Published in final edited form as:

Liver Transpl. 2017 June ; 23(6): 762–768. doi:10.1002/lt.24688.

Hemophilia Liver Transplantation Observational Study (HOTS)

Margaret V. Ragni, MD, MPH¹, Abhinav Humar, MD², Peter G. Stock, MD, PhD³, Emily A. Blumberg, MD⁴, Bijan Egtesad, MD⁵, John J. Fung, MD, PhD⁵, Valentina Stosor, MD⁶, Nicholas Nissen, MD⁷, Michael T. Wong, MD⁸, Kenneth E. Sherman, MD, PhD⁹, Donald M. Stablein, PhD¹⁰, and Burc Barin, MS¹⁰

¹Division Hematology/Oncology, University of Pittsburgh and Hemophilia Center of Western Pennsylvania, Pittsburgh, PA

²Division of Transplant Surgery, Starzl Transplant Institute, University of Pittsburgh

³Division of Transplant Surgery, University of California, San Francisco, CA

⁴Division of Infectious Diseases, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

⁵Transplant Center and Department of General Surgery, Cleveland Clinic Foundation, Cleveland, OH

⁶Divisions of Infectious Diseases and Organ Transplantation, Northwestern University, Feinberg School of Medicine, Chicago, IL

⁷Division Transplant Surgery, Cedars-Sinai Medical Center, Los Angeles, CA

⁸Division of Transplant Medicine, Beth Israel Deaconess Medical Center, Boston MA

⁹Division of Digestive Disorders, University of Cincinnati, Cincinnati OH

¹⁰Emmes Corporation, Baltimore, MD

Abstract

Hepatitis C (HCV) infection is the leading cause of liver disease in hemophilia. In those with HIV/HCV co-infection, the rate of liver disease progression is greater than in HCV mono-infected individuals. Despite antiretroviral therapy which slows HCV liver disease progression, some require transplantation. Whether transplant outcomes are worse in hemophilic (H) than non-hemophilic (NH) candidates is unknown. In order to determine rates and predictors of pre- and

Address of Corresponding Author: Margaret V. Ragni, MD, MPH, Professor of Medicine and Clinical Translational Science Department of Medicine, Division of Hematology/ Oncology, University of Pittsburgh Medical Center; Director, Hemophilia Center of Western PA, 3636 Boulevard of the Allies, Pittsburgh, PA 15213-4306; Phone: 412-209- 7288; Fax: 412-209-7281; ragni@dom.pitt.edu.

Author Contribution

MR designed the study, assisted in data collection, analyzed and interpreted the data, and wrote the manuscript. AH, PS, EB, BE, JF, VS, NN, MW, and KS collected the data and reviewed the manuscript. DS and RW reviewed the data and manuscript. BB designed the study, maintained data files, performed the data analyses, and reviewed the manuscript.

Disclosure

The authors have no conflicts of interest to disclose.

Conflicts of Interest:

None of the authors declares any conflicts of interest.

post-transplant survival, we conducted a retrospective observational study utilizing United Network for Organ Sharing (UNOS) national transplant registry data, comparing HCV+ H and NH candidates. We identified 2,502 HCV+ liver transplant candidates from eight U.S. university-based transplant centers, between January 1, 2004 to December 31, 2010, including 144 HIV+ (6%) and 2,358 HIV-; 36 H (1%) and 2,466 NH; 1,213 (48%) transplanted and 1,289 not transplanted. Other than male predominance and younger age, each $p < 0.001$, baseline data were comparable between H and NH. In univariate analysis, 90-day pre-transplant mortality was associated with higher baseline MELD, $HR = 1.15$, $p < 0.001$, lower baseline platelet count, $HR = 1.11$ per 25k/JL, $p = 0.04$, and having HIV/HCV+ hemophilia, $p = 0.003$. In multivariate analysis, pre-transplant mortality was associated with higher MELD ($p < 0.001$) and was significantly greater in HIV+ than HIV- groups ($p = 0.001$), but did not differ between HIV+ H and NH, $HR = 1.7$, $p = 0.36$. Among HIV/HCV+, post-transplant mortality was similar between H and NH, despite lower CD4 in H, $p = 0.04$.

Conclusions—This observational study confirms that hemophilia per se does not have a specific influence on transplant outcomes, and that HIV infection increases the risk of mortality in both H and NH patients.

Keywords

bleeding disorders; HCV infection; HIV infection; pre-transplant survival; UNOS

Introduction

Hepatitis C (HCV) is the major cause of chronic liver disease and mortality among adults with hemophilia (1, 2). Approximately 90% of hemophilic men exposed to HCV through clotting factor concentrates prior to the AIDS era, became infected with HCV (3, 4), and up to 80% of HCV-infected hemophilic men were co-infected with HIV (1, 3). HIV accelerates HCV liver disease progression (1, 2, 5–7), and, although combination antiretroviral therapy (cART) improves HIV survival (8), slows HCV progression to end-stage liver disease (ESLD), and improves ESLD-free survival (9–11), some ultimately require liver transplantation. After 25 years of HIV/HCV co-infection, about one-fourth have biopsy-proven fibrosis (2) and 5–10% have progressed to ESLD (1, 2), consistent with findings in other risk groups (6, 11).

In contrast to other risk groups, however, individuals with hemophilia have 1) longer duration HCV infection, with acquisition via clotting factor typically in the first year of life (12); and 2) greater bleeding risk and occurrence of bleeding complications (1, 2, 7, 13) due to factor VIII (or IX) deficiency in the setting of thrombocytopenia and prolonged INR in end-stage liver disease (ESLD). These risks are important as duration of HCV infection has been shown to be a significant predictor of liver disease progression (1, 6, 14), and increased bleeding frequency, including gastrointestinal bleeding (7, 13) increases post-transplant mortality (7, 15, 16).

Several studies have shown that post-transplant survival is shorter in HIV/HCV co-infected than HCV mono-infected candidates, and not different between HIV/HCV hemophilic and non-hemophilic recipients (7, 17, 18), pre-transplant survival in HIV/HCV co-infected

candidates with hemophilia is shorter than in non-hemophilic candidates (19). As the latter studies were small, analysis for predictors of pre-transplant survival was limited. Thus, we sought to evaluate pre-transplant outcomes using a larger national database of U.S. transplant candidates, the United Network for Organ Sharing (UNOS), collaborating with the eight transplant centers of the original HIV solid organ transplant study (HIV-TR) with hemophilia transplant candidates (18).

Methods

Subjects

We identified 2,817 subjects in the UNOS (United Network for Organ Sharing) database (20) by the following criteria: all HCV+ liver transplant candidates listed or transplanted at one of the eight centers, participating in the HIV-TR Study (18) between January 1, 2004 and December 31, 2010, and who did not have hepatocellular carcinoma or a MELD/PELD exclusion anytime on the waiting list. HCV+ subjects were identified as any candidate or corresponding recipient who had a diagnosis for transplant related to hepatitis C or who at the time of transplantation was HCV seropositive. A 7-item case report form was completed on each subject by respective transplant centers. UNOS datasets were provided to each of the eight centers to identify each subject by 1) hemophilia status (hemophilia A, ICD 286.0; hemophilia B, ICD 286.1); 2) hepatocellular carcinoma status; 3) HIV status; 4) CD4+ count; 5) HIV RNA PCR; 6) HCV RNA PCR; and 7) platelet count, the latter four labs at listing and at transplantation. Data were entered by participating sites on the Emmes online data entry system, cleaned, and verified. After eliminating 315 cases for other hepatocellular cancer (HCC) cases identified in the UNOS datasets (N=287), missing records, missing HIV status, missing hemophilia status, or hemophilia C, a total of 2,502 liver transplant candidates remained for analysis.

Statistical Analysis

We performed univariate proportional hazards models for pre-transplant mortality within 90 days of listing, which included group and baseline factors (Table 1). Variables with $p < 0.1$ from the univariate models were included in an initial multivariate model. Kaplan-Meier time to-event curves were constructed for liver transplant candidates, including time to death, time to transplant, and time to MELD 25; and for liver transplant recipients, including time to death and time to graft loss. Statistical analysis was carried out using SAS version 9.3, Cary NC.

Results

We identified 2,502 HCV+ liver transplant candidates, including 144 (6%) with HIV infection and 36 (1%) with hemophilia, and 1,213 (48%) transplant recipients (Table 1). Baseline data among groups were comparable, although, as expected, the proportion of males was significantly higher in those with hemophilia, as compared with non-hemophilic groups, and age was significantly lower in the HIV+ hemophilia group, as compared with the other three groups, $p < 0.001$. Among HIV+ groups, BMI was lower than in the HIV-

groups, $p<0.001$, and log HCV RNA was higher in the HIV+ non-hemophilic group than in the other three groups, $p<0.001$.

Clinical outcomes are shown in Table 2. A total of 1,289 pre-transplant candidates were not transplanted (18 H, 1271 NH); 771 remained alive or were removed from listing pre-transplant (13 H, 758 NH); and 518 expired pre-transplant (5 H, 513 N). The most common causes of pre-transplant death included multi-organ failure in 113 (22%) (1 H, 112 NH); sepsis or infection in 86 (17%) (0 H, 86 NH); other causes in 157 (30%) (3 H, 154 NH); or unknown causes in 162 (31%) (1 H, 161 NH).

Among the transplant candidates, the overall pre-transplant patient survival at 90 days and 6 months from listing did not differ significantly between H and NH groups (Table 3). In the first 90-days post-listing, time-to-event curves for death and elevated MELD 25 were significantly different between groups, log-rank, $p<0.001$ and 0.02, respectively. Time-to-event curves for transplant within the first 90 days were not significantly different between the four groups, $p=0.26$ (Figures 1 and 2).

In univariate proportional hazards models, pre-transplant mortality within 90-days of listing was associated with higher baseline MELD (HR=1.15, $p<0.001$), and lower baseline platelet count (HR=1.11 per 25k/JL, $p=0.04$) (Table 4). Compared with the HIV- NH group, HIV+ H candidates (HR=5.1, $p=0.001$) and HIV+ NH candidates (HR=1.8, $p=0.04$) had a significantly higher hazard of pre-transplant mortality, marginally worse in HIV+ H candidates than in HIV+ NH candidates (HR=2.8, $p=0.08$). Factors with $p<0.1$ from the univariate model were included in an initial multivariate model: after dropping platelet count (<100 K vs. 100 K), $p=0.67$, the model was refit. In the final multivariate model, higher MELD score was significantly associated with pre-transplant mortality ($p<0.001$), and the two HIV+ groups combined had significantly worse pre-transplant survival within 90 days of listing than the two HIV- groups combined, $p=0.001$. The hazard of pre-transplant mortality, however, was not significantly worse in HIV+ H than HIV+ NH (HR=1.7, $p=0.36$).

Clinical outcomes among transplant recipients are shown in Table 2. Of 2,502 transplant candidates, 1,213 underwent liver transplantation (18 H and 1,195 NH), of whom 943 remain alive (12 H and 931 NH); and 270 expired post-transplant (6 H and 264 NH). The most common causes of post-transplant death were multi-organ failure in 40 (15%) (0 H, 40 NH); sepsis or infection in 54 (20%) (3 H, 51 NH); other causes in 148 (55%) (3 H, 145 NH); or unknown cause in 28 (10%) (0 H, 28 NH). Among the 1,213 liver transplant recipients, post-transplant mortality at one-year and three-years after transplantation did not differ significantly between H and NH groups (combined log-rank, $p=0.31$), and, similarly, post-transplant graft survival did not differ between H and NH groups (combined log-rank, $p=0.62$) (Table 5). In the first three years post-transplant, Kaplan-Meier time-to-death was significantly different between HIV+ and HIV- groups (combined log-rank, $p=0.002$, as was time-to-graft loss, $p=0.002$ (Figure 2). Time to death was significantly different only between HIV+ NH and HIV- NH groups (log-rank, $p=0.01$), but not between HIV+ H and HIV- H groups ($p=0.40$), likely due to small hemophilia sample size. Similarly, graft

survival was significantly different between HIV+ NH and HIV– NH groups (log-rank, $p=0.003$), but not between HIV+ H and HIV– H group ($p=0.40$).

Discussion

This retrospective observational study was designed to determine the predictors of poor pre-transplant survival in hemophilic men, using UNOS national transplant registry data from eight U.S. transplant centers. Given the importance of age (14) and bleeding risk (15, 16) in HCV outcome and in ESLD thrombocytopenia (1, 2, 7, 13) and the recognized longer duration of HCV infection (1, 2, 17) in those with hemophilia than in non-hemophilic transplant candidates, we identified a hazard ratio of 2.0 for pre-transplant mortality, comparing HIV+ hemophilic and non-hemophilic transplant candidates. While the increased risk was large, it was not significant and could be the result of the small number of HIV/HCV+ transplant candidates. Our previous solid organ transplant HIV-TR sub-study (19) did identify significantly poorer pre-transplant survival in hemophilia, but as it was a small pilot study, we sought to confirm the findings in a larger study. Utilizing the large UNOS database, we hypothesized that MELD was not as good a predictor of pre-transplant mortality in hemophilic than non-hemophilic candidates, and that hemophilia status itself shortens pre-transplant survival because of longer HCV duration and greater bleeding in the setting of ESLD thrombocytopenia.

The HOTS study also found that survival in HIV+ candidates was poorer than in HIV– candidates, which differs from the findings of the larger HIV-TR study (18), likely related to differences between the studies. First, the HOTS analysis was of four comparison groups, including hemophilia status, while the HIV-TR study was only a two-comparison group analysis, HIV+ vs HIV-. Secondly, while our study focused on HCV+, non-HCC candidates, the HIV-TR study included HCV– and HCC candidates: it is well-known that pre-transplant outcomes are worse in HCV+, non-HCC candidates who have HIV co-infection. However, both studies showed increased mortality in HIV+ pre-transplant candidates, which, while not significant in the previous HIV-TR study, was significant in this study, likely related to the small number of hemophilic transplant candidates. The greater risk of pre-transplant death in HIV+ than HIV- patients was independent of the MELD score, as indicated in multivariate analysis. Thus, exception MELD points might be given to HIV+ candidates to mitigate this disadvantage.

The current study has several limitations. The first is the small sample size, especially the small number of hemophilia candidates, some of whom may have been missed by retrospective ICD classification, limiting the power to address hemophilia-specific questions. Second, although direct acting antiviral agents are now available to treat HCV, many hemophilic men may not have received and benefitted from them. Thus, this study is relevant and timely.

One potential approach to address these limitations is by implementation of ICD classification codes for hemophilia, hemophilia A, 286.0 (D66), hemophilia B, 286.1 (D67), in the UNOS transplant registry. While hemophilia is a rare disease characterized by fewer than 1 in 50,000 male births, it is of note that hemophilic men who develop ESLD account

for 10% of all liver transplants performed in HIV/HCV co-infected individuals in the U.S. (1, 17, 18). In addition, in hemophilia patients with ESLD who develop bleeding complications, e.g. gastrointestinal tract bleeding, mortality may increase while awaiting transplantation (7, 15, 16), confirming the importance of early, aggressive factor replacement. Third, as new direct acting antiviral agents (DAA) are incorporated into pre- and post-transplant management, the proportion requiring transplant should be monitored, as well as outcome among those who undergo transplant. Increasingly, evidence indicates DAAs not only provide excellent control of chronic HCV infection, but also improve post-transplant survival and pre-transplant outcomes, with some candidates no longer requiring transplantation (21).

In summary, this observational study confirms hemophilia per se does not have significant influence on pre-transplant and post-transplant outcomes, and that HIV infection increases mortality in both H and NH patients.

Acknowledgments

Grant: This research was funded by Grant H30MC24050 PA-00024104 from HRSA Health Resources and Services Administration, Rockville MD, U.S. Department of Health and Human Services (DHHS), Region III Federally Funded Hemophilia Treatment Centers.

We thank the Participating Sites and Personnel for their outstanding work gathering and interpreting the data to accomplish this study: *University of Pittsburgh Medical Center, Pittsburgh, PA:* Abhi Humar, MD; Megan Basch BSN; Sheila Fedorek BSN; Roy Hill, BS; *Beth Israel Deaconess Medical Center, Harvard Medical School, Boston MA:* Michael Wong, MD; Susan McDermott, BSN, Julia Moore, BS; *Cedars Sinai Medical Center, University of California, Los Angeles:* Nicholas Nissen, MD; Janet Clarke-Platt, RN; *Cleveland Clinic Foundation, Cleveland OH:* Bijan Eghestad, MD; John Fung, MD, PhD; Mary Oldenburgh, RN; *Northwestern University, Chicago IL:* Valentina Stosor, MD; Jane Charette, RN; Emma Hoffman, RN; *University of Pennsylvania, Philadelphia PA:* Emily Blumberg, MD; Maryann Najdzinowicz, BSN; *University of California, San Francisco, CA:* Peter Stock, MD, PhD; Rodney Rogers, RN; *University of Cincinnati, OH:* Kenneth Sherman MD, PhD; Carrie Jennings, CNP; *Emmes Corporation:* Donald Stablein, PhD; Burc Barin, MS; Roe Wright, BS.

Abbreviations

cART	combination antiretroviral therapy
CD4	cluster differentiation 4/ helper T cells
DAA	direct-acting antiviral agents
ESLD	end-stage liver disease
H	hemophilia
HCC	hepatocellular cancer
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-TR	HIV solid organ transplant study
HR	hazard ratio
NH	non-hemophilia

MELD	model for end-stage liver disease
OLT	orthotopic liver transplantation
PELD	pediatric end-stage liver transplantation
UNOS	United Network for Organ Sharing

References

1. Ragni MV, Belle SH. Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C infection. *J Infect Dis*. 2001; 183:1112–1115. [PubMed: 11237838]
2. Ragni MV, Moore CG, Soadwa K, Nalesnik MA, Zajko AB, Cortese-Hassett A, et al. Impact of HIV on liver fibrosis in men with hepatitis C infection and hemophilia. *Hemophilia*. 2011; 17:103–111.
3. Ragni MV, Winkelstein A, Kingsley LA, Spero A, Lewis JH. 1986 Update of HIV seroprevalence, seroconversion, AIDS incidence and immunologic correlates of HIV infection in hemophiliacs. *Blood*. 1987; 70:786–790. [PubMed: 2887224]
4. Ragni MV, Ndimbe OK, Rice EO, Bontempo FA, Nedjar S. Presence of antibody to hepatitis C virus (HCV) in hemophilic men with HCV 'seroreversion'. *Blood*. 1993; 82:1010–1015. [PubMed: 7687887]
5. Hay CRM, Preston FE, Trigger DR, Underwood JCE. Progressive liver disease in hemophilia: an understated problem? *Lancet*. 1985; 1:1495–1498. [PubMed: 2861420]
6. Pineda JA, Romero-Gomez M, Diaz-Garcia F, Girón-González JA, Montero JL, Torre-Cisneros J, et al. HIV co-infection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. *Hepatology*. 2005; 41:779–789.
7. Ragni MV, Eghtesad B, Schlesinger KW, Dvorchik I, Fung J. Pre-transplant survival is shorter in HIV-positive than in HIV-negative subjects with end-stage liver disease. *Liver Transplant*. 2005; 11:1425–1430.
8. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity among patients with advanced human immunodeficiency virus infection. *N Engl J Med*. 1998; 338:853–860. [PubMed: 9516219]
9. Ragni MV, Nalesnik MA, Schillo R, Dang Q. Highly active antiretroviral therapy improves ESLD-free survival in HIV-HCV co-infection. *Haemophilia*. 2009; 15:552–558. [PubMed: 19347994]
10. Qurishi N, Creuzberg C, Luchters G, Effenberger W, Kupfer B, Sauerbruch T, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus co-infection. *Lancet*. 2003; 362:1708–1713. [PubMed: 14643119]
11. Mehta SH, Thomas DL, Torbenson M, Brinkley S, Mirel L, Chaisson RE, et al. The effect of antiretroviral therapy on liver disease among adults with HIV and hepatitis C co-infection. *Hepatology*. 2005; 41:123–131. [PubMed: 15619237]
12. Kasper CK, Kipnis SA. Hepatitis and clotting factor concentrates. *JAMA*. 1972; 221:510.
13. Mehta KD, Ragni MV. Bleeding and liver transplantation outcomes in hemophilia. *Blood*. 2016; in press. doi: 10.1111/hae.13104
14. Kirk GD, Mehta SH, Astemborski J, Balai N, Washington J, Higgins Y, et al. HIV, age, and the severity of hepatitis C virus-related liver disease: A cohort study. *Ann Intern Med*. 2013; 158:658–666. [PubMed: 23440167]
15. Gamil ME, Pirenne J, Malenstein HV, Verhaegen M, Desschans B, Monbaliu D, et al. Risk factors for bleeding and clinical implications in patients undergoing liver transplantation. *Transplant Proc*. 2012; 44:2857–2860. [PubMed: 23146542]
16. Bleibel W, Caldwell SH, Curry MP, Northup PG. Peripheral platelet count correlates with liver atrophy and predicts long-term mortality on the liver transplant waiting list. *Transplant International*. 2014; 26:435–442.
17. Ragni MV, Belle SH, Im K, Neff G, Roland M, Stock P, et al. Survival in HIV-infected liver transplant recipients. *J Infect Dis*. 2003; 188:1412–1420. [PubMed: 14624365]

18. Terrault NA, Roland ME, Schiano T, Dove L, Wong MT, Poordad F, et al. Outcomes of liver transplantation in HCV-HIV co-infected recipients. *Liver Transplant*. 2012; 18:716–726.
19. Ragni MV, DeVera M, Roland ME, Wong MT, Stosor V, Sherman KE, et al. Liver transplant outcomes in HIV-infected hemophilic men. *Haemophilia*. 2013; 19:134–140. [PubMed: 22762561]
20. Organ procurement and transplantation network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN / SRTR 2010 Annual Data Report. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; http://www.srtr.org/annual_reports/2010/ [Accessed July 2012]
21. Stock PG, Terrault NA. Human immunodeficiency virus and liver transplantation: hepatitis C is the last hurdle. *Hepatology*. 2015; 61:1747–1754. [PubMed: 25292153]

Figure 1. Pre-transplant Outcomes in HIV/HCV Co-Infected Candidates

Figure 1a: Time to Death in Liver Transplant Candidates

This figure shows Kaplan-Meier time-to-death curves for all four groups, including HIV+ hemophilic, HIV+ non-hemophilic, HIV- hemophilic, and HIV- non hemophilic candidates, $p < 0.001$, for overall comparison in the first 90 days post-listing.

Figure 1b: Time to Transplant in Liver Transplant Candidates

This figure shows Kaplan-Meier time-to-transplant curves for all four groups, including HIV + hemophilic, HIV+ non-hemophilic, HIV- hemophilic, and HIV- non-hemophilic candidates, $p = 0.26$, for overall comparison in the first 90 days post-listing.

Figure 1c: Time to Elevated MELD (25) in Liver Transplant Candidates

This figure shows Kaplan-Meier time-to-MELD 25 curves for all four groups, including HIV+ hemophilic, HIV+ non-hemophilic, HIV-hemophilic, and HIV- non- hemophilic candidates, $p = 0.02$, for overall comparison in the first 90 days-post- listing.

Figure 2. Post-transplant Outcomes in HIV/HCV Co-Infected Recipients

Figure 2a: Time to Death in Liver Transplant Recipients

This figure shows Kaplan-Meier time-to-death curves for all four groups, including HIV+ hemophilic, HIV+ non-hemophilic, HIV– hemophilic, and HIV– non-hemophilic recipients, $p=0.02$, for overall comparison in the first 3 years post-transplant.

Figure 2b: Time to Graft Loss in Liver Transplant Recipients

The figure shows Kaplan-Meier time-to-graft loss curves for all four groups, including HIV+ hemophilic, HIV+ non-hemophilic, HIV– hemophilic, and HIV– non-hemophilic recipients, $p=0.02$, for overall comparison in the first 3 years post-transplant.

Table 1

Baseline Demographics of HCV Liver Transplant Candidates

All Transplant Candidates					
	HIV+ H	HIV+ NH	HIV- H	HIV- NH	p-value
Transplant Candidates	18	126	18	2340	
Pre-Transplant					
Alive/Discontinued Follow-up	5	57	8	701	
Expired	4	32	1	481	
Transplanted	9	37	9	1,158	
Gender (Male)	18 (100%)	98 (78%)	18 (100%)	1634 (70%)	p<0.001
Race					p=0.60
Caucasian	16 (89%)	81 (64%)	15 (83%)	1681 (72%)	
Black	1 (6%)	19 (15%)	1 (6%)	280 (12%)	
Asian	0 (0%)	5 (4%)	0 (0%)	57 (2%)	
Other	1 (6%)	21 (17%)	2 (11%)	2018 (1%)	
Age (Median)	41	48	51	53	p<0.001
BMI	25	25	29	28	p<0.001
CD4⁺ (No./μl)	242	316	-	-	p=0.16
Platelet ($\times 10^3$/L)	68	77	64	74	p=0.91
Platelet <100K	0(0%)	6 (5%)	1(6%)	178 (8%)	p=0.97
MELD	21	16	15	16	p=0.12
HIV RNA (+)	6(33%)	28(22%)	-	-	p=0.38
HCV RNA (+)	12(67%)	93(74%)	11(61%)	1444(62%)	p=0.10

H = Hemophilic; NH = Non-Hemophilic; BMI is body-mass index; MELD is model for end-stage liver disease.

Table 2

Clinical Outcomes in Liver Transplant Candidates

	HIV+ H (N=18)	HIV+ NH (N=126)	HIV- H (N=18)	HIV- NH (N=2,340)	p-value
No. Pre-Transplant Not Transplanted	9 (50%)	89 (71%)	9 (50%)	1182 (51%)	
No. Alive/ <u>Discontinued Follow-up</u>	5 (28%)	57 (45%)	8 (44%)	701 (30%)	
Deteriorated, too sick to transplant	1 (20.0%)	13 (23%)	0 (0%)	184 (26%)	
Improved, transplant not needed	0 (0%)	5 (9%)	1 (13%)	35 (5%)	
Other causes	1 (20%)	14 (25%)	2 (25%)	175 (25%)	
Refused transplant	0 (0%)	4 (7%)	0 (0%)	18 (3%)	
Still waiting transplant	1 (20%)	11 (19%)	2 (25%)	150 (21%)	
Transferred to another center	0 (0%)	4 (7%)	1 (13%)	54 (8%)	
Transplanted at another center	2 (40%)*	2 (40%)	1 (13%)	45 (6%)	
Unable to contact	0 (0%)	4 (7%)	1 (13%)	40 (6%)	
No. Expired Pre-Transplant	4 (22%)	32 (25%)	1 (6%)	481 (21%)	
Cause of Pre-Transplant Death					p=0.85
Sepsis, infection	0 (0%)	3 (9%)	0 (0%)	83 (17%)	
Multi-organ failure	1 (25%)	9 (28%)	0 (0%)	103 (21%)	
Other causes	2 (50%)	11 (34%)	1 (100%)	143 (30%)	
Unknown	1 (25%)	9 (28%)	0 (0%)	152 (32%)	
No. Transplanted	9 (50%)	37 (29%)	9 (50%)	1158 (49%)	
No. Alive/ Discontinued Follow-up	5 (56%)	57 (62%)	7 (78%)	908 (78%)	
No. Expired Post-Transplant	4 (44%)	14 (38%)	2 (22%)	250 (22%)	
Cause of Post-Transplant Death					p=0.57
Sepsis, infection	3 (75%)	3 (21%)	0 (0%)	48 (19%)	
Multi-organ failure	0 (0%)	2 (14%)	0 (0%)	38 (15%)	
Other causes	1 (25%)	7 (50%)	2 (100%)	138 (55%)	
Unknown	0 (0%)	2 (14%)	0 (0%)	26 (10%)	

H = Hemophilic, NH = Non-Hemophilic

Table 3

Clinical Outcomes in Pre-Transplant Candidates

Time Point	Group	Pre-Transplant Subject Survival	Pre-Transplant Not Transplanted	Pre-Transplant MELD<25
90-day	HIV+ H	77% (CI 49,91)	72% (CI 41,89)	44% (CI 21,65)
	HIV+ NH	89% (CI 82,94)	82% (CI 74,88)	72% (CI 63,79)
	HIV- H	100% (CI 100,100)	83% (CI 57,94)	89% (CI 61,97)
	HIV- NH	94% (CI 93,95)	74% (CI 72,76)	72% (CI 70,74)
6-month	HIV+ H	77% (CI 49,91)	56% (CI 26,78)	44% (CI 21,65)
	HIV+ NH	89% (CI 82,94)	71% (CI 62,79)	65% (CI 56,73)
	HIV- H	100% (CI 100,100)	83% (CI 57,94)	89% (CI 61,97)
	HIV- NH	90% (CI 89,91)	66% (CI 64,68)	67% (CI 65,69)

Table 4

Proportional Hazards Regression Models for Pre-Transplant Death

Univariate Predictor	HR (95% CI)	p-value
Group (Comparison group: HIV-NH)		0.003
HIV+ H	5.1 (1.9, 13.9)	0.001
HIV+ NH	1.8 (1.02, 3.3)	0.04
HIV– H	#	0.97
MELD Score *	1.15 (1.14, 1.17)	<0.001
Platelet Count (continuous, per 25k/JL)	0.9 (0.8, 0.99)	0.04
Platelet Count <100k	1.53 (1.01, 2.33)	0.047
Male gender	1.2 (0.8, 1.8)	0.40
Black race	1.2 (0.7, 2.1)	0.40
Age	1.01 (0.99, 1.03)	0.40
Estimated Duration of HCV Infection	1.01 (0.99, 1.04)	0.24
BMI	0.98 (0.95, 1.01)	0.25
Combined Kidney-Liver candidate	1.4 (0.9, 2.4)	0.15
Detectable HCV viral load	1.8 (0.7, 4.5)	0.19
Log HCV RNA	1.0 (0.8, 1.2)	0.88
CD4 Count (per 50 cells/JL) §	1.0 (0.9, 1.1)	0.90
Detectable HIV viral load §	1.0 (0.2, 4.4)	0.96
Log HIV RNA §	1.3 (0.9, 1.9)	0.14
Multivariate Predictors	HR (95% CI)	p-value
MELD Score *	1.16 (1.14, 1.17)	<0.001
Group (compared to HIV-Non-Hemophilic) **		0.003
HIV+ Hemophilic	4.3 (1.6, 11.8)	0.004
HIV+ Non-hemophilic	2.2 (1.2, 4.0)	0.01
HIV– Hemophilic	#	0.98

* Within 90 days prior to enrollment;

§, including HIV+ groups only;

did not converge.

** The hazard of pre-transplant mortality was not significantly worse in HIV+ hemophilic than HIV+ non-hemophilic, HR=1.7, 95% CI (0.5, 5.6), p=0.36. The two HIV+ groups combined had significantly worse pre-transplant survival within 90 days of listing compared to the two HIV- groups combined, HR=2.5, 95%CI (1.5, 4.3), p=0.001.

Table 5

Clinical Outcomes in Liver Transplant Recipients

Time Point	Group	Post-Transplant Subject Survival	Post-Transplant Graft Survival	Time Point*	Post-Transplant Rejection
1-year	HIV+ H	78% (CI 36,94)	78% (CI 36,94)	6-month	14% (CI 0,58)
	HIV+ NH	65% (CI 47,79)	61% (CI 44,75)		6% (CI 0,27)
	HIV-H	78% (CI 36,94)	78% (CI 36,94)		29% (CI 4,71)
3-year	HIV-NH	86% (CI 83,88)	82% (CI 79,84)	1-year	10% (CI 8,12)
	HIV+ H	56% (CI 20,80)	56% (CI 20,80)		14% (CI 0,58)
	HIV+ NH	59% (CI 40,73)	52% (CI 35,67)		6% (CI 0,30)
	HIV-H	78% (CI 36,94)	78% (CI 36,94)		33% (CI 4,78)
	HIV-NH	77% (CI 74,79)	72% (CI 70,75)		13% (CI 11,16)

* Recorded for 6-month and 1-year time points in the UNOS database; exact timing not known.