphisms were excluded from this list.

During the study period, the majority (88.6%) of the genotyped specimens were wild-type (Table 3.5). Mutations conferring resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) were most common among drug resistant specimens. Multidrug resistance (MDR; viruses with mutations conferring resistance to at least two classes of drugs), was identified in 0.4% of genotyped specimens. The presence of mutations conferring antiretroviral resistance in persons who have never received treatment suggests that transmission of drug resistant HIV is occurring.

There was no trend in the proportion of specimens with transmitted drug resistance over time (Table 3.6). However, transmitted drug resistance was higher among children and young adults: 19.2% of specimens among adolescents aged 15 to 19 years had antiretroviral resistance. Among adults aged 30 years or older, the proportion with transmitted drug resistance was approximately 10% (Table 3.7). Transmission of MDR strains was highest among persons aged 20 to 39 years.

Table 3.8 shows the distribution of transmitted drug resistance in pre-treatment specimens of persons with recent compared to established HIV infection. The proportion with resistant strains was similar in both groups. Mutations associated with NNRTI resistance were more common among recent infections, whereas those associated with NRTI resistance were higher among established infections.

## Discussion and Conclusion

To place the Quebec data presented in this report in proper context, it is important to reiterate that in Quebec, samples submitted for HIV genotyping are not usually the same specimens as those collected for laboratory confirmation of HIV infection. In addition, HIV-positive persons may be asymptomatic and only become aware of their serostatus several years later. From the time of infection to the initiation of antiretroviral treatment, some mutations associated with drug resistance, especially those that reduce viral fitness may disappear from circulating subtypes in the absence of selective pressure exercised by drugs. For example, the M184V mutation, which confers resistance to lamivudine, quickly disappears after treatment is stopped. On the other hand, mutations in positions 103, 181 and 190 that are induced by NNRTIs may persist for several months or years, even in the absence of selective pressure.

In summary, aggregate data presented by the Quebec provincial program on HIV drug resistance testing show an evolving distribution of HIV subtypes. Subtype B was most prevalent among adults over 50 years of age; however, the relative proportion decreased in younger age groups. This coincides with evolution of the HIV epidemic over the past decade, which has been impacted by changes in patterns of HIV transmission and international travel. Transmitted drug resistance did not appear to increase during the period studied. New treatment options that facilitate compliance, as well as the introduction of new classes of drugs will likely contribute to a reduction in therapeutic failure, which in turn may decrease the transmission of antiretroviral resistant viruses. Nonetheless, continued epidemiological monitoring is essential as it allows for improvement in treatment options for postexposure prophylaxis.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### Distribution of HIV-1 Subtypes

## Table 3.1: Distribution of HIV-1 subtypes among antiretroviral treatment-naive persons newly diagnosed with HIV in Quebec, 2001-2008

| HIV-1 subtype | Number | Proportion (%) | % in non-B samples |
|---|---|---|---|
| B | 5324 | 88.4 | - |
| C | 255 | 4.2 | 36.5 |
| A/AE | 168 | 2.8 | 24.1 |
| AG | 120 | 2.0 | 17.2 |
| D | 49 | 0.8 | 7.0 |
| F | 14 | 0.2 | 2.0 |
| G | 26 | 0.4 | 3.7 |
| H | 5 | < 0.1 | 0.7 |
| K | 6 | < 0.1 | 0.9 |
| Others CRF[1] | 36 | 0.6 | 5.1 |
| Indet. (non-B) | 19 | 0.3 | 2.7 |
| Total | 6022 | | |

[1] CRF refers to recombinant forms

## Table 3.2: Number and proportion of HIV-1 subtypes by year of first genotyping test

| | HIV-1 subtype | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | B (%) | C | A/AE | AG | D | F | G | H | K | Others CRF[1] | Indet. | Total |
| Before 2002 | 255 (92.1) | 5 | 6 | 5 | 3 | 1 | 1 | 0 | 0 | 0 | 1 | 277 |
| 2002 | 833 (93.0) | 25 | 17 | 10 | 3 | 0 | 5 | 0 | 0 | 1 | 2 | 896 |
| 2003 | 675 (89.3) | 40 | 11 | 13 | 6 | 1 | 3 | 0 | 1 | 3 | 3 | 756 |
| 2004 | 677 (85.4) | 52 | 22 | 11 | 8 | 1 | 5 | 1 | 1 | 8 | 7 | 793 |
| 2005 | 678 (89.2) | 35 | 19 | 11 | 7 | 1 | 3 | 1 | 0 | 4 | 1 | 760 |
| 2006 | 711 (86.2) | 33 | 23 | 26 | 12 | 3 | 3 | 1 | 0 | 8 | 5 | 825 |
| 2007 | 757 (87.6) | 34 | 27 | 22 | 8 | 1 | 4 | 2 | 3 | 6 | 0 | 864 |
| 2008 | 738 (86.7) | 31 | 43 | 22 | 2 | 6 | 2 | 0 | 1 | 6 | 0 | 851 |
| Total | 5,324 (88.4) | 255 | 168 | 120 | 49 | 14 | 26 | 5 | 6 | 36 | 19 | 6,022 |

[1] CRF refers to recombinant forms

## Table 3.3: Number and proportion of HIV-1 subtypes by sex and year

| | HIV-1 subtype | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | B (%) | C | A/AE | AG | D | F | G | H | K | Others CRF[1] | Indet. | Total |
| Men | 4,465 (94.0) | 111 | 73 | 48 | 12 | 8 | 12 | 1 | 2 | 10 | 11 | 4,753 |
| Women | 833 (67.6) | 141 | 90 | 72 | 36 | 6 | 14 | 4 | 4 | 24 | 8 | 1,232 |
| Unknown | 26 (70.3) | 3 | 5 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 37 |
| Total | 5,324 (88.4) | 255 | 168 | 120 | 49 | 14 | 26 | 5 | 6 | 36 | 19 | 6,022 |

[1] CRF refers to recombinant forms

## Table 3.4: Number and proportion of HIV-1 subtypes by age group

| | HIV-1 subtype | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age group** | **B (%)** | **C** | **A/AE** | **AG** | **D** | **F** | **G** | **H** | **K** | **Others CRF[1]** | **Indet.** | **Total** |
| <15 | 63 (65.0) | 15 | 8 | 5 | 1 | 1 | 2 | 0 | 0 | 1 | 1 | 97 |
| 15-19 | 38 (71.7) | 5 | 3 | 1 | 2 | 2 | 0 | 0 | 0 | 1 | 1 | 53 |
| 20-29 | 537 (78.4) | 53 | 35 | 31 | 10 | 2 | 6 | 1 | 0 | 9 | 2 | 685 |
| 30-39 | 1,603 (86.2) | 86 | 58 | 50 | 14 | 7 | 11 | 3 | 4 | 14 | 9 | 1,859 |
| 40-49 | 2,055 (92.5) | 69 | 47 | 24 | 13 | 1 | 3 | 1 | 1 | 6 | 2 | 2,222 |
| 50-59 | 796 (93.8) | 14 | 12 | 8 | 8 | 1 | 4 | 0 | 0 | 3 | 3 | 849 |
| 60+ | 220 (94.8) | 4 | 5 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 232 |
| Total | 5,312 (88.6) | 246 | 167 | 120 | 48 | 14 | 26 | 5 | 5 | 35 | 19 | 5,997 |

[1] CRF refers to recombinant forms

### Primary HIV-1 drug resistance

## Table 3.5: Number and proportion of specimens by transmitted drug resistance category, September 2001-December 2008

| Transmitted drug resistance | Number | Proportion (%) |
|---|---|---|
| Wild type[1] | 1,715 | 88.6 |
| NRTI[2] | 46 | 2.4 |
| NNRTI[3] | 98 | 5.1 |
| PI[4] | 30 | 1.5 |
| NNRTI/NRTI | 20 | 1.0 |
| PI/NNRTI | 4 | 0.2 |
| PI/NRTI | 15 | 0.8 |
| MDR[5] | 8 | 0.4 |
| Total | 1,936 | 100 |

[1] No major mutations associated with drug resistance were identified.

[2] Nucleoside reverse transcriptase inhibitor

[3] Non-nucleoside reverse transcriptase inhibitor

[4] Protease inhibitor

[5] Multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to at least two of the three classes of antiretroviral drugs (NRTIs, NNRTIs and protease inhibitors).

## Table 3.6: Distribution of transmitted drug resistance among treatment-naïve individuals, by year, September 2001-December 2008

| | Transmitted drug resistance | | | | | |
|---|---|---|---|---|---|---|
| **Year** | **Wild type[1] (%)** | **NRTI[2]** | **NNRTI[3]** | **PI[4]** | **MDR[5]** | **Total** |
| Sept-Dec 2001 | 10 (76.9) | 0 | 0 | 0 | 3 | 13 |
| 2002 | 70 (88.6) | 2 | 3 | 1 | 3 | 79 |
| 2003 | 106 (84.1) | 3 | 8 | 3 | 6 | 126 |
| 2004 | 165 (88.7) | 3 | 12 | 4 | 2 | 186 |
| 2005 | 221 (88.4) | 5 | 13 | 6 | 5 | 250 |
| 2006 | 318 (88.3) | 14 | 14 | 2 | 12 | 360 |
| 2007 | 376 (89.5) | 7 | 23 | 6 | 8 | 420 |
| 2008 | 449 (89.4) | 12 | 25 | 8 | 8 | 502 |
| Total | 1,715 (88.6) | 46 | 98 | 30 | 47 | 1,936 |

[1] No major mutations associated with drug resistance were identified.

[2] Nucleoside reverse transcriptase inhibitor

[3] Non-nucleoside reverse transcriptase inhibitor

[4] Protease inhibitor

[5] Multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to at least two of the three classes of antiretroviral drugs (NRTIs, NNRTIs and protease inhibitors).

## Table 3.7: Distribution of transmitted drug resistance among treatment-naïve individuals, by age group

| | Transmitted drug resistance | | | | | |
|---|---|---|---|---|---|---|
| **Age group** | **Wild type[1] (%)** | **NRTI[2]** | **NNRTI[3]** | **PI[4]P** | **MDR[5]** | **Total (%)** |
| <15 | 9 (80.8) | 0 | 1 | 0 | 1 | 11 (19.2) |
| 15-19 | 15 (80.0) | 0 | 2 | 1 | 1 | 19 (20.0) |
| 20-29 | 286 (85.1) | 8 | 27 | 3 | 12 | 336 (14.9) |
| 30-39 | 549 (88.4) | 17 | 28 | 12 | 15 | 621 (11.6) |
| 40-49 | 587 (90.3) | 15 | 30 | 10 | 8 | 650 (9.7) |
| 50-59 | 199 (88.8) | 6 | 7 | 3 | 9 | 224 (11.2) |
| 60+ | 58 (92.1) | 0 | 3 | 1 | 1 | 63 (7.9) |
| Total | 1,703 (88.5) | 46 | 98 | 30 | 47 | 1,924 (11.5) |

[1] No major mutations associated with drug resistance were identified.

[2] Nucleoside reverse transcriptase inhibitor

[3] Non-nucleoside reverse transcriptase inhibitor

[4] Protease inhibitor

[5] Multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to at least two of the three classes of antiretroviral drugs (NRTIs, NNRTIs and protease inhibitors).

## Table 3.8: Distribution of transmitted drug resistance by recent versus established infection, 2001-2008

| | Transmitted drug resistance | | | | | |
|---|---|---|---|---|---|---|
| **Time of infection** | **Wild type[1] (%)** | **NRTI[2]** | **NNRTI[3]** | **PI[4]** | **MDR[5]** | **Total** |
| Recent infection | 806 (87.1) | 17 | 62 | 17 | 23 | 925 |
| Established infection | 909 (89.9) | 29 | 36 | 13 | 24 | 1,011 |
| Total | 1,715 (88.6) | 46 | 98 | 30 | 47 | 1,936 |

[1] No major mutations associated with drug resistance were identified.

[2] Nucleoside reverse transcriptase inhibitor

[3] Non-nucleoside reverse transcriptase inhibitor

[4] Protease inhibitor

[5] Multi-drug resistance and includes mutations in HIV-1 that are associated with resistance to at least two of the three classes of antiretroviral drugs (NRTIs, NNRTIs and protease inhibitors).

# SECTION IV: SUMMARIES OF KEY SDR STUDIES

## Table 4.1: 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 (NRTI) | 1.9 | 0.2 | 3.5 |
| BC[2] | 1997-1998 | Mixed | 479 | 3.4 | 3.8 | 0.2 | 6.3 |
| BC[3] | 1996-2007 | IDU | 128 | 1.6 (NRTI)<br>3.1(NNRTI) | None | None | 4.7 |
| QC[4] | 1997 | MSM (54.4%) | 50 | 12 (NRTI)<br>0 (NNRTI) | 5 | ~5 | 14.0 |
| | 1998 | | 42 | ~5 (NRTI)<br>0 (NNRTI) | 0 | 0 | - |
| | 1999 | | 17 | ~18 (NRTI)<br>~13 (NNRTI) | ~18 | ~12 | 23.5 |
| | 2000 | | 18 | ~12 (NRTI)<br>~6 (NNRTI) | ~6 | ~5 | 11.1 |
| | 2001 | | 18 | 0 (NRTI)<br>0 (NNRTI) | ~6 | 0 | 5.6 |
| | 2002 | | 18 | 0 (NRTI)<br>~6 (NNRTI) | ~0 | 0 | 5.6 |
| | 2003 | | 17 | 0 (NRTI)<br>0 (NNRTI) | 0 | 0 | 0.0 |
| QC[5] | 1997-2005 | Mixed | 230 | - | - | - | 8.0 |
| Canada[6] | 2004 | Mixed | 537 | - | - | - | 9.7 |
| BC, AB, SK, MB[7] | 2000-2001 | Mixed | 715 | 4.1 (NRTI)<br>1.4 (NNRTI) | 1.5 | 1.0 | 8.1 |
| BC, AB, SK, MB, ON, NS[8] | 1996 | Mixed | 35 | 8.6 (NRTI)<br>0 (NNRTI) | 5.7 | 14.3 | 28.6 |
| | 1997 | | 38 | 0 | 0 | 0 | 0 |
| | 1998 | | 88 | 3.4 (NRTI)<br>0 (NNRTI) | 1.1 | 0 | 4.5 |
| | 1999 | | 307 | 5.9 (NRTI)<br>0.3 (NNRTI) | 1.6 | 1.0 | 8.8 |
| | 2000 | | 440 | 3.9 (NRTI)<br>0.5 (NNRTI) | 1.1 | 1.1 | 6.6 |
| | 2001 | | 349 | 4.6 (NRTI)<br>2.3 (NNRTI) | 1.7 | 1.1 | 9.7 |
| | 2002 | | 160 | 1.2 (NRTI)<br>1.9 (NNRTI) | 4.4 | 1.9 | 9.3 |
| | 2003 | | 241 | 3.3 (NRTI)<br>2.1 (NNRTI) | 4.6 | 0.8 | 10.8 |
| | 2004 | | 611 | 3.3 (NRTI)<br>2.8 (NNRTI) | 1.6 | 1.3 | 9.0 |
| | 2005 | | 49 | 6.1 (NRTI)<br>2.0 (NNRTI) | 2.0 | 6.1 | 16.3 |
| | 1996-2005 | | 2318 | 3.9 (NRTI)<br>1.6 (NNRTI) | 2.1 | 1.4 | 9.0 |

* BC=British Columbia, QC=Quebec, 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

† Sample size consists of those who were successfully genotyped.

‡ 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 4.2: 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* | SampleSize** | RTIs† (%) | PIs‡ (%) | MDR§ (%) | Total (%) |
|---|---|---|---|---|---|---|---|
| United States[1] | 1989-1998 | MSM (80%) | 141 | 3.0 (NRTI)<br>17 (NNRTI) | 10.0 | 2.0 | 26.0 |
| United States[2] | 1995-1999 | MSM (94%) | 80 | 12.5 (NRTI)<br>7.5 (NNRTI) | 2.5 | 3.8 | 16.3 |
| United States[3] | 1997-2001 | Mixed | 1082 | 6.4 (NRTI)<br>1.7 (NNRTI) | 1.9 | 1.3 | 8.3 |
| United States[4] | 1998 | Mixed | 238 | 3.4 (NRTI)<br>0.4 (NNRTI) | 0 | 0 | 3.8 |
| | 1999 | | 240 | 8.3 (NRTI)<br>2.1 (NNRTI) | 1.7 | 1.7 | 10.0 |
| | 2000 | | 245 | 6.9 (NRTI)<br>1.2 (NNRTI) | 2 | 1.2 | 9.0 |
| | 1998-2000 | | 723 | 6.2 (NRTI)<br>1.2 (NNRTI) | 1.2 | 1.0 | 7.6 |
| United States[5] | 2003-2004 | Mixed | 539 | 7.1 (NRTI)<br>9.1 (NNRTI) | 3.2 | 3.2 | 15.2 |
| United States<br>(with samples from Canada)[6] | 1995-1998 | Mixed | 213 | 8.5 (NRTI)<br>1.7 (NNRTI) | 0.9 | 3.8 | 8.0 |
| | 1999-2000 | | 88 | 15.9 (NRTI)<br>7.3 (NNRTI) | 9.1 | 10.2 | 22.7 |
| | 1995-2000 | | 301 | 10.9 (NRTI)<br>3.5 (NNRTI) | 3.3 | 5.6 | 12.3 |
| United States[7] | 1996-1997 | Mixed | 40 | 25.0 (NRTI)<br>0.0 (NNRTI) | 2.5 | 2.5 | 25.0 |
| | 1998-1999 | | 94 | 7.4 (NRTI)<br>6.4 (NNRTI) | 5.3 | 1.1 | 18.1 |
| | 2000-2001 | | 91 | 20.9 (NRTI)<br>13.2 (NNRTI) | 7.7 | 14.3 | 27.4 |
| | 1996-2001 | | 225 | 16.0 (NRTI)<br>8.0 (NNRTI) | 5.8 | 6.7 | 23.1 |
| United States[8] | 2004 | Youth | 55 | 4.0 (NRTI)<br>15 (NNRTI) | 4.0 | 2.0 | 18.0 |
| United States[9] | 1995-1998 | MSM (97%) | 76 | 11.8 (NRTI)<br>2.6 (NNRTI) | 1.3 | 2.6 | 13.2 |
| | 1999-2000 | | 71 | 15.5 (NRTI)<br>5.5 (NNRTI) | 5.6 | 5.6 | 19.7 |
| | 2001-2002 | | 102 | 8.8 (NRTI)<br>7.8 (NNRTI) | 4.9 | 3.9 | 16.7 |
| | 2003-2004 | | 112 | 16.1 (NRTI)<br>13.4 (NNRTI) | 7.1 | 9.8 | 24.1 |
| | 1995-2004 | | 361 | 13.1 (NRTI)<br>8.0 (NNRTI) | 5.0 | 5.8 | 18.8 |

| Country | Year of diagnosis | Risk Exposures* | SampleSize** | RTIs† (%) | PIs‡ (%) | MDR§ (%) | Total (%) |
|---|---|---|---|---|---|---|---|
| United States[10] | 2004 | Mixed | 129 | 6.2(NRTI)<br>8.5 (NNRTI) | 2.3 | 3.1 | 13.2 |
| United States [11] | 1997-1999 | MSM (84%) | 69 | 4 (NRTI)<br>2.9 (NNRTI) | - | - | 7 |
| United States [12] | 1999-2003 | MSM | 195 | 8.7 (NRTI)<br>6.7(NNRTI) | 5.6 | 3.6 | 15.9 |
| United States [13] | 2004 | Mixed | 22 | 4.5 (NRTI)<br>9.1 (NNRTI) | | 13.6 | 27.3 |
| United States [14] | 2002-2006 | MSM | 117 | - | - | | 12.5 |
| United States [15] | 1998-1999 | Mixed | 199 | 14.0(NRTI)<br>16.0 (NNRTI) | 3.0 | - | - |
| United States [16] | 1999-2001 | MSM (69%) | 491 | 7.8 (NRTI)<br>3.0 (NNRTI) | 0.7 | 0.7 | 11.6 |
| United States[17] | 2003 | Mixed | 317 | 3.0 (NRTI)<br>6.0 (NNRTI) | 2.0 | none | 10.0 |
| United States [18] | 2005 | Mixed | 103 | *30.1 (NRTI)<br>*22.3 (NNRTI) | *5.8 | 6.8 | 25.0 |
| United States [19] | 1998-2007 | Mixed | 253 | 7.5 (NRTI)<br>9.5 (NNRTI) | 3.2 | 2.4 | 17.8 |
| United States[20] | 2002 | MSM (96%) | 372 | 6 (NRTI)<br>~6 (NNRTI) | 15 | - | 19 |
| | 2003 | | | 4 (NRTI)<br>~3 (NNRTI) | ~4 | - | 7 |
| | 2004 | | | ~7 (NRTI)<br>~5 (NNRTI) | ~4 | - | ~12 |
| | 2005 | | | ~14 (NRTI)<br>~9 (NNRTI) | ~5 | - | ~21 |
| | 2006 | | | 16 (NRTI)<br>~4 (NNRTI) | ~7 | - | ~20 |
| | 2007 | | | ~8 (NRTI)<br>13 (NNRTI) | ~6 | - | 24 |
| | 2008 | | | ~3 (NRTI)<br>~10 (NNRTI) | ~5 | - | 15 |
| | 2009 | | | 11 (NRTI)<br>8 (NNRTI)* | ~6 | - | 15 |
| | 2002-2009 | | | - | - | - | 16 |
| United States[21] | 2006 | Mixed | 1997 | 5.6 (NRTI)<br>7.8 (NNRTI) | 4.5 | 2.6 | 14.6 |
| Germany [22] | 1996-1999 | Mixed | 64 | 6.3 (NRTI)<br>3.1 (NNRTI) | 1.6 | 1.6 | 12.5 |

| Country | Year of diagnosis | Risk Exposures* | SampleSize** | RTIs† (%) | PIs‡ (%) | MDR§ (%) | Total (%) |
|---|---|---|---|---|---|---|---|
| Germany[23] | 2001 | Mixed | 83 | ~4.5 (NRTI) | 0.0 | 0.0 | - |
| | 2002 | | 123 | ~5.8 (NRTI)<br>~2.5 (NNRTI) | ~2.0 | ~2.0 | - |
| | 2003 | | 138 | ~4.2 (NRTI)<br>~3.8 (NNRTI) | ~3.0 | ~1.8 | - |
| | 2004 | | 242 | ~7.0 (NRTI)<br>~3.2 (NNRTI) | ~3.5 | ~2.0 | - |
| | 2005 | | 245 | ~5.0 (NRTI)<br>~4.0 (NNRTI) | ~2.8 | ~1.5 | - |
| | 2001-2005 | | 831 | 5.4 (NRTI)<br>3.0 (NNRTI) | 2.4 | 1.3 | 9.0 |
| Germany [24] | 2001-2003 | Mixed | 269 | 8.6 (NRTI)<br>3.7 (NNRTI) | 1.5 | 1.5 | 11.2 |
| Germany[25] | 1999-2003 | Mixed | 49 | 12.2 (NRTI)<br>10.2 (NNRTI) | 2 | - | 20.4 |
| Germany[26] | 1996-2007 | MSM (88%) | 1276 | 7.5 (NRTI)<br>3.5 (NNRTI | 2.9 | 1.2 | 12.4 |
| Belgium[27] | 2000 | Mixed | 83 | 5 (NRTI)<br>2.5 (NNRTI) | 1.2 | 1.3 | 7.2 |
| Belgium[28] | 2003 | MSM (55%) | 73 | 5.5 (NRTI)<br>2.7 (NNRTI) | 1.4 | - | 6.8 |
| | 2004 | | 72 | 11.1 (NRTI)<br>6.9 (NNRTI) | 2.8 | - | 15.3 |
| | 2005 | | 79 | 6.3 (NRTI)<br>1.3 (NNRTI) | 0.0 | - | 6.3 |
| | 2006 | | 61 | 4.9 (NRTI)<br>3.3 (NNRTI) | 3.3 | - | 9.8 |
| | 2003-2006 | | 285 | 7.0 (NRTI)<br>3.5 (NNRTI | 1.8 | 2.4 | 9.5 |
| France[29] | 1995 | Mixed | 12 | 25.0 | 0.0 | - | 25.0 |
| | 1996 | | 14 | 21.4 | 0.0 | - | 21.4 |
| | 1997 | | 18 | 11.1 | 5.6 | - | 16.7 |
| | 1998 | | 4 | 0.0 | 0 | - | 0.0 |
| | 1995-1998 | | 48 | 17.0 | 2.0 | - | 18.7 |
| France[30] | 1999-2000 | Mixed | 251 | 8.0 (NRTI)<br>4.0 (NNRTI) | 5.0 | 5.0 | 10 |
| France[31] | 2001-2002 | Mixed | 666 | 2.4 (NRTI)<br>0.3 (NNRTI) | 1.2 | 7.2 | 11.3 |

| Country | Year of diagnosis | Risk Exposures* | SampleSize** | RTIs† (%) | PIs‡ (%) | MDR§ (%) | Total (%) |
|---|---|---|---|---|---|---|---|
| France[32] | 1999-2000 | Mixed | 249 | 8.0 (NRTI)<br>4.0 (NNRTI) | 6.0 | 5.0 | 10.0 |
| France[33] | 1996-2004 | Mixed | 518 | 5.2 (NRTI)<br>2.5 (NNRTI) | 4.4 | 3.1 | 8.5 |
| France[34] | 1996-1999 | Mixed | 204 | *12.7 (NRTI)<br>*8.8 (NNRTI) | *6.4 | 4.4 | 8.8 |
| France[35] | 1996-2005 | MSM (62%) | 172 | 11.6 (NRTI)<br>6.4 (NNRTI) | 4.1 | - | 13.4 |
| France [36] | 2003-2004 | Mixed | 323 | 6.0 (NRTI)<br>5.9(NNRTI | 3.4 | 3.0 | 12.3 |
| France[37] | 1987-1997 | Mixed | 90 | 5.6(NRTI) | - | - | - |
| France[38] | 1998 | Mixed | 391 | 3.3(NRTI)<br>0.8 (NNRTI) | 1.9 | 0.3 | 3.7 |
| France[39] | 2006-2007 | Mixed | 466 | 5.8 (NRTI)<br>2.8 (NNRTI) | 4.7 | - | 10.6 |
| Spain[40] | 1998 | Mixed | 52 | 17.0 ( NRTI) | 6.0 | 1.9 | - |
| Spain[41] | 1997-1999 | Mixed | 31 | 29.0.(NRTI)<br>3.2 (NNRTI) | 9.7 | 0 | 25.8 |
| | 2000-2001 | | 21 | 0 (NRTI)<br>0 (NNRTI) | 4.8 | 0 | 4.8 |
| Spain[42] | 2004 | Mixed | 182 | 2.2 (NRTI)<br>1.1 (NNRTI) | 0.5 | 0.6 | 3.8 |
| Spain[43] | 1997 | Mixed | 9 | 33.3 (NRTI)<br>0 (NNRTI) | 0 | - | 33.3 |
| | 1998 | | 17 | 29.4 (NRTI)<br>5.9 (NNRTI) | 5.9 | - | 29.4 |
| | 1999 | | 5 | 20 (NRTI)<br>0 (NNRTI) | 0 | - | 20 |
| | 2000 | | 7 | 0 (NRTI)<br>0 (NNRTI) | 14.3 | - | 14.3 |
| | 2001 | | 30 | 3.3 (NRTI)<br>0 (NNRTI) | 0 | - | 3.3 |
| | 2002 | | 28 | 10.7 (NRTI)<br>3.6 (NNRTI) | 3.6 | - | 14.3 |
| | 2003 | | 50 | 8 (NRTI)<br>4 (NNRTI) | 0 | - | 10.0 |
| | 2004 | | 52 | 3.8 (NRTI)<br>7.7 (NNRTI) | 2.0 | - | 7.7 |
| | Total | | 198 | 9.6 (NRTI)<br>4.0 (NNRTI) | 2.0 | - | 12.1 |

| Country | Year of diagnosis | Risk Exposures* | SampleSize** | RTIs† (%) | PIs‡ (%) | MDR§ (%) | Total (%) |
|---|---|---|---|---|---|---|---|
| Switzerland[44] | 1996 | Mixed | 35 | 5.6 | 3.0 | - | 8.6 |
| | 1997 | | 41 | 6.9 | 7.7 | - | 14.6 |
| | 1998 | | 60 | 6.8 | 2.0 | - | 8.8 |
| | 1999 | | 61 | 3.1 | 1.9 | - | 5.0 |
| | 1996-1999 | | 197 | - | - | - | 8.8 |
| Switzerland[45] | 1999-2001 | Mixed | 200 | 7.0(NRTI)<br>0.5 (NNRTI) | 1.0 | 1.5 | 10.0 |
| Switzerland[46] | 1999-2001 | Mixed | 225 | 8.6 (NRTI)<br>0.9 (NNRTI) | 2.3 | 1.4 | 10.5 |
| Switzerland[47] | 1996-2005 | Mixed | 822 | 5.5 (NRTI)<br>1.9 (NNRTI | 2.7 | 2.0 | 7.7 |
| Netherlands[48] | 1994 | MSM (56%) | 13 | ~22.5 (NRTI)<br>~9.0 (NNRTI) | 0.0 | 0.0 | - |
| | 1995 | | 12 | ~16.0 (NRTI)<br>0.0 (NNRTI) | ~8.0 | 0.0 | - |
| | 1996 | | 13 | ~15.0 (NRTI)<br>0.0 (NNRTI) | 0.0 | 0.0 | - |
| | 1997 | | 12 | ~8.0 (NRTI)<br>0.0 (NNRTI) | 0.0 | 0.0 | - |
| | 1998 | | 7 | 0.0 (NRTI)<br>0.0 (NNRTI) | 0.0 | 0.0 | - |
| | 1999 | | 10 | ~10.0 (NRTI)<br>0.0 (NNRTI) | 0.0 | 0.0 | - |
| | 2000 | | 7 | 0.0 (NRTI)<br>0.0 (NNRTI) | 0.0 | 0.0 | - |
| | 2001 | | 10 | ~9.0 (NRTI)<br>~11.0 (NNRTI) | 0.0 | 0.0 | - |
| | 2002 | | 16 | 0.0 (NRTI)<br>0.0 (NNRTI) | 0.0 | 0.0 | - |
| | 1994-2002 | | 100 | 10.0 (NRTI)<br>2.0 (NNRTI) | 1.0 | 0.0 | 13.0 |
| United Kingdom[49] | 1996-2000 | Mixed | 60 | 5 (NRTI)<br>6.7 (NNRTI | 1.7 | - | 7.0 |

| Country | Year of diagnosis | Risk Exposures* | SampleSize** | RTIs† (%) | PIs‡ (%) | MDR§ (%) | Total (%) |
|---|---|---|---|---|---|---|---|
| United Kingdom[50] | 1996-1997 | Mixed | 310 | ~7 (NRTI)<br>~1 (NNRTI) | ~1 | - | ~8.5 |
| | 1998 | | 340 | ~8 (NRTI)<br>~2 (NNRTI) | ~3 | - | ~10 |
| | 1999 | | 358 | ~10 (NRTI)<br>~5 (NNRTI) | ~2.5 | - | ~11 |
| | 2000 | | 457 | ~9 (NRTI)<br>~5 (NNRTI) | ~3.5 | - | ~14 |
| United Kingdom[51] | 2001 | Mixed | 516 | ~9 (NRTI)<br>~5 (NNRTI) | ~4 | - | ~13 |
| | 2002 | | 520 | ~11.5 (NRTI)<br>~6.5 (NNRTI) | ~5 | - | ~16 |
| | 2003 | | 764 | ~7.5 (NRTI)<br>~6 (NNRTI) | ~3 | - | ~12.5 |
| | 2004 | | 1185 | ~4 (NRTI)<br>~4 (NNRTI) | ~2.5 | - | ~9 |
| | 2004-2005 | | 180 | 3.3 (NRTI)<br>2.8 (NNRTI) | 1.7 | 0.6 | 7.2 |
| United Kingdom [52] | 1996-2003 | Mixed | 2357 | 9.9 (NRTI)<br>4.5 (NNRTI) | 4.6 | 3.3 | 14.2 |
| United Kingdom[53] | 2005-2006 | Mixed | 149 | 3.4 (NRTI)<br>4.7 (NNRTI) | 0.7 | 0.7 | 9.4 |
| Italy[54] | 1996-2001 | Mixed | 112 | 11.6 (NRTI)<br>0.9 (NNRTI) | 2.7 | 1.8 | 16.1 |
| Italy [55] | 1996-2007 | Mixed | 1690 | 11.0 (NRTI)<br>6.0 (NNRTI | 4 | 3.7 | 15.1 |
| Italy[56] | 2004-2008 | Mixed | 108 | 8.3 (NRTI)<br>10.2 (NNRTI | 2.8 | 7.4 | 15.7 |
| Portugal[57] | 2003 | Mixed | 180 | 3.9 (NRTI)<br>1.7 (NNRTI | - | 2.2 | 7.8 |
| Luxembourg[58] | 1983-2000 | Mixed | 299 | 9.8 (NRTI)<br>0.0 (NNRTI) | - | - | 2.2 |
| Europe/Canada[59] | 1987-1995 | Mixed | 69 | 2.9 (NRTI)<br>0 (NNRTI) | - | - | 2.9 |
| | 1996-1998 | | 145 | 7.6 (NRTI)<br>1.4 (NNRTI) | 2.1 | - | 10.3 |
| | 1999-2003 | | 224 | 5.4 (NRTI)<br>5.8 (NNRTI) | 4.5 | - | 12.5 |
| | <1996-2003 | | 438 | 5.7 (NRTI)<br>3.4 (NNRTI) | 3.0 | 1.2 | 10.3 |
| Europe[60] | 1996-2002 | Mixed | 2208 | 7.6 (NRTI)<br>2.9 (NNRTI) | 2.5 | 3.5 | 10.4 |
| Europe[61] | 2000-2004 | Mixed | 698 | 6.2 (NRTI)<br>4.0 (NNRTI) | 1.9 | - | 10.0 |

| Country | Year of diagnosis | Risk Exposures* | SampleSize** | RTIs† (%) | PIs‡ (%) | MDR§ (%) | Total (%) |
|---|---|---|---|---|---|---|---|
| Europe[62] | 2002-2003 | Mixed | 1050 | 5.4 (NRTI)<br>2.6 (NNRTI) | 3.0 | 1.4 | 9.1 |
| Europe & Israel[63] | 2002-2005 | Mixed | 2793 | 4.7 (NRTI)<br>2.3 (NNRTI) | 2.9 | 1.1 | 8.4 |

*Note: Drug resistance was reported for each drug class whenever possible. In some instances, there was some overlap among the study sample participants, as a participant may have had more than one resistant strain within the same drug class. In these circumstances, where we could not distinguish between the participant and the strain, we opted not to report the value. In other circumstances where the values were reported, we provided this caveat to interpret with caution as there may have been some overlap among the study sample.

**Sample size consists of those who were successfully genotyped.

† 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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# APPENDIX A: OVERVIEW OF THE CANADIAN HIV STRAIN AND DRUG RESISTANCE SURVEILLANCE PROGRAM

The Canadian HIV Strain and Drug Resistance Surveillance Program (SDR), initiated in 1998, is based in the Centre for Communicable Diseases and Infection Control (CCDIC) at the Public Health Agency of Canada in Ottawa, Ontario. It is a collaborative effort between six provinces in Canada, the CCDIC, and the National HIV and Retrovirology Laboratories. The SDR forms a key component in a national system for the enhanced surveillance of HIV/AIDS, emerging retroviruses, and other sexually transmitted blood-borne pathogens. 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. With both genetic and epidemiological components, its initial aim is to monitor and characterize the genetic diversity of HIV in Canada.

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 atypical test results, undertaking quality assurance, and monitoring diagnostic kits. Using knowledge of the circulating HIV strains, modifications can be made to current tests to ensure that testing accurately detects all HIV-positive individuals.

### 2) To inform vaccine development

The genetic diversity of HIV-1 is a major challenge to vaccine development. Information on the distribution of the viral subtypes can be used to target vaccine development and testing, since the efficacy and effectiveness of any vaccine that is developed would likely be subtype specific.

### 3) To assess genetic markers of HIV drug resistance

Highly active antiretroviral therapy (HAART) has significantly decreased mortality and morbidity among people with HIV type 1 (HIV-1) infection and is associated with a significant recovery of the compromised immune function. However, these benefits can be adversely affected by the development of drug-resistant forms of the 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 little consensus on whether differences in HIV subtypes 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, 2008, British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, and Nova Scotia currently participate 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 December 31, 2008. 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.

# APPENDIX B: 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 purpose of diagnostic testing was available to send to the National HIV and Retrovirology Laboratories (NHRL) and, of these, the subset for whom subtype analysis and/or primary drug resistance testing was performed by genotyping. The quality of samples received by the 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. Obtaining results was largely dependent on specimen quality, which includes antecedent storage conditions and specimen volume.

The epidemiologic data collected through the SDR Program contain information included in the National HIV/AIDS Case 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. 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 Public Health Agency of Canada's CCDIC.

### 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 Reports* detail this hierarchy and are available by contacting the CCDIC or by visiting its Web site at http://www.phac-aspc.gc.ca/aids-sida/publication/survreport/2009/dec/index-eng.php.

### Interpretation of Drug Resistance

Drug resistance for each specimen was obtained by analyzing the genotype and looking for mutations or genetic changes that result in drug resistance. There are a number of organizations that have produced lists of mutations, which based upon the interpretation of the evidence, confer resistance to various drugs (e.g. Stanford HIV Database, International AIDS Society, Agence nationale de recherches sur le SIDA, and the Rega Institute). In addition, there are commercial entities such as Monogram Biosciences and Virco that provide both interpretations and complete genotyping. As of 2009, the NHRL have exclusively used the Stanford Calibrated Population Resistance tool to measure drug resistance (http://cpr.stanford.edu/cpr/servlet/CPR). This database uses the World Health Organization's *List of mutations for surveillance of transmitted drug resistant HIV: 2009 update*, which is intended to provide a simple, unambiguous and standardized measure of transmitted drug resistance in HIV-1 (Bennett et al). The list is updated annually with the goal of ensuring that mutations present as polymorphisms in the population are not falsely counted as occurring as the result of drug exposure. Conversely, the list also identifies mutations that are of limited clinical significance but only arise in the setting of drug exposure. A common set of mutations, as defined in Bennett et al, was applied to all historical specimens and analyzed to determine trends over time.

**Reference**

Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, Kiuchi M, Heneine W, Kantor R, Jordan MR, Schapiro JM, Vandamme AM, Sandstrom P, Boucher CA, van de Vijver D, Rhee SY, Liu TF, Pillay D, Shafer RW. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. PLoS One. 2009;4(3):e4724. Epub 2009 Mar 6.

# APPENDIX C: 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 were provided to the Public Health Agency of Canada (PHAC) from provincial partners participating in the Canadian HIV Strain and Drug Resistance Surveillance (SDR) Program. Consequently, if serologic assays in the province failed to detect a new HIV variant, then the specimen was not sent to PHAC for analysis.

- The data are based on convenience sampling and, therefore, do not include all newly diagnosed cases in a given population for any specific year. Furthermore, there is variable representation in the SDR database among provinces, which hampers commentary on national rates of HIV drug resistance. Although no biases are anticipated as a result of the convenience sampling in individual provinces, it bears keeping 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 Quebec and may not be representative of all cases newly diagnosed in Ontario. Together, these two provinces represent about two thirds of reported HIV infections in Canada. Work is underway on mechanisms to include representative data from these provinces. In this report, we present a separate section (Section III) containing data from the Quebec program for HIV drug resistance testing, which describe the range of subtypes and primary drug resistance in this province.

- This report deals solely with transmitted drug resistance (i.e. resistance 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 British Columbia are likely to have been collected from individuals who have received treatment.

- Missing or unknown epidemiologic data remain problematic, particularly information on previous HIV testing, date of first positive HIV test, ethnicity, risk behaviour, CD4 and viral load at diagnosis, and previous antiretroviral treatment. To address this, the SDR Program validates cases with the participating provinces, regularly updating reported variables, and removing duplicates as well as cases that may not be new diagnoses.

- Subtype identification is performed on sequence from the *pol* gene. Subtypes A-H have *pol* sequences consistent with their subtype. This is probably true for most circulating recombinant forms. In cases where the laboratory encounters a non-identified subtype, other parts of the genome are analyzed to help with recombinant identification. However, there still remains the potential for misclassification of subtypes, especially in the case of novel recombinants.

- The initial serological assays (Abbott 3A11-LS™ or the bioMérieux Vironostika HIV-1-LS™) that were developed to detect recently acquired infections were based on subtype B-derived antigens and have been shown to occasionally misdiagnose incident non-B infections as established infections. The currently used HIV-1 BED Incidence assay is an IgG-capture EIA using a multi-subtype gp41 peptide and can be used for both subtype B and non-subtype B population studies. This assay still has limitations, and reviews of the accuracy of serological tests for recent infections have found that a significant percentage of people with long-term HIV infections (including AIDS) may be misclassified as recently infected. Efforts should be made to exclude people with AIDS or low CD4 counts to increase the predictive value.

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