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

Annual Report 2018

BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS

Providence HEALTH CARE
How you want to be treated.

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 for HIV treatment. 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, all those who report adverse drug-related events and Drug Treatment Program participants.

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 3 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:**
    - **Prescription:** All requests for new antiretroviral regimens must be reviewed and approved by the BC-CfE Drug Treatment Program. The 'Prescription Request' form includes a section for reporting adverse drug-related events.
    - Prescribers may also document adverse drug-related events on refill prescriptions for ongoing regimens.
    - **Therapy Interruption Alert/ Late refill notification:** BC-CfE mails Therapy Interruption Alerts to prescribers if the patient's refill history suggests a >2 month gap in therapy for HIV treatment or >3 month gap for PrEP. 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.
- **HIV-tx, HIV Treatment:** Use of combination ART for the treatment of HIV infection (in HIV-positive persons).
- **PrEP, Pre-exposure Prophylaxis:** Use of certain ARVs for the prevention of HIV infection (in HIV-negative persons).

Reports of Adverse Drug-Related Events Associated with Antiretroviral Medications

Table 1a. Adverse Drug-Related Events Associated with ART for HIV treatment – Five year summary

Year	Number of persons receiving antiretroviral treatment	Adverse Drug-Related Event reports All categories, excluding duplicates	
		Total per year	Average per month
2014	7363	945	79
2015	7624	812	68
2016	7803	841	70
2017	7909	952	79
2018	**8005**	**927**	**77**

Table 2a. Adverse drug-Related Events Associated with ART for HIV treatment- 2018

Information Category	Reports including duplicates N= 929 n(%)	Reports excluding duplicates N= 927 n(%)
Event Type		
Adverse Drug Reaction	695 (74.8)	693 (74.8)
Adverse Drug Reaction Prevention	89 (9.6)	89 (9.6)
Drug Interaction Prevention	145 (15.6)	145 (15.6)
Information Source		
Prescription	922 (99.2)	*
Therapy Interruption Alert	3 (0.3)	*
Spontaneous Report	4 (0.4)	*
Reporter Type		
Physician	664 (71.5)	*
Pharmacist	264 (28.4)	*
Other Reporter	1 (0.1)	*

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

Table 1b. Adverse Drug-Related Events Associated with ARVs for PrEP– Five year summary

Year	Number of persons receiving PrEP	Adverse Drug-Related Event reports All categories, excluding duplicates	
		Total per year	Average per month
2014	No data		
2015	No data		
2016	No data		
2017	No data		
2018	**3186**	**26**	**2**

Table 2b. Adverse Drug-Related Events Associated with ARVs for PrEP- 2018

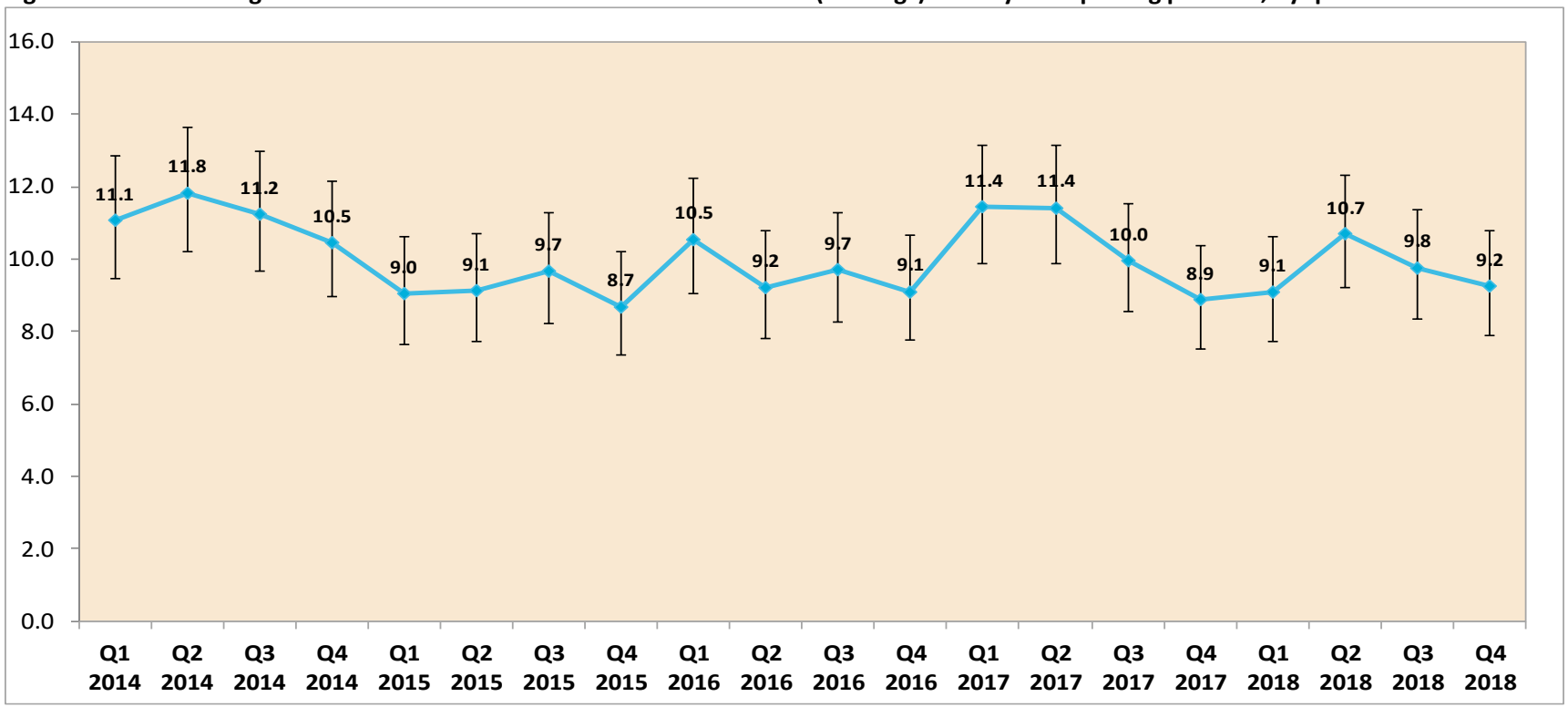
Information Category	Reports including duplicates N= 26 n(%)	Reports excluding duplicates N= 24 n(%)
Event Type		
Adverse Drug Reaction	25	23
Adverse Drug Reaction Prevention	0	0
Drug Interaction Prevention	1	1
Information Source		
Prescription	10	*
Therapy Interruption Alert	12	*
Spontaneous Report	4	*
Reporter Type		
Physician	22	*
Pharmacist	4	*

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

Adverse Drug Reactions (ADRs) associated with ART for HIV treatment

Unless otherwise specified, the inclusion and exclusion criteria for the 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. Adverse Drug Reactions associated with ART for HIV treatment (all drugs) – Five year reporting patterns, by quarter



ADR rates are calculated as follows: Within each quarter (3 month period), 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 quarter. 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.

Adverse Drug Reaction (ADR) Rates by Antiretroviral Drug Class

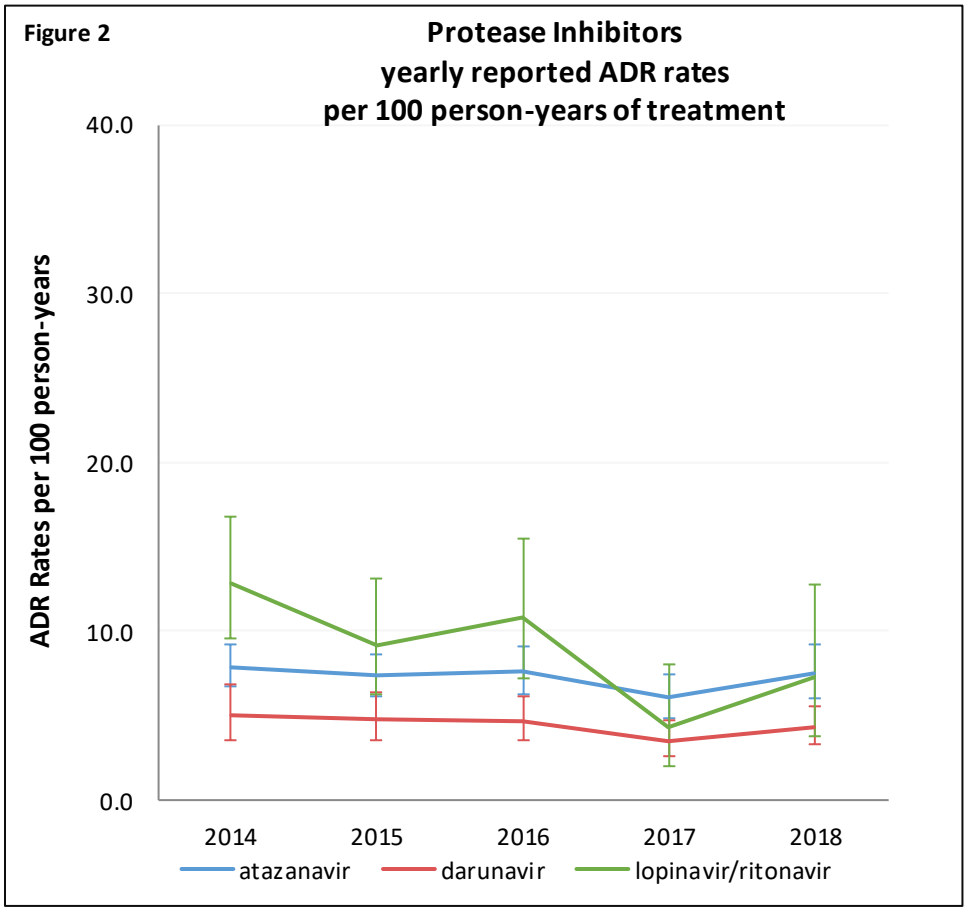
This section focuses on ART for HIV treatment. Information regarding PrEP is included in the relevant sections.

Figures 2 to 5 display annual ADR rates over the past five years. 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.

In all analyses in this section (Figs 2-5), 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. Duplicate reports of the same event, ADRs with a causality assessment of "unlikely" and reports of therapy change to prevent ADRs or drug interactions are excluded.

See Appendix for details regarding calculation of rates.

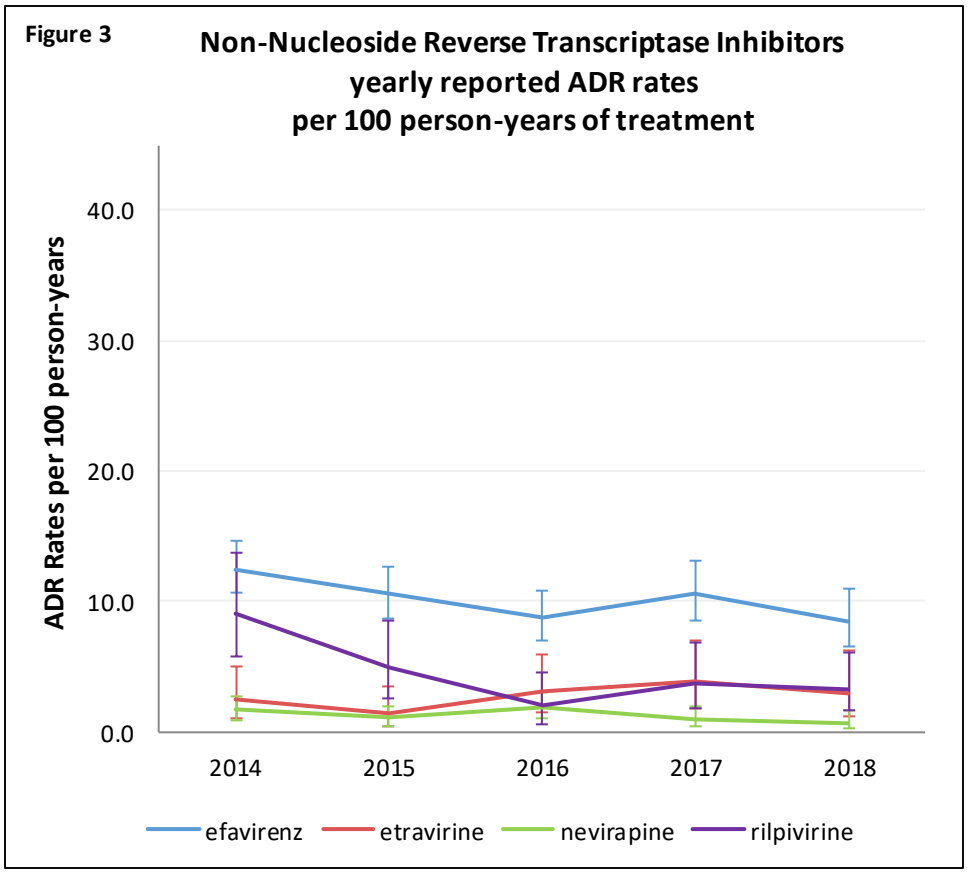
Figure 2. Protease Inhibitors Adverse Drug Reactions (ADRs) associated with ART for HIV treatment



Number of Adverse Drug Reaction (ADR) reports / Total patient-years drug exposure					
	2014	**2015**	**2016**	**2017**	**2018**
atazanavir	163/ 2069	136/ 1854	122/ 1605	82/ 1359	84/ 1125
darunavir	39/ 784	47/ 972	54/ 1154	45/ 1282	58/ 1354
lopinavir	53/ 414	31/ 337	29/ 268	9/ 211	12/ 165

Graph does not display data for years in which there was less than 100 person-years drug exposure.

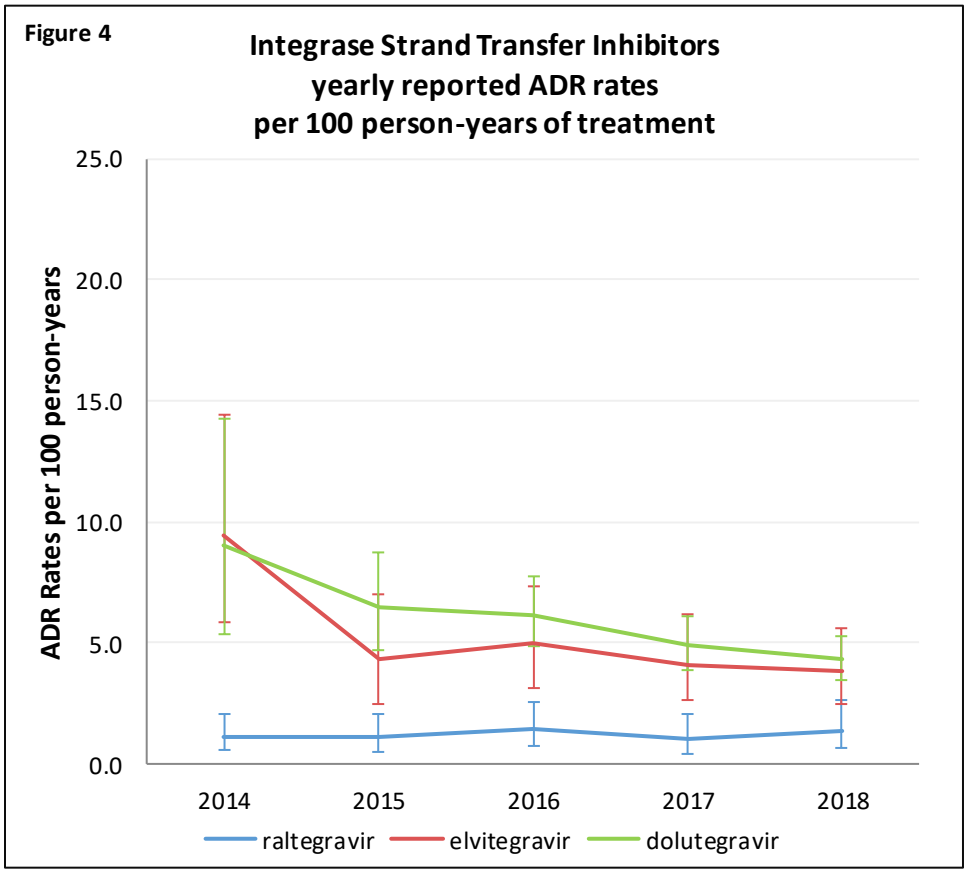
Figure 3. Non-Nucleoside Reverse Transcriptase Inhibitors ADRs associated with ART for HIV treatment



Number of Adverse Drug Reaction (ADR) reports / Total patient-years drug exposure					
	2014	**2015**	**2016**	**2017**	**2018**
efavirenz	153/ 1224	114/ 1080	82/ 942	87/ 820	59/ 697
etravirine	7/ 289	4/ 297	9/ 288	10/ 262	7/ 233
nevirapine	15 /911	9/ 863	15/ 818	7/ 768	5/ 710
rilpivirine	22/ 243	12/ 245	5/ 253	10/ 271	10/ 301

Graph does not display data for years in which there was less than 100 person-years drug exposure.

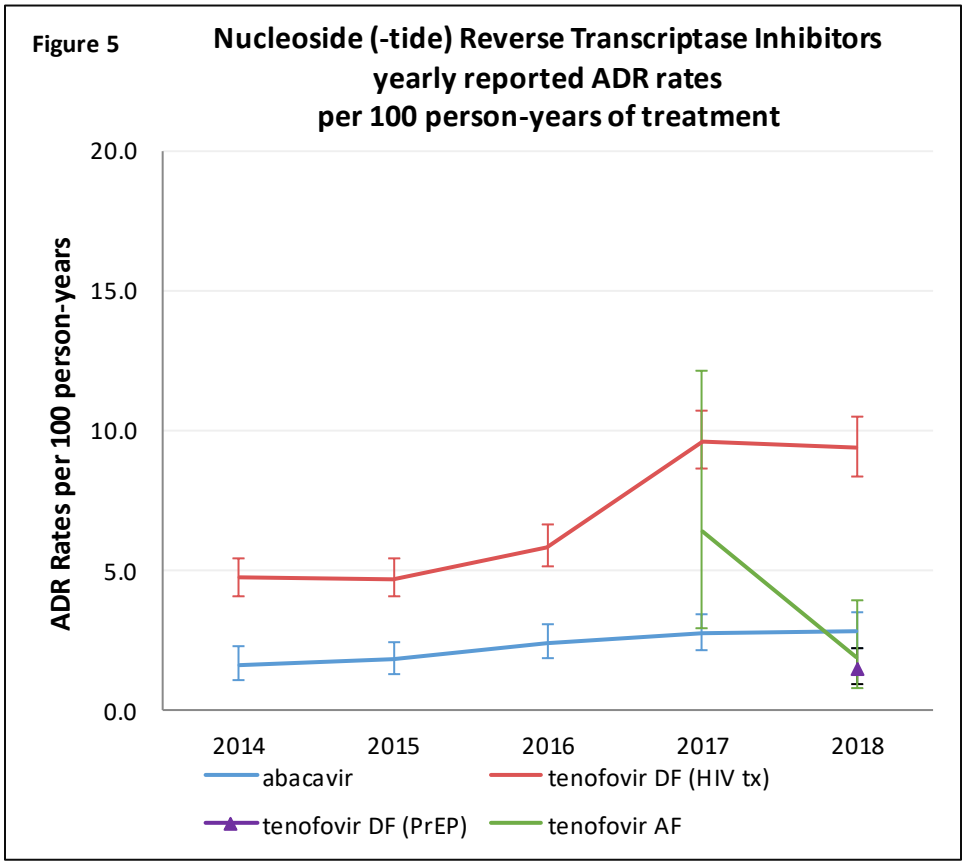
Figures 4. Integrase Strand Transfer Inhibitor ADRs associated with ART for HIV treatment



Number of Adverse Drug Reaction (ADR) reports / Total patient-years drug exposure					
	2014	**2015**	**2016**	**2017**	**2018**
raltegravir	10/ 882	9/ 828	11/ 762	7/ 691	9/ 645
elvitegravir	21/ 222	16/ 369	24/ 484	23/ 561	24/ 636
dolutegravir	18/ 200	45/ 692	73/ 1182	82/1671	89/ 2087

Graph does not display data for years in which there was less than 100 person-years drug exposure.

Figures 5. Nucleoside (-tide) Reverse Transcriptase Inhibitor ADRs associated with ART for HIV treatment or PrEP



Number of Adverse Drug Reaction (ADR) reports / Total patient-years drug exposure					
	2014	**2015**	**2016**	**2017**	**2018**
abacavir	32/ 1998	40/ 2226	60/ 2508	76/ 2796	85/ 3035
tenofovir DF (HIV tx)	193/ 4082	190/ 4054	229/ 3920	353/ 3667	309/ 3299
tenofovir DF (PrEP)	no data	no data	no data	no data	22/ 1505
tenofovir AF	no data	no data	1/ 13	9/ 141	7/ 370

Graph does not display data for years in which there was less than 100 person-years drug exposure.

Tenofovir AF, tenofovir alafenamide; Tenofovir DF, tenofovir disoproxil fumarate.

ADR rates associated with use of tenofovir DF for HIV treatment (HIV-tx) and pre-exposure prophylaxis (PrEP) are reported separately

Adverse Drug Reaction Rates by Symptom Category, associated with ART for HIV treatment

This section focuses on ART for HIV treatment.

Figures 6a-6c display annual ADR rates over the past five years by clinical effect.

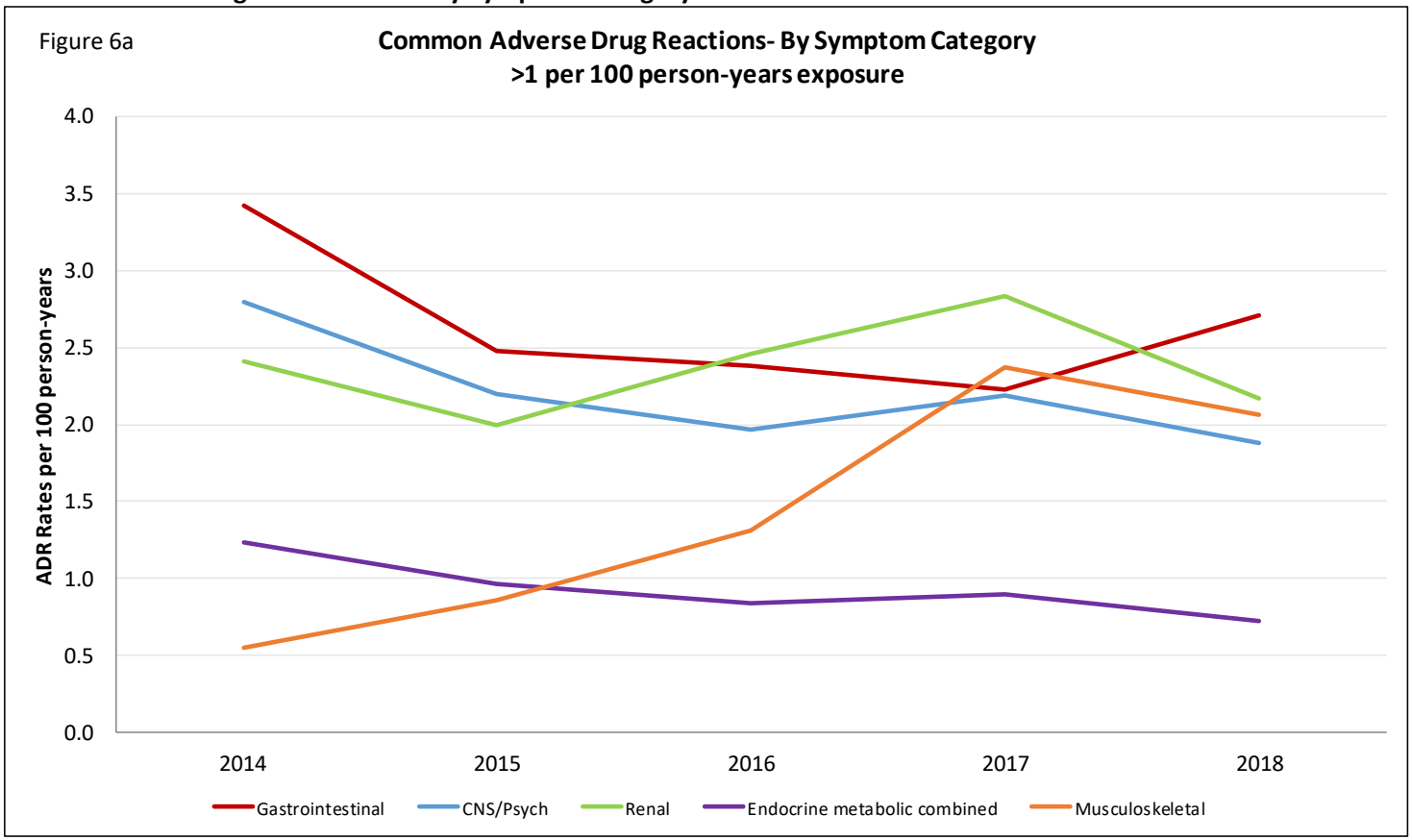
ADR rates are shown for the total population of persons receiving antiretrovirals for treatment of HIV. Symptom categories are organized by body system (renal, hepatic, gastrointestinal, etc.) and stratified into common (>1), uncommon (0.1-1.0) and rare (<0.1) ADR events per 100 person-years of ART exposure.

In all analyses in this section (Figs 6a-6c), ADR reports involving more than one clinical category are counted once in each clinical category per person per year. Duplicate reports of the same event, ADRs with a causality assessment of "unlikely" and reports of therapy change to prevent ADRs or drug interactions are excluded.

See Appendix for details regarding calculation of rates.

Adverse Drug Reaction Rates by Symptom Category, associated with ART for HIV treatment
Figures 6a-6c. Adverse Drug Reaction Rates by Symptom Category

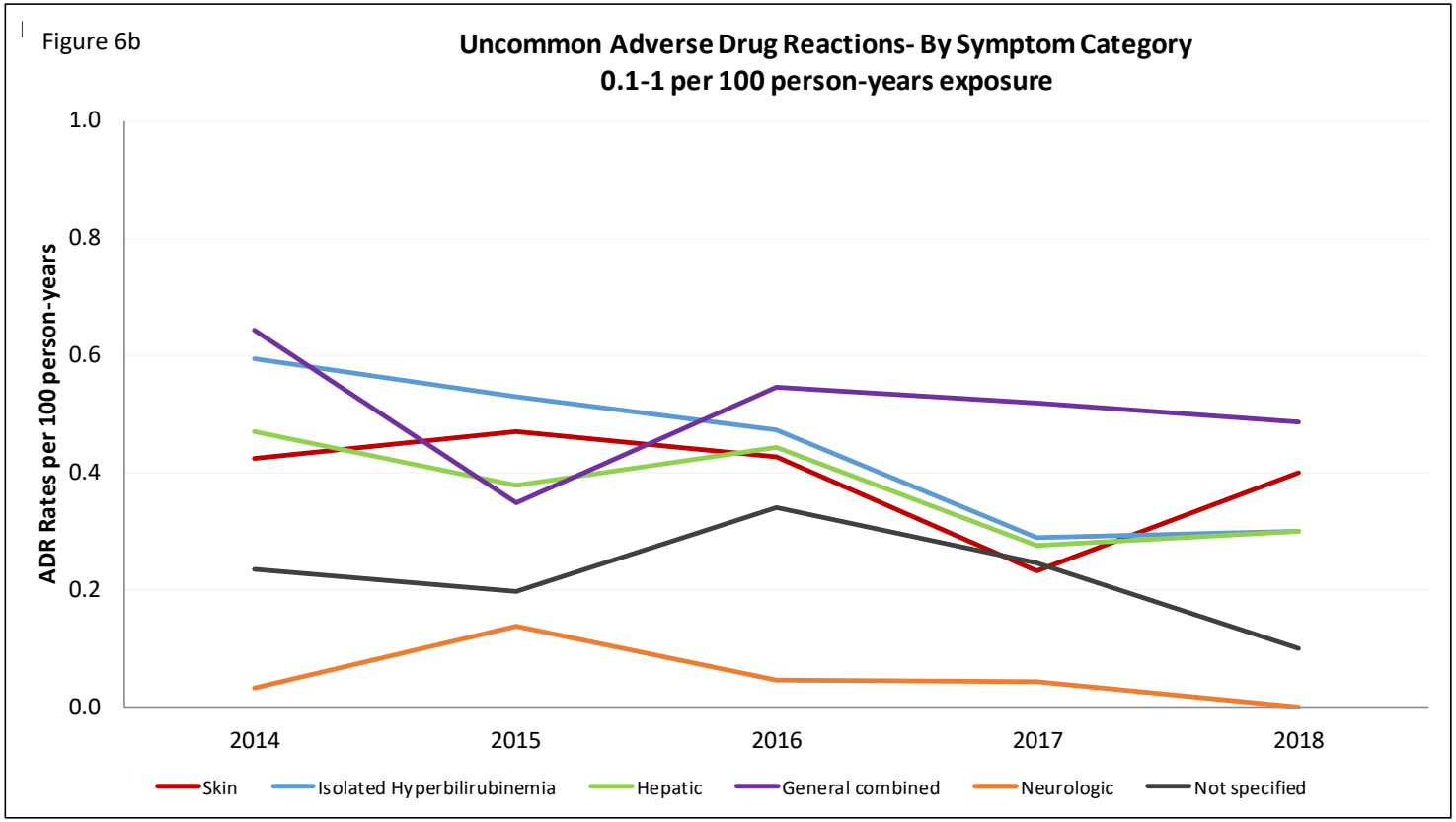
Figure 6a



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

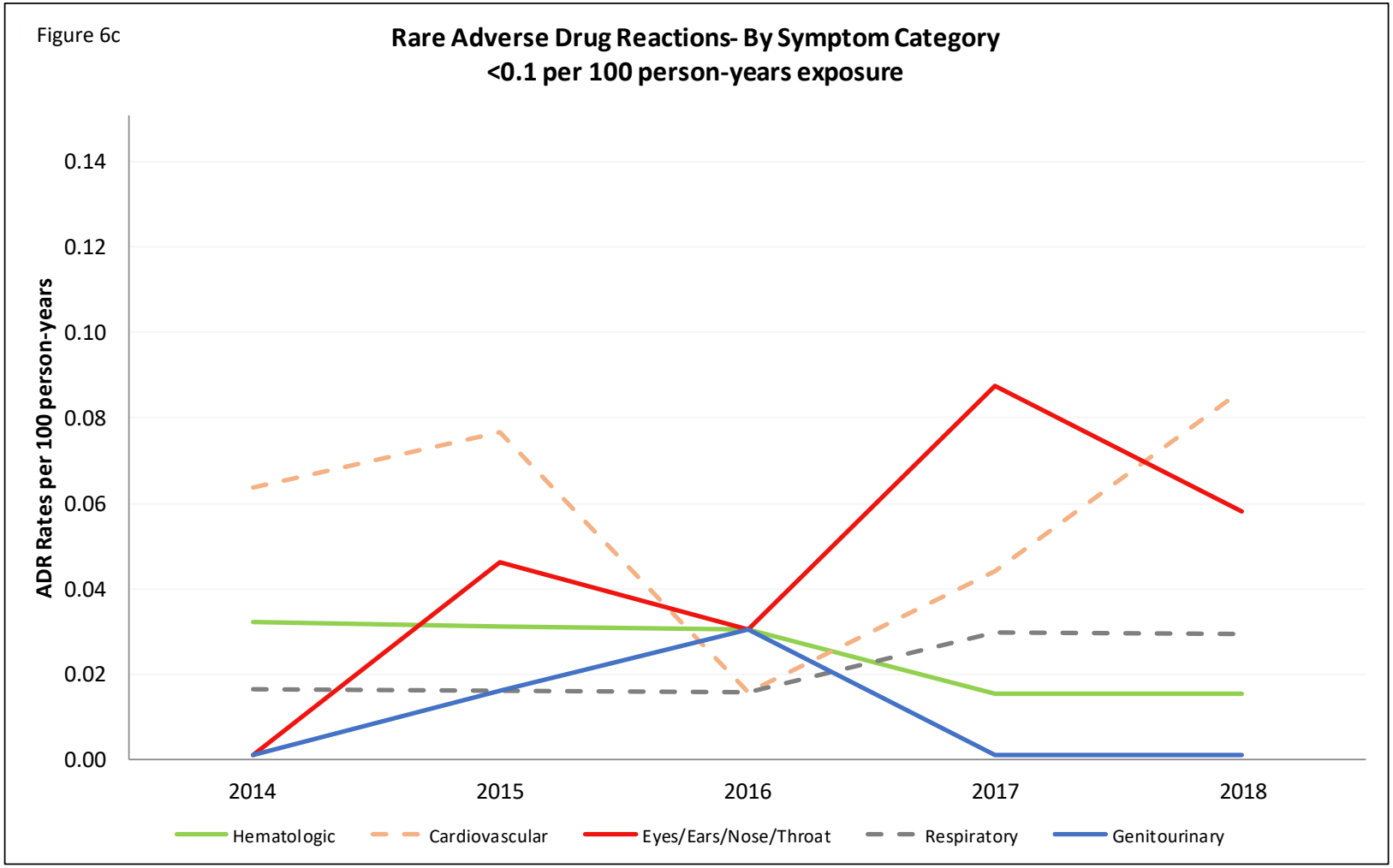
Figure 6b



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 Associated with ART for HIV Treatment or PrEP

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.

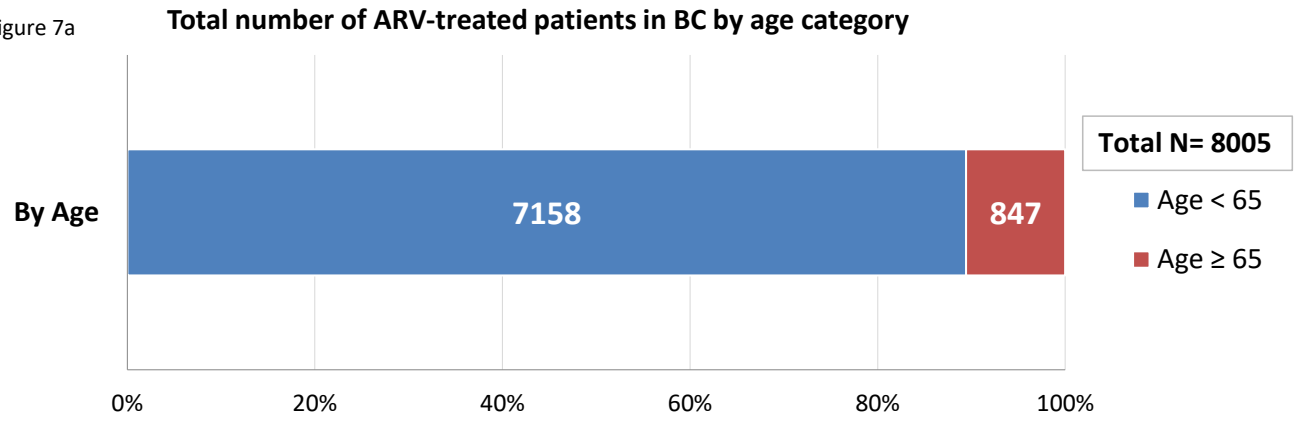
In 2018, 11/681 (1.6%) of adverse drug reaction reports (excluding duplicates and "unlikely" causality) were classified as serious. A total of 38/681 (5.6%) ADR reports were submitted to Health Canada, including two adverse reactions to PrEP medication. As part of a focused monitoring initiative regarding generic ARVs, sixteen reports submitted to Health Canada involved reported intolerance of a generic medication following switch from brand name product. These included several reports of minor, non-specific symptoms and one complaint subsequently evaluated as unlikely related to the antiretroviral medicine.

Adverse Drug Reactions Associated with ART for HIV Treatment in Special Populations

Figures 7a-8b examine ADR reports stratified by age and sex.

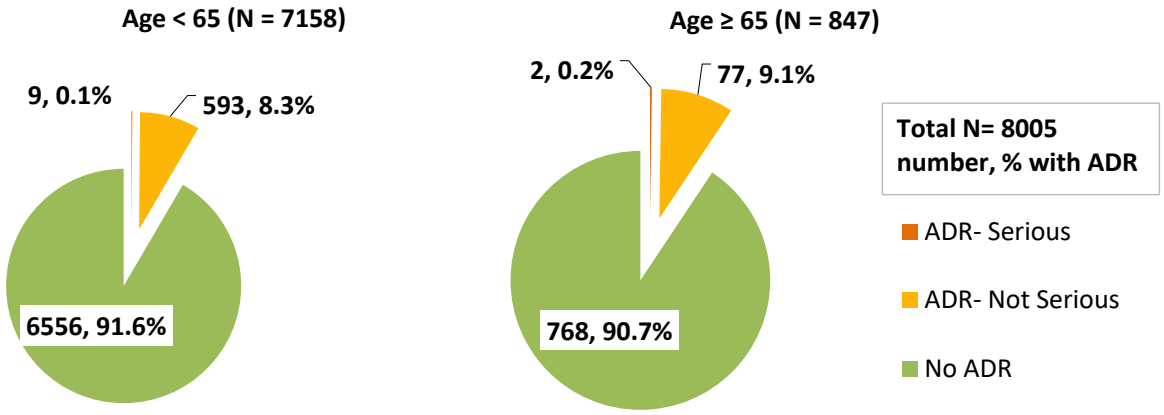
Adverse Drug Reactions associated with ART for HIV treatment, stratified by age category

Figure 7a



Proportion of ADR reports in ART-treated persons by age

Figure 7b



Summary: Seniors ≥65 years of age represent approximately 11% of the total ARV-treated population. The proportion of seniors with a reported ARV ADR in 2018 was slightly higher than for younger persons, but this difference was not statistically significant. ADRs most commonly reported in seniors were similar to the general population, with renal, gastrointestinal, musculoskeletal (bone health) and central nervous system symptoms accounting for the majority of reports.

Figure 8. Adverse Drug Reactions associated with ART for HIV treatment, stratified by biological sex

Figure 8a

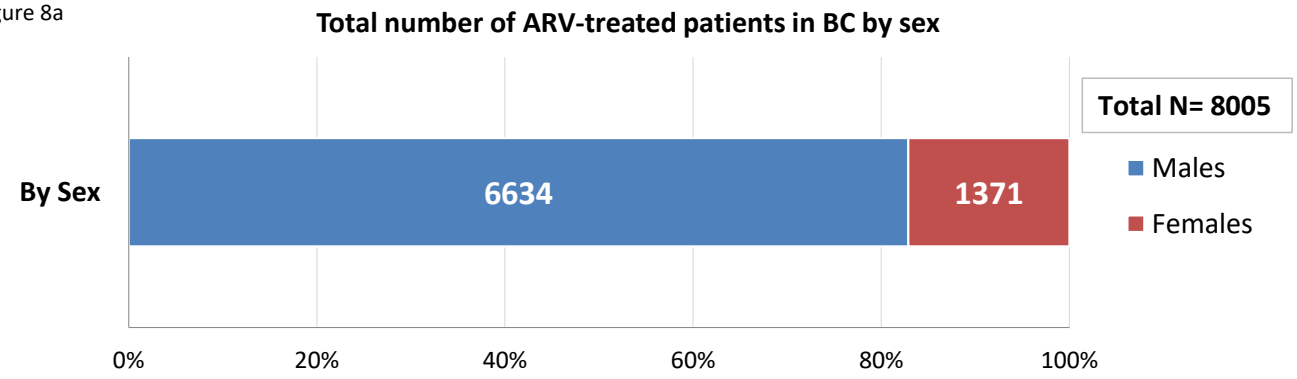
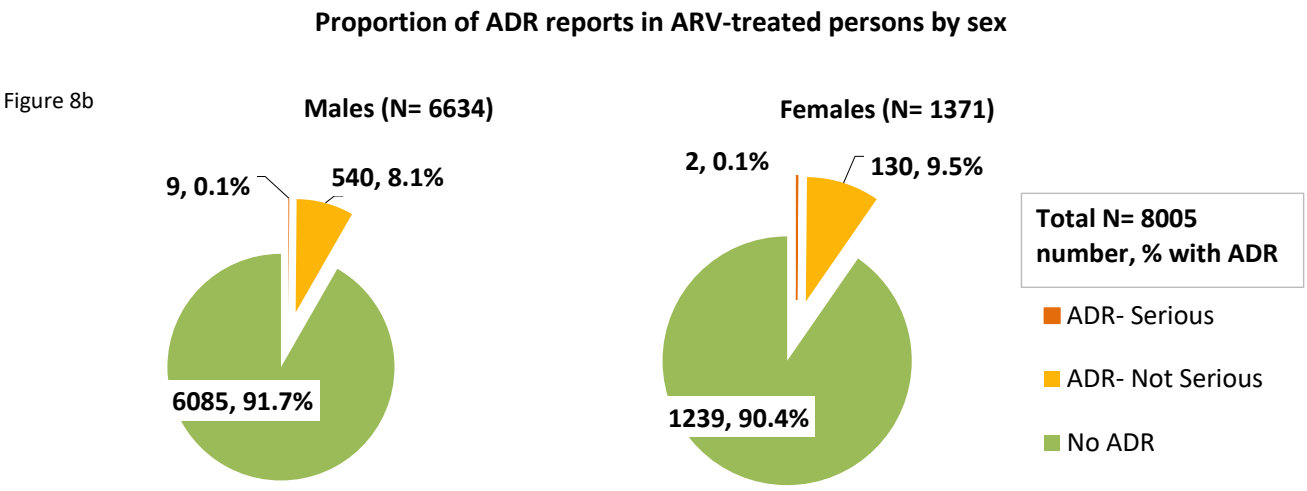


Figure 8b

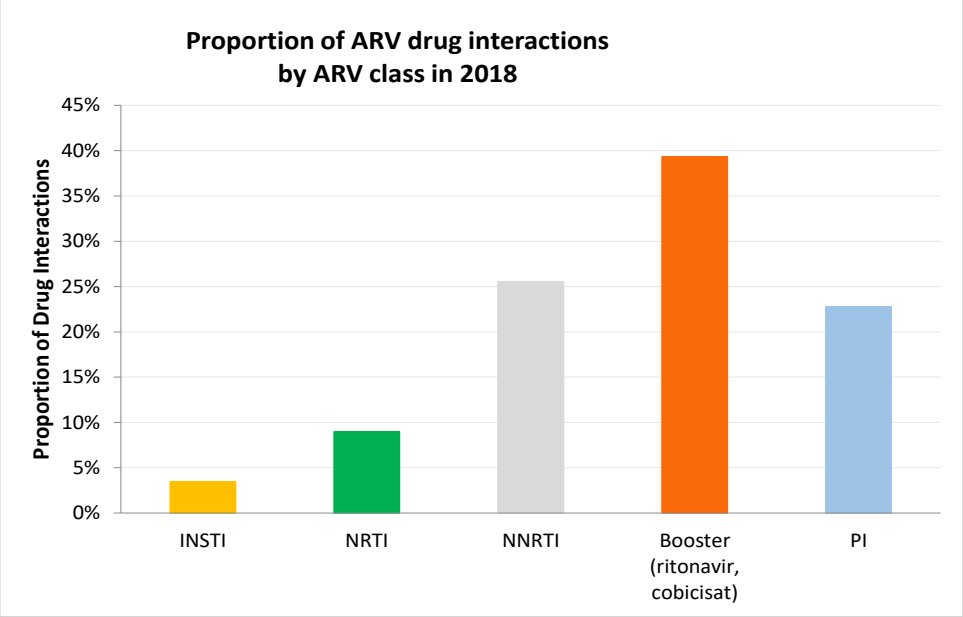


Summary: Females represent approximately 17% of the total ARV-treated population. The proportion of females with a reported ARV ADR was slightly higher than for males in 2018, but this difference was not statistically significant. ADRs most commonly reported in females were similar to the general population, with renal, gastrointestinal, musculoskeletal (bone health) and central nervous system symptoms accounting for the majority of reports.

Drug Interactions Associated with ART for HIV Treatment

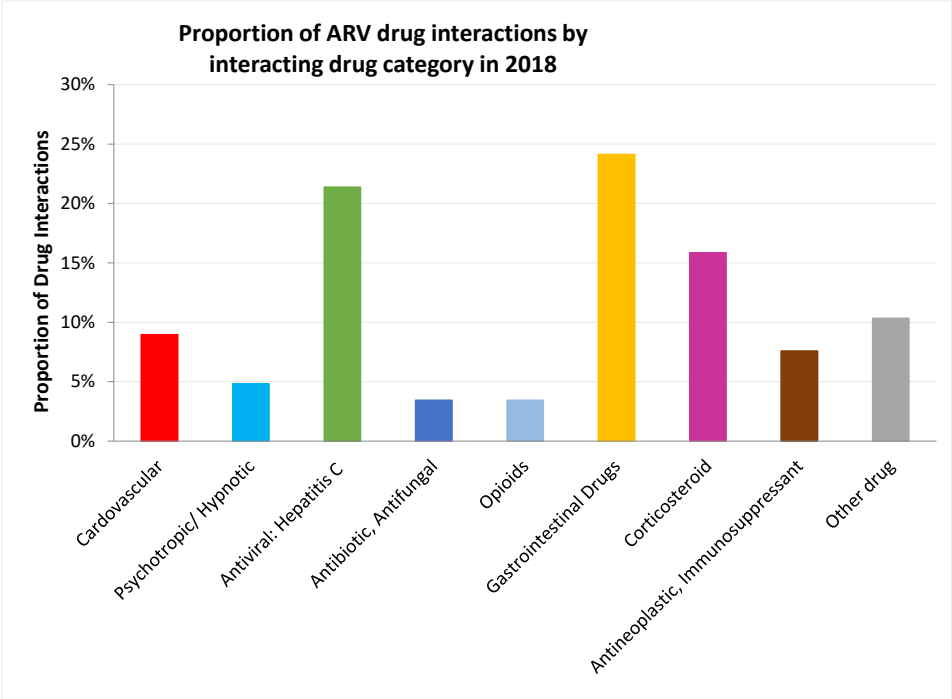
Figures 9 and 10 summarize antiretroviral drug interaction reporting patterns in 2018

Figure 9. Antiretroviral Drug interactions by ARV class



INSTI Integrase strand transfer inhibitor; NRTI Nucleoside(tide) reverse transcriptase inhibitor; NNRTI Non-nucleoside(tide) reverse transcriptase inhibitor; PI Protease inhibitor; "Booster" pharmacokinetic enhancer

Figure 10 Antiretroviral Drug Interactions by interacting drug category



As shown in Figures 9 and 10, above, pharmacokinetic 'boosters' (ritonavir and cobicistat), protease inhibitors (primarily atazanavir) and Non-nucleoside(tide) reverse transcriptase inhibitors (primarily efavirenz and nevirapine) account for the majority of antiretroviral drug interactions reported to the Pharmacovigilance initiative.

Drug interactions with gastrointestinal drugs (particularly gastric acid suppressing drugs) remain common, but are declining secondary to declines in prescribing of susceptible antiretrovirals (e.g. atazanavir). A high proportion of reported drug interactions continue to involve proactive changes in ART to avoid drug interactions with hepatitis C treatment. Interactions with cardiovascular drugs such as anticoagulant and antiplatelet medications are becoming more common, possibly associated with the evolving comorbidities in the aging cohort of persons living with HIV in BC. Drug interactions between the strong cytochrome P-450 CYP-3A inhibitors ritonavir or cobicistat and corticosteroids continue to be the most common drug interaction leading to adverse clinical effects (adrenal suppression).

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 taking antiretroviral medication for HIV treatment or prevention (PrEP) 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.
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.

Figure 1-5: Calculation of ADR rates, by antiretroviral drug: 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.

Figures 6a-c. Calculation of ADR Rates by symptom category: ADR reports contribute data for each relevant clinical category once per person in the calendar year the ADR was reported.
ADR rates are calculated as follows: In each calendar year, the numerator is the number of ADR reports specifying an adverse reaction for the symptom class of interest. The denominator is the total number of patient-years exposure to antiretroviral therapy for treatment of HIV during the calendar year. The resulting 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.