e-poster #EPB124

Low incidence of adverse drug reactions associated with generic-equivalent antiretroviral product substitutions in a publicly-funded HIV treatment program

O.L. Hunt[1], K.J. Lepik[1,2], N. Bacani[1] , L. Wang[1] , J. Toy[1,2], P. Sereda[1] , T. McLinden[1], L. Akagi[1,2], M. Harris[1,3], E. Ready[2] , J. Trigg[1] , J.S.G. Montaner[1,3], R. Barrios[1,3]

[1] BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; [2] St Paul's Hospital, Pharmacy, Vancouver, Canada, University of British Columbia, [3] UBC Faculty of Medicine, Vancouver, Canada

Background

- In British Columbia, Canada, persons living with HIV (PLWH) receive antiretroviral medications (ARVs) free-of-charge through a publicly-funded HIV Drug Treatment Program (DTP).
- Generic ARVs provide low-cost alternatives to brand-name products. To support program sustainability, brand-name products are automatically switched to available generic equivalents, in accordance with Ministry of Health policies.
- Adverse drug reactions attributed specifically to a generic version of a product are termed generic **"Product Substitution Issues" (PSIs)**.
- We describe the incidence and type of PSIs reported to the DTP's Pharmacovigilance service during the first year of product availability for:
  - "Generic-1" (initial brand-to-generic drug formulary transition)
  - "Generic-2" (subsequent generic-1 to generic-2 drug formulary transition)

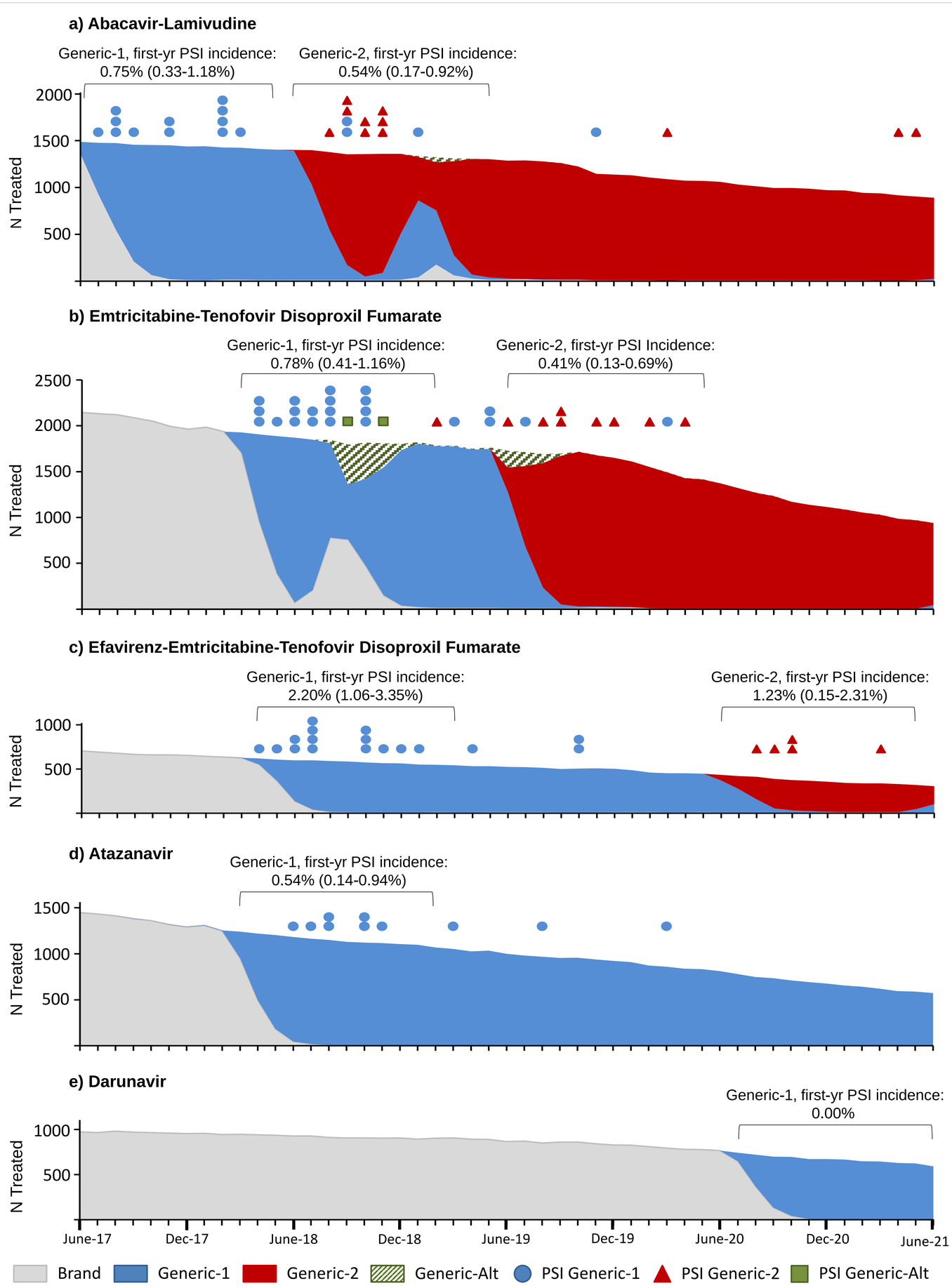
Methods

- We included PLWH age ≥19 years who received ≥1 of the five most commonly used generic ARVs between 01-Jun-2017 and 30-Jun-2021:
  - Abacavir-Lamivudine (ABC-3TC)
  - Emtricitabine-Tenofovir Disoproxil Fumarate (FTC-TDF)
  - Efavirenz-Emtricitabine-Tenofovir Disoproxil Fumarate (EFV-FTC-TDF)
  - Atazanavir
  - Darunavir
- All data were extracted from DTP databases. Antiretroviral use and PSIs were summarized monthly.
- PSI incidence proportion and 95% confidence interval (95%CI; Wald Confidence Limits for binomial proportions), were calculated during the first year following each generic transition (product rollout) date.
- After pooling across products, a logistic regression model (using generalized estimating equations with robust standard errors) compared PSI incidence proportion for generic-2 versus generic-1.
- Symptoms associated with PSIs reported in the first year following generic product transition were summarized by product, pooling generics -1 and -2.

Results

- Between 01-Jun-2017 and 30-Jun-2021, 5560/8842 (63%) of ARV-treated PLWH received generic ARVs, of whom 5421/5560 (98%) received ≥1 of the generics studied. Of N=5421, 83% were male, median (Q1-Q3) age 52 (43-58) years. Overall, 27% received one, 40% two, and 33% three or more different generics.
- Prior use of generic ARVs increased over time, with only 7% of PLWH having prior generic ARV experience at the time of ABC-3TC introduction in 2017, while 72% of PLWH who switched to generic darunavir in 2020 had previously used other generic ARVs (**Table 1**).
- **Figure 1a-1e** shows longitudinal ARV usage and first-year PSI incidence, which was <1% for most generics. Of 93 PSIs, 71/93 (76%) were reported within the first year post-generic transition. Within the first year of product use, the median time to PSI report was 2-3 months after the initial dispensing date (**Table 1**).
- Pooled analysis of ABC-3TC, FTC-TDF and EFV-FTC-TDF showed significantly lower first-year PSI incidence for generic-2 (0.55%, 95%CI=0.31-0.78%) versus generic-1 (0.98%, 95%CI=0.69-1.27%), p=0.029 (**Table 1**).
- Common PSI-related symptoms included mild-moderate gastrointestinal, central nervous system (CNS, predominantly efavirenz-related), dermatologic, and general (unwellness/malaise) effects (**Table 2**).

Figure 1: Longitudinal antiretroviral product usage, generic product substitution issue (PSI) frequency, and PSI incidence (fist year following each generic product transition)



***Definitions*. Generic product transition date:** 1st day of the month when Generic-1 or -2 product dispensing began. If product usage began near month-end, the "transition date" was considered day 1 of the following month for study purposes. **Brand**, Originator brand-name product; **Generic-1**, first generic version (brand-to-generic transition); **Generic 2**, second generic version (generic-to-generic transition); **Generic-Alt,** alternate (non-formulary) generic, excluded from PSI analysis; **PSI**, Product Substitution Issue, adverse drug reaction specifically attributed to a generic product; **first-yr PSI incidence**; PSI incidence proportion, expressed as % (95% confidence interval) of generic-treated persons, measured in the 1st year following product transition date.

Table 1. Summary of generic ARV product use and product substitution issue incidence in the first year following each generic product transition

Variable	Abacavir-Lamivudine		Emtricitabine-Tenofovir DF		Efavirenz-Emtricitabine-Tenofovir DF		Atazanavir	Darunavir
	Generic-1	Generic-2	Generic-1	Generic-2	Generic-1	Generic-2	Generic-1	Generic-1
Generic antiretroviral product use in the first year following the generic product transition date (overall N=5421)								
First year period	Jun'17-May'18	Jun'18-May'19	Mar'18-Feb'19	Jun'19-May'20	Apr'18-Mar'19	Jun'20-May'21	Mar'18-Feb'19	Jul'20-Jun'21
N, generic-treated	**1596**	**1472**	**2167**	**1951**	**635**	**406**	**1293**	**757**
Prior use of ARV product; n (%)	1480 (93)	1389 (94)	2018 (93)	1801 (92)	607 (96)	391 (96)	1265 (98)	728 (96)
Prior use of other generic ARVs; n(%)	109 (7)	1410 (96)	220 (10)	1781 (91)	12 (2)	391 (96)	495 (38)	548 (72)
Generic product substitution issues (PSIs) in the first year following the generic product transition date (overall N=71)								
N, generic PSIs	**12**	**8**	**17**	**8**	**14**	**5**	**7**	**0**
Median (Q1-Q3) days to PSI	74 (32-206)	70.5 (44-94)	65 (39-115)	76 (20-151)	93 (53-159)	39 (34-53)	91 (85-190)	0
1st-year PSI incidence proportion, % (95%CI)	0.75% (0.33-1.18%)	0.54% (0.17-0.92%)	0.78% (0.41-1.16%)	0.41% (0.13-0.69%)	2.20% (1.06-3.35%)	1.23% (0.15-2.31%)	0.54% (0.14-0.94%)	0

Tenovovir DF, tenofovir disoproxil fumarate

Table 2. Summary of symptoms associated with generic product substitution issues

Variable	Abacavir-Lamivudine	Emtricitabine-Tenofovir DF	Efavirenz-Emtricitabine-Tenofovir DF	Atazanavir	Darunavir
N, generic-related PSIs	**20**	**25**	**19**	**7**	**0**
PSI Symptoms (n, % of N PSIs)					
Gastrointestinal	15 (75)	13 (52)	9 (47)	4 (57)	-
Central Nervous System	4 (20)	1 (4)	9 (47)	1 (14)	-
Skin Rash	1 (5)	6 (24)	3 (16)	1 (14)	-
General	3 (15)	2 (8)	2 (11)	1 (14)	-
Other/ Unspecified	1 (5)	6 (24)	3 (16)	1 (14)	-

Tenovovir DF, tenofovir disoproxil fumarate. Reported product substitution issue (PSI) symptoms are pooled for generic-1 and -2 versions of each product. Each PSI event may have symptoms in more than one category. Central nervous system symptoms included sleep disturbances, grogginess, headache, altered mood; Gastrointestinal symptoms included nausea, abdominal discomfort/ bloating, diarrhea, not tolerating tablet taste/smell. General symptoms included fatigue, malaise, low energy, feeling unwell.

Discussion

- The transition from brand-to-generic and between different generic versions of ARVs was generally well tolerated. Overall PSI incidence was <1% of generic ARV-treated PLWH within the first year following generic product transition. EFV-FTC-TDF had a slightly higher PSI incidence (1-2%), with approximately half the cases involving CNS effects.
- For the three products with two different generic versions, PSI incidence was lower with the second generic-to-generic transition than with the initial brand-to-generic transition. The most recently introduced generic, darunavir, had no reported PSIs.
- Overall, we report a low incidence of adverse drug reactions attributed to generic ARV product substitution.

Presented at the 24th International AIDS Conference (AIDS 2022)

Correspondence to: Dr. Rolando Barrios (rbarrios@bccfe.ca)

Providence HEALTH CARE How you want to be treated.

BRITISH COLUMBIA CENTRE *for* EXCELLENCE *in* HIV/AIDS

AIDS 2022 29 July – 2 August