Treatment of HCV-Uninfected Transplant Recipients Receiving Organs From HCV-Viremic Donors

With the large disparity between patients in need of organ transplantation and available donor organs, many transplant programs are turning to the use of organs from HCV-viremic donors. In the past, organs from HCV-viremic donors were primarily used in recipients with chronic hepatitis C or discarded. With the advent of safe and effective HCV DAA regimens, however, organs from HCV-viremic donors may be considered for use in recipients without HCV infection. Use of these organs increases the pool of available organs, patient access to transplantation (Sageshima, 2018), and potentially reduces waitlist time (Bhamidimarri, 2017; Scalea, 2015) and related mortality (Sawinski, 2019; Shelton, 2018; Kucirka, 2012; Altshuler, 2022).

All organ donors undergo HCV-antibody and HCV nucleic acid testing (NAT). Nonhepatic donors who are HCV antibody positive but HCV RNA negative likely pose a negligible risk of HCV transmission to the recipient, although more data are needed to confirm this. However, among increased-risk donors (as defined by the US Public Health Service [PHS] guidelines) who had a recent HCV exposure, HCV RNA may not yet be detectable and transplant recipients from these donors should be monitored for HCV in addition to HBV and HIV per the increased-risk donor testing protocols (Levitsky, 2017; Seem, 2013b). Transplant recipients who receive a liver from an HCV-antibody–positive/HCV-RNA–negative donor should be monitored more closely after transplantation given the potential risk for HCV transmission (Bari, 2018; Sobotka, 2021). Donors who are HCV RNA positive (with or without anti-HCV) pose the highest risk for HCV transmission to transplant recipients. Because of the significant risk for HCV infection when transplanting an organ from an HCV-viremic donor into an HCV-uninfected recipient, rigorous informed consent, including discussion of potential secondary risks to caregivers from needlestick exposures (Kim, 2022), and post-transplantation, HCV-related follow-up processes are recommended.

### Recommendations When Considering Use of HCV-Viremic Donor Organs in HCV-Uninfected Recipients

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<thead>
<tr>
<th>RECOMMENDED</th>
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<tr>
<td>Informed consent should include the following elements:</td>
<td>I, C</td>
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<tr>
<td>• Risk of transmission from an HCV-viremic donor</td>
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<tr>
<td>• Risk of liver disease if HCV treatment is not available or treatment is unsuccessful</td>
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<tr>
<td>• Risk of graft failure</td>
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<tr>
<td>• Risk of extrahepatic complications, such as HCV-associated renal disease</td>
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<tr>
<td>• Risk of HCV transmission to partner</td>
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<tr>
<td>• Benefits, specifically reduced waiting time and possibly lower waiting list mortality</td>
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<tr>
<td>• Other unknown long-term consequences (hepatic and extrahepatic) of HCV exposure (even if cure is attained)</td>
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<td>Transplant programs should have a programmatic strategy to:</td>
<td>I, C</td>
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<tr>
<td>• Document informed consent</td>
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<tr>
<td>• Assure access to HCV treatment and retreatment(s), as necessary</td>
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<tr>
<td>• Ensure long-term follow-up of recipients (beyond SVR12)</td>
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Recent data indicate increasing acceptance of organs from HCV-viremic donors among HCV-uninfected recipients (Cotter, 2019; Potluri, 2019; Bowering, 2018). Although no published data are available regarding the long-term (beyond 1 to 2 years) consequences to HCV-negative recipients transplanted with organs from HCV-viremic donors who are treated post-transplant with DAAs, limited short-term data from liver, kidney, heart, and lung transplant programs are encouraging.

Liver Transplantation

Among 10 HCV-negative liver transplant recipients of organs from HCV-viremic donors, 100% achieved SVR12 with 12 to 24 weeks of various DAA regimens (Kwong, 2019). The median time from transplantation to treatment initiation was 43 days (interquartile range [IQR] 20-59 days). Noteworthy was the high rate of acute cellular or antibody-mediated rejection (30%) during or after DAA therapy in this study. In another study of 14 HCV-negative liver transplant recipients from HCV-viremic donors, treated with glecaprevir/pibrentasvir for 12 weeks starting within 5 days of transplant, SVR rates were 100% and only one patient experienced acute rejection (Bethea, 2020). In another single-center experience, 61 HCV-negative recipients of liver allografts from HCV-viremic donors were compared to 231 HCV-negative recipients of liver allografts from HCV-negative donors (Bohorquez, 2021a). Of the 61 patients in the study group, 56 received antiviral therapy; treatment was initiated a median of 66.9 days following transplantation. Four study group participants died (within 1 year following liver transplantation), one was persistently aviremic, and another experienced a complex post-operative course. Of the 51 patients with complete treatment data, 64% were treated with glecaprevir/pibrentasvir and 36% received sofosbuvir/velpatasvir. All patients achieved SVR12; one participant required retreatment with sofosbuvir/velpatasvir/voxilaprevir after relapse. There were no significant differences between recipients of allografts from HCV-viremic vs HCV-negative donors in terms of other clinical outcomes such as acute cellular rejection, kidney dysfunction, or survival. A retrospective study of deceased donor liver transplantations in the US from January 2008 through January 2018 demonstrated that 2-year graft survival was similar, regardless of HCV status concordance or discordance between the allograft donor and recipient (Cotter, 2019). In a single-center retrospective study of 21 HCV-seronegative recipients who received a liver transplant from HCV-viremic donors, 20 (95%) of recipients had confirmed HCV viremia and 100% of the 15 patients with available data achieved SVR12 after DAA treatment. There were equivalent rates of post-transplant complications between the 21 recipients who received a liver from HCV-viremic donors when compared to 21 recipients who received a liver from HCV antibody positive / NAT negative donors (Sobotka, 2021).

In a prospective, multicenter (n=6), single-arm, open-label clinical trial, 13 HCV-negative liver transplant recipients received allografts from HCV-viremic donors. Participants were treated with 12 weeks of sofosbuvir/velpatasvir; the median time from transplantation to antiviral therapy was 7 days (Terrault, 2020). All liver transplant recipients achieved SVR12. Serious adverse events possibly related to study participation among the liver recipients included antibody mediated rejection, biliary sclerosis, cardiomyopathy, and graft-versus-host disease (which eventually led to the patient’s death). In a prospective multicenter (n=3) observational study, 20 HCV-negative patients received a liver transplant from HCV-viremic donors and all recipients had HCV viremia confirmed within 3 days post-transplant and achieved SVR12 after receiving DAA treatment (median 27.5 days post-transplant) (Aqel, 2021). One patient who was started on DAA treatment on post-op day 24 developed end-stage renal disease secondary to HCV-related acute membranous nephropathy and died 14 months post-transplant due to septic shock from a presumed infection.

Unlike with other organs, shorter durations of HCV therapy should not be used in recipients of livers from HCV-viremic donors because of the large reservoir of HCV in the transplanted organ. Additionally, although prophylactic/pre-emptive therapy has not been as strongly stressed for recipients of liver grafts from HCV-viremic donors, a case report noted the development of acute kidney injury (with proteinuria) in the first month posttransplant due to HCV-associated focal proliferative glomerulonephritis. This case report highlights the potential for HCV-related, extrahepatic manifestations in the early posttransplant setting (Bohorquez, 2021b). The prospective multicenter noted above (Aqel, 2021) also highlights the importance of considering the initiation of DAA treatment earlier post-transplant given that one liver transplant recipient had biopsy-proven acute HCV-related glomerulonephritis on post-op day 18, which was 6 days prior to the initiation of
DAA treatment, and went on to develop end stage renal disease despite having achieved SVR12. This patient died due to presumed infectious complications. The possible high risk for immunologic complications (eg, rejection) in liver recipients from HCV-viremic donors treated with DAA therapy requires further study but vigilance is appropriate.

**Recommendation Regarding Timing of DAA Therapy for HCV-Negative Recipients of HCV-Viremic Liver Transplant**

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
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<tbody>
<tr>
<td>Early(^a) treatment with a pangenotypic DAA regimen is recommended when the patient is clinically stable.</td>
<td>II, B</td>
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</table>

\(^a\) Early treatment refers to starting within the first 2 weeks after liver transplant but preferably within the first week when the patient is clinically stable.

**Recommended regimens listed by pangenotypic, evidence level and alphabetically for:**

**Treatment of HCV-Uninfected Recipients of Liver Grafts from HCV-Viremic Donors**

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
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<tbody>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)(^b)</td>
<td>12 weeks</td>
<td>I, C</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, C</td>
</tr>
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</table>

\(^a\) Other considerations in selection of the DAA regimen:

- Presence of liver dysfunction (eg, elevated bilirubin) as protease inhibitors should be avoided
- Specific drugs that are contraindicated or not recommended with specific DAA agents, including but not limited to:
  - High-dose antacid therapy (eg, twice daily proton pump inhibitor)
  - Amiodarone (contraindicated with sofosbuvir-inclusive regimens; see prescribing information)
  - Specific statins (eg, atorvastatin)
- Consideration of immunosuppressive drugs and DAA interactions (see below)

\(^b\) Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

**Transplantation of Other Organs**

In the THINKER trial, 10 HCV-uninfected kidney transplant recipients received allografts from genotype 1 HCV-viremic donors and were treated with 12 weeks of elbasvir/grazoprevir; 100% achieved SVR (Goldberg, 2017). In a 1-year follow-
up study that included 10 additional participants (n=20) who received 12 to 16 weeks of elbasvir/grazoprevir (± ribavirin), all achieved SVR12. Kidney function in those who received kidneys from HCV-infected donors was comparable to matched controls who received allografts from HCV-uninfected donors (Reese, 2018). A separate open-label trial similarly demonstrated 100% SVR12 with 12 weeks of elbasvir/grazoprevir (± sofosbuvir) therapy initiated immediately prior to transplantation in 10 HCV-uninfected kidney transplant recipients of allografts from HCV-viremic donors (Durand, 2018). Notably, organ recipients in this study received the first dose of elbasvir/grazoprevir on call to the operating room. Of the 10 patients treated, only 3 had detectable HCV viremia compared to 100% in the THINKER trial, which utilized the same regimen but initiated therapy on day 3 after transplantation.

In a prospective, multicenter (n=7) study to transplant hepatitis C-infected kidneys (ie, the MYTHIC trial), 30 HCV-negative recipients received kidney allografts from HCV-viremic donors. Early initiation of glecaprevir/pibrentasvir (target was within 3 days posttransplant) for 8 weeks resulted in 100% SVR12; there were no significant treatment-related adverse events (Sise, 2020). Three episodes of acute rejection were noted but all patients had good graft function at 6 months follow-up. Three patients developed transient BK viremia and 4 (40%) of the 10 recipients who were CMV donor seropositive, CMV recipient seronegative developed CMV disease within the first-year post-transplant. One-year survival was 93% and 1-year graft function was excellent (median creatinine 1.17; IQR: 1.02-1.38 mg/dl) (Sise, 2021).

A prospective, multicenter, single-arm, open-label clinical trial evaluated the safety and efficacy 12 weeks of sofosbuvir/velpatasvir among 11 HCV-negative kidney transplant recipients who received grafts from HCV-viremic donors (Terrault, 2020). The median time from transplant to initiation of DAA therapy was 16.5 days; all kidney transplant recipients in this study achieved SVR12. No serious adverse events related to study participation were noted in the kidney recipients in this study. The REHANNA trial evaluated a shortened 4-week course of glecaprevir/pibrentasvir treated (compared to the standard 8 weeks) among HCV-negative kidney transplant recipients who received grafts from HCV-viremic donors. The first dose was administered prior to organ perfusion. All 10 patients achieved SVR12 and there were no adverse outcomes noted (Durand, 2021). Other studies in HCV discordant kidney donors and transplant recipients have also demonstrated high SVR12 rates without any treatment-related toxicities (Franco, 2019); (Friebus-Kardash, 2019). A single-center, retrospective cohort study compared 1-year outcomes for 65 transplant recipients who received a kidney from HCV viremic donors to 59 recipients who received a kidney from HCV negative donors (Molnar, 2021). Allograft biopsy findings and kidney allograft function during the first-year post-kidney transplantation were assessed and there were no statistically significant differences between the HCV positive and HCV negative cohorts with regards to delayed graft function rates, estimated glomerular filtration rates (eGFR), and proportions of patients with cellular rejection, antibody mediated rejection, or de novo DSAs.

A study of HCV-uninfected recipients who received a heart transplant from an HCV-viremic donor showed that using a 12-week course of elbasvir/grazoprevir initiated a few days after transplantation (once the recipient became viremic) resulted in SVR12 in 9 out of the 10 evaluable patients (McLean, 2019). In the DONATE HCV trial, 44 HCV-uninfected lung (n=36) and heart transplant (n=8) recipients from HCV-viremic donors sofosbuvir/velpatasvir was administered prophylactically/preemptively, starting within a few hours after transplantation and continued for 4 weeks (compared to the standard 12-week course). Among the initial 35 patients with at least 6 months of follow-up after transplantation, 100% achieved SVR and had excellent graft function (Woolley, 2019). There was an increase in the proportion of the HCV-viremic lung cohort who had acute cellular rejection compared to the non-HCV lung cohort, although this finding was not statistically significant and longer-term follow-up is needed to assess for chronic rejection. In a study of 20 HCV-uninfected heart transplant recipients of allografts from HCV-viremic donors, patients were treated prophylactically/preemptively with glecaprevir/pibrentasvir beginning just prior to transplantation and continued for 8 weeks. All participants achieved SVR12, and patient and graft survival were 100% with a median follow-up of 10.7 months (Bethea, 2019). Another clinical trial evaluated 22 HCV-uninfected lung transplant recipients of allografts from HCV-viremic donors; the 20 patients who became viremic after transplantation were treated with 12 weeks of sofosbuvir/velpatasvir beginning 2 to 6 weeks after transplantation (median 21 days; IQR 16.76-24.75 days). All lungs from HCV-viremic donors were treated with ex-vivo lung perfusion ± ultraviolet C perfusate irradiation to reduce HCV RNA concentration and infectivity, likely contributing to a slower rise in HCV viral load among recipients. Although all 20 DAA-treated patients had undetectable HCV RNA at the end of treatment, 2 patients experienced post-treatment relapse. One patient experienced severe hepatitis with early signs
of fibrosing cholestatic hepatitis [FCH] on liver biopsy, and both patients exhibited complex NS3A and NS5A RASs at relapse. Both relapsed patients were successfully retreated with 24 weeks of sofosbuvir/velpatasvir/voxilaprevir plus ribavirin and achieved SVR12 (Cypel, 2019).

A study of 22 heart transplants from HCV-viremic donors evaluated an 8-week course of glecaprevir/pibrentasvir initiated 6–11 days after transplantation, once the viremia developed. Two patients had DAA interruptions. No differences were noted between the HCV-viremic vs HCV-aviremic donor cohorts in terms of survival or rejection (Reyentovich, 2020). Another study evaluated 38 thoracic organ transplants (22 heart; 16 lung) from HCV-viremic donors. Treatment with glecaprevir/pibrentasvir was initiated at the time of detectable viremia (mean 7 days) among the heart recipients and within 3 days after transplantation for the lung recipients; all participants achieved SVR12 (Smith, 2021). DAA treatment interruption occurred in 2 patients due to hyperbilirubinemia. One patient resumed treatment within a few days; the other patient’s treatment course was shortened to 10 days. Both patients still achieved SVR12. In the heart transplant recipients, all patients became viremic within the first week after transplantation. In contrast, only 11 of the 16 lung transplant recipients developed viremia. Overall, investigators noted reduced HCV transmission, lower viral loads, and more rapid clearance in the lung transplant patients who received earlier treatment (Smith, 2021). In both of these studies, initiation of treatment within a few days after transplantation was associated with an occasional need for treatment interruption, although all recipients still achieved SVR12 (Reyentovich, 2020); (Smith, 2021).

A separate study conducted among 50 heart transplant recipients (22 received hearts from HCV-viremic donors), an 8-week course of glecaprevir/pibrentasvir was initiated once viremia developed (mean 7.2 days) (Gidea, 2020). Investigators noted a higher proportion of acute cellular rejection in the HCV-viremic vs HCV-aviremic donor study groups (14/22 vs 5/28, respectively; p=0.001) in the first 2 months and at 180 days (17/22 vs 12/28, respectively; p=0.02). These findings raise concern about a potential association between HCV-viremic donors and rejection.

While these early results are encouraging, the overall number of published cases is small and treatment approaches notably variable. Known reported risks include DAA treatment failure with emergence of complex RASs and possible severe or rapidly progressive liver disease (fibrosing cholestatic hepatitis) (Cypel, 2019); (Kapila, 2019); (Molnar, 2019). Additionally, ethical and scientific issues remain, including avoidance of selection bias, optimal timing of DAA therapy, and long-term graft and patient outcomes. Due to the limited and heterogeneous experience and lack of longer-term safety data, strong consideration should be given to performing these transplantations with a rigorous informed consent process as recommended by the American Society of Transplantation consensus panel (Levitsky, 2017).

In addition, there have been an increasing number of dual organ transplants performed from HCV-viremic donors for heart-kidney recipients nationally between August 2015 and August 2020. Analyses from the UNOS registry demonstrated similar 1-year survival between 90 HCV donor seropositive and 896 HCV donor seronegative heart-kidney recipients using unadjusted and adjusted Cox-proportional hazards-regression models including in propensity-score matched cohorts (Madan, 2021); (Diaz-Castrillon, 2022).

### Recommendation Regarding Timing of DAA Therapy for HCV-Negative Recipients of HCV-Viremic Non-Liver Solid Organ Transplant

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<tr>
<th>RECOMMENDED</th>
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<tr>
<td>Prophylactic(^a)/preemptive(^b) treatment with a pangenotypic DAA regimen is recommended.</td>
<td>II, B</td>
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</table>

\(^a\) Prior to HCV RNA results, typically immediately pre-transplant or day 0 post-transplant  
\(^b\) Day 0 to within the first week post-transplant, typically as soon as the patient is deemed clinically stable
### Treatment of HCV-Uninfected Recipients of Non-Liver Organs from HCV-Viremic Donors

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<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
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<tbody>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)</td>
<td>8 weeks</td>
<td>I, C</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, C</td>
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</tbody>
</table>

**a** Other considerations in selection of the DAA regimen:

- Presence of liver dysfunction (eg, elevated bilirubin) as protease inhibitors should be avoided
- Specific drugs that are contraindicated or not recommended with specific DAA agents, including but not limited to:
  - High-dose antacid therapy (eg, twice daily proton pump inhibitor)
  - Amiodarone (contraindicated with sofosbuvir-inclusive regimens; see prescribing information)
  - Specific statins (eg, atorvastatin)
- Consideration of immunosuppressive drugs and DAA interactions (see below)

**b** 8 weeks is recommended for prophylactic/preemptive treatment approaches. However, if treatment initiation is delayed beyond the first week after transplant, treatment should be continued for 12 weeks. Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Initiation of DAA therapy for HCV-negative recipients of a non-liver allograft from an HCV-viremic donor can occur prophylactically/preemptively (ie, perioperatively without confirmation of viremia in the recipient) or reactively after documentation of HCV viremia. The goal is to undertake DAA therapy as early as clinically possible to minimize the duration of HCV viremia in the recipient and avoid the development of acute hepatitis and other non-hepatic complications of HCV infection. Initiating prophylactic/preemptive DAA therapy before viremia occurs may reduce the likelihood of complications, such as FCH, acute HCV-related glomerulonephritis, acute pancreatitis, acute cellular rejection, and allograft vasculopathy (Gidea, 2020; Schlendorf, 2020; Bethea, 2019; Cypel, 2019; Kapila, 2019; Woolley, 2019; Molnar, 2019; Durand, 2018). A prophylactic/preemptive treatment approach may also allow for a shorter duration of DAA therapy in non-liver transplant recipients of organs from HCV-viremic donors (Woolley, 2019). A recent trial evaluated the use glecaprevir/pibrentasvir combined with ezetimibe 10 mg (as an inhibitor of HCV entry) in 30 recipients of nonhepatic organs (lung, heart, kidney) from HCV-viremic donors. The drugs were administered with 1 dose before and for 7 days after transplantation. With this short therapy, none of the 30 individuals developed chronic HCV infection. It is unknown if infection occurred and was rapidly cleared or if it was prevented entirely (Feld, 2020). Although intriguing, short duration approaches are not currently recommended outside of a clinical trial setting and have only been studied in the context of non-liver transplantation.

Though initiating HCV treatment as early as possible post-transplant may be clinically beneficial, barriers to initiating DAA treatment prophylactically/preemptively include the cost of DAA treatment and protracted insurance authorizations. One study compared the clinical and financial impact between an institution-subsidized course of initial DAA treatment with an insurance approval process for DAA coverage once HCV viremia was documented in the recipient. The timing of DAA initiation, duration of recipient viremia, and associated costs incurred by the patient and the institution were assessed in...
89 abdominal organ transplant recipients who did not have their DAA treatment subsidized compared to 62 thoracic organ transplant recipients who received DAA treatment that was initially subsidized by the institution. Their analysis showed that by not waiting to initiate DAA treatment for insurance authorization after HCV viremia was documented in the recipient enabled earlier treatment initiation (median, 4 days [IQR, 2-7] vs 10 days [IQR, 8-13]; p <0.001) and shorter duration of viremia (median, 16 days [IQR, 12-29] vs 36 [IQR, 30-47]; p <0.001) (Stewart, 2021).

Selection of the DAA therapy for HCV-negative recipients of a non-liver allograft(s) from an HCV-viremic donor should follow the same principles as for those who develop recurrent HCV infection post liver transplantation (see Patients Who Develop Recurrent HCV Infection Post Liver Transplantation). Importantly, since genotyping of HCV-viremic donors is not routinely performed, only pangenotypic regimens should be utilized if a prophylactic/preemptive treatment approach is used. If treatment is delayed until the recipient has quantifiable HCV RNA, the recipient’s genotype can be used to guide DAA treatment selection if a pangenotypic regimen is not used. Selection of regimens that avoid the use of ribavirin (to reduce ribavirin-associated side effects) and regimens that do not require baseline RAS testing are preferred. Thus, although there are data supporting the safety and efficacy of elbasvir/grazoprevir among HCV-negative kidney and heart transplant recipients of allografts from HCV-viremic donors, the regimen is designated an alternative regimen due to the necessity for baseline RAS testing and its limited genotype coverage. Similarly, ledipasvir/sofosbuvir is designated as an alternative regimen due to lack of pangenotypic coverage.

Notably, organs from HCV-viremic donors may be used in transplant candidates with current or prior HCV infection (see Patients Who Develop Recurrent HCV Infection Post Liver Transplantation).

Drug-Drug Interactions Between DAAs and Calcineurin Inhibitors

The interactions of DAA agents and calcineurin inhibitors are complex and unpredictable without formal studies of drug-drug interactions. A summary of interactions between calcineurin inhibitors and DAAs with recommended dosing is provided in the DAA Interactions With Calcineurin Inhibitors table.

Based on the metabolism of grazoprevir and elbasvir, a 15-fold increase in grazoprevir AUC and a 2-fold increase in elbasvir AUC can be expected with cyclosporine coadministration. Therefore, this combination should be avoided. Since a 40% to 50% increase in tacrolimus level is predicted with coadministration of grazoprevir, no dosing adjustments are anticipated but tacrolimus levels should be monitored. No clinically significant drug-drug interactions have been observed between sofosbuvir-inclusive regimens and tacrolimus.

**Last update:** October 24, 2022

**Related References**


