# Co-prescription of benzodiazepines and opioids on hospitalization rates among people living with HIV in British Columbia, Canada

L Ti[1,2], S Nolan[1,2], B Nosyk[1,3], M Ye[1], J Aghajanian [1], Z Cui[1], R Barrios[1,4], J Montaner[1,2], on behalf of the STOP HIV/AIDS Study Group

1. British Columbia Centre for Excellence in HIV/AIDS; 2. University of British Columbia; 3. Simon Fraser University; 4. Vancouver Coastal Health

## Background

- Co-prescription of benzodiazepines and opioids, which are prescribed primarily for anxiety and pain, respectively, are associated with various health harms.
- Even when prescribed appropriately, research studies have demonstrated that drug-drug interactions with the combination of these medications can result in high rates of morbidity, including respiratory depression, coma, and mortality.
- People living with HIV (PLHIV) are often prescribed these medications given the intersections between HIV/AIDS, mental health, pain, and addiction, making them particularly vulnerable to these harms.
- While studies have examined the use of opioids on hospitalization rates, little is known about the effect of benzodiazepine and opioid co-prescription on this outcome.

## Objective

- The objective of this study was to examine whether co-prescription of benzodiazepines and opioids was associated with higher hospitalization rates among PLHIV in British Columbia (BC), Canada.

## Methods

- The STOP HIV/AIDS in BC cohort is a provincial-level linkage of a series of surveillance, laboratory, and health administrative databases of all identified PLHIV in BC.
- We included individuals following the first dispensation of HAART.
- Co-prescription of benzodiazepines and opioids was defined as an overlapping prescription of at least one day of both medications. We categorized the main explanatory measure into four categories: 1) co-prescription of both medications; 2) benzodiazepine only; 3) opioid only; and 4) neither medication.
- We excluded methadone and buprenorphine as opioids of interest.
- Bivariable and multivariable generalized estimating equation regression models with Poisson distribution were constructed to determine the relationship between co-prescription of benzodiazepines and opioids on all-cause hospitalization rates.

## Results

- Between 1996 and 2014, 9,512 individuals were included in the study (Table 1); 1,776 (18.7%) were female and the median age at ART initiation was 40 years (Q1-Q3: 33-47 years).

**TABLE 1. Characteristics of study sample at baseline**

| Characteristic | Total (%) (*n* = 9512) | Hospitalized | |
|---|---|---|---|
| | | Yes (%) (*n* = 2909) | No (%) (*n* = 6603) |
| Drug prescribed | | | |
| Co-prescription of benzodiazepine and opioid | 256 (2.7) | 20 (7.8) | 236 (92.2) |
| Benzodiazepine only | 600 (6.3) | 65 (10.8) | 535 (89.2) |
| Opioid only | 398 (4.2) | 44 (11.1) | 354 (88.9) |
| Neither medication | 8258 (86.8) | 2780 (33.7) | 5478 (66.3) |
| Female sex | 1776 (18.7) | 698 (39.3) | 1078 (60.71) |
| Age at ART initiation (median, Q1-Q3) | 40 (33-47) | 40 (33-49) | 40 (33-47) |
| Calendar year (median, Q1-Q3) | 2005 (1999-2010) | 2005 (1999-2009) | 2005 (1998-2010) |
| History of IDU | 3261 (34.3) | 1043 (32.0) | 2218 (68.0) |
| Charlson comorbidity index (median, Q1-Q3) | 4 (4-4) | 4 (4-4) | 4 (4-4) |
| CD4 cell count (cells/mm3) (median, Q1-Q3) | 360 (180-560) | 270 (100-480) | 390 (230-590) |
| Viral load (log10 copies/mL) (median, Q1-Q3) | 2.7 (1.7-4.7) | 2.9 (1.7-5.0) | 2.4 (1.7-4.5) |

Q: quartile; ART: antiretroviral therapy; IDU: injection drug use

## Results cont'd

- At baseline, 2,909 (30.6%) individuals were hospitalized.
- Indicated in Table 2, bivariable analyses indicated a positive relationship between prescription of benzodiazepines and/or opioids and hospitalization rates compared to not being prescribed either medication: co-prescription of both medications (rate ratio [RR] = 2.64; 95% confidence interval [CI]: 2.39 – 2.91); benzodiazepine only (RR = 1.79; 95% CI: 1.67 – 1.92); and opioid only (RR = 2.83; 95%CI: 2.65 – 3.03).
- In a multivariable model adjusted for various demographic and clinical confounders (Table 2), there remained a positive association between the prescription of benzodiazepines and/or opioids and hospitalization rates compared to not being prescribed either medication: co-prescription of both medications (adjusted rate ratio [ARR] = 1.81; 95% confidence interval [CI]: 1.63 – 2.02); benzodiazepine only (ARR = 1.40; 95%CI: 1.31 – 1.51); and opioid only (ARR = 1.96; 95%CI: 1.83 – 2.11).
- Compared to those who were co-prescribed both medications, hospitalization rates among those prescribed an opioid only was not statistically significantly different (ARR = 1.08; 95%CI: 0.97 – 1.21), however those prescribed a benzodiazepine only was significantly lower (ARR = 0.77; 95%CI: 0.69 – 0.87; data not shown).

**TABLE 2. Bivariable and multivariable generalized estimating equation modeling of factors associated with all-cause hospitalization rates (n = 9512)**

| Characteristic | Rate Ratio (RR) | |
|---|---|---|
| | Unadjusted RR (95% CI) | Adjusted RR (95% CI) |
| **Main exposure** | | |
| Drug prescribed | | |
| Co-prescription of both medications vs. neither medication | 2.64 (2.39 – 2.91) | 1.81 (1.63 – 2.02) |
| Benzodiazepine only vs. neither medication | 1.79 (1.67 – 1.92) | 1.40 (1.31 – 1.51) |
| Opioid only vs. neither medication | 2.83 (2.65 – 3.03) | 1.96 (1.83 – 2.11) |
| **Confounders** | | |
| Sex (female vs. male) | 1.64 (1.52 – 1.76) | 1.40 (1.30 – 1.50) |
| Age at ART initiation (per 10-year increase) | 1.07 (1.04 – 1.11) | 1.15 (1.11 – 1.18) |
| Calendar year (per 10-year increase) | 1.26 (1.20 – 1.33) | 1.61 (1.52 – 1.69) |
| History of IDU | | |
| Yes vs. no | 2.32 (2.18 – 2.48) | 1.47 (1.37 – 1.57) |
| Unknown vs. no | 1.37 (1.24 – 1.50) | 1.31 (1.20 – 1.44) |
| Charlson comorbidity index | 1.37 (1.20 – 1.56) | 1.19 (1.06 – 1.34) |
| CD4 cell count (per 100 cells/mm3 increase) | 0.80 (0.79 – 0.81) | 0.87 (0.85 – 0.88) |
| Viral load (per log10 copies/mL increase) | 1.42 (1.40 – 1.45) | 1.31 (1.28 – 1.34) |

CI: confidence interval; ART: antiretroviral therapy; IDU: injection drug use

## Discussion

- In this study, we found that PLHIV who were co-prescribed benzodiazepines and opioids had higher hospital utilization rates, which consequently exacerbates the burden on the healthcare system.
- The findings should be interpreted with caution – in particular, co-prescription of these medications is not necessarily always inappropriate.
- However, these findings demonstrate the need for systems- and policy-level interventions to monitor and tease out inappropriate prescribing practices in this setting.

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