POPULATIONS AT RISK

Hepatitis C Virus Infection in San Francisco's HIV-infected Urban Poor

High Prevalence but Low Treatment Rates

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OBJECTIVE: **To measure Hepatitis C Virus (HCV) prevalence, incidence, and initiation of HCV therapy in a representative HIV-infected cohort of the urban poor.**

DESIGN: **Cohort analysis.**

SETTING: **The Research and Access to Care for the Homeless (REACH) Cohort is a systematic sample of HIV-infected marginally housed individuals identified from single-room occupancy hotels, homeless shelters, and free lunch programs in San Francisco.**

PARTICIPANTS: **Two hundred forty-nine participants with 28.9 months (median) of follow-up were studied. Mean age was 44 (range 24 to 75, standard deviation ±8.4) years. Eighty-two percent were male, 43% were African-American, 64% were lifetime injection drug users, and 24% had been on the street or in a shelter in the prior month.**

INTERVENTIONS: **We measured HCV testing and treatment history with structured interviews; additionally, participants were tested for HCV antibodies (EIA-2) with RNA viral load confirmation.**

MAIN RESULTS: **At baseline, 172 (69.1%) were HCV-positive and 182 (73.1%) were HCV-positive at follow-up, including 155 (62.2%) with viremia. HCV-positive status was associated with having injected drugs, elevated serum alanine aminotransferase, homelessness in the last 1 year, and more severe depressive symptoms. The incidence of new HCV infection was 4.63% per person-year (ppy; 95% confidence interval, 2.31 to 8.13) in the entire cohort and 16.77% ppy among injection drug users. The prevalence of HCV antibody-negative HCV-viremia was 13.2% (10/76). Nonwhites were less likely to receive HCV testing and subspecialty referral, controlled for drug use and other confounders. Sixty-eight percent (123/182) were aware treatment was available; however, only 3.8% (7/182) or 1.16% ppy received HCV treatment.**

CONCLUSIONS: **While HCV infection is common, HCV treatment is rare in the HIV-HCV coinfected urban poor. Urban poor, nonwhite individuals are less likely to receive HCV testing and subspecialty referral than their white counterparts. Antibody-negative infection may complicate screening and diagnosis in HIV-infected persons.**

KEY WORDS: **hepatitis C; HIV infection; HIV/HCV coinfection; HCV treatment; homelessness.**
J GEN INTERN MED 2004;19:357–365.

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The hepatitis C virus (HCV) is an RNA virus recognized as a leading cause of chronic hepatitis. Infecting approximately 4 million persons in the United States, it is 5 times more prevalent than HIV.[1–3] HCV is particularly common in HIV-infected people[4–6] and other marginalized populations.[7–11] Compared to their counterparts infected with HCV only, HIV/HCV-coinfected poor persons are more likely to be minority, report present or past injection drug use (IDU), and/or have a history of multiple sexual partners.[12] The annual cost burden of untreated HCV in the United States has been estimated at $5.5 billion, similar to that of asthma,[13] though recent studies demonstrate the cost effectiveness of treating HCV infection, even among those with HIV coinfection.[14,15]

HIV-HCV coinfection leads to more severe and complicated disease than either infection alone. HIV accelerates HCV disease progression and can lead to more rapid development of cirrhosis, hepatocellular carcinoma, and end-stage liver disease.[16,17] Conversely, HCV may accelerate HIV disease progression[18] and increase morbidity and mortality related to HIV.[19–21] Due to increased hepatotoxicity of antiretroviral therapy (ART) in coinfected individuals, HCV may also complicate successful management of HIV infection.[22,23]

Treatment of HCV with pegylated interferon (IFN) and ribavirin leads to viral clearance in roughly half of HIV-negative individuals[24] and up to 44% of HIV/HCV-coinfected persons.[25] Thus, more rapid disease progression, higher mortality, and increased ART hepatotoxicity warrants an aggressive approach to HCV diagnosis and treatment in HIV/HCV-coinfected individuals.

While the urban poor likely represent a significant reservoir for HCV infection, social instability and chaotic health service utilization complicate its evaluation and treatment.[26–28] HCV treatment in the urban poor may also be challenging because racial minorities, overrepresented among the urban poor, have commonly been undertreated for numerous diseases including HIV, coronary artery disease, bone fractures, alcoholism, chronic renal failure, and breast cancer.[29–35] For these reasons, we investigated HCV prevalence, incidence, and treatment in a representative HIV-infected cohort of the urban poor.

METHODS

Representative Sampling Strategy

The Research and Access to Care for the Homeless (REACH) Cohort is a systematic sample of San Francisco's HIV-infected marginally housed population generated from homeless shelters, free-lunch programs, and select residential hotels as previously described.[36] Adapted from Burnam and Koegel,[37] participants were recruited from single-room occupancy (SRO) hotels, facilities maintaining 73% of San Francisco's shelter beds, and venues providing 88% of free lunches throughout 11 census tracts. Individuals from shelters and lunch lines were identified by structured selection of shelter beds, and a proportional-to-size sample of residents of low-income SRO hotels charging less than $500 per month was conducted. Recruitment occurred in two waves, between July 1996 and May 2000.[38]

Self-reported and Laboratory Data Collection

Baseline information, collected upon cohort entry, included sociodemographics, residential history, health services utilization, primary care provider, health status, HIV medications, drug use, and sexual behavior. Responses to these items were monitored at quarterly visits thereafter. Participants were reimbursed $15 for each encounter.

For this analysis, study participants visited a project field site to complete a consent procedure, HCV antibody and RNA testing of stored baseline samples, and a standardized questionnaire concerning history of HCV testing and treatment as well as subsequent medical evaluation and follow-up. Repeat HCV antibody and confirmatory tests were performed. In a follow-up session, participants were provided test results, post-test counseling, and referrals. Depression symptoms were evaluated separately using the Beck Depression Inventory (BDI-II).[39] Depressive symptoms were classified as "minimal" (BDI score less than 14), "mild-moderate," (24–28) or "severe" (greater than 28). Adherence to HIV antiretroviral therapy was measured by unannounced pill count, as previously described.[40] The University of California San Francisco Committee on Human Research approved all study procedures.

Laboratory Methods

Using standard collection supplies (Vacutainer Systems, Becton Dickinson, Franklin Lakes, NJ), blood was collected from participants directly following administration of the survey instrument. Samples were stored at –70°C initially, and they were processed within 4 hours of collection. For prior negatives, samples were stored until confirmation of negative result and then discarded.

Hepatitis C-testing Algorithm

HCV antibody was detected using an enzyme immunoassay (EIA; Hepatitis C Enzyme Immunoassay 2.0, Abbott Laboratories, Emeryville, Calif) that was performed on samples collected at cohort enrollment and at the time of interview regarding HCV testing and treatment history. Individuals with positive baseline EIA results were retested at interview with a polymerase chain reaction (PCR) assay to detect HCV RNA (viral load; Amplicor Monitor Hepatitis C Virus Test, version 2.0, Roche Molecular Systems, Inc., Branchburg, NJ). If viral load was undetectable, a recombinant immunoblot assay (RIBA; HCV 3.0 strip immunoblot assay, Chiron Corporation, Emeryville, Calif) was performed to distinguish resolved infections from false positives. Individuals with negative baseline results were retested at interview with EIA to confirm negative status; if positive upon repeat, the preceding algorithm was employed. Individuals with indeterminate baseline EIA results were retested with EIA and, if positive, with confirmatory assays as above.

In addition, all baseline samples, as well as follow-up samples from repeat EIA-negative participants, were retested with a quantitative branched DNA signal amplification assay (bDNA; VERSANT HCV RNA 3.0 Assay, Bayer Diagnostics, Pittsburgh, Pa) to confirm baseline classification and to detect those with seronegative viremia.

Based on this algorithm, "HCV-positive" was defined as evidence of HCV infection by either confirmed antibody or viral RNA tests. "Subjective positives" were HCV-positive persons self-reporting positive status. "HCV-infected" was defined as detectable HCV RNA level. "Incident" individuals were those without evidence of HCV infection at baseline who subsequently were found to be HCV-positive at follow-up.

Hepatitis B surface antibody testing was performed on samples sent for HCV viral load, and a liver function panel was performed on all individuals. To estimate presence of sustained virologic response (SVR) in individuals treated for HCV, a stored blood sample from 6 to 12 months following self-reported treatment termination was sent for HCV RNA determination.

Statistical Analysis

Participants' questionnaire responses and laboratory test results were analyzed along with their demographic characteristics. Data were analyzed using SAS (SAS Institute, Cary, NC) and SPSS (SPSS Inc., Chicago, Ill) statistical analysis software. In univariate analysis, a χ^2 test (or Fisher's exact test when expected cell size was less than 5) was used for comparing categorical variables, whereas

the nonparametric Wilcoxon two-sample test was used to compare continuous variables. Multivariate analysis was performed using logistic regression modeling.

The rate of new HCV infections was calculated using person-time of observation, and a 95% confidence interval (CI) was calculated assuming an exponential distribution. The observation time was that between the initial negative HCV result and the midpoint between such test and a subsequent positive HCV result. The HCV treatment initiation rate was calculated by dividing the number of individuals having initiated interferon treatment by the sum of accumulated treatment-free years of observation in persons who were HCV-positive at baseline.

RESULTS

Study Participants

During initial cohort screening, all consenting participants (4,682) found HIV-positive (386) were recruited into the REACH Cohort; 330 individuals consented to participate at baseline. By the time of this analysis, 81 persons were inaccessible, including those deceased (43), relocated out-of-area (16), lost to follow-up (15), withdrawing participation (5), and incarcerated (2), leaving 249 (87% of living participants) available.

The subgroup in this analysis was comparable to the overall REACH Cohort with respect to baseline characteristics including age, gender, ethnicity, initial HCV antibody status, CD4 count, lifetime IDU status, and the proportion homeless over 1 year ($P > .05$ for all comparisons). Participants inaccessible for the study were more likely to have had a higher baseline HIV viral load (86,054 vs 51,369 copies/ml; $P = .029$). Otherwise, there were no statistically significant differences between the original and subsequent samples.

At follow-up, the mean age was 44 (range 24 to 75, standard deviation [SD] ± 8.4) years; 82% were male; 43% were African American and 6% were Latino; 64% had ever injected drugs, whereas 21% had injected in the prior 30 days; and 24% had spent a night on the street or in a shelter in the last 30 days. Forty-eight percent were on ART, and the overall mean CD4 was 419 cells/μl (SD ± 304). Ninety-four percent had a primary care provider and 40% had a case manager. Seventy-three percent were patients in the public health care system and 3% were patients in Veterans Affairs facilities. Other participant characteristics are shown in Table 1.

Prevalence of HCV Infection

Of 249 persons studied, 172 (69.1%; 95% CI, 63.3 to 74.8) were found HCV-positive by either antibody or RNA tests at baseline along with 182 (73.1%; 95% CI, 67.6 to 78.6) at follow-up. At follow-up, 155 of 249 (62.2%; 95% CI, 56.2 to 68.3) had active viremia. In univariate analysis, HCV-positive persons at follow-up were more likely current and past injection drug users ($P < .001$), not on ART ($P = .007$), more depressed (mean BDI; $P = .007$), and homeless over 1 year at study baseline ($P = .020$). They also had higher levels of alanine aminotransferase (ALT; $P < .001$) and HIV RNA ($P = .014$). In multivariate analysis, significant independent risk factors of HCV status at follow-up were a history of IDU (OR, 14.0; 95% CI, 7.0 to 28.0) and not receiving ART (OR, 2.1; 95% CI, 1.1 to 4.0).

Of 155 viremic individuals, the median HCV RNA was 1,310,100IU/ml (SD ± 1.11 M). In univariate analysis, HCV and HIV viral load were significantly correlated with one another ($r = .14$; $P = .047$, by Spearman rank correlation test), but there was no significant association between HCV viral load and ALT, CD4, age, or other demographic characteristics.

New HCV Infections

During a median follow-up interval of 28.9 months (range 16 to 60), 10 of 76 (13.2%) HCV-negative individuals became infected as seen by HCV RNA testing, and 8 of 76 (10.5%) developed a positive HCV antibody test, thereby yielding a new infection rate of 4.63% per person-year (ppy; 95% CI, 2.31 to 8.13 ppy).

Of the 22 of 158 persons who were both HCV-negative at baseline and who reported a lifetime history of IDU, 8 of 22 (36.4%) new infections were identified, at a rate of 16.77% ppy (95% CI, 7.62 to 31.27 ppy). Newly infected persons were younger ($P = .004$), reported IDU ($P < .01$), had higher mean ALT ($P < .001$), and had worse depressive symptoms ($P = .014$). In multivariate analysis, significant independent risk factors of incident HCV infection were a history of IDU (OR, 15.5; 95% CI, 2.6 to 91.7; $P < .001$) and age younger than 35 (OR, 7.9; 95% CI, 1.5 to 41.4; $P = .001$).

Among those HCV antibody-positive at baseline, 26 of 173 (15.0%; 95% CI, 9.7 to 20.4) untreated individuals had no evidence of active viremia at follow-up, suggesting resolution of HCV infection without therapy. Lower ALT ($P = .031$) and homelessness over 1 year at baseline ($P = .047$) were significant predictors of undetectable HCV viral load. Among baseline HCV-positives, one person was later classified as a false positive on the basis of RNA and RIBA assays.

Seronegative HCV Infection

At the time of interview, 76 participants had no evidence of antibodies to HCV according to a second-generation ELISA. Among them, HCV RNA was detected in 10 individuals for which antibody tests were negative on 2 occasions (8/10) or once following a prior indeterminate result (2/10). The overall prevalence of those with seronegative viremia was 4.0% (10/249; 95% CI, 1.6 to 6.5%), 13.2% (10/76; 95% CI, 5.6 to 20.8) in the subset of those with negative antibody results. Among seronegatives, median HCV viral load was 2,090,380 IU/ml (SD ± 2.00 M). RNA was detected in 2 of 10 at follow-up only; presence of virus without detectable antibody may have reflected acute infection. In the remaining 8, RNA was detected 41.7 (mean) months prior to the last negative HCV antibody result. In

Table 1. Population Characteristics of HIV-positive Homeless and Marginally Housed Persons in San Francisco, 1997–2000, by HCV Infection Status at Follow-up

Characteristic		HCV Infection Status		
	All *N* = 249	Positive *N* = 182	Incident *N* = 10	Negative *N* = 67
Mean age, y (±SD), range	44 ± 8.4, 24 to 75	44 ± 7.6, 28 to 67	35 ± 6, 30 to 49*	45 ± 10, 24 to 75
Mean CD4, cells/mm^3 (±SD)	419 ± 304	401 ± 282	436 ± 105	467 ± 354
Mean HIV RNA, c/ml (±SD)	23,091 ± 33K	26,247 ± 34K*	20,008 ± 22K	14,482 ± 28K
Mean ALT, IU/L (±SD)	42 ± 40	48 ± 44*	71 ± 72*	27 ± 23
	n (%)	*n* (%)	*n* (%)	*n* (%)
Gender				
Male	205 (82)	145 (80)	9 (90)	60 (90)
Female	44 (18)	37 (20)	1 (10)	7 (10)
Race/ethnicity				
White	103 (41)	78 (43)	5 (50)	25 (37)
African American	106 (43)	75 (41)	3 (30)	31 (46)
Latin	16 (6)	10 (6)	0	6 (9)
Other	24 (10)	19 (10)	2 (20)	5 (8)
Sexual orientation				
Heterosexual	90 (37)	72 (40)	4 (40)	18 (27)
Bisexual	87 (35)	60 (34)	3 (30)	27 (40)
Homosexual	68 (28)	46 (26)	3 (30)	22 (33)
IDU history				
Yes	158 (64)	144 (79)*	8 (90)*	14 (21)
No	91 (36)	38 (21)	2 (20)	53 (79)
Current IDU (last 30 days)				
Yes	53 (21)	49 (27)*	4 (40)*	4 (6)
No	196 (79)	133 (73)	6 (60)	63 (94)
Current HAART†				
Yes	120 (48)	78 (43)*	5 (50)	42 (63)
No	129 (52)	104 (57)	5 (50)	25 (37)
In primary medical care‡				
Yes	235 (94)	172 (94)	10 (100)	63 (94)
No	14 (6)	10 (6)	0	4 (6)
In public health care system§				
Yes	181 (73)	133 (73)	5 (50)	48 (72)
No	68 (27)	49 (27)	5 (50)	19 (28)
Homeless over 1 year‖				
Yes	142 (57)	112 (62)*	5 (50)	30 (45)
No	106 (43)	69 (38)	5 (50)	37 (55)
Alcohol use (days of last 30)				
none	153 (61)	114 (63)	6 (60)	40 (60)
1–4	39 (16)	28 (15)	2 (20)	11 (16)
>4	56 (23)	40 (22)	2 (20)	16 (24)
Depression (BDI score)¶				
Minimal (<14)	114 (46)	75 (41)	3 (30)	39 (58)
Mild-moderate (14–28)	79 (32)	63 (35)	4 (40)	16 (24)
Severe (>28)	25 (10)	20 (11)	3 (30)	5 (8)
Mean BDI ± SD	14.7 ± 10.6	15.9 ± 10.5*	20.8 ± 12.6*	11.6 ± 10.2

* P < *.05, compared to HCV-negatives. Characteristics determined within 28 days (median) of HCV data collection, unless otherwise noted.*
† *Minimum of 3 antiretroviral drugs.*
‡ *Contact with provider within the last 6 months.*
§ *The SFDPH Community Health Network.*
‖ *Self-report at cohort baseline.*
¶ *Reflects those participants undergoing BDI assessment within 102 days (median) of HCV data collection.*

this group of persistently seronegative persons, mean HIV RNA was 38,012 copies/ml (vs 14,483 in all negatives; *P* = .041) and mean CD4 was 215 cells/μl (vs 467; *P* = .052). HCV seronegative viremia was not significantly associated with ALT, CD4, age, or other demographic characteristics.

Concordance of Self-reported and Objective Findings

Among HCV-positive individuals, 64% (117/182) reported receiving a positive test result prior to interview. Of

these, the median self-reported duration of positive status was 2.61 years, 85% (100/117) had a lifetime history of IDU, and 32% (37/117) were currently injecting. Reporting a prior positive antibody test result had a positive predictive value of 98% among the 62% (154/249) who recalled receiving a test result; reporting a negative test result among such persons had a predictive value of 74%.

Thirty-five percent (64/182) of the HCV-positive individuals were unaware of their HCV status. Overall, 12% (29/249) were unsure whether they had undergone testing or were unable to recall their test result. Thirty-two percent (79/249), including 24% (43/182) of HCV-positives, had not been tested. Four percent (11/249) inaccurately stated their test result.

HCV Counseling and Testing

Overall, 61% (152/249) of participants reported having discussed HCV with a health care provider. HCV antibody-positive persons were more likely to identify such encounters (65% vs 49%; $P = .026$); 76% (139/182) of HCV antibody-positive persons reported having been tested for HCV. In multivariate analyses, nonwhite individuals (OR, 0.26; 95% CI, –0.11 to 0.62; $P = .002$) and individuals reporting never using injection drugs (OR, 0.14; 95% CI, –0.19 to 0.92; $P = .03$) were independently associated with not receiving HCV testing.

Forty-seven percent of individuals with prior HCV diagnosis (55/117) indicated behavioral advice had been discussed with a provider, 37% (43/117) had been advised to avoid drinking alcohol, and 30% (35/117) were advised to avoid injection drug use. Concurrently, 38% (45/117) had consumed alcohol at least 1 day in the prior month, though consumption was not significantly associated with secondary prevention advice ($P = .668$), nor were there significant differences in self-reported drinking compared to HCV antibody-negative persons ($P = .661$). Forty-nine percent of individuals (57/117) recalled being vaccinated for either hepatitis A or B or both. In serologic testing, 37% (68/182) HCV antibody-positive individuals had evidence of hepatitis B surface antibodies, reflecting either prior HBV exposure or previous vaccination.

Evaluation and Treatment of HCV Infection

Thirty-eight (21%) HCV-positive persons reported referral to a gastroenterology (GI) specialist. Thirteen (7%) had declined liver biopsy, while 21 (12%) had undergone the procedure. Whites were significantly more likely to receive GI referral in a multivariate analysis (OR, 2.86; 95% CI, 1.36 to 5.99; $P = .006$). Receipt of testing, referral, biopsy, and treatment according to participant characteristics is detailed in Table 2.

Seven (3.8%; 95% CI, 1.1 to 6.6) HCV-positive persons reported having undergone treatment. Among persons HCV-positive at baseline, 3.5% (6/173) underwent treatment, a crude treatment initiation rate of 1.16% ppy (95% CI, 0.46 to 2.35 ppy). In total, only 18% (32/182) reported having been offered therapy; at follow-up, no one was currently receiving HCV treatment. Of those treated, 4 reported aborted treatment courses ranging from 1 to 6 months (mean 2.75 months) in duration. Three individuals had completed 12 months of treatment with interferon and ribavirin, yet only 1 individual had an undetectable HCV viral load in the 6- to 12-month period following self-reported treatment termination.

Sixty-eight percent (123/182) of HCV-positive persons interviewed were aware HCV treatment was available; however, 3.3% (6/182) indicated that they had declined treatment and 6.6% (12/182) reported their providers had discussed but deferred initiation of therapy. Additionally, 7.7% (14/182) indicated that a plan was made to start therapy in the ensuing 6 months. Finally, to facilitate HCV therapy, 3.8% (7/182) reported treatment for depression, and 1.6% (3/182) reported referral for substance abuse treatment.

DISCUSSION

Using serial laboratory measurements and individual self-reports, we examined HCV prevalence, incidence, and treatment penetration in a representative cohort of the HIV-infected urban poor. We found that HCV infection was common in this population: 73% percent of individuals were infected with HCV, and the new infection rate was 4.6% ppy among those not yet infected and 16.8 ppy in the subgroup of injection drug users. While our incidence rate for injectors is similar to those previously reported,[41–44] ours are the first estimates of HCV incidence and prevalence in a representative sample of HIV-infected urban poor individuals, a group in which injection drug use is common, but not universal.

Current Treatment Efforts

In contrast to the high prevalence and incidence of HCV,[45] treatment for infection was rare and several-fold less than the rate of new infections. The indolent nature of the disease, complexities of diagnosis and therapy, frequency of significant side effects, and low therapeutic response rates complicate selection of patients eligible for treatment initiation.[46,47] While not all patients with HCV require treatment and the incidence of HCV may be declining,[44,48,49] our findings suggest that the emergence of new infections outpaces treatment, and the urban poor will remain a significant and growing reservoir of HCV infection. This is important particularly for HIV/HCV-coinfected individuals in whom HCV infection complicates successful HIV therapy and leads to increased morbidity and mortality.

Barriers to HCV Treatment

Barriers to treatment of chronic illnesses, including HIV, have been clearly demonstrated in marginalized populations, particularly injection drug users. Active drug using[50,51] and HCV infection itself[52] have been shown to be negatively associated with receipt of ART. Data reported here

Table 2. Receipt of HCV Testing, Gastrointestinal Referral, Liver Biopsy, and HCV Treatment by HIV-positive Homeless and Marginally Housed Persons in San Francisco, 1997–2000, According to Selected Population Characteristics at Study Follow-up

		HCV-tested	Referred to GI	Liver biopsied	Offered therapy	HCV-treated
HCV-positives	**182**	**139**	**38**	**21**	**32**	**7**
	***n* (%)**	**% (*n*/*N*)**	**% (*n*/*N*)**	**% (*n*/*N*)**	**% (*n*/*N*)**	**% (*n*/*N*)**
Gender						
Male	145 (80)	75 (109)	21 (31)	12 (17)	19 (27)	5 (7)
Female	37 (20)	81 (30)	19 (7)	11 (4)	14 (5)	0
Age						
<40	58 (32)	72 (42)	21 (12)	7 (4)	12 (7)	2 (1)
40–46	60 (33)	80 (48)	23 (14)	10 (6)	18 (11)	5 (3)
>46	64 (35)	77 (49)	19 (12)	17 (11)	22 (14)	5 (3)
Race/ethnicity						
White	78 (43)	90 (70)	31 (24)*	13 (10)	18 (14)	4 (3)
African American	75 (41)	71 (53)*	16 (12)	11 (8)	17 (13)	4 (3)
Latin	10 (6)	50 (5)	10 (1)	0	30 (3)	0
Other	19 (10)	58 (11)	3 (1)	16 (3)	10 (2)	5 (1)
IDU history						
Yes	144 (79)	81 (117)*	23 (33)	12 (17)	16 (23)	3 (4)
No	38 (21)	58 (22)	13 (5)	10 (4)	24 (9)	8 (3)
Current IDU (last 30 day)						
Yes	49 (27)	84 (41)	22 (11)	14 (7)	18 (9)	8 (4)
No	133 (73)	74 (98)	20 (27)	10 (14)	17 (23)	2 (3)
Current HAART[†]						
Yes	78 (43)	73 (57)	20 (16)	13 (10)	19 (15)	3 (2)
No	104 (57)	79 (82)	21 (22)	11 (11)	16 (17)	5 (5)
ART adherence[‡]						
>90%	10 (13)	90 (19)	50 (5)	30 (3)	20 (2)	10 (1)
70–90%	21 (27)	76 (17)	19 (4)	5 (1)	14 (3)	0
<70%	34 (44)	68 (23)	15 (5)	18 (6)	21 (7)	0
In primary medical care[§]						
Yes	172 (94)	78 (134)	22 (38)	12 (21)	17 (30)	4 (7)
No	10 (6)	50 (5)	0	0	20 (2)	0
In public health care system[‖]						
Yes	133 (73)	80 (100)	18 (23)	11 (14)	14 (17)	3 (4)
No	49 (27)	69 (34)	29 (14)	14 (7)	26 (13)	6 (3)
Homeless over 1 year[¶]						
Yes	112 (62)	72 (81)	20 (22)	9 (10)	16 (18)	3 (3)
No	69 (38)	83 (57)	23 (16)	16 (11)	20 (14)	6 (4)
Alcohol use (days of last 30)						
none	114 (63)	75 (85)	20 (23)	11 (13)	18 (20)	4 (5)
1–4	28 (15)	79 (22)	29 (8)	18 (5)	21 (6)	4 (1)
>4	40 (22)	80 (32)	18 (7)	8 (3)	15 (6)	3 (1)
Depression (BDI score)[#]						
Minimal (<14)	75 (41)	72 (54)	21 (16)	12 (9)	12 (9)	1 (1)
Mild-moderate (14–18)	63 (35)	76 (48)	21 (13)	8 (5)	21 (13)	6 (4)
Severe (>28)	20 (11)	90 (18)	20 (4)	10 (2)	20 (4)	5 (1)

* P < *.05, compared within characteristic group for service analyzed. Characteristics determined within 28 days (median) of HCV data collection, unless otherwise noted.*

[†] *Minimum of 3 drugs.*

[‡] *Based on available pill count from ART adherence substudy.*

[§] *Contact with provider within the last 6 months.*

[‖] *The SFDPH Community Health Network.*

[¶] *Self-report at cohort baseline.*

[#] *Reflect those participants undergoing Beck Depression Inventory (BDI) assessment within 102 days of HCV data collection.*

and elsewhere confirm that there are formidable barriers to effective diagnosis and treatment of hepatitis C.[12,53–57]

The National Institutes of Health have recently called for expanded treatment of injection drug users and people with HIV.[58,59] To date, treatment of marginalized populations has been uneven because of limited health care access, provider bias toward certain behavioral traits, and concerns about adherence, reimbursement factors, health system barriers such as resource limitations, poor relationships with health care providers, and competing needs.

In this study, the low rate of HCV treatment did not result from lack of access to primary medical care; nearly all individuals had a primary care provider, most of these in the public health system. Of particular concern, nonwhite individuals in our cohort were statistically less likely to undergo HCV testing and referral. Ethnicity did not predict treatment, possibly because so few people of any ethnic origin received treatment. However, these findings echo observations of racial differences in evaluation for renal transplant and cardiac catheterization,[60,61] though further research is necessary to characterize more fully the ethnic disparities observed here.

Certainly, marginalized housing status may impose a barrier to HCV care among the HIV-infected poor. One study of HCV treatment penetration among ostensibly housed HIV-infected veterans (mean and nadir CD4 330 and 177 cells/μl, respectively) demonstrated that only 3% received HCV treatment.[57] Given low rates of HCV treatment overall, the effect of housing status on HCV treatment is difficult to isolate.

Despite more than three fifths of persons in this study having a lifetime history of IDU, over three quarters reported current abstinence, yet they still had not received HCV therapy. Edlin and others have argued that active drug use should not automatically preclude eligibility for HCV treatment,[62] and successful HCV treatment in active injection drug users has been demonstrated in two small cohorts.[63,64] While additional research may be necessary to clarify the indications for HCV treatment in active drug users, our data suggest that regardless of current drug use status, few HIV/HCV-coinfected urban poor people are receiving treatment.

Some providers may believe coinfected patients—particularly injection drug users—lack the ability to adhere to HCV therapy. In our cohort, unannounced pill counts in HCV-positive persons on ART exceeded 70% in roughly half, consistent with our prior estimates[40] and those of other investigators.[65–69] Elsewhere, we have demonstrated that provider estimates of adherence to ART are imprecise.[70] We suggest that predicting adherence to HCV therapy will be equally difficult and that all otherwise eligible individuals should have a trial of therapy after addressing modifiable barriers to adherence.[71]

HCV-positive persons in our cohort had more severe symptoms of depression. Chronic HCV infection itself may cause cognitive and affect disturbances.[72] Interferon use may exacerbate preexisting depressive symptoms and, in extreme cases, give rise to suicidality.[73,74] Still, interferon therapy may improve health-related quality of life in some HCV-treated persons.[75,76] Several studies have indicated that depression is undertreated in HIV-positive individuals.[77,78] Our study confirms these findings and suggests that failure to treat depression is a significant barrier to receiving HCV therapy. Clinicians must carefully assess patients' mental health before beginning hepatitis C treatment, and should monitor symptoms and provide necessary interventions while on therapy.

Patient Reticence

Despite efforts to expand access to HCV therapy, if eligible patients do not perceive its potential benefits as exceeding its risks and discomforts, they will not choose it. While some have demonstrated substantial willingness among active injectors to initiate HCV therapy,[79] others have shown that providers routinely underestimate patient reticence.[80] Only 19% of our cohort reported declining therapy when offered. Thus, more research is needed to better understand willingness of patients to accept current conventional therapy.

Screening for HCV

Our data indicate that 13% of seronegative persons, identified using a conventional assay, had evidence of HCV infection with a more sensitive viral detection assay. Based on longitudinal analysis, the majority had persistently high levels of HCV viremia while remaining antibody negative for over 3 years and therefore were unlikely to have been infected recently. Furthermore, HIV disease stage was only marginally worse in this subset, in contrast to prior studies in which acute seroconverters and the severely immunosuppressed accounted for the majority of those with seronegative infection.[81,82] Given the conventional usage of second-generation antibody tests in screening coinfected and other persons at high risk, improved testing algorithms are needed to identify more accurately HCV infection in HIV-infected individuals.

Study Limitations

This study has several important limitations. These results are only generalizable to HIV-positive urban poor persons in San Francisco. Because San Francisco has one of the most extensive public heath systems in the United States, we suggest that treatment rates are unlikely to be higher in other metropolitan areas where HCV is common. Some of our findings rely on participants' recall of events, such as provider interactions and vaccinations. While treatment and evaluation rates may be underestimated by reliance on such self-reports, medical therapy of these individuals was reviewed on a monthly basis. Because both liver biopsy and interferon treatment are likely to be recalled, we believe significant misclassification of treatment status is unlikely. Finally, our crude HCV therapy initiation rate does not take into account treatment eligibility factors such as hepatic fibrosis score, viral genotype, unusual clinical circumstances, individual provider practices, and patient acceptance.

Broadening HCV Therapy

Historically, the provision of ART to marginalized HIV-infected persons has required substantial dialogue, amelioration of provider biases, and persuasive cost analyses.[83–85] This study highlights similar public health shortcomings with respect to HCV therapy, which involves

a life-threatening, chronic infection in a vulnerable population with frequent comorbid illnesses. Further dialogue, based on empiric studies of treatment response and clinical outcomes, is required in order to more effectively deliver HCV treatment advances to all of those who may benefit.

Drs. Tomás Aragón, Brian Edlin, Elise Riley, and Kimberly Page-Shafer provided important critique of the analysis and presentation. In addition, sincere appreciation goes to Richard Clark, Nelia de la Cruz, David Guzman, Tarek Elbeik, Paula Zenti, Sandra Monk, John Day, James McDonald, Gina Hobson, Kelly Winslow, William Benjamin, and Johanna Crane who were responsible for data collection.

Supported by the Centers for Disease Control and Prevention Post-doctoral Fellowship Training Program in Infectious Diseases, National Institute of Mental Health, The Doris Duke Charitable Foundation, and an unrestricted grant from Agouron Pharmaceuticals, Inc. Agouron representatives did not participate in data collection, analysis, drafting of manuscript or decision to submit the manuscript for publication.

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