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Trends in hepatitis C treatment initiation among HIV/hepatitis C virus-coinfected men engaged in primary care in a multisite community health centre in Maryland: a retrospective cohort study

Yun-Chi Chen,[1] Chloe L Thio,[2] Andrea L Cox,[2] Sebastian Ruhs,[3] Farin Kamangar,[1] Kjell J Wiberg[4]

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[1]Department of Biology, Morgan State University, Baltimore, Maryland, USA
[2]Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA
[3]Chase Brexton Health Care, Baltimore, Maryland, USA
[4]Department of Medicine, Sinai Hospital, Baltimore, Maryland, USA

Correspondence to
Yun-Chi Chen;
yunchi.chen@icloud.com

ABSTRACT

Objectives Little is known about the cascade of hepatitis C care among HIV/hepatitis C virus (HCV)-coinfected patients in community-based clinics. Thus, we analysed our data from the interferon era to understand the barriers to HCV treatment, which may help improve getting patients into treatment in the direct-acting antivirals era.

Design Retrospective cohort study.

Setting Four HIV clinics of a multisite community health centre in the USA.

Participants 1935 HIV-infected men with >1 medical visit to the clinic between 2011 and 2013. Of them, 371 had chronic HCV and were included in the analysis for HCV care continuum during 2003–2014.

Outcome measures HCV treatment initiation was designated as the primary outcome for analysis. Multivariate logistic regression was performed to identify factors associated with HCV treatment initiation.

Results Among the 371 coinfected men, 57 (15%) initiated HCV treatment. Entering care before 2008 (adjusted OR [aOR, 3.89; 95% CI, 1.95 to 7.78), higher educational attainment (aOR, 3.20; 95% CI, 1.59 to 6.44), HCV genotype 1 versus non-1 (aOR, 0.21; 95% CI, 0.07 to 0.65) and HIV suppression (aOR, 2.13; 95% CI, 1.12 to 4.06) independently predicted treatment initiation. Stratification by entering care before or after 2008 demonstrated that higher educational attainment was the only factor independently associated with treatment uptake in both periods (aOR, 2.79; 95% CI, 1.13 to 6.88 and aOR, 4.10; 95% CI, 1.34 to 12.50, pre- and post-2008, respectively). Additional associated factors in those entering before 2008 included HCV genotype 1 versus non-1 (aOR, 0.09; 95% CI, 0.01 to 0.54) and HIV suppression (aOR, 2.35; 95% CI, 1.04 to 5.33).

Conclusions Some traditional barriers predicted HCV treatment initiation in those in care before 2008; however, the patients' level of educational attainment remained an important factor even towards the end of the interferon era. Further studies will need to determine whether educational attainment persists as an important determinant for initiating direct-acting antiviral therapies.

Strengths and limitations of this study

- The primary care setting provided 'real-world' data on HCV care continuum in a cohort of HIV-positive men belonging to diverse racial, socioeconomic and behavioural risk groups.
- The HCV screening rate was high (99%) in this study cohort, thereby minimising selection bias.
- The study period encompassed an earlier period and last until the end of the interferon era, allowing the analysis for trends in HCV treatment initiation.
- This is a retrospective study based on medical chart review, limiting the analysis for certain behavioural and socioeconomic factors.
- This study did not include HIV-infected women or adolescents/children.

INTRODUCTION

Hepatitis C virus (HCV) and HIV share routes of transmission, leading to high prevalence of HCV coinfection among HIV-infected individuals.[1–4] Chronic HCV-induced liver disease progression is accelerated and severity exacerbated in people with HIV coinfection compared with those without HIV.[4–6] In fact, chronic HCV has become one of the major causes for morbidity and mortality among HIV-infected persons receiving antiretroviral therapy.[3 4 6]

Both the traditional interferon (IFN)-based therapy and the newly available IFN-free, direct-acting antiviral (DAA) regimens could result in HCV eradication, known as sustained virologic response (SVR), in infected persons.[7 8] In contrast to the highly effective and well-tolerated DAA regimens, IFN-based treatment had a much lower SVR rate, and the efficacy was dependent on HCV genotype, host age and genetics and HIV coinfection.[9] For HCV genotype 1, the SVR

rates are <30% with IFN-based therapy and >95% with DAA regimens.[10 11]

A few studies have examined the HCV care continuum among HIV-infected patients during the IFN era, and very low rates of treatment uptake were consistently observed in these studies.[12–18] Due to the poor efficacy, extended course of treatment and considerable side effects associated with IFN-based therapy, many patients were deferred for new IFN-free DAA treatment in the years before the approval of the regimens for treating HCV in HIV-coinfected patients in 2015.[19–21] Despite removal of many barriers of IFN-based therapy, recent studies have shown that treatment uptake remained low in era of DAA regimens.[22–24] In addition to new barriers, such as high cost, that have emerged with DAA therapy, it is possible that some barriers of the IFN era persist.[25 26] Indeed, some barriers unrelated to the side effects of IFN-based therapy have been identified, including race, substance abuse, neuropsychiatric condition, detectable HIV RNA, AIDS, unstable housing and excessive missed clinic visits.[12 13 18 25 27]

To examine treatment barriers, we characterised the HCV cascade of care and determined factors associated with HCV treatment uptake among HIV-infected men receiving primary care in a multisite community health centre from 2003 to 2014, a point right before the inception of the DAA era. Identification of barriers and gaps in the HCV care continuum during the IFN era that are not specific to the therapy itself will provide crucial clues for improving HCV care and eradication among HIV-infected individuals with the advent of DAA regimens.

METHODS

Study population

HIV-infected men who were >17 years old, had at least two medical visits to Chase Brexton Health Care (CBHC) between 2011 and 2013, had positive anti-HCV and HCV RNA tests after entering care at CBHC and who were verified to have chronic HCV were included. Patients who only attended the clinic prior to 2010 were excluded because the medical records of these 'inactive' patients could not be retrieved from the Electronic Medical Record (EMR) database (Centricity).

CBHC is a multisite community health centre with one clinic in downtown Baltimore City, two clinics in suburban Baltimore and one clinic in rural Eastern Shore in the State of Maryland of the USA. CBHC was founded in Baltimore in the 1970s as a volunteer-run gay men's clinic. It has become one of the first, longest-serving and largest clinics in Baltimore and surrounding areas to deliver HIV care to the lesbian, gay, bisexual, transgender and intersex (LGBTI) community and people of various minorities and underserved groups. The comprehensive HIV care provided in CBHC included case management/social work services, mental healthcare, addiction treatment/rehabilitation and LGBTI support services in addition to regular medical care. The HIV care provided in rural Eastern Shore included one clinic at Easton and specialist visits to the Health Departments in different counties. To increase routine screening for anti-HCV in high-risk HIV-infected patients, a pop-up reminder was set up in the EMR since 2010.

There were at least two infectious disease (ID) specialists at CBHC at any point during 2003–2014. Most, but not all, of the HIV-infected patients were referred to the ID specialists, who also managed their HCV care. For the patients whose primary care providers (PCPs) were not ID specialists, their HCV infection was evaluated by the PCPs or the ID specialists after referral. All patients who initiated HCV treatment were treated at CBHC and all received IFN-based therapies. Some patients with decompensated liver cirrhosis were referred to gastroenterologists outside of CBHC and none of them initiated HCV treatment.

Data collection and definitions

Data on demographic, socioeconomic, clinical and behavioural characteristics were collected from 2003 to 2014 from the EMR database, using comprehensive medical chart reviews as previously described.[28]Patient data obtained from outside of CBHC were abstracted from the original documents scanned and stored in the EMR. The baseline data included age, race, educational attainment, employment status, Body Mass Index (BMI), HIV RNA level and CD4+ T cell counts and were collected at the initial clinic visit. Because CBHC did not adopt the EMR until 2003, the first clinic visit in year 2003 was considered as the initial visit for those who entered care

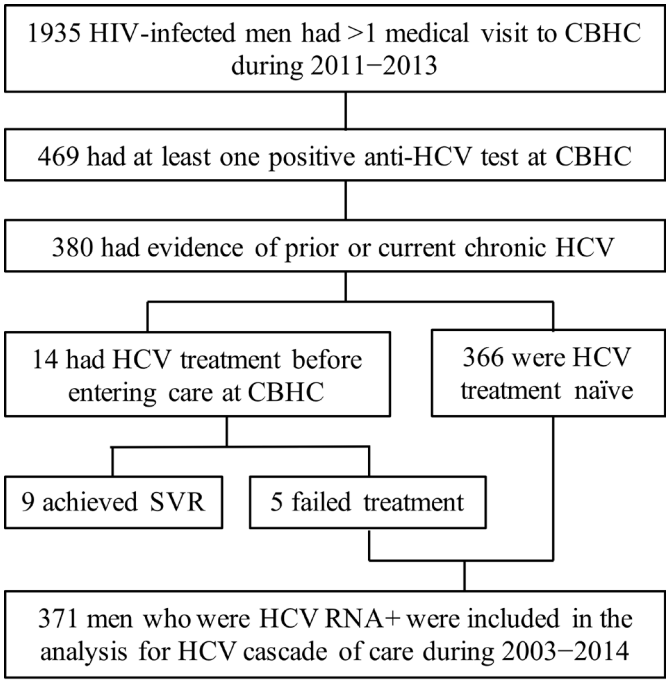

Figure 1 Flow chart showing the inclusion of HIV-infected men with chronic hepatitis C virus (HCV) infection in the analyses for HCV cascade of care. CBHC, Chase Brexton Health Care; SVR, sustained virologic response.

Table 1 Hepatitis C cascade of care in HIV-infected men engaged in care at CBHC (n=371)

	Starting	Fibrosis staging*		Treatment initiated		Treatment completed		SVR achieved	
	No.	No.	(%)	No.	(%)	No.	(%)	No.	(%)
All HCV RNA+ men	371	283	(76)	57	(15)	32	(9)	22	(6)
Age									
<40	64	46	(72)	12	(19)	9	**(14)***	8	**(13)***
40–49	174	134	(77)	29	(17)	16	(9)	10	(6)
≥50	133	103	(77)	16	(12)	7	(5)	4	(3)
Race									
Black	315	244	(77)	43	(14)	22	(7)	14	(4)
White	51	36	(71)	14	**(27)***	10	**(20)****	8	**(16)****
Other	5	6	(30)	0	(0)	0	(0)	0	(0)
Clinic sites									
Baltimore	326	249	(76)	49	(15)	29	(9)	19	(6)
Eastern Shore	45	34	(76)	8	(18)	3	(7)	3	(7)
Entering care at CBHC									
Before 2008	182	140	(77)	41	**(23) *** **	23	**(13) ** **	15	(8)
2008–2013	189	143	(76)	16	(8)	9	(5)	7	(4)
Education	n=360								
≤12 years	277	207	(75)	31	(11)	18	(6)	11	(4)
>12 years	83	68	(82)	24	**(29)*****	14	**(17)****	11	**(13)****
Employment									
Unemployed	263	196	(75)	31	(12)	18	(7)	12	(5)
Employed	108	87	(81)	26	**(24)****	14	(13)	10	(9)
Type of insurance									
Private	58	51	**(88)***	16	**(28)****	12	**(21)****	9	**(16)****
Medicare	125	93	(74)	19	(15)	7	(6)	8	(6)
Medicaid	148	119	(80)	18	(12)	11	(7)	4	(3)
Other	40	20	(50)	4	(10)	2	(5)	1	(3)
Ever illicit drug use									
Yes	339	256	(76)	50	(15)	29	(9)	19	(6)
No	32	27	(84)	7	(22)	3	(9)	3	(9)
Ever IDU									
Yes	269	205	(76)	36	(13)	20	(7)	13	(5)
No	102	78	(76)	21	(21)	12	(12)	9	(9)
Sexual behaviour									
Non-MSM	260	199	(77)	32	(12)	18	(7)	12	(5)
MSM	111	84	(76)	25	**(23)***	14	(13)	10	(9)
Baseline BMI	n=368								
<18.5 or >25	186	141	(76)	35	(19)	18	(10)	10	(5)
18.5–25	182	142	(78)	22	(12)	14	(8)	12	(7)
HIV RNA at initial visit									
≥400 copies/mL	227	167	(74)	29	(13)	16	(7)	11	(5)
<400 copies/mL	144	116	(81)	28	(19)	16	(11)	11	(8)
Baseline CD4 count									
<200 cell/mm^3	104	72	(69)	12	(12)	7	(7)	4	(4)
200–499 cell/mm^3	162	130	(80)	24	(15)	12	(7)	9	(6)
≥500 cell/mm^3	105	81	(77)	21	(20)	13	(12)	9	(9)
Nadir CD4 count									
<200 cell/mm^3	213	154	(72)	32	(15)	19	(9)	11	(5)

Continued

Table 1 Continued

	Starting	Fibrosis staging*		Treatment initiated		Treatment completed		SVR achieved	
	No.	No.	(%)	No.	(%)	No.	(%)	No.	(%)
≥200 cell/mm^3	158	129	**(82)***	25	(16)	13	(8)	11	(7)
Prevalent/incident HCV									
Prevalent	345	266	(77)	52	(15)	28	(8)	18	(5)
Incident	26	17	(65)	5	(19)	4	(15)	4	(15)
HCV genotype	n=355								
Genotype 1	334	264	(79)	49	(15)	26	(8)	16	(5)
Non-genotype 1	21	14	(67)	8	**(38)***	6	**(29)****	6	**(29)*****
Fibrosis staging*									
Ever	283	–	–	44	(16)	24	(8)	17	(6)
No or unknown	88	–	–	13	(15)	8	(9)	5	(6)
Peak fibrosis stage†	n=275								
F0–F2	148	–	–	18	(12)	9	(6)	6	(4)
F3–F4	127	–	–	22	(17)	11	(9)	8	(6)

Each data point represents the number and % of men involved in a particular step of the care cascade in the full cohort or in designated subgroups.
Boldface type indicates that the proportion is significantly higher than that of the other subgroup (in the case of two comparison subgroups) or that of all other subgroups combined (in the case of >2 comparison subgroups) in the specified step of the cascade.
Statistically significant differences between comparison subgroups in the specified step of cascade are depicted by *p<0.05, **p<0.01 or ***p<0.001.
*Fibrosis staging included the Fibrosure test and/or liver biopsy.
†Results derived from the Fibrosure test.
BMI, Body Mass Index; CBHC, Chase Brexton Health Care; HCV, hepatitis C virus; IDU, injection drug use; MSM, men who have sex with men.

at CBHC before 2003. The data on sexual behaviours and illicit drug use, including injection and non-injection drug use, were collected from the baseline through the last clinic visit. The nadir CD4 T cell count was determined by reviewing all available data on CD4 T cell count of the patient. The type of insurance usage represented the one at the last clinic visit.

The male sex was defined as the gender assigned at birth. Being retired at baseline was considered as being employed, as these patients had had stable employment. Normal BMI was within the range of 18.5 and 24.9. Because the sensitivity of HIV RNA tests improved and the undetectable level changed from <400 to <50 copies/mL over the period of 2003–2013, HIV suppression at baseline was defined as HIV RNA <400 copies/mL. The patients were considered to be men who have sex with men (MSM) if they ever reported such sexual behaviour. Those who reported past or current drug use were considered to have had a history of drug use. The definition of prevalent and incident HCV has been described previously.[28] For the patients with incident HCV, the clinic visit of the first anti-HCV positive test was considered as the baseline visit.

Chronic HCV infection is defined as having at least one positive HCV RNA test >6 months after the positive anti-HCV test. The patients (n=9) who had their chronic HCV cured before seeking care at CBHC were all confirmed to have anti-HCV and undetectable HCV RNA. Because different HCV genotypes responded differently to IFN, blood HCV RNA was analysed for genotypes of the infecting HCV. To assess the severity of HCV-induced liver damage/fibrosis, a Fibrosure test was employed, which measures the liver fibrosis-related biomarkers in the blood. The scores of the Fibrosure test represent the clinical stages of liver fibrosis, from F0 (no fibrosis), F1 (mild fibrosis), F2 (intermediate fibrosis), F3 (severe fibrosis) to F4 (liver cirrhosis).[29] Chronic hepatitis C evaluation is defined as having HCV genotyping and/or liver fibrosis staging. An inconclusive Fibrosure test was considered as not having the staging.

Statistical analysis

The cascade of HCV care was defined as the process from hepatitis C evaluation, treatment initiation and treatment completion, through SVR attainment. HCV treatment initiation was designated as the primary outcome for analysis. Patients who received at least one dose of IFN were considered to have had treatment initiation. The secondary outcomes included (1) completion of the full course (48 weeks) of treatment and (2) achievement of SVR, defined as the absence of HCV RNA in the blood for ≥24 weeks after the last IFN injection. The patients whose therapy was terminated due to lack of an early virologic response were considered as not having treatment completion (n=4); however, SVR attainment was evaluated in these patients. Because the study period ended in 2014, for those who commenced HCV treatment in 2013 or 2014, the data on treatment completion and SVR were reviewed and confirmed in November 2016.

The proportion (%) of men involved in each step of the care cascade was calculated by comparing to the starting population. The difference between comparison subgroups in each step of the cascade was assessed using χ^2 analysis for categorical variables. Multivariate logistic

regression analyses were performed to determine the adjusted OR (aOR) and 95% CI for the association of HCV treatment uptake with selected independent variables. In the initial models, we included variables selected a priori, including age and race, in addition to factors that were statistically significant (p<0.05) in the univariate analysis, followed by stepwise model selections. Due to collinearity between employment and private insurance usage, only insurance was included in the models. Preliminary analyses showed higher rates of HCV treatment uptake among those who entered care at CBHC in earlier years, and the difference was most remarkable between those who entered care before 2008 and those who entered care during 2008–2013. Thus, the study cohort was divided into two subgroups: the <2008 enrollees and the 2008–2013 enrollees. All statistical analyses were performed using Stata software V.14.

Patient and public involvement

This is a retrospective study based on patients' medical chart review. Therefore, there is no direct involvement of patients or public in the initiation, design, recruitment to and conduct of the study.

RESULTS

There were 1935 HIV-infected men who had at least two medical visits to CBHC between 2011 and 2013 (figure 1). Of them, 1908 (99%) had at least one anti-HCV test at CBHC since the clinic entry (from <2003 to 2013) and 469 had ever tested positive for anti-HCV. Of the anti-HCV+ men, 98 (21%) were HCV RNA negative at baseline or at >6 months after the positive anti-HCV test. Nine of these 98 attained SVR prior to entering care at CBHC. The other 371 men were confirmed HCV RNA positive at >6 months after the positive anti-HCV test. Of them, 366 (99%) were HCV treatment-naïve and 5 (1%) had failed prior treatment before entering care. The median age was 47 (range, 24–71), and 315 (85%), 51 (14%) and 5 (1%) were of black, white or other race, respectively (table 1). In addition, 277 (75%) had never attended college, 263 (71%) were unemployed, 273 (74%) used public insurance and 269 (73%) ever had injection drug use (IDU). Moreover, 12 (3%) had chronic hepatitis B virus (HBV) coinfection.

The 371 HCV RNA+ men were monitored for participation in the HCV cascade of care from baseline through 2014. Most of the HCV/HIV-coinfected men had HCV genotyping results (n=355, 96%). Of them, 334 (94%), 14 (4%), 6 (2%) and 1 (<1%) had HCV genotype 1, 2, 3 or 4, respectively. However, a lower proportion of these coinfected men had liver fibrosis staging (n=283, 76%), as shown in table 1. Of them, 275 had at least one Fibrosure test and 44 had liver biopsy assessment. Remarkably, only 57 (15%) achieved treatment initiation, the primary outcome. Of those, only 32 (9%) and 22 (6%) achieved the secondary outcomes of treatment completion and/or SVR, respectively. Two patients who did not complete the full course of treatment attained SVR. Two of the five patients who failed HCV treatment prior to entering care at CBHC reinitiated the treatment and one achieved SVR. Only two of the 12 men with HIV/HBV/HCV triple coinfection embarked on HCV treatment and one attained SVR.

Initiation of HCV treatment was more likely to occur in those who were white, entered care before 2008, had >12 years of education, were employed, used commercial insurance or were infected with non-genotype 1 HCV (table 1). Although 29% of the patients with >12 years of education had treatment initiation, only 11% of those with ≤12 years of education initiated HCV treatment (p<0.001). Moreover, the rate of HCV treatment uptake was significantly higher in the pre-2008 cohort (23%) than that in the post-2008 cohort (8%; p<0.001). No differences in treatment uptake were observed between those with and without liver fibrosis staging or between those with and without advanced liver fibrosis/cirrhosis. Notably, none of the 24 (6%) HIV treatment-naïve patients ever embarked on HCV treatment.

Table 2 Analyses for factors associated with HCV treatment initiation among all HIV-infected men (n=371)

	Univariate analysis			Multivariate analysis*		
Characteristics	**OR†**	**(95% CI)**	**P value**	**aOR**	**(95% CI)**	**P value**
≥50 years old	0.66	(0.35 to 1.21)	0.19	0.76	(0.37 to 1.56)	0.45
Black race	0.48	(0.24 to 0.97)	**0.041**	0.76	(0.32 to 1.79)	0.53
Entering care before 2008	3.14	(1.70 to 5.96)	**<0.001**	3.89	(1.95 to 7.78)	**<0.001**
>12 years of education	3.22	(1.74 to 5.90)	**<0.001**	3.20	(1.59 to 6.44)	**0.001**
Private insurance	2.52	(1.27 to 4.87)	**0.009**	1.14	(0.51 to 2.54)	0.74
HIV suppression at baseline	1.65	(0.93 to 2.92)	0.09	2.13	(1.12 to 4.06)	**0.022**
HCV genotype 1	0.28	(0.11–0.75)	**0.012**	0.21	(0.07–0.65)	**0.007**

Boldface type indicates p<0.05.
*Adjusted for other variables in the table.
†An OR<1 represents a decreased likelihood of initiating treatment.
aOR, adjusted OR; HCV, hepatitis C virus.

Among the 57 men who initiated HCV treatment, the rates of SVR were higher for those who were younger, had incident HCV, had non-genotype 1 HCV, had normal BMI or used private insurance. For the 19 patients who had documented causes for treatment discontinuation, the most common reasons were intolerance to side effects (n=13) and lack of virologic responses after 3–6 months post-treatment initiation (n=4). Other reasons included non-adherence to treatment (n=2), severe comorbidity (n=1) and incarceration (n=1).

Multivariate analysis demonstrated that entering care at CBHC before 2008 (aOR, 3.89; 95% CI, 1.95 to 7.78), >12 years of education (aOR, 3.20; 95% CI, 1.59 to 6.44), HIV suppression at baseline (aOR, 2.13; 95% CI, 1.12 to 4.06) and infection with genotype 1 HCV (aOR, 0.21; 95% CI, 0.07 to 0.65) independently predicted HCV treatment uptake (table 2). Notably, HIV suppression was an independent predictor, even though it was not significantly associated with treatment initiation in the univariate analysis. Moreover, non-black race and usage of private insurance were no longer associated with treatment uptake after adjusting for other factors.

Stratification by entering care before or after 2008 demonstrated that among the earlier enrollees, HIV suppression at baseline (aOR, 2.35; 95% CI, 1.04 to 5.33), genotype 1 HCV (aOR, 0.09; 95% CI, 0.01 to 0.54) and higher level of education (aOR, 2.79; 95% CI, 1.13 to 6.88) independently predicted treatment uptake (table 3). However, higher educational attainment (aOR, 4.10; 95% CI, 1.34 to 12.50) was the only independent predictor for treatment initiation among the 2008–2013 enrollees.

There were 351 men who remained HCV RNA-positive at their last visit to CBHC before the end of 2014, including two men who were reinfected with HCV (re-emergence of HCV RNA with simultaneous elevation of alanine aminotransferase

level and self-reported risk exposure)>2 years after achieving SVR. Of them, 29 (8%) died, leaving 322 men who were subject to follow-up for receiving DAA therapies (table 4). Notably, a high proportion of these men either lacked liver fibrosis staging (23%) or had advanced liver fibrosis/cirrhosis (Fibrosure score, F3 or F4; 35%). Considering that having a Fibrosure score of F2 or higher was among the general eligibility criteria for insurance to subsidise the DAA therapies in the inception of the DAA era, we estimated that, as of 1 January 2015, 179 (56%) of these men would be eligible for treatment, and 162 (50%) might achieve SVR, assuming a 90% success rate.[10 30 31]

DISCUSSION

Monitoring the hepatitis C cascade of care is an integral part of the effort toward HCV eradication. Despite the high prevalence of HCV in HIV-infected individuals, few studies have evaluated the HCV care continuum in this population of patients. This study showed that only 15% of these community clinic patients initiated HCV

Table 3 Analyses for factors associated with HCV treatment uptake among the men who entered care before 2008 and the men who entered care between 2008 and 2013

	<2008 enrollees (n=182)						2008 – 2013 enrollees (n = 189)					
	Univariate analysis			Multivariate analysis*			Univariate analysis			Multivariate analysis*		
	OR†	(95% CI)	P value	aOR	(95% CI)	P value	OR	(95% CI)	P value	aOR	(95% CI)	P value
≥50 years old	0.84	(0.36 to 1.86)	0.69	0.80	(0.32 to 2.02)	0.64	0.56	(0.17 to 1.65)	0.30	0.64	(0.19 to 2.08)	0.45
Black race	0.43	(0.17 to 1.10)	0.08	0.69	(0.23 to 2.07)	0.51	0.41	(0.13 to 1.40)	0.14	0.76	(0.18 to 3.15)	0.71
>12 years of education	2.74	(1.26 to 5.93)	**0.012**	2.79	(1.13 to 6.88)	**0.026**	4.30	(1.45 to 12.75)	**0.009**	4.10	(1.34 to 12.50)	**0.013**
Private insurance	2.64	(1.16 to 5.92)	**0.022**	1.17	(0.44 to 3.15)	0.75	1.67	(0.35 to 6.00)	0.46	1.03	(0.23 to 4.49)	0.97
HIV suppression at baseline	2.42	(1.17 to 5.00)	**0.018**	2.35	(1.04 to 5.33)	**0.040**	1.53	(0.53 to 4.51)	0.43	1.67	(0.57 to 4.87)	0.35
HCV genotype 1	0.09	(0.01–0.46)	**0.003**	0.09	(0.01–.54)	**0.009**	0.50	(0.11 to 3.58)	0.41	0.48	(0.07 to 3.13)	0.44

Boldface type indicates p<0.05.
*Adjusted for other variables in the table.
†An OR<1 represents a decreased likelihood of initiating treatment.
aOR, adjusted OR; HCV, hepatitis C virus.

Table 4 The HIV-infected men who remained HCV RNA-positive at the last clinic visit (n=322)*

Characteristics	Number	(%)
Median age (IQR) as of 1 January 2015	54.3	(49.8–58.9)
Black race	278/322	(86%)
≤12 years of education	244/314	(78%)
Unemployed	228/322	(71%)
Insurance		
Private	49/322	(15%)
Medicare	103/322	(32%)
Medicaid	140/322	(44%)
Other	30/322	(9%)
Ever illicit drug use	295/322	(92%)
Ever IDU	234/322	(73%)
MSM	94/322	(29%)
Previous HCV treatment failure	38/322	(12%)
Previous HCV cure†	2/322	(<1%)
HCV treatment naïve	282/322	(88%)
HCV genotype		
Genotype 1	297/322	(92%)
Other genotype	12/322	(4%)
Unknown	13/322	(4%)
Peak Fibrosure score		
F0–F1	58/322	(18%)
F2	80/322	(25%)
F3	32/322	(10%)
F4	79/322	(25%)
Unknown	73/322	(23%)
Estimation of the number (%) of men, as of 1 January 2015, who would be eligible for DAA treatment and subsequently achieve SVR‡		
Treatment uptake	179/322	(56%)
SVR	161/322	(50%)

*This population of patients excluded those who were known to be deceased (n=29) before 1 January 2015. Each data point represents the number and % unless otherwise stated.
†These two men had acute HCV reinfection after >2 years of achieving SVR.
‡Based on the general eligibility criteria as of 1 January 2015, in which a Fibrosure score of F2 or higher was a prerequisite for insurance to subsidise the DAA therapies.
DAA, direct-acting antiviral; HCV, hepatitis C virus; IDU, injection drug use; MSM, men who have sex with men; SVR, sustained virologic response.

treatment during the IFN era. Our results also demonstrated that HIV suppression and favourable HCV genotype predicted treatment initiation only in an earlier period, but not towards the end, of the IFN era. To our knowledge, this study established for the first time that the educational attainment of patients was strongly associated with HCV treatment uptake, even in the face of increasing deferral for new DAA therapies in the final years of the IFN era.

We showed that the major lapse in the HCV care cascade was the initiation of treatment. Indeed, almost all of the patients had HCV genotyping (96%), though a lower proportion of them had liver fibrosis staging (76%), in part due to insurance coverage. A similar rate (~15%) of treatment uptake among HCV/HIV-coinfected patients was reported in a recent study conducted in the Owen HIV clinic in San Diego, California and was also noted in a liver/gastroenterology referral clinic and an open prospective HIV outpatient cohort.[13–15] Nevertheless, the rate of treatment uptake was higher in this study than those (1%–7%) observed in other HIV primary care settings before 2005.[16–18 27]

Surprisingly, recent studies have shown that the uptake rates of DAA treatment remained alarmingly low in the USA and other high-income countries.[22–24 32–35] The results from multiple community-based healthcare systems in the USA revealed that, although the treatment rates significantly improved from pre-DAA to post-DAA era, only about one in five HCV-infected patients embarked on DAA therapy.[32 33] For HCV/HIV-coinfected patients, the uptake rates of DAA treatment were <20%, with African Americans and Medicaid holders having much lower treatment rates.[22 24] In Europe, the rates were similarly low, ranging from <10% to 25%, depending on the countries.[23 34]

Our observations that HIV suppression and HCV genotype were independent predictors for HCV treatment uptake were consistent with the data that those with treated HIV and non-1 HCV genotype responded better to HCV treatment with an IFN-based regimen.[12 36] Although the reasons for not initiating treatment were not systemically documented for most of the patients in the study population, substance abuse, non-compliance to HIV care, comorbid conditions or deferral for new therapies have been noted in the EMR. The treatment decisions might have varied among different practitioners, depending on the perception, training and experience in HCV care.[12 36–39] Nonetheless, we did not find major differences in the number of patients receiving HCV treatment among different ID specialists during the study period.

In the study population, marked differences were noted in several characteristics between the patients with higher and lower levels of education (online supplementary table S1). Nevertheless, when these factors were incorporated into the multivariate regression model, either individually or together, educational attainment remained significantly associated with treatment uptake. Thus, our results strongly suggested that the patients' level of educational attainment was an important independent predictor for HCV treatment initiation, and the association was not due to type of insurance or to employment status. It is possible that patients with higher educational attainment were more likely to recognise the health consequences of chronic HCV and value the long-term benefits above

the risks of receiving HCV treatment, making them more motivated and proactive in seeking treatment. By contrast, patients with lower educational attainment might be more reluctant to undergo treatment even when they were eligible.[12 39 40] Whether this persists into the DAA era will require further study. However, this study highlights education level as a factor that needs to be considered in evaluation of the HCV cascade of care and hepatitis C programming effectiveness.

The increased treatment uptake in the pre-2008 cohort was likely because providers were deferring treatment as DAAs came closer to approval. It is unlikely that age or liver fibrosis stage played a role in deferral because the 2008–2013 enrollees were older at clinic entry than the pre-2008 enrollees and they did not have more advanced liver fibrosis (online supplementary table S2). Although the HCV genotype distributions were similar between these two subgroups, HCV genotype was not predictive of treatment initiation among the 2008–2013 enrollees, possibly as a result of deferral awaiting DAA therapy.

Since all patients had at least two medical visits between 2011 and 2013, those who enrolled before 2008 were engaged in care at CBHC for an extended period of time. This could be beneficial in establishing trust between patients and practitioners,[12 40] thereby increasing the likelihood of initiating HCV treatment. By contrast, the 2008–2013 enrollees were in care at CBHC for a shorter period and in the years approaching the DAA era. For them, only educational attainment was independently associated with treatment uptake. Indeed, among the 16 treated patients, 11 enrolled in care between 2010 and 2013 and 6 (55%) of them had >12 years of education. Furthermore, HIV suppression had no effect on HCV treatment uptake among the 2008–2013 enrollees, possibly due to a higher number of patients with HIV suppression in this subgroup (online supplementary table S2).

Race, illicit drug use, psychiatric or medical contraindications (eg, mental illnesses, depression or other chronic comorbidities), and unstable socioeconomic circumstances (eg, homeless, incarceration or low income) have been linked to low rates of HCV treatment uptake among HIV-coinfected patients in previous studies.[12 13 15 25 27 40] Notably, some of these traditional factors still posed barriers to DAA treatment initiation, regardless of HIV coinfection.[22 24 32 33 41] Usage of Medicaid or Medicare could serve as a proxy for low income and/or certain medical or psychiatric comorbid conditions.[42] Indeed, only 11% of the Medicare enrollees in the study cohort were above 65 years old as of 2014. However, using private insurance was not independently associated with treatment initiation. Our study also did not find an association of race or illicit drug use, including IDU, with HCV treatment uptake. Indeed, the association between race and treatment uptake remained non-significant after removal of HCV genotype and other variables individually from the multivariate regression model. The lack of associations of HCV treatment uptake with these traditional factors could be unique to this study cohort/setting or due to a lower number of patients achieving the primary outcome.

Our results showed that most of the HIV-infected men who remained HCV RNA+ at the end of the study were of socioeconomically disadvantaged, vulnerable and 'difficult-to-treat' populations (table 4). Recent studies have shown that these patients could greatly benefit from DAA treatment with high SVR rates if the treatment was given and completed.[24 30 31 33 43] However, given current restrictions by public insurance and some private insurance to approve DAA treatment with stage 2 or greater liver disease, it is estimated that <60% of these HCV/HIV-coinfected men would be eligible for DAA treatment. Thus, although DAA therapy is substantially more effective at curing HCV than IFN-based therapy, the cascade of care would still not show the majority receiving treatment,[22 24 32] which could potentially lead to worsening liver disease and ongoing HCV transmission. We believe that routine liver fibrosis staging and enhancing HCV awareness education could help overcome these barriers and improve DAA uptake rate among these patients. Considering that the criteria for insurance approval of DAA treatment varied by providers and states in the USA, it would be interesting to determine the impact of such policy variation on DAA uptake rates compared with the universal healthcare system in countries such as the UK and Australia.[34 44 45]

This study has some limitations. First, data on psychiatric illnesses and active alcohol consumption were not collected. The history of illicit drug use, including IDU, did not discern past and current use and could not measure the extent of abuse. We did not have data on the number/frequency of missed visits or related factors, such as incarceration and unstable housing, and thus could not assess the association between adherence and HCV care continuum. Nor did we have data on the calendar year in which the patients commenced HCV treatment to analyse the length of time between entering care/diagnosis of chronic HCV and treatment initiation. The data on CD4+ T cell counts and HIV RNA levels were collected at the initial visit and thus did not reflect adherence to HIV care at CBHC. However, HIV suppression at baseline indicated that the patients had been compliant to the antiretroviral treatment. In addition, the data on types of employment were unavailable. It is possible that the patients with hourly paid jobs might be less willing to initiate IFN treatment than those with salaried jobs, who might be able to take sick leaves without loss of income. Finally, this study focused only on male patients. Future studies are needed to examine the HCV treatment cascade and barriers among HIV-infected women.

For HCV/HIV-coinfected patients receiving HIV primary care, HIV services present a setting to engage them in HCV care. Indeed, a recent study assessing access to HCV care among injection drug users found that those who were HIV-infected were more likely to receive HCV care due to engaging in HIV care.[46] Inasmuch as the emerging sexual HCV transmission among HIV-infected MSM, HCV-related education and support services

should target this high-risk group,[47 48] and DAA treatment should be considered for coinfected MSM as a strategy of 'treatment-as-prevention'.[49] A community health centre that fulfils the functions of LGBTI organisation and HIV clinic could be of great utility to deliver such public health services en route to HCV eradication.

In conclusion, although the coinfected patients were actively engaged in HIV primary care, whether or not they initiated HCV treatment was highly dependent on their levels of educational attainment. This effect persisted when HIV suppression and HCV genotype no longer predicted treatment uptake at a later time of the IFN era. Thus, the influence of educational attainment on HCV care continuum needs to be determined in the DAA era. Notwithstanding, education on HCV-related health outcomes and long-term benefits of treatment should be intensified for all coinfected patients, especially those who refuse or are ineligible to receive DAA therapies.[50] Community-based strategic plans/programmes of HCV education should also be implemented as an integral part of the public health effort toward HCV eradication, especially for those with lower attainment of education.

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