MAJOR ARTICLE

Predicting Risk of End-Stage Liver Disease in Antiretroviral-Treated Human Immunodeficiency Virus/Hepatitis C Virus-Coinfected Patients

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Background. End-stage liver disease (ESLD) is an important cause of morbidity among human immunodeficiency virus (HIV)/hepatitis C virus (HCV)-coinfected patients. Quantifying the risk of this outcome over time could help determine which coinfected patients should be targeted for risk factor modification and HCV treatment. We evaluated demographic, clinical, and laboratory variables to predict risk of ESLD in HIV/HCV-coinfected patients receiving antiretroviral therapy (ART).

Methods. We conducted a retrospective cohort study among 6016 HIV/HCV-coinfected patients who received ART within the Veterans Health Administration between 1997 and 2010. The main outcome was incident ESLD, defined by hepatic decompensation, hepatocellular carcinoma, or liver-related death. Cox regression was used to develop prognostic models based on baseline demographic, clinical, and laboratory variables, including FIB-4 and aspartate aminotransferase-to-platelet ratio index, previously validated markers of hepatic fibrosis. Model performance was assessed by discrimination and decision curve analysis.

Results. Among 6016 HIV/HCV patients, 532 (8.8%) developed ESLD over a median of 6.6 years. A model comprising FIB-4 and race had modest discrimination for ESLD (c-statistic, 0.73) and higher net benefit than alternative strategies of treating no or all coinfected patients at relevant risk thresholds. For FIB-4 >3.25, ESLD risk ranged from 7.9% at 1 year to 26.0% at 5 years among non-blacks and from 2.4% at 1 year to 14.0% at 5 years among blacks.

Conclusions. Race and FIB-4 provided important predictive information on ESLD risk among HIV/HCV patients. Estimating risk of ESLD using these variables could help direct HCV treatment decisions among HIV/HCV-coinfected patients.

Keywords. end-stage liver disease; hepatic decompensation; HIV; hepatitis C; HIV/HCV coinfection.

Chronic hepatitis C virus (HCV) coinfection is common among patients with human immunodeficiency virus (HIV) infection [1]. Liver fibrosis progression is accelerated in HIV/HCV-coinfected patients [2], and

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rates of hepatic decompensation are higher among coinfected than HCV-monoinfected patients, even if HIV RNA is fully suppressed on antiretroviral therapy (ART) [3], Consequently, end-stage liver disease (ESLD) has emerged as an important cause of morbidity in this population [3–5].

Despite the clinical impact of HCV-related ESLD in coinfected patients, no models have been developed using readily available demographic, clinical, and laboratory characteristics to predict the risk of ESLD within a specified time period. Quantifying ESLD risk over time could prompt clinicians and patients to aggressively address modifiable risk factors for this condition (e.g., hazardous alcohol use; uncontrolled diabetes; severe anemia; detectable HIV viremia due to ART nonadherence; and/or resistance [3]) and identify subgroups of patients who should be followed closely for liver complications. Because highly efficacious and well tolerated, but costly, all-oral direct-acting antivirals for HCV treatment are now available [6, 7], a prognostic model for ESLD in coinfected patients could help prioritize the need for HCV therapy among HIV/HCV patients, who have an urgent need for HCV treatment [3].

We previously identified important risk factors for hepatic decompensation among HIV/HCV patients on ART [3]. In this study, we evaluated and compared alternative models comprising demographic, clinical, and laboratory variables to determine which combination of predictors can best classify HIV/HCV patients according to their risk of progression to ESLD over time. Because liver fibrosis stage is an important factor used to determine the urgency and timing of HCV therapy [8], we first evaluated the prognostic ability of 2 noninvasive markers of hepatic fibrosis (FIB-4 and aspartate aminotransferase-to-platelet ratio index [APRI]) that can be calculated from routinely measured laboratory data (i.e., liver aminotransferases, platelet count). We then evaluated whether the addition of clinical and demographic variables improved the predictive ability of these indices.

METHODS

Study Design and Data Source

We conducted a retrospective cohort study among ART-treated HIV/HCV-coinfected patients in the Veterans Aging Cohort Study (VACS) between January 1, 1997 and September 30, 2010 [9]. The Veterans Aging Cohort Study consists of electronic medical record data from HIV-infected patients receiving care at Veterans Affairs (VA) medical facilities across the United States. Data include demographic characteristics, hospital and outpatient diagnoses (recorded using International Classification of Diseases, Ninth Revision [ICD-9] codes), procedures, laboratory results, and dispensed medications. Clinically confirmed cancer diagnoses are identified using the VA Central Cancer Registry. Date of death was ascertained from the VA Vital Status file [10]. The underlying cause of death was determined by linkage with the National Death Index (NDI). [11] This study was approved by the Institutional Review Boards of the University of Pennsylvania and Philadelphia VA Medical Center.

Study Patients

Coinfected patients were included if they had: (1) HIV (identified using a validated algorithm [9]), (2) detectable HCV RNA, and (3) received ART, defined as use of at least 3 antiretrovirals from 2 different classes [12], for at least 12 months. We included only coinfected patients on ART because current guidelines recommend ART in all HIV/HCV patients regardless of CD4 count [12]. The majority of Veterans receive their medications from VA pharmacies [13, 14], and prior studies have shown the validity of VA dispensing data as a surrogate of actual adherence [15–18]. Patients were excluded if prior to start of follow-up (defined below), they had ESLD or received interferon-based therapy (because such treatment can affect noninvasive markers of hepatic fibrosis and reduces risk of ESLD [19]).

Follow-up began after 12 months on ART. The 12 months before the start of follow-up represented the baseline period, during which predictors were ascertained. Follow-up continued until study endpoint, death, initiation of HCV therapy, or last visit before September 30, 2010.

Main Study Outcome

The primary endpoint was ESLD, defined as hepatic decompensation, hepatocellular carcinoma, or liver-related death. Hepatic decompensation was determined by 1 hospital discharge ICD-9 diagnosis or 2 or more outpatient ICD-9 diagnoses of ascites, spontaneous bacterial peritonitis, or esophageal variceal hemorrhage (Supplementary Appendix 1). The requirement of 2 outpatient diagnoses aimed to exclude events that were suspected, but not subsequently confirmed, at follow-up visits. We validated this definition in a prior survey, with 91% of events confirmed by medical records [20]. Based on the results of the prior validation study [20], we did not include ICD-9 diagnoses for hepatic encephalopathy or jaundice, which could indicate decompensation, because these diagnoses were often linked to unrelated conditions (e.g., narcotic overuse, stroke recorded as encephalopathy; biliary obstruction, atazanavir-associated hyperbilirubinemia recorded as jaundice). The date of decompensation was defined as the hospital discharge date (if identified by hospital diagnosis) or initial outpatient diagnosis date (if identified by outpatient diagnoses). Hepatocellular carcinoma was determined using the VA Central Cancer Registry, which confirms diagnoses by histology, cytology, or consistent radiography. Deaths were considered liver-related if the underlying cause of death in the NDI was hepatic decompensation, liver cancer, alcoholic liver disease, viral hepatitis, or nonalcoholic liver disease [3]. The date of ESLD was defined as the initial date of hepatic decompensation, hepatocellular carcinoma, or death from liver disease, whichever occurred first.

Data Collection

Baseline variables evaluated as predictors of ESLD included the following: FIB-4 (<1.45; 1.45–3.25; >3.25), APRI (<1.0; 1.0–2.0; >2.0), age, body mass index ([BMI] <18.5; 18.5–24.9; 25.0–30.0; >30.0 kg/m^2), severe anemia (hemoglobin <10 g/dL), CD4 cell count <200 cells/mm^3, HIV RNA >400 copies/mL, alcohol dependence/abuse, diabetes mellitus, hepatitis B coinfection, and nonblack race, which have been shown to be risk factors for advanced liver disease in coinfected patients [3, 19, 21]. FIB-4 is a measure of liver fibrosis stage that was developed and validated compared with liver biopsy in HIV/HCV-coinfected patients [22]. It is calculated from age, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count: FIB-4 = (age [years] × AST [U/L])/((platelet count [10^9/L]) × (ALT [U/L])$^{1/2}$). FIB-4 <1.45 identifies no/minimal FIB, whereas results >3.25 indicate advanced hepatic FIB/cirrhosis [22]. APRI, another noninvasive measure of hepatic fibrosis, uses AST and platelet count: APRI = ([AST [U/L]/upper limit of normal [considered as 40 U/L])/platelet count (10^9/L)] × 100 [23]. An APRI >2.0 identifies cirrhosis in chronic HCV, and APRI <0.5 identifies no or minimal FIB [23]. We collected ALT, AST, platelet count, body weight, hemoglobin, CD4 count, and HIV RNA results measured closest to, but prior to, the start of follow-up. Alcohol dependence/abuse was defined by previously validated ICD-9 diagnoses (Supplementary Appendix 1) [24]. Diabetes was defined by random glucose ≥200 mg/dL, ICD-9 diagnosis, and/or antidiabetic medication use [25]. Hepatitis B coinfection was defined by a positive hepatitis B surface antigen. Additional variables collected at baseline for descriptive purposes included sex, HCV genotype, and HCV RNA.

Statistical Analysis

We used Cox regression to estimate the relative hazards of ESLD (with 95% confidence intervals) for the predictors of interest [26]. We also evaluated FIB-4, APRI, hemoglobin, CD4 count, and HIV RNA level as continuous variables.

Next, because the stage of hepatic fibrosis is a strong determinant of ESLD [3, 19] and an important factor in the decision to initiate HCV therapy [8], we initially created separate models comprising FIB-4 and APRI alone. We then developed 2 separate lines of prognostic models with FIB-4 and APRI as the base models, respectively. Various combinations of the other predictors were added to the base models, including an interaction term for race. Age is a component of FIB-4 and so was not included in FIB-4 models.

Each model's performance was assessed by statistical significance and discrimination, using the concordance statistic (c-statistic) as an index of the model's ability to separate persons who will develop ESLD from those who will not [27]. We favored simpler models with fewer predictors that had appreciably different c-statistics from those of FIB-4 or APRI-based

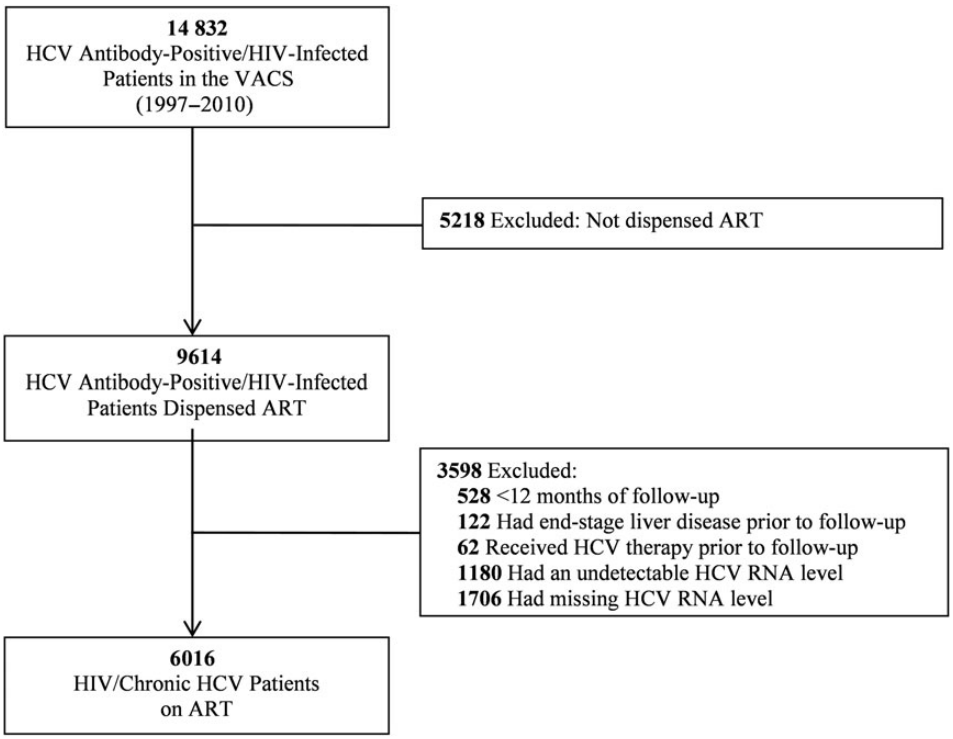


Figure 1. Selection of Veterans Aging Cohort Study (VACS) human immunodeficiency virus (HIV)/hepatitis C virus (HCV)-coinfected patients for inclusion in the study. Abbreviation: ART, antiretroviral therapy.

Table 1. Baseline Characteristics of the HIV/Hepatitis C Virus (HCV)-Coinfected Patients Included in the Study Sample, Overall and By End-Stage Liver Disease Status[a]

Characteristic	Overall (n = 6016)	End-Stage Liver Disease (n = 532)	No End-Stage Liver Disease (n = 5484)	*P* Value
Median age (years, IQR)	48 (44–53)	49 (45–53)	48 (44–52)	.061
Male sex	5929 (98.6)	532 (100.0)	5397 (98.4)	.003
Race/ethnicity				<.001
Black	3794 (63.1)	264 (49.6)	3530 (64.4)	
Caucasian	1474 (24.5)	164 (30.8)	1310 (23.9)	
Hispanic	576 (9.6)	89 (16.7)	487 (8.9)	
Other/Unknown	172 (2.9)	15 (2.8)	157 (2.9)	
Body mass index				.64
<18.5 kg/m^2	179 (3.0)	13 (2.4)	166 (3.0)	
18.5–24.9 kg/m^2	3045 (50.6)	259 (48.7)	2786 (50.8)	
25–29.9 kg/m^2	1969 (32.7)	188 (35.3)	1781 (32.5)	
≥30 kg/m^2	661 (11.0)	56 (10.5)	605 (11.0)	
Missing weight and/or height	162 (2.7)	16 (3.0)	146 (2.7)	
Diabetes mellitus	483 (8.0)	47 (8.8)	436 (8.0)	.47
History of alcohol dependence/abuse	1506 (25.0)	132 (24.8)	1374 (25.1)	.90
HCV genotype				.18
1 or 4	3553 (59.1)	306 (57.5)	3247 (59.2)	
2 or 3	456 (7.6)	31 (5.8)	425 (7.7)	
Other	14 (0.2)	2 (0.4)	12 (0.2)	
No result available	1993 (33.1)	193 (36.3)	1800 (32.8)	
HCV RNA[b]				.005
≥400 000 IU/mL and/or ≥ 1 000 000 copies/mL	4514 (75.0)	371 (69.7)	4143 (75.5)	
<400 000 IU/mL and/or <1 000 000 copies/mL	647 (10.8)	62 (11.7)	585 (10.7)	
Qualitative HCV RNA result only	855 (14.2)	99 (18.6)	756 (13.8)	
Hepatitis B surface antigen				.031
Positive	263 (4.4)	33 (6.2)	230 (4.2)	
Negative	5268 (87.6)	466 (87.6)	4802 (87.6)	
No result available at baseline	485 (8.1)	33 (6.2)	452 (8.2)	
Median HIV RNA (copies/mL, IQR)	400 (75–4870)	400 (179–3726)	400 (75–4905)	.080
HIV RNA				.66
>400 copies/mL	2534 (42.1)	233 (43.8)	2301 (42.0)	
≤400 copies/mL	3245 (54.0)	277 (52.1)	2968 (54.1)	
No result available at baseline	237 (3.9)	22 (4.1)	215 (3.9)	
Median CD4 cell count (cells/mm^3, IQR)	320 (180–491)	294 (159–484)	322 (182–492)	.043
CD4 cell count				.23
≥500 cells/mm^3	1377 (22.9)	113 (21.2)	1264 (23.0)	
350–499 cells/mm^3	1156 (19.2)	94 (17.7)	1062 (19.4)	
200–349 cells/mm^3	1544 (25.7)	135 (25.4)	1409 (25.7)	
<200 cells/mm^3	1629 (27.1)	166 (31.2)	1463 (26.7)	
No result available at baseline	310 (5.2)	24 (4.5)	286 (5.2)	
Hemoglobin				.29
<10 g/dL	161 (2.7)	18 (3.4)	143 (2.6)	
≥10 g/dL	5820 (96.7)	509 (95.7)	5311 (96.8)	
No result available at baseline	35 (0.6)	5 (0.9)	30 (0.5)	
APRI				<.001
<1.0	4095 (68.1)	209 (39.3)	3886 (70.9)	
1.0–2.0	1003 (16.7)	153 (28.8)	850 (15.5)	
>2.0	591 (9.8)	142 (26.7)	449 (8.2)	
No result available at baseline	327 (5.4)	28 (5.3)	299 (5.5)	

Table 1 continued.

Characteristic	Overall (n = 6016)	End-Stage Liver Disease (n = 532)	No End-Stage Liver Disease (n = 5484)	*P* Value
FIB-4				<.001
<1.45	2160 (35.9)	92 (17.3)	2068 (37.7)	
1.45–3.25	2561 (42.6)	205 (38.5)	2356 (43.0)	
>3.25	968 (16.1)	207 (38.9)	761 (13.9)	
No result available at baseline	327 (5.4)	28 (5.3)	299 (5.5)	

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range.

[a] Data are presented as number (%) unless otherwise specified.

[b] Based on highest baseline HCV RNA result.

models alone. Performance of promising models was further compared by decision curves [28, 29], a graphical approach for evaluating and comparing prognostic models that considers the inherent trade-offs of false-positive versus false-negative classifications arising out of varying risk thresholds. Details appear in Supplementary Appendix 2. From the final model selected, we plotted Kaplan-Meier failure curves. Differences in ESLD by FIB-4 categories were estimated using log-rank tests.

To ensure that missing data did not affect the validity of our results, in a sensitivity analysis, we generated 10 imputed datasets, each with completed data on all predictors [30]. Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC) and Stata 13.1 (Stata Corporation, College Station, TX).

RESULTS

Patient Characteristics

Between 1997 and 2010, a total of 6016 ART-treated HIV/HCV-coinfected patients met our inclusion criteria (Figure 1). Absence of HCV RNA assessment was a common reason for exclusion (18%), but there were no clinically relevant differences in the characteristics between included patients and those excluded due to missing HCV RNA (data not shown).

The cohort (Table 1) was predominantly male and black, and one quarter of the patients had a history of alcohol dependence/abuse. Most patients were infected with HCV genotype 1 and had a high baseline HCV RNA level. The patients were followed for a median of 6.6 (interquartile range, 3.4–9.8) years. During follow-up, 482 (8.0%) patients initiated HCV therapy during and were censored. End-stage liver disease occurred in 532 (8.8%) patients during follow-up. At the time of the first ESLD event, a diagnosis indicative of hepatic decompensation was recorded in 397 (6.6%) patients, hepatocellular carcinoma was recorded in 63 (1.0%) patients, and liver-related death was recorded in 72 (1.2%) patients. Among the 397 patients with an incident hepatic decompensation event, 335 (84.4%) had ascites, 71 (17.9%) had spontaneous bacterial peritonitis, and 110 (27.7%) had variceal hemorrhage. Overall, 1936 (32.2%) patients died during follow-up, of which 164 (8.5%) were liver-related deaths (Supplementary Appendix 3).

Performance and Comparison of Prognostic Models for End-Stage Liver Disease

Baseline FIB-4, baseline APRI, and nonblack race were the strongest factors associated with ESLD among the variables evaluated in Cox regression analyses (Supplementary Appendix 4). Interactions

Table 2. Candidate Prediction Models for End-Stage Liver Disease Among 6016 Antiretroviral-Treated HIV/Hepatitis C Virus-Coinfected Patients[a]

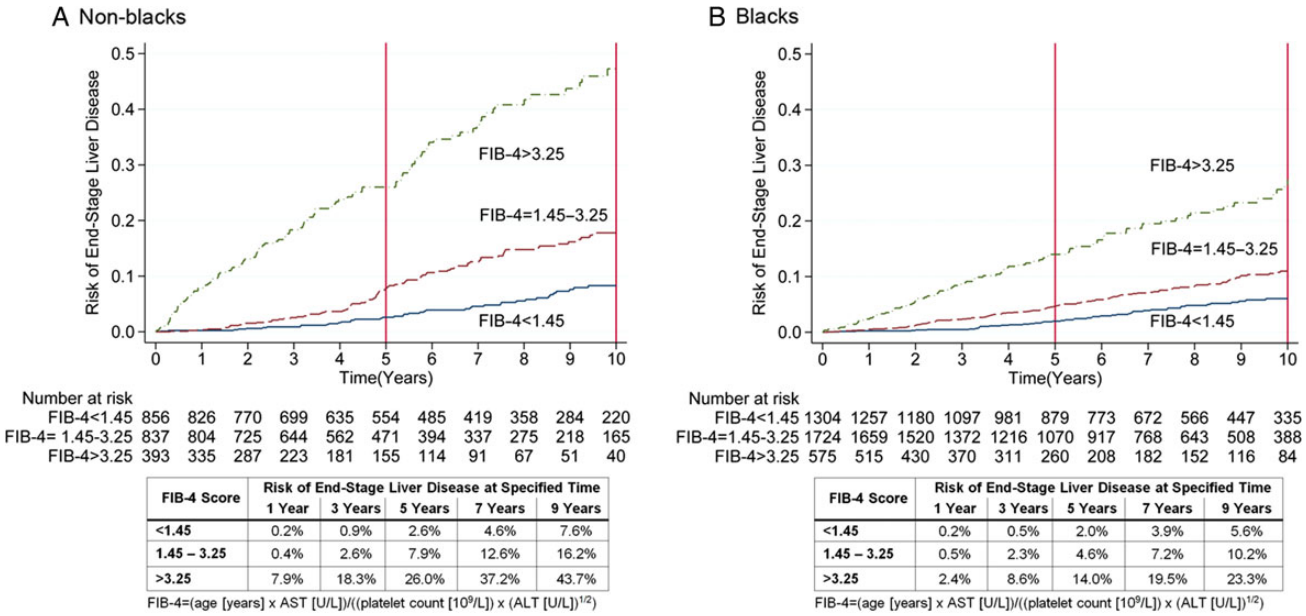
Prediction Model	C-Statistic	
	FIB-4-Based Model	APRI-Based Model
No additional predictors included (FIB-4 or APRI alone)	0.70	0.71
Alcohol included	0.71	0.72
Age included	–[b]	0.73
Race included	0.73	0.72
Age + race included	–[b]	0.74
Race + diabetes + hepatitis B + anemia included	0.74	0.74
Age + race + diabetes + hepatitis B + anemia included	–[b]	0.75
All predictors included[c]	0.74[b]	0.75

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

[a] C-statistics for the base prognostic models consisting of FIB-4 (categorized as follows: <1.45; 1.45–3.25; >3.25) and APRI (categorized as follows: <1.0; 1.0–2.0; >2.0) alone are presented in the top row. C-statistics for alternative prognostic models comprising FIB-4 or APRI plus select combinations of the other predictors are presented in subsequent rows below. Models with FIB-4 did not include age because age is a component of FIB-4.

[b] C-statistic was not evaluated within the FIB-4-based models because age is a component of FIB-4.

[c] Covariates included age (for APRI-based model only), body mass index, anemia (hemoglobin <10 g/dL), CD4 cell count <200 cells/mm^3, HIV RNA >400 copies/mL, history of alcohol dependence/abuse, diabetes mellitus, hepatitis B coinfection, and non-black race. FIB-4, APRI, hemoglobin, CD4 cell count, and HIV RNA level were also evaluated as continuous variables.



FIB-4 Score	Risk of End-Stage Liver Disease at Specified Time				
	1 Year	3 Years	5 Years	7 Years	9 Years
<1.45	0.2%	0.9%	2.6%	4.6%	7.6%
1.45 – 3.25	0.4%	2.6%	7.9%	12.6%	16.2%
>3.25	7.9%	18.3%	26.0%	37.2%	43.7%

FIB-4=(age [years] x AST [U/L])/((platelet count [10^9/L]) x (ALT [U/L])$^{1/2}$)

FIB-4 Score	Risk of End-Stage Liver Disease at Specified Time				
	1 Year	3 Years	5 Years	7 Years	9 Years
<1.45	0.2%	0.5%	2.0%	3.9%	5.6%
1.45 – 3.25	0.5%	2.3%	4.6%	7.2%	10.2%
>3.25	2.4%	8.6%	14.0%	19.5%	23.3%

FIB-4=(age [years] x AST [U/L])/((platelet count [10^9/L]) x (ALT [U/L])$^{1/2}$)

Figure 2. Risk of end-stage liver disease among antiretroviral-treated non-black (A) and black (B) HIV/hepatitis C virus-coinfected patients, by fibrosis (FIB)-4 score. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

with race were not observed for FIB-4 or APRI. Discrimination was similar for models with FIB-4 (c-statistic, 0.70) and APRI (c-statistic, 0.71) alone (Table 2). Alternative models comprising FIB-4 and race (c-statistic, 0.73) and APRI, age, and race (c-statistic, 0.74) had higher discrimination, but further addition of other combinations of predictors did not result in appreciably increased model discrimination (Table 2). Results of the decision curve analysis are shown in Supplementary Appendix 5. Because the model with FIB-4 + race had comparable discriminative ability and was simpler than the one with APRI + age + race, the model with FIB-4 + race was selected as the final model.

The risk of ESLD among non-blacks and blacks by category of FIB-4 is shown in Figure 2A and B, respectively (log-rank test among non-blacks, $P < 0.001$; log-rank test among blacks, $P < 0.001$). The risk at 5 years ranged from 2.6% to 26% among non-blacks (Figure 2A) and 2.0% to 14.0% among blacks (Figure 2B) across FIB-4 levels. Analyses using imputed data produced similar results.

DISCUSSION

This study evaluated prognostic models for determining the risk of developing ESLD in ART-treated HIV/HCV-coinfected patients. A prognostic model for risk of developing ESLD comprising FIB-4 and race had better discriminative accuracy than FIB-4 or APRI alone, and it was comparable to the APRI, age, and race model, but simpler. Using established cut-points of FIB-4, we determined the risk of ESLD over time in non-blacks and blacks. Despite including a number of additional variables associated with progression to ESLD (Supplementary Appendix 3), a model with all candidate predictors did not appreciably increase prognostic ability.

More importantly, our analyses in Figure 2 demonstrated that for HIV/HCV-coinfected individuals with moderate fibrosis by FIB-4 (i.e., results ranging from 1.45–3.25), there remains a significant risk of ESLD for non-blacks (>16% at 10 years) and blacks (>10% at 10 years). These results provide additional evidence that coinfected patients with at least moderate (F2) or higher liver fibrosis should be strongly considered for HCV treatment and should not be deferred until the development of more advanced liver disease, where the risk of ESLD will be even higher.

With the availability of all-oral direct-acting anti-HCV regimens that have high virologic cure rates and tolerability, but which are very costly, determining the rational use of these agents is imperative [31]. Quantifying the absolute risk of ESLD over time using a simple prognostic model comprising FIB-4 and race could have important clinical implications for the management of coinfected patients. Identifying coinfected patients at higher risk of ESLD could help prioritize HCV treatment in those who would benefit from it most and inform the need for close monitoring for liver-related complications. Alternatively, in those with a low risk of ESLD, emphasis could be placed on the modification of other risk factors for ESLD, including the reduction of alcohol consumption, control of diabetes, and HIV suppression, as well as clinical monitoring for liver disease progression. Analogous to other quantitative risk assessment tools, such as the Framingham Coronary Heart Disease Risk Score [32] and World Health Organization Fracture Risk Assessment Tool [33], which estimate the

10-year risk of cardiovascular disease and fracture, respectively, use of this ESLD risk model could aid the management of chronic HCV in patients with HIV, more than simply knowing which factors are predictive of developing ESLD.

If validated, this model could contribute to an individualized approach to HCV treatment among HIV/HCV patients. We sought to develop a simple model that reports ESLD risk over a 10-year period in both graphical and tabular form to allow easy interpretation by coinfected patients and their providers. Because the exact risk of ESLD that should prompt initiation of HCV treatment remains unclear, providers could use these results to discuss a patient's likelihood of developing ESLD over time and consider what risk of ESLD, in conjunction with other clinical and demographic factors, would prompt their initiation of HCV therapy.

FIB-4 is clinically credible as a predictor, easy to compute, and could be used in clinical practice in developed and developing world settings. Prior studies in coinfected patients have demonstrated that the baseline stage of hepatic fibrosis is strongly associated with ESLD [3, 19]. A separate analysis among coinfected women showed that FIB-4 was associated with all-cause mortality [34]. Among HIV-infected patients, baseline FIB-4 is associated with hepatocellular carcinoma risk [35]. In addition, FIB-4 uses a limited set of variables that are routinely and inexpensively measured in the outpatient setting, making this a useful option for resource-limited settings and practices where other noninvasive modalities of liver fibrosis assessment (e.g., transient elastography) might not be available.

Race is also credible as a predictor of ESLD. Recent studies in coinfected patients reveal that persons of non-black race have a higher risk of hepatic decompensation [3] and liver-related death [36]. A recent cohort study among 149 407 chronic HCV patients showed that blacks had lower rates of cirrhosis and hepatocellular carcinoma than non-Hispanic whites, even after adjustment for HCV genotype, HCV treatment, diabetes, and BMI [37]. Non-black HCV-infected patients have been reported to have stronger HCV-specific immunity than blacks [38], which could result in increased immune-mediated hepatic inflammation and accelerated liver fibrosis progression. Recent analyses in HCV-monoinfected and HIV/HCV-coinfected patients suggest that interleukin-28B CC genotype, which is common in non-blacks, is associated with increased hepatic inflammation and worse hepatic outcomes than those with CT or TT genotypes [39, 40]. Differences in the distribution of other genetic and non-genetic factors may also explain the disparity in ESLD risk between blacks and nonblacks. In future analyses, such factors may prove to be better indicators of ESLD risk than race.

This study has several potential limitations. First, we might have missed hepatic decompensation events and underestimated ESLD risk, because our decompensation definition did not include hepatic encephalopathy and because some patients did not have a confirmed cause of death. However, the incidence of ESLD among HIV/HCV patients in this study (8.8%) was similar to that reported in other cohort studies of coinfected patients [5, 19]. Furthermore, we previously evaluated the incidence rate of decompensation within VACS, US Medicare, and US Medicaid data using the validated ICD-9 definition (to capture outcomes occurring at non-VA hospitals that did not result in transfer to a VA facility). The incidence rate of decompensated cirrhosis was almost identical to that within the VACS alone, suggesting that few ESLD events were missed [3]. Second, our sample included mostly male US Veterans, and results may not be generalizable to women or to non-Veteran populations. Future analyses should evaluate the ability of FIB-4 and race to predict ESLD among coinfected women and non-Veterans. Third, differences by race in receiving HCV treatment (and being censored) should not affect our results because we stratified our analysis by race. Fourth, external validation of the prognostic model to predict ESLD in other coinfected populations is essential to ensure reproducibility of our findings across varied settings. Finally, although we considered many potential predictors during model development, data on liver stiffness measurement (using transient elastography) and genetic markers, such as interleukin-28B genotype and interferon lambda-4 deltaG genotype [40, 41], were not assessed. Future models evaluating ESLD risk in coinfected patients could determine whether these factors improve accuracy and utility. However, FIB-4 and race have the advantage of being simple predictors. Furthermore, because our final model included 2 categorical predictors, a simple Kaplan-Meier plot allows users to estimate risk easily for any given time frame.

CONCLUSIONS

In summary, FIB-4 and race can be used to quantify the risk of ESLD among HIV/HCV-coinfected patients on ART. Such information could prompt coinfected patients to reduce their risk factors for liver disease progression and aid HCV treatment decisions for both clinicians and patients. Future studies should evaluate the classification performance of FIB-4 and race in other coinfected populations, compare the performance of FIB-4 using the established cutoff points versus alternative thresholds, and determine whether its use improves outcomes.

Supplementary Material

Supplementary material is available online at *Open Forum Infectious Diseases* (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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