B.C. Centre for Excellence in HIV/AIDS Pharmacovigilance Initiative

Annual Report 2016

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in HIV/AIDS

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Disclaimer:
The BC Centre for Excellence in HIV/AIDS (BC-CfE) Pharmacovigilance Initiative receives reports of suspected adverse drug reactions, drug interactions and other adverse drug-related events associated with the use of antiretroviral medications. The information provided in this report summarizes post-marketing experience with antiretroviral therapy in persons who receive HIV medications through the BC-CfE Drug Treatment Program. Reports of adverse drug-related events are voluntarily submitted by health care providers, patients and care-givers and are not systematically evaluated for accuracy or for the strength of evidence regarding the causal relationship between drug exposure and observed effect.

Information from reports of adverse drug-related events is stored in the BC-CfE Registry, a secure, computerized database. This database is updated on a regular basis. Figures and tables provided in the Annual Report represent the best estimates available at the time this document was published.

Figures and graphs presented in this document are best viewed in colour.

Statement of Confidentiality:

The personal information of patients and their health care providers is private and confidential. De-identified data are used for the purpose of drug safety surveillance in accordance with British Columbia Privacy legislation and ethical approval granted by the University of British Columbia-Providence Healthcare Research Ethics board.

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Introduction

The BC-CfE Pharmacovigilance Initiative collects, evaluates, and analyzes reports of drug toxicity and other adverse drug-related events and uses this information to understand and prevent drug-related problems.

Adverse drug reactions ("side-effects") to antiretroviral medications and interactions between antiretroviral medications and other drugs can affect patients' health and interfere with treatment success. All drugs are tested for safety before they are approved for sale in Canada; however, pre-marketing clinical trials cannot study enough patients to be able to detect adverse drug-related events that are rare, take a long time to develop, or mainly affect particular groups of patients (e.g. females, seniors, or specific ethnic groups). These toxicities are usually discovered after a drug is used in the general population.

Ongoing monitoring of adverse drug-related events is required to detect unexpected toxicities as soon as possible, so that health care providers and patients can be warned of new safety concerns.

Acknowledgement

The Pharmacovigilance Initiative acknowledges with thanks the support provided by clerical staff, data analysts and programmers at the BC Centre for Excellence in HIV/AIDS, the staff of the St Paul's Hospital Ambulatory Pharmacy and all those who report adverse drug-related events.

Conflict of Interest Declaration

The BC-CfE Pharmacovigilance Initiative does not receive pharmaceutical industry funding. The authors of this report have no conflicts of interest to declare within the past two years**.**

Definitions and Abbreviations

The following definitions and abbreviations apply to terms used throughout this document. Terms that relate to a particular section of the report are defined within that section.

- **BC-CfE:** BC Centre for Excellence in HIV/AIDS

- **Adverse Drug-Related Event.** Any untoward event associated with a medication. The BC-CfE captures events including (but not limited to) the following event categories*:*
    - **Adverse Drug Reaction (ADR):** A suspected adverse drug reaction (unintended, undesirable effect of an antiretroviral medication) attributed to one or more antiretroviral drugs. Includes events in which the medication is continued, dose adjusted or discontinued.
    - **ADR Prevention:** Antiretroviral therapy is changed to prevent a potential adverse drug reaction.
    - **Drug Interaction, symptomatic:** An adverse drug reaction resulting from a drug interaction between an antiretroviral medication and another drug.
    - **Drug Interaction Prevention:** Antiretroviral medication is discontinued or the dose is adjusted to prevent a potentially harmful drug interaction with another medication (no ADR occurred).

- **Adverse drug-related event information source:**
    - **New Prescription:** An application for a new antiretroviral medication regimen submitted to the BC-CfE Drug Treatment Program. Forms include a section for reporting adverse drug-related events.
    - **Refill Prescription:** Refill of an ongoing antiretroviral medication regimen. Prescribers may add information regarding drug tolerability.
    - **Therapy Interruption Alert:** BC-CfE mails Therapy Interruption Alerts to prescribers if the patient's refill history suggests a >2 month gap in therapy. Forms include a section for reporting adverse drug-related events.
    - **Spontaneous Report:** A report voluntarily submitted directly to the BC-CfE Pharmacovigilance Initiative

- **ARV, Antiretroviral Drug:** Medications used to treat Human Immunodeficiency Virus infection.
- **ART, Antiretroviral Therapy:** Combination of ARVs comprising the treatment regimen

Reports of Adverse Drug-Related Events Associated with Antiretroviral Therapy

As summarized in Table 1, Table 2 and Figure 1, Total Adverse drug reaction and drug interaction reporting remains stable over the past five years, with minor fluctuations between years and between quarterly (3 month) periods.

Table 1. Adverse Drug-Related Events – Five year reporting patterns

Year	Number of patients receiving antiretroviral treatment	Adverse Drug-Related Event reports All categories, excluding duplicates	
		Total per year	Average per month
2012	6807	760	63
2013	7067	764	64
2014	7363	945	79
2015	7632	812	68
2016	**7803**	**841**	**70**

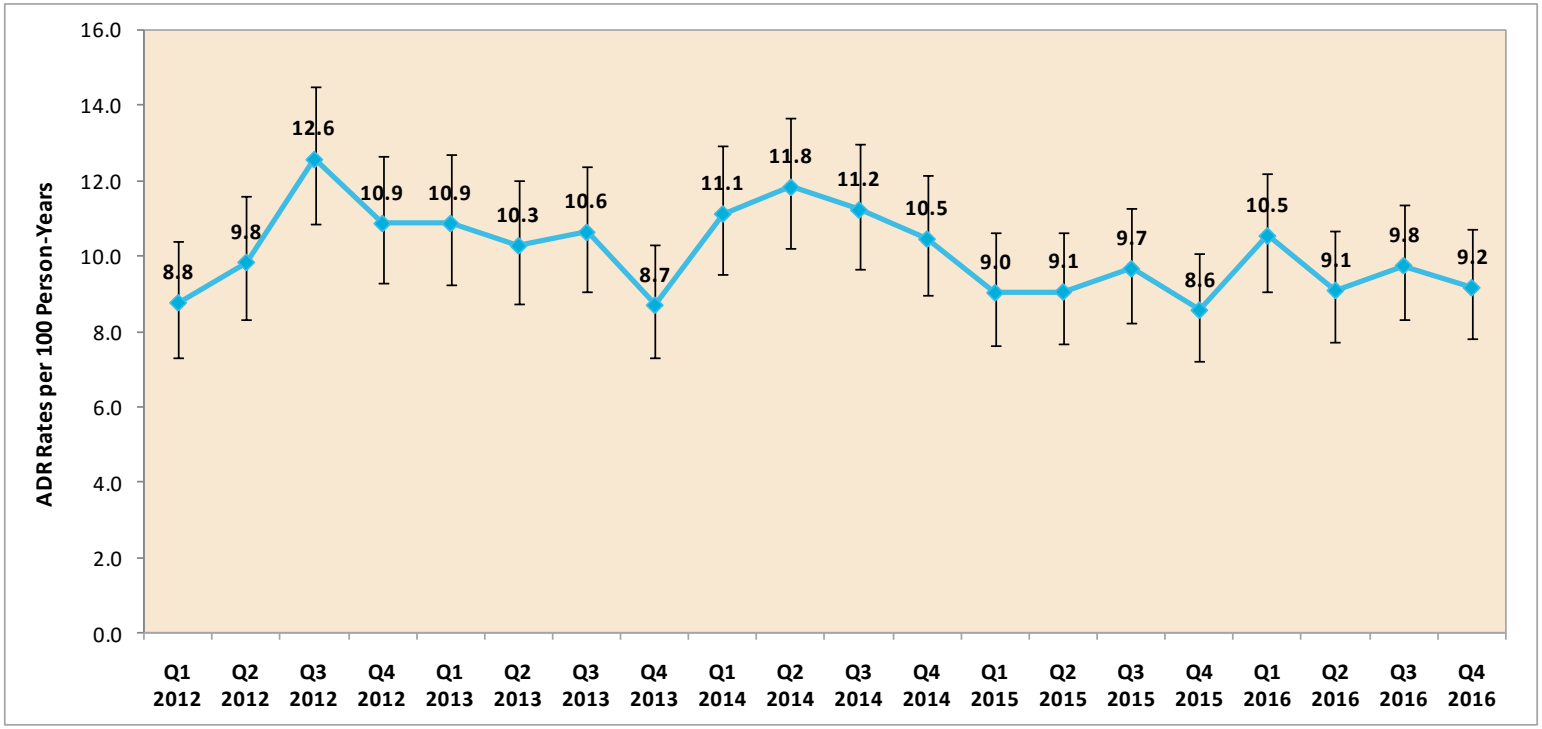
Table 2. Adverse Drug-Related Events Associated with Antiretroviral Therapy – 2016

Information Category	Reports Including duplicates N= 847 n(%)	Reports Excluding duplicates N= 841 n(%)
Event Type		
Adverse Drug Reaction	663 (78.3)	658 (78.2)
Adverse Drug Reaction Prevention	58 (6.8)	57 (6.8)
Drug Interaction, Symptomatic	4 (0.5)	4 (0.5)
Drug Interaction Prevention	122 (14.4)	122 (14.5)
Information Source		
New Prescription	836 (98.7)	*
Refill Prescription	2 (0.2)	*
Therapy Interruption Alert	6 (0.7)	*
Spontaneous Report	3 (0.4)	*
Reporter Type		
Physician	616 (72.7)	*
Pharmacist	230 (27.2)	*
Nurse	0	*
Other Reporter	1 (0.1)	*

*Not applicable; multiple reporter or information source categories are possible for each event

Adverse Drug Reactions (ADRs)

Figure 1. Adverse Drug Reactions, all drugs – Five year reporting patterns, by quarter

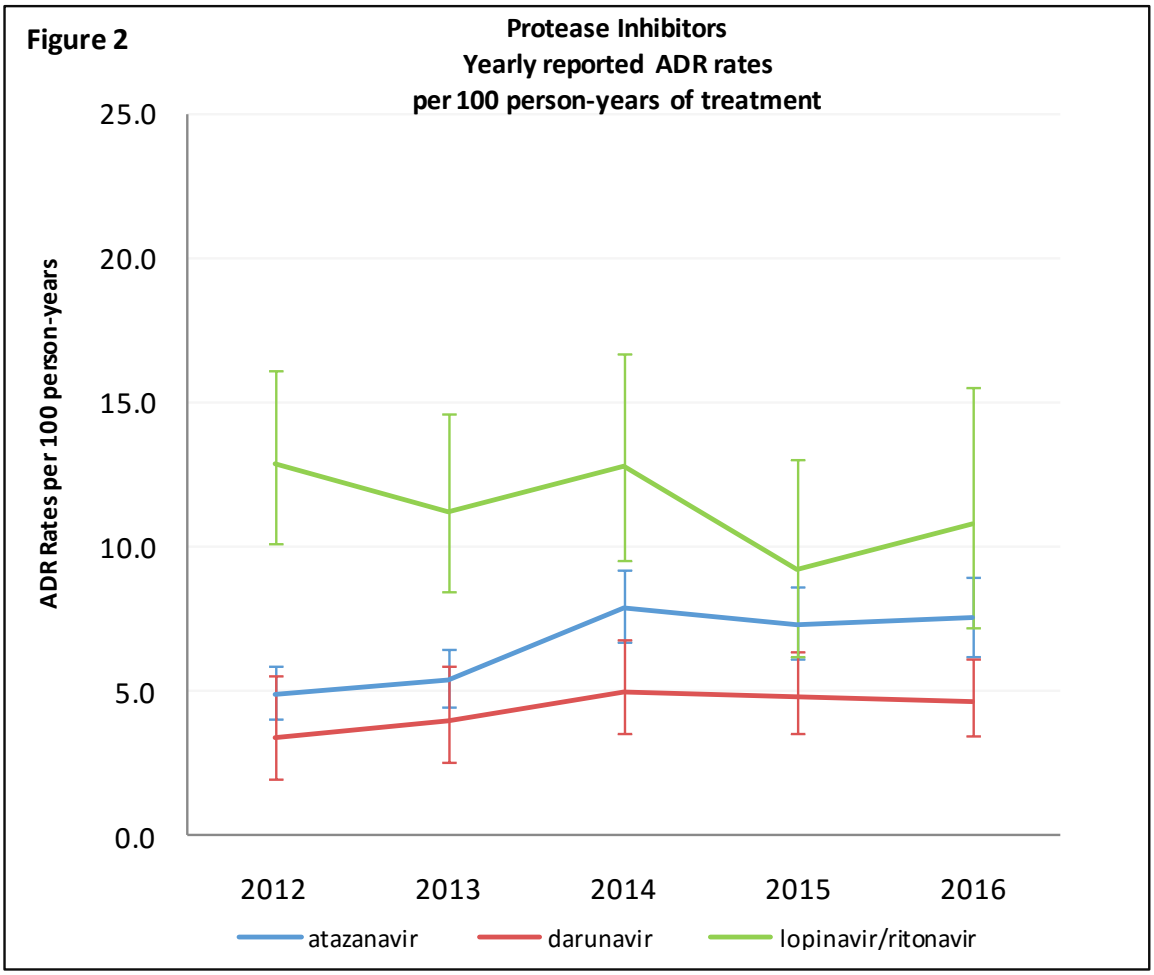


Adverse Drug Reaction (ADR) Rates by Antiretroviral Drug Class

Figures 2 to 5 display annual ADR rates over the past five years, by antiretroviral drug class. ADR rates are shown for the total ART-treated population.

Although some ADRs may not manifest until years after therapy initiation, many commonly reported ADRs typically occur within the first few months of therapy, and may result in early medication discontinuation. The influence of early ADRs introduces potential bias when comparing the ADR rates of different drugs over time. A newly marketed drug will have a high proportion of drug-exposed persons who have recently started the medication, and may appear to have a higher ADR rate than older drugs in the same class, where the majority of drug-exposed persons are the self-selected group who have tolerated these medications long-term.

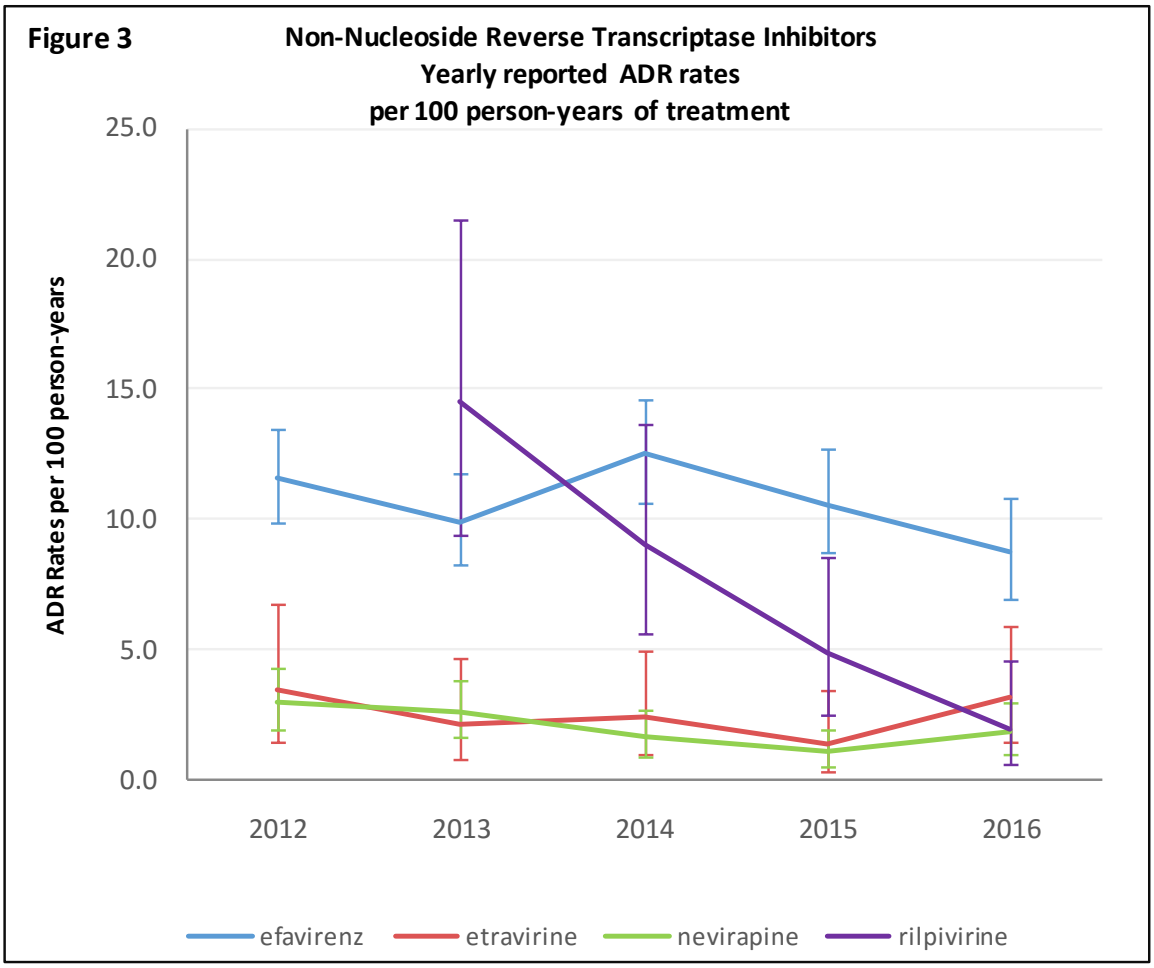
Figure 2. Protease Inhibitors Adverse Drug Reactions (ADRs)



Results are not reported in years with less than 100 person-years drug exposure.

The increase in atazanavir ADR rates between 2012 and 2016 is associated with increased reporting of renal and gall stones.

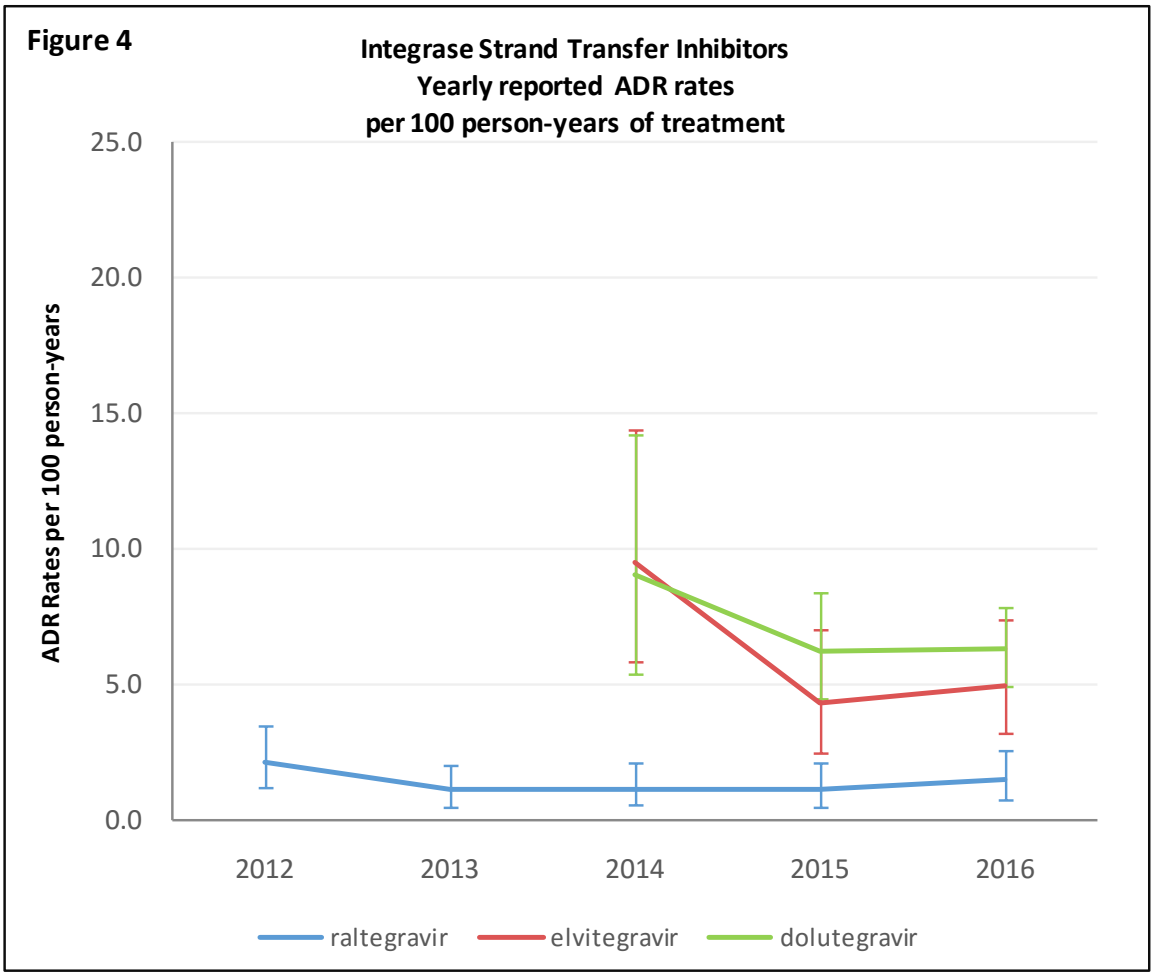
Figure 3. Non-Nucleoside Reverse Transcriptase Inhibitors Adverse Drug Reactions (ADRs)



Results are not reported in years with less than 100 person-years drug exposure.

The apparent decline of rilpivirine ADR rates (Figure 3) between 2013 and 2016 may be influenced by a small number of rilpivirine-exposed persons in 2013 (n=172), and an increasing number of persons on long-term rilpivirine treatment over time, which could reduce the proportion of those experiencing a new ADR (see page 5 discussion of newly marketed drugs).

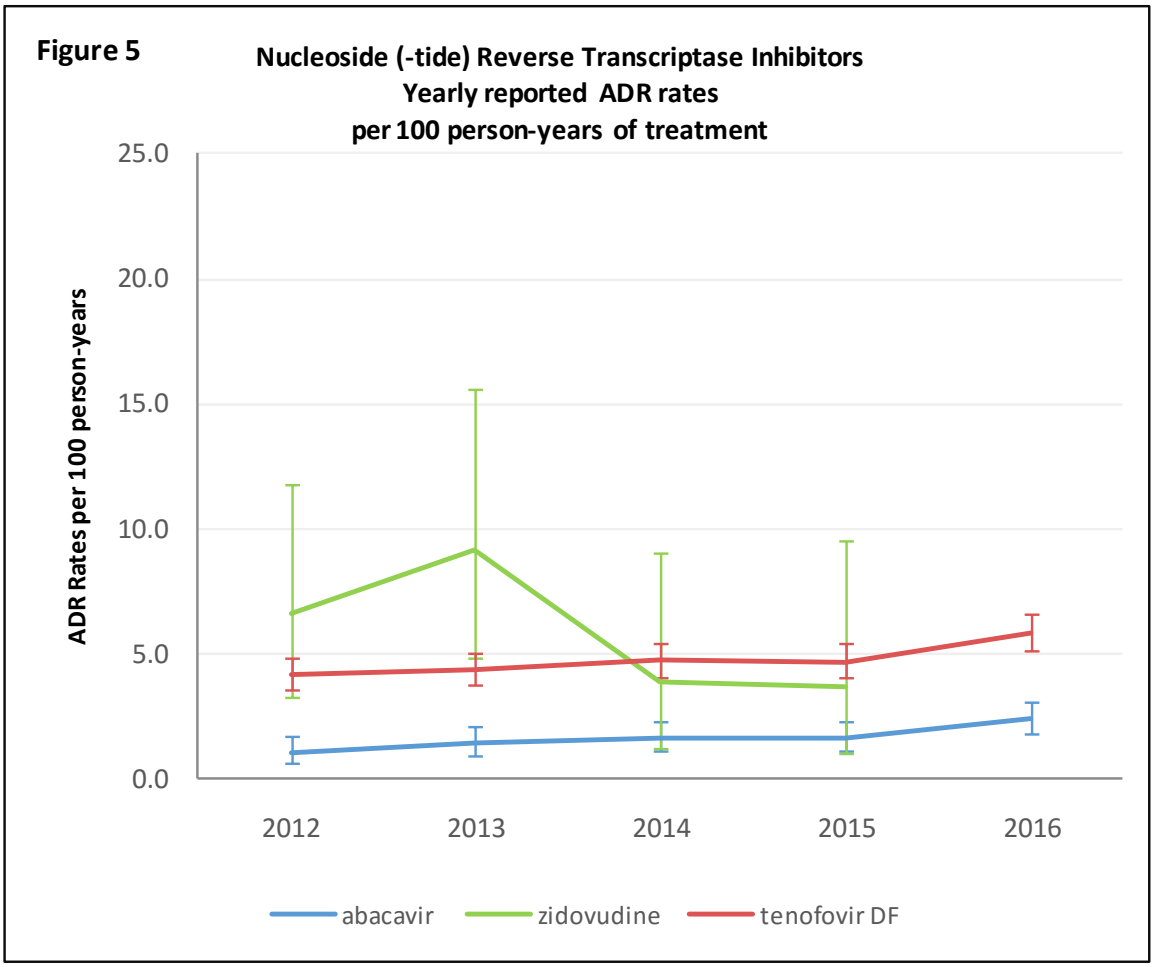
Figures 4. Integrase Strand Transfer Inhibitors Adverse Drug Reactions (ADRs)



Results are not reported in years with less than 100 person-years drug exposure.

The apparently higher ADR rates for dolutegravir and elvitegravir relative to elvitegravir (Figure 4) may be influenced by the relatively higher proportion of persons newly treated with the newer drugs (elvitegravir, dolutegravir) compared to a higher proportion of raltegravir-treated persons on long term therapy (see page 5 discussion of newly marketed drugs). Monitoring is ongoing.

Figures 5. Nucleoside (-tide) Reverse Transcriptase Inhibitor Adverse Drug Reactions (ADRs)



Results are not reported in years with less than 100 person-years drug exposure.

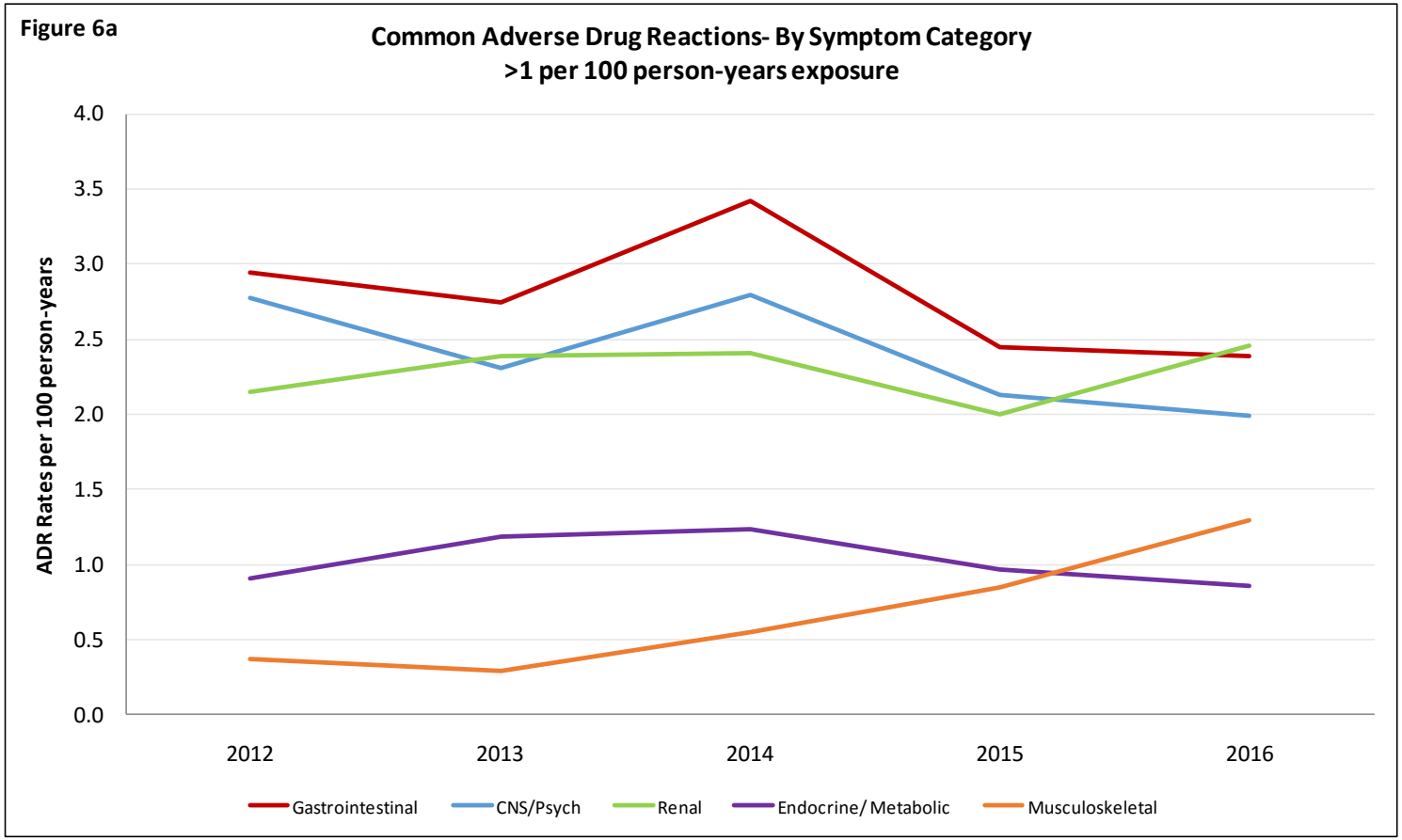
Due to declining use of zidovudine, ADR data is not reported after 2015.

Adverse Drug Reaction (ADR) Rates by Symptom Category

Figures 6 a-c display annual ADR rates over the past five years, by the type of symptoms reported. ADR rates are shown for the total ART-treated population, and for all antiretroviral drugs.

Despite changing patterns of ART prescribing during the past 5 years, rates of most ADR symptoms remain stable. The most commonly reported ADRs remain gastrointestinal upset, neuropsychiatric (CNS/Psych) and renal effects (Figure 6a). The increase in musculoskeletal ADRs in recent years is largely due to increased reporting of osteopenia/ osteoporosis associated with tenofovir disoproxil fumarate (tenofovir DF).

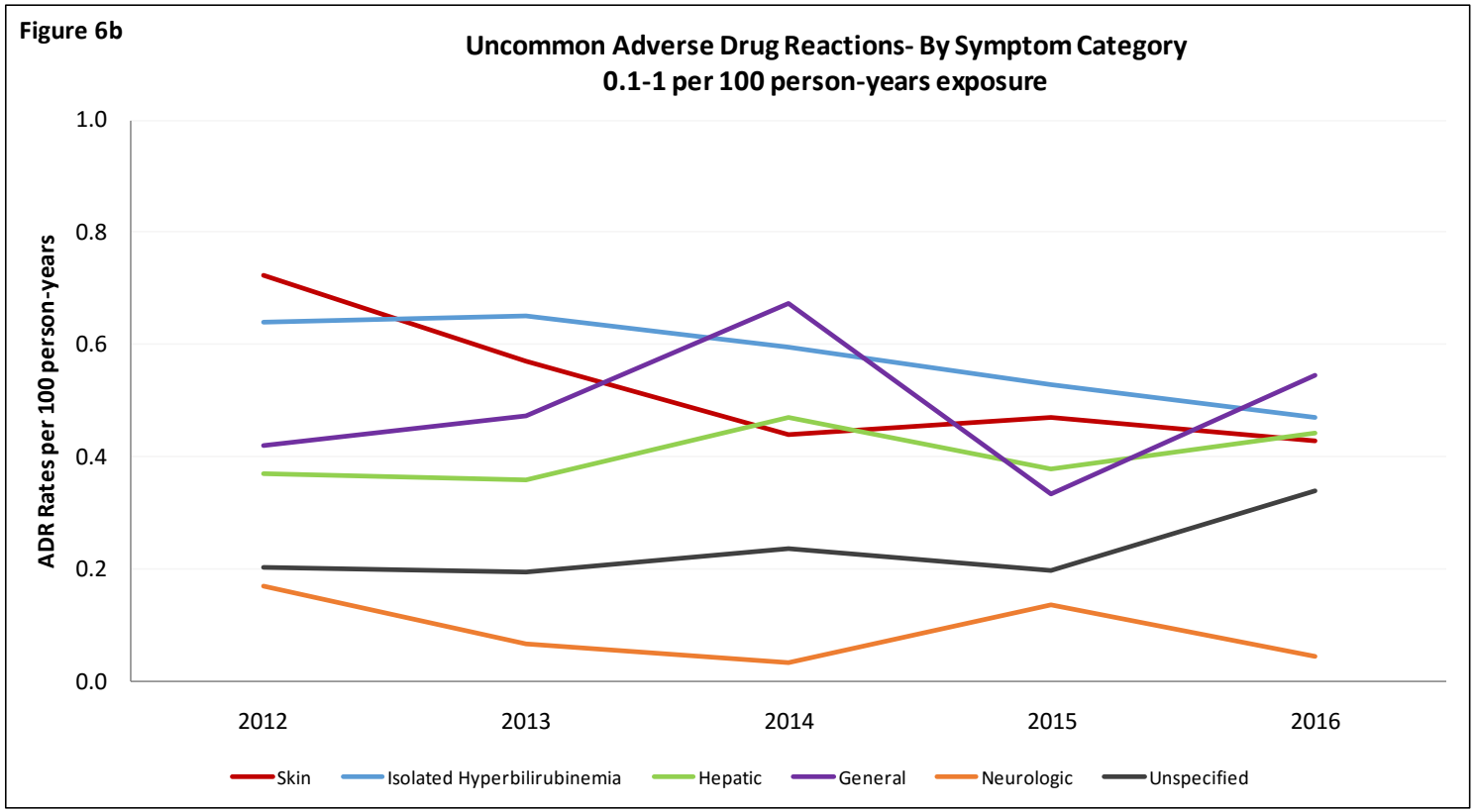
Figures 6a-c. Adverse Drug Reaction Rates by Symptom Category



Symptoms under these category headings may include the following. This is not a comprehensive list of all symptoms included:

Gastrointestinal:	nausea, vomiting, diarrhea, constipation, difficulty swallowing medication, gastro-esophageal reflux
CNS/Psych:	nightmares/vivid dreams, insomnia/ sleep disorder, altered mood, altered mental status, headaches, hallucinations
Renal:	serum creatinine elevated/GFR low, nephrolithiasis, elevated urinary albumin:creatinine ratio, Fanconi syndrome
Endocrine/Metabolic:	lipid abnormalities, lipodystrophy, serum phosphorus low, triglycerides elevated, cholesterol elevated
Musculoskeletal:	bone mineral loss (osteopenia, osteoporosis), myalgia/arthralgia

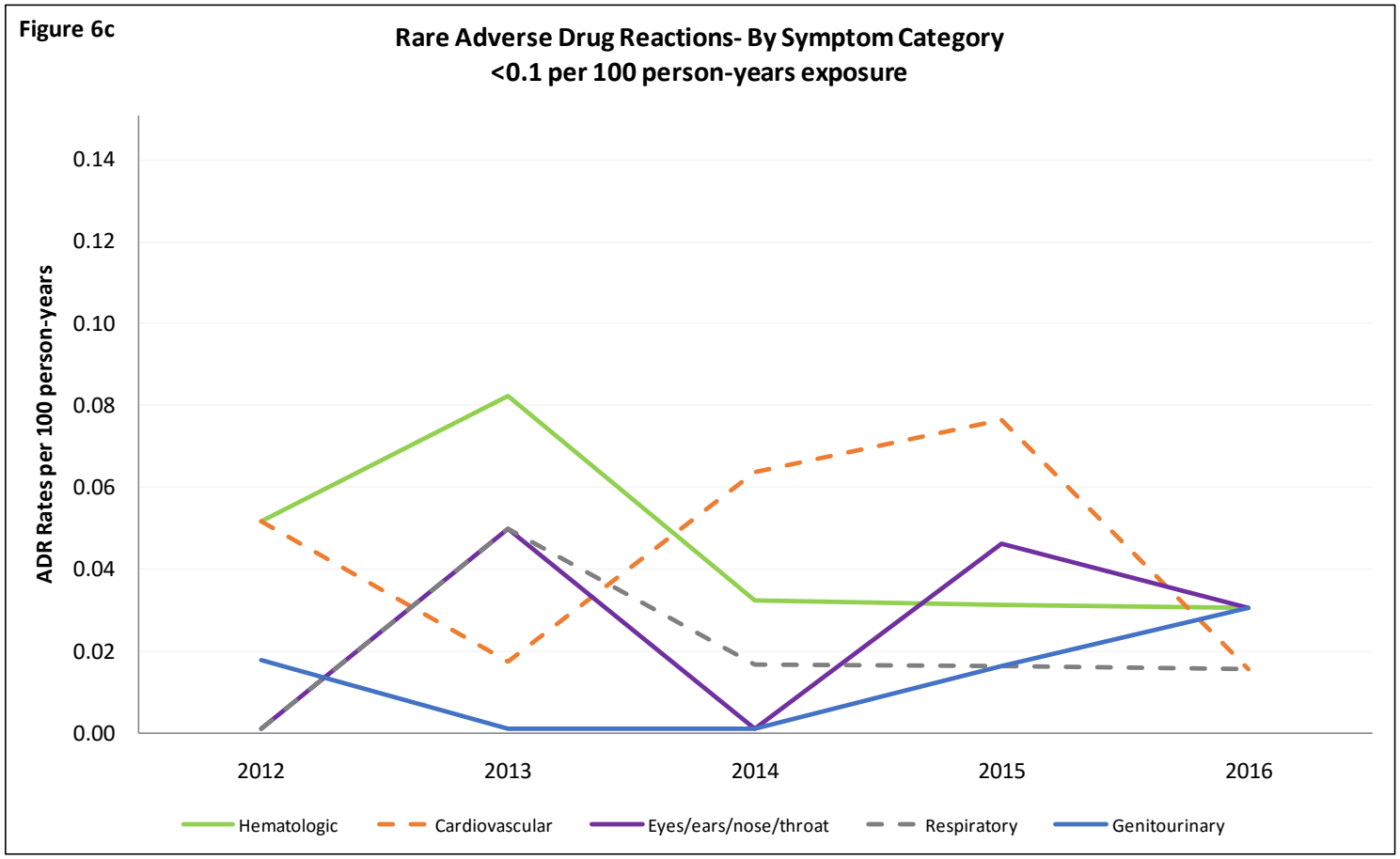
Figure 6b



Symptoms under these category headings may include the following. This is not a comprehensive list of all symptoms included:

Skin:	rash/hives, itching (no lesions)
Isolated Hyperbilirubinemia:	hyperbilirubinemia ± jaundice
Hepatic:	elevated hepatic transaminases, abnormal liver function tests (unspecified), cholelithiasis, albumin low
General:	fatigue/malaise/low energy, weight gain/loss (unintentional), allergic reaction
Neurologic:	peripheral neuropathy, neuromuscular weakness
Unspecified:	reaction not otherwise specified

Figure 6c



Symptoms under these category headings may include the following. This is not a comprehensive list of all symptoms included:

Hematologic:	neutropenia, pancytopenia, anemia/low hemoglobin
Cardiovascular:	cardiovascular risk (prevention) hypertension, hypotension, cardiac dysrhythmia
Eyes/ears/nose/throat:	visual changes, tinnitis, taste or smell disturbances
Respiratory:	cough (persistent/chronic), bronchospasm (not anapyhlaxis), shortness of breath/dyspnea
Genitourinary:	sexual dysfunction, urinary frequency/urgency/hesitancy, menstrual difficulties

Serious or Unexpected Adverse Drug Reactions

Reports Submitted to Health Canada Vigilance

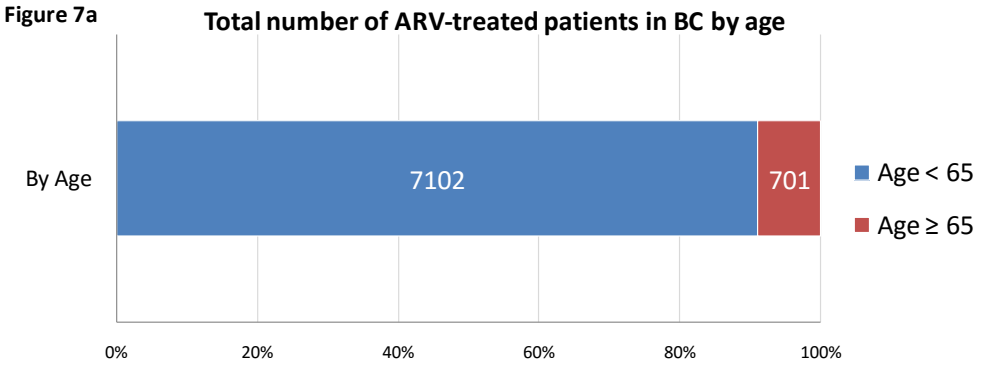
In support of national and international drug safety monitoring programs, the BC-CfE Pharmacovigilance Initiative reports serious or unexpected adverse drug reactions to the Health Canada Vigilance Program, which in turn submits reports to the World Health Organization. Serious adverse drug reactions include those of grade IV severity and/or those resulting in hospital admission, prolongation of hospital stay or death. Unexpected reactions include clinically important events associated with newly marketed drugs, or rare adverse reactions associated with established drugs.

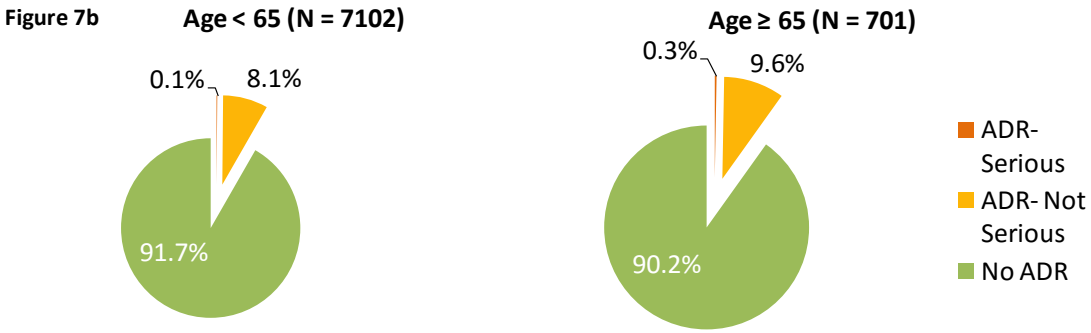
In 2016, 12/655 (1.8%) of adverse drug reaction reports (excluding duplicates and "unlikely" causality) were classified as serious. A total of 38/655 (5.8%) of ADR reports were submitted to Health Canada.

Adverse Drug Reactions in Special Populations

As shown in Figure 7a-b, seniors ≥65 years of age represent approximately 9% of the total ARV-treated population. The proportion of seniors with a reported ARV ADR in 2016 was slightly higher than for younger persons; however, there were no statistically significant differences between groups.

Figure 7a-b. Adverse Drug Reactions in BC stratified by age category





Females represent approximately 17% of the total ARV-treated population. The proportion of females with a reported ARV ADR was slightly, but statistically significantly ($p<0.5$ Pearson's Chi Square) higher than for males in 2016. See Figure 8 a-b.

Figure 8. Adverse Drug Reactions in BC by biological sex

Figure 8a

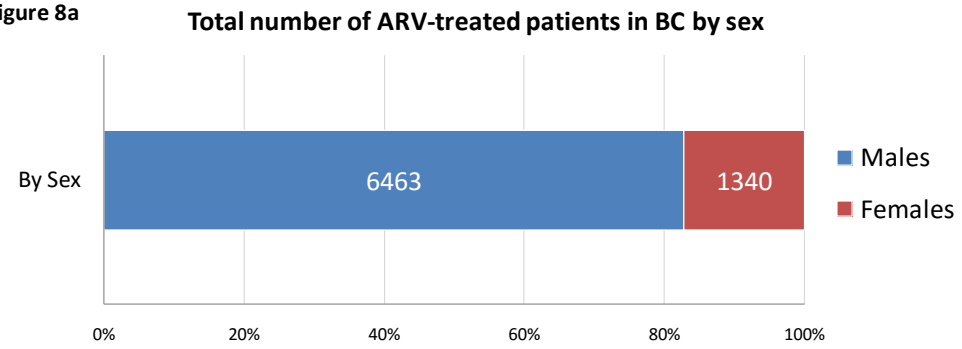
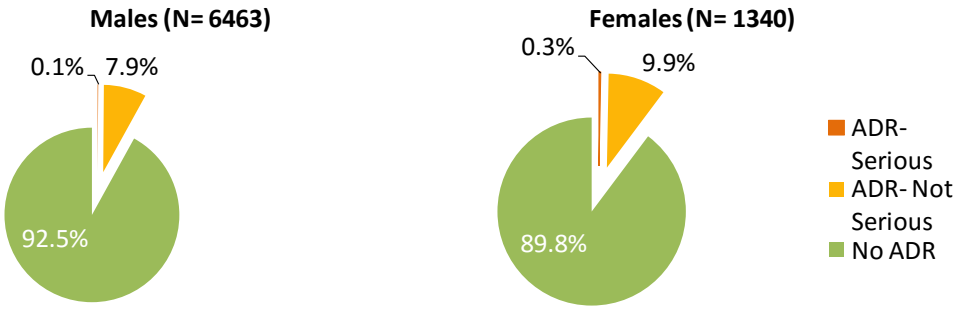


Figure 8b



Drug Interactions

Drug interactions between ARVs and other medicines may result in treatment failure (loss of virologic suppression or development of ARV drug resistance), or may increase the risk of side effects from either the ARVs or the other drugs. Figure 9 and 10 summarize ARV drug interaction reporting patterns for 2016.

Figure 9. Antiretroviral Drug Interactions – By ARV category

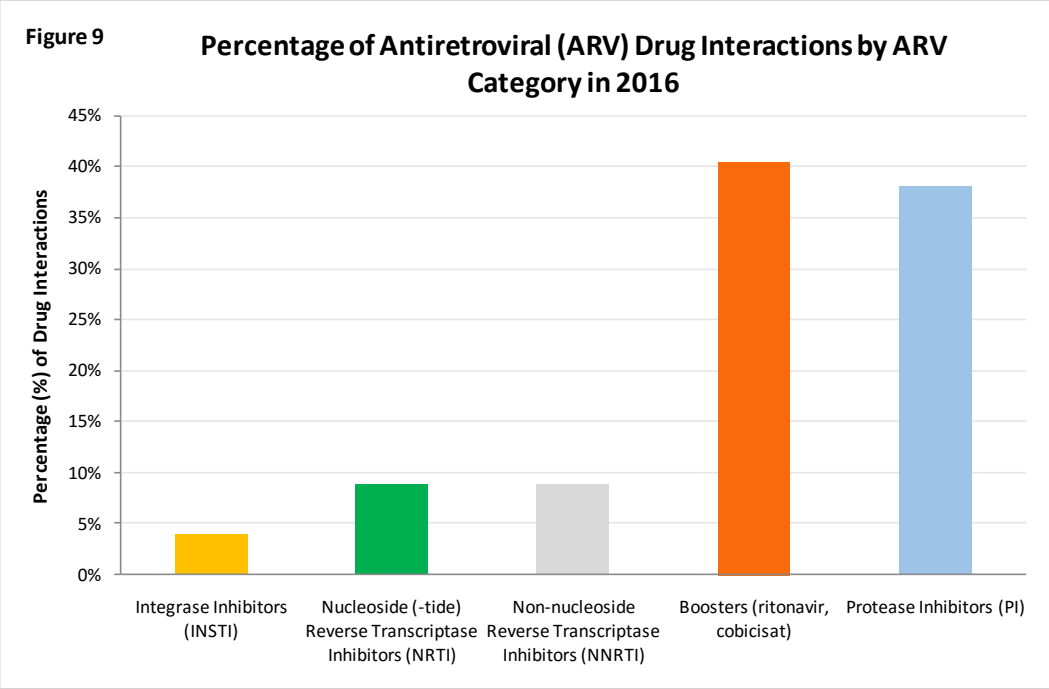
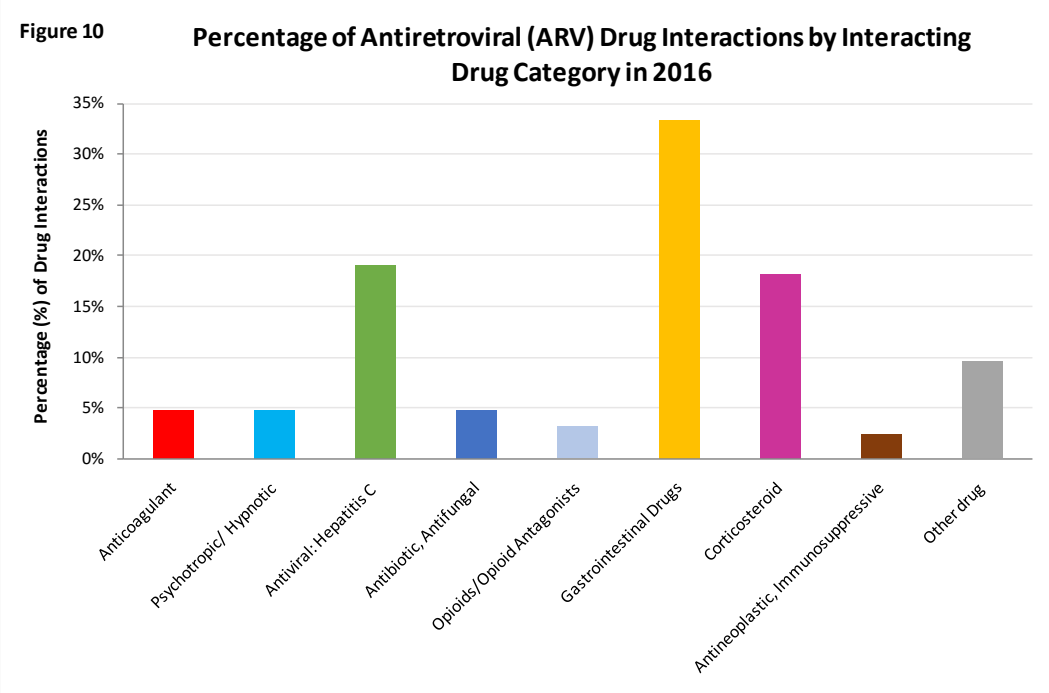


Figure 10. Antiretroviral Drug Interactions – By interacting drug category



The most common, clinically important drug interactions reported by the BC-CfE Pharmacovigilance Initiative are summarized in Table 3, below. These accounted for 70% of the drug interaction reports in 2016.

Table 3. Common, clinically important drug interactions

Antiretroviral Drug (Drug class)	Other Drug or Drug class	Clinical effect
Ritonavir (booster, PI) Cobicistat (booster)	Corticosteroids, including Asthma inhalers and nasal sprays (e.g. fluticasone) Intra-articular injections (e.g. triamcinolone)	Increase systemic corticosteroid, which can lead to Cushingoid symptoms and/or adrenal suppression
Atazanavir (PI) Rilpivirine (NNRTI)	Gastric acid suppressing drugs: Proton Pump Inhibitors (e.g. omeparazole), H2 blockers (e.g. ranitidine)	Decrease absorption of the ARV drug, which can result in treatment failure
Ritonavir or cobicistat (booster), efavirenz (NNRTI), tenofovir (NRTI) and others	Hepatitis C therapy (various drugs)	Drug toxicity or loss of therapeutic effectiveness (various)

How to report an Adverse Drug Reaction to BC-CfE Pharmacovigilance

Reports of suspected ADRs may be submitted to the BC-CfE Pharmacovigilance Initiative in several ways:

Any health care provider or person living with HIV or their caregiver may report an antiretroviral ADR by completing an **Antiretroviral Adverse Drug Reaction Report** form and faxing or mailing it to the address shown on the form. Click to Download ADR report form.

Health care providers may choose to report suspected ADRs to the BC-CfE Pharmacovigilance initiative in the following ways, instead of completing the ADR Report form:

Report on the HIV Drug Treatment Program Prescription Request:

The HIV Drug Treatment Program Prescription Request form is completed by the patient's physician whenever a change in antiretroviral regimen is requested. Click to download prescription request form. Describe the suspected drugs and reaction in the "Reason(s) for medication change" section of this prescription form. The majority of ADR reports received by BC-CfE Pharmacovigilance come from prescriptions requesting an ARV regimen change.

Report on the HIV Drug Treatment Program Antiretrovrial Treatment Interruption/Adherence Alert:

If a person living with HIV does not refill his or her ARV medication for more than two months after the expected refill date, an HIV Drug Treatment Program Antiretrovrial Treatment Interruption/Adherence Alert is mailed to the person's health care provider to support continuity of care. If the person has stopped or is poorly adherent to antiretroviral medication due to a suspected antiretroviral ADR, describe the suspected drugs and reaction in the designated section of the form and mail or fax to the address on the top of the form.

Report by telephone:
To submit a confidential adverse drug reaction report by telephone, contact the BC-CfE Pharmacovigilance Initiative Research Coordinator at **604-806-8663**.

APPENDIX: Technical information

Analytical methods used in the preparation of this report are summarized below:

Unless otherwise specified, the inclusion and exclusion criteria for all Adverse Drug Reaction (ADR) analyses are as follows:
Include: Events categorized as ADR (including ADRs resulting from drug interactions), see Definitions.
Exclude: Duplicate reports of the same event, ADRs with a causality assessment of "unlikely" and reports of therapy change to prevent ADRs or drug interactions.

Figure 1-5: Calculation of ADR rates: Within each quarter (3 month period, Figure 1) or calendar year (Figures 2-5), the numerator is the number of ADR reports specifying an adverse reaction attributed to the drug of interest. The denominator is the total number of patient-years exposure to the drug, accrued during the time period. The resulting ADR rate is multiplied by 100 to give events per 100 person-years of treatment. Error bars around each point display the 95% confidence interval calculated by the Poisson method.

ADR rates are reported without consideration for the duration of drug therapy prior to the ADR report, or the duration of symptoms prior to the ADR report date.

Figures 6a-c. Adverse Drug Reaction Rates by Symptom Category: ADR reports involving more than one clinical category or more than one implicated drug are counted once in each clinical category and/ or each drug category.