

# Presumed Nonalcoholic Fatty Liver Disease Among Medicare Beneficiaries With HIV, 2006–2016

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**Background.** Newer treatments for HIV and hepatitis C virus (HCV) have decreased mortality in HIV/HCV patients. Nonalcoholic fatty liver disease (NAFLD) has increased globally; therefore, the prevalence and mortality of NAFLD among HIV (+) patients was assessed.

**Methods.** Using Medicare denominator, inpatient, and outpatient files (random 5% sample per year), serial cross-sectional analysis (2006 to 2016) was performed. Joinpoint trend analysis evaluated prevalence and mortality with average annual percent change (AAPC). HIV (+) patients and liver diseases (LDs) were identified using International Classification of Diseases 9/10 codes. NAFLD was presumed using diagnosis codes or codes for metabolic dysfunction and obesity in absence of other LDs. Liver-related HIV (+) indicated HIV (+) patients with LDs.

**Results.** Among 28 675 887 Medicare beneficiaries, 47 062 were HIV (+) (mean [SD] age, 51.4 [11.3] years); 11 920 had liver diseases (6923 HCV, 2019 hepatitis B virus [HBV], 2472 presumed NAFLD, 278 alcoholic liver disease [ALD], and 1653 other LDs); 2882 HIV (+) patients died; 1260 had LDs. The prevalence and mortality for non-liver-related HIV (+) decreased (AAPC, −1.1% and −9.1%). Liver-related HIV (+) increased (AAPC, 1.7%;  $P = .007$ ); mortality leveled off. Prevalence and mortality worsened for presumed NAFLD (AAPC, 9.7% and 10.0%) and improved for HBV and HCV (HBV: AAPC, −3.5% and −8.8%; HCV: AAPC, −0.7% and −4.9%). After adjustments, HCV (odds ratio [OR], 2.00; 95% confidence interval [CI], 1.24–1.72), HBV (OR, 2.40; 95% CI, 2.09–2.77), ALD (OR, 5.70; 95% CI, 4.34–7.48), and presumed NAFLD (OR, 1.46; 95% CI, 1.24–1.72) increased 1-year mortality.

**Conclusions.** Among HIV (+) subjects, viral hepatitis remains the leading LD for increased 1-year mortality, but the prevalence and mortality with presumed NAFLD are increasing.

**Keywords.** liver disease; mortality; HCV; HBV; trends.

In the United States, as of 2016, ~1 008 929 people were living with HIV [1]. As the HIV virus affects killer T cells, leaving the infected individuals unable to mount an effective response to infections, today's antiretroviral regimens for HIV are geared toward increasing the number of killer cells by stopping HIV transcription within the cells (viral suppression). In addition to the incidence of HIV declining in most groups, the use of highly effective antiretroviral regimens has combined to successfully increase patients' life expectancy from 12 years after diagnosis in the 1980s up to 47 years following a diagnosis in 2017 [1–4].

It is important to remember that HIV shares common risks with other blood-borne infections, specifically hepatitis B virus (HBV) and hepatitis C virus (HCV) [5, 6]. As treatment of HIV has changed over the years, this highly lethal disease has become a chronic and manageable disease. As such, HCV-related

liver disease then became a major cause of death among those who were co-infected with HCV [7]. However, this too is changing due to the advent of highly effective and well tolerated direct-acting antiviral agents (DAAs) for HCV, which have provided a curative option for all HCV-infected patients. In fact, DAAs provide a >95% cure rate regardless of HIV co-infection [8, 9]. Therefore, as HCV is being aggressively treated among HIV-infected patients, it is expected that the risk of liver disease from HCV in HIV-infected patients will fall [7].

In the United States, in addition to viral hepatitis, nonalcoholic fatty liver disease (NAFLD) is another very common liver disease [10]. NAFLD is associated with metabolic risk factors such as obesity and type 2 diabetes [11–13]. In this context, as survival increases among HIV-infected patients, they are now at risk for obesity and diabetes, similar to the rest of the population [14–17]. In addition, although most of the new antiretroviral agents don't cause metabolic disturbances, a few may still cause lipodystrophy, which can worsen the metabolic profile and predispose patients to NAFLD [15]. In fact, the newer combined antiretroviral therapies (cART) may be inducing an increase in weight gain beyond the “return to health,” exposing patients with HIV to the potential development of diabetes mellitus and cardiovascular disease [18–22]. Recent studies have indicated that treatment with nucleoside reverse transcriptase

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inhibitors (NRTIs) and protease inhibitors (PIs) increases the chance of developing metabolic syndrome by around 2.4 times [23]. Studies remain ongoing to determine the exact mechanisms by which cART may cause obesity, especially in the face of the obesity epidemic and fewer patients now appearing underweight for cART therapy, as was the hallmark of advanced HIV disease [24–27]. Nonetheless, these factors combined may increase the incidence and prevalence of NAFLD in this population independent of lipodystrophy.

The prevalence of NAFLD has been studied in subgroups, but the prevalence and outcomes data in HIV-infected patients have not been fully reported [28–34]. Therefore, the purposes of this study were to assess the prevalence and mortality outcomes and resource utilization of Medicare beneficiaries with HIV infection who also had NAFLD or other types of liver disease.

## METHODS

### Data Source and Study Population

This was a serial cross-sectional analysis of Medicare beneficiaries between 2006 and 2016 using Medicare denominator, inpatient, and outpatient files (a random 5% sample for each of our study years). Eligible patients were fee-for-service Medicare enrollees with a medical record (inpatient or outpatient) with an International Classification of Diseases (ICD) 9/10 code for HIV (042-044 in ICD 9 or B20-B24 in ICD 10 code) at any position. [Supplementary Table 1](#) displays the ICD 9/10 codes used to identify the liver diseases (such as hepatitis B virus [070.2, 070.3, 070.42, 070.52, V02.61, B16, B17.0, B18.0, B18.1, B19.1, Z2251], hepatitis C virus [070.7, 070.41, 070.44, 070.51, 070.54, V02.62, B17.1, B18.2, B19.2, Z2252], alcoholic liver disease [571.0–571.3 and K70], NAFLD, etc.).

At this point, we observed that NAFLD was underdiagnosed and undercoded in the Medicare data sets. Indeed, we found that the prevalence of NAFLD through ICD codes (K76.0 and K76.89) among Medicare beneficiaries in 2016 was 0.19. Therefore, we extended NAFLD cases with an ICD code for NAFLD and nonalcoholic steatohepatitis (NASH), an ICD code for “cryptogenic liver disease or cirrhosis,” and those with metabolic abnormality [35], defined as all 3 ICD codes for diabetes, hypertension, and hyperlipidemia or 2 ICD codes for diabetes and obesity. To reduce the possibility of misclassifying NAFLD, we excluded NAFLD cases with any other liver diseases (viral hepatitis, ALD, iron overload, autoimmune, Wilson disease, hemochromatosis, and alpha-1-antitrypsin deficiency) or alcohol abuse. This extended NAFLD definition was validated using the NHANES database with clinical and laboratory data. We found that 92.5% of Medicare-aged subjects from NHANES who fulfilled our last NAFLD definition had evidence of NAFLD, as determined by an improved Fatty Liver Index for the US population (US FLI), a surrogate for the clinical diagnosis of NAFLD using race, age, gamma glutamyltransferase, waist circumference, insulin, and glucose, in which a cutoff score of 30 was found to be the most accurate, with an area under the curve of

0.80 (95% confidence interval [CI], 0.77–0.83). ([Supplementary Table 2](#)) [36].

Liver-related HIV (+) subjects were identified as HIV (+) patients having liver diseases including hepatitis B and C virus (HBV and HCV), alcoholic liver disease (ALD), NAFLD, autoimmune liver disease, Wilson disease, hemochromatosis, iron overload, alpha-1-antitrypsin deficiency, liver disorder, or unknown etiologies in the presence of hepatocellular carcinoma, cirrhosis, or hepatic failure. Non-liver-related HIV (+) subjects were defined as HIV (+) patients without liver disease. [Figure 1](#) shows a flow diagram outlining the inclusion and exclusion criteria of the study cohort.

Mortality status was available within 1 year of an encounter per year. All Medicare expenditures were adjusted using the medical component of Consumer Price Index, with 2016 as the index year (<https://www.bls.gov/cpi/>). Charlson Comorbidity Index (CCI) was derived using the enhanced ICD 9/10 codes [37].

### Data Analysis

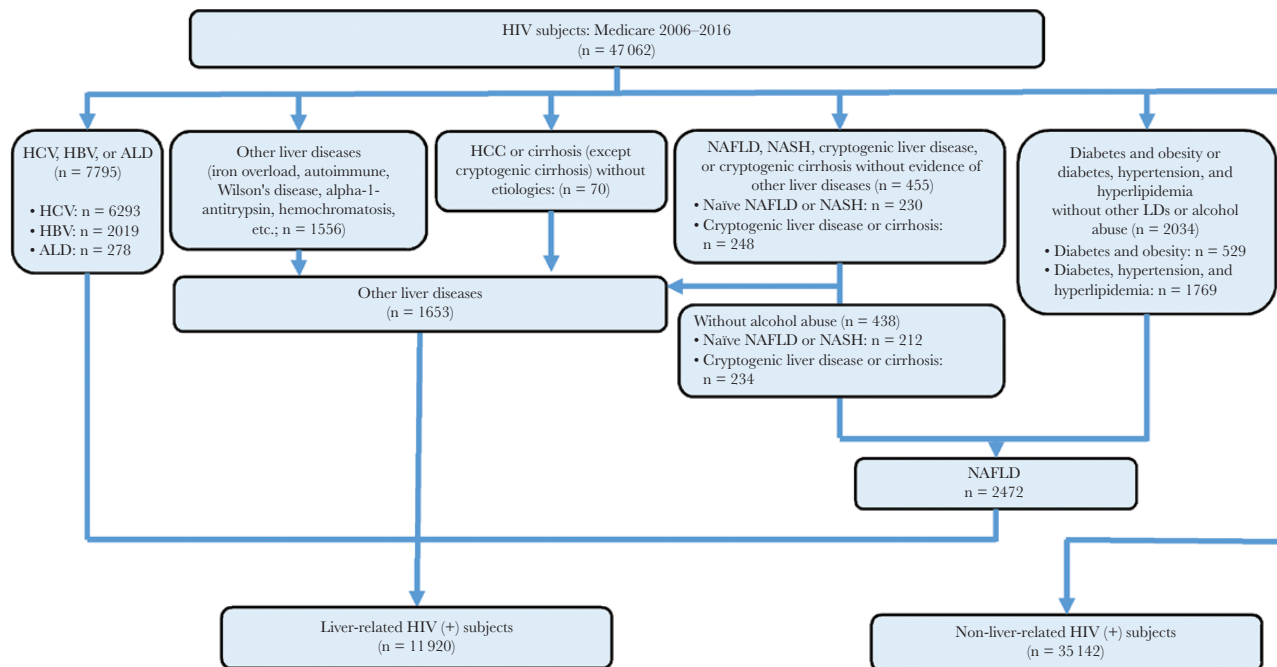
The present study was comprised of 2 components: (1) a trend analysis was performed for prevalence and mortality in Medicare patients positive for HIV with and without liver disease and (2) an association analysis was conducted to determine the impact of HIV and liver diseases on mortality and resource utilization. Temporal trend prevalence and death rates (per 100 000 Medicare population) were evaluated using the Joinpoint Regression Program (version 4.6.0.0; National Cancer Institute) with estimates of average annual percent change (AAPC). An increasing or decreasing trend was defined if the AAPC was significantly different from 0; otherwise, a stable or level trend was defined. The Cochran-Armitage test for linear trends in proportions was also performed.

After calendar year, age, gender, race/ethnicity, and beneficiary entitlement adjustments, multivariable regression analysis was performed on 1-year mortality (logistic model), charges (generalized linear regression model [GLM] with Gamma distribution), and length of stay (GLM with Poisson distribution) [38]. To show group homogeneity in our extended NAFLD definition, we performed sensitivity analyses for trends in prevalence and mortality among HIV (+) patients who were diagnosed with NAFLD through ICD codes, had cryptogenic liver disease and cirrhosis, or had a metabolic abnormality in the absence of any other cause of chronic liver disease or excessive alcohol consumption, as defined by ICD codes. All analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

### Demographics

Among 28 675 887 Medicare beneficiaries between 2006 and 2016, there were 47 062 HIV (+) patients (mean age [SD], 51.4 [11.3] years; non-Hispanic white 45.9%; non-Hispanic black 44.4%; Hispanic 6.6%; and male 74.2%). The majority of HIV



**Figure 1.** Flow diagram of the study cohort. Abbreviations: ALD, alcoholic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

(+) patients (84.9%) were receiving Medicare benefits under the category of disability or end-stage renal disease (ESRD). The highest number of HIV (+) patients observed was in the South (42.1%). Liver cancer was noted in 92 (0.2%), and cirrhosis was noted in 1319 (2.8%). The top 7 comorbidities were complications of hypertension (34.0%), followed by hyperlipidemia (27.0%), depression (15.8%), diabetes (15.4%), lung disease (14.6%), cardiovascular disease (25.6%), and renal disease (11.9%). Overall, 6.12% ( $n = 2882$ ) of HIV (+) patients died within 1 year of their encounter (Table 1).

#### Trend in Prevalence and Mortality for HIV (+) Patients in Medicare Beneficiaries

Between 2006 and 2017, the prevalence rate of HIV per 100 000 Medicare beneficiaries decreased 5.1%, with an AAPC of  $-0.5\%$  (95% CI,  $-0.8\%$  to  $-0.2\%$ ;  $P < .001$ ). The significant decrease in HIV rates occurred in 2011–2016 with an annual percent change (APC) of  $-1.9\%$ , after a continuous increase between 2006 and 2011 with an APC of  $1.0\%$ . The majority of cases occurred in males (271.1 cases per 100 000 compared with 76.9 cases per 100 000 for females). Interesting, although the HIV rate for males decreased continuously during the 2006–2016 (AAPC,  $-1.3\%$ ; 95% CI,  $-1.6\%$  to  $-1.0\%$ ;  $P < .001$ ), the rate for females actually increased until 2013 (APC,  $2.7\%$ ; 95% CI,  $1.4\%$  to  $4.0\%$ ;  $P = .002$ ) and then leveled off between 2013 and 2016 (APC,  $-3.0\%$ ; 95% CI,  $-7.0\%$  to  $1.2\%$ ;  $P = .129$ ). In fact, males and females experienced different trends for HIV ( $P < .001$ ). The rates for HIV with cardiovascular disease, diabetes, hypertension,

hyperlipidemia, and obesity (AAPC,  $3.9\%$ ,  $3.8\%$ ,  $4.1\%$ ,  $4.0\%$ , and  $15.7\%$ , respectively; all  $P < .001$ ) increased, whereas those with alcohol abuse and lipodystrophy plateaued ( $P = .112$  and  $.728$ , respectively) (Table 3). Characteristics of HIV (+) patients from 2006 to 2016 are reported in Supplementary Table 3.

The mortality rate for HIV (+) beneficiaries was 10.2 deaths per 100 000 Medicare population. The mortality rate significantly decreased from 12.5 cases in 2006 to 7.9 cases in 2016, with an AAPC of  $-5.3\%$  ( $-6.54\%$  to  $-4.04\%$ ;  $P < .001$ ). The mortality rate for HIV (+) males decreased (AAPC,  $-6.0\%$ ;  $P < .001$ ), whereas the rate for HIV (+) females leveled off ( $P = .058$ ). The mortality rates for HIV (+) with hyperlipidemia and obesity (AAPC,  $9.6\%$  and  $15.7\%$ , respectively; all  $P < .001$ ) increased, whereas the mortality rates for those with alcohol abuse decreased (AAPC,  $-4.7\%$ ;  $P = .039$ ) (Table 3).

#### Trends in Prevalence and Mortality for HIV (+) Patients by Liver Disease in Medicare Beneficiaries

During the study period, there were 11 920 (25.32%) HIV (+) beneficiaries (mean [SD] age, 51.4 [11.3] years) with liver diseases (6923 HCV, 2019 HBV, 2472 NAFLD, 278 ALD, and 1653 other liver diseases such as autoimmune, cholestatic, etc.). Compared with non-liver-related HIV (+) subjects, liver-related HIV (+) subjects were younger, more commonly male, more commonly non-Hispanic black, and less commonly non-Hispanic white, and had higher CCI scores and higher 1-year all-cause mortality (all  $P < .001$ ) (Table 1).

The overall age of liver-related HIV (+) subjects (SD) was 51.0 (11.6) years, with a range (SD) of 50.2 (9.9) for HBV to

**Table 1. Characteristics of HIV Patients, Stratified By Liver Disease Status: Medicare Population (2006–2016)**

	All HIV	Liver-Related HIV	Non-Liver-Related HIV	<i>P</i>
Subjects' Characteristics	47 062	11 920	35 142	
Age, mean ± SD, y	51.38 ± 11.28	51.01 ± 11.62	52.46 ± 10.14	<.0001
Age, No. (%)				
<65 y	40 428 (85.90)	10 394 (87.20)	30 034 (85.46)	<.0001
65–74 y	5594 (11.89)	1334 (11.19)	4260 (12.12)	.0066
≥75 y	1040 (2.21)	192 (1.61)	848 (2.41)	<.0001
Male, No. (%)	34 936 (74.23)	9065 (76.05)	25 871 (73.62)	<.0001
Race, No. (%)				
Non-Hispanic white	21 621 (45.94)	5147 (43.18)	16 474 (46.88)	<.0001
Non-Hispanic black	20 895 (44.40)	5583 (46.84)	15 312 (43.57)	<.0001
American Asian	388 (0.82)	81 (0.68)	307 (0.87)	.0429
Hispanic	3087 (6.56)	842 (7.06)	2245 (6.39)	.0101
American Native	278 (0.59)	105 (0.88)	173 (0.49)	<.0001
Other race	793 (1.69)	162 (1.36)	631 (1.80)	.0014
Region, No. (%)				
Northeast	11 887 (25.26)	3387 (28.41)	8500 (24.19)	<.0001
South	19 806 (42.08)	5095 (42.74)	14 711 (41.86)	.0920
Midwest	7044 (14.97)	1504 (12.62)	5540 (15.76)	<.0001
West	8158 (17.33)	1907 (16.00)	6251 (17.79)	<.0001
Entitlement, No. (%)				
Age	7094 (15.07)	1658 (13.91)	5436 (15.47)	<.0001
Disability/ERSD	39 968 (84.93)	10 262 (86.09)	29 706 (84.53)	<.0001
Liver cancer, No. (%)	92 (0.20)	92 (0.77)	0 (0.00)	<.0001
Cirrhosis, No. (%)	1319 (2.80)	1319 (11.07)	0 (0.00)	<.0001
Comorbidities, No. (%)				
Hypertension	15 992 (33.98)	6258 (52.50)	9734 (27.70)	<.0001
Diabetes	7225 (15.35)	3987 (33.45)	3238 (9.21)	<.0001
Hyperlipidemia	12 681 (26.95)	4262 (35.76)	8419 (23.96)	<.0001
Obese	2144 (4.56)	1027 (8.62)	1117 (3.18)	<.0001
Cardiovascular disease	6522 (13.86)	2773 (23.26)	3749 (10.67)	<.0001
Depression	7455 (15.84)	2740 (22.99)	4715 (13.42)	<.0001
Dementia	716 (1.52)	260 (2.18)	456 (1.30)	<.0001
Lung disease	6858 (14.57)	2705 (22.69)	4153 (11.82)	<.0001
Renal disease	5607 (11.91)	2628 (22.05)	2979 (8.48)	<.0001
Neurological disorder	3239 (6.88)	1337 (11.22)	1902 (5.41)	<.0001
Nonliver cancer	2101 (4.46)	751 (6.30)	1350 (3.84)	<.0001
Alcohol abuse	2193 (4.66)	1092 (9.16)	1101 (3.13)	<.0001
Lipodystrophy	687 (1.46)	251 (2.11)	436 (1.24)	<.0001
CCI, mean ± SD	7.00 ± 1.53	8.05 ± 1.84	6.64 ± 1.21	<.0001
1-y all-cause mortality, No. (%)	2882 (6.12)	1260 (10.57)	1622 (4.62)	<.0001

Abbreviations: CCI, Charlson comorbidity index; ESRD, end-stage renal disease.

56.1 (10.4) for NAFLD. The majority of liver-related HIV (+) patients were male (76.1%), with a range of 88.3% for HBV to 66.9% for NAFLD. The HIV (+) patients' race/ethnicity varied by liver disease. Non-Hispanic white and Hispanic more commonly had ALD, whereas non-Hispanic black less commonly had ALD (Table 2).

Among liver-related HIV (+) patients, 0.8% of HIV (+) patients had liver cancer, but 2.5% of HIV (+) patients with ALD had liver cancer. In addition, 11.1% had cirrhosis, but 75.5% of ALD-related HIV (+) subjects had cirrhosis. Among 5 etiology groups (NAFLD, HCV, HBV, ALD, and other liver diseases), NAFLD-related HIV (+) subjects were more likely to have hypertension,

diabetes, hyperlipidemia, and to be obese and had a higher mean CCI score (SD) of 8.5 (1.8) (Table 2). The characteristics of liver-related and non-liver-related HIV (+) patients from 2006 to 2016 are also reported in Supplementary Tables 4 and 5.

The prevalence rate for non-liver-related HIV (+) was 3 times higher than liver-related HIV (+) (123 vs 41.4 per 100 000). Between 2006 and 2016, the prevalence and mortality for non-liver-related HIV (+) decreased (AAPC, −1.1% and −9.1%; *P* values < .001). In contrast, liver-related HIV (+) prevalence increased (AAPC, 1.7%; *P* = .007) and mortality leveled off (*P* = .825) (Table 4). Joinpoint analysis showed that the prevalence rate for non-liver-related HIV (+) began to decrease

**Table 2. Characteristics of HIV Patients With Liver Disease, Stratified By Etiology: Medicare Population (2006–2016)**

	NAFLD	HCV	HBV	ALD	Other Liver Diseases <sup>a</sup>
Subjects, No.	2472	6293	2019	278	1653
Age, mean ± SD, y	56.12 ± 10.38	52.04 ± 8.97	50.18 ± 9.85	53.37 ± 9.38	50.70 ± 12.32
Age, No. (%)					
<65 y	1909 (77.22)	5708 (90.70)	1840 (91.13)	242 (87.05)	1419 (85.84)
65–74 y	474 (19.17)	546 (8.68)	158 (7.83)	30 (10.79)	187 (11.31)
≥75 y	89 (3.60)	39 (0.62)	21 (1.04)	6 (2.16)	47 (2.84)
Male, No. (%)	1654 (66.91)	4883 (77.59)	1783 (88.31)	241 (86.69)	1178 (71.26)
Race, No. (%)					
Non-Hispanic white	1073 (43.41)	2674 (42.49)	920 (45.57)	152 (54.68)	679 (41.08)
Non-Hispanic black	1109 (44.86)	2974 (47.26)	930 (46.06)	86 (30.94)	845 (51.12)
American Asian	26 (1.05)	38 (0.60)	11 (0.54)	3 (1.08)	8 (0.48)
Hispanic	190 (7.69)	484 (7.69)	116 (5.75)	25 (8.99)	89 (5.38)
American Native	15 (0.61)	61 (0.97)	23 (1.14)	11 (3.96)	8 (0.48)
Other race	59 (2.39)	62 (0.99)	19 (0.94)	1 (0.36)	24 (1.45)
Region, No. (%)					
Northeast	644 (26.05)	2093 (33.26)	533 (26.40)	62 (22.30)	317 (19.18)
South	1146 (46.36)	2474 (39.31)	815 (40.37)	121 (43.53)	845 (51.12)
Midwest	341 (13.79)	709 (11.27)	280 (13.87)	38 (13.67)	241 (14.58)
West	336 (13.59)	1001 (15.91)	388 (19.22)	56 (20.14)	245 (14.82)
Entitlement, No. (%)					
Age	600 (24.27)	662 (10.52)	196 (9.71)	37 (13.31)	237 (14.34)
Disability/ERSD	1872 (75.73)	5631 (89.48)	1823 (90.29)	241 (86.69)	1416 (85.66)
HCC, No. (%)	4 (0.16)	66 (1.05)	25 (1.24)	7 (2.52)	11 (0.67)
Cirrhosis, No. (%)	226 (9.14)	772 (12.27)	242 (11.99)	210 (75.54)	103 (6.23)
Etiology, No. (%)					
HCV	0 (0.00)	6293 (100.00)	647 (32.05)	127 (45.68)	0 (0.00)
HBV	0 (0.00)	647 (10.28)	2019 (100.00)	49 (17.63)	0 (0.00)
ALD	0 (0.00)	127 (2.02)	49 (2.43)	278 (100.00)	0 (0.00)
NAFLD	2472 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Other liver diseases <sup>a</sup>	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1653 (100.00)
Comorbidities, No. (%)					
Hypertension	2131 (86.21)	2712 (43.10)	869 (43.04)	133 (47.84)	792 (47.91)
Diabetes	2176 (88.03)	1199 (19.05)	350 (17.34)	68 (24.46)	367 (22.20)
Hyperlipidemia	1976 (79.94)	1370 (21.77)	490 (24.27)	65 (23.38)	513 (31.03)
Obese	574 (23.22)	261 (4.15)	81 (4.01)	15 (5.40)	128 (7.74)
Cardiovascular disease	712 (28.80)	1265 (20.10)	449 (22.24)	85 (30.58)	512 (30.97)
Depression	479 (19.38)	1549 (24.61)	476 (23.58)	91 (32.73)	401 (24.26)
Dementia	51 (2.06)	123 (1.95)	46 (2.28)	7 (2.52)	57 (3.45)
Lung disease	568 (22.98)	1435 (22.80)	451 (22.34)	81 (29.14)	411 (24.86)
Renal disease	651 (26.33)	1079 (17.15)	415 (20.55)	69 (24.82)	628 (37.99)
Neurological disorder	192 (7.77)	681 (10.82)	259 (12.83)	44 (15.83)	297 (17.97)
Nonliver cancer	160 (6.47)	326 (5.18)	168 (8.32)	17 (6.12)	141 (8.53)
Alcohol abuse	0 (0.00)	719 (11.43)	208 (10.30)	278 (100.00)	142 (8.59)
Lipodystrophy	116 (4.69)	93 (1.48)	24 (1.19)	1 (0.36)	24 (1.45)
CCI, mean ± SD	8.49 ± 1.80	7.84 ± 1.79	7.99 ± 1.92	9.45 ± 2.18	8.32 ± 1.95
CCI, median (Q1–Q3)	8 (7–9)	7 (7–9)	7 (7–9)	9 (8–11)	8 (7–9)
1-y all-cause mortality, No. (%)	173 (7.00)	640 (10.17)	274 (13.57)	85 (30.58)	268 (16.21)

Abbreviations: CCI, Charlson comorbidity index; ESRD, end-stage renal disease; LD, liver disease.

<sup>a</sup>Includes autoimmune, Wilson's disease, hemochromatosis, iron overload, alpha-1-antitrypsin deficiency, Budd-Chiari syndrome, cholangitis, liver disorders, and unknown etiologies for hepatocellular carcinoma, cirrhosis, and liver failure.

annually (APC,  $-2.4\%$ ;  $P < .001$ ) after a stable trend in the 2006–2010 period (APC,  $0.8\%$ ;  $P = .187$ ), whereas the prevalence for liver-related HIV (+) increased annually until 2012 (APC,  $1.7\%$ ;  $P < .001$ ) and then stabilized between 2012 and 2016 (APC,  $-0.5\%$ ;  $P = .676$ ) (Figure 2).

In 2016, HCV was the leading cause of liver-related HIV (+) (46.6%), followed by NAFLD (27.7%), HBV (14.3%), other LDs (13.5%), and ALD (2.5%) (Table 4). Among liver diseases, NAFLD was the driver of the increase in the prevalence rate for liver-related HIV (+) with an AAPC increase of  $9.7\%$  ( $P < .001$ ),

**Table 3. Prevalence and Mortality for those with HIV (per 100 000 Medicare Population): Medicare Population 2006–2016**

Prevalence of HIV (per 100 000): Medicare Population (2006–2016)				
	Count (Rate per 100 000), No. (%)			Average APC
	2006–2016a	2006	2016	
HIV	47 062 (164.36)	3702 (162.83)	4614 (154.45)	–0.49 (–0.75 to –0.22) <sup>b</sup>
Sex				
Female	12 126 (76.85)	857 (67.68)	1251 (77.13)	0.95 (–0.29 to 2.21)
Male	34 936 (271.06)	2845 (282.46)	3363 (246.32)	–1.34 (–1.63 to –1.04) <sup>b</sup>
HIV with				
Alcohol abuse	2193 (7.68)	209 (9.19)	222 (7.43)	–1.34 (–3.02 to 0.38)
CVD	6522 (22.50)	427 (18.78)	826 (27.65)	3.88 (2.84 to 4.94) <sup>b</sup>
Diabetes	7225 (24.93)	467 (20.54)	866 (28.99)	3.77 (2.82 to 4.73) <sup>b</sup>
Hypertension	15 992 (55.17)	956 (42.05)	1987 (66.51)	4.12 (2.86 to 5.40) <sup>b</sup>
Hyperlipidemia	12 681 (43.78)	717 (31.54)	1450 (48.54)	3.98 (2.63 to 5.35) <sup>b</sup>
Obese	2144 (7.20)	69 (3.03)	344 (11.52)	15.16 (12.16 to 18.24) <sup>b</sup>
Lipodystrophy	687 (2.42)	51 (2.24)	47 (1.57)	–1.31 (–8.40 to 6.32)
Mortality for HIV (per 100 000): Medicare Population (2006–2016)				
	Count (Rate per 100 000), No. (%)			Average APC
	2006–2016 <sup>a</sup>	2006	2016	
Overall	2882 (10.21)	284 (12.49)	237 (7.93)	–5.30 (–6.54 to –4.04) <sup>b</sup>
Sex				
Female	662 (4.25)	56 (4.42)	55 (3.39)	–3.69 (–7.40 to 0.16)
Male	2220 (17.49)	228 (22.64)	182 (13.33)	–5.98 (–7.05 to –4.89) <sup>b</sup>
HIV with:				
Alcohol abuse	250 (0.88)	31 (1.36)	18 (0.6)	–4.75 (–8.99 to –0.31) <sup>b</sup>
CVD	1161 (4.05)	90 (3.96)	126 (4.22)	–0.14 (–3.05 to 2.86)
Diabetes	653 (2.27)	44 (1.94)	63 (2.11)	1.39 (–1.96 to 4.85)
Hypertension	1396 (4.86)	101 (4.44)	144 (4.82)	0.40 (–1.78 to 2.62)
Hyperlipidemia	533 (1.81)	16 (0.7)	77 (2.58)	9.6 (5.24 to 14.15) <sup>b</sup>
Obese	94 (0.32)	1 (0.04)	12 (0.4)	21.75 (8.04 to 37.21) <sup>b</sup>

Average annual percent change is a weighted average of the APCs (a maximum of 2 joinpoints was allowed).

Abbreviations: APC, annual percent change; CVD, cardiovascular disease.

<sup>a</sup>Rates were averaged across 2006–2016.

<sup>b</sup>Significantly different from 0 ( $P < .05$ ).

whereas HBV had an AAPC decrease of –3.4% ( $P < .001$ ) and HCV, ALD, and other liver diseases were noted to have stable trends (Figure 3 and Table 4).

Of 2882 HIV (+) patients who died, 1260 had liver diseases (640 HCV, 274 HBV, 173 NAFLD, 85 ALD, and 268 other liver diseases). During the study period, worsening trends in mortality for NAFLD-related diagnosis in HIV (+) subjects were observed (AAPC, 10.0%;  $P = .018$ ), as compared with improving trends for HBV- and HCV-related HIV (+) (HBV: AAPC, –8.8%;  $P < .001$ ; HCV: AAPC, –4.9%;  $P = .033$ ) and stable trends for ALD and other-liver-related HIV (+) ( $P = .172$  and  $.068$ ).

As a sensitivity analysis, each classification used for our extended NAFLD definition experienced similar increasing trends in prevalence (pairwise comparison for test of parallelism: all  $P > .05$ ), demonstrating the homogeneity of our extended NAFLD definition (Supplemental Table 6). This result suggests that we did not inadvertently increase the

prevalence of NAFLD through the use of our NAFLD definition. In addition, similar increasing trends in mortality for each definition were also confirmed by biennial or triennial trend analyses. Of note, annual trend analysis was not possible because of a small event size (data not shown).

In the multivariate analysis after adjustments for calendar year, age, sex, race/ethnicity, region, and beneficiary entitlement, the presence of liver disease was associated with an increased risk of 1-year mortality compared with those with HIV but without liver disease: HCV (odds ratio [OR], 2.00; 95% CI, 1.24–1.72), HBV (OR, 2.40; 95% CI, 2.09–2.77), ALD (OR, 5.70; 95% CI, 4.34–7.48), and NAFLD (OR, 1.46; 95% CI, 1.24–1.72) (Table 5).

#### Health Care Utilization Among HIV (+) Patients With Liver Disease

Overall, 24.7% of HIV+ patients were hospitalized with a mean length of stay (LOS) of  $14.2 \pm 24.5$  days (median LOS [IQR],

**Table 4. Prevalence and Mortality for HIV, by Liver Diseases (per 100 000 Medicare Population (2006–2016))**

Prevalence for HIV, by Liver Diseases (per 100 000 Medicare Population (2006–2016))				
	Count (Rate per 100 000), No. (%)			Average APC
	2006–2016a	2006	2016	
Non-liver-related HIV	35 142 (122.99)	2868 (126.15)	3338 (111.74)	-1.13 (-1.63 to -0.63) <sup>c</sup>
Liver-related HIV	11 920 (41.37)	834 (36.68)	1276 (42.71)	1.68 (0.45 to 2.92) <sup>c</sup>
NAFLD	2472 (8.42)	92 (4.05)	353 (11.82)	9.72 (6.69 to 12.84) <sup>c</sup>
HCV	6293 (21.99)	519 (22.83)	595 (19.92)	-0.67 (-1.44 to 0.10)
HBV	2019 (7.11)	187 (8.23)	182 (6.09)	-3.46 (-4.81 to -2.08) <sup>c</sup>
ALD	278 (0.96)	21 (0.92)	32 (1.07)	1.93 (-1.50 to 5.48)
Other liver diseases <sup>b</sup>	1653 (5.71)	104 (4.57)	172 (5.76)	2.86 (-0.94 to 6.80)

Mortality for HIV, by Liver Diseases (per 100 000 Medicare population (2006–2016))				
	Count (Rate per 100 000)			Average APC
	2006–2016 <sup>a</sup>	2006	2016	
Non-liver-related HIV	1622 (5.81)	185 (8.14)	109 (3.65)	-9.14 (-11.02 to -7.22) <sup>c</sup>
Liver-related HIV	1260 (4.39)	99 (4.35)	128 (4.28)	-0.29 (-3.18 to 2.68)
NAFLD	173 (0.58)	1 (0.04)	22 (3.65)	10.01 (2.05 to 18.6) <sup>c</sup>
HCV	640 (2.26)	74 (3.25)	64 (2.14)	-4.85 (-9.00 to -0.51) <sup>c</sup>
HBV	274 (0.98)	33 (1.45)	20 (0.67)	-8.78 (-11.20 to -6.29) <sup>c</sup>
ALD	85 (0.3)	10 (0.44)	5 (0.17)	-6.37 (-15.32 to 3.52)
Other liver diseases <sup>b</sup>	268 (0.91)	9 (0.4)	27 (0.9)	7.2 (-0.51 to 15.51)

Average annual percent change is a weighted average of the APCs (a maximum of 2 joinpoints was allowed).

Abbreviations: ALD, alcoholic liver disease; APC, annual percent change; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease.

<sup>a</sup>Rates were averaged across 2006–2016.

<sup>b</sup>Include autoimmune, Wilson disease, hemochromatosis, iron overload, alpha-1-antitrypsin deficiency, Budd-Chiari syndrome, cholangitis, liver disorders, and unknown etiologies for HCC, cirrhosis, and liver failure.

<sup>c</sup>Significantly different from 0 ( $P < .05$ ).

7 [3–17] days), and 7.3% of patients died while hospitalized. The mean inpatient charge was \$116 234 ± \$218 248, whereas the mean inpatient payment was \$3646 ± \$52 356. On average, overall, HIV+ patients experienced 4.0 ± 4.3 (median [IQR], 3 [1–5] visits) outpatient visits per year with a mean outpatient charge of \$6450 ± \$18 225 and a mean outpatient payment of \$1423 ± \$4038 (Supplementary Table 7).

Among those who were HIV+ with LDs, those with HBV had the longest LOS at 19.3 ± 33.0 days, with 10.1% of this group dying while hospitalized, compared with those HIV (+) but without LDs, whose mean LOS was 12.6 ± 25.3 days (median [IQR], 6 [3–14] days; 6.1% died while hospitalized). The mean inpatient charges were also highest for those with HBV at \$165 621 ± \$230 073 (median [IQR], \$78 044 [\$33 676–\$205 663]) with a mean inpatient payment of \$53 352 ± \$63 925 (median [IQR], \$26 984 [\$16 063–\$65 417]), compared with those who were HIV (+) without LDs, whose mean inpatient charge was \$95 659 ± \$160 403 (median [IQR], \$44 993 [\$21 461–\$99 404]). (Supplementary Table 7).

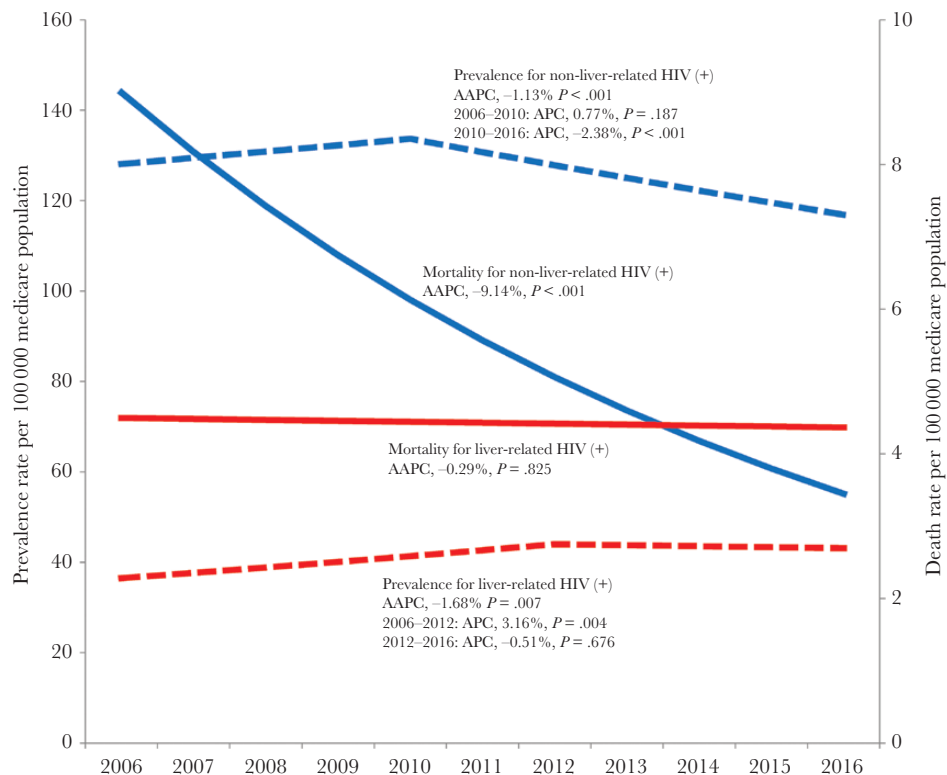
Predictors for longer inpatient stays are noted in Table 5. For both groups, those with HBV experienced greater odds of

having a longer length of stay and greater inpatient charges and outpatient charges.

## DISCUSSION

Over the past few decades, treatment of HIV infection has changed this highly lethal disease to a manageable chronic disease. Nevertheless, as AIDS-related deaths among HIV (+) patients have declined, death from HCV-related liver disease has become an important cause of death [14]. This paradigm has also shifted with the advent of the highly effective DAAs for HCV treatment [39–41]. In contrast, the epidemic of NAFLD is affecting all sectors of the society and may impact the long-term outcome of HIV-infected patients. Therefore, we sought to assess the prevalence and outcomes of different liver diseases in HIV (+) Medicare beneficiaries in the United States [42].

Overall, our results indicated that the prevalence of HIV among Medicare beneficiaries has been decreasing over the past decade (2006–2016). However, this overall decrease showed some gender differences, with leveling off of the rates of HIV positivity for female subjects. These same findings were noted when reviewing the deaths among Medicare beneficiaries with



**Figure 2.** Prevalence and mortality rates for HIV+ Medicare patients with/without liver disease from 2006 to 2016. Abbreviations: AAPC, average annual percent change; APC, annual percent change.

HIV. In this context, the overall deaths per 100 000 significantly decreased over the study time frame an average of 5.30% per year, primarily in men, without significant decreases in the female subjects.

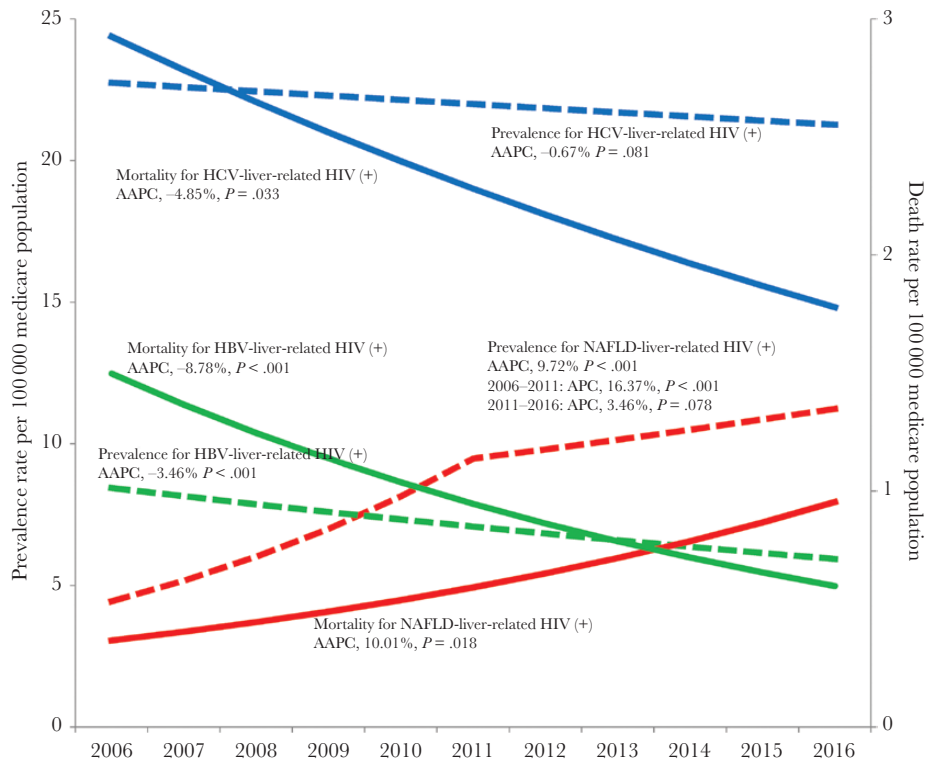
We also found that among this group of Medicare beneficiaries with HIV, 22% had some form of liver disease. Viral hepatitis was still the most prevalent disease, followed by NAFLD. Interestingly, although the prevalence of viral hepatitis decreased at an average rate of 0.9% per year, the prevalence of NAFLD significantly increased at an average of 7.2% per year, primarily between 2006 and 2011. This was not only significant for the prevalence rates of different liver diseases, but also death rates related to different types of liver disease. This may have important ramifications as HIV+ patients with NAFLD may have more rapid progression of their liver disease, so it becomes imperative to effectively work and counsel patients to provide the most appropriate treatment [42].

Although previous studies have suggested that the presence of viral hepatitis in HIV (+) patients hastens disease progression and possibly death [43–46], our study highlights the changing profile of liver disease from viral hepatitis to NAFLD in HIV (+) subjects. This is an urgent issue, as NAFLD is expected to become more common among those with HIV, who are now living longer and are thus more at risk for developing chronic diseases such as T2DM and NAFLD.

In addition, HIV (+) patients on the newer HIV treatments have been reported to be at a higher risk for obesity and type 2 diabetes, both metabolic conditions associated with NAFLD [20–24, 47]. In fact, in our study, we found that among those with HIV, the prevalence of obesity increased an average of 15.16% per year from 2006–2016, whereas lipodystrophy, a condition associated with the older HIV treatments, has plateaued. The change in the prevalence of obesity carried over to mortality, where among those with HIV and obesity there was an increasing trend of mortality, an average of 21.75% per year. Nevertheless, it is important to recognize that the sample size is small and caution must be exercised when interpreting these results. Type 2 diabetes mellitus and cardiovascular disease followed the same stable trends over time. Nonetheless, we recommend further study to investigate the impact of the newer HIV therapies, the obesogenic environment, and genetic links on this rapid rise in obesity, especially as it is obesity, which is helping to drive the global increase in NAFLD [11, 12, 20–24, 47].

On the other hand, it is important to note that our results suggest a significant decrease in the prevalence and death rates from viral hepatitis in HIV (+) patients. This trend is probably a result of the new curative treatment regimens for HCV that have been shown to be very successful in patients coinfecting with HIV while at the same improving patients' health-related quality of life, work





**Figure 3.** Prevalence and mortality rates for HIV+ Medicare patients with nonalcoholic fatty liver disease, hepatitis C virus, and hepatitis B virus from 2006 to 2016. Abbreviations: AAPC, average annual percent change; APC, annual percent change; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease.

productivity, and levels of fatigue [39, 40, 42, 48]. The same holds true for those with HBV, as there are now excellent suppressive therapies for HBV infection. In fact, the nucleotide analogs such as tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) have activity against both HIV and HBV, and the recommended treatment regimen for patients with both HIV and HBV includes (TAF or TDF) plus emtricitabine (FTC) or lamivudine (3TC) as the nucleoside reverse transcriptase inhibitor [46].

In addition to mortality outcomes, we assessed resource utilization in this group of patients. Our analyses show that HIV (+) patients with liver diseases do have a significant health care resource utilization burden. As noted in this study, compared with those with HIV but without liver disease, HIV (+) patients with

liver disease had longer length of hospital stays, higher inpatient mortality, higher hospital charges, more outpatient visits, and higher outpatient charges. The exact mechanism of the increased utilization was not investigated in this study; however, as noted in previous studies, the likely causes may not be just liver related but rather related to the number of comorbidities that these patients may now have as they live longer, and as seen in the higher CCI among those with HIV and liver disease vs those without. This is especially concerning for those with HIV and NAFLD as the latest economic forecasts for patients with NAFLD indicate a significant economic burden by the year 2030 due to the vast number of people who may be affected by NAFLD unless better diagnostic tools and treatments become available [49, 50].

**Table 5. One-Year All-Cause Mortality, Total Charges, and Length of Stay Among HIV Patients, by Liver Diseases: Medicare Population (2006–2016)**

	1-y All-Cause Mortality	Length of Stay	Total Charges	
			Inpatient	Outpatient
	OR (95% CI)	% Change (95% CI)	% Change (95% CI)	% Change (95% CI)
NAFLD	1.46 (1.24 to 1.72)	24.58 (14.80 to 35.20)	58.73 (50.50 to 67.41)	12.31 (9.94 to 14.74)
HCV	2.00 (1.81 to 2.21)	39.61 (32.67 to 46.90)	50.82 (45.57 to 56.26)	29.65 (28.09 to 31.23)
HBV	2.40 (2.09 to 2.77)	45.26 (34.61 to 56.76)	75.70 (64.98 to 87.13)	48.99 (46.58 to 51.43)
ALD	5.70 (4.34 to 7.48)	15.26 (−0.50 to 33.53)	60.75 (26.4 to 104.43)	17.25 (13.32 to 21.31)

All models were adjusted for calendar year, age, sex, race/ethnicity, region, and beneficiary entitlement.

Abbreviations: ALD, alcoholic liver disease; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

There are several study limitations that we need to acknowledge. First, because the diagnoses of HIV positivity and liver diseases were based on electronic medical record and ICD codes, some misclassification may have occurred. In this context, there is a possibility of a systematic under- or overcoding of medical conditions known to be less or more common. Indeed, we found that hypertension, hyperlipidemia, obesity, alcohol abuse, and NAFLD were underestimated (ie, HIV patients with metabolic abnormalities were classified as not having these conditions). Such a misclassification would lead to an underestimation of such disease states and bias our results and potentially attenuate the effect of NAFLD on mortality and health utilization. This is an inherent limitation of Medicare data. Second, to mitigate the likelihood of misclassification of NAFLD, we extended the definition of NAFLD to include metabolic dysfunction and obesity in the absence of other cause of liver diseases or alcohol abuse. Our extended definition of NAFLD has been validated with the use of NHANES data and the USFLI, a reliable surrogate for the clinical diagnosis of NAFLD in the US population [36]. Unfortunately, we were not able to validate the definition with liver biopsies; however, this diagnostic method is impractical for population-based studies such as NHANES and Medicare. Therefore, we also conducted a sensitivity analysis on our extended NAFLD definition and determined the homogeneity of the NAFLD subgroup for temporal trends in prevalence and mortality. However, readers are cautioned to think of NAFLD as presumed NAFLD, as we discussed earlier.

Regardless of these efforts, there may remain potential biases where ALD may have been misclassified as NAFLD due to the known under-reporting of ALD and excessive alcohol use in Medicare data [51, 52]. As such, caution must be used when interpreting our resource utilization findings, as they may not be solely attributed to NAFLD. Third, our follow-up was only a year after the medical encounter and the specific cause of death was not available in the Medicare data, which limits any robust interpretation of the mortality study results. Fourth, it is important to note that we were unable to distinguish the presence of nonalcoholic steatohepatitis (NASH), the more progressive form of NAFLD, or the stage of fibrosis, which is the main driver of liver-related mortality in patients with NAFLD [53]. We do recognize that the use of our extended definition of NAFLD to include metabolic dysfunction and obesity may have led to a bias of overestimating the impact of NAFLD on mortality, although we do not believe this to be the case, as was demonstrated in our sensitivity analysis. But, as we have reported previously, among those with presumed NAFLD, we do acknowledge that the risk of mortality increases as the number of metabolic components present increases, a result that was also demonstrated in this study [54].

Finally, we recognize that our findings may not be generalizable to the general population as our patient population received their medical care through the governmental system,

Medicare, where the majority of patients' beneficiary status was based on their disability rather than age, such that their characteristics may be quite different than those patients whose health care expenses are covered through commercial or private insurance sectors. One must also keep in mind that some of the statistical results we have reported may be statistically significant but not relevant to clinical practice; for example, the ages at which we found a statistical difference between the groups were 51 vs 52. However, what is important to note is that the trend for aging was significant in that the HIV (+) population, which has become significantly older; this may hold clinical implications.

In summary, our results show that the prevalence of HIV among the Medicare population and the prevalence of liver disease among HIV (+) Medicare beneficiaries have decreased from 2011 to 2016. This decline in liver disease in HIV (+) subjects is most likely due to the introduction of curative treatment regimens for HCV and excellent viral suppressive drugs for HBV. However, despite the overall decrease, there was a significant increase in the prevalence of presumed NAFLD among those with HIV, a trend that is consistent worldwide for NAFLD alone. In fact, NAFLD may increase even more within the HIV (+) population compared with the general population due to newer cART therapy and its relationship with increased obesity. These results have substantial importance as the overall 1-year mortality decreased for all groups of HIV (+) patients with liver disease except for those with presumed NAFLD. In addition to prevalence and mortality, liver disease in HIV (+) Medicare beneficiaries was responsible for substantial high health care resource utilization. Given the increasing clinical and economic impact of NAFLD in HIV (+) patients, clinicians must be more vigilant in identifying and managing NAFLD in this patient population. Additionally, these data should inform policy-makers, payers, providers, and the pharmaceutical industry to better understand NAFLD among HIV (+) subjects and develop strategies to deal with NAFLD in a fashion similar to other important liver diseases such as HBV and HCV among patients with HIV.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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