

# HIV SEROSTATUS AND HAVING ACCESS TO A PHYSICIAN FOR REGULAR HEPATITIS C VIRUS CARE AMONG PEOPLE WHO INJECT DRUGS

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HIV, ACCESS TO HCV CARE AMONG PWID

## ABSTRACT

**Background:** People who inject drugs (PWID) and who are living with HIV and hepatitis C virus (HCV) infection are vulnerable to a range of health-related harms, including liver cirrhosis, hepatocellular carcinoma, and death. There is limited evidence describing how HIV serostatus shapes access to a physician for regular HCV care among PWID.

**Setting:** Data were collected through the Vancouver Injection Drug Users Study (VIDUS), the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), and the At-Risk Youth Study (ARYS), three prospective cohorts involving people who use illicit drugs in Vancouver, Canada, between 2005 and 2015.

**Methods:** Using generalized estimating equations, we examined the relationship between HIV-seropositivity and having access to a physician for regular HCV care. We conducted a mediation analysis to examine whether this association was mediated by increased frequency of engagement in healthcare.

**Results:** In total, 1627 HCV-positive PWID were eligible for analysis; 582 (35.8%) were HIV-positive at baseline and 31 (1.9%) became HIV-positive during follow-up. In multivariable analyses, after adjusting for a range of confounders, HIV serostatus (adjusted odds ratio [AOR] = 1.99; 95% confidence interval [CI]: 1.77-2.24) was significantly associated with having access to HCV care. Approximately 26% of the effect was due to mediation.

**Conclusion:** Our results demonstrate a positive relationship between HIV-seropositivity and having access to a physician for regular HCV care, which is partially explained through increased frequency of engagement in healthcare. These findings highlight the need to address patterns of inequality in access to HCV care among PWID.

**Word Count:** 248

**Keywords:** HIV; Hepatitis C; physician; linkage to care; Injection drug use

## INTRODUCTION

The advent of highly-active antiretroviral therapy (HAART) has led to significant reductions in HIV-related morbidity, mortality and viral transmission.<sup>1-5</sup> However, HCV-related complications have emerged as a greater relative contributor to disease burden among dually-infected individuals.<sup>5</sup> Globally, an estimated 170 million individuals are chronically infected with HCV,<sup>6</sup> of which one-third experience progression to liver fibrosis and cirrhosis over a 20-30 year period.<sup>7</sup> Moreover, an estimated 700,000 deaths each year are attributable to HCV-related complications.<sup>8</sup> Due to shared transmission pathways, recent data suggests that approximately 3-12% of the 36.9 million people living with HIV (PLWH) are co-infected with HCV.<sup>9</sup> Among PLWH who inject drugs, the prevalence of HCV co-infection is significantly higher, with estimates ranging between 50% and 90%.<sup>5</sup>

The HIV Treatment as Prevention (TasP) initiative aims to scale-up access to HAART, dramatically curbing morbidity, mortality and HIV transmission.<sup>3</sup> Endorsed by the UNAIDS 90-90-90 campaign,<sup>10</sup> TasP's efficacy and effectiveness has become increasingly apparent among marginalized populations. Encouragingly, there appear to be broader implications in the context of HCV co-infection.<sup>3</sup> The impact of increased engagement in healthcare on access to HCV care remains largely unexplored.

The advent of direct-acting antivirals (DAAs) for the treatment of HCV infection has resulted in remarkable improvements in rates of sustained virologic response (SVR) across all genotypes and among various populations, including PWID. Unfortunately, access and uptake of DAA therapy among PWID remains very low.<sup>11</sup> A growing body of literature indicates a number of barriers, including patient concerns over possible side effects, high cost of DAAs based therapy, fractured social networks, unstable housing, incarceration, and limited engagement in healthcare.<sup>12,13</sup> Furthermore, these factors may be coupled with reluctance on the part of healthcare professionals to initiate DAAs in active PWID due to concerns over HCV reinfection.<sup>14,15</sup> It is noteworthy that this reluctance may be partially attributed to historical HCV treatment guidelines which have traditionally excluded PWID.<sup>12,16</sup>

Understanding the multifaceted nature of barriers to DAA access among PWID will facilitate treatment scale-up. Although a growing body of literature has explored the patterns and correlates of HAART and DAA accessibility among PWID,<sup>17,18</sup> potential differences between DAA treatment and care among HIV-positive and HIV-negative individuals remains unclear.<sup>19</sup> Thus, in a setting where there are no financial barriers to HIV treatment and care, and where universal access to DAA treatment is occurring,<sup>20</sup> the objective of this study was to assess the effect of HIV serostatus on accessing HCV physician care among PWID in Vancouver, Canada.

## METHODS

### *Study design and population*

Data for this study were drawn from the Vancouver Injection Drug Users Study (VIDUS), the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), and the At-Risk Youth Study (ARYS), three prospective cohorts involving people who use illicit drugs in Vancouver, Canada. The methods for these studies have been described elsewhere.<sup>21-25</sup> To be eligible for VIDUS, participants must be  $\geq 18$  years of age and report injection drug use at least one month prior to enrollment. ACCESS participants must be  $\geq 18$  years of age and report using an illicit drug (other than or in addition to cannabis) in the month prior to enrollment. ARYS participants must be 14-26 years of age, street-involved, and report using an illicit drug other than or in addition to cannabis) in the month prior to enrollment. Recruitment was conducted through self-referral, street outreach, and snowball sampling.

The data collection instruments and procedures were harmonized across the three cohorts to allow for pooled analyses. At baseline and semi-annually, participants completed an interviewer-administered questionnaire that elicited information on socio-demographic characteristics, drug use patterns, and other relevant exposures and outcomes. Additionally, at each visit, participants provided blood samples for HIV and HCV serologic tests and HIV disease monitoring as appropriate. If participants are

tested positive for HIV and/or HCV, which are reportable diseases, the study team provides post-test counselling and linkage to care. A \$30 (CAD) honorarium was offered to participants upon completion of each study visit. All three cohorts have received ethical approval by the University of British Columbia/Providence Health Care Research Ethics Board.

### *Study sample*

For the present analysis, the sample was restricted to those who: 1) were HCV positive at baseline or those who seroconverted between September 2005 and May 2015; 2) completed at least one follow-up visit after the positive HCV test result; 3) tested positive for HCV and reported a history of injection drug use during the same visit; 4) had chronic HCV, defined as not having spontaneously cleared HCV (ascertained through self-report); and 5) did not die during the study period (or up until the date of death confirmed through BC's Vital Statistics database). For participants added to the sample during follow-up (i.e., those who HCV-seroconverted during follow-up), their data following seroconversion was included.

### *Variable selection*

The primary outcome of interest was access to a physician for regular HCV care, defined by any self-reported access to a doctor or a specialist for regular HCV care at

least once in the past six months. We felt that it was important to examine HCV care more broadly, including both access to primary care and specialist physicians given that in BC, treatment guidelines indicate that both practitioner types are allowed to prescribe DAA-based treatments. We did not restrict to treatment access given that fibrosis level restrictions to prescribing DAAs likely limited treatment availability during the study period. Regardless, HCV care linkage remains an important outcome measure. The primary explanatory variable was HIV-seropositivity, defined as a positive HIV antibody test. We also considered a selection of possible confounders, including: age (per year increase); sex (male vs. female); homelessness (yes vs. no); incarceration (yes vs. no);  $\geq$  daily opioid injection drug use (yes vs. no);  $\geq$  daily stimulant injection drug use (yes vs. no); enrollment in methadone maintenance therapy (yes vs. no); and hospitalized (yes vs. no). The potential mediator variable (frequency of engagement in healthcare) was defined as having had access to a doctor, clinic, specialist, jail doctor, healthcare outside of hospital/clinic/doctor's office, or other in the past six months (once vs. once every two-three months vs. once a month vs. every one-two weeks vs  $>$  once a week vs. no access). All variables except age and gender were considered as time-updated variables of events reported in the six months prior to interview.

### *Statistical analyses*

As a first step, we examined descriptive and socio-demographic characteristics of the sample, stratified by having had access to a physician for regular HCV care at least once during the study period. Next, we used bivariable generalized estimating equations (GEE) with logit link function and exchangeable working correlation structure to estimate the relationship between the outcome (i.e., access to a physician for regular HCV care) and all explanatory variables, including HIV-seropositivity. Then, a multivariable GEE model was constructed where all secondary variables significant at  $p < 0.05$  in bivariable analyses were included. Multicollinearity was also assessed using the variance inflation factor.

As a secondary analysis, we implemented methods developed by Imai, Keele, and Tingley<sup>26</sup> to explore whether the association of interest was mediated by an increased frequency of engagement in healthcare. To begin, we transformed our categorical variable (frequency of engagement) into a numeric variable (i.e., once every six months = 1, once every two-three months = 2, once a month = 3, every one-two weeks = 4, > once a week = 5, no access = 0), to estimate the overall mediation effect. Parameters of interest included: the Average Casual Mediation Effect (ACME), defined as the average mediated effect between the predictor (HIV-seropositivity) and the outcome via mediator (frequency of access); the Average Direct Effect (ADE), defined as the average direct effect of the predictor on the outcome; the Total Effect (TE), which



was the entire effect the predictor had on the outcome (i.e., ACME + ADE); and the Proportion Mediated (PM), which was the proportion of the causal effect of independent variable that was mediated by the mediator (i.e., ACME / TE). Averaged effects were calculated over 50 iterations. Finally, a sensitivity analysis was employed to identify the value of rho at which ACME = 0, which is the correlation between the error terms of the mediator and outcome models. Essentially, the sensitivity analysis was used to probe the plausibility of sequential ignorability (SI). Statistical significance was defined at the 0.05 level. All analyses were performed in RStudio© version 0.99.892 (Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Baseline descriptive and socio-demographic characteristics, stratified by the outcome are presented in Table 1. Of the 1627 participants eligible for inclusion, 582 (35.8%) were HIV-positive at baseline and an additional 31 (1.9%) became HIV-positive during follow-up. Five hundred seventy-three (35.2%) were female and the median age at baseline was 41 years (interquartile range: 47.4-33.5=13.9 years). Overall, participants contributed a total of 9212 person-years of follow-up. Of the 1627 participants, 943 (58.0%) were engaged in healthcare at least once a month and 274 (16.8%) reported no access to care. Of the 1357 participants with access to a physician for regular HCV care

at least once during the study period, 1161 reported access at baseline, and 525 (38.7%) were HIV-seropositive.

As presented in Table 2, in bivariable analyses, HIV serostatus was significantly and positively associated with access to a physician for regular HCV care (odds ratio [OR] = 2.17; 95% confidence interval [CI]: 1.93-2.44). This association remained largely unchanged in multivariable analysis even after adjusting for a range of possible confounders (adjusted odds ratio [AOR] = 1.99; 95% CI: 1.77-2.24).

Mediation analysis yielded a statistically significant ACME ( $\beta = 0.049$ ; 95% [CI]: 0.044-0.054), ADE ( $\beta = 0.141$ ; 95% [CI]: 0.111-0.170) and TE ( $\beta = 0.190$ ; 95% [CI]: 0.161-1.216), suggesting that for HIV-seropositive participants, an increased frequency of engagement in healthcare resulted in a higher likelihood of accessing HCV physician care, as compared to HIV-seronegative participants. Approximately 26% of the effect was attributable to mediation. As a sensitivity analysis, the mediation analysis was repeated using baseline (first available) follow-up data and results were largely unchanged (data not shown). The value of  $\rho$  at which ACME would be zero was 0.2. While this value indicates a seemingly low magnitude of hidden bias due to unobserved confounders, it cannot be calibrated in conjunction with results from studies of a similar construct, which leaves the mediator-outcome association indeterminate.

## DISCUSSION

In the present study, we observed a high proportion of participants who reported access to a physician for regular HCV care. We also found a positive and independent relationship between HIV-seropositivity and access to a physician for regular HCV care among PWID, after adjusting for various confounders. Additionally, our findings revealed that an increased frequency of engagement in healthcare mediated this relationship.

Traditionally, PWID were among the least likely to have access to HCV care.<sup>13,27</sup> Encouragingly, our findings suggest a marked shift in HCV care accessibility among co-infected PWID, with 242 (39.48%) of co-infected participants who reported having had access to regular HCV physician care at baseline in the past six months. Of 613 co-infected participants, 554 (90.4%) reported access to a physician for regular HCV care at least once during the study period. It is important to note that while there have been guideline changes to increase accessibility to HCV treatment, DAAs were not covered as part of the PharmaCare drug coverage program until 2015, which took place after the study period. Similarly to other countries that have moved towards universal coverage for HCV medications,<sup>28</sup> in April 2017, the BC government expanded DAA coverage to HIV/HCV co-infected individuals regardless of liver disease severity, and committed to provide universal DAA coverage for all BC residents with chronic HCV infection

starting in early 2018.<sup>29</sup> Future research should seek to assess the impact of policy change on uptake of HCV treatment and care among this population.

That HIV-seropositive PWID were more likely to engage in HCV care may be partially attributable to HIV care facilities which are operating under an integrated care model.<sup>30</sup> Previous research has demonstrated the importance of integrated care models on mitigating barriers to HCV care for HIV-seropositive populations. For example, a recent retrospective review of HIV/HCV co-infected patients in New York found that HCV therapy can be safely integrated into HIV primary care settings with encouraging SVR rates (92%).<sup>31</sup> Similarly, Brunner *et al.* demonstrated the feasibility of offering HCV and HIV care within opioid agonist treatment (OAT) programs. This integrated “one-stop-shop” approach yielded HCV treatment outcomes comparable to those in non-drug using populations.<sup>32</sup> In fact, a true “one-stop-shop” approach will also be pursuant to reducing frequency of healthcare engagement; lessening wasteful time, resources and spending.<sup>33</sup> In response, a number of international health organizations have recommended the integration of infectious disease (e.g., HIV, HCV, HBV) testing, treatment, and care among individuals with comorbid conditions.<sup>34,35</sup> Accordingly, the implementation of integrated care models for HIV/HCV co-infected PWID should be considered globally.<sup>34-36</sup>

That HIV-seronegative PWID were less likely to engage in HCV care reinforces an urgent need to look beyond conventional approaches to healthcare delivery.

Similarly to what was proposed previously, the integration of OAT and HIV-related services impacts positively on access to HIV care, adherence, and health outcomes, and this approach has been endorsed by the World Health Organization.<sup>37,38</sup> A growing body of evidence positions the integration of OAT and HCV related services as an advantageous undertaking in part, given its ability to remove barriers to HCV care among individuals who do not seek traditional healthcare services.<sup>39,40</sup> The availability of HCV-related services within OAT clinics eliminates the requirement for referrals to an HCV specialist and allows for the provision of immediate patient care.<sup>40</sup> Other successful low-threshold models of HCV care include healthcare delivery through community-based clinics, peer-based models of treatment and task shifting.<sup>41,42</sup> Researchers should seek to explore the impact of these diverse and innovative delivery strategies to improve uptake of HCV care for HCV monoinfected PWID.

Our study had several limitations. First, although HIV/HCV results were ascertained by laboratory assays, measurement of the outcome and confounder variables were reliant on self-reported data, which is susceptible to social desirability and recall bias. Second, despite adjusting models for known confounders, results may be subject to underlying residual and unmeasured confounding. Third, due to the observational nature of the VIDUS, ACCESS and ARYS studies, we were unable to definitively establish causation. Finally, this is a nonrandom sample that is not

representative of a larger population and therefore, the extent to which these results may be generalized beyond our sample is unclear.

Overall, our findings demonstrate an essential need for scaling-up equitable access to HCV therapies, with services delivery models tailored to the needs of PWID. A sustained commitment to address these contextual differences will be essential to mitigate the alarming rates of preventable HCV-related morbidity and mortality experienced among PWID.

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