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Journal
Current Opinion in Organ Transplantation, 20(3)

ISSN
1087-2418

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Publication Date
2015-06-01

DOI
10.1097/mot.0000000000000199

Peer reviewed

HHS Public Access

Author manuscript

Curr Opin Organ Transplant. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Curr Opin Organ Transplant. 2015 June ; 20(3): 276–285. doi:10.1097/MOT.0000000000000199.

Hepatitis C virus–HIV-coinfected patients and liver transplantation

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Abstract

Purpose of review—To review the experience to date and unique challenges associated with liver transplantation in hepatitis C virus (HCV)/HIV-coinfected patients.

Recent findings—The prevalence of cirrhosis and hepatocellular carcinoma is rising among HIV-infected individuals. With careful patient selection and in the absence of HCV infection, HIV-infected and HIV-uninfected liver transplant recipients have comparable posttransplant outcomes. However, in the presence of HCV infection, patient and graft survival are significantly poorer in HIV-infected recipients, who have a higher risk of aggressive HCV recurrence, acute rejection, sepsis, and multiorgan failure. Outcomes may be improved with careful recipient and donor selection and with the availability of new highly potent all-oral HCV direct acting antivirals (DAAs). Although all-oral DAAs have not been evaluated in HIV/HCV-coinfected transplant patients, HIV does not adversely impact treatment success in nontransplant populations. Therefore, there is great hope that HCV can be successful eradicated in HIV/HCV-coinfected transplant patients and will result in improved outcomes. Careful attention to drug–drug interactions with HIV antiretroviral agents, DAAs, and posttransplant immunosuppressants is required.

Summary—Liver transplant outcomes are poorer in HIV/HCV-coinfected recipients compared with those with HCV-monoinfection. The new HCV DAAs offer tremendous potential to improve outcomes in this challenging population.

Keywords

direct-acting antivirals; hepatitis C virus; HIV; liver transplantation

INTRODUCTION

Since the introduction of combined antiretroviral therapy (ART), the life expectancy of HIV-infected individuals has improved dramatically [1–3]. However, as AIDS-related mortality has decreased, chronic diseases such as liver and kidney disease have emerged as

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Financial support and sponsorship

JP discloses receiving a research grant from Gilead.

Conflicts of interest

AK discloses ownership interest in Gilead. JP discloses serving on an advisory board to Gilead and having ownership interest in Bristol-Myers Squibb, Johnson and Johnson, Merck, and Abbvie.

leading causes of morbidity and mortality in patients with HIV infection [4▪]. Consequently, there is a growing need for solid organ transplantation in this population. Before the advent of potent ART, HIV infection was considered an absolute contraindication to solid organ transplantation. This was largely due to concerns that posttransplant immunosuppression would compromise control of HIV infection leading to life-threatening opportunistic infections, as well as questions about the appropriateness of transplantation in HIV-infected recipients given the limited supply of organs and unknown clinical outcomes in this group.

Over the last decade, however, several studies have demonstrated that outcomes after solid organ transplant in select HIV-infected patients can be comparable with those of HIV-negative patients [5,6]. In patients with well controlled HIV on ART, rapid progression of HIV posttransplant has not been observed, with CD4 counts normalizing within 1 year of transplant, and opportunistic infections can be avoided with appropriate prophylaxis. Furthermore, drug–drug interactions (DDIs) between ART and immunosuppressive agents, previously a well recognized obstacle to posttransplant management [7], are becoming less of a barrier with the advent of newer ARTs with fewer cytochrome P450 (CYP450) interactions. Nevertheless, HIV and hepatitis C virus (HCV)-coinfected individuals have demonstrably poorer outcomes after liver transplant than HIV-uninfected and/or HCV-uninfected recipients. This article will review the experience to date with liver transplantation in HIV/HCV-coinfected patients and will discuss the critical role the new HCV direct-acting antivirals (DAAs) are expected to have in this challenging patient population.

KEY POINTS

- HIV is no longer a contraindication to solid organ transplantation.
- Outcomes after liver transplant are poorer in HIV/HCV-coinfected recipients than HCV-monoinfected recipients primarily due to more aggressive HCV recurrence.
- All-oral HCV DAAs have not been studied in HIV/HCV-coinfected transplant recipients, but HIV does not appear to negatively impact DAA efficacy.
- Careful attention must be paid to drug–drug interactions between HIV antiretroviral therapy, HCV DAAs, and immunosuppressive agents.
- Whether pre-or posttransplant HCV eradication will improve outcomes in HIV/HCV-coinfected recipients remains to be seen.

HIV AND LIVER DISEASE

Liver disease is a leading cause of morbidity and mortality among patients infected with HIV [4▪]. This is primarily due to a high prevalence of coinfection with HCV or hepatitis B virus (HBV) as a consequence of shared routes of transmission. Furthermore, HIV infection accelerates the natural history of viral hepatitis-related liver disease. Compared with individuals with HCV monoinfection, the risk of progression to end-stage liver disease in HIV/HCV-coinfected patients is six-fold higher [8–10], and once hepatic decompensation

has occurred, survival is significantly poorer [11–13]. Similarly, higher rates of liver-related mortality have been demonstrated in HIV/HBV-coinfected versus HBV-monoinfected individuals [14,15].

With the decline of competing AIDS-related mortality, as well as aging among the HIV-infected population in the USA, the prevalence of cirrhosis has risen 3.7-fold in this patient group over the last 10–15 years [16]. Rates of cirrhosis complications have also risen: Ioannou *et al.* [16] demonstrated a 23-fold rise in the prevalence of hepatocellular carcinoma (HCC) in the United States HIV/HCV-coinfected veteran population from 1996 to 2009, and a similar rise in HCC in the setting of HIV has been reported in Canada, Spain, and France [17–19]. Although it is unclear whether HIV increases the risk of developing HCC, HCC appears to occur at a younger age and is more aggressive in patients with HIV infection [17,19]. Given the rising prevalence of end-stage liver disease and HCC in HIV-infected patients as well as poorer survival in HIV/HCV-coinfected and HIV/HBV-coinfected patients with cirrhosis, there is a great need for liver transplantation in the HIV-infected population.

LIVER TRANSPLANTATION OUTCOMES IN HIV-INFECTED PATIENTS

HIV/hepatitis B virus coinfection

Multiple reports have demonstrated excellent outcomes after liver transplantation for patients with HIV/HBV coinfection [20,21]. The largest prospective cohort of liver transplantation in HIV/HBV coinfection demonstrated cumulative patient and graft survival rates of 100 and 85% in 20 HBV-monoinfected and 22 HIV/HBV-coinfected patients, respectively, at median follow-up of 42 months ($P = 0.08$) [20]. There were three deaths in the HIV/HBV-coinfected group, all in the first year after transplant and none related to HBV recurrence or AIDS-related opportunistic complications. No patients required retransplantation for graft loss. Combination prophylaxis with hepatitis B immunoglobulin and anti-HBV nucleoside or nucleotide analogues was used indefinitely posttransplantation. Although low-level HBV viremia was intermittently detected in 54% of coinfected recipients, HBV surface antigen (HBsAg) remained negative and alanine aminotransferase (ALT) was not elevated. A European prospective cohort study reported similarly outstanding outcomes among 13 HIV/HBV-coinfected patients, survival at median follow-up of 27 months was 100%, and no HBV viremia was detected posttransplant [21]. This experience confirms that liver transplantation is appropriate and feasible in select HIV-infected patients.

HIV/hepatitis C virus coinfection

In contrast to the experience with HIV/HBV coinfection, posttransplant outcomes in HIV/HCV-coinfected patients have been more sobering. In the absence of HIV, due to posttransplant HCV recurrence, HCV-infected liver transplant recipients have lower overall graft and patient survival compared with HCV-negative recipients [22]. However, patient and graft survival are even poorer in HIV/HCV-coinfected compared with HCV-monoinfected recipients [23–25]. In a French single center prospective cohort study of 79 HCV-infected liver transplant recipients, including 35 with HIV/HCV coinfection, 2-year

and 5-year survival was 73 and 51% in the HIV/HCV-coinfected group compared with 91 and 81% in the HCV-monoinfected group ($P = 0.004$) [23]. In a larger prospective United States multicenter cohort study including 89 HIV/HCV-coinfected recipients and 235 HCV-monoinfected controls, 3-year patient survival was 60% in the HIV/HCV-coinfected versus 79% in the HCV-monoinfected group ($P < 0.001$) (Fig. 1a) [25]. Three-year graft survival rates were similarly disparate at 53 versus 74% in the coinfected and monoinfected groups, respectively ($P < 0.001$) (Fig. 1b). These findings were corroborated in a Spanish multicenter cohort study including 84 HIV/HCV-coinfected recipients and 252 HCV-monoinfected controls, which found 5-year survival rates of 54 and 71% in the HCV/HIV-coinfected and HCV-monoinfected groups, respectively ($P = 0.008$) [24]. In all three of these cohort studies, HIV infection was an independent predictor of mortality, with a 1.9-fold to 2.3-fold increased risk in mortality [23–25].

Inferior liver transplant outcomes in HIV/HCV coinfection are primarily due to recurrence of HCV after liver transplantation (LT), which, although universal in HCV-infected recipients, is more aggressive in the setting of HIV [23,26]. In the French cohort study, progression to a fibrosis score at least F2 (on a scale of 4) in the HIV/HCV-coinfected recipients was 17 and 26% at 1 and 2 years posttransplant, respectively, as compared with 6 and 9% in the HCV-monoinfected group ($P < 0.0001$) [23]. Fibrosing cholestatic hepatitis, a severe early post-transplant complication characterized by portal fibrosis, cholestasis, and rapidly progressive deterioration in liver function, is estimated to occur in up to 20% in HIV/HCV-coinfected liver transplant recipients [27] in comparison with 2–9% in HCV-monoinfected recipients [28].

Rates of acute rejection are also significantly higher in HIV/HCV-coinfected transplant recipients, and rejection episodes tend to be more severe and occur earlier. Terrault *et al.* [25] demonstrated rejection rates of 39% at 3 years in HCV/HIV-coinfected patients compared with 24% in HCV-monoinfected patients ($P = 0.01$), with the majority of rejection episodes occurring within the first 21 days after transplant. Possible underlying mechanisms include HIV-mediated immune activation and dys-regulation, inadequate immunosuppression due to DDIs between ART medications and immunosuppressants, and crossreactivity with subsequent hepatocellular injury from memory alloreactive T cells generated from exposure to prior infections such as cytomegalovirus [7,29]. Importantly, in the setting of HCV infection, treatment of acute rejection has been associated with progression of fibrosis and poorer graft and patient survival [30,31].

Finally, HIV/HCV-coinfected liver transplant recipients are also at increased risk of mortality due to sepsis and multiorgan failure. Severe infections, including bacterial infections with severe sepsis or septic shock, invasive fungal or viral infections, and bloodstream infections, can increase mortality rates three-fold [25,32].

Given the overall poorer posttransplant outcomes in HIV/HCV-coinfected individuals, there has been hesitancy among many within the transplant community to allocate such a scare resource in this patient population. However, outcomes may be improved with careful recipient and donor selection and the administration of DAAs to prevent and treat posttransplant HCV recurrence.

RECIPIENT AND DONOR SELECTION FOR LIVER TRANSPLANTATION

In the United States, HIV-specific eligibility criteria have evolved with growing evidence showing the safety and efficacy of solid organ transplantation in HIV-infected patients. These criteria now include a CD4 T-cell count greater than 200 cells/μl, or greater than 100 cells/μl in liver transplant recipients without a history of opportunistic infections, and absence of HIV viremia pretransplant or predicted absence of HIV viremia on combined antiretroviral therapy (cART) posttransplant (Table 1). Although history of AIDS-defining illness is no longer an absolute contraindication to transplant [33], certain opportunistic infections do preclude transplant if there is no definitive posttransplant treatment, including history of progressive multifocal leukoencephalopathy, cryptosporidiosis, multidrug resistant fungal infections, primary CNS lymphoma, and visceral Kaposi's sarcoma [34].

Both recipient and donor factors have emerged as predictors of adverse outcomes in HIV/HCV-coinfected liver transplant recipients, and based on this evidence many centers that perform these transplants have additional recipient and donor criteria for their HIV/HCV-coinfected patients (Table 1). Recipient severity of illness, including BMI less than 21 kg/m^2 and need for kidney transplant, is associated with both poorer patient and graft survival [25]. Similar to the HCV-monoinfected transplant literature, older donor age and higher donor risk index are associated with increased posttransplant mortality in the setting of HIV/HCV-coinfection [23–25]. In contrast, although the use of HCV-infected donors has not impacted graft or patient survival in HCV-monoinfected recipients [35], donor HCV-positivity is an independent predictor of poorer outcomes in HIV/HCV-coinfected recipients [25]. The use of these recipient and donor factors as criteria for transplant criteria in HIV/HCV coinfection is center-specific and may change with the availability of effective HCV treatment.

DIRECT ACTING ANTIVIRAL USE IN HIV/HEPATITIS C VIRUS LIVER TRANSPLANT PATIENTS

The introduction of the new, potent all-oral DAAs with high efficacy and tolerability offers the opportunity to improve outcomes of HIV/HCV-coinfected transplant recipients. The two main HCV treatment strategies in the liver transplant setting are to treat individuals prior to transplant, with the goal of sustained virologic response (SVR) or achieving undetected HCV RNA levels for long enough to prevent posttransplant HCV recurrence, or to treat individuals after transplant. The optimal strategy remains unclear and will depend on a variety of factors, including anticipated waiting list times, severity of cirrhosis, comorbid conditions such as renal insufficiency, and availability of HCV-infected donors [36].

Among HCV-monoinfected patients, outcomes with all-oral DAA regimens in the setting of liver transplant have been promising. Among patients of any genotype with mildly decompensated cirrhosis and small HCC awaiting transplant who were treated with sofosbuvir with ribavirin for up to 48 weeks, 90% were HCV RNA negative at the time of transplant, and 60% achieved posttransplantation virologic response at 12 weeks after transplant [37▪▪]. Posttransplant sofosbuvir and ribavirin dual therapy is also well tolerated and effective; in a prospective, multicenter cohort study of 40 posttransplant patients with

recurrent HCV infection of any genotype treated for 24 weeks, SVR12 was achieved by 70% of patients with minimal side-effects [38▪▪].

Even more effective all-oral DAA regimens are now available for genotype 1 transplant patients. The SOLAR-1 (ledipasvir-sofosbuvir with ribavirin for the treatment of HCV in patients with post transplant recurrence: preliminary results of a prospective, multicenter study) trial evaluated ledipasvir/sofosbuvir and ribavirin for 12 or 24 weeks in 223 HCV-mono-infected post-LT patients with genotype 1 and 4 [39▪]. Of those with F0–F3 fibrosis or Child Pugh A cirrhosis, SVR12 rates were 96–98%. Serious adverse events were rare, and the most common adverse events were fatigue, anemia, headache, and nausea.

An alternative regimen in transplant patients with recurrent HCV genotype 1 and without cirrhosis is daily fixed-dose combination of paritaprevir/ritonavir/ombitasvir along with twice-daily dosed dasabuvir with ribavirin. Among 34 HCV-monoinfected post-transplant patients with no or mild fibrosis (Metavir stage F0–F2) who received this combination for 12 or 24 weeks, 95% achieved SVR12 [40]. One patient discontinued the regimen due to adverse events, 15% required erythropoietin though no participants required blood transfusions, and the most common adverse effects were fatigue, headache, and cough. Finally, preliminary ‘real world’ data of sofosbuvir and simeprevir with or without ribavirin to treat post-liver transplant recurrent HCV genotype 1 demonstrate SVR rates of around 90% [41,42]. The most significant side-effects with this regimen included anemia requiring erythropoeitin (EPO) and/or blood transfusion, serious adverse side-effects were rare.

At present, there is very limited published experience on the use of all-oral DAA regimens in the HIV/HCV-coinfected liver transplant population. Successful treatment of two HIV-infected patients with post-transplant recurrent HCV genotype 1a using sofosbuvir, simeprevir, and ribavirin [43] and one HIV-infected patient with posttransplant fibrosing cholestatic HCV genotype 4 using sofosbuvir and ribavirin dual therapy has been reported [44▪]. Despite the paucity of data regarding the DAAs in the HIV/HCV-coinfected transplant population, results from HCV-monoinfected transplant recipients can help inform the management of HIV/HCV-coinfected patients in similar clinical settings.

Indeed, in the nontransplant population, efficacy of the all-oral DAA regimens appears to be comparable regardless of HIV status [45▪▪], suggesting that HIV infection does not impair antiviral response to the DAAs as it does with interferon [46] (Table 2). In the PHOTON-1 (All-Oral Therapy With Sofosbuvir Plus Ribavirin For the Treatment of HCV Genotype 1, 2, and 3 Infection in Patients Co-infected With HIV) and PHOTON-2 studies, sofosbuvir and ribavirin dual therapy for 12–24 weeks was evaluated in 497 HIV-infected patients with HCV genotypes 1–4 [59]. Overall SVR12 rates were 81% for genotype 1, 89% for genotype 2, and 84% each for genotypes 3 and 4 and were lowest in two patient subgroups: genotype 1a with cirrhosis (65%) and treatment-experienced genotype 3 (79%) [59].

The ERADICATE (High Efficacy of Sofosbuvir/Ledipasvir for the Treatment of HCV Genotype 1 in Patients Coinfected With HIV on or off Antiretroviral therapy: Results from the NIAID ERADICATE Trial) study evaluated sofosbuvir/ledipasvir for 12 weeks in 50 non-cirrhotic, treatment naive HIV-infected individuals with HCV genotype 1. Thirteen

patients were ART-naive, and 37 had well controlled HIV on tenofovir-based regimens with efavirenz, raltegravir, or rilpivirine. Overall SVR12 was 98% [64]. The regimen was well tolerated with no discontinuations and, importantly, was safely administered in combination with several ART regimens. In the first part of the TURQUOISE-I (Safety and efficacy of ABT-450/r/Ombitasvir, Dasabuvir, and Ribavirinin patients co-infected with hepatitis C and HIV-1) trial evaluating paritaprevir/ritonavir/ombitasvir along with twice-daily dosed dasabuvir with ribavirin for 12 or 24 weeks among patients with HCV genotype 1 and HIV infection on atazanavir-based or raltegravir-based ART, SVR12 rates were high in both treatment durations 94% (29/31) with 12 weeks and 95% (19/20) with 24 weeks [54]. The regimen was well tolerated, and no serious adverse events were reported. Five patients developed transient detectable HIV-1 RNA (<200 copies/ml) on treatment; in all cases HIV viral resuppression was achieved without discontinuing HCV treatment or adjusting ART.

Given comparable observed treatment responses to the all-oral DAAs in HCV-monoinfected and HIV/HCV-coinfected study populations, the American Association for the Study of Liver Diseases and Infectious Diseases Society of America recommendations for sofosbuvir and ribavirin for HIV/HCV-coinfected patients are the same as for HCV-monoinfected patients (Table 2).

Finally, although not yet approved, the combination of grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin was evaluated in both HCV-monoinfected and HIV/HCV-coinfected treatment-naive genotype 1 noncirrhotic patients in the phase 2 C-WORTHY (A Study of the Combination Regimen Grazoprevir (MK-5172) and Elbasvir (MK-8742) ± Ribavirin in Participants With Chronic Hepatitis C (MK-5172-035)) trial [65]. With 12 weeks of treatment, SVR12 in HCV-monoinfected and HIV/HCV-coinfected patients in the dual therapy arm was 98% (43/44) and 87% (26/30), respectively, and in the ribavirin arm was 93% (79/85) and 97% (28/29), respectively. Treatment was generally well tolerated, regardless of ribavirin use or HIV status. The most common adverse events were fatigue, headache, nausea, and diarrhea, and serious adverse events occurred in only three patients.

Several additional interferon-free DAA combinations are currently under investigation in HIV/HCV-coinfected patients, fixed-dose combination of sofosbuvir/ledipasvir (400/90 mg) one tablet daily for 12 weeks in genotype 1 or 4 patients (ION-4 (A Phase III, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Coinfection) trial, NCT02073656), sofosbuvir along with daclatasvir once daily for 8 or 12 weeks in genotype 1–6 patients (ALLY-2 (Daclatasvir in Combination With Sofosbuvir for HIV/HCV Coinfection) trial, NCT02032888), and asunaprevir and daclatasvir with or without Bristol-Myers Squibb (BMS)-791325 in genotype 1 patients (NCT02124044).

Notably, the HIV/HCV-coinfected patients included in DAA clinical trials are a selected population with well controlled HIV, most on ART with HIV RNA less than 50 copies/ml and CD4 count greater than 200 cells/mm^3. Although the HIV/HCV-coinfected liver transplant candidates are also carefully selected with well controlled HIV on ART, data

regarding the efficacy of DAAs in HIV/HCV-coinfected patients with cirrhosis (even compensated cirrhotics) are scarce. Thus, the generalizability of the HIV/HCV-coinfected clinical trial results to the liver transplant setting is unclear.

DRUG–DRUG INTERACTIONS AND POSTTRANSPLANT MANAGEMENT IN HIV/HEPATITIS C VIRUS COINFECTION

A unique challenge in managing HIV/HCV-coinfected patients is the potential for DDIs between ART and DAAs (Table 3). Sofosbuvir is not metabolized by CYP450 and therefore has few clinically significant DDIs with ART. However, it should not be used with tipranavir, which can induce the p-glycoprotein drug transporter, of which sofosbuvir is a substrate [66]. In addition to tipranavir, the sofosbuvir/ledipasvir combination is not recommended with cobicistat and elvitegravir. Ledipasvir also increases tenofovir levels when coadministered with certain ART medications, particularly ritonavir-boosted HIV protease inhibitors [67▪▪]. Therefore, patients receiving sofosbuvir/ledipasvir while on a tenofovir-containing HIV regimen should have close monitoring of their renal function while on treatment, with tenofovir dose adjustment as appropriate based on creatinine clearance, and concomitant use with ritonavir-boosted HIV protease inhibitors should be avoided when possible. If tenofovir-induced renal toxicity is suspected, tenofovir should be discontinued immediately as renal damage may be irreversible. Although Atripla (emtricitabine/tenofovir/efavirenz) reduces ledipasvir concentrations by approximately 30%, there are no recommendations to avoid Atripla with sofosbuvir/ledipasvir, and this combination has been used in studies of HIV/HCV-coinfected patients to date.

The regimen of paritaprevir/ritonavir/ombitasvir along with dasabuvir with ribavirin is not recommended with efavirenz, rilpivirine, darunavir, and ritonavir-boosted lopinavir, or in patients not on ART, and the ritonavir dosage used for boosting other HIV protease inhibitors may require adjustment [67▪▪]. In some cases, the removal of ritonavir from the HIV regimen is necessary. Simeprevir is not recommended with efavirenz, etravine, nevirapine, cobicistat, or any HIV protease inhibitors. Finally, when ribavirin is used, didanosine, stavudine, or zidovudine should not be administered due to increased risk for mitochondrial toxicity and hematotoxicity.

Given these DDIs, often the ART regimen must be changed prior to initiating HCV treatment. In this case, it is recommended that the patient be placed on the new ART regimen for at least 1 month prior to initiating HCV treatment to confirm continued HIV viral suppression [68▪]. If the original ART regimen is resumed after completion of HCV treatment, the modified ART regimen should be continued for at least 2 weeks due to the prolonged half-life of some DAAs [68▪]. Importantly, ART interruptions should not be made to allow for HCV treatment, as episodic antiviral therapy increases the risk of opportunistic infection or death from any cause [69] and increases the risk of liver fibrosis progression in HIV/HCV coinfection [70].

In addition to the interactions of the DAAs with ART, careful attention must be paid to their potential interactions with posttransplant immunosuppressants (Table 3). Adding another layer of complexity is the potential DDIs between ART medications and posttransplant

immunosuppression and the need to balance the goals of HIV suppression and maintaining appropriate levels of immunosuppression. The HIV protease inhibitors are CYP450 inhibitors and thus increase levels of immunosuppressive agents, particularly calcineurin inhibitors and mammalian target of rapamycin inhibitors, which often require a greater than 50% dose reduction [7,71–73]. In contrast, nonnucleoside reverse transcriptase inhibitors, particularly efavirenz, induce the CYP450 system and have the opposite effect on calcineurin inhibitors and mammalian target of rapamycin inhibitor levels. However, this effect is not as potent as the opposing effect of the protease inhibitors, patients on both nonnucleoside reverse transcriptase inhibitors and protease inhibitors tend to take similar doses of immunosuppressants as those solely on protease inhibitors [7]. Given these issues, when feasible many transplant centers transition patients from protease inhibitor-based ART regimens to integrase inhibitors, such as raltegravir, which is not a substrate of CYP450 [74]. Prevention of HIV-specific opportunistic infection prophylaxis is achievable in the posttransplant setting with appropriate use of antibiotic and antifungal therapy [75] (Table 4). However, these prophylactic medications also may have DDIs with posttransplant immunosuppressants.

CONCLUSION

Over the last decade, the need for liver transplantation in the HIV/HCV-coinfected population has increased due to the rising prevalence of cirrhosis and HCC. Many transplant centers have adopted liver transplantation in HIV-infected individuals, and in the absence of HCV coinfection outcomes are comparable with HIV-negative recipients [6,20]. However, HIV/HCV-coinfected patients have the poorest post-transplant outcomes, primarily due to more rapid and aggressive recurrence of HCV posttransplant.

The availability of all-oral DAA regimens to successfully eradicate HCV in HIV-infected transplant patients will likely lead to improved posttransplant outcomes in this challenging population. Data are lacking on the safety and efficacy of these new agents in HIV/HCV-coinfected transplant patients. However, these regimens are highly effective in the HCV-monoinfected transplant population, and in the nontransplant population treatment efficacy appears comparable among HIV/HCV-coinfected and HCV-monoinfected patients. This provides great hope that with the treatment of HCV pretransplant and posttransplant and judicious recipient and donor selection, patient and graft survival in HIV/HCV-coinfected transplant recipients will reach levels equivalent to those of HIV-uninfected recipients. Additional studies, including clinical trials and ‘real world’ data in this special population are needed.

Acknowledgments

The authors thank Aileen Chi, Pharm. D, for her assistance reviewing the section on drug–drug interactions. A.A.K. discloses ownership interest in Gilead. J.C.P. discloses serving on an advisory board to Gilead, receiving a research grant from Gilead, and having ownership interest in Bristol-Myers Squibb, Johnson and Johnson, Merck, and Abbvie. The authors thank Aileen Chi, Pharm. D, for her assistance reviewing the section on drug–drug interactions.

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▪▪ of outstanding interest

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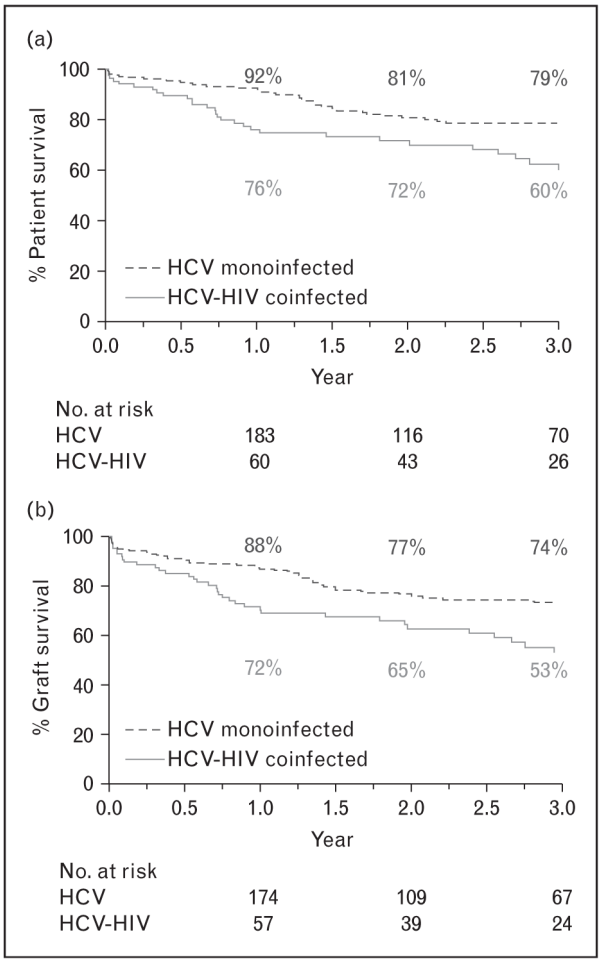

FIGURE 1.

(a) Cumulative patient survival in HIV/HCV-coinfected and HCV-monoinfected liver transplant recipients in a multicenter United States cohort ($P < 0.001$). Reproduced with permission [25]. (b) Cumulative graft survival in HIV/HCV-coinfected and HCV-monoinfected liver transplant recipients in a multicenter United States cohort ($P < 0.001$). Reproduced with permission [25].

Table 1

Recipient and donor criteria for HIV-infected liver transplant recipients

Established HIV-related criteria	**Evolving criteria specific to HIV/HCV coinfection[a]**
Recipient	Recipient
$CD4^+$ T-cell count >100 cells/mm^3 (>200 cells/mm^3 if prior opportunistic infection or malignancy)	BMI >21 kg/m^2
HIV RNA suppressed on ART (or predicted suppression posttransplant)	No need for combined liver–kidney transplant
Stable ART regimen	Low MELD
No active opportunistic infection or neoplasm	Donor
No history of chronic cryptosporidiosis, primary CNS lymphoma, or progressive multifocal leukoencephalopathy	Age <50 years old
No history of multidrug resistant fungal infections	Absence of anti-HCV positivity

ART, antiretroviral therapy; CNS, central nervous system; HCV, hepatitis C virus; MELD, model of end-stage liver disease.

[a]Varies by transplant center and may change with the availability of HCV direct acting antivirals.

Table 2

Sustained virologic response rates of American Association for the Study of Liver Diseases/Infectious Diseases Society of America recommended hepatitis C virus regimens, by HIV status

		SVR12	
Regimen	**Treatment duration**	**HCV monoinfection**	**HIV/HCV coinfection**
Genotype 1			
Sofosbuvir/ledipasvir ± weight-based RBV	Noncirrhoticor treatment-naive compensated cirrhotic: 12 weeks Treatment-experienced compensated cirrhotic or decompensated cirrhotic: 12 weeks with RBV or 24 weeks without RBV	Overall: 94–99% [47,48] Compensated cirrhotic: 92–100% [49] Decompensated cirrhotic: 87–89% [39▪]	Noncirrhotic: 98%
Paritaprevir/ritonavir/ombitasvir along with twice-daily dasabuvir ± weight-based RBV	Noncirrhotic: 12 weeks with RBV (genotype 1a) or without RBV (genotype 1b) Cirrhotic[a]: 24 weeks with RBV (genotype 1a) or 12 weeks with RBV (genotype 1b)	Noncirrhotic: 96–100% [50–52,53▪▪] Cirrhotic: 95–99% [55]	Overall: 92% [54]
Sofosbuvir + simeprevir ± weight-based RBV	Noncirrhotic: 12 weeks Cirrhotic[a]: 24 weeks	Overall: 93–96% Cirrhotic: 93% [56]	No data
Genotype 2			
Sofosbuvir + weight-based RBV	Noncirrhotic: 12 weeks Cirrhotic: 16 weeks	Noncirrhotic: 96–98% Cirrhotic: 78–91% [57,58]	Noncirrhotic: 88% Cirrhotic: 100% [59]
Genotype 3			
Sofosbuvir + weight-based RBV	Noncirrhotic and cirrhotic: 24 weeks	Overall: 85% Noncirrhotic: 87–95% Cirrhotic: 62–92% [60]	Noncirrhotic: 91–95% Cirrhotic: 79–100% [59]
Genotype 4			
Sofosbuvir and weight-based RBV	Noncirrhotic and cirrhotic: 24 weeks	Noncirrhotic: 90–95% Cirrhotic: 67–100% [61]	Noncirrhotic: 83% Cirrhotic: 88% [59]
Sofosbuvir/ledipasvir ± weight-based RBV	Noncirrhotic and cirrhotic: 12 weeks	Overall: 95% [62]	No data
Paritaprevir/ritonavir/ombitasvir along with twice-daily dasabuvir + weight-based RBV	Noncirrhotic and cirrhotic[a]: 12 weeks	Overall: 100% [63]	No data

HCV, hepatitis C virus; RBV, ribavirin; SVR12, sustained virologic response 12 weeks after treatment discontinuation.

[a] Not recommended in patients with decompensated cirrhosis.

Table 3

Drug–drug interactions between direct acting antiviral regimen, antiretroviral therapy, and posttransplant immunosuppressants

Regimen	Interactions with ART	Interactions with posttransplant immunosuppressants
Sofosbuvir + weight-based RBV	Not recommended with tipranavir [66]	
	Due to interaction with RBV, not recommended with didanosine, stavudine, or zidovudine [67▪▪]	
Sofosbuvir/ledipasvir ± weight-based RBV	Not recommended with cobicistat, elvitegravir, or tipranavir	
	If HIV regimen includes ritonavir-boosted protease inhibitors and tenofovir, use an alternative HCV therapy or change to an HIV regimen without tenofovir. If unable to change HIV regimen and coadministration required, monitor for tenofovir- associated renal adverse events. There is no automatic adjustment of tenofovir when used with ritonavir	
	If RBV is used, not recommended with didanosine, stavudine, or zidovudine [66,67▪▪,68▪]	
Paritaprevir/ritonavir/ombitasvir along with twice-daily dasabuvir ± weight-based RBV	If HIV regimen includes ritonavir-boosted protease inhibitor, remove ritonavir from the HIV regimen or adjust the ritonavir dose	Dose adjustments are recommended for tacrolimus, cyclosporine, and mTOR inhibitors due to interaction with ritonavir.
	Not recommended with efavirenz, rilpivirine, darunavir, or ritonavir-boosted lopinavir	
	Not recommended in patients not on ART [67▪▪]	
Sofosbuvir + simeprevir ± weight-based RBV	Not recommended with efavirenz, etravirine, nevirapine, cobicistat, tipranavir, or any HIV protease inhibitors	Avoid with cyclosporine
	If RBV is used, not recommended with didanosine, stavudine, or zidovudine [67▪▪]	Monitor mTOR inhibitor levels

ART, antiretroviral therapy; HCV, hepatitis C virus; mTOR, mammalian target of rapamycin; RBV, ribavirin.

Table 4

Opportunistic infection prophylaxis for HIV-infected transplant recipients, by CD4 T-cell count

CD4 T-cell count	Primary prophylaxis	Secondary prophylaxis
Any CD4 count	*Pneumocystis jiroveci*[a]	*Pneumocystis jiroveci*[a]
<200	*Toxoplasmosis gondii*[b]	*Toxoplasmosis gondii*[c]
		Cryptococcosis, extrapulmonary[c]
<75–100		Cytomegalovirus
<50	Mycobacterium avium complex[d]	*Mycobacterium avium* complex[d]

[a] Indicated for life; initiate immediately posttransplant.

[b] In toxoplasmos is immunoglobulin G-positive patients.

[c] Discontinue when CD4 T-cell count greater than 200 cells/mm^3 for 3–6 months.

[d] Discontinue when CD4 T-cell count greater than 100 cells/mm^3 for 3–6 months.