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### Title

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### Permalink

<https://escholarship.org/uc/item/9f68w12s>

### Journal

AIDS (London, England), 34(11)

### ISSN

0269-9370

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### Publication Date

2020-09-01

### DOI

10.1097/qad.0000000000002610

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Peer reviewed



Published in final edited form as:

*AIDS*. 2020 September 01; 34(11): 1681–1683. doi:10.1097/QAD.0000000000002610.

## The Role of Barriers to Care on the Propensity for HCV Non-referral among People Living with HIV

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### Abstract

Twenty-five percent of HIV/HCV co-infected patients were not referred for HCV treatment despite unrestricted access in California to direct-acting antivirals (DAA) in 2018. Having unstable housing and ongoing drug use directly affected HCV treatment non-referral. However, psychiatric history and alcohol use impacted HCV treatment non-referral through the mediation of not being engaged in HIV care. Achieving HCV elimination requires DAA treatment outside conventional health settings, including substance rehabilitation centers, mental health crisis houses, and homeless shelters.

### Keywords

HIV; HCV referral; engagement in care; barriers to care; DAA; mediation analysis

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Sub-optimal hepatitis C virus (HCV) linkage to care is a key obstacle to global HCV elimination efforts[1]. In the early direct-acting antivirals (DAA) years, it was problematic to disentangle reasons influencing the individual components of HCV linkage to care among people living with HIV (PLWH) as multiple barriers limited access to DAA[2,3]. These limitations likely influenced the HIV medical provider's attitude towards HCV treatment referral and the patient's willingness to attend their intake HCV care appointments. Since

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Edward Cachay: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, obtained funding, study supervision, approved the final submission

Francesca Torriani: patient recruitment, critical revision of the manuscript, approved the final submission

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Wm. Christopher Mathews: Contributed to study design, complex mediation analysis, and interpretation of data, drafting of the paper, critical revision of the manuscript, approved the final submission.

January 2018, there are no restrictions for DAA access in California[4]. We investigated factors associated with HCV non-referral at the University of California, San Diego (UCSD).

We hypothesized that four potential barriers to care (drug use, unstable housing, alcohol use, and psychiatric disease) would affect the clinician's propensity to refer for DAA treatment. Effects on HCV non-referral would be mediated in part through HIV non-engagement in care. Thus, we designed a causal mediation model using a cohort of adult PLWH under care at UCSD in 2018 with detectable HCV viral load. Information on proposed barriers to care was abstracted from electronic medical records (EMR) using diagnosis codes. We also reviewed EMR for documentation of urine toxicology results for drug use; Substance Abuse and Mental Health Services Administration's patient self-report definition of heavy drinking[5]; short stays (up to 2 weeks) in motels or different friends or family members' houses for unstable housing; and PHQ-9 scores for depression. Engagement in HIV care was defined as having 2 visits with an HIV provider separated by three or more months per calendar year during the study period[6]. Additional covariates that could influence propensity for HCV non-referral included demographics, insurance type, CD4+ count, HIV viral load, HCV genotype, cirrhosis status, and liver decompensation history. UCSD Human Research Protection Program approved the study.

We separately fit four causal mediation models to examine the effects of each barrier to care (independent variables) on the outcome HCV treatment non-referral, with HIV non-engagement in care as the mediating variable. Each modeled variable was binary coded. We used the Stata mediation analysis *paramed.ado* program to fit models that estimated direct(DE), indirect(IE), and total effects(TE) as odds ratios (OR)[7]. The TE of each barrier to care on the OR scale is estimated as the product of the natural DE and IE. The proportion of the TE mediated by engagement in care is calculated as the ratio of the natural logs of the OR for the natural IE over the TE[8]. Mediation models were first fit with the inclusion of a potential barrier-to-care:engagement interaction. If the independent variable:mediator interaction was not significant ( $p < 0.10$ ), final models were estimated for the main effects. Bias-corrected confidence intervals for effects were estimated using bootstrap standard errors (500 replications). Analyses were performed using Stata Statistical Software, release 16.1; StataCorp, College Station, TX).

Among 3258 PLWH enrolled in care, 143 had active HCV infection, of whom 35 (24.5%) were not referred for HCV treatment. Patients eligible for HCV treatment had a median age of 49 years; 36% of them were non-white, 18% were female. According to their HCV risk factor, 64% were men who have sex with men, of whom 37% had a history of injecting drug use (IDU) and 27% did not have an IDU history. Along the HIV continuum of care, 59% were not engaged in HIV care; 93% were prescribed antiretroviral therapy, but only 51% of them had an undetectable HIV viral load. There were no differences in sociodemographics, insurance type, HIV or HCV risk factors, HIV or HCV virologic characteristics, cirrhosis diagnosis, or liver decompensation status between those referred or not for HCV treatment. PLWH with ongoing drug use, unstable housing, alcohol use, psychiatric disease, and those not engaged in care were less likely to be referred for HCV treatment (supplementary table).

In bivariate analysis, ongoing drug use, having unstable housing, and alcohol use were significantly associated with HIV non-engagement in care. There was no evidence of barrier-to-care:engagement interaction in any of the four initial mediation models. Mediation models showed significant total, and indirect (mediated) effects for each barrier to care, with the percent mediated by non-engagement in care varying from 48% (drug use) to 56% (unstable housing). Also, significant direct effects on HCV non-referral were found for ongoing drug use (OR: 6.30, 95% CI: 2.31–27.84) and unstable housing (OR: 3.99, 95% CI: 1.43–11.20), see Table.

In summary, we found that 25% of PLWH with HCV infection were not referred for DAA treatment in 2018 despite unrestricted access to DAA. Patient characteristics associated with HCV non-referral included ongoing drug use, alcohol use, having unstable housing, and history of psychiatric disease. Having unstable housing and ongoing drug use had direct effects on HCV treatment non-referral; 47% of drug use effect on HCV treatment non-referral was mediated through non-engagement in care. In contrast, psychiatric history and alcohol use increased the odds of HCV treatment non-referral mainly through the mediation of HIV non-engagement in care, likely reflecting limited opportunities for being referred to HCV treatment.

The finding that ongoing drug use and unstable housing directly predict HCV non-referral may reflect provider implicit or unconscious biases[9] that are not valid in the context of high treatment success rates when adequate psychosocial support is provided[10,11]. Our observation that psychiatric disease and alcohol use mediate their effects on HCV treatment non-referral primarily through HIV non-engagement in care calls for action to scale-up DAA treatment in other settings, including alcohol, drug rehabilitation centers, mental health crisis houses, and homeless shelters[12–16].

Our study is single-site, and its geographical location may limit generalizability to other clinical settings. Nevertheless, our observation that 25% of PLWH were not linked to HCV treatment despite unrestricted DAA access is consistent with a report documenting 20%–40% of PLWH with HCV failing to link to HCV care in countries with universal health-care systems and no DAA restrictions[17].

We conclude that HIV engagement in care and physician training regarding the ability of patients to succeed with DAA may both be critical to achieving HCV elimination.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments:

We would like to thank our patients, whose resilience and perseverance continue to inspire us to improve our clinical services.

**Funding Support:** This work was supported in part by NoCo Grant funded by Gilead Sciences (IN-US-334–4481), the University of California San Diego Center for AIDS Research [AI036214], and the Pacific AIDS Education and Training Center (PAETC). NM was additionally supported by NIAID/NIDA grant R01AI147490. The funders had no role in study design, decision to publish, or preparation of the manuscript.

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**Table:**

Odd Ratios with confidence intervals for indirect, direct, and total effects of barriers to care on HCV non-referral.

Barriers to care	Odds Ratios for HCV non-referral (95% confidence interval)
<b>Drug use</b>	
Natural DE	6.30 (2.31–27.84) <sup>§</sup>
Natural IE	5.42 (2.95–12.28) <sup>§</sup>
Total effect	34.16 (10.09–226.13) <sup>‡</sup>
Percent mediated	47.86%
<b>Unstable housing</b>	
Natural DE	3.99 (1.43–11.20) <sup>§</sup>
Natural IE	5.93 (3.31–18.46) <sup>‡</sup>
Total effect	23.62 (7.92–87.04) <sup>‡</sup>
Percent mediated	56.27%
<b>Alcohol use</b>	
Natural DE	2.85 (0.80–8.97)
Natural IE	3.13 (1.48–6.93) <sup>§</sup>
Total effect	8.93 (2.12–31.66) <sup>§</sup>
Percent mediated	52.13%
<b>Psychiatric disease</b>	
Natural DE	2.34 (0.87–10.41)
Natural IE	2.48 (1.13–6.97) <sup>*</sup>
Total effect	5.84 (1.27–30.15) <sup>*</sup>
Percent mediated	51.42%

\* p < 0.05

§ p < .01

‡ p < 0.001

DE: Direct effect, IE: Indirect effect

Bias-corrected confidence intervals based on bootstrap standard errors with 500 replications

Proportion mediated calculations used the Vanderweele formula (2010), reference N<sup>o</sup>10.

Proportion Mediated = ln(OR<sub>NIE</sub>)/ln(OR<sub>TE</sub>)

Total effect = OR<sub>NDE</sub> \* OR<sub>NIE</sub>