



Primary HIV Antiretroviral Drug Resistance in Canada

At a Glance

- The Canadian HIV Strain and Drug Resistance Surveillance Program (SDR program) monitors and assesses HIV strains and the transmission of HIV drug resistance among individuals with newly diagnosed and not yet treated HIV infection in Canada.
- Preliminary observations from the SDR program of HIV drug resistance among treatment-naïve individuals with newly diagnosed HIV infection in Canada (i.e. primary drug resistance) are as follows:
 - The overall prevalence of primary drug resistance to at least one antiretroviral drug is 9%.
 - The overall prevalence of multidrug resistance to two or more classes of antiretroviral drugs is approximately 1%.
- Available data suggest that the prevalence of primary drug resistance in Canada is similar to that observed in other developed countries where highly active antiretroviral treatment is widely used.

Introduction

Highly-active antiretroviral therapy (HAART) has significantly decreased mortality and morbidity among people with HIV type 1 (HIV-1) infection¹⁻⁶ and is associated with a significant recovery of the compromised immune function.^{7,8} However, these benefits can be adversely affected by the development of drug-resistant forms of the virus.

Drug resistance is classified into categories of primary or secondary drug resistance. Secondary drug resistance refers to resistance that develops in individuals already receiving treatment. Primary drug resistance is resistance observed in treatment-naïve individuals with newly diagnosed HIV infection, 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 antiretroviral therapy (ART), have important implications for HIV-related morbidity and mortality, and may result in increased health care costs.⁹⁻¹⁴ 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.¹⁵

This *Epi Update* provides a summary of primary HIV drug resistance in Canada and in other developed countries and includes an overview of data from the Canadian Strain and Drug Resistance Surveillance (SDR) program, a collaboration between the provinces and the Public Health Agency of Canada (the Surveillance and Risk Assessment Division and the National HIV and Retrovirology Laboratories). Note that additional, more detailed, information from the SDR program will be available in the next edition of the report entitled *HIV-1 Strain and Primary Drug Resistance in Canada* (with anticipated publication in the fall of 2010; the current edition of this report was published in 2006¹⁶).

Evolution of Drug Resistance

ART is directed toward inhibition of vital steps in the life cycle of the virus. The most commonly used drugs used in ART target the reverse transcriptase (RT) and protease enzymes. Drug resistance largely results from changes (mutations) in the genetic material that code for these enzymes, rendering ART less effective. Although newer classes of drugs are available, the most commonly used drugs approved for the treatment of HIV infection fall into three classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs).

The HIV virus is constantly changing, and mutations in the virus's genetic material occur on a daily basis. Most mutations do not result in the development of drug resistance, as they are lethal, reduce fitness, or even if not affecting viral growth, occur at sites that are not targeted by ART. However, under conditions in which treatment does not completely inhibit viral replication, a virus with drug-resistant mutations may begin to thrive, resulting in treatment failure. For some drugs in particular (e.g. NNRTIs), a single mutation may be associated with a high level of resistance to drugs from that same class.

Methods to Identify Drug Resistance

Genotypic tests identify mutations in the viral genetic material through sequencing the viral genes of interest. By comparing the generated sequences with databases containing resistance-conferring mutations, the presence or absence of drug resistance can be determined.

Phenotypic tests assess growth of a virus containing the genes of interest in the presence of drugs against which resistance is being determined. This test is similar in concept to antibiotic-resistance testing in bacterial culture.

Drug Resistance in Untreated Individuals (Primary Drug Resistance)

Mutations associated with drug resistance in individuals with newly diagnosed but untreated infection is thought to be the result of the transmission of a drug-resistant virus from a treated individual or from other treatment-naïve individuals (onward transmission).¹⁷⁻¹⁹ Several studies from Europe and the United States have reported mutations associated with drug resistance ranging from as low as 3.8% to as much as 20% and higher in untreated, early or acute HIV-1 infections.²⁰⁻²⁶

Primary drug resistance in Canada

Cumulative results from the available data of the SDR program show that the overall prevalence of primary drug resistance to at least one antiretroviral drug is 9% (see Table 1 for primary drug resistance results by drug class).

Regarding the time of infection, SDR program data reveal that to date the proportion of primary drug resistance among recent infections is higher than among established infections.^{16,27} This is consistent with the

Table 1. Distribution of primary drug resistance among treatment-naïve individuals with newly diagnosed infection (1996-December 2008)

	Frequency	Percentage
Wild type ^a	3,781	91.0
NRTI ^{***}	150	3.6
NNRTI [†]	108	2.6
PI [‡]	78	1.9
NNRTI/NRTI	20	0.5
PI/NNRTI	6	0.1
PI/NRTI	9	0.2
PI/NNRTI/NRTI	5	0.1
TOTAL	4,157	100.0

^aWild type includes polymorphisms and minor mutations in the protease gene not associated with drug resistance.

^{***}Refers to nucleoside reverse transcriptase inhibitors.

[†]Refers to non-nucleoside reverse transcriptase inhibitors.

[‡]Refers to protease inhibitors.

Note: 1- Included in the analysis, data from participating provinces in the SDR program: BC, AB, SK, MB, ON and NS.

2- Quebec drug resistance data are not included in the analysis but will be included in the next edition of the report entitled *HIV-1 Strain and Primary Drug Resistance in Canada* (with anticipated publication in the fall of 2010).

Data source: Public Health Agency of Canada. Unpublished data to the end of 2008 from the Canadian HIV Strain and Drug Resistance Surveillance Program. Ottawa: Surveillance and Risk Assessment Division, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada.

findings of most²⁷⁻³⁰ but not all studies,^{31,32} which report a higher prevalence of primary drug resistance among recently infected individuals relative to individuals with untreated and chronic HIV-1 infection.

More detailed information and analysis will be available in the next edition of the report entitled *HIV-1 Strain and Primary Drug Resistance in Canada*.

Summary of Key Studies on the Prevalence of Primary Drug Resistance

This section summarizes findings regarding the prevalence of primary drug resistance in individuals not yet treated (treatment-naïve patients) in North America and in Western Europe.

Primary drug resistance in Canada

Data collected during the periods 1996-1998 and 1997-2005 from different cohorts in Canada have shown a prevalence of primary drug resistance ranging from 2% to 8%.³³⁻³⁵ In a study of drug resistance in newly HIV-1 infected individuals in Montreal over the period 1996-2003, the prevalence of drug resistance among recently infected patients decreased from 13% in 1997-2000 to 4.0% in 2001-2003.³⁶

Data collected through the SDR program assessed the regional variation in HIV strain and drug resistance from treatment-naïve individuals whose infection was diagnosed in 2004. Sequence information was obtained from 537 serum samples. Overall, the prevalence of drug resistance was 9.7%; however, the range varied from 5.6% to 18.4% among provinces.³⁷ An earlier analysis of data from this program found that the prevalence of primary drug resistance was higher among Caucasian men who have sex with men and higher in recent than in established infections.²⁷

A recent study by Tossonian et al.³⁸ found the prevalence of primary HIV drug resistance to be 4.7% in a population of treatment-naïve individuals who injected drugs and attended a community health centre in Vancouver. The prevalence of resistance to various drug classes in this population was 3.1% for NNRTIs and 1.6% for NRTIs, and there were no cases of resistance to PIs or of multidrug resistance.³⁸

Primary drug resistance in the United States

Different estimates of the prevalence of primary drug resistance in the United States have been reported. Overall, the prevalence among treatment-naïve individuals recently or chronically infected varied from as

low as 7% to as much as 27.3%, depending on the characteristics of the population studied, study design, sampling strategies, methods and criteria used to score the transmission of a resistant virus, survey period and geographic region.^{20-22,26,39-43} For example, studies in the last decade have reported high prevalence rates of primary drug resistance in San Diego (25%)⁴⁴ and in New York City (24.1%).⁴⁵ Other recent studies in the US among different risk groups have also found a high prevalence of primary drug resistance, which varied between 11.6% and 18%.^{29,41,42,46-48} A more recent study by Hurt et al.⁴⁹ found a prevalence of 17.8% of primary drug resistance in North Carolina patients with acute or recent HIV infections diagnosed between 1998 and 2007. NNRTI mutations were detected in 9.5% of the people infected, NRTIs in 7.5% and PIs in 3.2% of persons.

Primary drug resistance in western Europe

Overall, studies conducted in western European countries have shown variation in the reported prevalence of primary drug resistance, in line with some North American reports. This variation reflects the heterogeneity of the study design, the demographic characteristics of the population and resistance detection methodology.

Findings from two large multicentre studies suggest that the prevalence of primary drug resistance in western Europe from 1996 to 2003 was approximately 10% among recently or chronically infected individuals, and the prevalence of resistance varied according to drug class. In addition, a higher prevalence of primary drug resistance was reported in people infected with subtype B virus than in people infected with non-B subtypes.^{28,50,51}

A number of studies have found prevalence rates of less than 10%. Between 2002 and 2005, the SPREAD (Strategy to Control SPREAD of HIV Drug Resistance) Programme⁵² examined 2,793 patients with newly diagnosed HIV-1 infection in 20 European countries and in Israel, and found an overall prevalence of primary drug resistance of 8.4%. NRTI resistance was present in 5% of patients, whereas 2% had resistance to NNRTIs and 3% were resistant to PIs. A 10-year study (1996-2005) in Switzerland found rates of 7.7% for any drug, 5.5% for NRTIs, 1.9% for NNRTIs and 2.7% for PIs.⁵³ Multiple drug resistance was observed in 2% of patients. A number of other studies conducted in western European countries, including the United Kingdom, Germany, Portugal, Belgium, Italy, France and Luxembourg, have found prevalence rates of primary drug resistance ranging from 5% to 10%,^{31,54-59} whereas in other studies the reported prevalence was lower than 5%.^{25,60}

However, several studies have found higher prevalence rates of primary drug resistance in western European countries. A 2003 British study found a rate of 19.2% for any drug resistance mutation, 12.4% for NRTIs, 8.1% for NNRTIs and 6.6% for PIs.⁶¹ Similarly, a large Italian cohort of 1,690 treatment-naïve patients from 1996 to 2007 had a 15% prevalence of primary drug resistance, with a prevalence of 7% of non-B subtypes and 17.3% of B subtype samples.⁶² A number of other studies in different western European countries have also found prevalence rates higher than 10% among acutely, recently or chronically infected people and among those with newly diagnosed infection.^{62,63}

Comments

Primary HIV drug resistance has been observed in most countries where HAART is used. 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. Continued surveillance of primary drug resistance is needed not only to develop guidelines for initial therapy but also to better understand and prevent the transmission of resistant HIV.

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