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Stability of liver fibrosis among HCV-infected injection drug users

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Abstract

Background—There are few published data characterizing patterns of liver stiffness measurements (LSMs) among HCV-infected persons and their potential impact on clinical decisions (for example, deferring treatment and hepatocellular carcinoma surveillance).

Methods—A total of 591 HCV-infected injection drug users (IDUs) in a community-based cohort had four LSMs. We used semi-parametric latent class growth modelling to identify patterns, which then became a gold standard against which we characterized validity of information from the initial measurements.

Results—Median age was 49, 68% were male, 92% African-American and 33% HIV-coinfected. The median LSM at visit 1 was 6.7 kPa (IQR 5.3–8.8). Over a median 1.75 years, LSM measures were stable; median change between visits was 0 kPa (IQR -1.4–1.7). Only 3% had evidence of fibrosis progression. Other groups included stable patterns of 1) no fibrosis (59%), 2) moderate fibrosis (21%), 3) severe fibrosis (7%) and 4) cirrhosis (9%). Individuals with fibrosis progression were more likely to be HIV-infected than those with stable low fibrosis ($P<0.001$). The diagnostic accuracy of the first LSM for identification of need for cancer surveillance (cirrhosis 12.3 kPa) was high (positive predictive value = 97%). Although no single low LSM had high negative predictive value for significant fibrosis (metavir <2), individuals with two or more low results rarely had progression.

Conclusions—These data underscore the stability of liver fibrosis in a cohort of predominantly African-American HCV-infected persons over 1.75 years, support using LSMs to monitor untreated persons at risk for progression and assess need for hepatocellular carcinoma surveillance.

Introduction

Management of liver disease and determination of treatment urgency among persons infected with HCV requires knowledge of fibrosis stage. HCV treatment outcomes have improved and are anticipated to improve further with approval of direct acting antiviral

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agents [1,2]. However, some individuals want to know if they can safely wait for interferon-sparing treatment and, for the foreseeable future, some form of liver fibrosis staging will be needed, irrespective of the success of HCV treatment, in order to ascertain the need for surveillance for hepatocellular carcinoma and oesophageal varices (currently only recommended in those with cirrhosis) [3].

Liver biopsy has long been considered the gold standard for assessment of fibrosis stage [4–6]. However, liver biopsy is invasive, expensive and subject to measurement error, and cannot be safely repeated frequently in persons choosing to postpone treatment [7,8]. Over the past decade, a number of surrogate non-invasive methods for ascertaining fibrosis have been investigated, including blood tests, algorithms based on the results of multiple serum markers [9–15] and transient elastography [16]. Liver stiffness measurements (LSMs) via elastography have good diagnostic accuracy for both fibrosis and cirrhosis [17–19] and elastography can be performed rapidly and repeatedly in clinic settings. However, there is a paucity of information on longitudinal LSM measures. Understanding longitudinal patterns is important because the diagnostic accuracy of the long-term pattern of some screening tests, like the serum alanine aminotransferase level (ALT), is much better than a single determination [20].

The objective of this analysis was to characterize longitudinal patterns of LSM among a cohort of HCV-infected persons and to use the information from the long-term patterns to retrospectively assess the validity of fewer measurements.

Methods

Study population

The AIDS Linked to the IntraVenous Experience (ALIVE) study is a community-based cohort of injection drug users (IDUs) in Baltimore, MD that has been previously described [21]. Briefly, between 1988–1989, 2,946 IDUs were recruited through community outreach and followed at six-month intervals. All participants were 18 years of age or older, acknowledged non-medical injection drug use in the prior 11 years and were free of AIDS at entry. Additional persons were recruited into the cohort in 1994–1995 ($n=391$), 1998 ($n=244$) and 2005–2008 ($n=875$). At all study visits, participants underwent a blood draw and questionnaire that included a combination of interviewer-administered questions and audio computer-assisted self-interview. Samples were stored frozen at -70°C in a repository for future testing. HCV antibody testing was performed retrospectively on frozen specimens using a second- or later- generation enzyme immunoassay (Ortho Diagnostics, Raritan, NJ, USA). Beginning in October 2005, we measured liver stiffness by elastography on all participants in follow-up at six-month intervals. In total, 1,418 participants had at least one LSM, of whom 1,184 were HCV-antibody-positive. Participants were eligible for this analysis if they were HCV-positive and had at least four valid LSMs that occurred within 4 and 23 months of each other. Patients with HIV or who were hepatitis B surface antigen positive (HBsAg) were *not* excluded. Of the 1,184, 664 had four measurements; 63 were excluded because 1 of the measurements was invalid and 10 were excluded because they did not have four measurements within the specified time range, leaving 591 eligible participants.

Liver stiffness measurements

Liver stiffness was assessed by transient elastography (Fibroscan; EchoSens, Paris, France) [22,23] as previously described [24]. Briefly, an ultrasound transducer probe is mounted on the axis of a vibrator allowing vibrations of mild amplitude and low frequency to induce an elastic shear wave that propagates through liver tissue. Pulse-echo ultrasound acquisitions

are used to follow propagation of the shear wave and measure its velocity. Results are received as single quantitative LSMs, reported in kilopascals (kPa). All elastography measurements were performed by certified operators who were trained by the manufacturer in the research clinic. During the course of the study, seven operators performed measurements. The median number of examinations performed per operator was 968. Examinations were considered to be valid if they met three criteria: (1) number of valid shots at least eight, (2) success rate (ratio of valid shots to the total number of shots) at least 60% and (3) IQR, which reflects the variability of measurements, less than 30% of the median LSM value (for example, $IQR/LSM < 30\%$) [25]. Of the 5,173 measurements taken among those with at least four valid measurements, 759 (14.7%) were excluded because they failed to meet the criteria. Of these, 214 (4.1%) were excluded for not having eight valid results, 306 (5.9%) for a success rate $<60\%$ and 559 (10.8%) because of the IQR. Of note, some persons failed to meet multiple criteria. Among the valid 4,414 measurements, we selected the first four available measurements for analysis ($n=2,364$).

Statistical analysis

Our analysis of longitudinal data focused on detecting underlying patterns of liver disease and asking whether this instrument could detect those patterns in this measurement interval. We used semi-parametric latent class growth modelling (also known as finite mixture models) which represent an extension of conventional maximum likelihood methods [26]. The goal of these methods is to identify membership in latent groups defined by distinctive longitudinal patterns [27]. While these models have been best characterized in the context of developmental trajectories in relation to psychology and life course studies, they are easily extendable to biomarker data [28]. The latent group in this case is liver fibrosis and the information used to determine these groups are the LSMs. The number of patterns is typically hypothesized *a priori*, but this hypothesis can also be tested through [the method](#). We hypothesized that there would be four patterns: 1) no fibrosis, stable; 2) significant fibrosis, stable; 3) cirrhosis, stable; and 4) disease progression. However, we tested for up to six patterns.

The outcome of the analysis was the absolute LSM in kPa. In order to account for the skewed nature of LSM data, we reclassified all measurements >15 kPa (consistent with liver cirrhosis) as 15. Although values >12.3 kPa have previously been found in this cohort to be consistent with cirrhosis [24], an upper limit of 15 was chosen to account for measurement error. Time was measured through study visits scheduled to occur at six-month intervals. We generated a series of models varying the number of groups from 1 to 6 and compared the results of the models using three criteria: 1) Bayesian information criteria, 2) the average posterior probabilities of the groups and 3) substantive knowledge including the clinical and practical applicability of the groups [29]. For the third criteria, we considered the number of individuals in each class, the number of estimated parameters and the degree of similarity across groups. Posterior probabilities for group membership were calculated and individuals were assigned to the group with the highest probability of measurement. We used backwards selection of the time parameters to determine the shape of the trajectories (for example, cubic reduced to quadratic to linear) and final choice of shape parameter was based on statistical significance ($P>0.05$).

Once groups were defined, we assessed whether one or two LSMs could identify individuals who were indicated for surveillance for hepatocellular carcinoma (with cirrhosis) and who could safely wait for treatment (rule out significant fibrosis). For this analysis, we considered the groups identified by the model described above to be the gold standard; these groups were based on all four measurements. We characterized the diagnostic performance of one and two LSMs by calculating the sensitivity and positive predictive value (PPV) for identifying cirrhosis and the specificity and negative predictive value (NPV) for ruling out

cirrhosis and significant fibrosis relative to the gold standard defined above. We first explored cutoffs identified in a previous validation study which compared LSM to biopsy in this cohort to be indicative of significant fibrosis (9.3 kPa) and cirrhosis (12.3 kPa) [24] as well as other cutoffs driven by the longitudinal data. A sensitivity analysis considered measurements separated by one year rather than six months. Mortality rates (per 100 person-years [PY]) were compared across different groups defined by the data. Deaths were ascertained by linkages with the National Death Index; information on deaths was available through December 2008. All analyses were performed in SAS vs. 9.2 (SAS Institute, Cary, NC, USA).

Results

Study population

The median age of the 591 HCV-antibody-positive participants was 49 years (IQR 44–53; Table 1); 68% were male and 92% were African-American. The median body mass index (BMI) at the time of the first LSM was 24.1 (IQR 21.8–27.4); 33% were coinfecting with HIV. The median CD4⁺ T-cell count among those infected with HIV was 296 (IQR 164–463). In total, 49% reported drinking alcohol at the time of the first measurement and 49% reported active drug injection. Only 13 (2%) reported receiving HCV treatment during the study period. The median LSM at the first visit was 6.7 kPa (IQR 5.3–8.8; range 3–75).

Patterns of liver stiffness measurements

The vast majority of LSM results remained unchanged over a median 1.75 years (IQR 1.50–2.05). The median change in LSM from visit 1 to visit 2 was 0.05 kPa (IQR -1.2–1.5); from visit 2 to visit 3, -0.1 kPa (IQR -1.3–1.3) and from visit 3 to visit 4, 0 kPa (IQR -1.2–1.4). Overall, from the first to the last visit, the median change in LSM was 0 kPa (IQR -1.4–1.7).

When four results on all subjects were considered, the model which best fit the data suggested that there were 5 distinct groups (Figure 1). Four groups were defined by stable LSM results: 1) no fibrosis ($n=349$, 59%), 2) moderate fibrosis ($n=126$, 21%), 3) severe fibrosis ($n=44$, 7%) and 4) cirrhosis ($n=53$, 9%). The median LSM values at all four visits in these four groups were 5.6 kPa (IQR 4.7–6.5), 8 kPa (IQR 6.8–9.3), 11.4 kPa (IQR 9.4–13.1) and 22.4 kPa (IQR 16.8–35.3), respectively. With this model, fibrosis progression was detected in only 19 (3%); the median LSM value in this group was 10.6 kPa (IQR 7.9–14.9). All groups demonstrated high median classification probabilities meaning their group assignment fit their actual LSM values: group 1, 0.99; group 2, 0.91; group 3, 0.93; group 4, 0.97; and group 5, 0.99. The variability between individual measurements was least in group 1 and greatest in groups 3–5 (Figure 2).

The median (IQR) ALT and aspartate aminotransferase (AST) values in IU/l across all visits by group were as follows, 1) no fibrosis: ALT 25 (19–38), AST 30 (24–41); 2) moderate fibrosis: ALT 33 (26–51), AST 39 (29–58); 3) severe fibrosis: ALT 47 (29–71), AST 53 (35–75); 4) cirrhosis: ALT 56 (38–79), AST 73 (47–131). Overall, 14 (0.7%) experienced an AST>200 IU/l during follow-up and (0.8%) an ALT>200 IU/l. ALT>200 IU/l was similar across groups but AST>200 IU/l was significantly higher in groups 4 (cirrhosis; 4%) and 5 (disease progression; 3%). Only 2 individuals experienced an ALT or AST>500 IU/l during follow-up.

Within the group of 19 identified by the model to have evidence of disease progression (Figure 3), 12 had classification probabilities that exceeded 0.90, thus indicating good fit in the group. Among these 12, 9 had LSMs<9.3 at their first measurement and values consistent with cirrhosis (12.3) at their fourth measurement. The other three had values consistent with severe fibrosis (9.3–12.2) at their first visit and cirrhosis at their fourth. The

median age of these 12 individuals was 50 years. In total, 83% were male, 83% were African-American and 50% were HIV-coinfected. The remaining seven individuals in the progression group with lower classification probabilities also had values consistent with cirrhosis at their fourth measurement but the trajectory was not as steep. When we compared the 19 with evidence of progression to those who remained either at no or moderate fibrosis, there were no statistically significant differences with respect to age, race, gender or recent drug and alcohol use, but those who progressed were significantly more likely to be HIV-positive (63% versus 28%; $P<0.001$). Predictive value of LSM for identification of need for cancer surveillance (cirrhosis)

Using the model-based pattern as the gold standard, we assessed the performance of one to two LSMs for identifying severe fibrosis/cirrhosis (sensitivity and PPV). We also considered specificity and NPV (for excluding severe fibrosis/cirrhosis). Based on the model, the groups determined to be consistent with severe fibrosis/cirrhosis were 4 and 5. Using the cutoffs that have been previously validated in this cohort with liver biopsy, 70 had a first LSM consistent with cirrhosis (≥ 12.3 kPa, 11.8%) [24]. Of the 70 persons with LSM ≥ 12.3 kPa at the first visit, 60 (86%) had at least one additional measurement ≥ 12.3 kPa. Considering groups 4 and 5 (from the model) to be the gold standard for the diagnosis of severe fibrosis/cirrhosis, one measurement ≥ 12.3 had a PPV of 97% for identifying severe fibrosis/cirrhosis and a sensitivity of 70%. One measurement <12.3 had a NPV of 94% and a specificity of 100%. If we had classified severe fibrosis/cirrhosis on the basis of this one measurement, we would have missed 29 persons with severe fibrosis/cirrhosis and identified 2 persons as having severe fibrosis/cirrhosis when they had less significant disease. In total, 23 of the 29 misclassified as not having severe fibrosis/cirrhosis were in group 4 and 6 were in group 5; 18 (62%) of the 29 had a second LSM that was consistent with severe fibrosis/cirrhosis. Classification of severe fibrosis/cirrhosis was not improved greatly with requirement of two measurements or lower cutoffs. The use of two measurements for excluding cirrhosis would have an NPV of 98% and a specificity of 98%. With two measurements, we would have missed 11 persons with cirrhosis and identified 7 persons as having cirrhosis when they did not.

Predictive value of LSM for treatment deferral, excluding significant fibrosis

We further assessed the accuracy of one to two measurements in their ability to identify persons *without* significant fibrosis. Based on the model, the group considered to be consistent with no significant fibrosis was group 1. Considering group 1 from the model to be the gold standard for the designation of no significant fibrosis, we first tested the performance of a previously validated (against the biopsy) cutoff for exclusion of significant fibrosis in this population (<9.3 kPa). This cutoff had an NPV (for being in group 1, representing absence of significant fibrosis) of 73% and a specificity of 96%. NPV improved when lower cutoffs for excluding significant fibrosis were incorporated (Figure 4). For example, at a cutoff of 8 kPa, NPV was improved to 80% with some cost to specificity (86%). NPV improved further when it was required that two measurements be below 8 kPa (88%) with little cost to specificity (83%).

Applying this cutoff of <8 kPa to the data, 404 persons had an initial measurement <8 kPa and 349 had two consecutive measurements <8 kPa. Of the 404 whose first measurement was <8 kPa, 309 (76%) remained <8 kPa at all three subsequent visits. Of the 349 who had two consecutive measurements <8 kPa, 309 (89%) remained <8 kPa at the next two visits. While all of the remaining 40 had 1 measurement ≥ 8 kPa, all were classified in groups 1–3. No deaths were observed among the 349 with two consecutive measurements <8 kPa compared to three in the group where both measurements were ≥ 8 kPa (mortality rate [MR] 1.03 per 100 PY) and two in the group where one measurement was ≥ 8 kPa (MR 0.74 per 100 PY).

More variability existed in the measurements in the 8–12.3 kPa range. In total, 117 (20%) had an initial measurement that was 8–12.3 kPa. All had one subsequent measurement that was 8 kPa, but 56 (48%) also had a measurement that was <8 kPa. Further, 26 (22%) had at least one subsequent measure that was indicative of cirrhosis (>12.3 kPa). Importantly, of these 22, >50% had an initial measurement that was >10 kPa.

Discussion

The results of this study underscore that liver fibrosis did not progress over a short interval in this sample of HCV-infected individuals. Further, our longitudinal LSM results support the diagnostic accuracy of a single measure greater than 12.3 kPa for detection of cirrhosis and need for hepatocellular carcinoma surveillance. Finally, these data suggest that LSMs may also be reliably used to monitor individuals who choose to postpone treatment, especially those coinfecting with HIV in whom fibrosis progression is more likely.

It has been suggested that disease staging for HCV-associated liver disease may become less important as new, more efficacious, and better tolerated drugs are approved for HCV treatment. Specifically, as treatment outcomes for genotype 1 HCV approach what is achieved with genotype 2 or 3 HCV infection, liver biopsy may be considered optional for disease staging in some settings. Nonetheless, it is important, even if a sustained virological response is achieved, to monitor cirrhotic patients for hepatocellular carcinoma [30]. Our data support the use of elastography for identification of persons in need of screening for hepatocellular carcinoma and oesophageal varices. Although long-term studies will be needed to establish a direct link between elastography score and liver cancer, a single measurement had high diagnostic accuracy for detection of cirrhosis in this population.

These data may also be important for management of HCV-infected individuals without cirrhosis, who wish to postpone treatment while they are waiting for safer and/or more efficacious medications. Some may even wish to postpone treatment even after the anticipated approval of several new agents in 2011 to avoid pegylated interferon- α and ribavirin, which are not tolerated by approximately 10% of patients selected for clinical trials [31,32]. While interferon-sparing HCV treatment trials have begun [33], proof of efficacy and regulatory approval is years away. In addition, even with newer regimens, treatment is expected to be less efficacious in some populations, including African-Americans and those coinfecting with HIV [2]. In other individuals, deferral of treatment may be necessary while other medical (for example, psychiatric) and social issues (for example, homelessness, incarceration or drug use) are stabilized. Treatment has previously been shown to be more effective when these barriers have been addressed first [34,35]. These barriers become even more important in the context of protease inhibitors where resistance will be a likely consequence of sub-optimal adherence and treatment failure. Thus, despite the advances in HCV therapeutics, it is likely that at least for the next several years, many may still opt to wait for treatment.

On the one hand, The stability of LSM measures in most individuals suggests that there is a subset of individuals for whom treatment could be safely postponed. This finding is consistent with the predominance of no liver fibrosis at baseline despite >20 years of infection in most individuals in this cohort [20], as well as prior observations that natural history of liver disease progression is generally slow [36]. In contrast, these findings also demonstrate that it is important to monitor persons who opt to postpone treatment. Sustained virological response rates are higher in persons without cirrhosis and are also likely to be higher in persons with lower levels of liver stiffness, so identifying persons before they progress to a point of impaired treatment response is important. Further, a small subset of subjects had clear evidence of progression; the rate of progression in this cohort has been

previously shown to be low, so potentially higher progression rates might be expected in other populations, particularly those coinfecting with HIV. Indeed, disease progression appeared to be more common among HIV/HCV-coinfecting persons, reinforcing the need for ongoing monitoring and potentially more aggressive treatment in this group. Even among others who did appear to have evidence of progression, there was diagnostic uncertainty, particularly among those with measurements in the 8–12.3 kPa range. It appears that at least some of this uncertainty/measurement error can be removed with serial measurements.

Measurements were most consistent when they were in the low/normal range; the majority of persons who had low measurements had stable results. While this finding may reflect an intrinsic property of the test itself, it would also be expected in a low disease burden population in which an NPV would be expected to exceed PPV. Conversely, in populations with a higher prevalence of disease, we would expect improved PPV for elevated measurements. Importantly, despite the increased variability at higher LSMs, when measurements were elevated to a level consistent with cirrhosis, they were far more consistent than those in the intermediate/significant fibrosis range.

A challenge in interpreting these results relates to the cutoffs that were applied and identified in this population versus others. Collectively, across 50 studies among which 23 included HCV-infected individuals, the range of LSM cutpoints for F2 fibrosis was 4.5–11.2 kPa and for cirrhosis was 10.1–19 kPa. Even in our study, while the previously validated cutpoint for cirrhosis appeared accurate, the optimal cutpoint identified in this analysis appeared lower than the previously validated cutpoint. On the one hand, the cutpoint of <8 kPa was more comparable to what has been identified in other studies [17]. In contrast, the heterogeneity, even within the same study population, highlights one of the major challenges for widespread application of liver elastography.

We were limited in this study by not having biopsy results on all individuals to compare with the patterns that were suggested by the LSM results. However, we and others, have previously demonstrated good correlation of LSM results when compared to the liver biopsy [16,23,24]. When these results, careful calculations of the diagnostic accuracy of biopsy [37], and size of the cohort were considered, we concluded that the error of the biopsy and lack of a clear ‘tie breaker gold standard’ would make the scientific value of repeating biopsies on all these individuals too low to justify the risk. Future studies will be focused on clinical outcomes to validate elastography results.

Our population had a low prevalence of significant fibrosis and cirrhosis compared with other samples, particularly those that are clinic-based. Possible explanations for this, and consequences, need to be considered. First, we did not have data on HCV RNA for all participants so our sample likely included HCV-antibody-positive persons with and without viraemia; lower prevalence of disease would be expected in those who were not viraemic. Second, we cannot rule out the possibility of selection bias given that this study was nested in a cohort that has been ongoing since 1988. It is possible that those with rapid disease progression died before 2005 and thus were not included in this analysis. However, we have previously demonstrated low rates of liver mortality in this cohort [36] and >50% of those included in this analysis were newly recruited into the cohort in 2005. The difference in disease prevalence has implications for generalizing the findings to other populations beyond African-Americans with a history of injection drug use. In particular, as both PPVs and NPVs are affected by disease prevalence, the cutoffs described in this population may behave differently in populations with substantially higher disease prevalence. We were also unable to characterize demographic, behavioural and clinical patterns associated with the observed patterns, particularly disease progression, because of the small numbers in some

groups. Future studies will examine the role of such factors, including, in particular, HIV and alcohol use on stiffness patterns.

Finally, there are other important limitations to use of elastography relative to liver biopsy (the current gold standard) that should be considered. There are some conditions under which LSM cannot be performed (for example, ascites) or tend to result in failure (for example, overweight or obesity). Further, in addition to providing an assessment of fibrosis, liver biopsy provides simultaneous evaluation of necroinflammation, steatosis, steatohepatitis and iron overload that cannot be evaluated by LSM. No assessment of these conditions can be obtained through LSM. Nonetheless, newer LSM probes will address some of these limitations, and our current results support the use of elastography in identifying subgroups of patients for therapeutic intervention.

One way to address some of the limitations of elastography on its own is to consider application in combination with other non-invasive markers or biopsy. Others have suggested the optimal diagnostic accuracy may be achieved when multiple diagnostic tests are combined. For example, Vergniol demonstrated that the highest diagnostic accuracy for clinical outcomes was achieved by combining LSM with FibroTest and ActiTest [38]; overall predictive accuracy for this combination exceeded that of liver biopsy. Others have suggested combination algorithms that include serum markers (for example, APRI, FibroTest), LSM and biopsy [39]. We were limited in this analysis by not having data on other non-invasive markers (for example, APRI, FibroTest) to assess the combined predictive accuracy; future studies should consider looking at combinations of markers longitudinally.

In conclusion, we observed that liver fibrosis was stable in the majority of HCV-infected persons over a short interval. Our results support the use of LSM to monitor persons for hepatocellular carcinoma surveillance and to support treatment deferral in those who may wish to wait. While a single elevated measurement may be sufficient to identify persons for hepatocellular carcinoma screening, it appears that at least two consecutive measurements should be considered for lower disease states.

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Measurements >15 kPa were assigned a value of 15 kPa.

Figure 1.
Trajectories of liver stiffness measurements among 591 HCV-antibody-positive persons

Figure 2.

Difference between consecutive liver stiffness measurements by model-based trajectory

n=19.

Figure 3.
Liver stiffness measurements over time among persons identified as having evidence of disease progression

The definition of significant fibrosis is based on the model-based pattern (groups 2–5). Specificity and negative predictive value (NPV) of 1–2 measurements for excluding significant fibrosis are presented across a range of cutoff values of liver stiffness measurements (LSMs; <6 to <9.3 kPa).

Figure 4.
Diagnostic accuracy of LSM for exclusion of significant fibrosis

Table 1

Description of population at first Fibroscan assessment

Characteristic	Value
Median age, years	49 (44–53)
Female gender	189 (32)
African-American race	542 (92)
Body mass index, kg/m ²	24.1 (21.8–27.4)
HIV-positive	193 (33)
Median CD4 ⁺ T-cell count ^a , cells/mm ³	296 (164–463)
Alcohol use	
None	391 (51)
<Daily	126 (21)
>Daily	163 (28)
Injection drug use	
None	302 (51)
<Daily	126 (21)
>Daily	163 (28)
Aspartate aminotransferase, U/l ^b	34 (26–51)
Alanine aminotransferase, U/l ^b	30 (21–49)
Total bilirubin, mg/dl	0.5 (0.4–0.7)
Albumin, mg/dl	4.1 (3.8–4.3)

n=591. Values are *n* (%) or median (IQR).^aFor HIV-positive patients only.^bMissing for 48 persons.