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Shingo Shimada
Henry Ford Health, sshimad1@hfhs.org

Tommy Ivanics
Henry Ford Health, tivanic1@hfhs.org

Toshihiro Kitajima
Henry Ford Health, tkitaji1@hfhs.org

Tayseer Shamaa
Henry Ford Health, tshamaa1@hfhs.org

Michael Rizzari
Henry Ford Health, MRizzar1@hfhs.org

See next page for additional authors

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Authors

Shingo Shimada, Tommy Ivanics, Toshihiro Kitajima, Tayseer Shamaa, Michael Rizzari, Kelly Collins, Atsushi Yoshida, Marwan S. Abouljoud, Dilip Moonka, Jiaqi Zhang, Mei Lu, and Shunji Nagai

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ORIGINAL ARTICLE

Improvements in liver transplant outcomes in patients with HCV/HIV coinfection after the introduction of direct-acting antiviral therapies

Shingo Shimada[1] | Tommy Ivanics[1] | Toshihiro Kitajima[1] | Tayseer Shamaa[1] | Michael Rizzari[1] | Kelly Collins[1] | Atsushi Yoshida[1] | Marwan Abouljoud[1] | Dilip Moonka[2] | Jiaqi Zhang[3] | Mei Lu[3] | Shunji Nagai[1]

[1]Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, Michigan, USA

[2]Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, Michigan, USA

[3]Department of Public Health Sciences, Henry Ford Hospital, Detroit, Michigan, USA

Correspondence
Shunji Nagai, Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202, USA.
Email: snagai1@hfhs.org

Abstract

Background: In recipients with HCV/HIV coinfection, the impact that the wider use of direct-acting antivirals (DAAs) has had on post-liver transplant (LT) outcomes has not been evaluated. We investigated the impact of DAAs introduction on post-LT outcome in patients with HCV/HIV coinfection.

Methods: Using Organ Procurement and Transplant Network/United Network for Organ Sharing data, we compared post-LT outcomes in patients with HCV and/or HIV pre- and post-DAAs introduction. We categorized these patients into two eras: pre-DAA (2008-2012 [pre-DAA era]) and post-DAA (2014–2019 [post-DAA era]). To study the impact of DAAs introduction, inverse probability of treatment weighting was used to adjust patient characteristics.

Results: A total of 17 215 LT recipients were eligible for this study (HCV/HIV [$n = 160$]; HIV mono-infection [$n = 188$]; HCV mono-infection [$n = 16\,867$]). HCV/HIV coinfection and HCV mono-infection had a significantly lower hazard of 1- and 3-year graft loss post-DAA, compared pre-DAA (1-year: adjusted hazard ratio [aHR] 0.29, 95% confidence interval (CI) 0.16–0.53 in HIV/HCV, aHR 0.58, 95% CI 0.54–0.63, respectively; 3-year: aHR 0.30, 95% CI 0.14–0.61, aHR 0.64, 95% CI 0.58–0.70, respectively). The hazards of 1- and 3-year graft loss post-DAA in HIV mono-infection were comparable to those in pre-DAA. HCV/HIV coinfection had significantly lower patient mortality post-DAA, compared to pre-DAA (1-year: aHR 0.30, 95% CI 0.17–0.55; 3-year: aHR 0.31, 95% CI 0.15–0.63).

Conclusions: Post-LT outcomes in patients with coinfection significantly improved and became comparable to those with HCV mono-infection after introducing DAA therapy. The introduction of DAAs supports the use of LT in the setting of HCV/HIV coinfection.

KEYWORDS
direct-acting antivirals, hepatitis C virus, human immunodeficiency virus, liver transplantation, posttransplant outcome

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immune deficiency syndrome; cART, combination antiretroviral therapy; DAAs, direct-acting antivirals; DCD, donation after circulatory death; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTIs, integrase strand transfer inhibitors; IPTW, inverse probability of treatment weighting; LT, liver transplantation; MELD, model for end-stage liver disease; OPTN, Organ Procurement and Transplant Network; SVR, sustained virological response; UNOS, United Network for Organ Sharing; US, United States

1 | INTRODUCTION

Liver transplantation (LT) for patients with human immunodeficiency virus (HIV) was initially considered a contraindication due to high mortality from acquired immune deficiency syndrome (AIDS).[1] Nevertheless, the number of LTs for patients with HIV has been increasing. Prior to 1996, anti-HIV drugs such as HIV reverse transcriptase inhibitors were used that were less potent and well tolerated.[2] The introduction of the protease inhibitor in the mid-1990s allowed the use of highly effective combination antiretroviral therapy (cART), which was key in treating HIV and improving life expectancy of those living with HIV.[2,3] In the current era cART is very potent at maintaining virologic suppression and is associated with near normal life expectancy in those living with HIV.[4] In line with these change, post-LT outcomes in these patients have also improved.[5]

In the United States about 20% of people living with HIV have either evidence of past or current hepatitis C virus (HCV) infection, although this does vary substantially depending on the risk group such as intravenous drug users.[6,7] Infection with both HIV and HCV is called HIV/HCV coinfection, according to the Centers for Disease Control and Prevention.[8] In general, HIV coinfection worsens the general survival in patients with HCV because the HIV leads to rapid progression of hepatitis, increases the risk of viral persistence, and accelerates the development of cirrhosis and hepatocellular carcinoma (HCC) than in HCV mono-infected patients.[9–11] Compared to patients with HCV mono-infection, the risk of progression to end stage liver disease is six-fold more rapid in patients with HCV/HIV coinfection.[12] Post-LT survival rates were significantly lower in recipients with HCV/HIV coinfection than in HCV mono-infection due to a higher incidence of severe forms of recurrence of HCV such as fibrosing cholestatic hepatitis and the rapid progression of fibrosis.[5,13] While only strictly selected recipients with HCV/HIV coinfection could showed similar post-LT outcome to the US LT recipients, post-LT graft survival in overall recipients with HCV/HIV coinfection was worse than those in recipients with HCV mono-infection according to US multicenter trial.[14]

Emerging direct-acting antivirals (DAAs) regimens, introduced in late 2013, have dramatically changed the outcome and care in patients with HCV infection.[15,16] Before 2013, interferon and ribavirin-based treatment regimens were mainly used for patients with HCV, which had limited efficacy and debilitating side effects, making them contraindicated in patients with decompensated cirrhosis.[17] DAAs have a remarkably high sustained virological response (SVR) rate 12 weeks after treatment completion, resulting in significant reductions in morbidity in patients with HCV.[15] DAAs have been used for LT candidates and recipients with HCV, which successfully prevent post-LT recurrence of HCV.[18,19] While the safety and efficacy of DAAs for LT patients with HCV mono-infection is well reported and has been associated with improvements in post-LT outcomes,[18–20] the impact of DAA introduction on post-LT outcomes in recipients with HCV/HIV coinfection remains to be elucidated.

We hypothesized that DAA introduction would dramatically improve the post-LT outcomes in not only patients with HCV mono-infection but also patients with HCV/HIV coinfection, and that the effects of DAA introduction might be different between patients with HCV mono-infection and patients with HCV/HIV coinfection. The aim of this study is to investigate possible different impact of DAAs on post-LT outcomes in patients with HCV/HIV coinfection compared to those with HCV mono-infection. To study these aims, possible improvements in cART during the study period should be acknowledged, which might have synergetic effects with DAA and further improve post-transplant outcomes in patients with HCV/HIV coinfection. To address possible confounding effects of recent improvement in HIV therapies, post-transplant outcomes were compared between the following three groups: HCV/HIV coinfection, HCV mono-infection, and HIV mono-infection.

2 | MATERIALS AND METHODS

2.1 | Patient

We analyzed the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) Standard Transplant and Research files for LT from January 1, 2008, to December 31, 2019. Patients 18 years or older at LT and patients with HCV and/or HIV were included for this study.

Patients who had diagnosis code(s) of 4104 (acute hepatic necrosis [AHN]: type C), 4106 (AHN: type B and C), 4204 (cirrhosis type C), 4206 (cirrhosis: type B and C), and/or 4593 (hepatitis C: chronic or acute) were classified as HCV infection. Patients with HIV positive serostatus were classified as HIV infection. Patients who were re-transplanted or had transplants combined with other organs were excluded (Figure 1).

The study period was classified into two eras to assess possible impact of DAAs on post-LT outcomes in recipients with HCV/HIV coinfection: a pre-DAA era (pre-DAA), which included patients transplanted from January 1, 2008 to December 31, 2012, and a post-DAA era (post-DAA), which included patients transplanted from January 1, 2014 to December 31, 2019. To allow a washout period of the effect of DAAs, patients transplanted in 2013 were excluded because DAAs became available in 2013.[21] Patients were censored on the last day of each era (December 31, 2012, in the pre-DAA or December 31, 2019, in the post-DAA, respectively) in the post-LT outcome analysis to eliminate impact on DAA on post-LT outcomes of patients in the pre-DAA. Continuous covariates included age, model for end stage liver disease (MELD) score, serum albumin, and cold ischemia time. Gender, moderate/severe ascites, encephalopathy, life support requirement, portal vein thrombosis, donation after circulatory death (DCD) donor, and donor HCV status were considered as binary variables. Categorical variables included Karnofsky score (10-30%, 40%–60%, and 70%–100%), MELD (MELD-Na) score (6–29, 30–34, 35 or higher), serum albumin value (<3.0 mg/dl, 3.0–3.9 mg/dl, and 4.0 mg/dl or higher), and cold ischemia time (<6 h, 6–7.9 h, and 8h or higher). The categorized recipient and donor age (<30 years old [yo], 30–39 yo, 40–49 yo, 50–59 yo, 60–69 yo, 70 yo, or higher) were used for inverse probability of treatment weighting (IPTW) estimation. This study was approved for an institutional review board (IRB) waiver after IRB review.

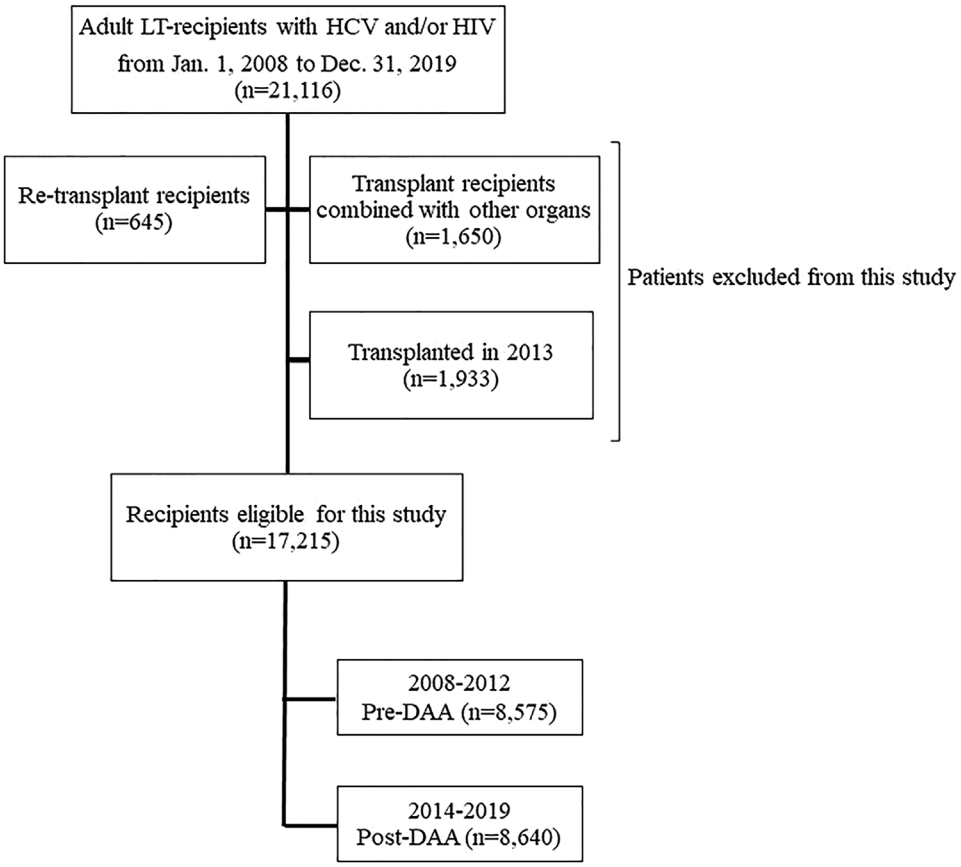

FIGURE 1 Flow chart of study population selection

2.2 | Outcome of interest

The study evaluated the impact of DAA therapy on post-LT outcomes, which might be influenced by infection status. Within each era, we classified patients into three infection status categories: HCV, HIV monoinfection, and HIV/HCV coinfection. One- and three-year graft loss and patient mortality were compared between eras in each infection status group.

2.3 | Statistical analysis

Descriptive analyses, for example, continuous variables were shown as median with interquartile range, categorical discrete variables were shown as percentage. The Mann–Whitney *U* test for continuous variables and chi-square were used to test the population difference between the pre- and post-DAA. Kaplan–Meier curve analysis was used for posttransplant survival and compared by log-rank tests. For risk analyses, we used the IPTW score-a weighted propensity-score approach[22] for the entire population to adjust for characteristic differences between the era (pre-DAA) without and with the introduction of DAAs (post-DAA). We used standardized mean difference to examine the balance of each covariate between two ears before and after IPTW.

The variables used to calculate the IPTW are shown in Table 1. The probability of a subject to be assigned into post-DAA, defined as p, was estimated using logistic regression with post-DAA regressed on observed baseline characteristics such as age, gender, liver laboratory results, and donor information before LT. Each subject's weight was calculated as $1/p$ if the subject was in the post-DAA or $1/(1-p)$ if subject was in pre-DAA. If there were no significant differences between the two eras after adjusting for IPTW, the two populations were balanced, or post-DAA selection bias was controlled. To estimate the risk of viral infection and DAAs induction, multivariable Cox regression with IPTW was used. A p-value $< .05$ was considered significance. All variables or variable-by-DAAs interactions with p-value $< .05$ were retained in the final multivariable model; estimated adjusted hazard ratios (aHR) were illustrated. All statistical analyses were completed using SPSS version 27 (IBM, Chicago, USA), R version 3.5.1 (R Foundation for Statistical Computing, Vienna Austria), and SAS 9.4 (SAS Institute, Cary NC, USA).

3 | RESULTS

3.1 | Study population and patient characteristics

Between January 1, 2008 and December 31, 2019, 21 116 adult patients with HCV and/or HIV received LT. Patients combined with

TABLE 1 Comparisons of patient characteristics in pre- and post-DAA eras and adjustment by inverse probability of treatment weighting

	Group	Pre-DAA $n = 8575$	Post-DAA $n = 8640$	p Crude	SMD Unweighted	SMD Weighted
Patients group (infectious status), *n* (%)	HCV/HIV	63 (0.7)	97 (1.1)	<.001	0.082	0.0
	HIV mono	46 (0.5)	142 (1.6)			
	HCV mono	8466 (98.7)	8401 (97.2)			
Age (year) group, *n* (%)	<30	35 (0.4)	27 (0.3)	<.001	0.587	0.0
	30–<40	106 (1.2)	106 (1.2)			
	40–<50	1004 (11.7)	486 (5.6)			
	50–<60	5008 (58.4)	3197 (37.0)			
	60–<70	2250 (26.2)	4538 (52.5)			
	70 or higher	172 (2.0)	286 (3.3)			
Gender, *n* (%)	Male	6270 (73.1)	6475 (74.9)	.006	0.041	0.011
	Female	2305 (26.9)	2165 (25.1)			
Serum albumin (mg/dl) group, *n* (%)	<3.0	4269 (49.8)	2998 (34.7)	<.001	0.336	0.030
	≥3.0, < 4.0	3430 (40.0)	4042 (46.8)			
	≥4.0	876 (10.2)	1600 (18.5)			
Grade 3/4 encephalopathy, *n* (%)		850 (9.9)	598 (6.9)	<.001	−0.107	−0.068
Moderate/severe ascites, *n* (%)		2405 (28.0)	1823 (21.1)	<.001	−0.161	−0.013
Karnofsky score, *n* (%)	10%-30%	1740 (20.3)	1390 (16.1)	<.001	0.153	0.027
	40%–60%	3100 (36.2)	3701 (42.8)			
	70%–100%	3735 (43.5)	3549 (41.1)			
MELD score group, *n* (%)	6–29	6966 (81.2)	7329 (84.8)	<.001	0.129	0.081
	30–34	676 (7.9)	449 (5.2)			
	35+	933 (10.9)	862 (10.0)			
Serum sodium group (mEq/L), *n* (%)	<135	2953 (34.4)	2172 (25.1)	<.001	0.199	0.0
	135–144	5401 (63.0)	6234 (72.2)			
	145 or higher	221 (2.6)	234 (2.7)			
Portal vein thrombosis, *n* (%)		794 (9.3)	1259 (14.6)	<.001	0.165	0.186
Life support requirement, *n* (%)		363 (4.2)	353 (4.1)	.63	0.007	0.026
Cold ischemia time (hours) group, *n* (%)	<6	3611 (42.1)	4511 (52.2)	<.001	0.238	0.0
	≥6, < 8	2578 (30.1)	2538 (29.4)			
	≥8	2386 (27.8)	1591 (18.4)			
DCD graft, *n* (%)	Yes	486 (5.7)	622 (7.2)	<.001	0.062	0.051
Donor age (year) group, *n* (%)	<30	2578 (30.1)	2268 (26.2)	<.001	0.215	0.0
	30–<40	1317 (15.3)	1739 (20.1)			
	40–<50	1853 (21.6)	1589 (18.4)			
	50–<60	1849 (21.6)	1794 (20.8)			
	60–<70	799 (9.3)	982 (11.4)			
	70 or higher	179 (2.1)	268 (3.1)			
Donor gender, *n* (%)	Male	5108 (59.6)	5237 (60.6)	.16	0.021	0.043
	Female	3467 (40.4)	3403 (39.4)			

Abbreviations: DAA, direct-acting antivirals; DCD, donation after circulatory death; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MELD, model for end-stage liver disease; SMD, standardized mean difference.

other organs ($n = 1650$), re-transplants ($n = 645$), and transplants in 2013 ($n = 1933$) were excluded. The remaining 17 215 patients were eligible for this study. Patients were divided into two groups; patients received LT in the pre-DAA ($n = 8575$) and those in the post-DAA ($n = 8640$) (Figure 1). Patient characteristics are shown in Table 1. The rates of patients with HCV/HIV coinfection undergoing LT increased from 0.7% in pre-DAA to 1.1% in post-DAA. The rates of patients with HIV mono-infection undergoing LT increased from 0.5% to 1.6% ($p < .001$).

There were significant differences in patient characteristics between pre- and post-DAA (Table 1). Compared with patients that underwent LT in pre-DAA, the proportions of DCD LT were significantly higher post-DAA (5.7%–7.2%, $p < .001$). The proportions of patients with Grade 3/4 encephalopathy (9.9%–6.9%, $p < .001$), moderate/severe ascites (28.0%–21.1%, $p < .001$), and Karnofsky score 10%–30% (20.3%–16.1%, $p < .001$) were significantly lower in the post-DAA.

3.2 | Patient characteristics in each viral status pre- versus post-DAA

Comparison of patient characteristics in each viral status between pre- and post-DAA are shown in Tables 2 and 3 and Table S1. In patients with HCV/HIV coinfection, patients received an LT in the post-DAA had lower proportions of patients with serum sodium group <135 mEq/L (42.9% vs. 24.7%, $p = .02$), and a higher proportion of liver graft receipt from HCV-antibody positive donors (9.5% vs. 23.7%, $p = .02$). The annual number of HCV/HIV coinfection cases was similar between the two eras (median: 12 cases/year in pre-DAA versus 14 cases/year in post-DAA, $p = .31$) (Table 2). In patients with HIV mono-infection, the annual number of cases with HIV mono-infection per year was significantly higher in post-DAA (median: nine cases/year in pre-DAA versus 16 cases/year in post-DAA, $p = .006$) (Table S1). Patients with HCV mono-infection received LT in the post-DAA had significantly lower proportions of patients with grade ¾ encephalopathy (9.9% vs. 6.9%, $p < .001$), moderate/severe ascites (28.1% vs. 21.2%, $p < .001$), Karnofsky score 10%–30% (20.3% vs. 16.0%, $p < .001$) compared with patients who received LT in the pre-DAA. There was no significant difference in the annual number of cases with HCV mono-infection (median: 1689 cases vs. 1410 cases, $p = .27$) (Table 3).

3.3 | The risks of graft loss and patient mortality between each era in viral infectious status

The populations were balanced after adjusting for IPTW (Table 1). The risks of graft loss in patients who received LT in the post-DAA were significantly lower in patients with HCV/HIV coinfection and HCV mono-infection (HCV/HIV coinfection; 1-year: aHR 0.29, 95% confidence interval (CI) 0.16–0.53, 3-year: aHR 0.30, 95% CI 0.14–0.61, HCV mono-infection; 1-year: aHR 0.58, 95% CI 0.54–0.63, 3-year: aHR 0.64, 95% CI 0.58–0.70 [ref. pre-DAA]) (Figure 2A). The risks of 1-year and 3-year graft loss in patients received LT in the post-DAA were not significantly different from those in the pre-DAA in patients with HIV mono-infection. Similar trends were observed when comparing 1-year patient mortality between eras in each viral status (Figure 2B). In terms of causes of death within 3-year after LT in patients with HCV/HIV coinfection, no graft failure due to recurrence of HCV was found in the post-DAA (45.0% pre-DAA vs. 0% post-DAA, $p = .01$). AIDS-related death within 3-year after LT was 15.4% in the post-DAA while it was 0% in the pre-DAA ($p = .29$) (Table 4). In patients with HCV mono-infection, there were 19 cases of graft failure within 3-year after LT due to recurrence of HCV in the post-DAA while there were 342 cases of graft failure due to recurrence of HCV in the pre-DAA (19.3% vs. 1.8%, $p < .001$) (Table S2).

3.4 | The risks of graft loss and patient mortality stratified by the viral infectious status in each era

In the pre-DAA, the adjusted risks for 1- and 3-year graft loss in patients with HCV/HIV coinfection were significantly higher than those with HCV mono-infection (1-year: aHR 2.79, 95% CI 1.94–3.98, 3-year: aHR 2.48, 95% CI 1.80–3.40) or HIV mono-infection (1-year: aHR 4.05, 95% CI 1.97–8.32, 3-year: aHR 2.76, 95% CI 1.59–4.78) (Figure 3A). In the post-DAA, no statistically significant difference was observed in the risk of 1- and 3-year graft loss between the groups (Figure 3B). Figures S1 and S2 show graft survival curves for these viral infection groups in each era.

Similarly, in the pre-DAA, the adjusted risks of 1-year and 3-year patient mortality in patients with HCV/HIV coinfection were significantly higher than those with HCV mono-infection (1-year: aHR 2.60, 95% CI 1.82–3.72, 3-year: aHR 2.36, 95% CI 1.72–3.23) or HIV mono-infection (1-year: aHR 4.72, 95% CI 2.26–9.87, 3-year: aHR 2.62, 95% CI 1.56–4.39) (Figure 3C). In the post-DAA, no statistically significant difference was observed in the risk of 1-year and 3-year patient mortality among each viral status (Figure 3D). Figures S3 and S4 show patient survival curves for these viral infection groups in each era.

4 | DISCUSSION

This study revealed that post-LT outcomes in patients with coinfection significantly improved and became comparable to those with HCV mono-infection after introducing DAA therapy. Post-LT outcomes in patients with HCV/HIV coinfection have become equivalent to those with HCV or HIV mono-infection in the post-DAA era. Because of the significantly worse post-LT outcomes in this particular population, indications of LT for patients with HIV/HCV coinfection needed to be more carefully assessed. The findings in this study indicate that, after DAAs introduction, patients who have end stage liver disease associated with HCV/HIV coinfection could be considered as LT candidates similarly to those with HCV or HIV mono-infection.

The risks of post-LT patient mortality and graft loss were significantly lower in the post-DAA era in patients with coinfection and

TABLE 2 Comparisons of characteristics of patients with HCV/HIV coinfection between eras

	Group	Pre-DAA *n* = 63	Post-DAA *n* = 97	*p*-Value
Annual number of cases, median (IQR)		12 (9, 16)	14 (12, 20)	.31
Age (year), median (IQR)		54.0 (49.5, 57.0)	57.0 (52.0, 62.0)	.001
Gender, *n* (%)	Male	48 (76.2)	72 (74.2)	.93
	Female	15 (23.8)	25 (25.8)	
Serum albumin (mg/dl) group, *n* (%)	<3.0	28 (44.4)	31 (32.0)	.16
	≥3.0, <4.0	20 (31.7)	45 (46.4)	
	≥4.0	15 (23.8)	21 (21.6)	
Grade 3/4 encephalopathy, *n* (%)		5 (7.9)	6 (6.2)	.91
Moderate/severe ascites, *n* (%)		15 (23.8)	12 (12.4)	.09
Karnofsky score, *n* (%)	10%–30%	9 (14.3)	15 (15.5)	.19
	40%–60%	23 (36.5)	48 (49.5)	
	70%–100%	31 (49.2)	34 (35.0)	
MELD score group, *n* (%)	6–29	51 (81.0)	80 (82.5)	.91
	30–34	5 (7.9)	6 (6.2)	
	35+	7 (11.1)	11 (11.3)	
Serum sodium group (mEq/L), *n* (%)	<135	27 (42.9)	24 (24.7)	.02
	135–144	36 (57.1)	69 (71.1)	
	145 or higher	0 (0)	4 (4.1)	
Portal vein thrombosis, *n* (%)		6 (9.5)	10 (10.3)	1.00
Life support requirement, *n* (%)		1 (1.6)	3 (3.1)	.94
Cold ischemia time (hours) group, *n* (%)	<6	31 (49.2)	44 (45.4)	.38
	≥6, <8	21 (33.3)	27 (27.8)	
	≥8	11 (17.5)	26 (26.8)	
DCD graft, *n* (%)		4 (6.3)	7 (7.2)	1.00
Donor age (year), median (IQR)		42.0 (27.5, 53.0)	38.0 (29.0, 52.0)	.76
Donor gender, *n* (%)	Male	34 (54.0)	59 (60.8)	.49
	Female	29 (46.0)	38 (39.2)	
Donor HCV, *n* (%)		6 (9.5)	23 (23.7)	.02

Note: Data were summarized using the median with IQR for continuous variables and using percentage for discrete variables. Continuous variables were analyzed using the Mann–Whitney *U* test, and discrete variables were analyzed using a chi-square test.

Abbreviations: DAA, direct-acting antivirals; DCD, donation after circulatory death; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; MELD, model for end-stage liver disease.

HCV mono-infection. Due to differences in the patient characteristics between the pre- and post-DAA eras, IPTW was used to adjust for possible confounding effects to evaluate causal impacts of DAAs on the post-LT outcomes. IPTW is a causal inference method developed to emulate randomized controlled studies using observational data.[23,24] After the risk adjustment, in patients with HCV mono-infection, the risk of graft loss and patient mortality were approximately 50% lower in the post-DAA era, whereas the risk of graft loss and patient mortality were 70% lower in patients with HCV/HIV coinfection. Patients with HIV mono-infection did not show significant improvements in posttransplant outcomes, especially in 3-year patient and graft survival. The findings from those comparisons between 3 groups further supported our hypothesis that DAA had different prognostic effects in HCV/HIV coinfection group, compared to HCV mono-infection group.

According to the previous report, which investigated LT-recipients with HIV infection, HCV recurrence as cause of death has decreased in HCV mono-infected patients, but not in HCV/HIV coinfected patients.[25] Meanwhile, there was no graft failure due to recurrence of HCV for the cause of death in the post-DAA era in the HCV/HIV coinfection group in our study, despite contributing to nearly half of all graft losses in the pre-DAA era. Similarly, a significant decrease in the HCV mono-infection group was noted. These effects are likely related to the introduction of DAA therapy. Possible reasons for the worse post-LT outcomes in patients with coinfection might be associated with HIV status and control. Recently, simplified regimens that

TABLE 3 Comparisons of characteristics of patients with HCV mono-infection between eras

	Group	Pre-DAA $n = 8466$	Post-DAA $n = 8401$	p-Value
Annual number of cases, median (IQR)		1689 (1666, 1692)	1410 (1216, 1645)	.27
Age (year), median (IQR)		56.0 (52.0, 60.0)	60.0 (56.0, 64.0)	<.001
Gender, *n* (%)	Male	6184 (73.0)	6290 (74.9)	.007
	Female	2282 (27.0)	2111 (25.1)	
Serum albumin (mg/dl) group, *n* (%)	<3.0	4222 (49.9)	2911 (34.6)	<.001
	≥3.0, <4.0	3386 (40.0)	3940 (46.9)	
	≥4.0	858 (10.1)	1550 (18.5)	
Grade 3/4 encephalopathy, *n* (%)		835 (9.9)	577 (6.9)	<.001
Moderate/severe ascites, *n* (%)		2381 (28.1)	1780 (21.2)	<.001
Karnofsky score, *n* (%)	10%–30%	1718 (20.3)	1345 (16.0)	<.001
	40%–60%	3058 (36.1)	3592 (42.8)	
	70%–100%	3690 (43.6)	3464 (41.2)	
MELD score group, *n* (%)	6–29	6881 (81.3)	7142 (85.0)	<.001
	30–34	667 (7.9)	428 (5.1)	
	35+	918 (10.8)	831 (9.9)	
Serum sodium group (mEq/L), *n* (%)	<135	2914 (34.4)	2110 (25.1)	<.001
	135–144	5337 (63.1)	6067 (72.2)	
	145 or higher	215 (2.5)	224 (2.7)	
Portal vein thrombosis, *n* (%)		782 (9.2)	1221 (14.5)	<.001
Life support requirement, *n* (%)		357 (4.2)	336 (4.0)	.50
Cold ischemia time (hours) group, *n* (%)	<6	3565 (42.1)	4383 (52.2)	<.001
	≥6, <8	2544 (30.0)	2475 (29.5)	
	≥8	2357 (27.8)	1543 (18.3)	
DCD graft, *n* (%)		480 (5.7)	604 (7.2)	<.001
Donor age (year), median (IQR)		42.0 (27.0, 53.0)	42.0 (29.0, 54.0)	<.001
Donor gender, *n* (%)	Male	5050 (59.7)	5090 (60.6)	.22
	Female	3416 (40.3)	3311 (39.4)	
Donor HCV, *n* (%)		638 (7.5)	1431 (17.0)	<.001

Note: Data were summarized using the median with IQR for continuous variables and using percentage for discrete variables. Continuous variables were analyzed using the Mann–Whitney *U* test, and discrete variables were analyzed using a chi-square test.

Abbreviations: DAA, direct-acting antivirals; DCD, donation after circulatory death; HCV, hepatitis C virus; IQR, interquartile range; MELD, model for end-stage liver disease.

TABLE 4 Comparisons of the causes of death after liver transplantation in patients with HCV/HIV coinfection between eras

	1-year			3-years		
	Pre-DAA n = 13	Post-DAA n = 8	p-value	Pre-DAA n = 20	Post-DAA n = 13	p-value
Graft failure due to recurrence of HCV, *n* (%)	5 (38.5)	0 (0)	.14	9 (45.0)	0 (0)	.01
AIDS-related, *n* (%)	0 (0)	0 (0)	–	0 (0)	2 (15.4)	.29
Malignancy, *n* (%)	0 (0)	2 (25.0)	.26	1 (5.0)	3 (23.1)	.31
Infection, *n* (%)	5 (38.5)	3 (37.5)	1.00	6 (30.0)	3 (23.1)	.97
Others, *n* (%)	3 (23.0)	3 (37.5)	.83	4 (20.0)	5 (38.5)	.45

Abbreviations: AIDS, acquired immune deficiency syndrome; DAA, direct-acting antivirals; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

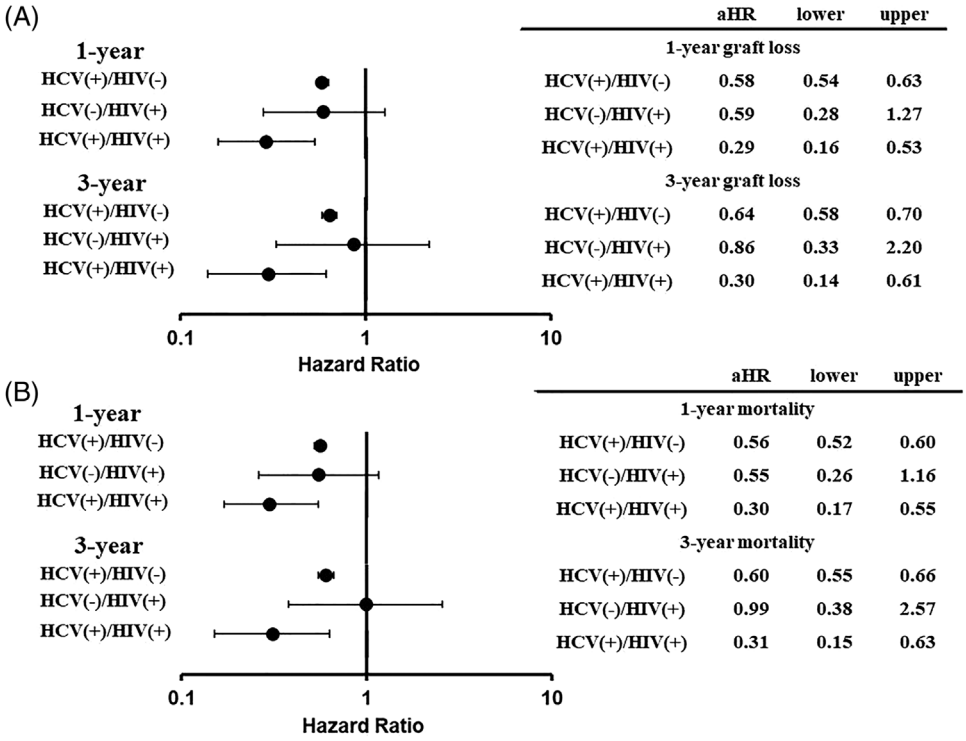

FIGURE 2 Adjusted hazards of graft loss and mortality in patients transplanted in post-direct-acting antiviral (DAA) (ref. Pre-DAA) among each viral infectious status. (A) 1-year and 3-year graft loss. (B) 1-year and 3-year mortality. Hepatitis C virus (HCV)(+)/human immunodeficiency virus (HIV)(+), HCV/HIV coinfection; HCV(+)/HIV(−), HCV mono-infection; HCV(−)/HIV(+), HIV mono-infection

can enhance medication compliance and lower drug toxicities with newer cART have been observed, which might have contributed to the greater improvement in posttransplant outcomes of patients with HCV/HIV coinfection.[26] To examine these possible effects of cART, we compared the post-LT outcomes in patients with HIV mono-infection. However, there was no difference in their risks of graft loss between eras. These results may suggest that the outcome improvements in HIV/HCV coinfection patients would be independent of cART. When patients with coinfection developed liver graft dysfunction due to post-LT HCV recurrence, they were unlikely to have received cART appropriately, potentially leading to a further deterioration in their clinical condition secondary to uncontrolled HIV. It is speculated that better control of HCV status by DAA therapy may have allowed sufficient and timely cART post-LT, leading to more significant improvements in the outcomes of patients with HIV/HCV coinfection in the post-DAA era.

HCV/HIV coinfection was a well-known risk factor for graft loss and mortality after LT.[27] This study corroborates this elevated risk for mortality and graft loss compared to recipients with HIV or HCV mono-infection. After the wider use of DAAs, the outcomes in patients with coinfection have become similar to the other two groups. Two recent papers reported that HCV/HIV coinfected LT-recipient outcomes have significantly improved, and HCV coinfection was not associated with graft failure among HIV infected LT recipients in post-DAA era.[28,29] Our study showed same results after control for characteristic differences between the era and also compared by both each viral infectious status and each era. Cotter et al. compared the risks for graft failure after LT by Cox regression model using OPTN/UNOS file according to the infectious status in pre- and post-DAA era, separately.[28] However, they did not compare the risk between pre- and post-DAA era, because of possible confounders between eras (e.g., improved medical care, LT recipient selection changes). In our study, a comparison of risk between pre- and post-DAA era in each infection type was evaluated. To reduce the impact of confounders and significant changes in patient characteristics between pre- and post-DAA eras, risk analyses for graft loss were performed after controlling possible characteristics differences between the era using IPTW approach. Recipient and donor characteristics were successfully controlled after the matching. These results further supported the different impact of DAA on posttransplant outcome between patient with HCV/HIV coinfection and with HCV mono-infection. Although HCV/HIV coinfection represents a rare indication for LT, individual transplant centers are unlikely to have sufficient experience to allow an investigation of the risks and benefits of LT for this population. Consequently, the historically poor post-LT outcomes may raise concerns when considering LT in these patients.[5,13] However, based on those findings, it should be acknowledged that this particular patient population can achieve satisfactory post-LT outcomes. While the number of LT patients with HCV mono-infection has decreased, 1.2 million people are infected with HIV in the USA, and about 25% of people with HIV in the United States also have HCV. There will be occasions for transplant practitioners in which LT needs to be considered to those with coinfection. This study thus provides essential insights

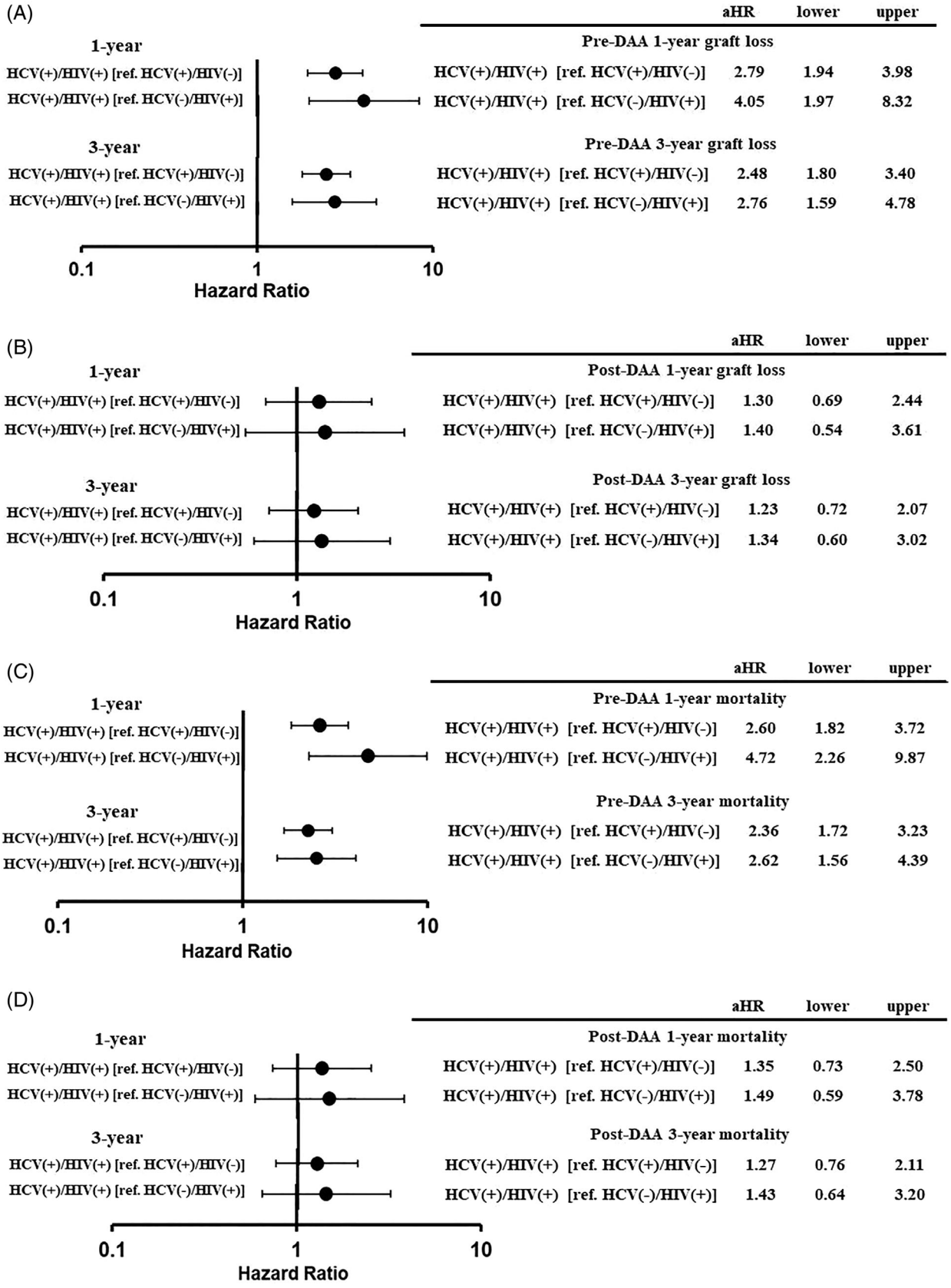

FIGURE 3 Adjusted hazards of graft loss and mortality in patient's viral infectious status in pre- and post-direct-acting antiviral (DAA). (A) Graft loss in pre-DAA. (B) Graft loss in post-DAA. (C) Patient mortality in pre-DAA. (D) Patient mortality in post-DAA. Hepatitis C virus (HCV)(+)/human immunodeficiency virus (HIV)(+), HCV/HIV coinfection; HCV(+)/HIV(-), HCV mono-infection; HCV(−)/HIV(+), HIV mono-infection

into the outcomes after LT for patients with this condition to improve patient counseling and help inform decision making.

The timing of DAA therapies (i.e., pre-LT or post-LT) for patients with coinfection and HCV mono-infection might have impacted their post-LT outcomes. There were reports, which showed the validity of pre-LT DAA treatment for patients with HCV mono-infection.[30,31] Although pre-LT DAA treatment might be beneficial, SVR rates are lower in patients with diminished liver function.[32] In addition, patients with advanced cirrhosis may not have enough time to complete DAA treatment before LT. Therefore, according to the International Liver Transplantation Society's consensus statement, it has been recommended that HCV-infected patients with advanced decompensated cirrhosis (MELD 30 or higher) or those expected to undergo LT within 3 months not to undergo antiviral therapy before transplant.[33] In the same consensus statement, pre-LT HCV antiviral therapies have been recommended for patients with coinfection to prevent liver disease progression and decompensation while awaiting an LT.[33] Of note, anti-HIV medications for cART have interactions with many drugs such as immunosuppressants, interferon, and DAAs.[34] The combination of cART and ribavirin has been associated with an increased risk of lactic acidemia.[35] Because patients with HIV/HCV coinfection continue to receive cART after LT, they might be better treated with DAAs before LT to reduce the complexity and interactions in post-LT medication regimens. When comparing the outcomes after LT in patients with HIV mono-infection between pre- and post-DAA eras, the risks of 1-year graft loss and mortality in post-DAA era tended to be lower. This might be due to increased use of integrase strand transfer inhibitors (INSTIs) in cART in these patients. In 2016, INSTIs were recommended as first line regimens for cART-naïve patients by Department of Health and Human Services guidelines.[36] Hence, INSTIs are often used for cART, recently.[37] INSTIs have fewer side effects drug interactions with anti-rejection medications and DAAs compared to older cART regimens.[38] This might give the positive impact on patients with HIV mono-infection. Of note, the improvement was not obvious in 3-year patient and graft outcomes. Detailed clinical information regarding HCV and/or HIV therapies is not available in the OPTN/UNOS registry. Future studies should therefore address the possible effects of timing and regimens of antiviral treatments.

Limitations of this study should be acknowledged. This is a retrospective study that might contain the potential for unmeasured and residual confounding even despite the IPTW analyses performed. Due to the lack of information in the OPTN/UNOS registry, the actual treatment histories for HCV and/or HIV, HCV genotype, also whether patients received DAA treatment or not were not evaluated in this study.

In conclusion, post-LT outcomes in patients with coinfection significantly improved and became comparable to those with HCV mono-infection after introducing DAA therapy. Because the outcomes of patients with HCV/HIV coinfection were similar to those in patients with HIV or HCV mono-infection after the widespread use of DAAs, LT should be more eagerly sought as a definitive treatment for this unique patient population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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None.

AUTHOR CONTRIBUTIONS

Writing of the manuscript: Shingo Shimada. *Review of the manuscript*: Tommy Ivanics, Toshihiro Kitajima, Tayseer Shamaa, Michael Rizzari, Kelly Collins, Atsushi Yoshida, Marwan Abouljoud, Dilip Moonka, and Shunji Nagai. *Study design and interpretation of the data*: Shingo Shimada, Mei Lu, and Shunji Nagai. *Data analysis*: Shingo Shimada, Jiaqi Zhang, and Mei Lu.

REFERENCES

1. Tzakis AG, Cooper MH, Dummer JS, Ragni M, Ward JW, Starzl TE. Transplantation in HIV+ patients. *Transplantation*. 1990;49:354-358.
2. Maeda K, Das D, Kobayakawa T, Tamamura H, Takeuchi H. Discovery and development of anti-HIV therapeutic agents: progress towards improved HIV medication. *Curr Top Med Chem*. 2019;19:1621-1649.
3. Mocroft A, Brettle R, Kirk O, et al. Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. *AIDS*. 2002;16:1663-1671.
4. Teeraananchai S, Kerr SJ, Amin J, Ruxrungtham K, Law MG. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. *HIV Med*. 2017;18:256-266.
5. Sawinski D, Goldberg DS, Blumberg E, Abt PL, Bloom RD, Forde KA. Beyond the NIH multicenter HIV transplant trial experience: outcomes of HIV+ liver transplant recipients compared to HCV+ or HIV+/HCV+ coinfected recipients in the United States. *Clin Infect Dis*. 2015;61:1054-1062.
6. Kim AY, Onofrey S, Church DR. An epidemiologic update on hepatitis C infection in persons living with or at risk of HIV infection. *J Infect Dis*. 2013;207(Suppl 1):S1-S6.
7. Crowell TA, Berry SA, Fleishman JA, et al. Impact of hepatitis coinfection on healthcare utilization among persons living with HIV. *J Acquir Immune Defic Syndr*. 2015;68:425-431.
8. CDC. Treatment, care, and prevention for people with HIV. Accessed July 2, 2021. https://www.cdc.gov/hiv/clinicians/treatment/coinfections.html.
9. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA*. 2000;284:450-456.
10. Goedert JJ, Eyster ME, Lederman MM, et al. End-stage liver disease in persons with hemophilia and transfusion-associated infections. *Blood*. 2002;100:1584-1589.
11. Thomas DL, Shih JW, Alter HJ, et al. Effect of human immunodeficiency virus on hepatitis C virus infection among injecting drug users. *J Infect Dis*. 1996;174:690-695.
12. Soto B, Sánchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modified the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol*. 1997;26:1-5.
13. Miro JM, Montejo M, Castells L, et al. Outcome of HCV/HIV-coinfected liver transplant recipients: a prospective and multicenter cohort study. *Am J Transplant*. 2012;12:1866-1876.
14. Terrault NA, Roland ME, Thomas Schiano T, et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. *Liver Transpl*. 2012;18:716-726.

15. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med*. 2015;373:2618-2628.
16. Flemming JA, Kim WR, Brosgart CL, Terrault NA. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. *Hepatology*. 2017;65:804-812.
17. Hezode C, Fontaine H, Dorival C, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *J Hepatol*. 2013;59:434-441.
18. Cotter TG, Paul S, Sandıkçı B, et al. Improved graft survival after liver transplantation for recipients with hepatitis C virus in the direct-acting antiviral era. *Liver Transpl*. 2019;25:598-609.
19. Arora SS, Axley P, Ahmed Z, et al. Decreasing frequency and improved outcomes of hepatitis C-related liver transplantation in the era of direct-acting antivirals - a retrospective cohort study. *Transpl Int*. 2019;32:854-864.
20. Young K, Liu B, Bhuket T, Wong RJ. Lower likelihood of post-transplant graft failure, death, and retransplantation in the era of direct-acting antivirals. *J Clin Exp Hepatol*. 2020;10:581-589.
21. Bittermann T, Reddy KR. In the era of direct-acting antivirals, liver transplant delisting due to clinical improvement for hepatitis C remains infrequent. *Clin Gastroenterol Hepatol*. 2020;S1542-3565(20):31294-31295. https://doi.org/10.1016/j.cgh.2020.09.033.
22. Steventon A, Grieve R, Sekhon J. A comparison of alternative strategies for choosing control populations in observational studies. *Health Serv Outcomes Res Methodol*. 2015;15:157-181.
23. Hernan MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183:758-764.
24. Harms MH, van Buuren HR, Corpechot C, et al. Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. *J Hepatol*. 2019;71:357-365.
25. Campos-Varela I, Dodge JL, Berenguer M, et al. Temporal trends and outcomes in liver transplantation for recipients with HIV infection in Europe and United States. *Transplantation*. 2020;104(10):2078-2086.
26. Bloch M, John M, Smith D, Rasmussen TA, Wright E. Managing HIV-associated inflammation and ageing in the era of modern ART. *HIV Med*. 2020;21(Suppl 3):2-16.
27. Miro JM, Stock P, Teicher E, Duclos-Vallée JC, Terrault N, Rimola A. Outcome and management of HCV/HIV coinfection pre- and post-liver transplantation. A 2015 update. *J Hepatol*. 2015;62:701-711.
28. Cotter TG, Wang J, Lieber SR, et al. Raising HOPE": improved outcomes for HIV/HCV-coinfected liver transplant recipients in the direct-acting antiviral era. *Transplant Direct*. 2021;7(7):e707.
29. Campos-Varela I, Dodge JL, Terrault NA, Brandman D, Price JC. Non-viral liver disease is the leading indication for liver transplant in the United States in persons living with human immunodeficiency virus. *Am J Transplant*. 2021;21(9):3148-3156.
30. Curry MP, Forns X, Chung RT, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. *Gastroenterology*. 2015;148(1):100-107.
31. Pascasio JM, Vinaixa C, Ferrer MT, et al. Clinical outcomes of patients undergoing antiviral therapy while awaiting liver transplantation. *J Hepatol*. 2017;67(6):1168-1176.
32. Cheung MC, Walker AJ, Hudson BE, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol*. 2016;65:741-747.
33. Terrault NA, McCaughan GW, Curry MP, et al. International liver transplantation society consensus statement on hepatitis C management in liver transplant candidates. *Transplantation*. 2017;101(5):945-955.
34. eacsociety. EACS guidelines 2020 version 10.1. Accessed July 1, 2021. https://www.eacsociety.org/files/guidelines-10.1_30032021_1.pdf.
35. Lafeuillade A, Hittinger G, Chadapaud S. Increased mitochondrial toxicity with ribavirin in HIV/HCV co-infection. *Lancet*. 2001;357:280-281.
36. Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Accessed January 14, 2022. http://img.thebody.com/hivatis/pdfs/adult_guide.pdf.
37. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet*. 2017;390:2063-2072.
38. Werbel WA, Durand CM. Solid organ transplantation in HIV-infected recipients: history, progress, and frontiers. *Curr HIV/AIDS Rep*. 2019;16:191-203.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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