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Healthcare utilisation and costs associated with adherence to antipsychotics among people living with HIV/AIDS and schizophrenia: a population-based cohort study in British Columbia, Canada

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ABSTRACT

Objectives Non-adherence to antipsychotics is the greatest obstacle to treating schizophrenia. We assessed the economic and clinical impacts of adherence to antipsychotics among people living with HIV/AIDS (PLWH) and schizophrenia in British Columbia, Canada.

Design and setting A population-based cohort study in British Columbia, Canada.

Methods Eligible PLWH were enrolled in the Seek and Treat for Optimal Prevention of HIV/AIDS population-based cohort during 2001–2016, diagnosed with schizophrenia, on antipsychotics for ≥1 day, and followed for ≥1 year from schizophrenia diagnosis date or 1 January 2001, whichever occurred last.

Primary and secondary outcome measures A two-part model assessed the marginal effect of adherence on healthcare costs (in 2016 Canadian dollar), while logistic regression examined the effect on virological failure, and generalised linear mixed models examined the effect on hospital readmissions within 30 days and length of hospital stay.

Results Among 726 PLWH with schizophrenia, ≥80% adherence to antipsychotics increased from 25% (50/198) in 2001 to 41% (225/554) in 2016. In most years, we observed no difference in adherence to antipsychotics among those who used only injectables, only non-injectables, and a combination of both, or among those who have ever consumed typical/first-generation antipsychotics and who consumed only atypical/second-generation antipsychotics. Overall healthcare costs were higher in the non-adherent group ($C2185), driven by the average annual hospitalisation costs ($C5517), particularly among women ($C8806) and people who ever injected drugs (PWID) ($C5985). Non-adherent individuals also experienced higher hospital readmissions (adjusted odds ratio (aOR) 1.48, 95% CI 1.23 to 1.77), and longer hospital stays (adjusted mean ratio 1.23, 95% CI 1.13 to 1.35) in comparison to adherent individuals. We found no difference in virological failure by adherence groups, except when we stratified by gender where the aOR for women was 2.48 (95% CI 1.06 to 5.82).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This retrospective cohort study estimated the effect of non-adherence (<80%) to antipsychotics on healthcare costs and various clinical and healthcare-related outcomes among people living with HIV and schizophrenia in British Columbia, Canada.

⇒ We used the Seek and Treat for Optimal Prevention of HIV/AIDS cohort data which was derived from confidential linkages among several provincial administrative healthcare databases.

⇒ Adherence to antipsychotics was measured using the interval-based average proportion of days covered methodology, as recommended by the Pharmacy Quality Alliance.

⇒ Although we excluded transient psychotic episodes or episodes of insufficient chronicity, a risk of misclassification and/or misdiagnosis of schizophrenia remains, especially given the overlapping symptoms with other mental health disorders, particularly bipolar disorder.

⇒ Our findings may only be generalisable to settings with universal healthcare and similar access to healthcare services and medications.

Conclusions Our results showed that implementing strategies and interventions to increase antipsychotic adherence, particularly among women and PWID, will be critical in addressing this public health challenge.

INTRODUCTION

Schizophrenia is a complex mental health disorder with potential lifelong implications on morbidity, mortality and overall quality of life.1 Those who live with schizophrenia are expected to live 10–25 years less than the general population.2 The lower life expectancy may be influenced by a higher risk
of suicide, comorbidities and bloodborne infectious diseases including HIV/AIDS. A population-based cohort study based in British Columbia (BC), Canada, found that people living with HIV (PLWH) were six times more likely to have a schizophrenia diagnosis than HIV-negative individuals. The higher diagnosis incidence may be attributed to high-risk behaviours in this population, including injection drug use and unprotected sex with multiple partners.

While schizophrenia only affects 1% of the Canadian population, it is associated with very high healthcare costs. Presently, there is no cure for schizophrenia, and existing treatments require a lifelong commitment. With consistent antipsychotics use, individuals can manage their symptoms and prevent relapse and rehospitalisation. Nevertheless, non-adherence remains the most significant global obstacle when treating schizophrenia. Non-adherence may be due to poor understanding of the disorder, prominent symptoms, unpleasant side effects of medication, social stigma, low social support and inadequate access to mental health services. Non-adherence to antipsychotics can lead to relapse, which is a key driver of increased healthcare utilisation, including physician visits, hospitalisations and prescription medication use. Non-adherence to antipsychotics is, therefore, an important and costly issue that has both direct implications on an individual’s life and the public health system.

Compared with HIV-negative individuals with schizophrenia, PLWH with schizophrenia have nearly three times higher odds of all-cause mortality. While never receiving antipsychotics is associated with adverse health outcomes in this population, the impact of non-adherence to antipsychotics has not been thoroughly studied. In addition, given that PLWH with mental health disorders have a higher rate of virological failure than those without, non-adherence to antipsychotics among PLWH with schizophrenia may exacerbate the clinical implications of HIV and its treatment.

Thus, in this population-based study, we assessed the impact of non-adherence to antipsychotics on economic and health-related outcomes, including healthcare costs, virological failure, hospital readmissions and length of hospital stay among PLWH with schizophrenia in BC.

**METHODS**

**Data source**

This study used data from the Seek and Treat for Optimal Prevention of HIV/AIDS (STOP HIV/AIDS) population-based cohort. The cohort’s longitudinal individual-level data on all diagnosed PLWH in BC from 1996 to 2016 were derived from the linkages of provincial treatment, surveillance and administrative databases. The detailed description of the STOP HIV/AIDS database can be found in online supplemental appendix note 1.

**Study design**

In this population-based cohort study, eligible individuals were: (1) in the STOP HIV/AIDS cohort from 1 January 2001 to 31 December 2016; (2) diagnosed with schizophrenia; (3) ≥18 years old; (4) followed for ≥1 year after schizophrenia diagnosis and (5) on antipsychotics for ≥1 day (online supplemental appendix figure 1 and table 1). A 5-year look-back observation window of administrative records was examined to ascertain the schizophrenia diagnosis date at index date. Individuals with a schizophrenia diagnosis were then followed from the date of diagnosis or 1 January 2001 (ie, index date), whichever occurred last. A schizophrenia diagnosis was identified using the BC Ministry of Health’s case-finding algorithm. However, diagnostic instability was common in this administrative database, and diagnostic codes slightly changed over time. Thus, modifications were made following recommendations from a psychiatrist practising in BC (JE) to capture all diagnoses that are within the schizophrenia spectrum. The modified case-finding algorithm is as follows: one hospitalisation or two physician visits within 1 year with the following International Classification of Diseases (ICD) 9 or 10 codes: 295.x—schizophrenic disorders, F20.x—paranoid schizophrenia or F25.x—schizoaffective disorders. Diagnostic codes F21.x and F23.x were excluded to avoid capturing transient or short-lived psychotic episodes, or those with symptoms better explained by a personality disorder.

**Exposure**

Our main exposure was adherence to antipsychotics, which was measured using the proportion of days covered (PDC) methodology, as recommended by the Pharmacy Quality Alliance as the preferred method for estimating adherence to chronic medications using administrative prescription data as in this study. This dataset contains detail information including drug identification number (DIN) or product identification number, medication brand and generic names, medication strength and form, the American Society of Health-System Pharmacists (AHFS) codes, medication dispensing date and quantity, among other fields. Given that individuals can receive different medications simultaneously in a given year, we adopted the interval-based average PDC method. Please note that for long-acting injectables, adherence was assumed to be 100%. We calculated the ratio of the number of days an individual is covered by medication in a period, as determined by pharmacy refills, to the number of days in the period. A literature-recommended cut-off of 80% was chosen to dichotomise individuals into ‘adherent’ and ‘non-adherent’ categories.

We used the estimated adherence (in per cent) during the calendar year to assign ‘adherent/non-adherent’ status to our population.

**Potential confounders**

Several demographic, clinical and HIV-related potential confounders were considered and measured at different
time points depending on the nature of the study outcomes. Selected confounders are listed underneath each table for multivariable models. Demographic potential confounders included gender (women/men), age in years (per 10 years) and HIV risk group (heterosexual/other, people who have ever injected drugs (PWIDs), gay, bisexual and other men who have sex with men (gbMSSM), MSM/PWID or unknown). Clinical and HIV-related potential confounders included: a mood and/or anxiety diagnosis (yes/no), years since schizophrenia diagnosis (continuous), antiretroviral therapy (ART) era (never initiated ART, ≤2000, 2001–2009 or 2010–2016), ART adherence (ART not initiated, 0%–39%, 40%–79%, 80%–94% or ≥95%), CD4 (≤50, 50–199, 200–349 or ≥350 cells/mm³; online supplemental appendix note 2), viral suppression (yes, no or viral load not measured; suppression defined by all viral load tests <200 copies/mL), viral load (log10 copies/mL transformed; online supplemental appendix note 2), reason for exiting hospital (discharged home, transferred to long-term care, hospital transfer). We examined the top 20 reasons for hospital readmissions using CIHI’s Case Mix Groups (CMG) methodology (online supplemental appendix note 4), which comprises various categories of diagnoses based on similar clinical course and resource requirements.21

All analyses were stratified by gender (women/men) and PWID status (PWID/non-PWID) to account for potential confounding by indication. We also investigated whether adherence to antipsychotics was influenced by whether the individual received a typical/first-generation or atypical/second-generation antipsychotic medication during follow-up.22 23 Typical, or first-generation, antipsychotics were first developed in the 1950s, and have a higher risk of side effects. Atypical, or second-generation, antipsychotics are more recent (since the 1990s), and most have higher efficacy and a lower risk of side effects.

**Statistical analysis**

Analyses were performed by using either R V.3.6.0 or STATA (Release 15., StataCorp). The statistical methodology used to analyse each outcome is explained below.

**Individual characteristics**

Characteristics of adherent and non-adherent PLWH and schizophrenia were compared. Categorical variables were compared using Fisher’s exact test (small cell counts) or the χ² test, and continuous variables were compared using the Kruskal-Wallis test.24 The significance level was set at 0.05.

**Healthcare costs**

Healthcare costs were adjusted for inflation to reflect the value of the 2016 Canadian dollar. Given a methodological change regarding the cost measurement of a standard hospital stay in 2009, we limited our cost analysis to 2009–2016. In estimating the marginal effect of adherence to antipsychotics on costs, a two-part model was used to account for excess annual zero cost observations.25 A generalised linear model with a binomial distribution and logit link function was specified in the first stage, followed by a model with gamma distribution and log link function. Pharmacy, total MSP and total healthcare costs did not have an excessive number of zero values. Thus, the effect of adherence to antipsychotics on these costs was measured using only a generalised linear model with a gamma distribution and log link function. The adjusted marginal effects of our main exposure on the annual healthcare costs were then estimated by using the margins post-estimation command following the twowpm command (for healthcare costs with excessive zeros) or the glm function (for healthcare costs without excessive zeros) in STATA.

**Virological failure**

The probability of experiencing virological failure was modelled using logistic regression, implemented in R.
### Table 1  Summary statistics of characteristics among people living with HIV with schizophrenia in our study at index date

<table>
<thead>
<tr>
<th>Individual characteristics</th>
<th>Whole sample N (%)</th>
<th>&lt;80% adherence N (%)</th>
<th>≥80% adherence N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.4963</td>
</tr>
<tr>
<td>Women</td>
<td>182 (25)</td>
<td>131 (72)</td>
<td>51 (28)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>544 (75)</td>
<td>375 (69)</td>
<td>169 (31)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td>0.0153</td>
</tr>
<tr>
<td>&lt;30</td>
<td>102 (14)</td>
<td>80 (78)</td>
<td>22 (22)</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>244 (34)</td>
<td>180 (74)</td>
<td>64 (26)</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>257 (35)</td>
<td>169 (66)</td>
<td>88 (34)</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>123 (17)</td>
<td>77 (63)</td>
<td>46 (37)</td>
<td></td>
</tr>
<tr>
<td>HIV risk group</td>
<td></td>
<td></td>
<td></td>
<td>0.8836</td>
</tr>
<tr>
<td>Heterosexual/other</td>
<td>49 (7)</td>
<td>35 (71)</td>
<td>14 (29)</td>
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</tr>
<tr>
<td>PWID</td>
<td>381 (52)</td>
<td>268 (70)</td>
<td>113 (30)</td>
<td></td>
</tr>
<tr>
<td>gbMSM</td>
<td>89 (12)</td>
<td>59 (66)</td>
<td>30 (34)</td>
<td></td>
</tr>
<tr>
<td>gbMSM/PWID</td>
<td>127 (17)</td>
<td>86 (68)</td>
<td>41 (32)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>80 (11)</td>
<td>58 (72)</td>
<td>22 (28)</td>
<td></td>
</tr>
<tr>
<td>Mood and/or anxiety disorder</td>
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<td></td>
<td></td>
<td>0.0516</td>
</tr>
<tr>
<td>No</td>
<td>157 (22)</td>
<td>99 (63)</td>
<td>58 (37)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>569 (78)</td>
<td>407 (72)</td>
<td>162 (28)</td>
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<tr>
<td>ART initiation era</td>
<td></td>
<td></td>
<td></td>
<td>0.0281</td>
</tr>
<tr>
<td>Never initiated ART</td>
<td>146 (20)</td>
<td>111 (76)</td>
<td>35 (24)</td>
<td></td>
</tr>
<tr>
<td>≤ 2000</td>
<td>221 (30)</td>
<td>136 (62)</td>
<td>85 (38)</td>
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<td>2001–2009</td>
<td>208 (29)</td>
<td>149 (72)</td>
<td>59 (28)</td>
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<td>2010–2016</td>
<td>151 (21)</td>
<td>110 (73)</td>
<td>41 (27)</td>
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<tr>
<td>ART adherence</td>
<td></td>
<td></td>
<td></td>
<td>0.0045</td>
</tr>
<tr>
<td>ART never initiated</td>
<td>318 (44)</td>
<td>236 (74)</td>
<td>82 (26)</td>
<td></td>
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<tr>
<td>≤ 39%</td>
<td>110 (15)</td>
<td>84 (76)</td>
<td>26 (24)</td>
<td></td>
</tr>
<tr>
<td>40%–79%</td>
<td>91 (13)</td>
<td>65 (71)</td>
<td>26 (29)</td>
<td></td>
</tr>
<tr>
<td>80%–94%</td>
<td>54 (7)</td>
<td>35 (65)</td>
<td>19 (35)</td>
<td></td>
</tr>
<tr>
<td>≥ 95%</td>
<td>153 (21)</td>
<td>86 (56)</td>
<td>67 (44)</td>
<td></td>
</tr>
<tr>
<td>CD4 nadir cells/mm³</td>
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<td></td>
<td>0.2261</td>
</tr>
<tr>
<td>≤ 49</td>
<td>35 (5)</td>
<td>29 (83)</td>
<td>6 (17)</td>
<td></td>
</tr>
<tr>
<td>50–199</td>
<td>99 (14)</td>
<td>68 (69)</td>
<td>31 (31)</td>
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</tr>
<tr>
<td>200–349</td>
<td>123 (17)</td>
<td>81 (66)</td>
<td>42 (34)</td>
<td></td>
</tr>
<tr>
<td>≥ 350</td>
<td>197 (27)</td>
<td>129 (65)</td>
<td>68 (35)</td>
<td></td>
</tr>
<tr>
<td>Not measured</td>
<td>272 (37)</td>
<td>199 (73)</td>
<td>73 (27)</td>
<td></td>
</tr>
<tr>
<td>CCI age-adjusted score</td>
<td></td>
<td></td>
<td></td>
<td>0.7038</td>
</tr>
<tr>
<td>6</td>
<td>400 (55)</td>
<td>285 (71)</td>
<td>115 (29)</td>
<td></td>
</tr>
<tr>
<td>7–8</td>
<td>224 (31)</td>
<td>156 (70)</td>
<td>68 (30)</td>
<td></td>
</tr>
<tr>
<td>9–10</td>
<td>74 (10)</td>
<td>47 (64)</td>
<td>27 (36)</td>
<td></td>
</tr>
<tr>
<td>≥11</td>
<td>28 (4)</td>
<td>18 (64)</td>
<td>10 (36)</td>
<td></td>
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<tr>
<td>Health authority of residence</td>
<td></td>
<td></td>
<td></td>
<td>0.9819</td>
</tr>
<tr>
<td>Fraser</td>
<td>145 (20)</td>
<td>104 (72)</td>
<td>41 (28)</td>
<td></td>
</tr>
<tr>
<td>Interior</td>
<td>31 (4)</td>
<td>22 (71)</td>
<td>9 (29)</td>
<td></td>
</tr>
<tr>
<td>Northern</td>
<td>26–29 (4–4)*</td>
<td>18–21 (70–75)*</td>
<td>6–9 (25–30)*</td>
<td></td>
</tr>
</tbody>
</table>

Continued
using the glm function. This analysis was exclusive to those who have ever achieved viral suppression (ie, two consecutive viral loads <200 copies/mL within 4 months).

Online supplemental appendix figure S2 details this analysis’ inclusion criteria.

**Hospital readmission**
A generalised linear mixed model with a binomial distribution, logit link function and random intercept term was used to model the probability of hospital readmission, implemented in R using the lme4 package.

**Length of hospital stay**
A generalised linear mixed model with a gamma distribution, log link function and random intercept term was used to model the length of hospital stay for acute care hospitalisations during the follow-up period, implemented in R using the lme4 package. Choosing a model based on a gamma distribution is an effective strategy to model the right-skewed inpatient length of hospital stay data. The exponentiated coefficient estimate from this model represents the multiplicative effect on the average outcome, and hereafter will be referred to as the mean ratio.

In all analyses, except for the cost analysis, we employed a selection approach published by our group to select the potential confounders for the final model. Considering the relative change in the coefficient of the exposure variable, potential confounders were discarded one at a time until the maximum change from the full model surpassed 5%. Given that this selection method can be challenging for our cost analysis, we selected the potential confounders a priori based on literature-informed knowledge. These included: gender, years since schizophrenia diagnosis, mood and/or anxiety disorder diagnosis, HIV risk group, ART era, and time-varying age, CCI, CD4 nadir, and viral suppression.

**Patient and public involvement**
Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

**RESULTS**

**Individual characteristics**
Of 13,641 PLWH in the cohort, 726 met inclusion criteria and were followed for a median of 7.2 years (25th–75th percentiles (Q1–Q3): 3.1–12.6). Among eligible individuals, at index date, 75% (544) were men, 52% (380) were ≥40 years old, 52% (381) were PWID, 50% (359) initiated ART after 2001, 78% (569) had mood and/or anxiety disorder diagnosis, 27% (197) had a nadir CD4 count of ≥350 cells/mm^3, 77% (559) were recently diagnosed with schizophrenia and 45% (326) had a CCI score >6 (table 1). Those non-adherent to antipsychotics were significantly more likely to be <30 years old, never initiate ART and be <40% ART-adherent (among those who initiated) (table 1). Online supplemental appendix table S3 shows the characteristics of our population at the end of follow-up.

**Adherence to antipsychotics**
The proportion of PLWH with schizophrenia who were ≥80% adherent to antipsychotics has steadily improved across the 16-year period, from 25% (50/198) in 2001 to 41% (225/554) in 2016 (figure 1, online supplemental
When stratified by gender and PWID status, women had the lowest proportion of individuals with ≥80% adherence for most years in the same time period (from 17% (7/41) in 2001 to 39% (54/138) in 2016). We observed no difference in adherence to antipsychotics among those who used only injectable form, only non-injectable form and a combination of both for most years, except in 2006–2009 (p<0.05) (online supplemental appendix table S5). Similarly, no difference in adherence was observed in most years among individuals who have ever consumed typical/first-generation antipsychotics and those who consumed only atypical/second-generation antipsychotics, except in 2008–2009 (p<0.05) (online supplemental appendix table S6). Further, a cross-tabulation of ART adherence by antipsychotic adherence demonstrated a significant association in most years (except 2001 and 2003); those with poor adherence to antipsychotics were also poorly adhered to ART, especially in the later study years (online supplemental appendix table S7).

**Healthcare costs**

Figures 2 and 3 (online supplemental appendix table S8–S12) present the cost analysis results. Marginal costs with a negative value suggest a lower average annual cost per individual among non-adherent compared with adherent (ie, reference) groups. A positive marginal cost suggests a higher average annual cost among non-adherent individuals. The total average annual cost was higher among the non-adherent group relative to the adherent group ($2185; 95% CI $180 to $4549), which may be influenced by a higher average annual hospitalisation cost among the non-adherent group ($5517; 95% CI $3991 to $7043). In comparison to adherent individuals, MSP costs were higher ($1052 (95% CI $755 to $1348)) and pharmacy costs were lower ($4020 (95% CI $5303 to $2738)) than the costs for those non-adherent.

The average annual total cost was higher among non-adherent men relative to adherent men ($1486; 95% CI $1089 to $4060) (figure 2). For non-adherent women, the total cost relative to adherent woman was much higher than what we found among men ($6163; 95% CI $1561 to $10766) (figure 2). Pharmacy costs aside, the disparities in total costs between adherent and non-adherent groups in men and women were largely driven by hospitalisation costs. In particular, the hospitalisation cost was $8806 (95% CI $5784 to $11828) higher among non-adherent women relative to adherent women. Among PWID and non-PWID, the annual total cost was higher among non-adherent individuals by $2137 (95% CI $815 to $5088) and $179 (95% CI $2695 to $3053), respectively (figure 3). Again, the cost difference was driven by hospitalisation costs.
For instance, hospitalisation costs were $5985 (95% CI $4079 to $7890) higher among non-adherent PWID compared with adherent PWID.

### Clinical outcomes

In total, 531 (73%) PLWH with schizophrenia achieved initial viral suppression. Overall, there was no difference in adjusted OR (aOR) between adherent and non-adherent individuals, even when stratified by PWID status (table 2). However, when stratified by gender, non-adherent women experienced higher odds of virological failure (aOR 2.48, 95% CI 1.06 to 5.82).

Overall, 5503 hospitalisations or 9533 hospitalisations/100 person-years (95% CI 92.81 to 97.84) were observed with a median length of stay of 6 days (Q1–Q3: 3.0–14.0). Non-adherent individuals had an increased average length of hospital stay (adjusted mean ratio 1.23, 95% CI 1.13 to 1.35) compared with adherent individuals (table 2). On stratification, the average length of hospital
stay remained higher in all non-adherent subgroups except for non-PWIDs.

We observed 1531 hospital readmissions within 30 days of the first hospitalisation (28% (1531/5503) of all hospitalisations). Overall, non-adherent individuals had 1.48 times (95% CI 1.23 to 1.77) the odds of hospital readmission of adherent individuals (table 2). Following stratification, the aOR of hospital readmission remained higher in all of the non-adherent subgroups, except non-PWIDs. Non-adherent individuals accounted for the majority of hospital readmissions (83%; 1278/1531), with 51% of the top 20 reasons for their readmissions, based on CMG classifications, being mental health related (online supplemental appendix table S13).

### DISCUSSION

To our knowledge, this population-based study is the first to explore the clinical and economic impacts of adherence to antipsychotics among PLWH with schizophrenia. The proportion of adherent individuals steadily increased from 2001 to 2016. PWID had the fastest growing proportion of adherent individuals across the study period. This result may be due to a combination of different factors. First, with the second generation of antipsychotics, adherence to these medications is supposed to improve, even though some studies have shown that this is not the case in other settings.28–31 Second, in BC, PLWH affected by schizophrenia tends to be a highly vulnerable and marginalised group of individuals, with a high percentage with substance use disorder.32 33 Thus, there have been several initiatives to support these individuals not only on their HIV adherence, but adherence to mental health and substance use disorder therapies.34 35 In addition, we have seen great benefits of community-based programmes designed to improve treatment access for individuals with substance use and concurrent psychiatric illness, such as Opioid Agonist Treatment Programmes.36

We further demonstrated that non-adherence to antipsychotics contributes to poor health outcomes and an excess of certain healthcare costs. Overall, non-adherent individuals had higher total costs driven by lower pharmacy costs (ie, from not taking the medications), and higher hospitalisation costs. We also observed disparities by gender and PWID status, particularly higher costs among non-adherent women and PWID. The higher cost among women may be explained by gender-based research indicating that women are more likely to seek mental health-related treatment than men.37 In addition, women in our cohort were more likely to be PWID compared with men. PWID, especially when non-adherent, are more likely to be hospitalised given the adverse outcomes associated with injection drug use, including drug overdoses, hepatitis C, bacterial infections and other mental health disorders.38 Note that in our cohort, the use of clozapine is

### Table 2

Multivariable models assessing the impact of adherence to antipsychotic medication on clinical outcomes (virological failure, hospital readmission and length of hospital stay) among PLWH with schizophrenia in our study population

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall</th>
<th>Women</th>
<th>Men</th>
<th>PWID</th>
<th>Non-PWID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological failure (viral load &gt;200 copies/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>1.32 (0.83 to 2.09)</td>
<td>2.48 (1.06 to 5.82)</td>
<td>0.94 (0.55 to 1.63)</td>
<td>1.30 (0.76 to 2.22)</td>
<td>0.82 (0.23 to 2.91)</td>
</tr>
<tr>
<td>≥80%</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Hospital readmission (within 30 days of discharge)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>1.48 (1.23 to 1.77)</td>
<td>2.09 (1.47 to 2.97)</td>
<td>1.36 (1.10 to 1.68)</td>
<td>1.58 (1.29 to 1.94)</td>
<td>1.19 (0.64 to 2.22)</td>
</tr>
<tr>
<td>≥80%</td>
<td>REF</td>
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<tr>
<td>Adjusted mean ratio (95% CI)</td>
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<tr>
<td>Length of hospital stay</td>
<td></td>
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<tr>
<td>&lt;80%</td>
<td>1.23 (1.13 to 1.35)</td>
<td>1.53 (1.31 to 1.79)</td>
<td>1.12 (1.04 to 1.20)</td>
<td>1.11 (1.04 to 1.19)</td>
<td>1.21 (0.98 to 1.50)</td>
</tr>
<tr>
<td>≥80%</td>
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The adjusted mean ratio coefficient estimate from the length of hospital stay analysis represents the multiplicative effect on the average outcome.

Confounders considered for virological failure: Gender (only for overall and PWID/non-PWID models), age (per 10 years), years since schizophrenia diagnosis, CD4 (closest to ART initiation), HIV risk group (only for overall and gender models), antiretroviral era, viral suppression (in year of hospitalisation), years since schizophrenia diagnosis, HIV risk group (only for overall and gender models), CD4 nadir (in the year of hospitalisation), CCI score (in year of hospitalisation), antiretroviral era, viral suppression (in year of the hospitalisation (all <200 copies/mL)), and reason for exiting hospital.

Confounders considered for hospital readmission: Gender (only for overall and PWID/non-PWID models), age (per 10 years, in year of hospitalisation), years since schizophrenia diagnosis, HIV risk group (only for overall and gender models), CD4 nadir (in year of hospitalisation), CCI score (in year of hospitalisation), antiretroviral era, viral suppression (in year of hospitalisation (all <200 copies/mL)), PLWH, people living with HIV/AIDS; PWID, people who have ever injected drugs.
low (≤5%), and, thus, does not explain adverse treatment outcomes.

We observed a significant increase in hospital readmissions within 30 days and length of hospital stay among non-adherent PLWH with schizophrenia. It was interesting to note that there was no difference in virological failure between adherent and non-adherent PLWH. Stratified analyses by gender and PWID status further revealed disparities in clinical outcomes. Non-adherent women had consistently worse outcomes compared with adherent women, and the effect on all outcomes was stronger than men in general. Not surprising, non-adherent PWID had worse outcomes than adherent PWID. However, it was interesting to note that although the expected length of hospital stay for non-adherent PWID was shorter than non-adherent non-PWID, the expected probability of being readmitted within 30 days of discharge among PWID was higher than non-adherent non-PWID.

The lack of similar studies among PLWH with schizophrenia limited the comparability of our results. Nonetheless, our findings are parallel with previous research among people living only with schizophrenia. A literature review of 28 studies concluded that non-adherence to antipsychotics among people living with schizophrenia generally resulted in lower overall healthcare costs, but greater non-pharmacy costs. Furthermore, a study found that people living with schizophrenia with <80% adherence to antipsychotics were 2.4 times more likely to be admitted to a hospital and have longer hospital stays. Markedly, we demonstrated that mental health-related causes accounted for 51% of hospital readmissions among PLWH with schizophrenia. The exacerbated healthcare utilisation may be prevented by improved adherence, thus underscoring the important individual and public health burden, with strong implications for targeted interventions.

Non-adherence to antipsychotics among PLWH with schizophrenia remains a prevalent and burdensome public health challenge. Considering the high proportion of non-adherent individuals in our cohort, stakeholders (eg, policy-makers and healthcare professionals) urgently need to collaborate and intensify efforts to increase adherence, improve health outcomes and decrease excess healthcare utilisation and corresponding economic burden. Expanding adherence retention support that addresses the specific needs of vulnerable subpopulations (eg, women and PWID) is crucial. Higher co-occurrence of mood and/or anxiety disorders in our cohort further highlights existing complex medical needs and competing priorities, which may impede the accessibility of care required. When considering interventions, stakeholders must acknowledge that HIV and schizophrenia are complex and stigmatised conditions. For instance, people living with schizophrenia face structural (eg, poverty, unstable housing, food insecurity), social (eg, lack of social support, stigma) and biological challenges (eg, medication side effects, substance use) that may hinder their ability to access and adhere to antipsychotics. Unquestionably, many PLWH experience the same barriers to HIV care and treatment. PLWH with schizophrenia may thus face amplified unique challenges, exemplified by the substantial proportion of those who have never initiated ART or achieved suboptimal ART adherence in our study. The integration of mental health and HIV interventions, while considering these contextual realities, is therefore critical.

This study thus offers a conceptual and methodological foundation to guide future research in this area. For example, further research is needed to identify additional health determinants contributing to non-adherence to antipsychotics among PLWH with schizophrenia. In addition, investigating methods that better integrate access to mental health services and improve antipsychotic adherence in this understudied population may result in better health outcomes and reduced preventative healthcare utilisation and costs.

LIMITATIONS
First, although administrative databases provide longitudinal health records of a large population, administrative data were not collected for research purposes and may suffer from coding errors. Second, although we excluded transient psychotic episodes or episodes of insufficient chronicity, a risk of misclassification and/or misdiagnosis of schizophrenia remains, especially given the overlapping symptoms with other mental health disorders, particularly bipolar disorder. Third, there is no gold standard to measure adherence. Although we chose the average PDC technique in our study to estimate adherence when an individual is receiving multiple medications, there are other methods (more and less conservative) that can be used to estimate adherence, which may influence some of the results in this study. Fourth, our findings may only be generalisable to settings with universal healthcare and similar access to ART, healthcare services and medications. Fifth, critical risk factors for non-adherence were dealt with as confounders in our analysis. However, understanding the degree and way in which these variables contribute to non-adherence is critical to improve adherence. Ideally, we would conduct further analyses to investigate the effect of these risk factors on non-adherence alone or as part of interaction terms, however, due to the limited sample size, and number of confounders, it was impractical. Thus, we decided to address some of the confounding by conducting stratified analyses by gender and history of injection drug use as these variables were key confounders in the association we were interested in. Finally, we were unable to capture other potentially influential confounders, including homelessness, access to mental health services (other than psychiatrists) and social support.
CONCLUSION
Our study shows that even in a universal healthcare setting, non-adherence to antipsychotics remains a prevalent public health issue that significantly contributes to poor clinical outcomes and is associated to an excess in non-pharmacy-related healthcare costs. We also observed disparities by gender and PWID status. Our results underline a need for strategic mental health and HIV integrated interventions to increase antipsychotic adherence among PLWH with schizophrenia, particularly those who are PWID and women.

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Contributors
Concept and design: VDL, SS, NGAN, MS-J and JE; acquisition, analysis, or interpretation of data: HMT, HN and VDL; drafting of the manuscript: SS, NGAN, MS-J, VDL; critical revision of the manuscript for important intellectual content: SS, NGAN, HMT, HN, MS-J, JE, TLP, WGH, JSGM, VDL; administrative, technical or material support: JSGM and VDL; guarantor: VDL. All authors (SS, NGAN, HMT, MS-J, HN, JE, TLP, WGH, JSGM and VDL) have read and approved the final manuscript.

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Competing interests
JSGM: Institutional grants have been provided by Gilead, Merck and ViV Healthcare. All other authors declare no competing interests.

Patient and public involvement
Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not applicable.

Ethics approval
The BC-CIE received approval for this study from the British Columbia Ethics Review Committee at the St. Paul’s Hospital, Providence Health Care site (H18-02206; H16-02030). This study was conducted using strictly anonymised laboratory and administrative databases, and thus informed consent was not required. This study complies with BC’s Freedom of Information and Protection of Privacy Act.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
No data are available. The British Columbia Centre for Excellence in HIV/AIDS (BC-CIE) is prohibited from making individual-level data available publicly due to provisions in our service contracts, institutional policy and ethical requirements. In order to facilitate research, we make such data available via data access requests. Some BC-CIE data are not available externally due to prohibitions in service contracts with our funders or data providers. Institutional policies stipulate that all external data requests require collaboration with a BC-CIE researcher. For more information or to make a request, please contact Mark Helberg, senior director, internal and external relations, and strategic development: mhelberg@bcce.ca.

Supplemental material
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