



BMJ Open 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

Sony Subedi,¹ Ni Gusti Ayu Nanditha ^{1,2}, Hiwot M Tafessu,¹ Hasan Nathani,¹ Martin St-Jean,¹ Julius Elefante,^{3,4} Thomas L Patterson,⁵ William G Honer,³ Julio S G Montaner,^{1,2} Viviane D Lima ^{1,2}

To cite: Subedi S, Nanditha NGA, Tafessu HM, *et al.* 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. *BMJ Open* 2023;13:e070680. doi:10.1136/bmjopen-2022-070680

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-070680>).

Received 01 December 2022
Accepted 04 April 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Viviane D Lima;
vlima@bccf.ca

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 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.^{3–5} 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.⁵ The higher diagnosis incidence may be attributed to high-risk behaviours in this population, including injection drug use and unprotected sex with multiple partners.⁶

While schizophrenia only affects 1% of the Canadian population,⁷ it is associated with very high healthcare costs.¹ Presently, there is no cure for schizophrenia, and existing treatments require a lifelong commitment.⁸ With consistent antipsychotics use, individuals can manage their symptoms and prevent relapse and rehospitalisation.¹ Nevertheless, non-adherence remains the most significant global obstacle when treating schizophrenia.^{9–10} 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.¹⁰ 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.¹¹ 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.⁵ 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,¹² 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.¹³ 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.¹⁴ 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.^{15–17} 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.¹⁶ 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.^{11–18} 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 (gbMSM), 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 $\geq 95\%$), 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, transferred to home with support services, transferred to 'other', or signed out against medical advice), and the Charlson Comorbidity Index (CCI) score (6, 7–8, 9–10 or ≥ 11). The CCI score predicts 1-year mortality using a scoring system for individuals who have comorbidities.¹⁹ An HIV/AIDS diagnosis corresponded to a CCI score of 6, which is the lowest score assigned in this study. The ICD-9 and ICD-10 codes employed to identify comorbidities to calculate the CCI are presented in online supplemental appendix table 2. Of note, ART adherence (%) was calculated during the year before the outcome of interest using the PDC method and the HIV risk group was self-reported.

Outcomes

Our main outcome was annual healthcare costs associated with adherence/non-adherence to antipsychotics among PLWH with schizophrenia. We explored three types of costs per individual: (1) Medical Services Plan (MSP) costs, defined as the total costs for fee-for-service services provided by general practitioners and specialists, and laboratory tests; (2) hospitalisation costs, defined as the total cost for acute care and day surgery hospitalisations and calculated using methodology from the Canadian Institute for Health Information (CIHI),²⁰ by multiplying resource intensity weights and the standard hospital stay cost corresponding to the specific hospitalisation record (online supplemental appendix note 3); (3) pharmacy costs, defined as the total cost related to pharmaceuticals and calculated by summing the medication cost claimed by the pharmacist, professional fee (ie, dispensing cost for technical/professional services) and special service fee.

We also investigated clinical outcomes, including virological failure, hospital readmission and length of hospital stay (days). Except for virological failure (ie, a measure of viral load ≥ 200 copies/mL), all other outcomes were measured longitudinally (ie, annually). Readmission

cases included acute care hospitalisations within 30 days of initial hospitalisations that did not result in in-hospital death or interhospital 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 χ^2 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 twopm 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

| Individual characteristics | Whole sample N (%) | <80% adherence N (%) | ≥80% adherence N (%) | P value |
|---------------------------------|-----------------------|-------------------------|-------------------------|---------|
| | N=726 (100) | 506 (70) | 220 (30) | |
| Gender | | | | 0.4963 |
| Women | 182 (25) | 131 (72) | 51 (28) | |
| Men | 544 (75) | 375 (69) | 169 (31) | |
| Age (years) | | | | 0.0153 |
| <30 | 102 (14) | 80 (78) | 22 (22) | |
| 30–39 | 244 (34) | 180 (74) | 64 (26) | |
| 40–49 | 257 (35) | 169 (66) | 88 (34) | |
| ≥50 | 123 (17) | 77 (63) | 46 (37) | |
| HIV risk group | | | | 0.8836 |
| Heterosexual/other | 49 (7) | 35 (71) | 14 (29) | |
| PWID | 381 (52) | 268 (70) | 113 (30) | |
| gbMSM | 89 (12) | 59 (66) | 30 (34) | |
| gbMSM/PWID | 127 (17) | 86 (68) | 41 (32) | |
| Unknown | 80 (11) | 58 (72) | 22 (28) | |
| Mood and/or anxiety disorder | | | | 0.0516 |
| No | 157 (22) | 99 (63) | 58 (37) | |
| Yes | 569 (78) | 407 (72) | 162 (28) | |
| ART initiation era | | | | 0.0281 |
| Never initiated ART | 146 (20) | 111 (76) | 35 (24) | |
| ≤2000 | 221 (30) | 136 (62) | 85 (38) | |
| 2001–2009 | 208 (29) | 149 (72) | 59 (28) | |
| 2010–2016 | 151 (21) | 110 (73) | 41 (27) | |
| ART adherence | | | | 0.0045 |
| ART never initiated | 318 (44) | 236 (74) | 82 (26) | |
| ≤39% | 110 (15) | 84 (76) | 26 (24) | |
| 40%–79% | 91 (13) | 65 (71) | 26 (29) | |
| 80%–94% | 54 (7) | 35 (65) | 19 (35) | |
| ≥95% | 153 (21) | 86 (56) | 67 (44) | |
| CD4 nadir cells/mm ³ | | | | 0.2261 |
| ≤49 | 35 (5) | 29 (83) | 6 (17) | |
| 50–199 | 99 (14) | 68 (69) | 31 (31) | |
| 200–349 | 123 (17) | 81 (66) | 42 (34) | |
| ≥350 | 197 (27) | 129 (65) | 68 (35) | |
| Not measured | 272 (37) | 199 (73) | 73 (27) | |
| CCI age-adjusted score | | | | 0.7038 |
| 6 | 400 (55) | 285 (71) | 115 (29) | |
| 7–8 | 224 (31) | 156 (70) | 68 (30) | |
| 9–10 | 74 (10) | 47 (64) | 27 (36) | |
| ≥11 | 28 (4) | 18 (64) | 10 (36) | |
| Health authority of residence | | | | 0.9819 |
| Fraser | 145 (20) | 104 (72) | 41 (28) | |
| Interior | 31 (4) | 22 (71) | 9 (29) | |
| Northern | 26–29 (4–4)* | 18–21 (70–75)* | 6–9 (25–30)* | |

Continued

Table 1 Continued

| Individual characteristics | Whole sample N (%) | <80% adherence N (%) | ≥80% adherence N (%) | P value |
|--|-----------------------|-------------------------|-------------------------|---------|
| Vancouver coastal | 429 (59) | 296 (69) | 133 (31) | |
| Vancouver Island | 89 (12) | 62 (70) | 27 (30) | |
| Unknown | <5† | <5† | <5† | |
| Total follow-up time in years (median (Q1–Q3)) | 7.2 (3.1–12.6) | 7.3 (3.1–12.9) | 6.7 (3.2–12.4) | 0.3704 |
| Years since schizophrenia diagnosis | | | | 0.6792 |
| 0 | 559 (77) | 383 (69) | 176 (31) | |
| 1 | 28 (4) | 21 (75) | 7 (25) | |
| 2 | 29 (4) | 20 (69) | 9 (31) | |
| 3 | 22 (3) | 16 (73) | 6 (27) | |
| 4 | 37 (5) | 30 (81) | 7 (19) | |
| 5 | 51 (7) | 36 (71) | 15 (29) | |

Index date is the date of diagnosis or 1 January 2001, whichever occurred last.

The lowest CCI score category starts at 6 since it is the score assigned to every individual diagnosed with HIV/AIDS. All results are significant at the $p < 0.05$.

*Due to data privacy, we provided a range due the cells with <5 participants.

†Due to data privacy, we replaced the exact numbers if the cell contained <5 participants.

ART, antiretroviral therapy; CCI, Charlson Comorbidity Index; gbMSM, gay, bisexual and other men who have sex with men; PLWH, people living with HIV; PWID, people who have ever injected drugs.

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.²⁶ 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.²⁷ 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, 27% (197) had a nadir CD4 count of ≥350 cells/mm³, 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

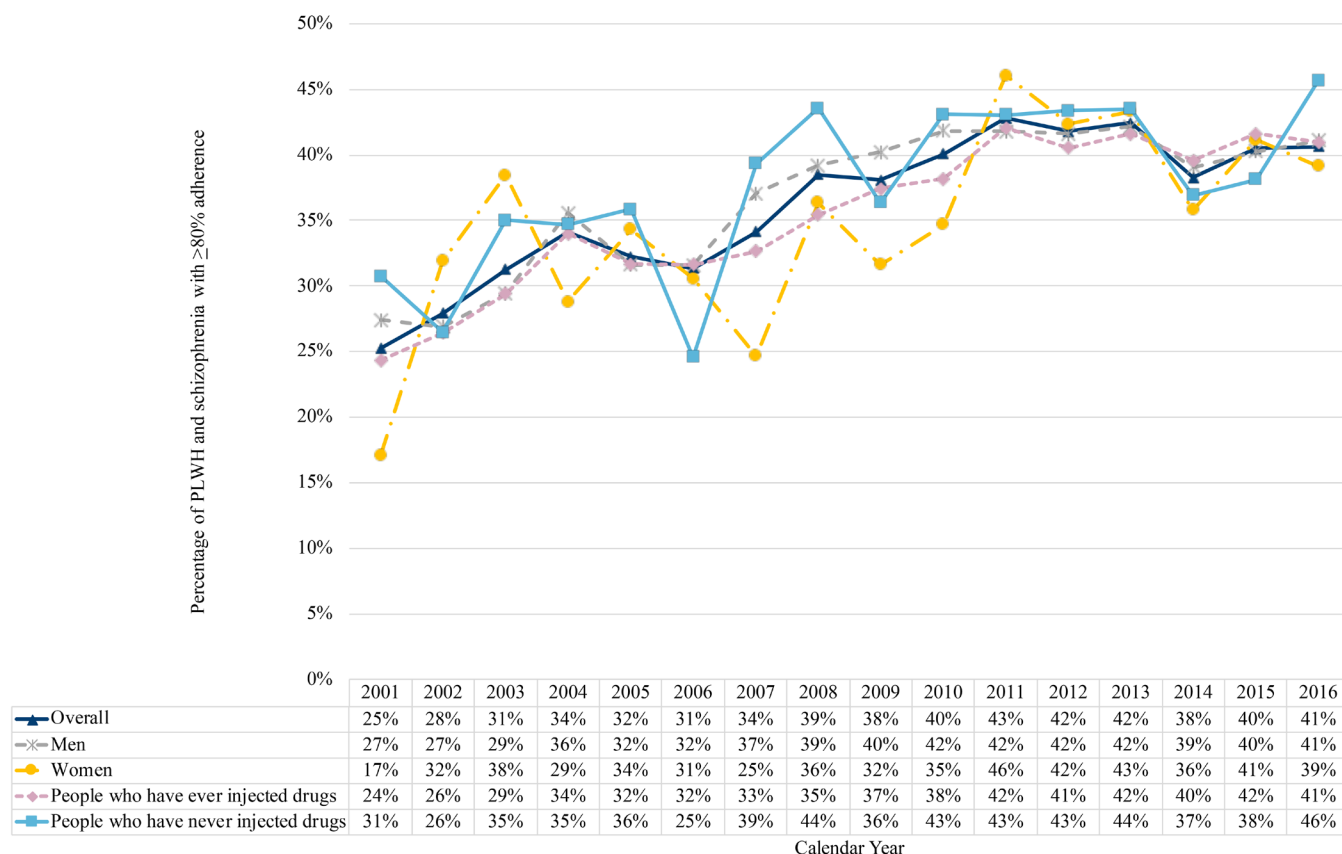


Figure 1 Comparison of the overall annual percentage of PLWH with schizophrenia with $\geq 80\%$ antipsychotic adherence in the study population, stratified by gender and injection drug use status. Data can be found in online supplemental appendix. PLWH, people living with HIV/AIDS.

appendix table S4). When stratified by gender and PWID status, women had the lowest proportion of individuals with $\geq 80\%$ 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 (\$C2185; 95% CI –\$C180 to \$C4549), which may be influenced by a higher average annual hospitalisation cost among the non-adherent group (\$C5517; 95% CI \$C3991 to \$C7043). In comparison to adherent individuals, MSP costs were higher (\$C1052 (95% CI \$C755 to \$C1348)) and pharmacy costs were lower –\$C4020 (95% CI –\$C5303 to –\$C2738) than the costs for those non-adherent.

The average annual total cost was higher among non-adherent men relative to adherent men (\$C1486; 95% CI –\$C1089 to \$C4060) (figure 2). For non-adherent woman, the total cost relative to adherent woman was much higher than what we found among men (\$C6163; 95% CI \$C1561 to \$C10 766) (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 \$C8806 (95% CI \$C5784 to \$C11 828) 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 \$C2137 (95% CI –\$C815 to \$C5088) and \$C179 (95% CI –\$C2695 to \$C3053), respectively (figure 3). Again, the cost difference was driven by hospitalisation costs.

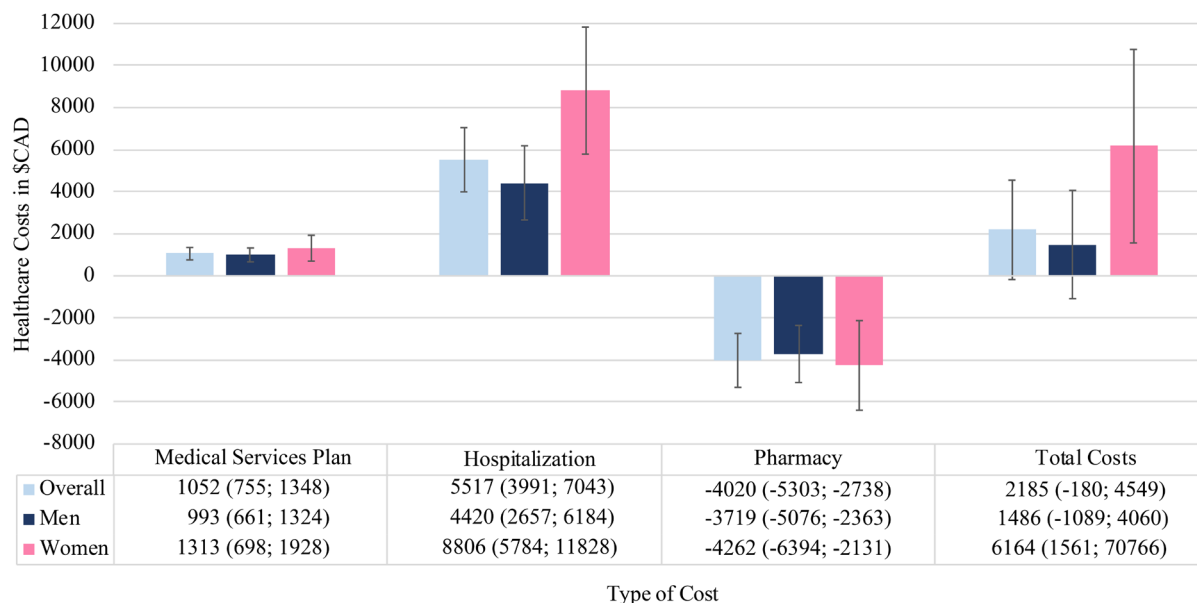


Figure 2 Marginal effect on annual healthcare costs among non-adherent PLWH with schizophrenia compared with their adherent counterparts in our study population, overall and stratified by gender (adjusted to 2016 Canadian dollar). The reference group is the adherent group for each stratified subgroup. The costs are presented in 2016 Canadian dollar. The range presented in the brackets are the 95% CIs. PLWH, people living with HIV/AIDS.

For instance, hospitalisation costs were \$C5985 (95% CI \$C4079 to \$C7890) 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

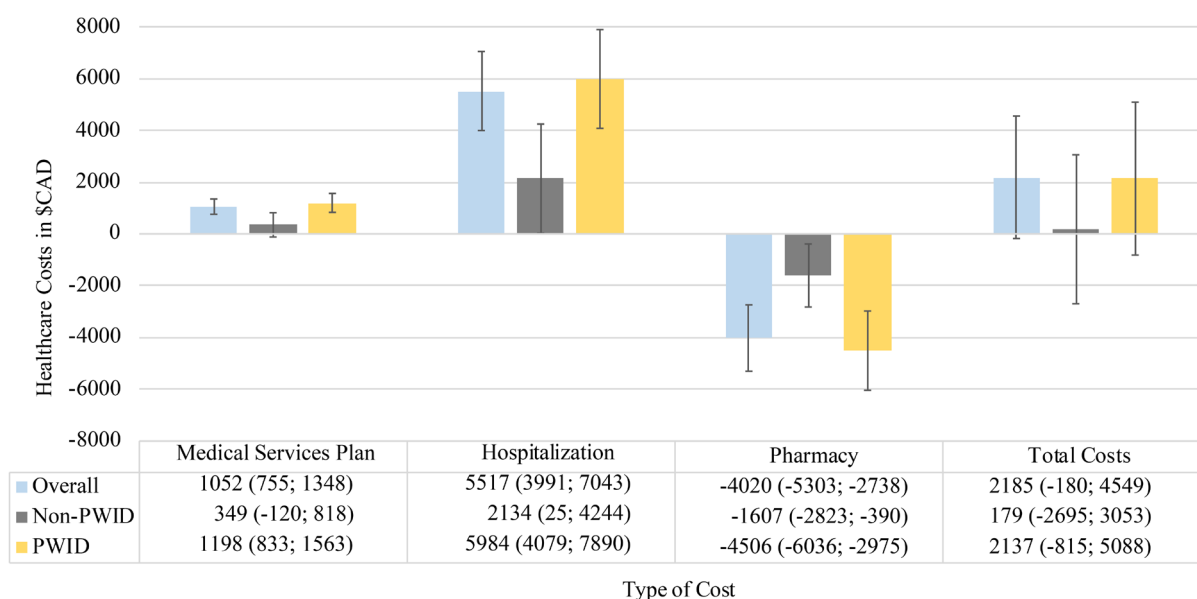


Figure 3 Marginal effect on annual healthcare costs among non-adherent PLWH with schizophrenia compared with their adherent counterparts in our study population, overall and stratified by PWID status (adjusted to 2016 Canadian dollar). The reference group is the adherent group for each stratified subgroup. The costs are presented in 2016 Canadian dollar. The range presented in the brackets are the 95% CIs. PLWH, people living with HIV/AIDS.

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

| Outcome | Overall | Women | Men | PWID | Non-PWID |
|--|---------------------|---------------------|---------------------|---------------------|---------------------|
| Adjusted OR (95% CI) | | | | | |
| Virological failure (viral load >200 copies/mL) | | | | | |
| <80% | 1.32 (0.83 to 2.09) | 2.48 (1.06 to 5.82) | 0.94 (0.55 to 1.63) | 1.30 (0.76 to 2.22) | 0.82 (0.23 to 2.91) |
| ≥80% | REF | REF | REF | REF | REF |
| Hospital readmission (within 30 days of discharge) | | | | | |
| <80% | 1.48 (1.23 to 1.77) | 2.09 (1.47 to 2.97) | 1.36 (1.10 to 1.68) | 1.58 (1.29 to 1.94) | 1.19 (0.64 to 2.22) |
| ≥80% | REF | REF | REF | REF | REF |
| Adjusted mean ratio (95% CI) | | | | | |
| Length of hospital stay | | | | | |
| <80% | 1.23 (1.13 to 1.35) | 1.53 (1.31 to 1.79) | 1.12 (1.04 to 1.20) | 1.11 (1.04 to 1.19) | 1.21 (0.98 to 1.50) |
| ≥80% | REF | REF | REF | REF | REF |

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, ART adherence (1 year prior to failure or end of follow-up), viral load (\log_{10}) closest to ART initiation.

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 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 length of hospital stay: 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.

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

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.³⁹ 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.⁴⁰ 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.¹¹ Unquestionably, many PLWH experience the same barriers to HIV care and treatment.⁴¹ 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 preventable 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.⁴² 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.

Author affiliations

¹British Columbia Centre for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada

²Division of Infectious Diseases, Department of Medicine, Faculty of Medicine, The University of British Columbia, Vancouver, British Columbia, Canada

³Department of Psychiatry, The University of British Columbia, Vancouver, British Columbia, Canada

⁴Department of Psychiatry, St Paul's Hospital, Vancouver, British Columbia, Canada

⁵Department of Psychiatry, University of California San Diego, La Jolla, California, USA

Acknowledgements We would like to thank all the participants included within STOP HIV/AIDS, the British Columbia Centre for Excellence in HIV/AIDS, the BC Ministry of Health, BC Vital Statistics Agency, PharmaNet and the institutional data stewards for granting access to the data. All inferences, opinions and conclusions drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the data stewards.

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.

Funding This work was supported by the following sources of funding: JSGM's Treatment as Prevention (TasP) research, paid to his institution, has received support from the BC Ministry of Health, Health Canada, Public Health Agency of Canada, Vancouver Coastal Health and VGH Foundation. VDL is funded by a grant from the Canadian Institutes of Health Research (PJT-148595), and the Canadian Foundation for AIDS Research (CANFAR Innovation Grant—30-101).

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

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

Patient consent for publication Not applicable.

Ethics approval The BC-CfE received approval for this study from the University of British Columbia Ethics Review Committee at the St. Paul's Hospital, Providence Health Care site (H18-02208; H16-02036). 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-CfE) 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-CfE 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-CfE researcher. For more information or to make a request, please contact Mark Helberg, senior director, internal and external relations, and strategic development: mhelberg@bccfe.ca.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Ni Gusti Ayu Nanditha <http://orcid.org/0000-0002-3723-6418>

Viviane D Lima <http://orcid.org/0000-0003-4943-091X>

REFERENCES

- Goeree R, Farahati F, Burke N, *et al*. The economic burden of schizophrenia in Canada in 2004. *Curr Med Res Opin* 2005;21:2017–28.
- Laursen TM, Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Curr Opin Psychiatry* 2012;25:83–8.
- Smith DJ, Langan J, McLean G, *et al*. Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. *BMJ Open* 2013;3:e002808.
- Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol* 2010;24:81–90.
- Closson K, McLinden T, Patterson TL, *et al*. HIV, schizophrenia, and all-cause mortality: a population-based cohort study of individuals accessing universal medical care from 1998 to 2012 in British Columbia, Canada. *Schizophr Res* 2019;209:198–205.
- Hughes E, Bassi S, Gilbody S, *et al*. Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness: a systematic review and meta-analysis. *Lancet Psychiatry* 2016;3:40–8.
- Simeone JC, Ward AJ, Rotella P, *et al*. An evaluation of variation in published estimates of schizophrenia prevalence from 1990–2013: a systematic literature review. *BMC Psychiatry* 2015;15:193.
- Crockford D, Addington D. Canadian schizophrenia guidelines: schizophrenia and other psychotic disorders with coexisting substance use disorders. *Can J Psychiatry* 2017;62:624–34.
- Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. *World Psychiatry* 2013;12:216–26.
- Velligan DI, Sajatovic M, Hatch A, *et al*. Why do psychiatric patients stop antipsychotic medication? A systematic review of reasons for nonadherence to medication in patients with serious mental illness. *Patient Prefer Adherence* 2017;11:449–68.
- Higashi K, Medic G, Littlewood KJ, *et al*. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. *Ther Adv Psychopharmacol* 2013;3:200–18.
- Pence BW, Miller WC, Gaynes BN, *et al*. Psychiatric illness and virologic response in patients initiating highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007;44:159–66.
- Heath K, Samji H, Nosyk B, *et al*. Cohort profile: seek and treat for the optimal prevention of HIV/AIDS in British Columbia (STOP HIV/AIDS BC). *Int J Epidemiol* 2014;43:1073–81.
- Chronic Disease Information Working Group (BCCDC). *BC chronic disease and selected procedure case definitions version 2017, last updated April 2019*. British Columbia, 2015.
- Bijlsma MJ, Janssen F, Hak E. Estimating time-varying drug adherence using electronic records: extending the proportion of days covered (PDC) method. *Pharmacoepidemiol Drug Saf* 2016;25:325–32.
- Choudhry NK, Shrank WH, Levin RL, *et al*. Measuring concurrent adherence to multiple related medications. *Am J Manag Care* 2009;15:457–64.
- Basak R, McCaffrey Iii DJ, Bentley JP, *et al*. Adherence to multiple medications prescribed for a chronic disease: a methodological investigation. *J Manag Care Spec Pharm* 2014;20:815–23.

- 18 Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. 2007. Available: <http://ep.yimg.com/ty/cdn/epill/pdcmp.pdf>
- 19 Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
- 20 Canadian Institute for Health Information. Understanding variability in the cost of a standard hospital stay Ottawa, ON. 2017. Available: https://secure.cihi.ca/free_products/cshs-variability-study-2017-en.pdf
- 21 Canadian Institute for Health Information. The case mix groups (CMG). n.d. Available: <https://www.cihi.ca/en/cmg>
- 22 Jibson MD. Second-generation antipsychotic medications: pharmacology, administration, and side effects: uptodate. n.d. Available: <https://www.uptodate.com/contents/second-generation-antipsychotic-medications-pharmacology-administration-and-side-effects>
- 23 Jibson MD. First-generation antipsychotic medications: pharmacology, administration, and comparative side effects: uptodate. n.d. Available: https://www.uptodate.com/contents/first-generation-antipsychotic-medications-pharmacology-administration-and-comparative-side-effects?topicRef=14776&source=see_link
- 24 McDonald JH. *Handbook of biological statistics*, 2nd ed. 2009. Available: <http://www.biostathandbook.com>
- 25 Belotti F, Deb P, Manning WG, *et al.* twopm: Two-part models. *Stata Journal* 2015;15:3–20.
- 26 Williford E, Haley V, McNutt LA, *et al.* Dealing with highly skewed hospital length of stay distributions: the use of gamma mixture models to study delivery hospitalizations. *PLoS One* 2020;15:e0231825.
- 27 Lima VD, Geller J, Bangsberg DR, *et al.* The effect of adherence on the association between depressive symptoms and mortality among HIV-infected individuals first initiating HAART. *AIDS* 2007;21:1175–83.
- 28 Awad AG, Voruganti LN. New antipsychotics, compliance, quality of life, and subjective tolerability—are patients better off? *Can J Psychiatry* 2004;49:297–302.
- 29 Bera RB. Patient outcomes within schizophrenia treatment: a look at the role of long-acting injectable antipsychotics. *J Clin Psychiatry* 2014;75 Suppl 2:30–3.
- 30 Burton SC. Strategies for improving adherence to second-generation antipsychotics in patients with schizophrenia by increasing ease of use. *J Psychiatr Pract* 2005;11:369–78.
- 31 Lian L, Kim DD, Procyshyn RM, *et al.* Long-acting injectable antipsychotics for early psychosis: a comprehensive systematic review. *PLoS One* 2022;17:e0267808.
- 32 Jones AA, Gicas KM, Seyedin S, *et al.* Associations of substance use, psychosis, and mortality among people living in precarious housing or homelessness: a longitudinal, community-based study in Vancouver, Canada. *PLoS Med* 2020;17:e1003172.
- 33 Honer WG, Cervantes-Larios A, Jones AA, *et al.* The hotel study—clinical and health service effectiveness in a cohort of homeless or marginally housed persons. *Can J Psychiatry* 2017;62:482–92.
- 34 British Columbia Centre for Excellence in HIV/AIDS. The hope to health research & innovation centre. 2021. Available: <http://bccfe.ca/hope-health-research-innovation-centre/about>
- 35 British Columbia Ministry of Health. Integrated models of primary care and mental health & substance use care in the community. 2012. Available: <https://www.health.gov.bc.ca/library/publications/year/2012/integrated-models-lit-review.pdf>
- 36 Provincial Health Services Authority. BC mental health & substance use services. Clinical & professional resources. 2020. Available: <http://www.bcmhsus.ca/health-professionals/clinical-professional-resources>
- 37 Matheson FI, Smith KWL, Fazli GS, *et al.* Physical health and gender as risk factors for usage of services for mental illness. *J Epidemiol Community Health* 2014;68:971–8.
- 38 Connor JP, Gullo MJ, White A, *et al.* Polysubstance use: diagnostic challenges, patterns of use and health. *Curr Opin Psychiatry* 2014;27:269–75.
- 39 Pennington M, McCrone P. Does non-adherence increase treatment costs in schizophrenia? *Pharmacoeconomics* 2018;36:941–55.
- 40 Valenstein M, Copeland LA, Blow FC, *et al.* Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. *Med Care* 2002;40:630–9.
- 41 Yehia BR, Stewart L, Momplaisir F, *et al.* Barriers and facilitators to patient retention in hiv care. *BMC Infect Dis* 2015;15:246.
- 42 Laursen TM, Agerbo E, Pedersen CB. Bipolar disorder, schizoaffective disorder, and schizophrenia overlap: a new comorbidity index. *J Clin Psychiatry* 2009;70:1432–8.