Published in final edited form as:

Drug Alcohol Depend. 2020 January 01; 206: 107670. doi:10.1016/j.drugalcdep.2019.107670.

Receipt of opioid agonist treatment halves the risk of HIV-1 RNA viral load rebound through improved ART adherence for HIV-infected women who use illicit drugs

Joëlla W. ADAMS¹, Brandon D.L. MARSHALL¹, Nur Afiah MOHD SALLEH^{2,3}, Rolando BARRIOS⁴, Seonaid NOLAN², M-J MILLOY^{2,5,*}

¹Brown University School of Public Health, Department of Epidemiology, 121 South Main Street, Providence, RI 02903, United States

²British Columbia Centre on Substance Use, 400-1045 Howe Street, Vancouver, BC V6Z 2A9, Canada

³Interdisciplinary Studies Graduate Program, University of British Columbia, 170-6371 Crescent Road, Vancouver, BC V6T 1Z2, Canada

⁴British Columbia Centre for Excellence in HIV/AIDS, 608-1081 Burrad Street, Vancouver, BC V6Z 1Y6, Canada

⁵Department of Medicine, University of British Columbia, 2775 Laurel Street, 10th Floor, Vancouver, BC V5Z 1M9, Canada

Abstract

Background: Women living with HIV who use illicit drugs may be particularly vulnerable to HIV-1 RNA viral load (VL) rebound.

Methods: We used longitudinal data from 2006–2017 to evaluate the impact of sociodemographic, behavioral, social-structural, and clinical factors on the hazard of viral rebound for women enrolled in the ACCESS study, a prospective cohort with systematic VL monitoring. Women were included if they achieved VL suppression (<50 copies/mL) following antiretroviral therapy (ART) initiation and had more than one study interview. Sociodemographic as well as substance use, social-structural, addiction treatment, and HIV clinical factors were evaluated as predictors of viral rebound (VL >1000 copies/mL). Cox regressions using a recurrent events framework, time-varying covariates, robust standard errors, and a frailty component were used.

Results: Of the 185 women included, 62 (34%) experienced at least one viral rebound event over an 11-year period, accumulating a total of 87 viral rebound events. In adjusted analysis, stimulant

*Corresponding author: Address: British Columbia Centre on Substance Use, 1045 Howe Street, Vancouver, BC, Canada, Tel: +1(604)806-9142, Fax: +1(604)806-9044, bccsu-mjmsm@bccsu.ubc.ca.

Contributors. JWA, MJM, and BDLM conceptualized this specific analysis. JWA performed the formal analysis with guidance of MJM and BDLM. JWA wrote the resulting manuscript while MJM, BDLM, NA.MS, SN, and RB provided feedback and edits. All authors reviewed and approved submission.

Publisher's Disclaimer: Disclaimer: Preliminary results for this work were presented at IAS 2019 Mexico City within a poster discussion section on July 24, 2019.

Conflict of Interest: No conflict declared.

use more than doubled the hazard of viral rebound (adjusted hazard ratio [AHR]: 2.35, 95% confidence interval [CI]: 1.07–5.14) while the only factor protective against viral rebound was receipt of opioid agonist treatment (OAT) in the past six months (AHR: 0.46, 95% CI: 0.26–0.81). After adjusting for ART adherence in the past six months, the effect of OAT was attenuated (AHR: 0.57, 95% CI: 0.32–1.02).

Conclusions: Efforts to improve access to and retention within OAT programs and decrease stimulant use may improve rates of viral suppression for HIV-positive women who use illicit drugs.

Keywords

opioid-related disorders; medication assisted treatment of opioid use disorder; women; illicit drugs; HIV-1

1. Introduction

Since the introduction of antiretroviral therapy (ART) for the treatment of HIV infection, cohort and surveillance-based studies conducted in North America and Europe have reported lower rates of optimal ART adherence and higher rates of HIV-1 RNA viral rebound in women compared to men (Crepaz et al., 2016; Kuyper et al., 2004; Lazo et al., 2007; O’Neil et al., 2012; Touloumi et al., 2006; Turner et al., 2003). A recent study using Centers for Disease Control and Prevention’s National HIV Surveillance System data over a two-year period concluded that women in the United States had a higher HIV viral burden and increased transmission risk potential compared to men (Crepaz et al., 2016). This gender difference was attributable to the decreased likelihood of durable viral suppression among women. Similarly, a longitudinal study based in British Columbia reported that 47% of women had a viral rebound within two years compared to 34% for men in a cohort of HIV-positive patients initiating ART and achieving viral suppression (Kuyper et al., 2004). Viral rebound can result in a drug-resistant virus, transmission to others, and HIV-related morbidity and mortality (2014).

Risk factors predictive of viral rebound may differ by gender (Lazo et al., 2007; Nicastrì et al., 2007). Psychosocial factors such as depression or a history of domestic abuse are reported predictors of ART discontinuation or viral rebound among women (Dale et al., 2014; Kuyper et al., 2004; Li et al., 2005). Stigma related to involvement in sex work may limit engagement in health care, which in turn, can lead to poor HIV treatment outcomes (Dale et al., 2014; King et al., 2013). Known predictors of viral rebound may also affect women to a lesser or greater degree than men. For example, recent injection drug use has been reported to influence the rate of viral rebound among women to a greater degree compared to men (Kuyper et al., 2004). Active use of illicit substances and injection drug use have been shown to predict ART treatment discontinuation (Lazo et al., 2007; Milloy et al., 2012). As women living with HIV who use illicit drugs may be particularly vulnerable to viral rebound, identifying risk factors for viral rebound specific to this sub-population can be used to guide clinical or behavioral intervention efforts. However, the majority of clinical studies are cross-sectional and not powered to detect gender differences in viral rebound by sociodemographic characteristics or lack longitudinal data to characterize viral load

dynamics over an extended period of time. Therefore, this study's objective was to evaluate the impact of sociodemographic, behavioral, and clinical factors on the hazard of viral rebound after achieving viral suppression for a cohort of women living with HIV who use illicit drugs over an eleven year period.

2. Material and methods

2.1. Sample and data source

We utilized longitudinal data from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) study. This ongoing prospective cohort study began as a virtual cohort of participants within the Vancouver Injection Drug Use Study (VIDUS), which first enrolled participants in 1996 (Strathdee et al., 1998). From 2006 onwards, ACCESS has operated as an open observational prospective cohort of HIV-positive people who use illicit drugs in Vancouver, Canada. As described previously, extensive community-based methods including street outreach was used to recruit individuals who were HIV-seropositive, over 18 years of age, used illicit drug other than cannabis in the previous month, and could provide written consent (Strathdee et al., 1998; Wood et al., 2004a). Upon recruitment, participants completed a baseline interview questionnaire on sociodemographic characteristics, details on substance use, access to services, and other relevant exposures. Thereafter, interviewer-administered questionnaires were given every six months alongside an examination by a study nurse and blood plasma draw. The University of British Columbia/Providence Healthcare Research Ethics Board approved the ACCESS study.

Universal health care coverage in Canada guarantees free healthcare services and, in the province of British Columbia, ART is provided at no cost for persons living with HIV. Delivery of HIV clinical care is not part of the ACCESS study protocol. However, a collaboration between the ACCESS study and the Drug Treatment Program of the British Columbia Centre for Excellence in HIV/AIDS, the local provider of all ART and HIV clinical monitoring, allows for linkage of HIV care treatment outcomes, including all HIV-1 viral loads (VL), CD4+ cell counts, and dispensation of ART, to participant interview data.

2.1.1. Analytic sample—For this analysis, we included all ACCESS participants who reported non-male gender at baseline; were either exposed to ART at baseline or initiated ART and achieved viral suppression (defined a VL <50 copies/mL) over the study period; and had a minimum of two study interviews following suppression from 2006–2017.

2.2. Outcome measure and covariates

Our outcome of interest, viral rebound, was defined as a lab result indicating a VL >1,000 copies/mL, the cut-off used previously by studies in this setting (Gross et al., 2006; Milloy et al., 2012). Time-invariant characteristics collected during the baseline study interview included sex at birth (female vs. male), ethnicity (white vs. non-white), education level (high school diploma vs. <high school diploma), sexual orientation (heterosexual vs. non-heterosexual), and a history of sexual abuse (yes vs. no, defined as ever experiencing sexual abuse).

The CD4+ cell count and HIV VL lab result closest to the time of the baseline interview were used as time-invariant variables. In addition, we included a categorical variable capturing the year of earliest ART dispensation (grouped into the following: 1993–2000, 2001–2005, 2006–2010, 2010–2017). Time-varying characteristics were updated at each study interview, where data was available, and included experiencing any of the following in the past six months: homelessness (defined as living on the street, yes vs. no); incarceration (defined as spending at least overnight in a youth detention facility, municipal jail, provincial prison or federal penitentiary, yes vs. no); licit employment (yes vs. no); sex work (defined as exchanging sex for gifts, food, or shelter, yes vs. no); suicidal ideation (defined as an affirmative response to “have you seriously thought about taking your own life?”); injection drug use; stimulant use (defined as reporting use of any of the following: cocaine, crack, or methamphetamine; heroin use (yes vs. no); binge alcohol use (defined as more than four drinks per day on average); binge drug use (defined as a period of above average illicit drug use); overdose (yes vs. no); opioid agonist treatment (OAT, defined as self-report of least one day of dispensation of methadone or buprenorphine, yes vs. no); and physical or sexual violence (defined as being attacked, assaulted, suffering violence, or being forced to have sex against one’s will). Using data from the linkage to the province-wide ART dispensary, we also measured adherence to ART in the previous 180 days, defined as the product of the number of days dispensed ART divided by the number of days since first dispensation of ART, capped at a maximum of 180. This product was dichotomized at <95% vs. 95%. This validated measure based on pharmacy refill data has been shown to predict HIV viral suppression and survival within this context (Milloy et al., 2012; Wood et al., 2003; Wood et al., 2004b).

2.3. Statistical Analyses

As a first step, we compared Kaplan-Meier survival curves for key explanatory variables of interest. We then used extended Cox regression models with a recurrent event framework to identify predictors of viral rebound. For these time-to-event analyses, time zero was considered to be the date of the first interview following a lab reporting viral suppression or the baseline interview (if the participant was suppressed upon recruitment using data from the confidential linkage to the HIV clinical monitoring and ART dispensary.) For those who experienced a viral rebound event, the date of viral rebound was defined as the mid-point between the first interview date following a lab reporting viral rebound and the previous interview. Participants who remained continually suppressed were right-censored at the last lab record in or before June 2017.

The first multivariable model used robust standard errors to account for correlation due to individual-level differences. Covariates were selected based on previous research in this setting and other studies identifying predictors of viral rebound (Crepaz et al., 2016; Kuyper et al., 2004; Lazo et al., 2007; Milloy et al., 2012; Richardson et al., 2015; Touloumi et al., 2006). The second multivariable model implemented a frailty component which introduces random variability to account for unobserved individual-level factors that are not captured by covariates within the model (Kleinbaum and Klein, 2010). The third multivariable model included time-varying ART adherence (i.e., 95% vs. <95% in the last six months). We performed a mediation analysis to determine whether significant associations found between

the exposure variables of interest and viral rebound were mediated by ART adherence, adapting the Baron Kenny approach to a Cox regression analysis (Baron and Kenny, 1986; Jung et al., 2012). In order to evaluate the extent to which ART adherence explained differences in time to viral rebound, we compared a model with all the covariates to a model with all the covariates and ART adherence (the hypothesized mediator) and examined the percentage change in adjusted hazard ratios. The percentage change was calculated using the following formula: $[(\text{HR without ART adherence} - \text{HR with ART adherence}) / (\text{HR without ART adherence} - 1.0)] \times 100$ (Jung et al., 2012; MacKinnon et al., 2007).

The multivariable analyses omitted the sex at birth variable due to small number of individuals reporting male sex at birth. We coded a missing response as affirmative for ten respondents who declined to answer the question regarding sexual abuse. A sensitivity analysis (results not shown) compared results for an analysis where missing responses were not coded as affirmative and demonstrated no difference in major findings and improvement in precision with the alternative coding strategy. All statistical analyses were performed using SAS software, version 9.4 (SAS, Cary, NC).

3. Results

3.1. Participants

Between 2006 and 2017, the ACCESS study recruited 947 participants, including 330 (35%) who self-identified as non-males. In this sample, 293 (89%) women were either exposed to ART at baseline or initiated ART during the study. Of these, 73 (25%) never achieved a VL <50 copies/mL and 14 (5%) only had one study interview. This resulted in a final study population of 206 women. Over half (111, 53%) of the women self-reported Indigenous ancestry, 9 (4%) were transgender women, and a quarter (51, 25%) self-identified as a sexual minority. At the baseline interview, 133 (65%) reported injection drug use in the past six months, 80 (39%) reported heroin use, 167 (81%) reported stimulant use, and 134 (66%) had received OAT in the past six months. Participants had an average of eight study interviews available (interquartile range [IQR]: 4, 13) and a median of 4.7 (IQR: 2.1, 7.3) person-years of follow-up. These analyses included 918 person-years of follow-up.

Of the 206 women eligible for analysis, 21 were excluded from multivariable analysis due to missing data on explanatory variables. Table 1 reports sociodemographic, substance use, and HIV clinical factors of the women included within the multivariable regression analysis, those women omitted, and the total study population. Excluded women were more likely to self-identify as heterosexual, to report being recently employed, to have an ART adherence level <95%, and less likely to be virally suppressed, report being incarcerated or ever being sexually abused at the baseline interview.

3.2. Viral rebound events

Of the remaining 185 women, 62 (34%) experienced at least one viral rebound event over the study period, accumulating a total of 87 viral rebound events. Among the 62 women with at least one rebound event during the study, 42 (68%) experienced a single event, 15 (24%) experienced two, and 5 (8%) experienced three viral rebounds over the study period. In

bivariable Cox regression analysis (Table 2), the hazard of viral rebound was negatively associated with OAT in the past six months, ART adherence, and the viral load closest to the baseline interview. Figure 1 displays a Kaplan-Meier survival curve plotting time in days from the first recorded VL <50 copies/mL or the baseline interview (if suppressed) until the first viral rebound event stratified by women who were enrolled within an OAT program at each study interview (n=87) compared to women who were never enrolled in an OAT program (n=50). At all time points, women who were continuously enrolled in an OAT program have a higher probability of remaining virally suppressed compared to women who are OAT-naïve.

3.3. Multivariable analyses

In multivariable analysis (Table 3), stimulant use in the past six months more than doubled the hazard of viral rebound. Even after adjusting for ART adherence, stimulant use was associated with viral rebound (adjusted hazard ratio [AHR]: 2.21, 95% confidence interval [CI]: 1.00–4.87). The only factor protective against viral rebound was receipt of OAT. Receipt of OAT halved the hazard of viral rebound within the marginal model analysis (AHR: 0.46, 95% CI: 0.26–0.82) as well as the model including a frailty component (AHR: 0.46, 95% CI: 0.26–0.81). For the third model, including time-varying ART adherence attenuated the effect of OAT (AHR: 0.57, 95% CI: 0.32–1.02), suggesting that the effect of OAT was mediated by ART adherence (Figure 2). Comparing a model that included all the covariates and receipt of OAT to a model with all the covariates, receipt of OAT, and ART adherence reduced the hazard of viral rebound associated with receipt of OAT by 24.5%.

4. Discussion

These longitudinal analyses of a community-recruited cohort of women living with HIV who use illicit drugs found that viral rebound was a common event among those who initially achieved virologic control. One-third of the analytic sample experienced at least one viral rebound event over follow-up. In multivariable models, we identified OAT as strongly linked to a reduced risk of virologic rebound, with receipt of OAT halving the hazard of viral rebound, and mediated by ART adherence, while use of stimulants increased the hazard of viral rebound.

Our findings are consistent with others noting low rates of viral suppression among women. A study by Crepaz et al. analyzing data on over 200,000 individuals receiving HIV care in the United States found that 64% of men had durable viral suppression (defined as all VL values over a two-year period <200 copies/mL) compared to 55% of women (Crepaz et al., 2016). The authors highlight the need for research to identify modifiable factors that impact durable viral suppression. An evaluation of the HIV care cascade for women in Canada found attrition at the VL suppression stage was highest in women who use illicit drugs compared to other vulnerable subgroups (Kerkerian et al., 2018). The same study further highlighted the significant association between current drug use and higher odds of non-adherence, suggesting the need for adherence support for this patient population.

Recent use of stimulants more than doubled the hazard of viral rebound, even after adjusting for ART adherence. Similar findings have been reported by other studies of women living

with HIV and using illicit drugs (Cook et al., 2008; Duncan et al., 2007; Kapadia et al., 2005). In particular, crack cocaine has been linked to accelerated HIV disease progression, even after controlling for ART adherence (Baldwin et al., 1998; Cabral, 2006), although studies predate modern ART formulations. Within our study, stimulant use was highly prevalent (over 80% of participants reported use in the past six months of at least one stimulant at baseline). Additional efforts are needed to provide ART adherence support for women using stimulants in addition to harm reduction interventions to foster recovery or reduce the harms associated with continuing stimulant use.

Medication-assisted treatment (MAT) for opioid use disorder, primarily with methadone and buprenorphine, can improve ART adherence for individuals living with HIV (Kapadia et al., 2008; Moatti et al., 2000; Nosyk et al., 2015; Palepu et al., 2006; Springer et al., 2010; Springer et al., 2012; Stein et al., 2000). Moatti *et al.* first reported that HIV-positive individuals who injected drugs and were receiving buprenorphine had higher levels of ART adherence compared to individuals who did not receive buprenorphine (Moatti et al., 2000). A more recent study using marginal structural modeling and causal inference methodology estimated that receipt of OAT increased the odds of ART adherence by 68% (Nosyk et al., 2015). Another study examining self-reported ART adherence using data from the Women's Interagency HIV Study found that women who were enrolled in medication-based treatment programs, including methadone, had improved ART adherence (Kapadia et al., 2008). Improved ART adherence is linked to viral suppression. A 2009 study by Roux *et al.* based in France found that retention within OAT programs was a significant predictor for long-term virological success (Roux et al., 2009). Despite substantial scholarship in this area, women are frequently under-represented in medication treatment studies and trials including persons with opioid use disorder. Additional efforts should be made to include women within these studies and to understand what factors influence their adherence to treatment for substance use.

The benefit of OAT on HIV treatment outcomes may be greater for women than men. A previously published study examining this cohort, including both men and women, from 1997–2009 found that viral rebound was associated with sex work involvement and recent incarceration while OAT was protective (AHR: 0.79, 95% CI: 0.66–0.94) (Milloy et al., 2012). Differences in effect size associated with OAT in the present analysis may be a function of a temporal trend or effect modification by gender.

Benefits of OAT include increased life stability, improved physical and mental health, and regular contact with counselors and healthcare delivery services; all of which, could contribute to improved likelihood of viral suppression (Brown et al., 2006). Findings from our analyses support the need for increased coordination of treatment for HIV care and co-morbid opioid use disorders as well as ensuring a low barrier entry into substance use treatment. Sites that co-locate OAT services and HIV clinical care can improve care engagement for individuals living with HIV who use illicit drugs (Bachiredy et al., 2014; Berg et al., 2011). Despite the proven benefits, OAT for women living with HIV is typically underutilized (Springer et al., 2015). Offering reproductive health services, trauma-informed care, childcare assistance and other services to facilitate health care engagement for women may help address this gap (Springer et al., 2015). In addition, there is a need to address

barriers resulting from the stigma and discrimination associated with substance use, including involvement in sex work (Lee and Boeri, 2017).

Notably, even in the context of free ART and HIV care services, a quarter of the women initiating ART never achieved viral suppression. A high proportion (63%) of these women reported receiving OAT in the six months preceding the interview following ART dispensation. However, when sub-setting to the women who had viral loads greater than 1,000 copies/mL, the percentage self-reporting recent OAT decreased to 52% and only 20% had an ART adherence level $\geq$ 95%. Even for women who achieved viral suppression, there was a substantial risk of viral rebound. While recent incarceration and recent homelessness did not reach the level of statistical significance within this analysis, these measures of marginalization and criminalization appear to impact the risk of viral rebound and warrant attention. Women who never achieved viral suppression more frequently reported experiencing homelessness and incarceration in the first interview following ART dispensation compared to women who achieved viral suppression. These findings suggest that women who use illicit drugs but who are not enrolled in an OAT program as well as women who've recently experienced incarceration or homelessness may require additional support for ART adherence to prevent HIV viral rebound. Previous studies have reported a correlation between incarceration and self-reported detectable levels of VL in 1,178 women living with HIV in three Canadian provinces, including British Columbia (Nadine et al., 2017). Periods of incarceration are known to disrupt ART continuity and engagement in HIV care could be further challenged by the limited availability of OAT within correctional settings (Iroh et al., 2015; Stephenson et al., 2005). A recent study based in Vancouver reported that utilization of OAT in correctional settings is low (Bozinoff et al., 2018). Additional research is needed to understand how OAT in correctional settings may benefit women living with HIV.

Variables hypothesized to have a gender-specific impact, including a history of sexual abuse and engaging in sex work, did not predict viral rebound within this cohort. However, it is notable that the majority of the cohort reported experiencing sexual abuse as a child (47%) or at some point in the past (67%). Therefore, there may not be enough variance in experience to assess the impact of these attributes. Regardless, the high prevalence of sexual abuse and experiences of violence supports the need for trauma-informed care when working with this population.

4.1. Limitations

Several limitations related to this study should be noted. First, misclassification of our exposure (i.e., receipt of OAT) is possible due to reliance on self-report, rather than records of medication dispensation, and the use of a binary variable to capture potentially complex OAT usage patterns. In addition, we were not able to validate use of OAT by a clinical diagnosis of opioid use disorder. However, misclassification likely biased the estimate to the null as women who only received one or two doses of OAT were grouped with women who received OAT throughout the six month period. Therefore, our estimated effect of OAT is likely conservative. In addition, OAT only included receipt of methadone or buprenorphine/naloxone; extended-release naltrexone is not available through regular clinical care and is

not used by study participants (Bruneau et al., 2018). Extended-release naltrexone has been shown to improve viral suppression in individuals with opioid use disorders, and while not included in the present study, studies suggest extended-release naltrexone can improve HIV care outcomes (Krupitsky et al., 2019; Springer et al., 2018). Second, we were unable to include all previously-identified risk factors for viral rebound within the multivariable analysis. For example, a variable indicating the specific ART regimen used was not included within analyses. These regimens likely changed throughout the study period, and could have influenced an individual's probability of viral rebound. However, we included year of first ART dispensation as a proxy for changing potency and tolerability of ART regimens over time. Pregnancy and the postpartum period are well-established predictors of falling out of HIV care and viral rebound (Adams et al., 2015; Huntington et al., 2015). However, the average age at the baseline interview was 42 years and the majority of the cohort were past reproductive age. Therefore, pregnancy and the postpartum period were unlikely exposures influencing viral rebound in this cohort. Results from this study may not be generalizable to younger women or HIV-positive women with illicit drug use living in other settings. For example, other factors influencing the probability of viral rebound may be more important predictors in Eastern Europe, especially in countries like Russia where OAT is generally not available, or lower-income countries. However, the expansion of OAT in lower-and middle-income countries is strongly recommended by the World Health Organization after a study found substantial benefits of OAT in culturally diverse settings (Lawrinson et al., 2008). While our study featured a relatively large cohort compared to many previous studies, our sample size may have limited our ability to identify predictors of viral rebound. Finally, we did not formally implement a formal causal mediation analysis as methods in this area are still developing for a time-varying exposure and non-rare outcome within a recurrent event framework (VanderWeele, 2011; Wang and Albert, 2017). Despite these limitations, this study has several strengths including the use of longitudinal data over an extended period of time, implementation of a recurrent event framework and frailty component, and an outcome based on laboratory values rather than self-report.

4.2. Conclusion

In summary, this study provides additional evidence that OAT can improve HIV treatment outcomes among women in a setting of universal healthcare coverage with free ART. Efforts to improve access to and retention in OAT programs as well as programs to address stimulant use may improve rates of viral suppression for women living with HIV who use illicit drugs.

Acknowledgements.

The authors thank the British Columbia Centre on Substance Use Data Analytical team for their guidance. We would also like to thank study participants for their contribution to the research, as well as current and past researchers and staff.

Role of Funding Source. The ACCESS study is supported by the National Institutes of Health [U01-DA0251525]. This analysis was supported by the National Institutes of Health [F31-MH114736-01A1, R25-DA037190, U01-DA0251525]. M-J Milloy receives support from a Scholar award from the Michael Smith Foundation for Health Research, and a New Investigator from the Canadian Institutes of Health Research. The University of British Columbia received an unstructured gift from NG Biomed Ltd., a private firm seeking a license to produce medical cannabis, to support him. He is the Canopy Growth professor of cannabis science at the University of British Columbia, a position created using unstructured gifts to the university from Canopy Growth, a licensed producer of

cannabis, and the Government of British Columbia's Ministry of Mental Health and Addictions. The funding sources had no involvement in the study design; the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

References

- Adams JW, Brady KA, Michael YL, Yehia BR, Momplaisir FM, 2015 Postpartum Engagement in HIV Care: An Important Predictor of Long-term Retention in Care and Viral Suppression. *Clin. Infect. Dis* 61, 1880–1887. [PubMed: 26265499]
- Bachiredy C, Soule MC, Izenberg JM, Dvoryak S, Dumchev K, Altice FL, 2014 Integration of health services improves multiple healthcare outcomes among HIV-infected people who inject drugs in Ukraine. *Drug and Alcohol Dependence* 134, 106–114. [PubMed: 24128379]
- Baldwin GC, Roth MD, Tashkin DP, 1998 Acute and chronic effects of cocaine on the immune system and the possible link to AIDS. *J. Neuroimmunol* 83, 133–138. [PubMed: 9610681]
- Baron RM, Kenny DA, 1986 The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J. Pers. Soc. Psychol* 51, 1173–1182. [PubMed: 3806354]
- Berg KM, Litwin A, Li X, Heo M, Arnsten JH, 2011 Directly observed antiretroviral therapy improves adherence and viral load in drug users attending methadone maintenance clinics: A randomized controlled trial. *Drug and Alcohol Dependence* 113, 192–199. [PubMed: 20832196]
- Bozinoff N, DeBeck K, Milloy MJ, Nosova E, Fairbairn N, Wood E, Hayashi K, 2018 Utilization of opioid agonist therapy among incarcerated persons with opioid use disorder in Vancouver, Canada. *Drug and Alcohol Dependence* 193, 42–47. [PubMed: 30340144]
- Brown LS Jr., Kritz SA, Goldsmith RJ, Bini EJ, Rotrosen J, Baker S, Robinson J, McAuliffe P, 2006 Characteristics of substance abuse treatment programs providing services for HIV/AIDS, hepatitis C virus infection, and sexually transmitted infections: the National Drug Abuse Treatment Clinical Trials Network. *J. Subst. Abuse Treat* 30, 315–321. [PubMed: 16716846]
- Bruneau J, Ahamad K, Goyer M-È, Poulin G, Selby P, Fischer B, Wild TC, Wood E, 2018 Management of opioid use disorders: a national clinical practice guideline. *Canadian Medical Association Journal* 190, E247. [PubMed: 29507156]
- Cabral GA, 2006 Drugs of abuse, immune modulation, and AIDS. *J Neuroimmune Pharmacol* 1(3), 280–295. [PubMed: 18040805]
- Centers for Disease Control and Prevention, 2014 Recommendations for HIV prevention with adults and adolescents with HIV in the United States, 2014.
- Cook JA, Burke-Miller JK, Cohen MH, Cook RL, Vlahov D, Wilson TE, Golub ET, Schwartz RM, Howard AA, Ponath C, Plankey MW, Levine AM, Grey DD, 2008 Crack cocaine, disease progression, and mortality in a multicenter cohort of HIV-1 positive women. *AIDS* 22, 1355–1363. [PubMed: 18580615]
- Crepaz N, Tang T, Marks G, Mugavero MJ, Espinoza L, Hall HI, 2016 Durable Viral Suppression and Transmission Risk Potential Among Persons With Diagnosed HIV Infection: United States, 2012–2013. *Clin. Infect. Dis* 63, 976–983. [PubMed: 27358354]
- Dale S, Cohen M, Weber K, Cruise R, Kelso G, Brody L, 2014 Abuse and resilience in relation to HAART medication adherence and HIV viral load among women with HIV in the United States. *AIDS Patient Care STDS* 28, 136–143. [PubMed: 24568654]
- Duncan R, Shapshak P, Page JB, Chiappelli F, McCoy CB, Messiah SE, 2007 Crack cocaine: effect modifier of RNA viral load and CD4 count in HIV infected African American women. *Front. Biosci* 12, 1488–1495. [PubMed: 17127396]
- Gross R, Yip B, Lo Re V 3rd, Wood E, Alexander CS, Harrigan PR, Bangsberg DR, Montaner JS, Hogg RS, 2006 A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 suppression. *J. Infect. Dis* 194, 1108–1114. [PubMed: 16991085]
- Huntington S, Thorne C, Newell ML, Anderson J, Taylor GP, Pillay D, Hill T, Tookey PA, Sabin C, Study, U.K.C.H.C., the, U.K., Ireland National Study of, H.I.V.i.P., Childhood, 2015 The risk of viral rebound in the year after delivery in women remaining on antiretroviral therapy. *AIDS* 29, 2269–2278. [PubMed: 26544700]

- Iroh PA, Mayo H, Nijhawan AE, 2015 The HIV care cascade before, during, and after incarceration: a systematic review and data synthesis. *American journal of public health* 105, e5–e16.
- Jung SY, Rosenzweig M, Linkov F, Brufsky A, Weissfeld JL, Sereika SM, 2012 Comorbidity as a mediator of survival disparity between younger and older women diagnosed with metastatic breast cancer. *Hypertension* 59, 205–211. [PubMed: 22184319]
- Kapadia F, Cook JA, Cohen MH, Sohler N, Kovacs A, Greenblatt RM, Choudhary I, Vlahov D, 2005 The relationship between non-injection drug use behaviors on progression to AIDS and death in a cohort of HIV seropositive women in the era of highly active antiretroviral therapy use. *Addiction* 100, 990–1002. [PubMed: 15955015]
- Kapadia F, Vlahov D, Wu Y, Cohen MH, Greenblatt RM, Howard AA, Cook JA, Goparaju L, Golub E, Richardson J, Wilson TE, 2008 Impact of drug abuse treatment modalities on adherence to ART/HAART among a cohort of HIV seropositive women. *Am. J. Drug Alcohol Abuse* 34, 161–170. [PubMed: 18293232]
- Kerkerian G, Kestler M, Carter A, Wang L, Kronfli N, Sereda P, Roth E, Milloy MJ, Pick N, Money D, Webster K, Hogg RS, de Pokomandy A, Loutfy M, Kaida A, 2018 Attrition Across the HIV Cascade of Care Among a Diverse Cohort of Women Living With HIV in Canada. *J. Acquir. Immune Defic. Syndr* 79, 226–236. [PubMed: 29916960]
- King EJ, Maman S, Bowling JM, Moracco KE, Dudina V, 2013 The influence of stigma and discrimination on female sex workers' access to HIV services in St. Petersburg, Russia. *AIDS Behav* 17, 2597–2603. [PubMed: 23525789]
- Kleinbaum DG, Klein M, 2010 *Survival analysis*. Springer.
- Krupitsky E, Blokhina E, Zvartau E, Verbitskaya E, Lioznov D, Yaroslavlseva T, Palatkin V, Vetrova M, Bushara N, Burakov A, Masalov D, Mamontova O, Langleben D, Poole S, Gross R, Woody G, 2019 Slow-release naltrexone implant versus oral naltrexone for improving treatment outcomes in people with HIV who are addicted to opioids: a double-blind, placebo-controlled, randomised trial. *The Lancet HIV* 6, e221–e229. [PubMed: 30880163]
- Kuyper LM, Wood E, Montaner JS, Yip B, O'Connell JM, Hogg RS, 2004 Gender differences in HIV-1 RNA rebound attributed to incomplete antiretroviral adherence among HIV-Infected patients in a population-based cohort. *J. Acquir. Immune Defic. Syndr* 37, 1470–1476. [PubMed: 15602125]
- Lawrinson P, Ali R, Buavirat A, Chiamwongpaet S, Dvoryak S, Habrat B, Jie S, Mardiaty R, Mokri A, Moskalewicz J, Newcombe D, Poznyak V, Subata E, Uchtenhagen A, Utami DS, Vial R, Zhao C, 2008 Key findings from the WHO collaborative study on substitution therapy for opioid dependence and HIV/AIDS. *Addiction* 103, 1484–1492. [PubMed: 18636999]
- Lazo M, Gange SJ, Wilson TE, Anastos K, Ostrow DG, Witt MD, Jacobson LP, 2007 Patterns and predictors of changes in adherence to highly active antiretroviral therapy: longitudinal study of men and women. *Clin. Infect. Dis* 45, 1377–1385. [PubMed: 17968839]
- Lee N, Boeri M, 2017 *Managing Stigma: Women Drug Users and Recovery Services*. Fusio : the Bentley undergraduate research journal 1, 65–94. [PubMed: 30140790]
- Li X, Margolick JB, Conover CS, Badri S, Riddler SA, Witt MD, Jacobson LP, 2005 Interruption and discontinuation of highly active antiretroviral therapy in the multicenter AIDS cohort study. *J. Acquir. Immune Defic. Syndr* 38, 320–328. [PubMed: 15735452]
- MacKinnon DP, Fairchild AJ, Fritz MS, 2007 Mediation analysis. *Annu. Rev. Psychol* 58, 593–614. [PubMed: 16968208]
- Milloy MJ, Kerr T, Buxton J, Rhodes T, Krusi A, Guillemi S, Hogg R, Montaner J, Wood E, 2012 Social and environmental predictors of plasma HIV RNA rebound among injection drug users treated with antiretroviral therapy. *J. Acquir. Immune Defic. Syndr* 59, 393–399. [PubMed: 22134149]
- Moatti JP, Carrieri MP, Spire B, Gastaut JA, Cassuto JP, Moreau J, 2000 Adherence to HAART in French HIV-infected injecting drug users: the contribution of buprenorphine drug maintenance treatment. The Manif 2000 study group. *AIDS* 14, 151–155. [PubMed: 10708285]
- Nadine K, Ashley L-D, Lu W, Alexandra d.P., Angela K,H,LC, Tracey C, Logan KV, N. BA, Wangari T, Neora P, Mary K, Paul S, Mona L, Team, o.b.o.t.C.R., 2017 Understanding the Correlates of

- Attrition Associated with Antiretroviral Use and Viral Suppression Among Women Living with HIV in Canada. *AIDS Patient Care and STDs* 31, 428–437.
- Nicastri E, Leone S, Angeletti C, Palmisano L, Sarmati L, Chiesi A, Geraci A, Vella S, Narciso P, Corpolongo A, Andreoni M, 2007 Sex issues in HIV-1-infected persons during highly active antiretroviral therapy: a systematic review. *J. Antimicrob. Chemother* 60, 724–732. [PubMed: 17715125]
- Nosyk B, Min JE, Colley G, Lima VD, Yip B, Milloy MJ, Wood E, Montaner JS, 2015 The causal effect of opioid substitution treatment on HAART medication refill adherence. *AIDS* 29, 965–973. [PubMed: 25915170]
- O'Neil CR, Palmer AK, Coulter S, O'Brien N, Shen A, Zhang W, Montaner JS, Hogg RS, 2012 Factors associated with antiretroviral medication adherence among HIV-positive adults accessing highly active antiretroviral therapy (HAART) in British Columbia, Canada. *J Int Assoc Physicians AIDS Care (Chic)* 11, 134–141. [PubMed: 22318879]
- Palepu A, Tyndall MW, Joy R, Kerr T, Wood E, Press N, Hogg RS, Montaner JS, 2006 Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: the role of methadone maintenance therapy. *Drug Alcohol Depend.* 84, 188–194. [PubMed: 16542797]
- Richardson LA, Kerr TH, Dobrer S, Puskas CM, Guillemi SA, Montaner JS, Wood E, Milloy MJ, 2015 Socioeconomic marginalization and plasma HIV-1 RNA nondetectability among individuals who use illicit drugs in a Canadian setting. *AIDS* 29, 2487–2495. [PubMed: 26558546]
- Roux P, Carrieri MP, Cohen J, Ravaux I, Poizot-Martin I, Dellamonica P, Spire B, 2009 Retention in opioid substitution treatment: a major predictor of long-term virological success for HIV-infected injection drug users receiving antiretroviral treatment. *Clin. Infect. Dis* 49, 1433–1440. [PubMed: 19807275]
- Springer SA, Chen S, Altice FL, 2010 Improved HIV and substance abuse treatment outcomes for released HIV-infected prisoners: the impact of buprenorphine treatment. *J. Urban Health* 87, 592–602. [PubMed: 20177974]
- Springer SA, Di Paola A, Azar MM, Barbour R, Biondi BE, Desabrais M, Lincoln T, Skiest DJ, Altice FL, 2018 Extended-Release Naltrexone Improves Viral Suppression Among Incarcerated Persons Living With HIV With Opioid Use Disorders Transitioning to the Community: Results of a Double-Blind, Placebo-Controlled Randomized Trial. *Journal of acquired immune deficiency syndromes (1999)* 78, 43–53. [PubMed: 29373393]
- Springer SA, Larney S, Alam-Mehrjerdi Z, Altice FL, Metzger D, Shoptaw S, 2015 Drug Treatment as HIV Prevention Among Women and Girls Who Inject Drugs From a Global Perspective: Progress, Gaps, and Future Directions. *Journal of acquired immune deficiency syndromes (1999)* 69 Suppl 2, S155–S161. [PubMed: 25978482]
- Springer SA, Qiu J, Saber-Tehrani AS, Altice FL, 2012 Retention on buprenorphine is associated with high levels of maximal viral suppression among HIV-infected opioid dependent released prisoners. *PLoS One* 7, e38335. [PubMed: 22719814]
- Stein MD, Rich JD, Maksad J, Chen MH, Hu P, Sobota M, Clarke J, 2000 Adherence to antiretroviral therapy among HIV-infected methadone patients: effect of ongoing illicit drug use. *Am. J. Drug Alcohol Abuse* 26, 195–205. [PubMed: 10852356]
- Stephenson BL, Wohl DA, Golin CE, Tien H-C, Stewart P, Kaplan AH, 2005 Effect of release from prison and re-incarceration on the viral loads of HIV-infected individuals. *Public health reports* 120, 84.
- Strathdee SA, Palepu A, Cornelisse PA, et al., 1998 Barriers to use of free antiretroviral therapy in injection drug users. *JAMA* 280, 547–549. [PubMed: 9707146]
- Touloumi G, Pantazis N, Antoniou A, Stirnadel HA, Walker SA, Porter K, Collaboration C, 2006 Highly active antiretroviral therapy interruption: predictors and virological and immunologic consequences. *J. Acquir. Immune Defic. Syndr* 42, 554–561. [PubMed: 16868497]
- Turner BJ, Laine C, Cosler L, Hauck WW, 2003 Relationship of gender, depression, and health care delivery with antiretroviral adherence in HIV-infected drug users. *J. Gen. Intern. Med* 18, 248–257. [PubMed: 12709091]

- VanderWeele TJ, 2011 Causal mediation analysis with survival data. *Epidemiology* (Cambridge, Mass.) 22, 582–585.
- Wang W, Albert JM, 2017 Causal Mediation Analysis for the Cox Proportional Hazards Model with a Smooth Baseline Hazard Estimator. *J. R. Stat. Soc. Ser. C. Appl. Stat* 66, 741–757.
- Wood E, Hogg RS, Bonner S, Kerr T, Li K, Palepu A, Guillemi S, Schechter MT, Montaner JS, 2004a Staging for antiretroviral therapy among HIV-infected drug users. *JAMA* 292, 1175–1177. [PubMed: 15353528]
- Wood E, Hogg RS, Yip B, Harrigan PR, O’Shaughnessy MV, Montaner JS, 2003 Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350×10^9 cells/L. *Ann. Intern. Med* 139, 810–816. [PubMed: 14623618]
- Wood E, Montaner JS, Yip B, Tyndall MW, Schechter MT, O’Shaughnessy MV, Hogg RS, 2004b Adherence to antiretroviral therapy and CD4 T-cell count responses among HIV-infected injection drug users. *Antiviral therapy* 9, 229–235. [PubMed: 15134185]

Highlights:

- Most studies aren't powered to examine risk factors for HIV viral rebound specifically for women
- Longitudinal analyses for a cohort of women living with HIV who use illicit drugs
- Opioid agonist treatment in the past six months halved the hazard of viral rebound
- Recent stimulant use more than doubled hazard of viral rebound

Figure 1.

Kaplan-Meier survival curve for time to first viral rebound following viral suppression for HIV-infected women who use illicit drugs by receipt of medication assisted treatment (consistently on OAT, $n = 87$ vs. never received OAT, $n = 50$).

Figure 2. Mediation pathways for antiretroviral therapy (ART) adherence on the relationship between receipt of opioid agonist treatment and plasma HIV-1 RNA viral rebound.

Table 1.

Sociodemographic, behavioral, clinical characteristics for 206 women living with HIV who use illicit drugs at first PROJECT ACCESS interview following viral suppression (viral load <50 copies/mL) by inclusion status.

	Included in multivariable analysis (n=185),	Not included in multivariable analysis (n=21),	Total (n=206),
<i>Sociodemographic characteristics^a</i>	n (%)	n (%)	n (%)
Age at first interview, mean (SD)	42 (7.8)	43 (8.6)	42 (7.8)
Sex at birth, n (%)			
Female	176 (95.1)	21 (100.0)	197 (95.6)
Male	9 (4.9)	0 (0.0)	9 (4.4)
Non-white race/ethnicity, n (%)			
Yes	105 (56.8)	9 (42.9)	114 (55.3)
No	80 (43.2)	12 (57.1)	92 (44.7)
Education level, n (%)			
Less than high school	108 (58.4)	7 (43.8)	115 (57.2)
High school completion	77 (41.6)	9 (56.3)	86 (42.8)
Sexual orientation, n (%)			
Self-identified straight	136 (73.5)	17 (89.5)	153 (75.0)
Self-identified LGBT	49 (26.5)	2 (10.5)	51 (25.0)
Homeless past six months, n (%)			
Yes	25 (13.5)	3 (14.3)	28 (13.6)
No	160 (86.5)	18 (85.7)	178 (86.4)
Incarcerated past six months, n (%)			
Yes	13 (7.1)	1 (4.8)	14 (6.9)
No	169 (92.3)	20 (95.2)	189 (93.1)
Employed past six months, n (%)			
Yes	20 (10.8)	5 (23.8)	25 (12.4)
No	165 (89.2)	16 (76.2)	181 (93.8)
Exchanged sex for gifts, food, or shelter in past six months, n (%)			
Yes	48 (26.5)	3 (14.3)	51 (25.3)
No	133 (73.5)	18 (85.7)	151 (74.8)
Suicidal ideation in past six months, n (%)			
Yes	13 (7.0)	0 (0)	13 (6.3)
No	172 (92.9)	21 (100)	193 (93.7)
<hr/>			
<i>Substance use^b</i>			
Injection drug use in past six months, n (%)			
Yes	120 (65.2)	13 (61.9)	133 (64.9)
No	64 (34.8)	8 (38.1)	72 (35.1)
Heroin use in the past six months, n (%)			
Yes	71 (38.4)	9 (42.9)	80 (38.8)
No	114 (61.6)	12 (57.1)	126 (61.2)

	Included in multivariable analysis (n=185),	Not included in multivariable analysis (n=21),	Total (n=206),
Stimulant use in the past six months, n (%)			
Yes	150 (81.1)	17 (80.9)	167 (81.1)
No	35 (18.9)	4 (19.1)	39 (18.9)
Binge alcohol use in past six months, n (%)			
Yes	8 (4.4)	0 (0.0)	8 (3.9)
No	176 (95.7)	21 (100.0)	197 (96.1)
Binge drug use in past six months, n (%)			
Yes	65 (35.5)	10 (47.6)	75 (36.8)
No	118 (64.5)	11 (52.38)	129 (63.2)
Overdose in past six months, n (%)			
Yes	6 (3.3)	0 (0.0)	6 (2.9)
No	177 (96.7)	21 (100.0)	198 (97.1)
Opioid agonist therapy in past six months, n (%)			
Yes	121 (66.5)	13 (61.9)	134 (66.0)
No	61 (33.5)	8 (38.1)	69 (34.0)
Age first injected an illicit drug, median (IQR)	18 (15, 24)	20 (15, 29)	19 (15, 24)
<i>Experiences with violence at first interview^c</i>			
Ever sexually abused, n (%)			
Yes	126 (68.1)	11 (52.4)	137 (66.5)
No	59 (31.9)	10 (47.6)	69 (33.5)
Physical or sexual violence in the last six months, n (%)			
Yes	29 (15.7)	1 (4.8)	30 (14.6)
No	156 (84.3)	20 (95.2)	176 (85.4)
<i>Clinical characteristics at first interview^d</i>			
ART adherence			
<95% ART adherence	51 (27.6)	3 (14.3)	54 (26.2)
95% ART adherence	134 (72.4)	18 (85.7)	152 (73.8)
Year of earliest ART dispensation			
1993–2000	62 (33.5)	2 (9.5)	64 (31.1)
2001–2005	44 (23.8)	3 (14.3)	47 (22.8)
2006–2010	53 (28.7)	8 (38.1)	61 (29.6)
2010–2017	26 (14.1)	8 (38.1)	34 (16.5)
CD4 Count at baseline interview, median (IQR)	330 (230, 470)	475 (420, 653)	338 (232, 480)
Viral load at baseline interview, median (IQR)	2699 (42, 30563)	5170 (287, 19310)	3337 (45, 29882)
Proportion with suppressed viral load (<50 copies/mL) at baseline interview	80 (43.2)	2 (10.5)	82 (40.2)

^aThe following self-reported measures were missing for a number of individuals: educational attainment (n=5), sexual orientation (n=2), incarceration in the past six months (n=3), exchanging sex for gifts, food, or shelter in past six months (n=4)

^bThe following self-reported measures were missing for a number of individuals: age at first injection (n=9), injection drug use in the past six months (n=1), binge alcohol use in the past six months (n=1), binge drug use in the past six months (n=1), overdose in the past six months (n=2), and medication assisted therapy in past six months (n=2)

^cThe following self-reported measures were missing for a number of individuals: childhood physical abuse (n=14), any physical abuse (n=15), childhood sexual abuse (n=13), any sexual abuse (n=10), sexual violence in the past 6 months (n=22), violence in the past 6 months (n=6)

^dThe following measures were missing for a number of individuals:, baseline CD4 count values (n=10) and baseline viral load values (n=1)

Table 2.

Unadjusted estimates of sociodemographic, behavioral, and clinical factors associated with viral rebound after achieving viral suppression for women living with HIV who use illicit drugs.

<i>Sociodemographic characteristics</i>	Hazard Ratio (HR)	95% Confidence Interval (CI)	P-value
Age (per year)	0.98	0.95–1.01	0.274
Sex at birth (male vs. female)	0.54	0.17–1.76	0.306
Non-white race/ethnicity (yes vs. no) *	1.52	0.92–2.51	0.104
Education level (less than high school vs. > high school completion) *	0.88	0.53–1.45	0.613
Sexual orientation (self-identified LGBT vs. self-identified straight) *	1.26	0.74–2.12	0.394
Homeless past six months (yes vs. no)	1.64	0.91–2.95	0.098
Incarcerated past six months (yes vs. no)	2.15	0.98–4.72	0.057
Employed past six months (yes vs. no)	0.86	0.41–1.80	0.696
Exchanged sex for gifts, food, or shelter in past six months (yes vs. no)	0.80	0.44–1.47	0.476
Suicidal ideation in past six months	1.16	0.54–2.58	0.709
<i>Substance use</i>			
Injection drug use in past six months (yes vs. no)	1.03	0.64–1.65	0.901
Stimulant use in past six months (yes vs. no)	1.53	0.87–2.72	0.143
Heroin use in past six months (yes vs. no)	0.91	0.57–1.47	0.710
Binge alcohol use in past six months (yes vs. no)	1.76	0.65–4.76	0.263
Binge drug use in past six months (yes vs. no)	0.81	0.63–1.43	0.807
Overdose in past six months (yes vs. no)	1.23	0.52–2.87	0.217
Opioid agonist therapy in past six months (yes vs. no)	0.51	0.31–0.82	0.006
<i>Experiences with violence at first interview</i>			
Ever sexually abused (yes vs. no) *	1.09	0.65–1.83	0.737
Physical or sexual violence in the last six months (yes vs. no)	1.13	0.65–1.94	0.668
<i>Clinical characteristics at first interview</i>			
ART adherence (<95% ART adherence vs. 95% ART adherence)	0.21	0.14–0.32	<0.0001
Year of earliest ART dispensation *			<i>0.123</i>
1993–2000 vs. 2010–2017	1.43	0.64–3.21	0.386
2001–2005 vs. 2010–2017	1.34	0.55–3.26	0.527
2006–2010 vs. 2010–2017	0.67	0.27–1.65	0.379
CD4 Count at baseline interview (per natural log10 increase)	0.95	0.69–1.32	0.774
Viral load at baseline interview (per natural log10 increase)	0.91	0.83–1.00	0.049

* Time invariant, measured at baseline interview upon entry into study

Table 3.

Adjusted estimates of sociodemographic, behavioral, and clinical factors associated with viral rebound after achieving viral suppression for women living with HIV who use illicit drugs (n=185) using extended Cox regression with recurrent event framework.

Sociodemographic characteristics	Model 1: Marginal Model Analysis		Model 2: Frailty Model Analysis		Model 3: Frailty with time-varying ART adherence	
	AHR	95% CI	AHR	95% CI	AHR	95% CI
Age (per year)	0.98	0.94–1.02	0.97	0.93–1.02	0.97	0.93–1.02
Non-white race/ethnicity (yes vs. no) *	1.60	0.87–2.93	1.49	0.77–2.88	1.58	0.83–2.98
Education level (less than high school (HS) vs. > HS) *	0.68	0.39–1.20	0.63	0.33–1.19	0.68	0.37–1.26
Sexual orientation (self-identified LGBT vs. self-identified straight) *	1.31	0.77–2.23	1.48	0.76–2.89	1.28	0.66–2.46
Homeless past six months (yes vs. no)	1.25	0.72–2.16	1.16	0.54–2.49	0.98	0.46–2.12
Incarcerated past six months (yes vs. no)	2.46	0.79–7.61	2.82	0.88–9.03	2.94	0.98–8.78
Employed past six months (yes vs. no)	0.79	0.36–1.73	0.67	0.32–1.40	0.79	0.38–1.64
Exchanged sex for gifts, food, or shelter in past six months (yes vs. no)	0.93	0.48–1.79	0.94	0.45–2.00	1.00	0.48–2.11
Suicidal ideation in past six months (yes vs. no)	1.17	0.53–2.59	1.09	0.45–2.62	0.97	0.40–2.37
<i>Substance use</i>						
Injection drug use in past six months (yes vs. no)	0.84	0.47–1.49	0.80	0.39–1.61	0.76	0.37–1.55
Stimulant use in past six months (yes vs. no)	2.36	1.15–4.85	2.35	1.07–5.14	2.21	1.00–4.87
Heroin use in past six months (yes vs. no)	0.88	0.48–1.60	0.89	0.46–1.72	0.89	0.46–1.72
Binge alcohol use in past six months (yes vs. no)	1.24	0.30–4.97	1.53	0.51–4.66	1.52	0.53–4.40
Binge drug use in past six months (yes vs. no)	0.83	0.54–1.29	0.79	0.46–1.35	0.72	0.42–1.24
Overdose in past six months (yes vs. no)	1.29	0.53–3.15	1.27	0.49–3.31	1.47	0.55–3.93
Opioid agonist therapy in past six months (yes vs. no)	0.46	0.26–0.82	0.46	0.26–0.81	0.57	0.32–1.02
<i>Experiences with violence</i>						
Ever sexually abused (yes vs. no) *	1.03	0.60–1.74	0.98	0.52–1.83	1.06	0.58–1.97
Physical or sexual violence in the last six months (yes vs. no)	1.19	0.66–2.15	1.26	0.64–2.49	1.38	0.69–2.76
<i>Clinical characteristics at first interview</i>						
Year of earliest ART dismenation *						
1993–2000 vs. 2010–2017	1.07	0.42–2.74	1.23	0.38–4.04	1.32	0.41–4.28
2001–2005 vs 2010–2017	0.74	0.26–2.09	0.77	0.23–2.54	0.86	0.26–2.83
2006–2010 vs. 2010–2017	0.48	0.17–1.35	0.50	0.14–1.74	0.50	0.15–1.72

<i>Sociodemographic characteristics</i>	Model 1: Marginal Model Analysis		Model 2: Frailty Model Analysis		Model 3: Frailty with time-varying ART adherence	
	AHR	95% CI	AHR	95% CI	AHR	95% CI
CD4 Count at baseline interview (per natural log 10 increase)	0.84	0.58–1.24	0.80	0.50–1.26	0.81	0.54–1.24
Viral load at baseline interview (per natural log 10 increase)	0.87	0.76–1.00	0.89	0.78–1.02	0.90	0.79–1.02
<i>Clinical characteristic at current interview</i>						
ART adherence (95% vs. <95%)	n/a	n/a	n/a	n/a	0.22	0.13–0.36

* Time invariant, measured at baseline interview upon entry into study.