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

Annual Report 2019

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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Table of Contents

Introduction

The BC-CfE Pharmacovigilance Initiative collects, evaluates, and analyzes reports of drug toxicity and other adverse drug-related events associated with antiretroviral medications, 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 for HIV treatment or prevention 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 or prevent Human Immunodeficiency Virus (HIV) 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.
- **Antiretroviral drug classes:**
    - NRTI: Nucleoside (-tide) Reverse Transcriptase Inhibitor
    - NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor
    - PI: Protease Inhibitor
    - INSTI: Integrase Strand Transfer Inhibitor
    - PK Enhancer: Pharmacokinetic Enhancer ("booster")

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 patients receiving antiretroviral treatment	Adverse Drug-Related Event reports All categories, excluding duplicates	
		Total per year	Average per month
2015	7624	812	68
2016	7803	841	70
2017	7905	952	79
2018	7995	927	77
2019	**8106**	**917**	**76**

Table 2a. Adverse Drug-Related Events Associated with ART for HIV treatment- 2019

Information Category	Reports including duplicates N= 921 n(%)	Reports excluding duplicates N= 917 n(%)
Event Type		
Adverse Drug Reaction	659 (71.2)	655 (71.4)
Adverse Drug Reaction Prevention	118 (13.1)	118 (13.0)
Drug Interaction, Symptomatic	1 (0.1)	1 (0.1)
Drug Interaction Prevention	143 (15.6)	143 (15.6)
Information Source		
Prescription	916 (99.5)	*
Therapy Interruption Alert	2 (0.2)	*
Spontaneous Report	3 (0.3)	*
Reporter Type		
Physician	671 (72.9)	*
Pharmacist	249 (27.0)	*
Other Healthcare Professional	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 patients receiving antiretroviral treatment	Adverse Drug-Related Event reports All categories, excluding duplicates	
		Total per year	Average per month
2015	No data		
2016	No data		
2017	No data		
2018	3186	22	2
2019	**5009**	**55**	**5**

Table 2b. Adverse Drug-Related Events Associated with ARVs for PrEP- 2019

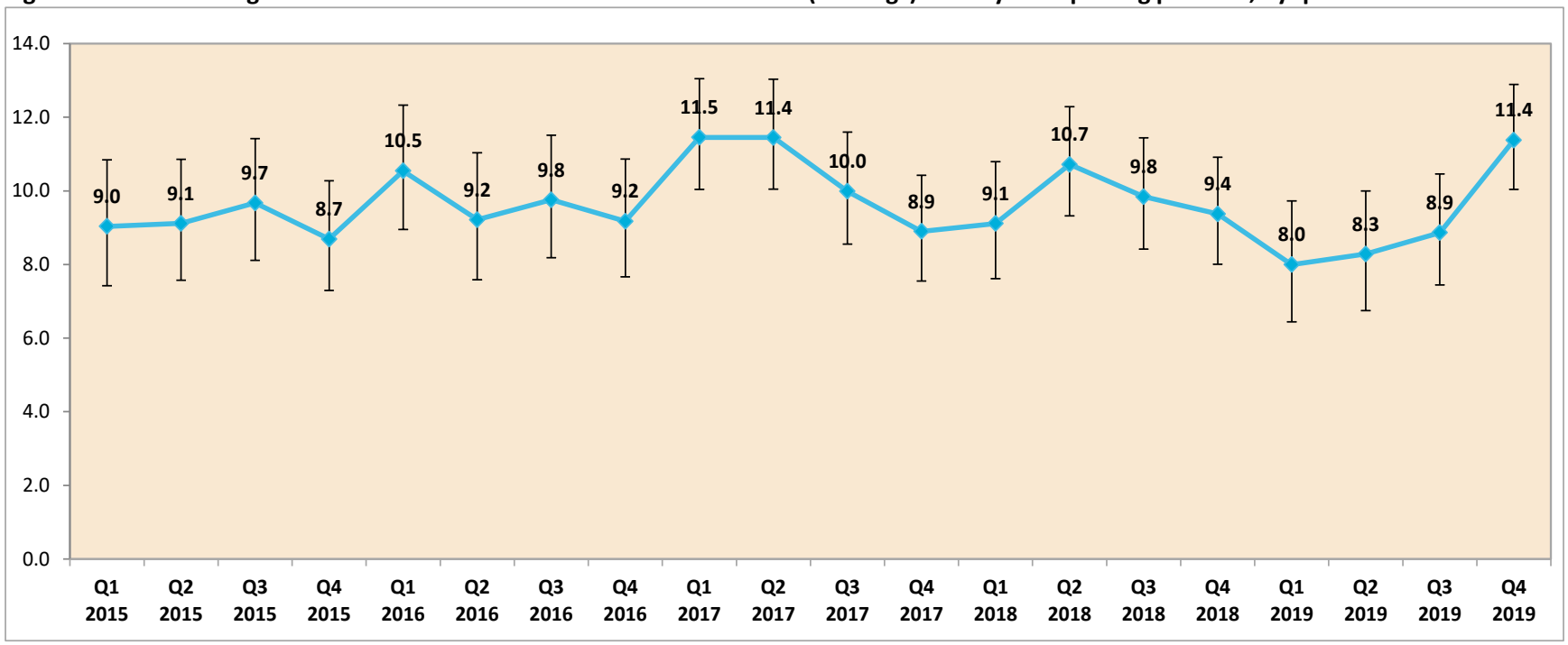
Information Category	Reports including duplicates N= 56 n(%)	Reports excluding duplicates N= 55 n(%)
Event Type		
Adverse Drug Reaction	54 (96.4)	53 (96.4)
Adverse Drug Reaction Prevention	2 (3.6)	2 (3.6)
Information Source		
Prescription	21 (37.5)	*
Therapy Interruption Alert	31 (55.4)	*
Spontaneous Report	4 (7.1)	*
Reporter Type		
Physician	47 (83.9)	*
Pharmacist	3 (5.3)	*
Other Healthcare Professional	4 (7.1)	*
Client/ Community member	2 (3.6)	*

*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



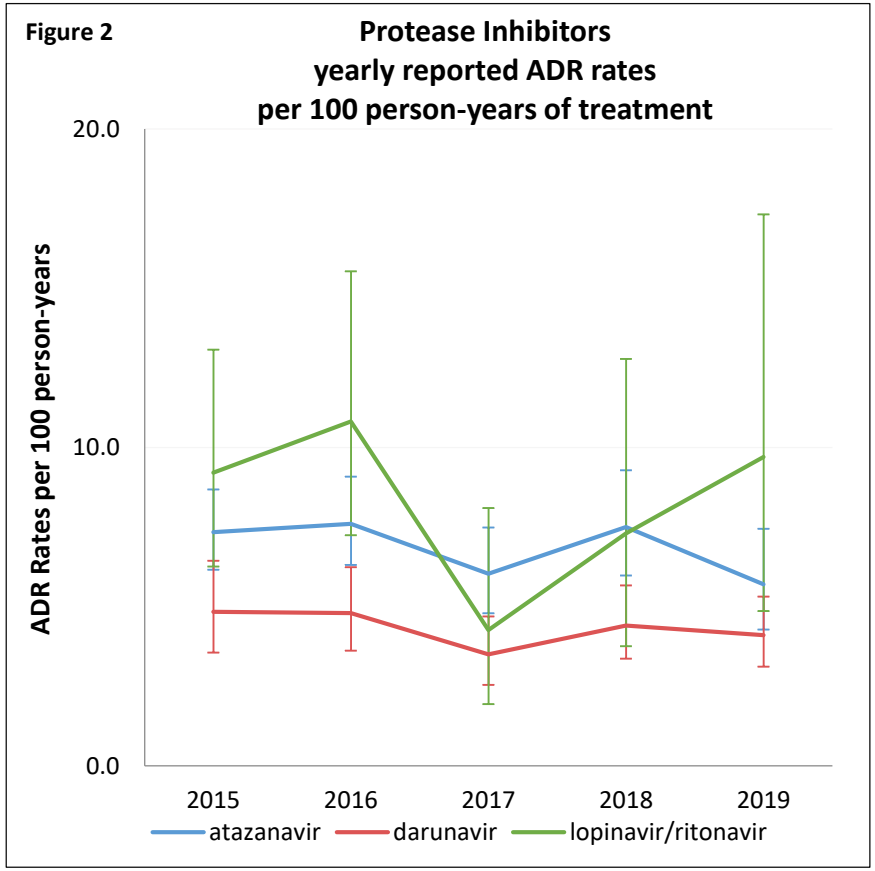
ADR rates are calculated as follows: Within each quarter (3 month period), the numerator is the number of ADR reports specifying an adverse reaction attributed to the drug of interest. The denominator is the total number of patient-years exposure to the drug, accrued during the quarter. The resulting 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.

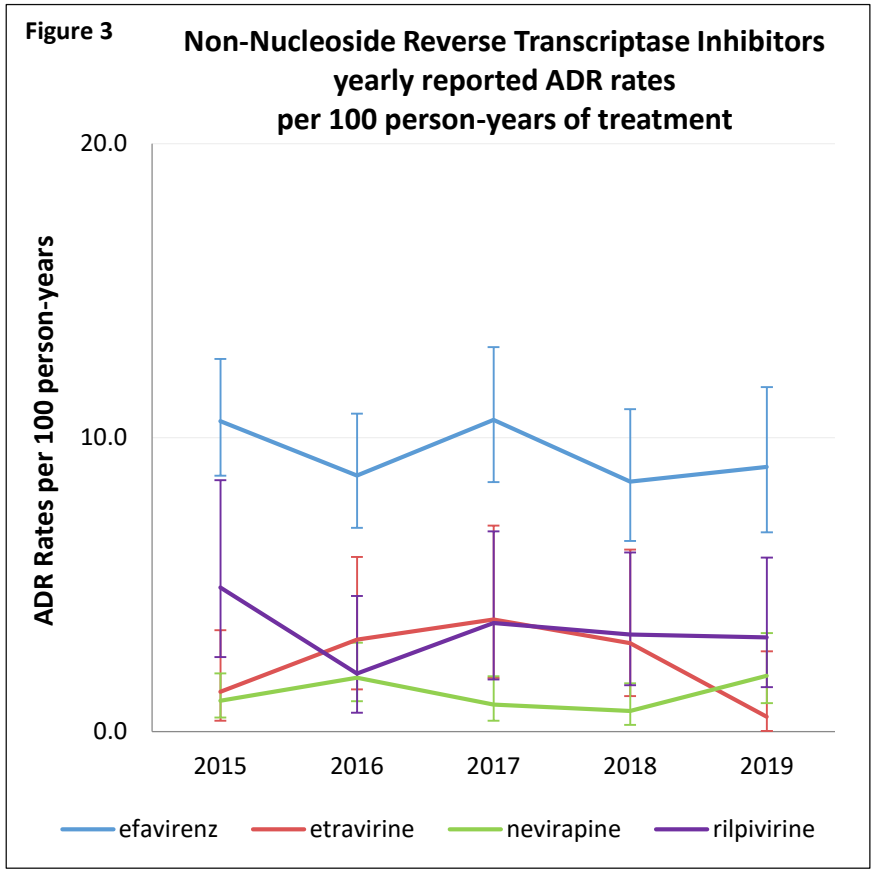
Figures 2 to 5 display annual ADR rates over the past five years for the most commonly used ARVs. For each ARV, ADR rates are shown for all persons treated during the calendar year. See Appendix for details regarding calculation of rates.

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



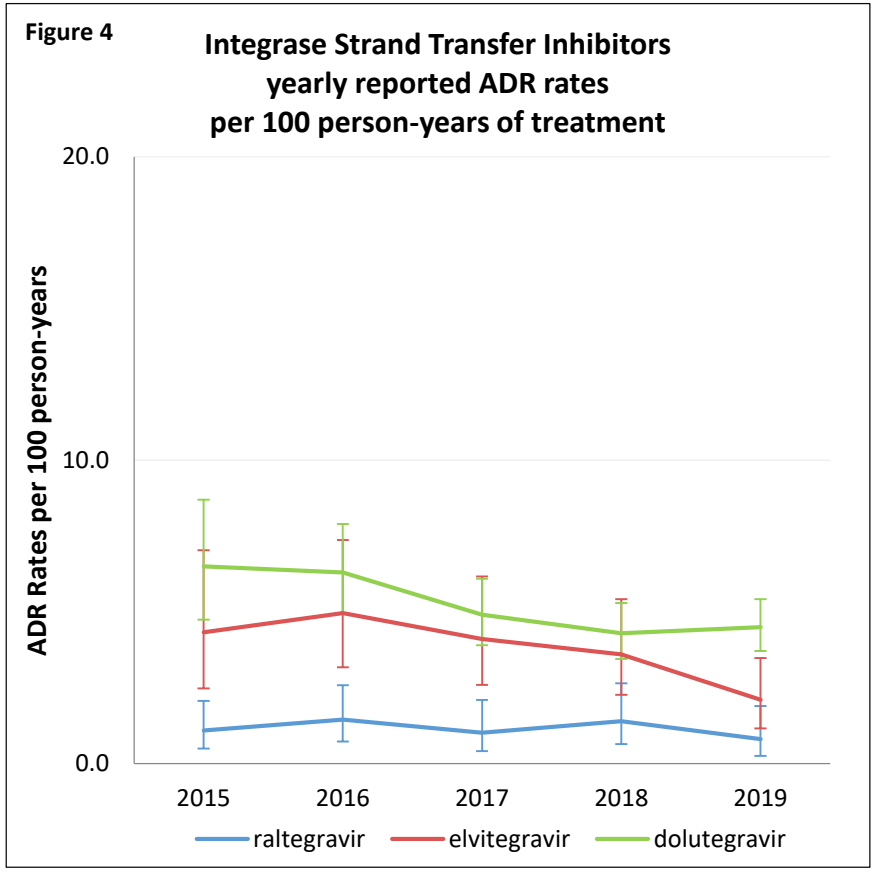
Number of Adverse Drug Reaction (ADR) reports / Total patient-years drug exposure					
	2015	**2016**	**2017**	**2018**	**2019**
atazanavir	136/ 1854	122/ 1604	82/ 1356	84/ 1122	54/ 948
darunavir	47/ 972	54/ 1153	45/ 1275	58/ 1349	57/ 1391
lopinavir	31/ 337	29/ 268	9/ 211	12/ 164	11/ 114

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					
	2015	**2016**	**2017**	**2018**	**2019**
efavirenz	114/ 1080	82/ 942	87/ 818	59/ 696	55/ 611
etravirine	<5/ 297	9/ 288	10/ 262	7/ 233	<5/ 205
nevirapine	9/ 863	15/ 818	7/ 768	5/ 710	12/ 618
rilpivirine	12/ 245	5/ 253	10/ 270	10/ 301	10/ 309

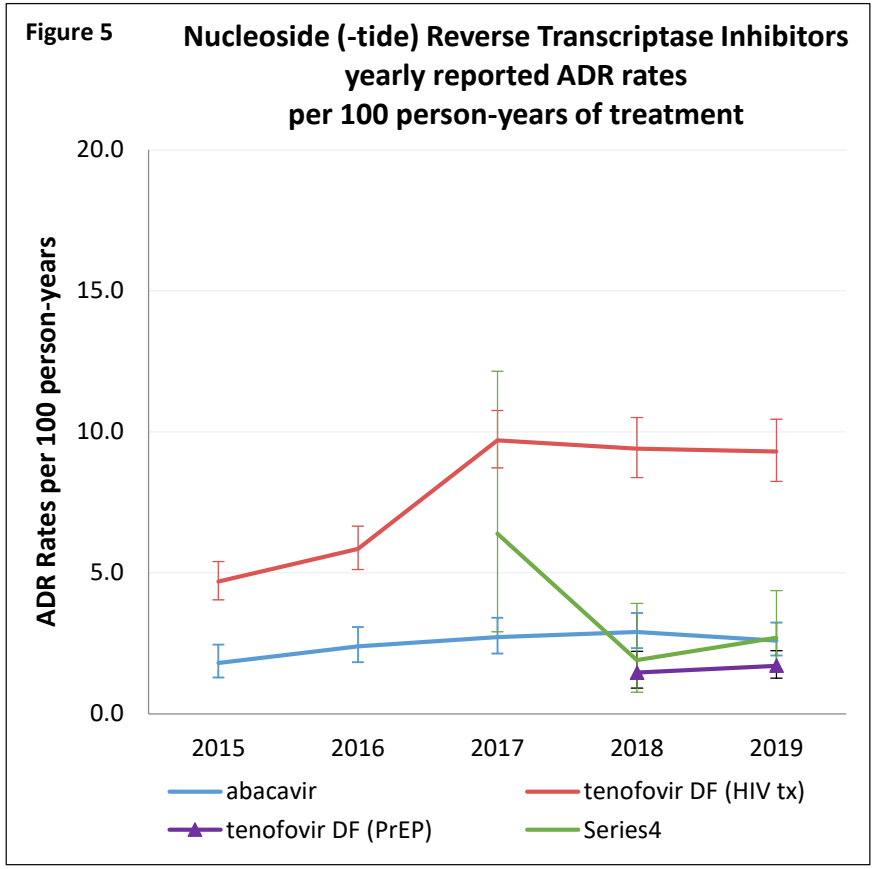
Figure 4. Integrase Strand Transfer Inhibitor ADRs associated with ART for HIV treatment



Number of Adverse Drug Reaction (ADR) reports / Total patient-years drug exposure					
	2015	**2016**	**2017**	**2018**	**2019**
raltegravir	9/ 828	11/ 761	7/ 690	9/ 644	5/ 609
elvitegravir	16/ 369	24/ 484	23/ 558	23/ 634	15/ 707
dolutegravir	45/ 692	74/ 1182	82/ 1666	90/ 2083	110/ 2468
bictegravir	no data	no data	no data	limited data	<5/ 35

Due to small numbers, data for bictegravir are displayed in tabular format, but omitted from the graph in Fig 4**.**

Figure 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					
	2015	**2016**	**2017**	**2018**	**2019**
abacavir	40/ 2226	60/ 2508	76/ 2789	87/ 3029	83/ 3168
tenofovir DF (HIV tx)	190/ 4054	229/ 3917	353/ 3654	310/ 3289	283/ 3036
tenofovir DF (PrEP)	no data	no data	no data	22/ 1505	52/ 3025
tenofovir AF	no data	limited data	9/ 141	7/ 370	16/ 598

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.

This section focuses on ART for HIV treatment.

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

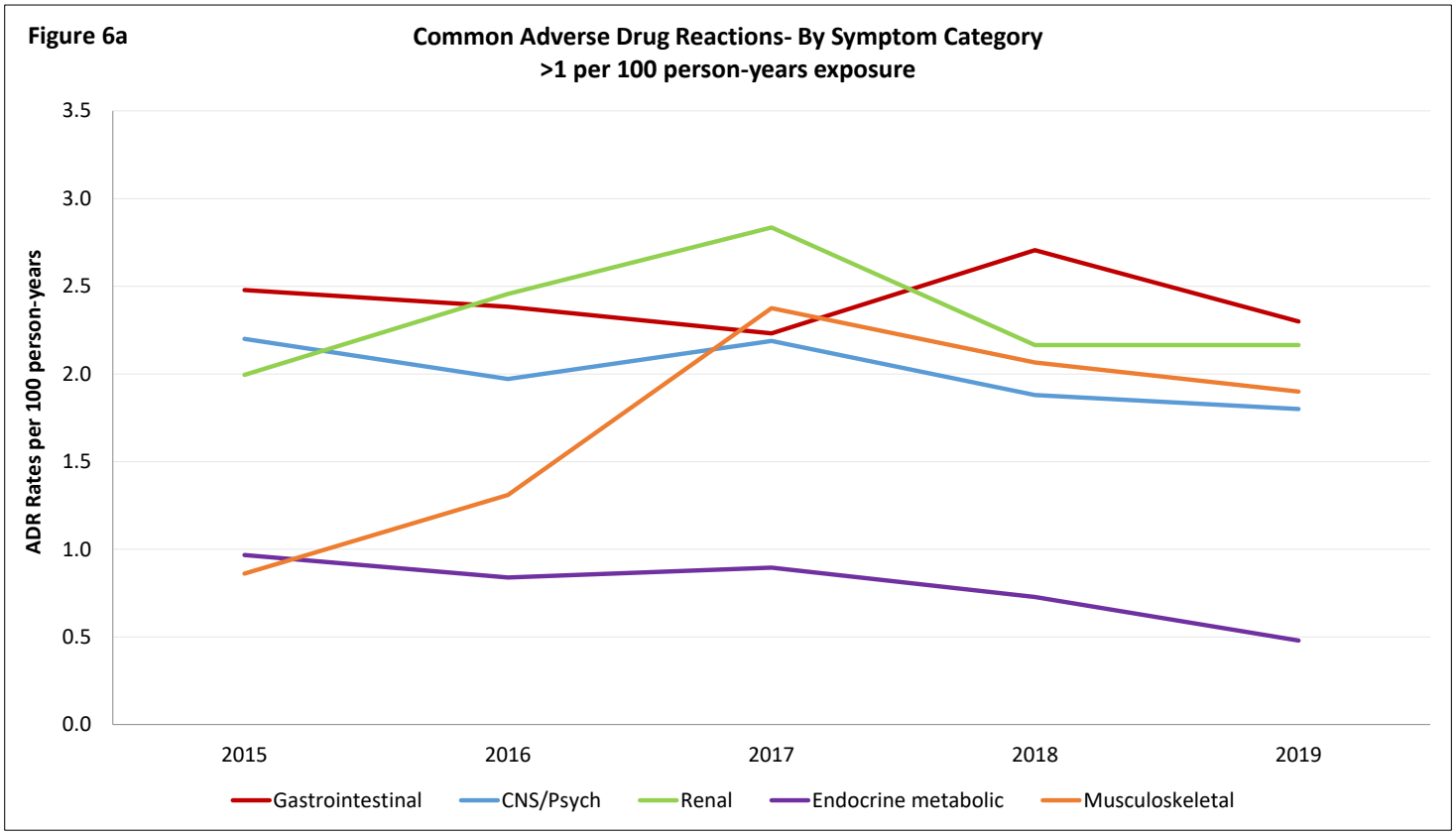
ADR rates are shown for the total population of persons receiving antiretrovirals for treatment of HIV. Symptom categories are organized by body system (renal, hepatic, gastrointestinal, etc.) and stratified into common (>1), uncommon (0.1-1.0) and rare (<0.1) ADR events per 100 person-years of ART exposure.

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

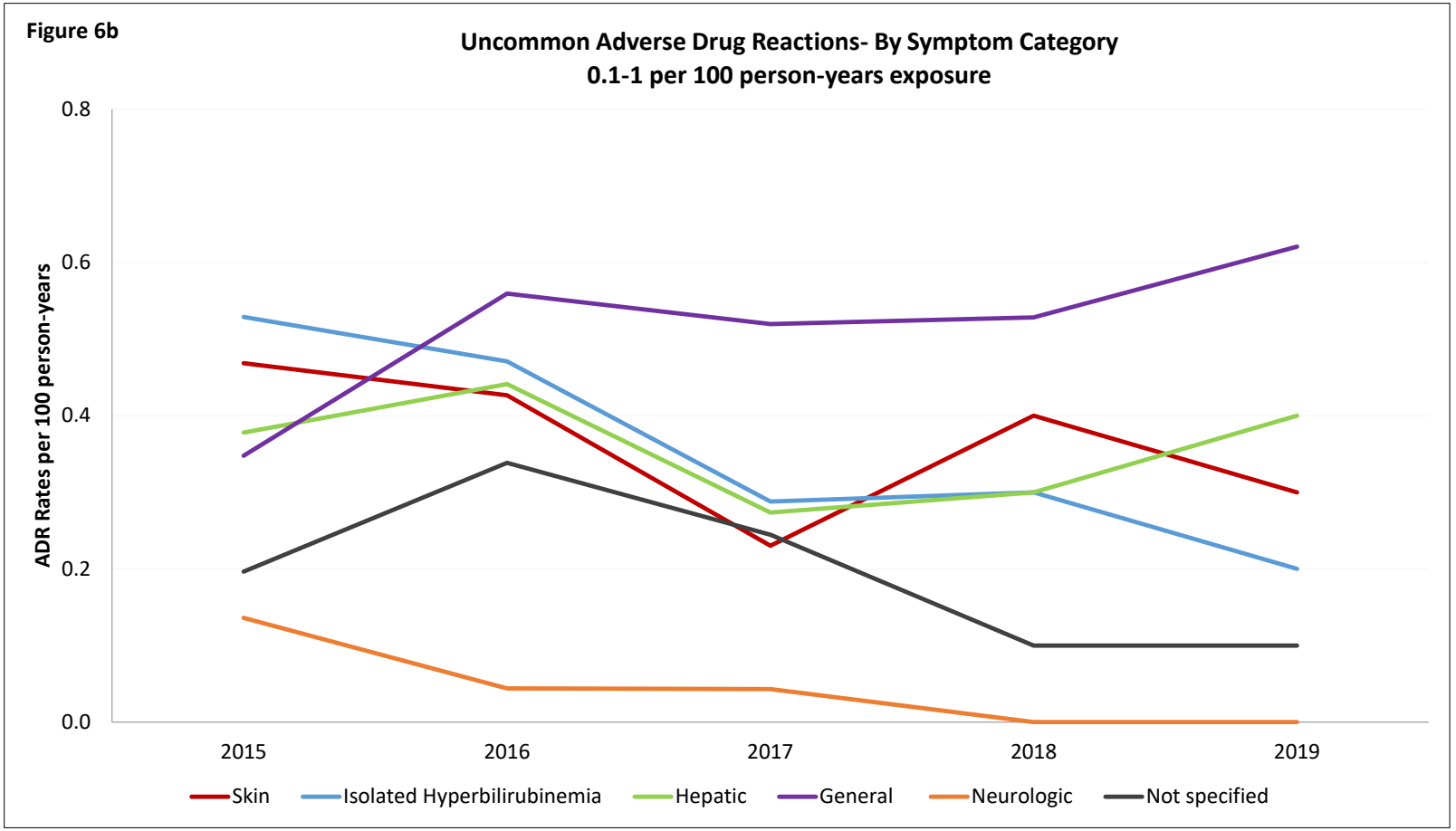
Figures 6a-6c. Adverse Drug Reaction Rates by Symptom Category



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, blood glucose elevated
Musculoskeletal:	bone mineral loss (osteopenia, osteoporosis), myalgia/arthralgia

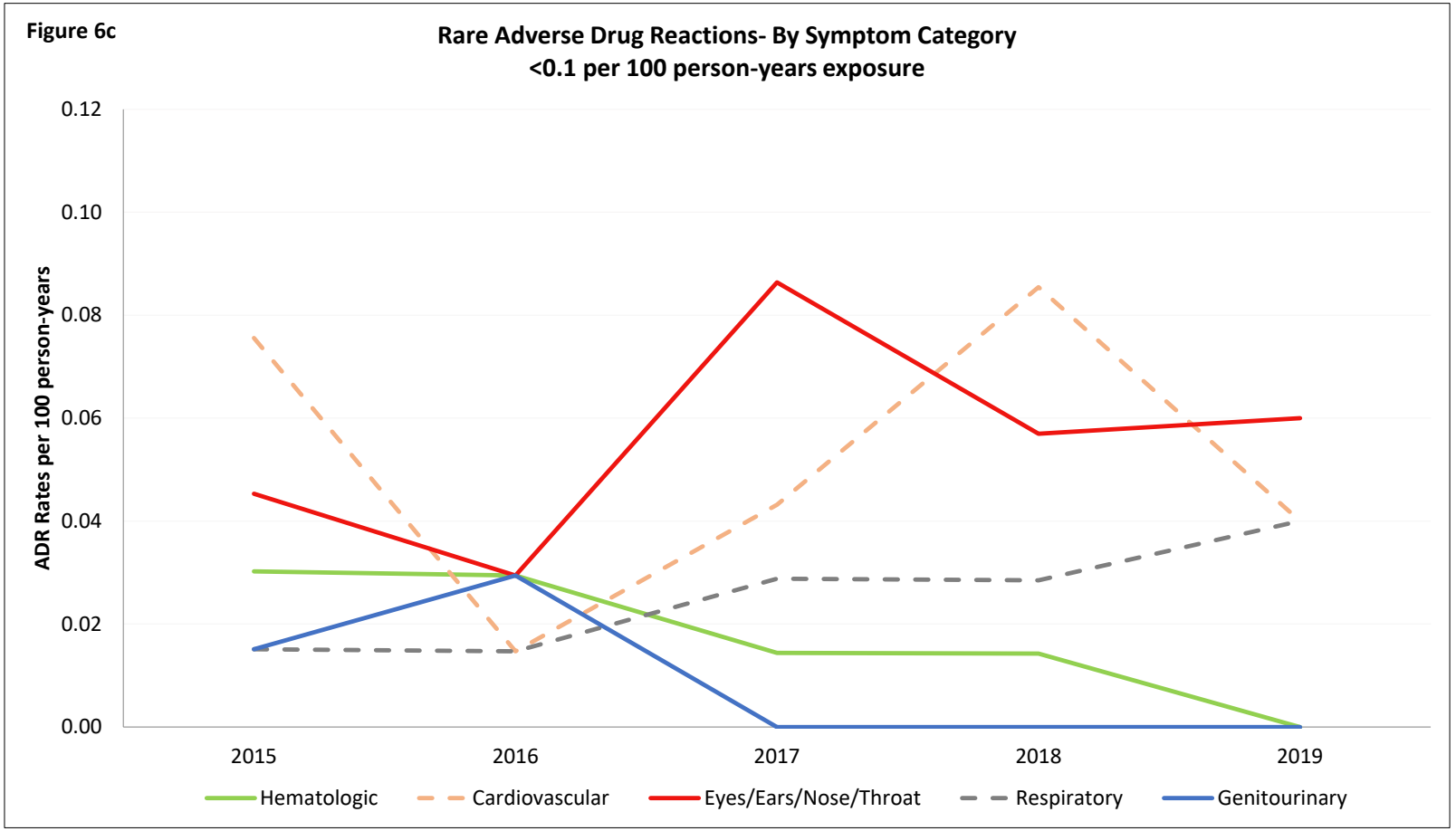
Figure 6b



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:	Abnormal liver function tests, bilirubin elevated, cholelithiasis, hepatic transaminase AST/ALT elevated
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:	hypertension, flushing, cardiotoxicity
Eyes/ears/nose/throat:	visual changes, nasal or sinus congestion, tinnitus, throat or mouth irritation
Respiratory:	cough (persistent/chronic), 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 2019, 21/648 (3.2%) of adverse drug reaction reports (excluding duplicates and "unlikely" causality) were classified as serious. A total of 47/648 (7.3%) ADR reports were submitted to Health Canada, including five adverse reactions to PrEP medication. As part of a focused monitoring initiative regarding generic ARVs, three reports submitted to Health Canada involved reported intolerance of a generic medication following a switch from the brand name product.

Adverse Drug Reactions Associated with ART for HIV Treatment in Special Populations
Figures 7a-8b examine ADR reports stratified by age and sex.

Figure 7a. Total Number of ART-treated Patients in BC by Age (N=8106)

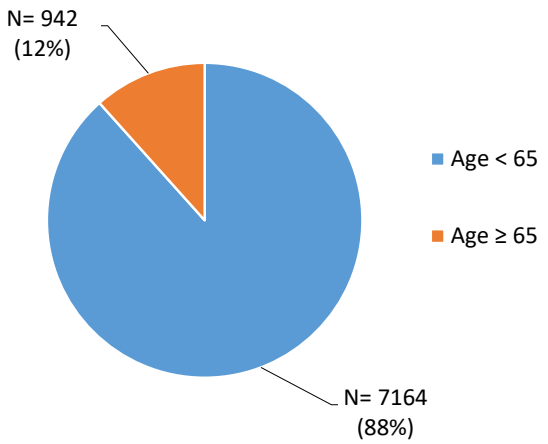
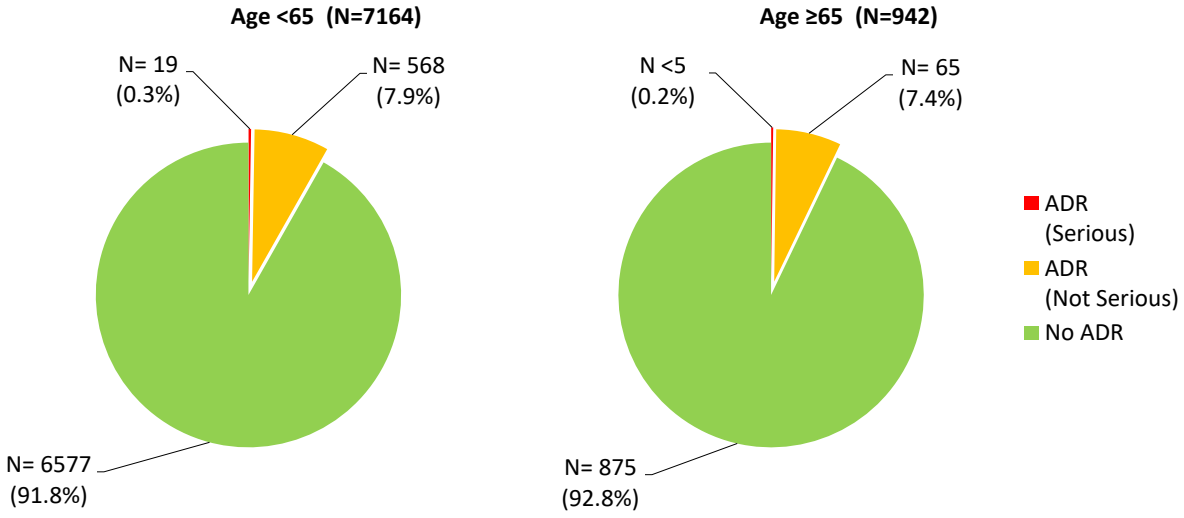


Figure 7b. Proportion of ADR Reports in ART-Treated Patients by Age



Summary: Seniors ≥65 years of age represent approximately 12% of the total ARV-treated population. The proportion of seniors with a reported ARV ADR in 2019 was slightly lower than for younger persons (7.1% and 8.2% respectively), but this difference was not statistically significant (p value= 0.252). ADRs most commonly reported in seniors were similar to the general population, with renal, central nervous, gastrointestinal, and musculoskeletal (bone health) system symptoms accounting for the majority of reports (listed in declining order of frequency).

Figure 8a. Total Number of ART-treated Patients in BC by Sex (N=8106)

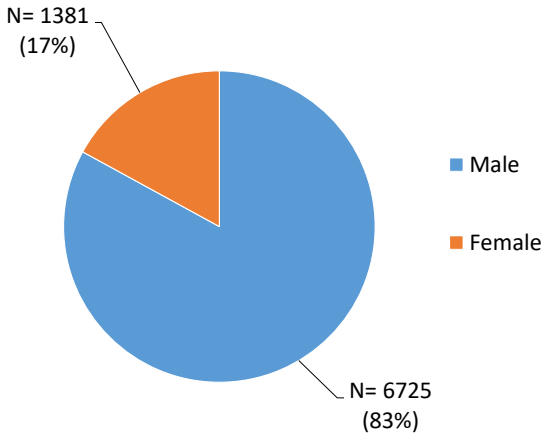
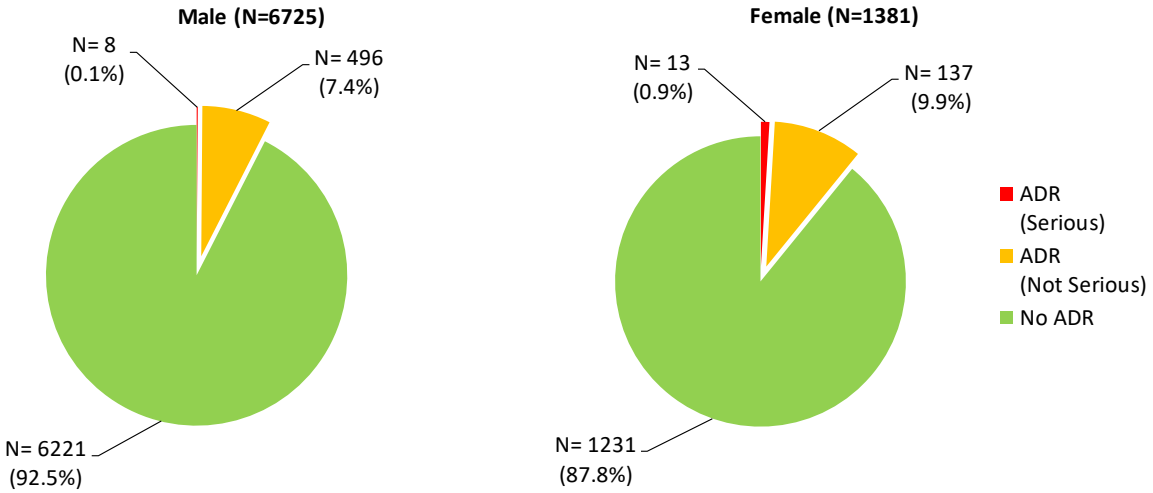


Figure 8b. Proportion of ADR Reports in ART-Treated Patients by Sex

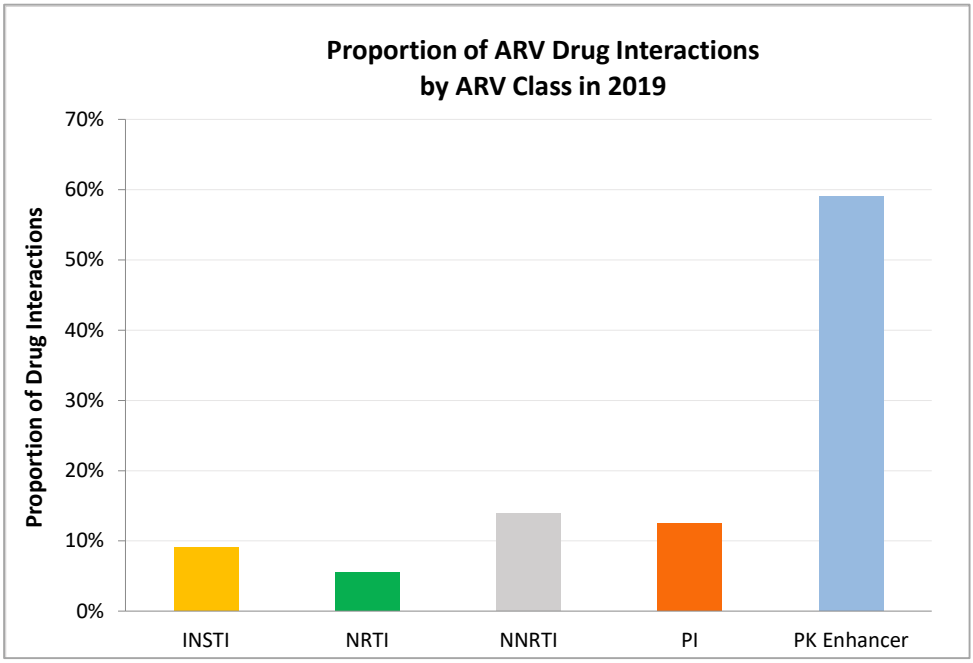


Summary: Females represent approximately 17% of the total ARV-treated population. In 2019, the proportion of females with a reported ARV ADR was higher than for males (10.9% and 7.5%, respectively), which was a statistically significant difference (p value <0.001). ADRs most commonly reported in females were similar to the general population, with gastrointestinal, musculoskeletal (bone health), renal, and central nervous system symptoms accounting for the majority of reports (listed in declining order of frequency)**.**

Drug Interactions Associated with ART for HIV Treatment

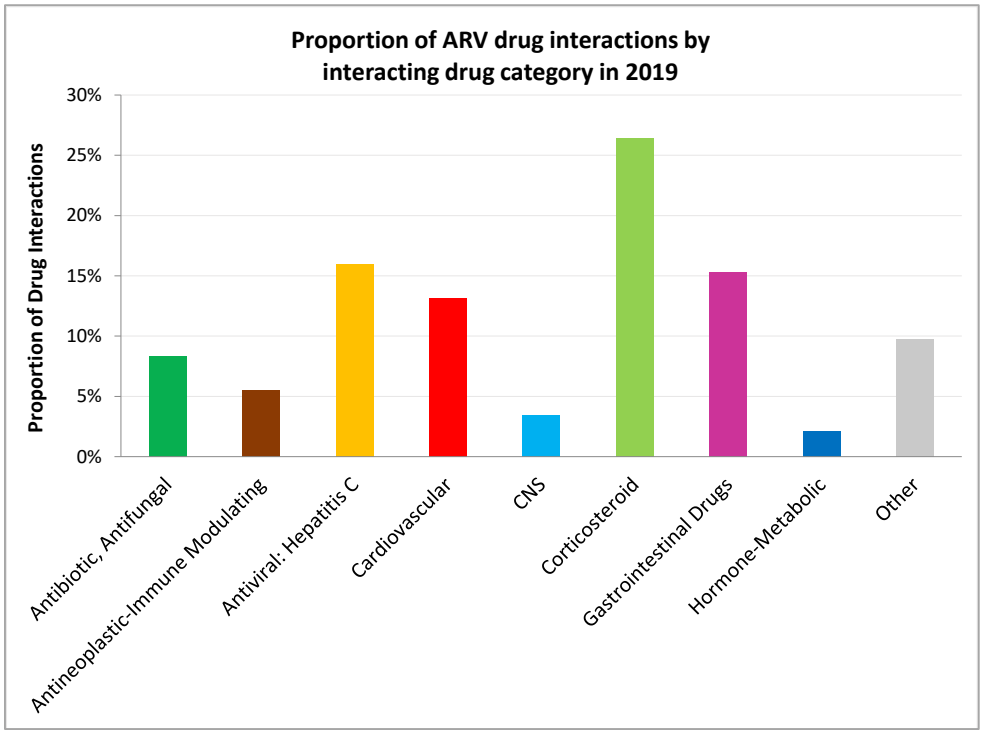
Figures 9 and 10 summarize antiretroviral drug interaction reporting patterns in 2018.

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; PK Enhancer: Pharmacokinetic enhancer

Figure 10. Antiretroviral Drug Interactions by interacting drug category



As shown in Figures 9 and 10, above, the pharmacokinetic enhancers ("boosters") cobicistat and ritonavir account for the majority of ART therapy changes related to drug interactions between HIV medications and other drugs. Interactions between ritonavir or cobicistat and corticosteroids continue to be the most common drug interaction leading to adverse clinical effects (adrenal suppression). Drug interactions with gastrointestinal drugs (particularly gastric acid suppressing drugs) are declining secondary to declines in prescribing of susceptible ARVs (e.g. atazanavir). Interactions with cardiovascular drugs (e.g. anticoagulant and antiplatelet medications) are becoming more common, possibly associated with the aging cohort of persons living with HIV in BC.

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.

For more information regarding adverse reaction reporting and HIV medication safety, refer to the BC-CfE website: http://bccfe.ca/hiv-drug-safety

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.