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

Annual Report: 2020

BRITISH COLUMBIA
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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 for HIV treatment and prevention. 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 or Pre-Exposure Prophylaxis (PrEP) 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, and all those who report adverse drug-related events and Drug Treatment Program and PrEP 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

Tables 1a, 2a and 1b, 2b summarize all reports of adverse drug related events associated with antiretroviral use for HIV treatment and Prevention, respectively. Overall reporting of events related to HIV treatment was increased in 2020, largely driven by an increase in preventative ART regimen changes to newer ARVs to minimize the risks of long-term ARV complications.

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
2016	7795	846	71
2017	7895	952	79
2018	7988	932	78
2019	8100	917	76
2020	**8111**	**1044**	**87**

Table 2a. Adverse Drug-Related Events Associated with ART for HIV treatment- 2020

Information Category	Reports including duplicates N= 1045 n(%)	Reports excluding duplicates N= 1044 n(%)
Event Type		
Adverse Drug Reaction	620 (59.3)	620 (59.3)
Adverse Drug Reaction Prevention	247 (23.6)	246 (23.6)
Drug Interaction, Symptomatic	6 (0.6)	6 (0.6)
Drug Interaction Prevention	172 (16.5)	172 (16.5)
Information Source		
Prescription	1042 (99.7)	*
Therapy Interruption Alert	2 (0.2)	*
Spontaneous Report	1 (0.1)	
Reporter Type		
Physician	671 (64.2)	*
Pharmacist	372 (35.6)	*
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
2016	No data		
2017	No data		
2018	3186	22	2
2019	5009	52	4
2020	**5335**	**33**	**3**

Table 2b. Adverse Drug-Related Events Associated with ARVs for PrEP- 2020

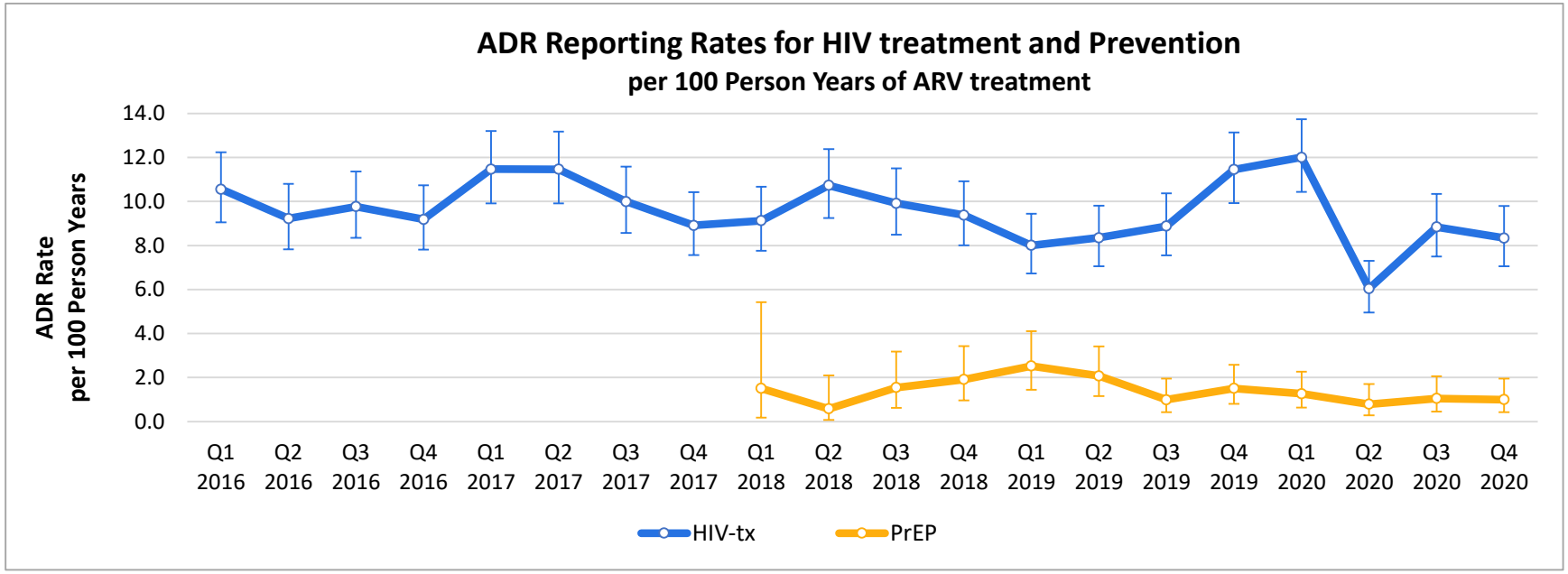
Information Category	Reports including duplicates N= 33 n(%)	Reports excluding duplicates N= 33 n(%)
Event Type		
Adverse Drug Reaction	33 (100)	33 (100)
Information Source		
Prescription	17 (51.5)	*
Therapy Interruption Alert	16 (48.5)	*
Reporter Type		
Physician	26 (78.8)	*
Pharmacist	1 (3.0)	*
Other Reporter	6 (18.2)	*

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

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

Figure 1 shows a sharp decline in ADR reporting related to ART for HIV treatment in April to June 2020 (second quarter), followed by a rebound in subsequent quarters. This transient decline was associated with healthcare system disruptions due to the COVID-19 pandemic.

Figure 1. Adverse Drug Reactions associated with ART for HIV treatment and PrEP (all drugs) – Five year reporting patterns, by quarter



Quarterly ADR rates in persons receiving ARVs for HIV treatment (HIV-tx) and prevention (PrEP). See Appendix for calculation method.

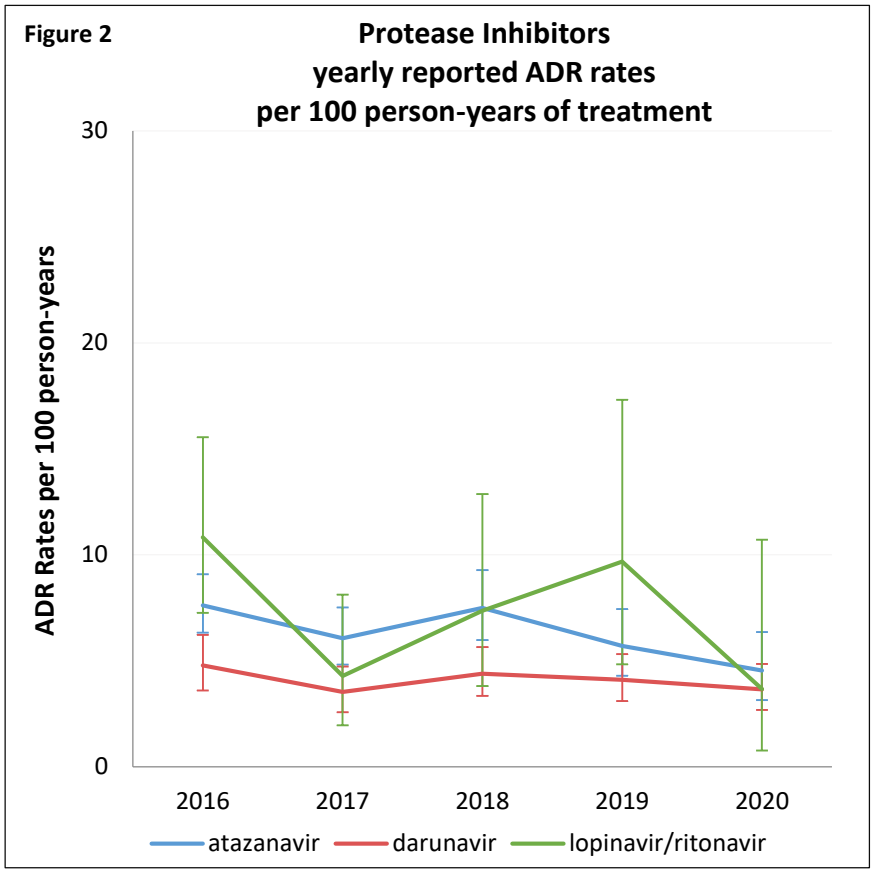
Adverse Drug Reaction (ADR) Rates by Antiretroviral Drug Class

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.

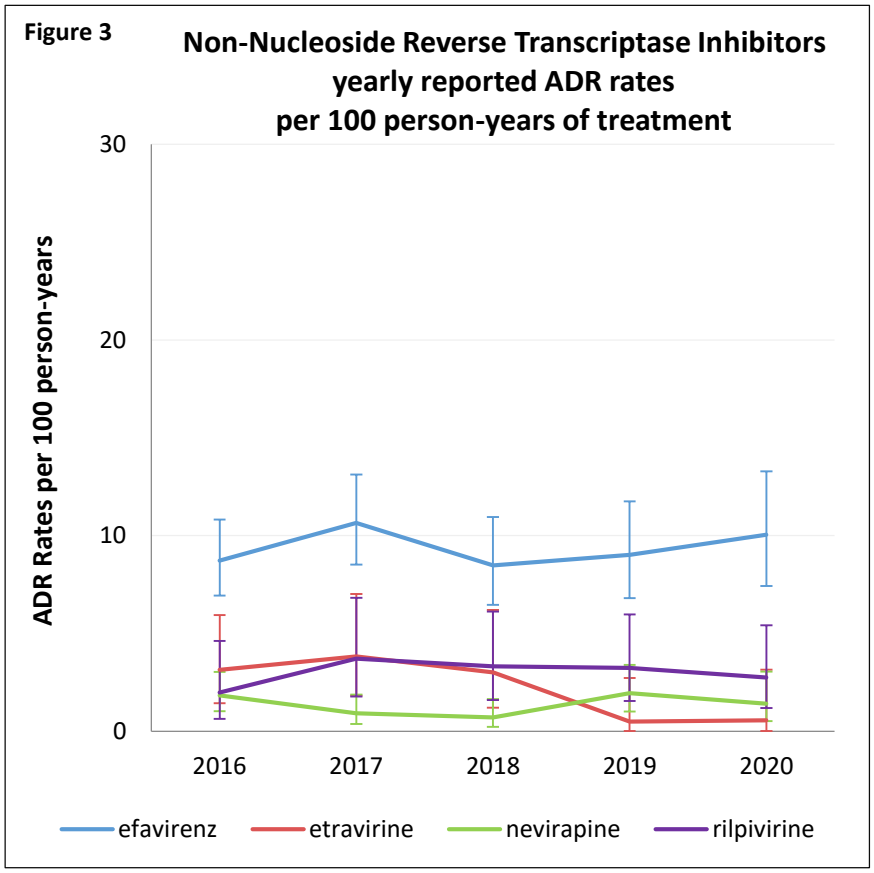
2020 reporting year highlights: The INSTI bictegravir recently became available in BC. The apparently higher ADR rates for bictegravir in 2019-2020 relative to other INSTIs (Figure 4) may represent a "new drug effect". Many ADRs manifest within the first few months following drug initiation, which may result in early medication discontinuation. In a given calendar year, a newly marketed drug may appear to have a higher ADR rate than established drugs, due to the disproportionate number of people who have recently started the newer medication and experienced early onset tolerability issues. Established drugs may appear to have a lower ADR rates if the majority of drug-exposed persons have been taking, and tolerating the medications long-term. Monitoring is ongoing.

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



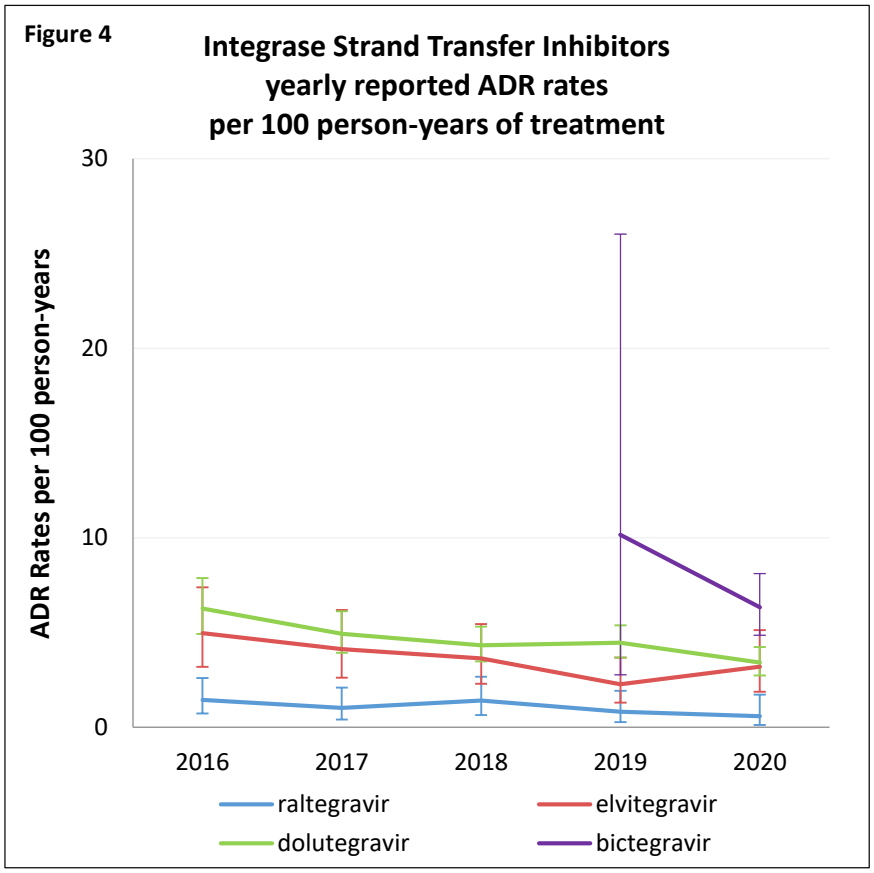
Number of Adverse Drug Reaction (ADR) reports / Total patient-years drug exposure					
	2016	**2017**	**2018**	**2019**	**2020**
atazanavir	122/ 1603	82/ 1354	84/ 1120	54/ 947	34/ 748
darunavir	55/ 1152	45/ 1274	59/ 1347	57/ 1390	47/ 1288
lopinavir	29/ 268	9/ 210	12/ 163	11/ 114	<5/ 82

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



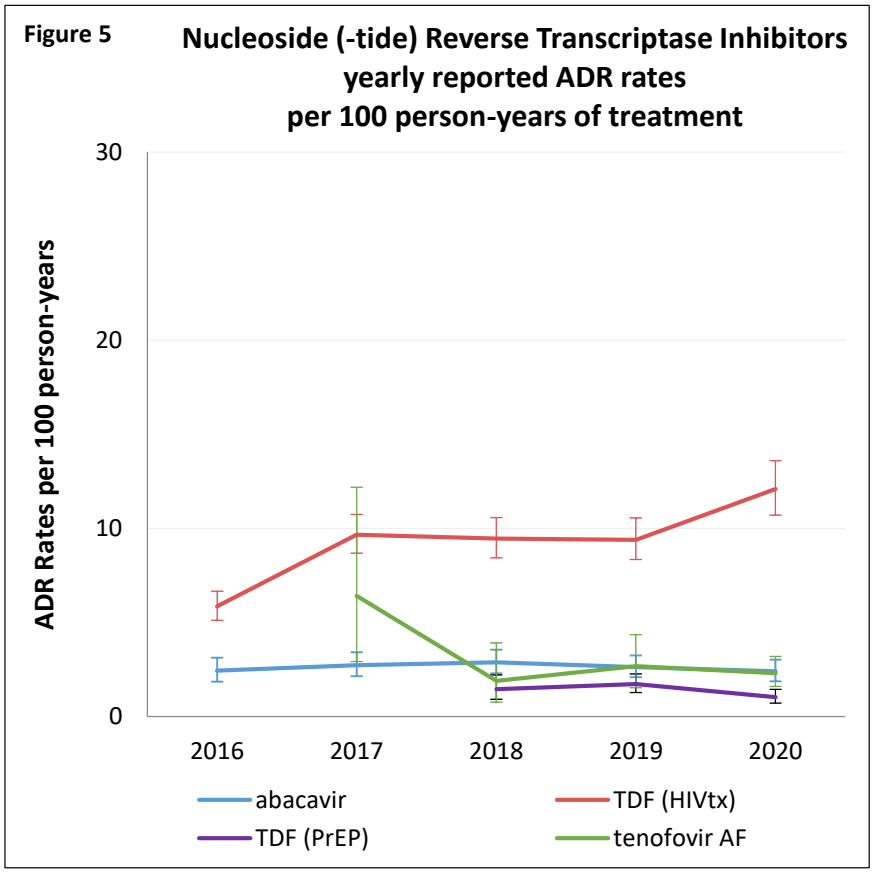
Number of Adverse Drug Reaction (ADR) reports / Total patient-years drug exposure					
	2016	**2017**	**2018**	**2019**	**2020**
efavirenz	82/ 940	87/ 818	59/ 695	55/ 610	49/ 488
etravirine	9/ 287	10/ 262	7 / 232	<5/ 204	<5/ 177
nevirapine	15/ 817	7/ 767	5/ 709	12/ 617	6/ 427
rilpivirine	5/ 253	10/ 270	10/ 301	10/ 308	8/ 291

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					
	2016	**2017**	**2018**	**2019**	**2020**
raltegravir	11/ 761	7/ 689	9/ 643	5/ 608	<5/ 512
elvitegravir	24/ 484	23/ 558	23/ 634	16/ 706	17/ 531
dolutegravir	74/ 1181	82/ 1664	90/ 2081	110/ 2464	83/ 2428
bictegravir	no data	no data	Limited data	<5/ 39	62/ 980

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					
	2016	**2017**	**2018**	**2019**	**2020**
abacavir	61/ 2506	76/ 2786	87/ 3025	83/ 3165	71/ 2951
tenofovir DF (HIV tx)	229/ 3913	353/ 3650	311/ 3287	285/ 3033	279/ 2307
tenofovir DF (PrEP)	no data	no data	22/ 1505	52/ 3025	33/ 3194
tenofovir AF	<5/ 13	9/ 140	7/ 369	16/ 597	35/ 1523

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 symptom category.

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.

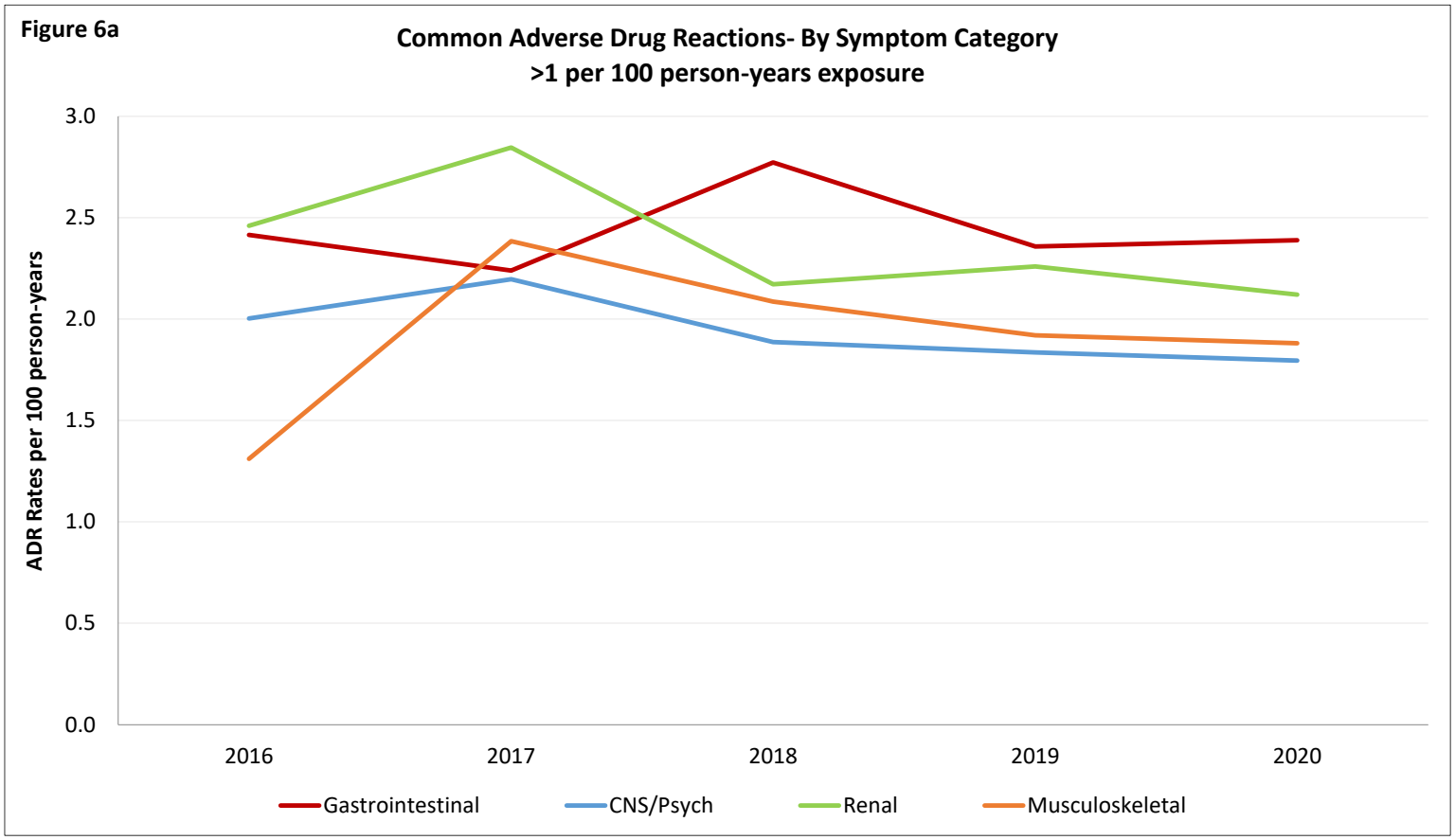
Symptom categories are organized by body system. For visual clarity, symptom categories are grouped into common (>1), uncommon (0.1-1.0) and rare (<0.1) ADR events per 100 person-years of ART exposure, displayed in Figures 7 a, b and c, respectively, and error bars are not displayed in the graphs.

See Appendix for details regarding calculation of rates.

2020 reporting year highlights: Gastrointestinal, central nervous system, renal and musculoskeletal (bone health) concerns continue to be the most commonly reported ARV-associated ADRs (Figure 7a). Endocrine and metabolic ADRs, such as lipid abnormalities or lipodystrophy continue to decline and, in 2020, have been moved from the summary of “common” ADRs (Figure 7a) to “uncommon” (Figure 7b).

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

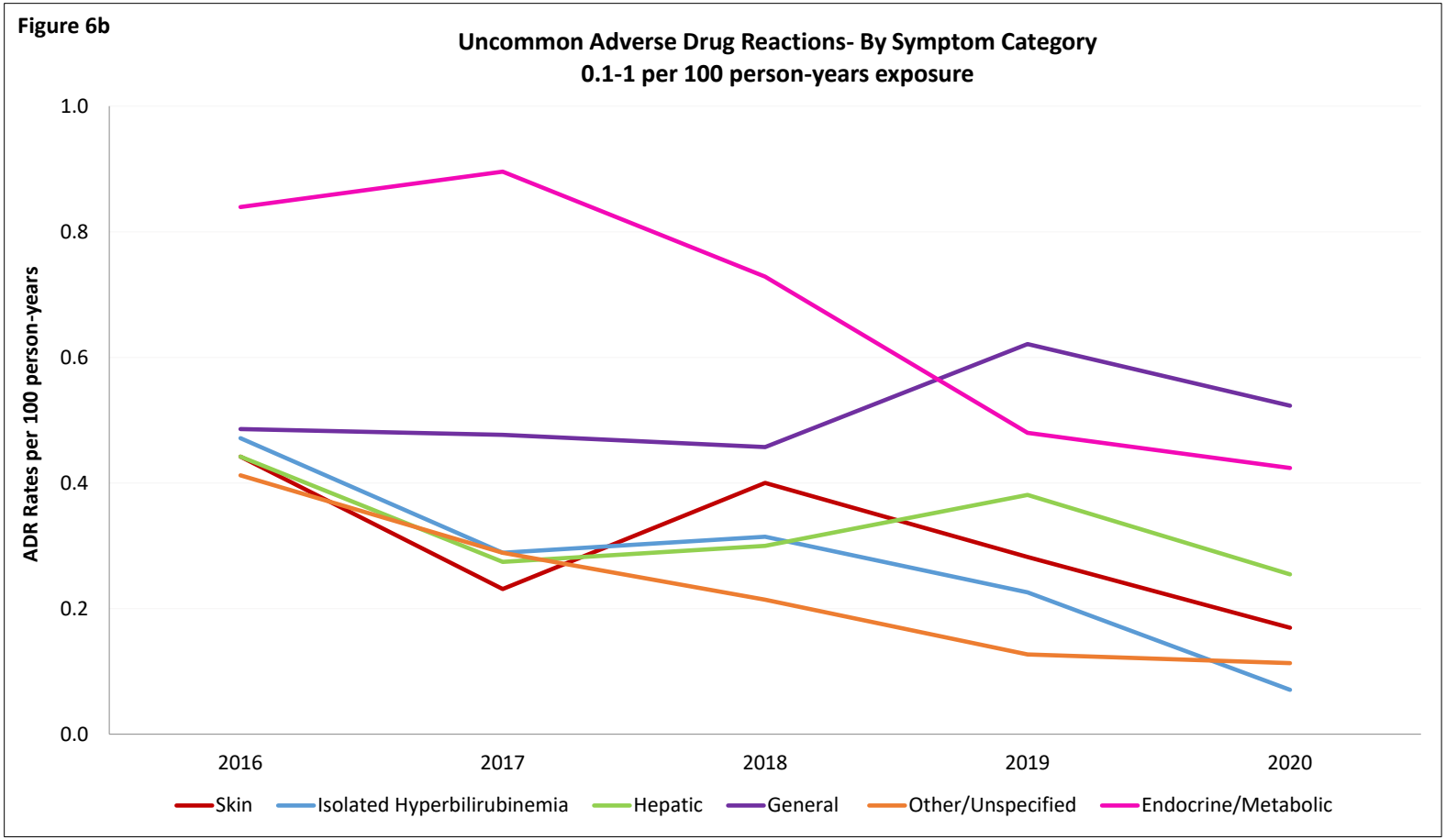
Figures 6a-6c. Adverse Drug Reaction Rates by Symptom Category



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

CNS/Psych:	Nightmares/vivid dreams, insomnia/ sleep disorder, altered mood, altered mental status, vertigo/ dizziness
Gastrointestinal:	Nausea, vomiting, diarrhea, GI upset/ discomfort, difficulty swallowing medication, pancreatitis, constipation
Musculoskeletal:	Bone mineral loss (osteopenia, osteoporosis), myalgia/arthralgia
Renal:	Serum creatinine elevated/GFR low, nephrolithiasis, Fanconi syndrome, proteinuria, cholelithiasis

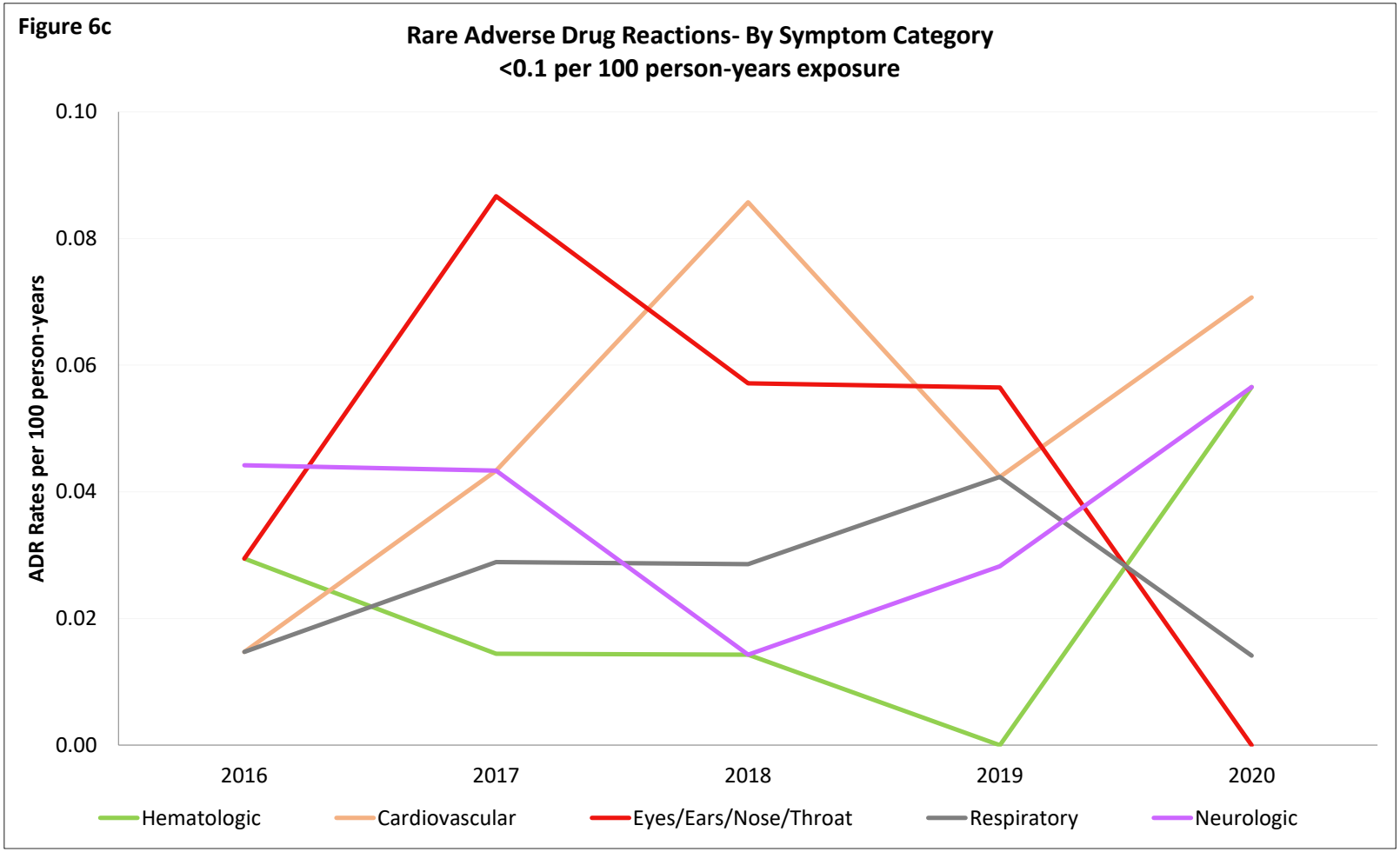
Figure 6b



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

Endocrine/ Metabolic:	Lipid abnormalities, lipodystrophy, serum phosphorus low
General:	Fatigue/malaise/low energy, weight gain/loss (unintentional), allergic reaction
Hepatic:	Abnormal liver function tests, bilirubin elevated, cholelithiasis, hepatic transaminase AST/ALT elevated
Isolated Hyperbilirubinemia:	Hyperbilirubinemia ± jaundice
Skin:	Rash/hives, itching (no lesions)
Other/ Unspecified:	Genitourinary, 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:

Cardiovascular:	Hypertension, flushing, cardiotoxicity
Eyes/ears/nose/throat:	Visual changes, nasal or sinus congestion, tinnitus, throat or mouth irritation
Hematologic:	Neutropenia, pancytopenia, anemia/low hemoglobin
Neurologic:	Peripheral neuropathy, neuromuscular weakness
Respiratory:	Cough (persistent/chronic), shortness of breath/dyspnea

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 (potentially life-threatening) 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 2020, 8/626 (1.3%) of adverse drug reaction reports (excluding duplicates and “unlikely” causality) were classified as serious. A total of 24/626 (3.8%) ADR reports were submitted to Health Canada for HIV treatment. No PrEP-related ADRs were submitted to Health Canada Vigilance in 2020.

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. ART-Treated Persons in BC, Stratified by Age

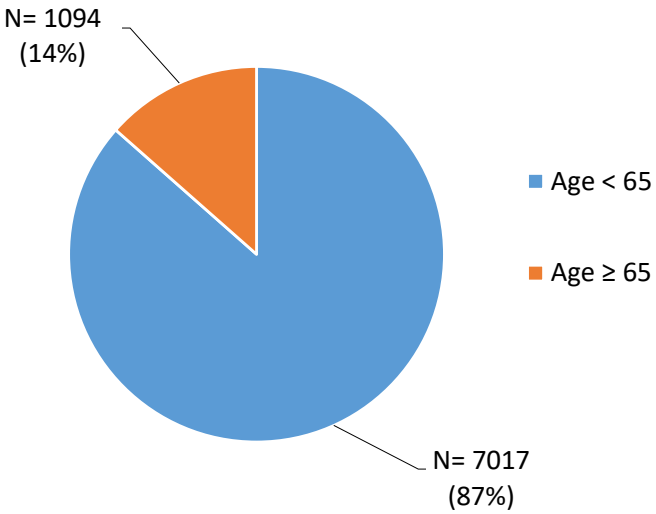
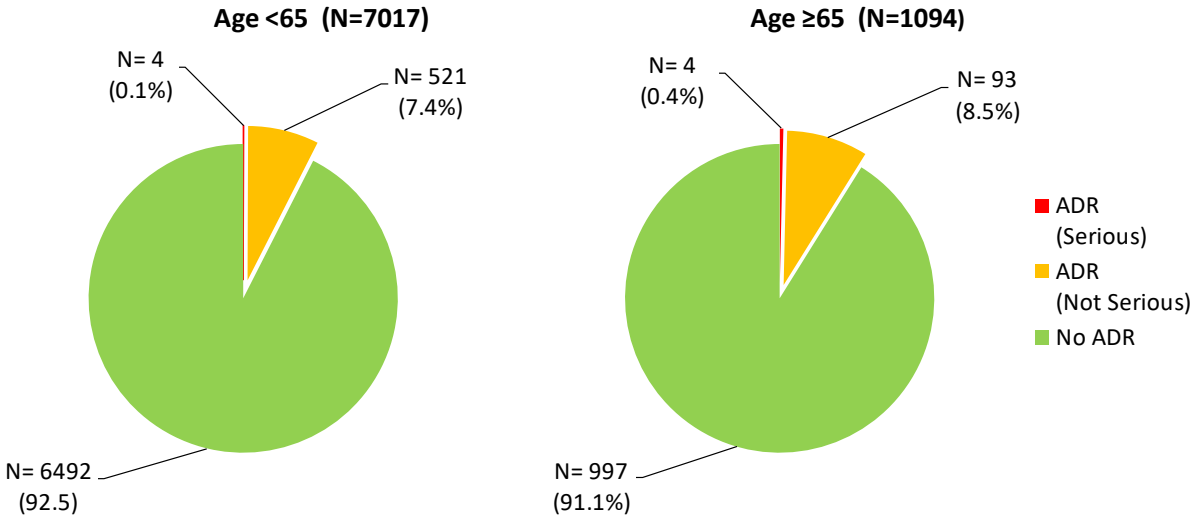


Figure7b. Proportion of ADR reports in ART-treated persons, stratified by age



Summary: Seniors ≥65 years of age represent approximately 14% of the total ARV-treated population. In 2020, the proportion of seniors with a reported ARV ADR was slightly higher than for younger persons (8.9% and 7.5% respectively), which was not a statistically significant difference (p = 0.109). ADRs most commonly reported in seniors were similar to the general population, with gastrointestinal, renal, musculoskeletal (bone health), and central nervous system symptoms accounting for the majority of reports (listed in declining order of frequency).

Figure 8a. ART-Treated Persons in BC, Stratified by Sex

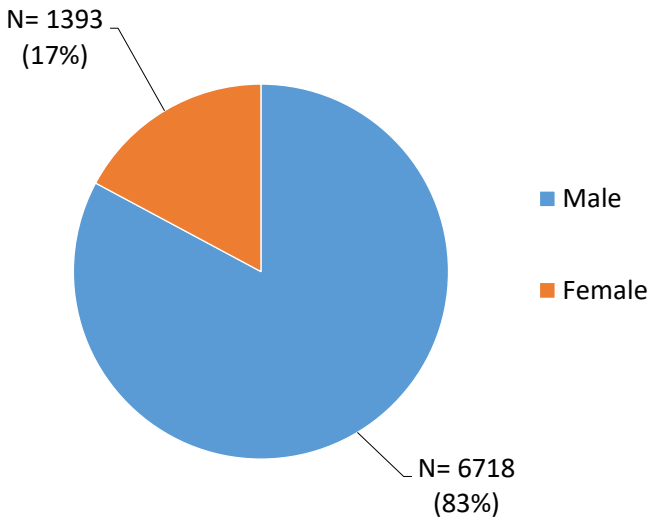
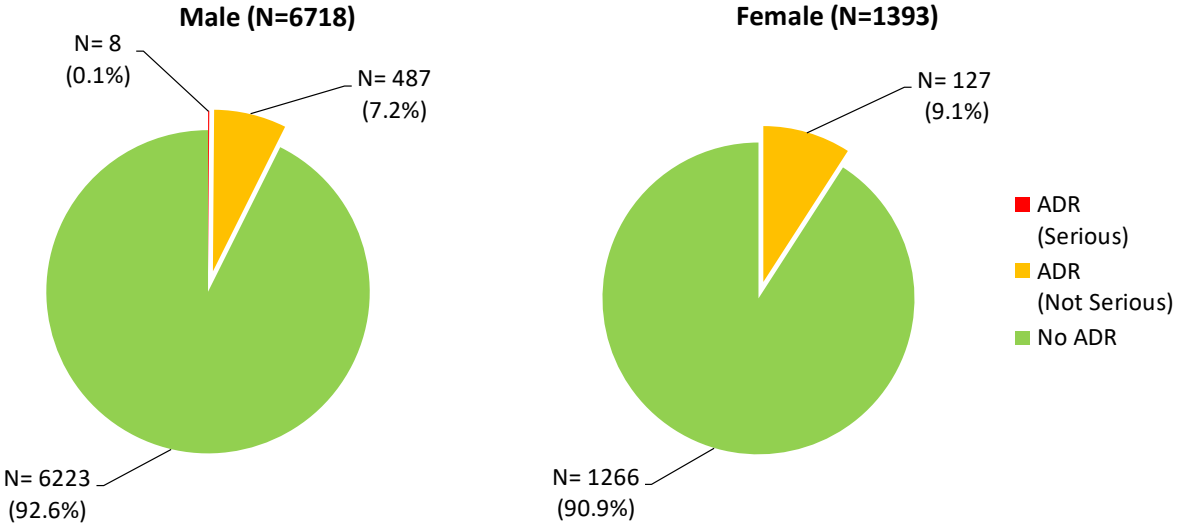


Figure 8b. Proportion of ADR reports in ART-treated persons by sex



Summary: Females represent approximately 17% of the total ARV-treated population. In 2020, the proportion of females with a reported ARV ADR was higher than for males (9.1% and 7.3%, respectively), which was a statistically significant difference (p= 0.026). 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). There were no serious ADRs reported for females in 2020.

Drug Interactions Associated with ART for HIV Treatment

Figures 9 and 10 summarize antiretroviral drug interaction reporting patterns in 2020.

Figure 9. Antiretroviral Drug interactions by ARV class

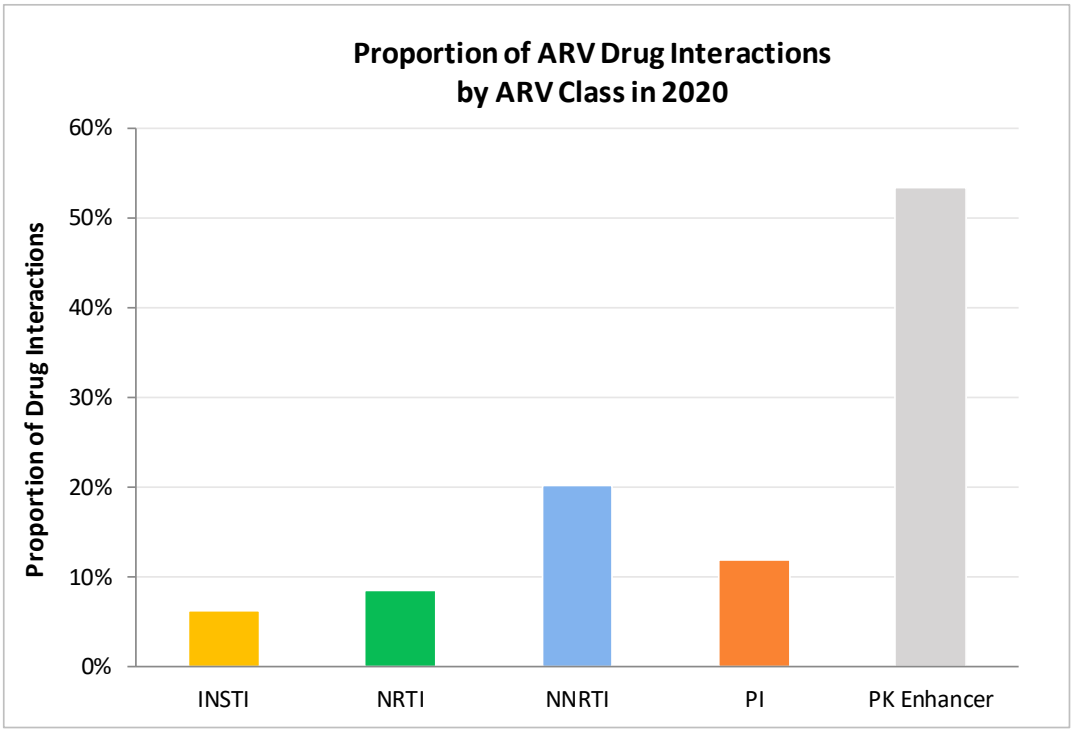
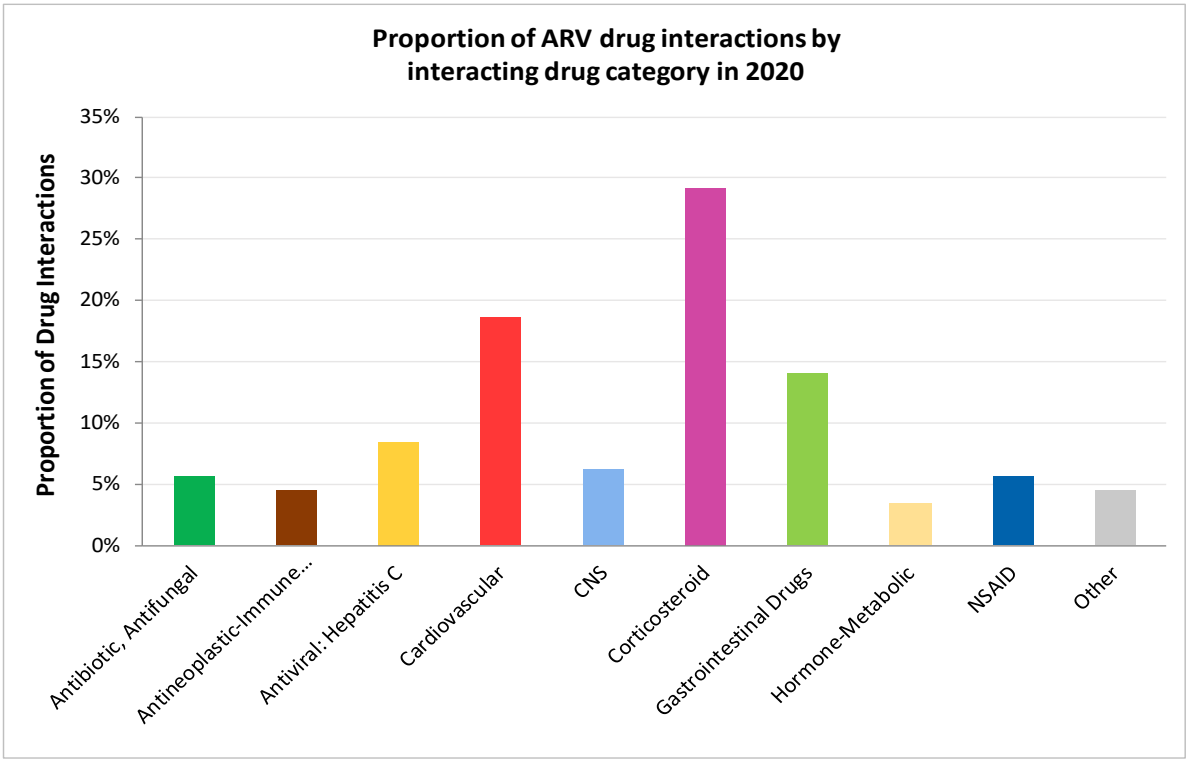


Figure 10. Antiretroviral Drug Interactions by interacting drug category



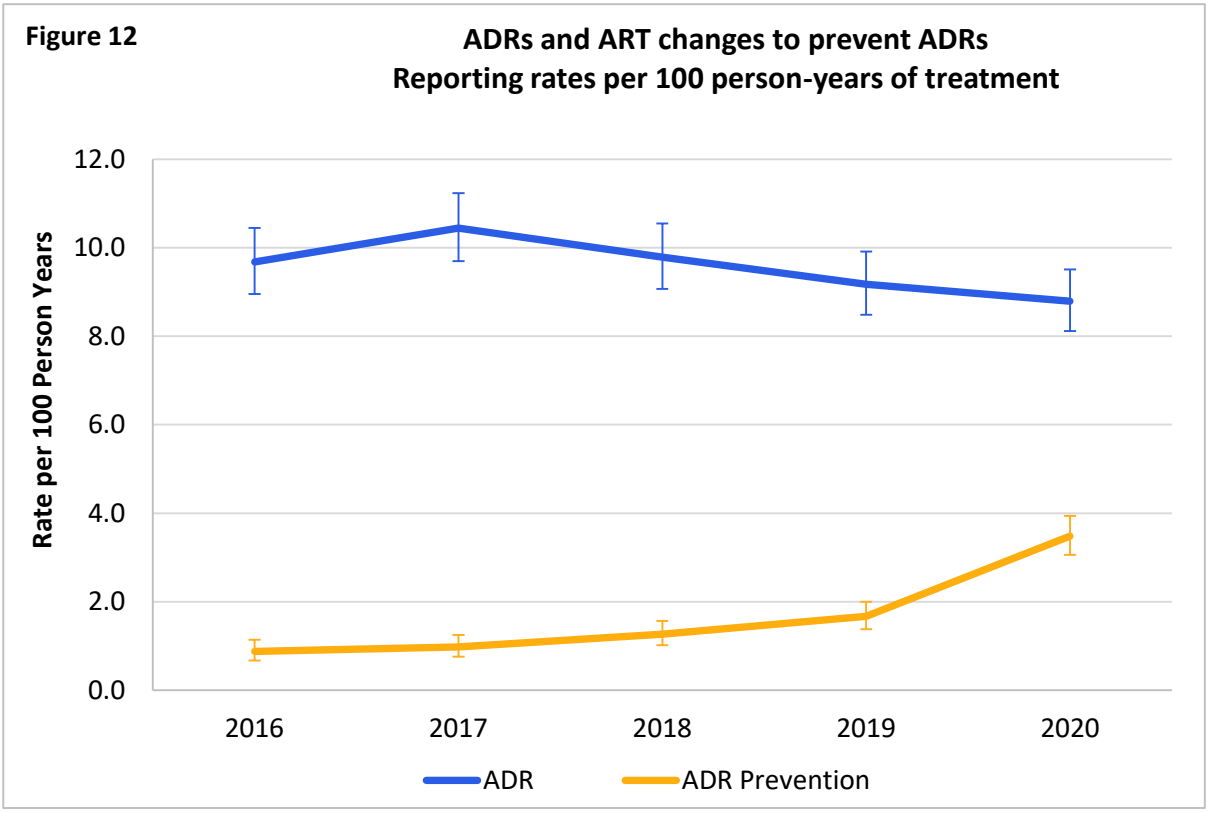
As shown in Figures 9 and 10 above, the pharmacokinetic enhancers ("boosters") cobicistat and ritonavir accounted for the majority of ART therapy changes related to drug interactions between HIV medications and other drugs. Interactions between ritonavir or cobicistat and corticosteroids continue to 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 the use 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. Interactions between INSTIs and polyvalent cations such as aluminum/ magnesium antacids, calcium or iron supplements are of emerging concern, due to the possible outcome of treatment failure secondary to reduced INSTI absorption.

ART changes for Prevention of Adverse Drug Reactions in persons receiving HIV treatment

Antiretroviral therapy changes for the purpose of preventing a potential ADR, such as reducing the long-term risk of renal injury, are documented as "ADR prevention", and monitored separately from symptomatic ADRs. Reports of ADR prevention are only captured when the prescriber documents this intention on a request for ARV regimen change, and therefore the actual incidence of preventative regimen changes is likely underestimated.

Figure 12 shows the pattern of ART changes for ADR prevention in relation to reports of ADRs. In recent years, ADR reports have been declining, while preventative regimen changes have been increasing, largely driven by the availability of newer ART alternatives. In 2020, the ARVs most commonly implicated in preventative changes are tenofovir DF (long term renal and bone health concerns) , abacavir (cardiovascular risk reduction), efavirenz (avoiding central nervous system effects), and atazanavir (avoiding risk of renal stones).

Figure 12. Five year reporting rates for ADRs and ART changes to prevent ADRs associated with ART for HIV treatment (all drugs)



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 Antiretroviral Treatment Interruption/Adherence Alert:

If a person living with HIV does not refill their ARV medications for more than two months after the expected refill date, an HIV Drug Treatment Program Antiretroviral 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" to be associated with ARV(s), 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: Calculation of overall ADR rates for HIV-treatment and PrEP patients. Within each quarter (3 month period), the numerator is the number of ADR reports for ART-treated persons. The denominator is the total number of patient-years of ART exposure 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.

Figure 2-5: **Calculation of ADR rates, by antiretroviral drug.** Within each calendar year, 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.