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3 AQ: 1 **MELD Score Is an Important Predictor of Pretransplantation Mortality in**
4 AQ: 2 **HIV-Infected Liver Transplant Candidates**
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18 **BACKGROUND & AIMS:** Human immunodeficiency
19 AQ: 3 virus (HIV) infection increases the rate of liver disease
20 progression in patients infected with hepatitis C virus
21 (HCV) and could shorten survival times of those awaiting
22 liver transplants. The Model for End-Stage Liver Disease
23 (MELD) predicts mortality in HIV-negative transplant
24 candidates, but its reliability in predicting mortality of HIV-
25 positive candidates has not been established. **METHODS:**
26 We evaluated predictors of pretransplantation mortality
27 in HIV-positive liver transplant candidates enrolled in
28 AQ: 4 the Solid Organ Multi-Site Transplant Study (HIVTR),
29 matched 1:5 by age, sex, race, and HCV infection with
30 HIV-negative controls from the United Network of Or-
31 gan Sharing. **RESULTS:** Of 167 HIVTR candidates, 24
32 died (14.4%); this mortality rate was similar to that of
33 controls (88/792, 11.1%, $P = .30$) with no significant differ-
34 ence in causes of mortality. A significantly lower proportion
35 of HIVTR candidates (34.7%) underwent liver transplan-
36 tation, compared with controls (47.6%, $P = .003$). In the
37 multivariate model for the combined cohort, baseline
38 AQ: 5 MELD score predicted pretransplantation mortality (hazard
39 ratio [HR], 1.27; $P < .0001$), whereas HIV infection was not
40 significantly associated with increased risk of pretransplan-
41 tation mortality (HR, 1.69; $P = .20$). After controlling for
42 pretransplantation CD4⁺ cell count and HIV RNA levels,
43 the only significant predictor of mortality in the HIV-in-
44 fected subjects was pretransplantation MELD (HR, 1.2; $P <$
45 $.0001$). **CONCLUSIONS: Pretransplantation mortality**
46 **characteristics are similar between HIV-positive and**
47 **HIV-negative candidates. Although lower CD4⁺ cell**
48 **counts and detectable levels of HIV RNA might be as-**
49 **sociated with a higher rate of pretransplantation mor-**
50 **tality, the baseline MELD score was the only significant**
51 **independent predictor of pretransplantation mortality**
52 AQ: 6 **in HIV-infected liver transplant candidates.**

17
18 drome (AIDS)-related death^{1,2} primarily related to com-
19 plications of chronic hepatitis B virus (HBV) or hepatitis
20 C virus (HCV) coinfection, as well as hepatotoxicity associ-
21 ated with antiretroviral therapy and alcohol use.³⁻⁵ Given
22 the improved survival now possible with use of highly
23 active antiretroviral therapy (HAART), many long-term
24 HIV-infected individuals are developing end-stage liver
25 disease (ESLD) and increasingly being considered for
26 liver transplantation.

27
28 Transplant programs have adopted the Model for End-
29 Stage Liver Disease (MELD), which was established in
30 HIV-uninfected patients and incorporates creatinine, bil-
31 irubin, and international normalized ratio to estimate
32 prognosis and determine the medical urgency for liver
33 transplantation, ensuring the appropriate organ alloca-
34 tion to those with the highest risk of death.⁶ Although
35 the MELD has been validated as a predictor of survival in
36 a wide variety of patients with ESLD,^{6,7} no data exist
37 regarding its use in HIV-infected patients with ESLD in
38 whom other factors (eg, HIV disease stage, CD4 cell
39 count, and antiretroviral therapy) may be important pre-
40 dictors of mortality. This is of concern because HIV-
41 infected patients with ESLD have a shortened survival
42 compared with HIV-negative patients with similar MELD
43 scores.⁸ Previous studies have suggested, in fact, that
44 predictors of mortality used for organ allocation in
45 HIV(-) liver transplant candidates may not be valid in
46 their HIV(+) counterparts.⁸⁻¹¹ Thus, it is timely to define
47 predictors of mortality in HIV(+) transplant candidates
48 to optimize organ allocation and clinical outcomes in
49 this group. The objectives of this study were to determine
50 the incidence of, time to, causes of, and risk factors for
51 pretransplantation mortality, including pretransplanta-

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53 *Abbreviations used in this paper:* HCC, hepatocellular cancer; HCV,
54 hepatitis C virus; HIV, human immunodeficiency virus; MELD, Model for
55 End-Stage Liver Disease; UNOS, United Network for Organ Sharing.

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55 **A**mong individuals with human immunodeficiency
56 virus (HIV) infection, liver-related death is the most
57 frequent cause of non-acquired immunodeficiency syn-

tion MELD, CD4⁺ count, HIV viral load (VL), HCV coinfection, and HAART therapy in HIV-infected liver transplant candidates and compare these with matched HIV(-) controls.

Patients and Methods

Study Subjects

The HIV in Solid Organ Transplantation Multi-Site Study (HIVTR) enrolled patients with HIV infection and ESLD who were candidates for liver transplantation at 20 transplant centers in the United States between February 2003 and September 2007 (clinicaltrials.gov, NCT00074386). Patients were required to meet standard site criteria for placement on the liver transplant wait list as well as HIV-specific study inclusion criteria, which included CD4⁺ cells >100/ μ L or >200/ μ L if there was a history of prior opportunistic infection or HIV-1 RNA <50 copies/mL or >50 copies/mL in those with hepatotoxicity or HAART intolerance in whom HIV suppression was predicted posttransplantation. Subjects with a history of progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, primary central nervous system lymphoma, multidrug-resistant fungal infections, or significant wasting were excluded from this study. Patients with hepatocellular carcinoma (HCC) were enrolled in the HIVTR protocol, although excluded from this analysis, because they are typically assigned a higher priority for liver transplantation regardless of MELD score.

Data Collection

Clinical and laboratory data were collected locally at screening, enrollment (time of placement on the transplant waiting list), and every 3 months until transplantation or death and entered into an online data collection system at each of 20 participating sites. Clinical variables included age, sex, race, liver disease etiology, antiretroviral medications, body mass index (BMI), and cause of death (when appropriate). Laboratory tests included CD4⁺ cell count, HIV RNA polymerase chain reaction (PCR), and serum chemistries for calculating MELD scores, as follows: MELD = $[0.957 \times \text{Ln}(\text{creatinine mg/dL, maximum } 4.0) + 0.378 \times \text{Ln}(\text{bilirubin mg/dL}) + 1.120 \text{ Ln}(\text{international normalized ratio}) + 0.643] \times 10$.

Control Subjects

Controls were HIV(-) liver transplant candidates enrolled in the United Network for Organ Sharing (UNOS)-administered Organ Procurement and Transplantation Network (OPTN) database during the same time frame as the HIV(+) study subjects from the HIVTR study. Each case subject was matched to up to 5 controls by age, sex, race, and HCV infection status, as defined by HCV antibody positivity. Controls with HCC were excluded. Other variables collected from the HIV(-) con-

trols included MELD scores and time to transplantation, death, or current wait listing.

Human Subjects Research

Written informed consent was obtained from all study subjects prior to enrollment in the HIV transplant protocol. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was reviewed by each site's institutional review board. No donor organs were obtained from executed prisoners or other institutionalized persons.

Statistical Analysis

Frequencies and percentages were calculated for categorical variables and medians and interquartile ranges (IQR) for continuous variables. Fisher exact test was used to analyze categorical data, and Wilcoxon rank-sum test was used to analyze continuous data. Trajectories for time-to-death, time-to-transplant, and time-to-MELD score ≥ 25 were calculated from date of placement on the transplant waiting list. Time-to-event distributions were estimated by the product-limit estimate method, and survival distributions were compared by log-rank test.

Univariate and multivariate proportional hazards models were developed to examine predictors of pretransplantation mortality. Models were developed for the overall cohort, the HCV-infected subgroup, and the HIV-infected subjects alone. The multivariate proportional hazards models for pretransplantation mortality included variables that were significant in the univariate analyses as well as important potential confounders. The MELD was examined as a dichotomous, a categorical, and a continuous variable. Respective hazard ratios (HR) were determined with 95% confidence intervals (CI). The statistical analysis was carried out using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Baseline Characteristics of Subjects and Controls

Of 196 HIV(+) liver transplant candidates enrolled during the study period, 167 (85.2%) were evaluable, and 29 (15%) with HCC were excluded from analysis. The 167 subjects were matched with 792 HIV(-) liver transplant candidate controls without HCC from the UNOS database. The median (IQR) follow-up time for HIV(+) subjects was similar to that of UNOS controls, 166 days (10-526) vs 194 days (35-598), $P = .09$. An additional 136 HIV(+) subjects with advanced liver disease who were screened did not become transplant candidates in this study, among whom, 31 (22.8%) died.

Of the HIV(+) subjects, 24 of 167 (14.4%) died prior to transplantation, similar to the mortality rate in the HIV(-) UNOS controls, 88 of 792 (11.1%), $P = .30$. Limiting the comparison with HCV(+) subjects only, the

Table 1. Characteristics of HIV(+) and UNOS HIV(-) Liver Transplant Candidates

	HIV (+) (n = 167)	UNOS (n = 792)	P value
Median (IQR), age, y	47 (42–52)	49 (43–53)	.06
No. (%) male sex	136 (81)	642 (81)	.83
Race, n (%)			.97
White	126 (75)	579 (73)	
African American	25 (15)	127 (16)	
Other	17 (10)	87 (11)	
Median (IQR), body mass index	24 (22–28)	28 (25–32)	<.0001
Health care coverage, n (%) ^a			<.0001
Private insurance	71 (43)	464 (64)	
Medicare	47 (28)	71 (10)	
Medicaid	34 (20)	153 (21)	
Other	15 (9)	42 (6)	
UNOS/OPTN region, n (%)			<.0001
1 (New England)	28 (17)	43 (5)	
2 (Mid-Atlantic)	50 (30)	111 (14)	
5 (Southwest)	47 (28)	121 (15)	
9 (New York)	22 (13)	63 (8)	
Other	20 (12)	454 (58)	

^aNot reported for 62 (8%) of the UNOS controls.

mortality rate was similar between the HIV(+) subjects, 18 of 125 (14.4%), and the UNOS controls, 62 of 592 (10.5%), $P = .28$. By contrast, although 75% of both groups were HCV(+), a significantly lower proportion of HIV(+) transplant candidates, 58 of 167 (34.7%), underwent liver transplantation, as compared with the HIV(-) UNOS controls, 377 of 792 (47.6%), during the study period, $P = .003$.

Table 2. Characteristics of Liver Transplant Candidates by Transplant Status

	Transplant	No Transplant	Died	P value ^a
No. enrolled, n (%)				
HIVTR	58 (35)	85 (51)	24 (14)	N/A
UNOS	377 (48)	327 (41)	88 (11)	N/A
Median (IQR), age, y				
HIVTR	47 (42–52)	47 (43–51)	50 (41–55)	.85
UNOS	48 (43–52)	50 (44–54)	49 (43–54)	.09
Race (white), n (%)				
HIVTR	41 (71)	68 (80)	16 (67)	.34
UNOS	275 (73)	239 (73)	69 (78)	.8
Male sex, n (%)				
HIVTR	44 (76)	71 (84)	21 (88)	.39
UNOS	309 (82)	254 (78)	75 (85)	.19
Median (IQR), baseline CD4				
HIVTR	315 (229–437)	264 (189–399)	237 (146–348)	.03
UNOS	—	—	—	—
No. (%) Detectable HIV RNA				
HIVTR	9 (16)	6 (7)	5 (21)	.09
UNOS	—	—	—	—
No. (%) HCV infection				
HIVTR	47 (81)	60 (71)	18 (75)	.37
UNOS	277 (73)	253 (77)	62 (70)	.3

^aFor tests comparing transplant, no transplant, and died groups within cohort.

Table 3. Causes of Pretransplantation Mortality in HIV(+) and HIV(-) Candidates

	HIVTR HIV(+) cases	UNOS HIV(-) controls
No. deaths (%)	24/167 (14.4)	88/792 (11.1)
Cause of death, n (%) ^a		
Sepsis, infection	6/24 (25.0)	18/88 (20.4)
Multiple organ failure	4/24 (16.7)	23/88 (26.1)
Gastrointestinal bleed	3/24 (12.5)	5/88 (5.7)
Other causes	7/24 (29.2)	24/88 (27.3)
Unknown	4/24 (16.7)	18/88 (20.4)

^a P value = .67 for comparison between HIVTR and UNOS.

The HIV(+) HIVTR and HIV(-) control subjects did not differ overall in most of the baseline characteristics (Tables 1 and 2). The 2 groups were similar in age, sex, and ethnicity. The proportion with private medical insurance coverage was significantly lower in HIV(+) than in HIV(-) control subjects, $P < .0001$. Another difference was the median baseline body mass index (BMI), significantly lower in HIV(+) than in HIV(-) control subjects, $P < .0001$. The geographic regions of the transplant centers also varied between both groups ($P < .0001$), with the majority of HIV(+) cases receiving a transplant in New England, New York, the mid-Atlantic states, and the Southwestern United States.

The primary causes of pretransplantation death—sepsis and multiple organ system failure—did not differ between groups (Table 3). No patients with HIV infection were reported to have died of opportunistic infections. A total of 34% (29/85) of HIV(+) subjects not undergoing transplantation was either removed early from the study

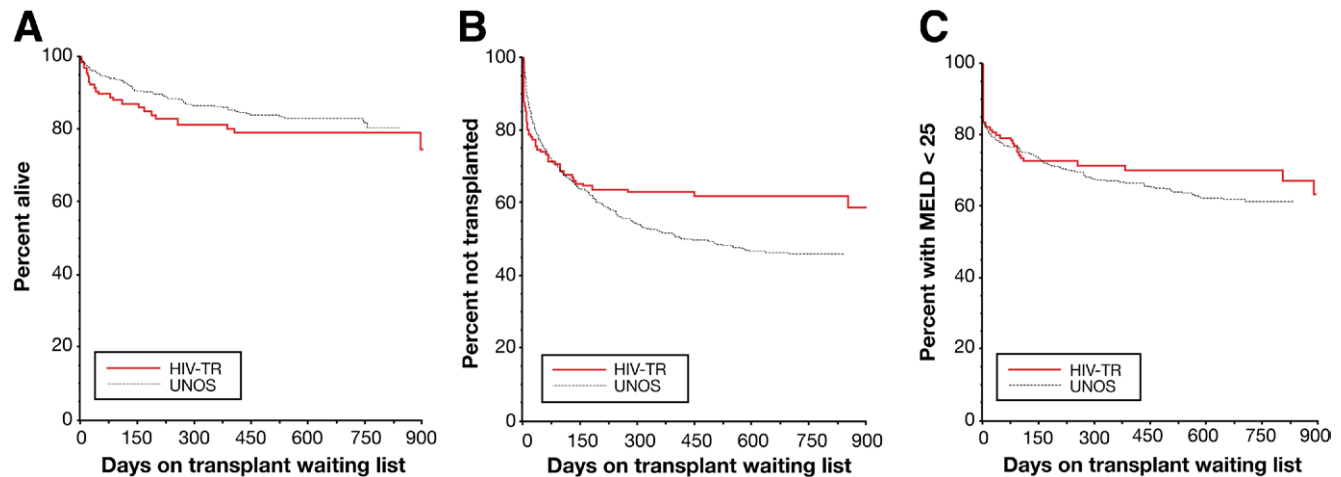


Figure 1. (A) Time to death in HIV(+) transplant candidates. This Kaplan Meier plot shows that time to death is similar in HIV(+) and HIV(-) transplant candidates, $P = .18$. (B) Time to transplantation in HIV(+) transplant candidates. This Kaplan Meier plot shows that time to transplantation is similar in HIV(+) and HIV(-) transplant candidates, $P = .13$. (C) Time to MELD score ≥ 25 in HIV(+) transplant candidates. This Kaplan Meier plot shows the time to elevation of MELD score to ≥ 25 is similar in HIV(+) and HIV(-) transplant candidates, $P = .13$.

or temporarily inactive on the liver transplant waiting list, primarily because of active illicit drug use or no longer meeting HIV-specific inclusion criteria. On review of the UNOS cohort group, 20% had a status of temporarily inactive on the liver transplant wait list as of the data cut-off date ($P = .01$).

Time to Elevated MELD Score and Death

Comparing time-to-event curves for death, transplant, and MELD score ≥ 25 between HIV(+) subjects and HIV(-) UNOS controls revealed no significant differences (Figure 1), even for the HCV-infected subgroups (data not shown).

HIV-Related Characteristics

Within the HIV-infected group, HIV-related variables were analyzed by transplant status, as shown in Table 2. HIV(+) subjects who died pretransplantation had a significantly lower median CD4 count at enrollment (237 cells/ μL) than those who received a transplant (315 cells/ μL , $P = .01$). No significant differences were observed in nadir CD4 count, proportion with detectable HIV RNA at enrollment, history of AIDS-related opportunistic infections, or use of protease-inhibitor containing initial antiretroviral regimen by transplant status, eg, expired vs receiving transplant. No specific antiretroviral medication or combination of medications was associated with death.

Predictors of Pretransplantation Mortality for the Overall Cohort

In multivariate proportional hazards regression models for the overall cohort and the HCV-infected subgroup, adjusting for the baseline MELD, BMI, and region, the hazard of pretransplantation mortality was not significantly higher in HIV(+) subjects (HR, 1.69; 95% CI:

0.76–3.75; $P = .20$) compared with HIV(-) subjects (HR, 1.71; 95% CI: 0.67–4.35; $P = .26$). An additional interaction term between HIV status and baseline MELD score was also nonsignificant ($P = .33$), ie, HIV status did not have a significant impact on the association between baseline MELD score and the hazard of death. In both multivariate models, the baseline MELD score was the only significant predictor of pretransplantation mortality (HR, 1.31; 95% CI: 1.21–1.41 and HR, 1.36; 95% CI: 1.22–1.51, respectively, $P < .0001$).

Predictors of Pretransplantation Mortality for HIV-Infected Subjects

In univariate proportional hazards models (Table 4), HCV infection, CD4 count at enrollment, and protease inhibitor use were not associated with increased risk of death or MELD score elevation of ≥ 25 . Detectable

Table 4. Risk Factors for Pretransplantation Mortality in HIV (+) Transplant Candidates

	HR for death	P value	HR, MELD score >25	P value
Univariate analysis				
Risk factor at enrollment				
MELD > 25	15.0	<.0001	—	
HCV coinfection	1.0	0.97	0.8	0.52
Protease inhibitor regimen	1.5	0.37	1.2	0.59
CD4 count < 200/ μL	1.1	0.74	1	0.94
Detectable HIV RNA	3.2	0.02	2.79	0.005
Multivariate analysis				
Risk factor at enrollment				
MELD score 15–19	5.7	0.005		
MELD score 20–24	21.4	<.0001		
MELD score ≥ 25	101.1	<.0001		
CD4 count < 200/ μL	2.4	0.07		
Detectable HIV RNA	1.0	0.98		

HIV RNA at baseline, however, increased the hazard of death (HR, 3.2; 95% CI: 1.2–8.6, $P = .02$) and rate of progression to MELD score ≥ 25 (HR, 2.79; 95% CI: 1.4–5.7, $P = .005$). Not surprisingly, high baseline MELD score (≥ 25) was also associated with greater hazard of death (HR, 15.0; 95% CI: 5.2–43.3, $P < .0001$).

In multivariate proportional hazards models for death, after controlling for CD4 count and detectable HIV RNA, the only significant predictor of mortality was pretransplantation MELD score. This was true for MELD score as a dichotomous variable < 25 and ≥ 25 (HR, 19.5; 95% CI: 5.8–66.0, $P < .001$) and as a 4-level categorical variable (Table 4). When MELD score < 15 was used as the reference category, relative hazard increased as MELD score increased. When baseline MELD score was examined as a linear variable, after adjusting for both CD4 count $< 200/\mu\text{L}$ and detectable baseline HIV RNA, each unit increase in MELD score was associated with a 20% increase in the risk of pretransplantation death ($P < .0001$).

Discussion

ESLD in patients coinfecting with HIV and HCV has only recently become an indication for liver transplantation.^{12–14} With the availability of HAART, the mortality from HIV is declining. It is projected, however, that mortality from HCV will continue to increase over the next 25 years.¹⁵ HIV is known to accelerate the progression of HCV-associated liver fibrosis, cirrhosis, hepatic encephalopathy, and death,^{9,16} whereas HAART may slow ESLD progression among coinfecting individuals.^{11,17} Unique risk factors for ESLD and liver-related mortality have been identified in HIV/HCV coinfecting patients, such as a limited CD4 improvement and failure to maintain an undetectable viral load on antiretroviral therapy.^{8–10} Despite these data suggesting that HIV disease stage and/or its treatment with antiretroviral therapy may impact mortality in HIV-infected patients considered for liver transplantation, organ allocation in most centers has been based on models derived from HIV-uninfected persons with ESLD. Importantly, our data demonstrate that, after controlling for variables such as CD4 count at the time of listing and HIV RNA level, baseline MELD score was the only independent predictor of pretransplantation mortality in HIV-infected liver transplant candidates.

A lower proportion of the HIV-infected patients underwent transplantation as compared with the UNOS controls. This may be partly explained by the regional variation of the participating transplant centers or complicating illness precluding transplantation. The majority of HIV-infected patients were located in regions of the country that historically have longer wait times for organs, whereas the UNOS controls were evenly distributed throughout the United States. A higher percentage of HIV-infected subjects were either on temporarily inactive status or removed from the wait list as compared with the UNOS controls, which may have led to the differ-

tial rates of transplant. There was, however, no difference in cause of death between both groups nor were there any deaths because of opportunistic infections in the HIV-infected patients. This cohort of patients was required to have a fairly robust CD4 count at entry and maintain it above 100 cells/mL to remain eligible for a transplant. This may explain the lack of opportunistic infections seen.

Interestingly, there was no significant difference in mortality in HIV-infected and uninfected patients waiting for liver transplantation. In contrast, previous reports have found shorter pretransplantation survival in HIV-positive liver transplant candidates, unrelated to severity of liver or HIV disease.^{8,9} Unlike these studies that included patients irrespective of stage of HIV disease, patients in our study met specific HIV disease criteria (eg, adequately controlled HIV replication and CD4 count $\geq 100/\mu\text{L}$) in addition to standard transplant criteria for other comorbid conditions. Furthermore, they were enrolled only at the time of placement on the transplant wait list and underwent rigorous routine pretransplantation evaluation, including cardiac stress tests and pulmonary function tests, with optimization of their overall health status by multiple subspecialty care providers. It is possible that lead bias affected our results, for example, if subjects in this study were at an earlier stage of ESLD than HIV-infected patients in the previous studies. Nonetheless, among HIV-infected persons considered for liver transplantation, our findings strongly support use of the MELD score to predict mortality and to guide the allocation of limited organs, given that each point increase in MELD score was associated with a 20% greater risk of death in our HIV-infected patients.

Patients with HCC were not included in this cohort because they receive priority for organ allocation, which could introduce bias when evaluating predictors of mortality. A recent case-control study of patients with HCC showed that those with HIV infection were usually younger and more likely symptomatic, but tumor staging and survival appeared to be similar in those with and without HIV infection.¹⁸ It will be important to prospectively study outcomes in HIV-infected patients with HCC.

The data we report have implications for monitoring and management of the HIV/HCV coinfecting individual. There may be better predictors of mortality in HIV/HCV coinfection, especially in patients with more advanced HIV disease, such as MELD score combined with CD4 count. Furthermore, MELD-Na, which incorporates serum sodium concentrations along with the traditional MELD calculations, may be a more accurate predictor.¹⁹ Unfortunately, we had insufficient data to determine whether any of these markers would have been better predictors of pretransplantation mortality.

Our study suggests a smaller proportion of coinfecting patients come to transplantation as compared with HCV

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monoinfected patients. Although the reasons for this are not known, it would seem prudent for HIV providers to calculate MELD scores on all HIV/HCV coinfecting patients during routine quarterly HIV monitoring to help guide decisions on prompt referral for transplant evaluation. Overall, this study demonstrates that pretransplantation mortality risks in HIV(+) transplant candidates with CD4 count >100, who meet criteria for placement on the liver transplant wait list, are similar to HIV(-) candidates. Because the MELD score is an equally reliable predictor in both groups, these data support the incorporation of MELD score as part of standard HIV medical management.

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Conflicts of interest

The authors disclose no conflicts.

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