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Social and environmental predictors of plasma HIV RNA rebound among injection drug users treated with antiretroviral therapy

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Abstract

Introduction—Evidence is needed to improve HIV treatment outcomes for individuals who use injection drugs (IDU). Although studies have suggested higher rates of plasma viral load (PVL) rebound among IDU on antiretroviral therapy (ART), risk factors for rebound have not been thoroughly investigated.

Methods—We used data from a long-running community-recruited prospective cohort of IDU in Vancouver, Canada, linked to comprehensive ART and clinical monitoring records. Using proportional hazards methods, we modeled the time to confirmed PVL rebound above 1000 copies/mL among IDU on ART with sustained viral suppression, defined as two consecutive undetectable PVL measures.

Results—Between 1996 and 2009, 277 individuals had sustained viral suppression. Over a median follow-up of 32 months, 125 participants (45.1%) experienced at least one episode of virologic failure for an incidence of 12.6 (95% Confidence Interval [CI]: 10.5 – 15.0) per 100 person years. In a multivariate model, PVL rebound was independently associated with sex trade involvement (Adjusted Hazard Ratio [AHR] = 1.40, 95% CI: 1.08 – 1.82) and recent incarceration (AHR = 1.83, 95% CI: 1.33 – 2.52). Methadone maintenance therapy (AHR = 0.79, 95% CI: 0.66 – 0.94) was protective. No measure of illicit drug use was predictive.

Conclusions—In this setting of free ART, several social and environmental factors predicted higher risks of viral rebound among IDU, including sex trade involvement and incarceration. These findings should help inform efforts to identify individuals at risk of viral rebound as well as targeted interventions to treat and retain individuals in effective ART.

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Keywords

human immunodeficiency virus (HIV) infection; antiretroviral therapy (ART); injection drug user (IDU); plasma HIV-1 RNA viral load; viral suppression; viral rebound

INTRODUCTION

Despite the advent of antiretroviral (ART) therapy, HIV-infected individuals who use injection drugs (IDU) continue to experience high levels of HIV/AIDS-related morbidity and mortality.[1,2] Central to these sub-optimal treatment outcomes are lower rates of access and adherence to ART.[3,4] Evidence is urgently required to identify and address barriers to retaining IDU in effective HIV treatment.[5]

The primary clinical goal of ART is to inhibit viral replication and suppress plasma viral load (PVL) to undetectable levels.[6] Longitudinal analyses of clinic-based studies have revealed that while a substantial proportion of individuals are able to achieve viral suppression with ART,[7,8] at least one in ten patients will experience at least one episode of viral rebound.[7] Clinical factors associated with a greater risk of rebound include shorter duration of viral suppression;[9,10] ART regimen composition;[7] and non-adherence to ART.[11,12]

Ongoing illicit drug use represents an added challenge in the medical management of HIV infection.[13] Previous studies have identified active alcohol and illicit drug use as risk factors for failure to achieve viral suppression[14–17] and avoid viral rebound.[12,18] However, the determinants of viral rebound among IDU on ART have not been completely investigated. In particular, consideration of the broader social and environmental factors that have been shown to determine vulnerability to HIV infection[19–21] have not been well evaluated as possible determinants of viral outcomes. Thus, given the urgent need to improve treatment access and delivery for HIV-seropositive IDU, we conducted the following study with the primary objective of identifying social and environmental risk factors for viral rebound among IDU on ART.

METHODS

In these analyses, we used data from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an ongoing prospective observational cohort of HIV-seropositive illicit drug users in Vancouver, Canada. The cohort was populated through community recruitment, as detailed previously;[22–24] briefly, we used snowball sampling and extensive street outreach beginning in 1996 focused on Vancouver's Downtown Eastside (DTES) neighborhood. The DTES includes a large and established open drug market and endemic levels of illicit drug use, poverty, poor housing and HIV infection.[22] Individuals are eligible for ACCESS if they are HIV-seropositive; are aged 18 years or older; have used illicit drugs other than cannibinoids in the previous month and can provide written informed consent. At recruitment and every six months thereafter, individuals answer an interviewer-administered questionnaire, undergo an examination by a study nurse and provide blood plasma samples for serologic and virologic analysis. Personal data on socio-demographic characteristics, drug-using behaviours and related exposures are gathered during the interview process by trained study staff. All HIV clinical care is delivered independently of the study, although study staff may provide referrals to clinicians and ancillary social or medical services including support for antiretroviral adherence. The University of British Columbia/ Providence Healthcare Research Ethics Board has approved the ACCESS study.

Data gathered during the interview process on sociodemographic, drug-using and other characteristics is augmented with comprehensive information on HIV care and treatment outcomes supplied by the Drug Treatment Programme (DTP) of the British Columbia Centre for Excellence in HIV/AIDS (BCCfE), a province-wide centralized HAART dispensary and HIV/AIDS clinical monitoring laboratory. For each participant, the BCCfE provides a complete prospective profile of CD4+ cell counts, PVL and exposure to specific antiretroviral agents (described in detail previously.)[22–24] Of note is the fact that all HIV care including antiretroviral medications are provided free-of-charge to all HIV-seropositive individuals in the province.

In this study, we included all individuals who were exposed to ART at baseline or who initiated ART over the study period; had at least one observation of CD4 cell count and PVL within 12 months of recruitment; and at least two consecutive measurements indicating suppression of PVL during the study period. Because the sensitivity of the viral load assays changed over the study period, we defined suppression as any measurement below 500 copies/mm^3 before April 1, 1999 and any measurement below 50 copies/mm^3 after April 1, 1999.

For all individuals included in these analyses, time zero was defined as the date of the first interview following the second measurement indicating suppression. The primary outcome of interest was confirmed viral rebound, defined as the date of the second of two consecutive measurements of PVL above 1000 copies/mL, consistent with a previous study from our setting.[25] Local treatment guidelines recommend that PVL be assessed at ART initiation, four weeks after starting treatment, and every three months thereafter. In this study, measures of PVL, CD4 cell count and other clinical indicators could be ordered by the participant's physician as well as study physicians.

Consistent with previous studies identifying clinical risk factors for viral rebound,[9,12,26] we considered the following explanatory variables: PVL at ART initiation (per log10 increase); presence of a protease inhibitor in the first ART regimen (yes vs. no); experience of participant's HIV physician (< 6 patients enrolled BCCfE treatment registry vs. ≥ 6 patients); CD4 cell count (per 100 cells); the time since ART initiation (per year increase); and adherence to ART (>95% vs. ≤95%). The presence of a PI, PVL at ART initiation and HIV physician experience were assessed at baseline and were time-invariant variables; the remaining were time-updated exposures and referred to the six month period prior to each participant's interview. CD4 cell count was defined as the mean of all observations in the previous six months or, if none were available, the most recent observation. Information on adherence to prescribed ART was gathered using the confidential linkage to the BCCfE's ART dispensation records.[3,24] These records contain details on all antiretrovirals used in the province, by recording medications delivered by the centralized dispensary to pharmacies in community as well as correctional settings. We defined adherence in each six month period as the number of days for which ART was dispensed over the number of days an individual was eligible for therapy and dichotomized the resulting proportion at >95% vs. ≤95%. We have previously demonstrated the clinical utility of this validated pharmacy refill measure and shown it reliably predicts viral suppression[27–29] and survival.[3,24]

Sociodemographic characteristics assessed at baseline included the participant's age, gender (female vs. male), whether the participant reported Aboriginal ancestry (yes vs. no) and educational attainment (< high school diploma vs. ≥ high school diploma). Patterns of illicit drug use were assessed longitudinally and included as time-updated variables. Consistent with a previous study on illicit drug use and viral suppression from our setting,[30] we characterized illicit drug use in the last six months as a three-level variable with abstinence as the reference level vs. any illicit drug use (excluding cannibinoids) vs. any injection drug

use. We also included recent binge drug use, defined as any period of more intense drug use than typical in the previous six months (yes vs. no).

As there is a growing interest in the role played by the contextual determinants of HIV vulnerability,[21,31] our choice of explanatory variables was informed by the risk environment framework.[32,33] This framework is increasingly used to understand the social, environmental and structural level forces that contribute to the risk of infection with HIV.[21] Specifically, we included these time-updated variables: living in unstable housing, defined as being homeless, living in a single-room occupancy hotel room, homeless shelter or transitional housing (yes vs. no); participating in the sex trade, defined as any sexual acts in exchange for money, drugs or other goods or favors (yes vs. no); engagement in methadone maintenance therapy (yes vs. no); and recent incarceration. Exposure to correctional environments was assessed using a three-level variable with a reference level of no incarceration overnight or longer in any facility vs. any incarceration overnight or longer in pre-trial detention vs. any incarceration overnight or longer in a provincial prison or federal penitentiary. With the exception of engagement in MMT, which referred to current status, all other time-updated characteristics referred to the six-month period prior to the follow-up interview.

To model the relationship between these explanatory variables and the time to viral rebound, we constructed a series of univariate and multivariate proportional hazards frailty models including a recurrent events framework. Frailty models are a class of survival statistical techniques that consider the effect of time-updated covariates as well as each individual's unobservable deviation from the baseline hazard function, consistent with each individual's inherent risk of viral rebound. Because each individual could experience multiple periods of viral suppression and viral failure, we included a recurrent events framework. All individuals were coded at risk for the outcome from the first time of suppression to the first rebound, if applicable; from then on, their observations were censored until the individual had two consecutive PVL observations indicating suppression at which time they were considered at risk for another failure event. This cycle was continued until the end of all available observations.

As a first step, we considered the relationship between all explanatory variables and the risk of rebound by estimating the hazard ratio (HR) with 95% confidence intervals (95% CI) and associated p-value using univariate frailty models. Next, we constructed a multivariate model including all variables with p-values less than 0.05 in univariate analyses except for adherence to prescribed HAART. In a secondary analysis, we fit the same multivariate model, adding the covariate for HAART adherence.

RESULTS

Between May 1996 and November 2008, 762 individuals were recruited into the study. Of these, 538 (70.6%) were ART-exposed, 274 (36.0%) prior to study recruitment and 264 (34.6%) following recruitment. Two hundred seventy-seven individuals (36.3%) had at least two consecutive PVL observations indicating suppression and complete clinical profiles and were included in these analyses. Over the study period, the 277 participants contributed 995 person-years of follow-up with a median follow-up time of 32 months (IQR: 6 – 64) per participant. One hundred twenty-five participants (45.1%) experienced at least one instance of viral rebound over follow-up, equal to a crude incidence of 12.6% (95% CI: 10.5–15.0).

The baseline characteristics of the participants, stratified by viral rebound over the study period, are presented in Table 1. Of note, participants who were younger, with less time

elapsed on treatment and lower CD4 cell counts at the time of ART initiation had a greater likelihood of failure.

The unadjusted estimates of the effect of the explanatory variables on the time to rebound are presented in Table 2. Younger individuals (HR = 0.98 [95% CI: 0.97 – 0.99]) and individuals reporting sex-trade participation (HR = 1.45 [95% CI: 1.15 – 1.84]) both faced elevated risks of viral rebound. Engagement in methadone maintenance therapy (HR = 0.75 [95% CI: 0.64 – 0.89]) was protective against treatment failure. Although exposure to pre-trial detention facilities was not associated with rebound, incarceration overnight or longer in a provincial prison or federal penitentiary (HR = 1.86 [95% CI: 1.37 – 2.52]) conferred a significant risk of failure. Interestingly, various patterns of illicit drug use, including any use, any injection drug use, and any binge drug use, were not associated with a greater risk of rebound.

The adjusted estimates of factors associated with time to treatment failure are presented in Table 3. In Model 1, the multivariate model including all variables significant in univariate analyses, sex trade participation (Adjusted Hazard Ratio [AHR] = 1.40 [95% CI: 1.08 – 1.82]) and incarcerations in a prison or penitentiary (AHR = 1.83 [95% CI: 1.33 – 2.52]) were each independently associated with treatment failure. Engagement in methadone maintenance therapy (AHR = 0.79 [95% CI: 0.66 – 0.94]) was negatively associated with viral rebound. This model was also adjusted for age and clinical predictors of viral rebound significant in univariate analyses, specifically CD4 cell count, treatment duration and the presence of a PI in the initial ART regimen. However, in the model including ART adherence (Model 2), neither age, sex trade participation nor methadone maintenance therapy remained independently associated with viral rebound. The association with provincial or federal incarceration remained, although the effect was substantially attenuated. The significant clinical correlates of rebound remained when adherence was included in the model.

In light of the independent relationship between engagement in methadone maintenance therapy, as well as a recent report identifying OST as a significant determinant of long-term virologic success,[34] we conducted a sub-analysis identifying the relationship between length of maintenance treatment and the hazard of viral rebound. In a Cox proportional hazards model, we observed that a greater number of consecutive follow-ups on MMT was marginally associated with a lower relative hazard of viral rebound (HR = 0.98, 95% Confidence Interval: 0.95 – 1.00, p = 0.094.)

DISCUSSION

In this study, the first to our knowledge to investigate social and environmental determinants of viral rebound among IDU on ART, loss of virologic control following suppression was common, with almost half of participants (45.1%) experiencing at least one episode of treatment failure over follow-up. While this rate of rebound is consistent with previous studies,[12,18] we found patterns of illicit drug use were not significant predictors of rebound. Instead, endogenous factors, including recent incarceration, participation in the sex trade, and engagement in methadone maintenance therapy emerged as independent risk factors for rebound. Providing validity to the model, established clinical determinants of viral rebound, specifically CD4 cell count and the length of treatment were also associated in multivariate models.

Comparison of the two multivariate models indicates the associations between several exposures and treatment failure are largely driven by poorer adherence to ART within those strata. When adherence to ART is added to the multivariate model (Model 2), several

associations in Model 1, specifically age, participation in the sex trade and engagement in MMT, are rendered non-significant. This is consistent with previous studies that found adherence to ART was typically lower among younger individuals[35] and those in the sex trade[36] while engagement in MMT was associated with better adherence.[37] Interestingly, although the strength of the effect of recent incarceration in a prison or penitentiary also declined, it remained significantly associated with rebound. This highlights the critical need to improve adherence in criminal justice settings.[38,39] Thus, our study supports the provision of increased and improved support for ART adherence among these younger drug users, those in the sex trade and the recently incarcerated, to reduce the risk of viral rebound.

In this study, we used the risk environment framework to analyse HIV disease progression among IDU. In the past, the risk environment framework has informed studies of the factors that shape the risk of HIV acquisition.[40–42] Specifically, the framework describes the interplay between exogenous forces, including micro- and macro-level political, social, economic and physical effects, and endogenous characteristics, including host and viral attributes, on the production of vulnerability to HIV infection.[21] In the current study, we observed that exposures previously linked with a higher risk of HIV infection were independently associated with higher rates of viral rebound, specifically incarceration[43] and participation in the sex trade.[44] As with HIV infection,[44] engagement in MMT was protective. Certainly, the causal pathways between these exposures and HIV infection differ from these exposures to treatment non-adherence and viral rebound. However, this study illustrates how the vulnerability produced by the social and structural context of healthcare can contribute to HIV disease progression. Thus, the risk environment framework may be a useful model to identify factors contributing to the elevated levels of HIV-related morbidity and mortality among drug users and inform evidence-based interventions in clinical practice, community settings and at the population level.

Consistent with previous studies from our setting describing how imprisonment complicates adherence[39,45] and inhibits suppression,[46] incarceration in a prison or penitentiary, but not in pre-trial detention, emerged as the strongest non-clinical predictor of viral rebound. Although health services are typically more rudimentary in local pre-trial facilities and lack the means to care for chronic conditions, the typically short duration of exposure likely minimizes the clinical consequences of any missed doses. Our finding of a deleterious effect of longer-term imprisonment on viral loads contradicts previous prison-based studies of HAART delivery in which prisoners achieved viral suppression.[47,48] This is likely related to the barriers to ART access and adherence presented in correctional facilities, including delays in dispensing appropriate antiretrovirals from prison pharmacies; possibly contentious relationships with prison-based healthcare providers and inmates; and the desire of some individuals to conceal their serostatus from other prisoners.[45] Our study underlines the challenges incarceration and transition between correctional and non-correctional environments pose to IDU on ART.[49]

To better understand the context of these findings, it is important to note that HIV care, including clinical monitoring and all medications, is provided free of charge to all individuals in our setting through the province's publicly-funded healthcare system. This commitment to universal HIV care was recently reaffirmed by an investment by the provincial government in a seek, test and treat intervention to increase the coverage of HAART among IDU.[50,51] Our findings highlight the apparent contradiction between government policies which, on one hand, seek to deliver HIV care to IDU and, on the other hand, criminalize drug users and undercut the effectiveness of ART. This conflict is sharpened by recent moves by Canada's federal government to enact mandatory minimum prison sentences for illicit drug-related offenses.[52] Future research should focus on the

possibly deleterious effect of these social, structural and environmental exposures on efforts to deploy HIV treatment as prevention among vulnerable and marginalized populations.

Substantial effort has been devoted to the development of prognostic tools to identify individuals on ART at heightened risk of viral failure using routinely collected data.[12,53] Our results, specifically the lack of an association with patterns of illicit drug use and the strong link with incarceration, participation in the sex trade and engagement in methadone maintenance therapy, suggest that these screens could be improved by the inclusion of these and other measures of vulnerability. Further, the finding that abstinent individuals did not significantly differ from active drug users in the likelihood of viral rebound builds on our previous report that ongoing drug use did not prevent viral suppression.[54] These studies are evidence against the blanket refusal to provide medically necessary ART to IDU, as is common in many jurisdictions.[5]

As in all observational studies, our study has several limitations. First, the study sample was not selected at random and our findings should not be generalized to other groups of IDU on ART. However, our use of snowball sampling and other community recruitment methods hopefully minimized the bias resulting from the selection procedures. Similarly, as with all observational studies, the relationships between the explanatory variables and the outcome of interest may be under the influence of unobserved confounding. We have sought to address this bias with multivariate adjustment of the covariate estimates and the selection of a broad set of possible confounders. We also recognize that many of our measures were self-reported and thus may be affected by social desirability bias. However the key variables emerging as significant in these analyses (sex trade involvement, recent incarceration and engagement in methadone maintenance therapy) were not likely to be differentially reported by individuals with greater or lesser likelihood of experiencing viral rebound. Finally, for historical reasons, we were forced to use a cut-off for PVL suppression of 500 copies / mm^3. Although we cannot know with certainty, we know of no reason why our results would differ had a cut-off of < 50 copies have been possible with our data.

To conclude, we assessed the patterns and predictors of viral rebound among community-recruited drug users on ART with suppressed PVL. Consistent with previous studies finding that exposure to characteristics of the risk environment framework were associated with vulnerability to HIV infection, we found that individuals engaged in the sex trade or recently incarcerated in a prison or penitentiary were at higher risk of viral rebound. Concurrently, active drug use was not associated with viral rebound. Our findings not only demonstrate the utility of the risk environment framework in analyzing patterns of HIV disease progression but also suggest that efforts to engage HIV-seropositive drug users in effective treatment should include consideration of the social, environmental and structural contexts of treatment delivery.

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TABLE 1

Baseline characteristics of HIV-seropositive injection drug users on antiretroviral therapy with durably suppressed HIV RNA levels (n = 277 participants)

Characteristic	No viral rebound over follow-up 152 (54.9%)	≥ 1 viral rebound over follow-up 125 (45.1%)	OR[1]	95% CI[2]	p-value
Age					
Median (IQR)	44.1 (38.7 – 49.6)	38.4 (32.7 – 44.1)	0.98	0.97 – 0.99	< 0.001
Gender					
Male	96 (63.2)	67 (53.6)	1.00		
Female	56 (36.8)	58 (46.4)	1.48	0.92 – 2.40	0.108
Aboriginal ancestry					
No	89 (58.6)	73 (58.4)	1.00		
Yes	63 (41.4)	52 (41.6)	1.01	0.62 – 1.62	0.978
Years since ART					
Median (IQR)	2.8 (0.0 – 5.9)	2.6 (0.9 – 4.3)	0.98	0.96 – 0.99	< 0.001
HIV RNA load (log10)[3]					
Median (IQR)	4.8 (4.5 – 5.2)	4.9 (4.4 – 5.3)	1.06	0.98 – 1.14	0.162
CD4 cell (per 100)[3]					
Median (IQR)	2.0 (1.2 – 2.8)	2.9 (1.5 – 4.2)	1.06	1.04 – 1.09	< 0.001
PI in first regimen[3]					
No	98 (64.4)	84 (67.2)	1.00		
Yes	54 (35.6)	41 (32.8)	0.89	0.54 – 1.46	0.634
HIV MD experience[3]					
≥ 6 patients	127 (83.6)	98 (78.4)	1.00		
< 6 patients	25 (16.4)	27 (21.6)	1.40	0.76 – 2.56	0.274

[1] Odds Ratio;

[2] 95% Confidence Interval;

[3] Observed at initiation of ART

TABLE 2

Unadjusted estimates of the behavioural, social and structural factors associated with viral rebound among 277 IDU on ART with suppressed viral loads at baseline in Vancouver, Canada

Characteristic	HR[1]	95% CI	p-value
Age[2]			
Per year older	0.98	0.97 – 0.99	< 0.001
Gender[2]			
Female vs. male	1.11	0.94 – 1.31	0.201
Aboriginal ancestry[2]			
Yes vs. no	0.89	0.75 – 1.05	0.171
Education[2]			
< HS dip vs. ≥ HS dip	1.04	0.88 – 1.24	0.651
Illicit drug use[3]			
None vs. any	0.93	0.15 – 5.74	0.591
None vs. injection	0.99	0.14 – 6.85	0.910
Binge drug use[3]			
Yes vs. no	1.23	0.99 – 1.52	0.060
Unstable housing[3]			
Yes vs. no	0.90	0.76 – 1.06	0.211
Sextrade participation[3]			
Yes vs. no	1.45	1.15 – 1.84	0.002
Methadone maintenance[3]			
Yes vs. no	0.75	0.64 – 0.89	< 0.001
Incarceration[3]			
None vs. pre-trial detention	1.07	0.72 – 1.61	0.726
None vs. prison or penitentiary	1.86	1.37 – 2.52	< 0.001
CD4 cell count[3]			
Per 100 cells	0.88	0.84 – 0.92	< 0.001
HIV MD experience[2]			
< 6 patients vs. ≥ 6	1.03	0.83 – 1.28	0.812
Time since initiation[3]			
Per year	0.89	0.85 – 0.93	< 0.001
PI in first regimen[2]			
Yes vs. no	1.32	1.11 – 1.56	0.001
pVL at ART initiation[2]			
Per log10 increase	0.97	0.88 – 1.08	0.574
ART adherence			

Characteristic	HR[1]	95% CI	p-value
>95% vs. ≤95%	0.16	0.12 – 0.21	< 0.001

[1]Hazard Ratio;

[2]Time invariant, measured at baseline;

[3]Time updated, refers to six-month period prior to follow-up interview

TABLE 3

Adjusted estimates of the behavioural, social and structural factors associated with viral rebound among 277 IDU on ART with suppressed viral loads at baseline in Vancouver, Canada

	Model 1			Model 2		
Characteristic	**AHR[1]**	**95% CI**	**p-value**	**AHR[1]**	**95% CI**	**p-value**
Age						
Per year older	0.98	0.97 – 1.00	0.006	1.00	0.99 – 1.02	0.602
Sextrade participation						
Yes vs. no	1.40	1.08 – 1.82	0.014	1.23	0.95 – 1.60	0.120
Methadone maintenance						
Yes vs. no	0.79	0.66 – 0.94	0.024	0.98	0.82 – 1.16	0.803
Incarceration						
None vs. pre-trial detent	1.09	0.71 – 1.67	0.846	1.14	0.74 – 1.75	0.563
None vs. prison or pen	1.83	1.33 – 2.52	0.003	1.45	1.05 – 2.01	0.025
CD4 cell count						
Per 100 cells	0.88	0.84 – 0.92	< 0.001	0.92	0.87 – 0.96	< 0.001
Time since initiation						
Per year	0.90	0.85 – 0.95	< 0.001	0.91	0.87 – 0.97	< 0.001
PI in first regimen						
Yes vs. no	1.22	1.01 – 1.46	0.131	1.06	0.88 – 1.28	0.538
ART adherence						
>95% vs. ≤95%				0.16	0.12 – 0.21	< 0.001

[1]Adjusted Hazard Ratio