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LONGER DURATION OF HOMELESSNESS IS ASSOCIATED WITH A LOWER LIKELIHOOD OF NON-DETECTABLE PLASMA HIV-1 RNA VIRAL LOAD AMONG PEOPLE WHO USE ILLICIT DRUGS IN A CANADIAN SETTING

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Abstract

Homelessness is common among people who use drugs (PWUD) and, for those living with HIV/AIDS, an important contributor to sub-optimal HIV treatment outcomes. This study aims to investigate the relationship between the duration of homelessness and the likelihood of plasma HIV-1 RNA viral load (VL) non-detectability among a cohort of HIV-positive PWUD. We used data from the ACCESS study, a long-running prospective cohort study of HIV-positive PWUD linked to comprehensive HIV clinical records including systematic plasma HIV-1 RNA VL monitoring. We estimated the longitudinal relationship between the duration of homelessness and the likelihood of exhibiting a non-detectable VL (i.e., <500 copies/mL plasma) using generalized linear mixed-effects modelling. Between May 1996 and June 2014, 922 highly active antiretroviral therapy-exposed participants were recruited and contributed 8188 observations. Of these, 4800 (59%) were characterized by non-detectable VL. Participants reported they were homeless in 910 (11%) interviews (median: six months, interquartile range: 6–12 months). A longer duration of homelessness was associated with lower odds of VL non-detectability (adjusted odds ratio = 0.71 per six-month period of homelessness, 95% confidence interval: 0.60–0.83) after adjustment for age, ancestry, drug use patterns, engagement in addiction treatment, and other potential confounders. Longer durations of episodes of homelessness in this cohort of HIV-positive illicit drug users were associated with a lower likelihood of plasma VL non-detectability. Our findings suggest that interventions that seek to promptly house homeless individuals, such as Housing First approaches, might assist in maximizing the clinical and public health benefits of antiretroviral therapy among people living with HIV/AIDS.

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Disclosure statement

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Keywords

Adherence; homelessness; injection drug use; viral load; viral suppression

INTRODUCTION

The development of highly active antiretroviral therapy (HAART) has significantly altered the course of the HIV/AIDS pandemic, dramatically reducing rates of HIV/AIDS-associated morbidity and mortality among many seropositive groups worldwide (Arts & Hazuda, 2012). In recent years, the potential of optimal engagement in HAART to virtually eliminate the risk of onward viral transmission has informed efforts to curb the incidence of new HIV infections through, in part, scaling up access to antiretroviral therapy (ART) (Montaner et al., 2006, 2010). Unfortunately, in many settings, HIV-positive people who use drugs (PWUD) have not fully benefited from the availability of HAART and continue to experience elevated levels of HIV/AIDS-associated morbidity, mortality, and onward viral transmission (Milloy, Marshall, Montaner, & Wood, 2012; Wood, Milloy, & Montaner, 2012).

To fully benefit from HAART, high levels of long-term adherence to treatment are required to experience non-detectable plasma HIV-1 RNA viral loads (VL) (Wood et al., 2003, 2008). A growing body of research has demonstrated a range of behavioural, social, and structural barriers to optimal HAART adherence among PWUD (Malta, Strathdee, Magnanini, & Bastos, 2008; Wolfe, Carrieri, & Shepard, 2010). Among these studies, housing has been identified as a crucial determinant of HIV/AIDS treatment outcomes; notably, homeless individuals are consistently at an elevated risk of suboptimal access and adherence to HAART (Malta et al., 2008; Wolfe et al., 2010). Homeless individuals have elevated exposure to factors that complicate HAART adherence and treatment outcomes, including engaging in illicit income-generating strategies such as sex work, limited access to healthcare services, and a high prevalence of co-morbid conditions (Milloy, Marshall, Montaner, et al., 2012). For example, in a survey of homeless decedents in Boston, USA, Baggett et al. (2013) reported high levels of drug overdose, cancer, and heart disease.

Although the link between homelessness and the risk of sub-optimal HAART adherence is well established, the effect of the duration of homelessness on VL dynamics among people living with HIV/AIDS has not been well explored (Coe et al., 2015; Waldrop-Valverde & Valverde, 2005). We have previously described how periods of homelessness are associated with lower likelihoods of optimal adherence, and how homelessness is a structural barrier to virologic response among individuals initiating HAART (Milloy, Kerr, Bangsberg, et al., 2012; Palepu, Milloy, Kerr, Zhang, & Wood, 2011). However, we are unaware of any longitudinal studies that have examined the relationship between entrenched homelessness and VL suppression. Thus, in this study, we sought to estimate the longitudinal effect of the duration of homelessness on the likelihood of non-detectable plasma HIV-1 RNA VL among HAART-exposed, HIV-positive PWUD in a setting of universal no-cost HIV/AIDS treatment and care.

METHODS

Data for these analyses were derived from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an ongoing prospective observational cohort of HIV-infected PWUD in Vancouver, Canada. A detailed description of the methods used by ACCESS is described elsewhere (Milloy et al., 2011; Wood et al., 2008). In brief, the cohort was recruited through snowball sampling and community outreach beginning in May 1996 with a focus on the Downtown Eastside of Vancouver, a central neighbourhood with high levels of illicit drug use, homelessness, and HIV infection. Eligibility criteria included: HIV seropositive, confirmed by serology; 18 years of age or older at study enrolment; illicit drug use other than or in addition to cannabis in the previous 30 days; and provision of written informed consent. Following recruitment, participants answer an interview-administered questionnaire detailing sociodemographic data, housing status, drug use patterns, addiction treatment and health care utilization, and other exposures and characteristics. Questionnaires are conducted at study entry (baseline) and during semi-annual follow-up interviews. Participants are reimbursed \$30 for each follow-up interview for their time. Participants are also examined by a study nurse and provide blood samples for HIV/AIDS clinical monitoring, including VL testing and CD4+ cell counts.

All information gathered at each interview is augmented with data on HIV/AIDS care and treatment outcomes from the Drug Treatment Program (DTP) from the British Columbia Centre for Excellence in HIV/AIDS. This province-wide, centralized HAART dispensary and HIV/AIDS clinical monitoring laboratory provides a complete retrospective and prospective profile, including all VL tests conducted through the study or by an individual's regular physician, as well as a record of HAART dispensations. Of note is the fact that all HIV/AIDS treatment and care, including all medications, are delivered for free through the setting's universal no-cost medical services plan. The University of British Columbia and Providence Healthcare Research Ethics Board has reviewed and approved the ACCESS study.

In this study, we included all individuals who had more than or equal to one day of HAART dispensation at baseline or who initiated HAART prior to their final study interview. Among these individuals, we included all observations following the earliest date of HAART dispensation. In addition, individuals must have contributed at least one VL observation and at least one CD4+ cell count within $\pm$ six months of the baseline interview. The primary outcome of interest in this analysis was HIV-1 RNA VL non-detectability, defined as a measurement of <500 copies/mL plasma, the lowest consistent level of detectability consistently available throughout the study period (i.e., May 1996 to June 2014). Since multiple VL measurements were recorded in the DTP database for some persons during a follow-up period, we defined VL as the mean of all observations available in the period beginning 180 days prior to the study interview, which was then categorized into either achieving non-detectable VL or not. For interviews lacking a VL observation in the previous 180 days, we defined the VL as <500 copies/mL only if pharmacy records indicated an individual was dispensed ART for more than or equal to 95% of the 180-day period prior to the interview.

Our primary explanatory variable was the duration of homelessness. As in previous analyses, we defined homelessness as living on the streets or with no fixed address (Wood et al., 2008) at the time of the interview. At each interview in which an individual reported being homeless, we calculated the duration of the current period of homelessness by referring to the last interview in which they reported being housed, or to the study baseline, if no instances of being housed were reported. To minimize the bias introduced by the fact that some participants did not complete all scheduled study interviews, we only counted uninterrupted periods of homelessness in contiguous observations.

To estimate the independent relationship between duration of homelessness and VL suppression, we analysed other variables that may have acted as possible confounders, including: age (per year older); gender (female vs. male); Caucasian ancestry (yes vs. no); education level (more than or equal to high school diploma vs. < high school diploma); and current engagement in addiction treatment (yes vs. no). We also assessed recent incarceration (yes vs. no); heroin injection (more than or equal to daily vs. <daily); cocaine injection (more than or equal to daily vs. <daily); and crack cocaine use (more than or equal to daily vs. <daily). These time-updated variables referred to behaviours or experiences occurring in the 180-day period prior to the study interview. Using data from clinical monitoring records, we also included CD4+ cell count (per 100 cells/mL) and VL levels at HAART initiation (copies/mL plasma, log10 transformed). For CD4 cell counts, for each individual we used the mean value of all observations in six-month period prior to the study interview or, if none were observed, the most recent measure. For VL at HAART initiation, we used the final measure prior to the date of the initiation of HAART. We also included a measure of adherence to HIV treatment using pharmacy dispensation records. As in previous analyses, for each six-month period, we calculated the quotient of the number of days that ART was dispensed divided by the total number of days since an individual had initiated HAART, capped at a maximum of 180 days (Coe et al., 2015; Waldrop-Valverde & Valverde, 2005). The resulting proportion was dichotomized at more than or equal to 95% vs. <95%. This measure has been used extensively and shown to predict VL suppression (Wood et al., 2003) and survival (Wood et al., 2008).

As a first step, we compared the values at the baseline interview for the covariates of interest, stratified by current homelessness, using chi-square tests (for categorical variables) and the Wilcoxon rank-sum tests (for continuous variables). To visualize the distribution of the duration of homelessness during the study period, we plotted the duration of current homelessness among the observations which reported homelessness (Figure 1). Next, to estimate the longitudinal relationships between the explanatory variables and the likelihood of VL non-detectability during the study period, we used generalized linear mixed-effects models, which account for the inherent non-independent nature of repeated measures gathered from individuals over time. To estimate the effect of the duration of homelessness on VL non-detectability, we fit a multivariable model using an a priori-defined manual stepwise procedure, based on changes in the value of the coefficient for the primary explanatory variable, as described in previous analyses (Milloy et al., 2011). First, we fit a full model that included all secondary explanatory variables with $p < .1$ in bivariable analyses noting the value of the coefficient associated with duration of homelessness. In a stepwise manner, we removed the secondary explanatory variable corresponding to the

smallest relative change in the effect of duration of homelessness on non-detectable VL from further consideration. We continued this iterative process until the maximum change of the value of the coefficient for duration of homelessness from the full model exceeded 5%. Remaining variables were considered confounders in the multivariable model. Because the duration of homelessness could be affected by the length of follow-up time observed, all bivariable and multivariable analyses were adjusted with a term for the number of follow-up interviews completed. ART adherence was not considered for inclusion in the multivariable model, as we hypothesized that this variable lay on the causal pathway between homelessness and viral detectability. We conducted all statistical analyses using R version 3.2.0 (The R Foundation, Vienna, Austria).

RESULTS

Between May 1996 and June 2014, 1078 HIV-positive individuals who use illicit drugs were recruited. Of these, 922 (86%) had more than or equal to 1 day of HAART dispensation prior to their final study interview as well as more than or equal to 1 CD4 and more than or equal to 1 VL observation within ± 180 days of their baseline interview and were included in these analyses. During the study period, these individuals completed 8188 interviews, or a median of 7 (interquartile range [IQR] = 3–11) per individual, resulting in 4094 person-years of observation. During this time, there were 15,824 VL observations, or a median of 2 (IQR = 1–3) per follow-up period. Among the 8188 observations, 4800 (59%) were characterized by VL < 500 c/mL. In total, 910 (11%) individuals reported they were currently homeless. Of the 922 HAART-exposed participants, 199 (22%) reported current homelessness at baseline and 402 participants (44%) reported that they were homeless at least once during the study period. Over the study period, the median duration of homelessness among the 922 participants was 6 months (IQR: 6–12 months).

Select sociodemographic, behavioural, and clinical characteristics at the baseline, stratified by current homelessness at baseline, are presented in Table 1. At baseline, currently homeless individuals were more likely to report being incarcerated in the previous six months (22% vs. 13%, $p = .003$), report more than or equal to daily heroin injection (24% vs. 13%, $p < .001$), report more than or equal to daily use of crack cocaine (35% vs. 23%, $p < .001$), and have lower levels of optimal ART adherence (48% vs. 59%, $p = .012$) and lower CD4 cell counts (310 cells/mL vs. 320 cells/mL, $p = .018$). Table 2 presents the results of the crude and adjusted longitudinal estimates of the odds of non-detectable VL. In bivariable analysis, longer duration of homelessness was associated with a lower likelihood of non-detectable VL (odds ratio = 0.60 per 6 months, 95% confidence interval [95% CI]: 0.52–0.70). In the multivariable analysis, after adjustment for age, Caucasian ancestry, heroin injection, cocaine injection, crack use, addiction treatment, and CD4 cell count, longer duration of homelessness remained associated with a lower likelihood of non-detectable VL (adjusted odds ratio [AOR] = 0.71, 95% CI: 0.60–0.83).

DISCUSSION

In this long-term prospective cohort study, we found that homelessness was common, with 11% of all observations containing a report of homelessness. In a multivariable model that

controlled for age, addiction treatment, high-intensity drug use patterns, and other confounders, longer duration of homelessness was independently and negatively associated with the likelihood of exhibiting a non-detectable VL (AOR = 0.71 per six-month period, 95% CI: 0.60–0.83).

Our main finding is consistent with previous studies that have described associations between being homeless or marginally housed and sub-optimal HIV/AIDS treatment (Carballo et al., 2004; Milloy, Kerr, Bangsberg, et al., 2012; Palepu et al., 2011; Sayles et al., 2012; Waldrop-Valverde & Valverde, 2005). For example, Sayles et al. found that lower levels of VL suppression were associated with poorer housing status in an analysis of poor and indigent people living with HIV/AIDS in Los Angeles, USA (2012). Nevertheless, care should be taken when comparing the effects of homelessness between settings with universal no-cost health insurance, like ours, and settings in which financial barriers might affect engagement in care. In a study of homeless and marginally housed individuals in San Francisco, USA, consistent coverage in health insurance was strongly associated with accessing health care and ART (Riley et al., 2011). Similarly, another San Francisco study found greater mortality and morbidity rates among homeless HIV-positive individuals, further exacerbated by a lack of consistent health coverage (Schwarcz et al., 2009). Our study of long-term VL suppression among HAART-exposed PWUD is consistent with an earlier local study that demonstrated homelessness to be a significant barrier to optimal virologic response among individuals initiating HAART (Milloy, Kerr, Bangsberg, et al., 2012).

Our findings have implications for current and future public policy. Treatment-as-Prevention (TasP) efforts seek to engage HIV-positive individuals in treatment in order to suppress VL to undetectable levels and reduce the incidence of HIV/AIDS morbidity, mortality, and viral transmission (Milloy, Montaner, & Wood, 2012; Montaner et al., 2010). Our study aligns with earlier work demonstrating that the attainment of optimal virologic status among PWUD at both individual and community levels is hindered by important social- and structural-level conditions, such as incarceration, inability to access evidence-based addiction treatment, and socioeconomic marginalization (Milloy, Marshall, Kerr, et al., 2012; Milloy, Kerr, Bangsberg, et al., 2012). Thus, efforts to expand TasP should consider these socio-structural barriers when attempting to engage members of traditionally hard-to-treat populations in HIV/AIDS treatment. One possible strategy to promote the individual and population-level benefits of TasP could be Housing First (HF), which aims to provide immediate, permanent, and unconditional housing to qualified individuals in need (Tsemberis & Elfenbein, 1999; Tsemberis, Gulcur, & Nakae, 2004). Beginning in 1992, HF models explicitly incorporate a harm reduction approach, and do not require abstinence from drug use participants (Milloy, Marshall, Montaner, et al., 2012; Milloy, Montaner, et al., 2012). Although exposure to HF has been shown to decrease psychiatric morbidity, findings from a recent randomized trial did not detect an effect on substance use patterns (Greenwood, Schaefer-McDaniel, Winkel, & Tsemberis, 2005; Somers, Moniruzzaman, & Palepu, 2015). Similarly, previous studies of housing on HIV treatment outcomes have not been conclusive, although there are some promising findings. In the only study, to our knowledge, of HF on VL, a very high proportion (69%) of residents at a harm reduction-based HF facility in the United States achieved an undetectable VL, although the study was

not experimental nor did it include a comparison group (Hawk & Davis, 2012). In a randomized controlled trial of supportive housing for HIV-positive homeless individuals, 36% of individuals in the intervention arm achieved non-detectable VL versus 19% in the non-intervention arm ($p = .051$) (Buchanan, Kee, Sadowski, & Garcia, 2009). Another randomized trial found that providing rental assistance to homeless and marginally housed people living with HIV resulted in significant improvements in CD4 cell count and VL (Wolitski et al., 2010). Although further research is needed to evaluate the effectiveness of housing interventions in improving HIV treatment outcomes, these and our findings suggest that interventions to prevent entrenched and chronic homelessness may contribute to TasP-based goals.

This study does have limitations that warrant discussion. Participants were not recruited through random sampling and therefore our sample population is not a representative sample of all HIV-positive PWUD. Therefore, our findings may not be generalizable to HIV-seropositive drug-using populations in local or other settings. A further limitation includes the self-reported nature of homelessness. In addition, to account for the possible bias introduced by the fact participants might miss scheduled follow-up interviews, we have only considered periods of homelessness in uninterrupted periods of follow-up. Also, because of the six-month observation window, we were unable to consider the impact of shorter periods of homelessness on viral status. Despite these limitations, we do not believe individuals differentially reported homelessness based on their VL status, which was ascertained through the local provider of all HIV/AIDS treatment and clinical monitoring. Finally, as with all observational studies, we cannot exclude the possibility that the observed association between duration of homelessness and non-detectable VL is influenced by residual confounding, although we sought to address this bias through multivariable adjustment of key demographic, behavioural, and social predictors of VL.

To conclude, we used data from a long-running study of HIV-positive individuals who use illicit drugs and found that, in both crude and adjusted analyses, increasing duration of homelessness was negatively associated with optimal VL status. Our findings have important implications for both the health of individuals and efforts to reduce community-level VLs to curb the HIV/AIDS pandemic. Specifically, efforts to maximise the beneficial impact of antiretroviral therapies among people who use illicit drugs must consider the deleterious impacts of homelessness and should promote initiatives that prioritize the provision of housing.

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Figure 1. Distribution of duration of homelessness episodes among 910 interview observations in which current homelessness was reported

Table 1

Sociodemographic, behavioural and clinical characteristics of 922 HAART-exposed participants at baseline, stratified by current homelessness

Baseline characteristic	Not homeless 723 (78%) n (%)	Homeless 199 (22%) n (%)	p-Value
Age			
Per year older	42 (35–48)	41 (34–46)	.167
Gender			
Male	466 (64.5)	137 (68.8)	
Female	257 (35.5)	62 (31.2)	.274
Caucasian ancestry			
No	313 (43.3)	83 (41.7)	
Yes	410 (56.7)	116 (58.3)	.746
Education			
High school diploma	414 (59.0)	103 (53.4)	
<High school diploma	288 (41.0)	90 (46.7)	.163
Incarceration^a			
No	628 (87.0)	156 (78.4)	
Yes	94 (13.0)	43 (21.6)	.003
Heroin injection^a			
<Daily	628 (86.9)	152 (76.4)	
Daily	95 (13.1)	47 (23.6)	<.001
Cocaine injection^a			
<Daily	603 (83.4)	165 (82.9)	
Daily	120 (16.6)	34 (17.1)	.915
Crack cocaine use^a			
<Daily	557 (77.0)	129 (64.8)	
Daily	166 (23.0)	70 (35.2)	<.001
Addiction treatment^a			
No	343 (47.4)	93 (46.7)	
Yes	380 (52.6)	106 (53.3)	.873
Plasma HIV-1 RNA^b			
Per log ₁₀ (copies/mL)	4.7 (4.0–5.0)	4.6 (4.0–5.0)	.379
ART adherence^a			
<95%	300 (41.5)	103 (51.8)	
95%	423 (58.5)	96 (48.2)	.012
CD4+ cell count			
Per 100 cells/mL	3.2 (2.1–4.5)	3.1 (1.6–4.0)	.006

^aRefers to the six-month period prior to the baseline interview.

^bMeasured at HAART initiation.

Table 2

Univariable and multivariable linear mixed-effects analyses of factors associated with non-detectable plasma HIV-1 RNA VL among 922 HAART-exposed individuals who use illicit drugs in Vancouver, Canada

Characteristic	OR	95% CI	p-Value	AOR	95% CI	p-Value
Homeless duration (per 6 months)	0.60	0.52–0.70	<.001	0.71	0.60–0.83	<.001
Age (per year)	1.20	1.17–1.24	<.001	1.17	1.14–1.20	<.001
Gender (female vs. male) ^a	0.29	0.18–0.47	<.001			
Caucasian (yes vs. no) ^a	1.53	0.99–2.37	.053	0.63	0.41–0.96	.031
Education (HS diploma vs. <HS) ^a	1.13	0.88–1.44	.330			
Heroin injection (daily vs. <daily)	0.34	0.26–0.45	<.001	0.46	0.34–0.62	<.001
Cocaine injection (daily vs. <daily)	0.58	0.44–0.75	<.001	0.77	0.58–1.02	.066
Crack use (daily vs. <daily)	0.54	0.44–0.67	<.001	0.75	0.60–0.94	.011
Addiction treatment (yes vs. no) ^b	1.42	1.15–1.75	.001	1.40	1.12–1.75	.003
Incarceration (yes vs. no) ^b	0.86	0.65–1.13	.278			
CD4 cell count (yes vs. no)	2.58	2.37–2.80	<.001	2.46	2.26–2.66	<.001
ART adherence (95% vs. <95%)	14.25	11.81–17.19	<.001			
HIV-1 RNA VL (per log10 copies/mL plasma) ^c	0.96	0.74–1.22	.717			

Note: OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio; HS, high school.

^aValue at baseline or time invariant.

^bRefers to the six-month period prior to the baseline interview.

^cMeasured at HAART initiation.