16. Hepatitis C in Solid Organ Transplantation

Table of Contents:

16.1 Guidelines and Consensus Recommendations
16.2 Abdominal
- **16.2.1 Kidney Transplant**
- **16.2.2 Pancreas Transplant**
- **16.2.3 Liver Transplant**

15.6 Cardiothoracic
- **16.3.1 Lung Transplant**
- **16.3.2 Heart Transplant**

16.4 Multi-Organ Studies
16.5 Post-transplant Outcomes and Complications
16.6 Medication Access and Cost Effectiveness
16.7 Pharmacokinetics/Drug Administration/Drug Interactions
16.8 Management of co-infection (HepC+ with HepB)

16.1 Guidelines and Consensus Recommendations

Recommendations for Testing, Managing, and Treating Hepatitis C. (2023). Retrieved from: http://www.hcvguidelines.org

- The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America practice guidelines for testing and treating hepatitis C virus infection

Bhattacharya D, et al. (2023). Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Clinical Infectious Diseases*, 2023, ciad319. Retrieved from: https://doi.org/10.1093/cid/ciad319

- Updated guidelines for testing, managing, and treating HCV from the American Association for the Study of Liver Diseases– Infectious Diseases Society of America

Stewart ZA, et al. (2021). Best practice recommendations for the use of hepatitis C viremic donor organs for hepatitis C virus naïve recipients. Clin Transplant. 2021;35(8):e14381. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34086371/

- Guidance developed by the American Society of Transplant Surgeons (ASTS) to aid transplant programs in developing protocols to utilize HCV+ donors in HCV- recipients.

Jones JM, et al. (2020). Assessing Solid Organ Donors and Monitoring Transplant Recipients for Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus Infection - U.S. Public Health Service Guideline, 2020. MMWR Recomm Rep. 2020;69(4):1-16. Published 2020 Jun 26. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32584804/

Aslam S, et al. (2020). Utilization of hepatitis C virus-infected organ donors in cardiothoracic transplantation: An ISHLT expert consensus statement. J Heart Lung Transplant. 2020;39(5):418-432. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32362393/

World Health Organization. (2018). Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Retrieved from: https://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2018/en/

- World Health Organization guidelines for screening and treatment of chronic hepatitis C infection

Levitsky J, et al. (2017). The American Society of Transplantation Consensus Conference on the use of Hepatitis C viremic donors in solid organ transplantation. Am J Transplantation. 17:2790-2802. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28556422

- Consensus document regarding availability and use of Hepatitis C positive donor organs as well as transmission and payor concerns.

Roth D, et al. (2016). KDOQI US Commentary on the 2018 KDIGO Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C. Am J Kidney Dis. 2020;75(5):665-683. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32279907/

16.2 Abdominal

16.2.1 Kidney Transplant

Kim MH, et al. (2023). Early initiation of glecaprevir/pibrentasvir after transplantation of HCV-viremic kidneys into HCV-negative recipients is associated with normalization in the altered inflammatory milieu. Clinical transplantation, 37(4), e14926. Retrieved from: https://doi.org/10.1111/ctr.14926

- Retrospective study evaluating treatment with glecaprevir/pibrentasvir in kidney transplant recipients from HCV+ donors and the effect on sustained changes in the soluble inflammatory milieu associated with HCV infection.

El Helou G, et al. (2022). Hepatitis C virus and kidney transplantation: Recent trends and paradigm shifts. Transplant Rev (Orlando);36(1):100677. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35063799/

- Review of HCV epidemiology, clinical outcomes, HCV treatment, studies on transplantation from positive donors to negative recipients, and evolving clinical management.

Fabrizi F, et al. (2021). Updated view on kidney transplant from HCV-infected donors and DAAs. Pharmaceutics. 13(4). Retrieved from: https://doi.org/10.3390/pharmaceutics13040496

- Review of 11 studies including 201 patients on the safety and efficacy of kidney transplant from HCV-viremic donors into HCV naïve recipients and the use of direct-acting antiviral agents in these patients.

Daloul R, et al. (2021). A review of kidney transplantation from HCV-viremic donors into HCV-negative recipients. Kidney Int. 1190-8. Retrieved from: https://doi.org/10.1016/j.kint.2021.06.034

- Review of published literature on safety and feasibility of transplanting HCV-viremic organs into HCV naïve recipients.

Terrault NA, et al. (2021). Prospective Multicenter Study of Early Antiviral Therapy in Liver and Kidney Transplant Recipients of HCV-Viremic Donors. Hepatology. 2021;73(6):2110-2123. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32926749/

- A prospective, multi-center (6 US transplant centers) trial evaluating 13 liver and 11 kidney transplant recipients treated with sofosbuvir-velpatasvir for 12 weeks starting once viremia was confirmed following transplant. Of the 24 patients transplanted (13 liver, of whom 2 had prior-treated HCV infection; 11 kidney), 23 became viremic after transplant. At the end of treatment, all LT recipients were HCV RNA-undetectable, whereas 3 (30%) of the kidney recipients still had detectable, but not quantifiable, viremia. All achieved sustained virologic response at 12 weeks following transplant

Jandovitz N, et al. (2021). Hepatitis C-positive donor to negative recipient kidney transplantation: A real-world experience. Transpl Infect Dis. 2021;23(3):e13540. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33259125/

- Retrospective, single center trial of 25 HCV NAT positive donor kidney transplants treated with DAAs; The most commonly prescribed DAA was ledipasvir/sofosbuvir (56%), followed by velpatasvir/sofosbuvir (32%), and then glecaprevir/pibrentasvir (12%). SVR 12 achieved in all patients except 1 due to missed mixed-genotype infection, subsequently treated with a pan genotypic agent and achieved SVR 12.

Durand CM, et al. (2021). Four-Week Direct-Acting Antiviral Prophylaxis for Kidney Transplantation From Hepatitis C-Viremic Donors to Hepatitis C-Negative Recipients: An Open-Label Nonrandomized Study. Ann Intern Med. 2021;174(1):137-138. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32894697/

- Single center trial evaluating 10 HCV D+R- renal transplant recipients utilizing glecaprevir/pibrentasvir as the Hep C anti-viral with first dose 6 hours post-op and the duration of therapy 4 weeks. All patients attained SVR12.

Sise ME, et al. (2020). Multicenter Study to Transplant Hepatitis C-Infected Kidneys (MYTHIC): An Open-Label Study of Combined Glecaprevir and Pibrentasvir to Treat Recipients of Transplanted Kidneys from Deceased Donors with Hepatitis C Virus Infection. J Am Soc Nephrol. 2020;31(11):2678-2687. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32843477/

- Prospective, multicenter (7 center) trial evaluating 30 HCV D+ (NAT+)/R- kidney recipients. DAA utilized was: Glecaprevir/pibrentasvir. Duration of therapy was 8 weeks (starting 3 days post-transplant) and all patients achieved SVR 12.

Kapila N, et al. (2020). Hepatitis C Virus NAT-Positive Solid Organ Allografts Transplanted Into Hepatitis C Virus-Negative Recipients: A Real-World Experience. Hepatology. 2020;72(1):32-41. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31659775/

- Single center, prospective, multi-organ transplant trial, that studied transplant recipients who were HCV nucleic acid test and anti-HCV antibody negative at the time of transplant and received an HCV-viremic organ. DAA regimen determined by hepatologist after HCV genotype and insurance approval. Duration of therapy ranged from 8-16 weeks depending on regimen.

Graham JA, et al. (2020). Transplantation of viral-positive hepatitis C-positive kidneys into uninfected recipients offers an opportunity to increase organ access. Clin Transplant. 2020;34(4):e13833. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32072689/

- Single center study evaluating a cohort of 30 HCV D+R- renal transplant recipient. DAAs utilized were: lecaprevir/pibrentasvir (29/30) and sofosbuvir/velpatasvir (1/30). Duration of therapy was 12 weeks and SVR 12 was obtained in all patients

Sise ME, et al. (2020). Preemptive Treatment With Elbasvir and Grazoprevir for Hepatitis C-Viremic Donor to Uninfected Recipient Kidney Transplantation. Kidney Int Rep. 2020;5(4):459-467. Published 2020 Jan 13. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32280841/

- Prospective, single center study evaluating 8 HCV D+R- renal transplant recipients. DAA utilized was elbasvir/grazoprevir where first dose was given on-call to OR. Duration was 12 weeks and SVR12 obtained in all patients.

Gupta G, et al. (2020). Ultra-short duration direct acting antiviral prophylaxis to prevent virus transmission from hepatitis C viremic donors to hepatitis C negative kidney transplant recipients. Am J Transplant. 2020;20(3):739-751. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31652392/

- Prospective, single center trial evaluating 50 HCV D+R- renal transplant recipients and using a pre-emptive strategy. In the pre-initiation phase, the first dose was 6 hours prior to transplant. DAA utilized was sofusbuvir/velpatasvir. Duration of pre-emptive strategy was 4 days. The 4 days of pre-emptive DAA prophylaxis resulted in a 7.5% transmission rate requiring a full course of DAA therapy based on genotyping.

Molnar MZ, et al. (2019). Transplantation of kidneys from hepatitis C-infected donors to hepatitis C-negative recipients: Single center experience. Am J Transplant. 2019;19(11):3046-3057. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31306549/

- Retrospective, single center, cohort study evaluating 53 HCV D+R- renal transplant recipients. DAAs utilized were: glecaprevir/pibrentasvir (47/53), velpatasvir/sofosbuvir (5/53), ledipasvir/sofosbuvir (1/53). Duration of therapy was 12 weeks and SVR 12 was obtained in all patients. One patient developed cholestatic hepatitis with resolution

Friebus-Kardash J, et al. (2019). Successful early sofosbuvir-based antiviral treatment after transplantation of kidneys from HCV-viremic donors into HCV-negative recipients. Transpl Infect Dis. 2019;21(5):e13146. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31306562/

- Prospective, single center trial in Germany evaluating 7 HCV D+R- renal transplants. DAAs utilized were sofosbuvir/ledipasvir (4/7) and sofosbuvir/velpatasvir (3/7). Duration was 8-12 weeks. Median time to start was 7 days (range 5-37 days) after transplant. All patients attained SVR12

Franco A, et al. (2019). Renal transplantation from seropositive hepatitis C virus donors to seronegative recipients in Spain: a prospective study. Transpl Int. 2019;32(7):710-716. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30773693/

- Prospective, observational, multicenter study in Spain, evaluating HCV NAT + and Ab+ donors. All patients obtained SVR12 and received glecaprevir/pibrentasvir for 8 weeks. Treatment was initiated 6 hours prior to transplant.

Durand CM, et al. (2018). Direct-Acting Antiviral Prophylaxis in Kidney Transplantation From Hepatitis C Virus-Infected Donors to Noninfected Recipients: An Open-Label Nonrandomized Trial. Ann Intern Med. 2018;168(8):533-540. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29507971/

- Prospective, single center trial evaluating 10 HCV D+R- renal transplant recipients. First dose of DAA was given on call to OR. DAA utilized was grazoprevir-elbasvir and sofosbuvir was added for Genotype 2 or 3. Duration of therapy was 12 weeks and 16 weeks for NS5a resistance. SVR 12 was obtained in all patients.

Reese P, et al. (2018) Twelve-month outcomes after transplant of hepatitis c-infected kidneys into uninfected recipients: a single group trial. Ann Intern Med;169(5):273-281. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30083748/

- Describes 12-month HCV treatment outcomes in an open-label, nonrandomized single center study of 20 HCV-negative transplant candidates (including the ten recipients of the THINKER-1 study)

Reau N, et al. (2018). Glecaprevir/Pibrentasvir Treatment in Liver or Kidney Transplant Patients With Hepatitis C Virus Infection. Hepatology. 2018;68(4):1298-1307. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29672891/

- This trial evaluated the safety and efficacy of glecaprevir/pibrentasvir for patients with chronic HCV GT1-6 infection who had received a liver or kidney transplant. MAGELLAN-2 was a phase 3, open-label trial conducted in patients who were ≥3 months posttransplant.

Goldberg DS, et al. (2017). Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients. N Engl J Med. 2017;376(24):2394-2395. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/28459186/

- An editor correspondence describing single center pilot trial of 10 kidney transplants recipients who were HCV negative and received their kidney from HCV positive donor. Elbasvir–grazoprevir was initiated once a patient became HCV viremic. Duration of therapy was 12 weeks and all patients obtained SVR 12.

Lubetzky M, et al. (2016). Safety and Efficacy of Treatment of Hepatitis C in Kidney Transplant Recipients with Directly Acting Antiviral Agents. Transplantation. 2016 Dec 22. doi: 10.1097/TP.0000000000001618. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28009781

- Retrospective, single-center, cohort analysis of kidney transplant recipients who received direct-acting antivirals for treatment of Hepatitis C. Endpoints included SVR at 12 weeks post completion of therapy and allograft function.

16.2.2 Pancreas Transplant

Lonze BE, et al. (2021). Pancreas transplantation from hepatitis C viremic donors to uninfected recipients. Am J Transplant. 2021;21(5):1931-1936. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33346951/

- A single center experience of HCV D+/R- pancreas transplants. All recipients in this series who received a HCV-positive pancreas allografts had undetectable HCV RNA levels by a mean of 23 days after initiation of HCV-directed therapy. All patients were started on a 12-week treatment course of DAA and DAAs utilized were glecaprevir/pibrentasvir (300 mg/120 mg; Mavyret®, AbbVie, Inc., North Chicago, IL) or sofosbuvir/velpatasvir (400 mg/100 mg; Epclusa®, Gilead Sciences, Inc., Foster City, CA).

16.2.3 Liver Transplant

Snyder HS, et al. (2022). A systematic review of direct acting antiviral therapies in hepatitis C virus-negative liver transplant recipients of hepatitis C-viremic donors. Pharmacotherapy, 42(12), 905–920. Retrieved from: https://doi.org/10.1002/phar.2742

- Systematic review evaluating the efficacy and safety of direct acting antiviral therapies in HCV-liver transplant recipients of HCV+ donors. Authors concluded DAA post-transplant is safe and effective, however the long-term outcomes are still unknown.

Terrault NA, et al. (2021). Prospective Multicenter Study of Early Antiviral Therapy in Liver and Kidney Transplant Recipients of HCV-Viremic Donors. Hepatology. 2021;73(6):2110-2123. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32926749/

- A prospective, multi-center (6 US transplant centers) trial evaluating 13 liver and 11 kidney transplant recipients treated with sofosbuvir-velpastasvir for 12 weeks starting once viremia was confirmed following transplant. Of the 24 patients transplanted (13 liver, of whom 2 had prior-treated HCV infection; 11 kidney), 23 became viremic after transplant. At the end of treatment, all LT recipients were HCV RNA-undetectable, whereas 3 (30%) of the kidney recipients still had detectable, but not quantifiable, viremia. All achieved sustained virologic response at 12 weeks following transplant

Anwar N, et al. (2020). Use of Hepatitis C Nucleic Acid Test-Positive Liver Allografts in Hepatitis C Virus Seronegative Recipients. Liver Transpl. 2020;26(5):673-680. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32125753/

- A matched cohort study was conducted examining post- liver transplantation outcomes of HCV NAT- patients who received HCV NAT+ organs (treatment group) compared with matched recipients with HCV NAT- organs (matched comparator group) between June 2018 to October 2019. The patients in the treatment group were prescribed a DAA regimen (glecaprevir/pibrentasvir, sofosbuvir/ velpatasvir, or sofosbuvir/ledipasvir) for 12 weeks

Bethea E, et al. (2020). Immediate administration of antiviral therapy after transplantation of hepatitis C-infected livers into uninfected recipients: Implications for therapeutic planning. Am J Transplant. 2020;20(6):1619-1628. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31887236/

- 14 HCV-negative patients underwent successful liver transplantation from HCVpositive donors. Nine patients received viremic (nucleic acid testing (NAT)-positive) livers and five patients received livers from HCV antibody-positive non-viremic donors and were followed using a

reactive approach. Survival in NAT-positive recipients is 100% at a median follow-up of 46 weeks. The DAA utilized was a 12-week course of oral glecaprevir-pibrentasvir within 5 days of transplant.

Kwong AJ, et al. (2019). Liver transplantation for hepatitis C virus (HCV) non-viremic recipients with HCV viremic donors. Am J Transplant. 2019;19(5):1380-1387. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30378723/

- A single center experience where 10 patients received livers from donors known to be infected with HCV based on positive nucleic acid testing. Seven had a prior diagnosis of HCV and were treated before liver transplantation. All recipients were non-viremic at the time of transplantation. All 10 recipients derived hepatitis C infection from their donor and achieved sustained virologic response at 12 weeks post-treatment with DAA-based regimens.

Reau N, et al. (2018). Glecaprevir/Pibrentasvir Treatment in Liver or Kidney Transplant Patients With Hepatitis C Virus Infection. Hepatology. 2018;68(4):1298-1307. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29672891/

- This trial evaluated the safety and efficacy of glecaprevir/pibrentasvir for patients with chronic HCV GT1-6 infection who had received a liver or kidney transplant. MAGELLAN-2 was a phase 3, open-label trial conducted in patients who were ≥3 months posttransplant.

Bari K, et al. (2018). Hepatitis C transmission from seropositive, nonviremic donors to non-hepatitis C liver transplant recipients. Hepatology;67(5):1673-82. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29205441/

- Prospective cohort study of HCV antibody-negative or NAT negative liver transplant recipients who received a liver graft from donors who were HCV antibody positive but NAT negative

Shoreibah M, et al. (2017). Ledipasvir/sofosbuvir without ribavirin is effective in the treatment of recurrent hepatitis C virus infection post-liver transplant. Hepatology International. 2017 Jan 12. doi: 10.1007/s12072-016-9778-6. [Epub ahead of print] Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28083718

- Retrospective, single-center study of liver transplant recipients who received ledipasvir/sofosbuvir without ribavirin for treatment of recurrent hepatitis C.

Levitsky J, et al. (2016). Perioperative ledipasvir-sofosbuvir for HCV in liver-transplant recipients. N Engl J Med;375(21):2106-8. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/27959735/

- Correspondence to the editor describing an open-label, multicenter, phase 2 study involving wait-listed patients with chronic HCV genotype 1 infection who were undergoing a first liver transplantation from an HCV-negative donor

Charlton M, et al. (2015). Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. *Gastroenterology*. 149(3):649-59. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25985734

- A phase 2, open-label study included enrolled 337 patients and assessed treatment with the NS5A inhibitor ledipasvir, the nucleotide polymerase inhibitor sofosbuvir, and ribavirin in patients infected with HCV genotypes 1 or 4

16.3 Cardiothoracic

16.3.1 Lung Transplant

Lewis TC, et al. (2022). One-year immunologic outcomes of lung transplantation utilizing hepatitis C-viremic donors. Clinical transplantation, 36(8), e14749. Retrieved from: https://doi.org/10.1111/ctr.14749

- Prospective, single-arm study evaluating the outcomes of lung transplant recipients from HCV+ donors after 1-year post-transplant. All donor-HCV+ recipients received 8-week treatment with glecaprevir-pibrentasvir immediately post-transplant. Authors concluded the frequency of acute cellular rejection and rejection requiring treatment was not statistically different between groups.

Smith DE, et al. (2020). Impact of Early Initiation of Direct-Acting Antiviral Therapy in Thoracic Organ Transplantation From Hepatitis C Virus Positive Donors. Semin Thorac Cardiovasc Surg. 2021;33(2):407-415. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32621962/

- A single center study that evaluated HCV transmission rates, viremia clearance, and short-term outcomes in HCV-negative patients who received HCV-positive thoracic organs (16 lungs and 22 hearts)

Cypel M, et al. (2020). Prevention of viral transmission during lung transplantation with hepatitis C-viraemic donors: an open-label, single-centre, pilot trial. Lancet Respir Med. 2020;8(2):192-201. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31606437/

- Single center, prospective, open-label, non-randomized trial in which donor lungs from HCV-viremic donors were transplanted into HCV-negative recipients. The aim of the study was to assess the safety and efficacy of lung transplantation in humans from HCV-positive donors to HCV-negative recipients after application of ex-vivo lung perfusion (EVLP) plus ultraviolet C (UVC) perfusate irradiation. Patients received Sofosbuvir 400 mg and velpatasvir 100 mg daily for 12 weeks and was started on therapy at least 2 weeks after transplant. SVR 12 was achieved in 18 patients (90% of the 20 patients).

Woolley AE, et al. (2019). Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients. N Engl J Med. 2019;380(17):1606-1617. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30946553/

- Single center pilot trial of shortened regimen for post-exposure prophylaxis for 36 lung transplants (and 8 heart transplants) completed from HCV NAT+ donors into NAT- recipients from March 1, 2017 – July 31, 2018

Abdelbasit A, et al. (2018). Lung Transplantation from Hepatitis C Viremic Donors to Uninfected Recipients. Am J Respir Crit Care Med. 2018;197(11):1492-1496. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29412687/

- A single center case series of five HCV viremic donors to negative recipients between November 2016-February 2017. Per center protocol, awaited viral load and genotyping before initiating therapy (24-92 days). Therapy and duration was determined based on genotype (sofosbuvir (400 mg) and ledipasvir (90 mg) daily or sofosbuvir (400 mg) and velpatasvir (100mg) daily). All patients achieved SVR 12.

16.3.2 Heart Transplant

Nunez M, et al. (2023). Hepatitis C and heart transplantation: An update. Clinical transplantation, 37(10), e15111. Retrieved from: https://doi.org/10.1111/ctr.15111

- Review of recent updates regarding the use of hepatitis C-viremic donors in heart transplant recipients.

Stachel MW, et al (2022). Long-term follow-up of acute and chronic rejection in heart transplant recipients from hepatitis C viremic (NAT+) donors. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 22(12), 2951–2960. Retrieved from: https://doi.org/10.1111/ajt.17190

- Prospective study evaluating the long term outcomes of heart transplant recipients from HCV+ donors compared to HCV- donors. Authors concluded there were no statistically significant differences in timing, severity, or frequency of ACR in NAT+ recipients compared with the NAT− cohort, nor were there differences in noninvasive measures of graft injury, incidence or severity of CAV, graft dysfunction, or mortality.

Villegas-Galaviz J, et al. (2022). Clinical outcomes of heart transplantation using hepatitis c-viremic donors: A systematic review with meta-analysis [published online ahead of print, 2022 Jan 15]. J Heart Lung Transplant;S1053-2498(22)00015-8. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35153130/

- Systematic review with meta-analysis of nonviremic recipients of heart transplants that had HCV viremic donors. Authors concluded that excellent clinical outcomes have been achieved in this population.

Siddiqi HK, et al. (2021). Hepatitis C Positive Organ Donation in Heart Transplantation. *Curr Transplant Rep.* Retrieved from: https://doi.org/10.1007/s40472-021-00350-1

- Review of studies and registry data for the use of HCV-positive donors in heart transplantation.

Smith DE, Chen S, Fargnoli A, et al. (2020). Impact of Early Initiation of Direct-Acting Antiviral Therapy in Thoracic Organ Transplantation From Hepatitis C Virus Positive Donors. Semin Thorac Cardiovasc Surg. 2021;33(2):407-415. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32621962/

- A single center study that evaluated HCV transmission rates, viremia clearance, and short-term outcomes in HCV-negative patients who received HCV-positive thoracic organs (16 lungs and 22 hearts)

Schlendorf KH, et al. (2020). Expanding Heart Transplant in the Era of Direct-Acting Antiviral Therapy for Hepatitis C. JAMA Cardiol. 2020;5(2):167-174. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31851352/

- A prospective, single-center observational study of 80 adult patients who underwent heart transplant using hearts from hepatitis C–positive donors between September 2016 and April 2019 at a large academic medical center. Among donors, who were considered hepatitis C–positive if results from hepatitis C antibody and/or nucleic acid testing were positive, 70 had viremia and 10 were seropositive but did not have viremia. Of the 70 recipients of HCV NAT+ hearts, 67 (95.7%) developed positive HCV PCR. There were no reported treatment failures, and all patients with at least 12 weeks of follow up after completion of DAA (67%) achieved SVR12. The DAAs utilized included ledipasvir-sofosbuvir for 27 patients (49%), sofosbuvir-velpatasvir for 16 patients (29.1%), and glecaprevir/pibrentasvir for 12 patients (21.8%).

Zhu Y, Shudo Y, Lee R, Woo YJ. (2020). Heart Transplant Using Hepatitis C-Seropositive and Viremic Organs in Seronegative Recipients. Ann Transplant. 2020;25:e922723. Published 2020 Jun 12. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32527989/

- This retrospective report describes all patients at a single center who received heart transplant from HCV antibody+ or NAT+ donor. The report included 3 patients who were treated with DAA during the modern era and achieved sustained viral response. One patient was treated with each of 3 different DAAs: ledipasvir-sofosbuvir, sofosbuvir-velpatasvir, and glecaprevir/pibrentasvir .

McLean RC, et al. (2019). Transplanting hepatitis C virus-infected hearts into uninfected recipients: A single-arm trial. Am J Transplant. 2019;19(9):2533-2542. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30768838/

- This is a single arm industry sponsored trial included 10 patients who underwent heart transplant from HCV NAT+ donors (inclusion: genotype 1 or 4 only; all patients were genotype 1a). All patients were treated with elbasvir/grazoprevir (Zepatier). Of the 10 patients, 9 completed treatment course and achieved SVR12, while one patient cleared viremia but died during treatment course from unrelated cause.

Woolley AE, et al. (2019). Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients. N Engl J Med. 2019;380(17):1606-1617. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30946553/

- Single center pilot trial of shortened regimen for post-exposure prophylaxis for 36 lung transplants (and 8 heart transplants) completed from HCV NAT+ donors into NAT- recipients from March 1, 2017 – July 31, 2018

Schlendorf KH, et al. (2018). Early outcomes using hepatitis C-positive donors for cardiac transplantation in the era of effective direct-acting anti-viral therapies. J Heart Lung Transplant. 2018;37(6):763-769. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29530322/

- This is a case series including 11 heart transplant recipients who received hearts from HCV NAT+ donors, with 9 developing viremia and undergoing treatment with DAA. The agents utilized included Ledipasvir-sofosbuvir (Harvoni) in 7 patients and sofosbuvir-velpatasvir (Epclusa) for 2 patients. Of the 9 treated patients, 8 achieved sustained viral response at 12 weeks (SVR12), and one patient died during treatment course from cause unrelated to HCV.

Stepanova M, et al. (2016). Long-term outcomes of heart transplant recipients with hepatitis C positivity: the data from the U.S. transplant registry. Clin Transplant, 30(12):1570-1577. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27739127

- Chronic hepatitis C infection is associated with a significantly increased post-transplant mortality in heart transplant recipients. The introduction of new direct-acting antiviral agents may provide a treatment option for HCV pre- or post-heart transplantation which could have a positive impact on patients' survival.

16.4 Multi-Organ Studies

Elbeshbeshy H, et al. (2024). Outcomes of kidney, liver, and simultaneous liver and kidney transplants from hepatitis c infected donors to hepatitis c naïve recipients: A large single center experience. Clinical transplantation, 38(1), e15161. Retrieved from: https://doi.org/10.1111/ctr.15161

- Retrospective, single-center observational study assessing outcomes of donor-positive recipient-naive patients who underwent simultaneous liver-kidney transplantation. Authors found no difference in graft failure, recipient death at 1 year, or complication as compared to donor-negative recipient-negative patients.

Ramirez-Sanchez C, et al. (2022). A Pilot Trial for Prevention of Hepatitis C Virus Transmission From Donor to Organ Transplant Recipient With Short-Course Glecaprevir/Pibrentasvir. Open forum infectious diseases, 9(11), ofac550. Retrieved from: https://doi.org/10.1093/ofid/ofac550

- Single-arm, single-center, open-label, pilot clinical trial enrolling patients that received any organ transplant from an HCV-viremic donor. Authors trialed a 7-day course of glecaprevir/pibrentasvir started in the preoperative period prevented transmission of hepatitis C virus (HCV) from viremic donors to 10 HCV-negative recipients (2 heart, 1 lung, 6 kidney, 1 heart/kidney) with 100% sustained virological response at 12 weeks.

McMaster WG Jr, et al. (2021). Early Outcomes of Multivisceral Transplant Using Hepatitis C-Positive Donors. Ann Thorac Surg. 2021;112(2):511-518. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33121968/

- A single-center series of heart/kidney transplant using HCV+ donors and compared them with recipients who received HCV- donors. HCV+ and HCV- groups had similar perioperative and early postoperative cardiac function and similar rates of delayed renal graft function. HCV+ recipients demonstrated higher creatinine levels at 3 months post-transplant compared with HCV- recipients, but by 1-year post-transplant, creatinine levels in both groups were similar. The groups had similar 30-day and 1-year survival. Recipients of organs with hepatitis C underwent weekly

viral load testing while inpatient and monthly viral load testing in the outpatient setting. In recipients who developed donor derived hepatitis C, DAA therapy was initiated under the guidance of transplant hepatology.

Weinfurtner K, et al. (2021). Hepatitis C viraemic organs in solid organ transplantation. J Hepatol, *74(3):*716–33. Retrieved from: https://doi.org/10.1016/j.jhep.2020.11.014

- Review on the practice of transplanting HCV-viremic organs into HCV naïve recipients, including a discussion of the barriers to implementation.

Feld JJ, et al. (2020). Short-course, direct-acting antivirals and ezetimibe to prevent HCV infection in recipients of organs from HCV-infected donors: a phase 3, single-centre, open-label study [published correction appears in Lancet Gastroenterol Hepatol. 2020 Jul;5(7):e6]. Lancet Gastroenterol Hepatol. 2020;5(7):649-657. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32389183/

- Single center, prospective observational study of 13 lung transplant HCV negative recipients (plus 10 kidney, 6 heart, and 1 kidney/pancreas transplant recipient) from HCV NAT+ donors. The aim of this study was to determine if antiviral drugs combined with an HCV entry blocker given before and for 7 days after transplant would be safe and reduce the likelihood of HCV infection in recipients of organs from HCV-infected donors. This study shows that an ultra-short course of

16.5 Post-transplant Outcomes and Complications

Molnar MZ, et al. (2021). Transplantation of Kidneys From Hepatitis C Virus-Infected Donors to Hepatitis C Virus-Negative Recipients: One-Year Kidney Allograft Outcomes. Am J Kidney Dis. 2021;77(5):739-747.e1. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33333148/

- Retrospective cohort study evaluating the comparison of biopsy findings compared between HCV D+R- and D-R- renal transplant recipients

Story MT, et al. (2021). Infiltrating Kaposi sarcoma presenting as acute kidney injury: An unexpected consequence of deliberate hepatitis C-positive organ transplantation. Transpl Infect Dis. 2021;23(2):e13481. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33012057/

- Two cases of donor-derived HHV-8 infection in HCV D+R- renal transplant

Aqel B, et al. (2021). Outcomes following liver transplantation from HCV-seropositive donors to HCV-seronegative recipients. J Hepatol. 2021;74(4):873-880. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33188903/

- 34 HCV-seronegative LT recipients received grafts from HCV-seropositive donors (20 HCV-viremic and 14 non-viremic). Six recipients underwent simultaneous liver-kidney transplant and 4 repeat LT. No recipient of an HCV-non-viremic graft developed HCV viremia. All 20 patients who received HCV-viremic grafts had HCV viremia confirmed within 3 days after LT. DAA treatment was started at a median of 27.5 days after LT. All (20/20) patients completed treatment and achieved SVR12. Glecaprevir/pibrentasvir was the preferred option, but other options were considered in the absence of any contraindications for their use

Weinberg EM, et al. (2021). Multicenter, Double-Blind, Randomized Trial of Emricasan in Hepatitis C–Treated Liver Transplant Recipients With Residual Fibrosis or Cirrhosis. Liver Transpl, *27*(4); 568–79. Retrieved from: https://doi.org/10.1002/lt.25934

- Multicenter, randomized, double-blind, placebo-controlled trial of emricasan in HCV liver transplant recipients with residual fibrosis or cirrhosis after achieving sustained virologic response to HCV therapy.

Kapila N, et al. (2020). Fibrosing cholestatic hepatitis after kidney transplantation from HCV-viremic donors to HCV-negative recipients: A unique complication in the DAA era. Am J Transplant. 2020;20(2):600-605. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31448549/

- Two cases of patients experiencing fibrosing cholestatic hepatitis (FCH) following HCV D+R- renal transplantation

Reau N, et al. (2018). Glecaprevir/Pibrentasvir Treatment in Liver or Kidney Transplant Patients With Hepatitis C Virus Infection. Hepatology. 2018;68(4):1298-1307. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29672891/

- This trial evaluated the safety and efficacy of glecaprevir/pibrentasvir for patients with chronic HCV GT1-6 infection who had received a liver or kidney transplant. Overall SVR12 was 98% (n=98/100; 95% CI, 95.3%-100%) Glecaprevir/pibrentasvir was initiated greater than or equal to 3 months post-transplant for a duration of 12 weeks.

Belli L, et al. (2018). Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol;69(4):810-817. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29940268/

- Cohort study based on data from the European Liver Transplant Registry (ELTR) analyzing evolution of indications and results of liver transplantation over 10 years in Europe, focusing on the changes induced by the advent of DAAs

Gupta G, Kang L, Yu JW, et al. (2017). Long-term outcomes and transmission rates in hepatitis C virus-positive donor to hepatitis C virus-negative kidney transplant recipients: Analysis of United States national data. Clin Transplant. 2017;31(10):10.1111/ctr.13055. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/28712111/

- Analysis of the national Organ Procurement and Transplant Network (OPTN) registry from 1994 to 2014 to compare the outcomes of HCV D+/R- (n = 421) to propensity-matched HCV-negative donor (D-)/R- kidney transplants, as well as with waitlisted patients who never received a transplant, in a 1:5 ratio (n = 2105, per matched group).

Irwin L, et al. (2017). Utilization of increased risk for transmission of infectious disease donor organs in solid organ transplantation: retrospective analysis of disease transmission and safety. Transplant Infectious Disease. 19(6): e12791. Retrieved from: https://onlinelibrary.wiley.com/doi/abs/10.1111/tid.12791

- Short communication reporting the use of increased risk donor organs. Describes a higher rate of use of increased risk donor organs compared to national rate of use.

Bowring M, et al. (2017). Changes in utilization and discard of hepatitis c-infected donor livers in the recent era. Am J Transplant;17(2):519-527. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/27456927/

- SRTR registry study analyzing the impact of DAAs on utilization and outcomes associated with HCV-positive deceased donor kidney transplant

Doucette KE, Halloran K, Kapasi A, Lien D, Weinkauf JG. (2016). Outcomes of Lung Transplantation in Recipients With Hepatitis C Virus Infection. Am J Transplant. 2016;16(8):2445-2452. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/26998739/

- A single-center study discussing the outcomes of patients with HCV who receive a lung transplant. In their cohort, HCV did not impact lung transplant outcomes

Leroy V, et al. (2015). Efficacy of Sofosbuvir and Daclatasvir in Patients With Fibrosing Cholestatic Hepatitis C After Liver Transplantation. Clinical gastroenterology and hepatology. 13(11):1993-2001. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26044317

- A study that evaluated the efficacy and safety of sofosbuvir- and daclatasvir-based regimens. It analyzed data from 23 patients with Fibrosing cholestatic hepatitis who participated in a prospective cohort study in France and Belgium and the effects of antiviral agents in patients with recurrence of HCV infection after liver transplantation

16.6 Medication Access and Cost Effectiveness

Bova S, et al. (2022). Access to direct-acting antivirals for hepatitis C-negative transplant recipients receiving organs from hepatitis C-viremic donors. Am J Health Syst Pharm. 2022;79(3):173-178. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33987658/

- A retrospective, single center, evaluating 38 HCV negative recipients receiving grafts from HCV-viremic or HCV-seropositive donors (25 liver, 6 lung, 4 simultaneous liver and kidney, 3 kidney transplants) and their access to DAAs. Of these patients, 23 had commercial insurance, 13 had Medicare, and 2 had Medicaid. All patients ultimately received insurance coverage for treatment; however, 36 (95%) required prior authorization and 9 (24%) required appeals to obtain insurance coverage.

Torabi J, et al. (2021). Commercial insurance delays direct-acting antiviral treatment for hepatitis C kidney transplantation into uninfected recipients. Transpl Infect Dis. 2021;23(1):e13449. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32810315/

- A retrospective, single center, evaluating 52 HCV D+R- kidney recipients receiving grafts from HCV-viremic or HCV-seropositive donors (25 liver, 6 lung, 4 simultaneous liver and kidney, 3 kidney transplants). Patients were grouped according to their prescription coverage plans, managed by either commercial or government pharmacy benefit managers (PBMs. All patients developed HCV viremia, but cleared the virus after treatment with DAA. Patients with government PBMs were treated earlier compared to those with commercial PBMs (11 days vs 26 days, P = .01).

Eckman MH, et al. (2020). Cost-effectiveness of Using Kidneys From HCV-Viremic Donors for Transplantation Into HCV-Uninfected Recipients. Am J Kidney Dis. 2020;75(6):857-867. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32081494/

- A study utilizing markov state transition decision model to exam cost-effectiveness of HCV D+R- kidney recipients. Authors concluded there was an increased quality-adjusted life expectancy and reduced costs when transplanting HCV D+R- renal transplant recipients compared to HCV D-R-

Crona L, Berry H, Byrns J, Campbell U. (2020). Clinical pharmacy programmatic perspectives on use of direct-acting antivirals for acquired hepatitis C infection in solid organ transplant recipients. Am J Health Syst Pharm. 2020;77(14):1149-1152. Retrieved from: https://academic.oup.com/ajhp/article-abstract/77/14/1149/5857376

- Description of a multi-organ transplant, single center experience with success and challenges to a posttransplant DAA workflow in approximately 50 HCV D+R- renal transplants. DAA prescribed based on D-D interactions and genotype. SVR 12 obtained in all patients

Gupta G, Zhang Y, Carroll NV, Sterling RK. (2018). Cost-effectiveness of hepatitis C-positive donor kidney transplantation for hepatitis C-negative recipients with concomitant direct-acting antiviral therapy. Am J Transplant. 2018;18(10):2496-2505. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30075489/

- A decision tree model was developed to analyze costs and effectiveness over a 5-year time frame between 2 choices: renal transplant (RT) using a Hep C D+ to R- strategy compared to continuing dialysis and waiting for a HCV-negative donor (D-/R-). The strategy of accepting a HCV+ organ then treating HCV was slightly more effective and substantially less expensive and resulted in an expected 4.8 years of life (YOL) with a cost of ≈$138,000 compared to an expected 4.7 YOL with a cost of ≈$329,000 for the D-/R- strategy.

Trotter PB, et al. (2018). Use of Organs From Hepatitis C Virus-Positive Donors for Uninfected Recipients: A Potential Cost-Effective Approach to Save Lives?. Transplantation. 2018;102(4):664-672. Retrieved form: https://pubmed.ncbi.nlm.nih.gov/29166338/

- The Potential Donor Audit of patients (<80 years) dying in UK critical care units and the UK Transplant Registry was searched to identify HCVpos potential and proceeding deceased donors. A cost analysis was performed by comparing the cumulative cost of direct-acting antivirals with

hemodialysis and renal transplantation. The additional costs of treating recipients exposed to HCV by receiving a HCVpos kidney was cost-neutral with dialysis 5 years from transplantation.

Kadatz M, Klarenbach S, Gill J, Gill JS. (2018). Cost-effectiveness of using kidneys from hepatitis C nucleic acid test-positive donors for transplantation in hepatitis C-negative recipients. Am J Transplant. 2018;18(10):2457-2464. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.14929

- A study using the Markov model to examine the cost-effectiveness of using deceased donors infected with HCV for kidney transplantation in uninfected waitlist candidates. In the primary analysis, this strategy was cost saving and improved health outcomes compared to remaining on the waitlist for an additional 2 or more years to receive a HCV-negative transplant.

16.7 Pharmacokinetics/Drug Administration/Drug Interactions

Laub M, Harris M, Sanoff S, Berg C, Byrns J. (2021). Effects of Sofosbuvir-Based Hepatitis C Treatment Regimens on Calcineurin Inhibitor Dosing in Liver and Kidney Transplant Recipients. Exp Clin Transplant. 2021;19(2):142-148. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31875466/

- The median percent difference in calcineurin inhibitor troughs from pretreatment to during treatment was -20.5% (interquartile range, -36.2% to 13.1%) and from pretreatment to posttreatment was -13.5% (interquartile range, -33.7% to 10.7%). Corresponding percent changes in calcineurin inhibitor doses were 0% (interquartile range, 0%-0%) and 0% (interquartile range, -10.5% to 33.3%), respectively. Patients on tacrolimus experienced statistically significant changes in troughs but not doses. During treatment, 65% of patients required no dose change, 23% underwent a dose increase, and 12% had a dose decrease. The sustained virologic response rate was 98%, and the biopsy-proven acute rejection rate was 0%.
- Hepatitis C direct-acting antiviral therapy may decrease calcineurin inhibitor levels, but this was not associated with clinically different dosing requirements or rejection rates

Lewis TC, et al. (2020). Management and tolerability of glecaprevir-pibrentasvir pharmacotherapy in hepatitis C viremic heart and lung transplant recipients. Clin Transplant. 2020;34(10):e14030. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32632929/

- Retrospective chart review, case-control format of heart and lung recipients previously enrolled in a single-center observational study. 24 heart and 22 lung transplant recipients of HCV NAT- organs were utilized as controls. This study cautioned using glecaprevir/pibrentasvir in combination with strong CYP3A4 inhibitors and noted the practice of dissolving glecaprevir/pibrentasvir in water for NG tube administration to prevent interruptions in therapy

Bellesini M, et al. (2020). Drug-Drug Interactions between Direct Oral Anticoagulants and Hepatitis C Direct-Acting Antiviral Agents: Looking for Evidence Through a Systematic Review. Clin Drug Investig. 2020;40(11):1001-1008. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32809123/

- This is the first systematic review assessing evidence about direct oral anticoagulants/direct-acting antiviral agents (DOACs/DAAs) drug–drug interactions (DDIs)
- Of 1386 identified references, four articles were finally included after applying the exclusion criteria. Three phase I clinical studies in healthy volunteers assessed interactions between dabigatran and glecaprevir/pibrentasvir, odalasvir/simeprevir, or sofosbuvir/velpatasvir/voxilaprevir, showing an increase in the dabigatran area under the concentration–time curve (AUC) by 138%, 103%, and 161%, respectively
- DAAs increase dabigatran concentration, while no studies were available for other DOACs

Woolley AE, et al. (2019). Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients. N Engl J Med. 2019;380(17):1606-1617. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30946553/

- Single center pilot trial of shortened regimen for post-exposure prophylaxis for 36 lung transplants (and 8 heart transplants) completed from HCV NAT+ donors into NAT- recipients. The article discusses the administration of DAA utilized. The DAA was crushed and mixed with saline and administered via an enteral (nasogastric, orogastric or percutaneous endoscopic gastrostomy) tube prior to extubation and transitioned to a pill when patients recovered their ability to swallow. The sofosbuvir/velpatasvir was given at least four hours prior to a proton pump inhibitor, or simultaneously with or 12 hours apart from an H2-receptor antagonist

Ortiz GA, Trivedi HD, Nader C. (2018). Pharmacokinetics and drug interactions of medications used to treat hepatitis C virus infection in the setting of chronic kidney disease and kidney transplantation. Hemodial Int. 2018;22 Suppl 1:S22-S35. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29694720/

- The review provides an overview of the essential pharmacokinetics and drug interactions of relevant antiviral therapies in the treatment of chronic hepatitis C in patients with advanced kidney disease and after kidney transplantation
- The results of the few trials and many observational studies included are encouraging in terms of the safety and efficacy of the coadministration of DAA with different immunosuppressants. However, frequent monitoring of drug concentrations as well as side effects is warranted

Wijarnpreecha K, et al. (2017). Efficacy and Safety of Direct-acting Antivirals in Hepatitis C Virus-infected Patients Taking Proton Pump Inhibitors. J Clin Transl Hepatol. 2017;5(4):327-334. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29226099/

- Nine cohort studies with 32,684 participants met the eligibility criteria and were included in the meta-analysis. The use of PPIs concomitant with DAAs among HCV-infected patients was associated with lower odds of achieving SVR compared with non-PPI users (pooled odds ratio (OR): 0.74, 95% confidence interval (CI): 0.63–0.88, I2 = 24%). Subgroup analysis addressed the association between PPIs use and SVR12 demonstrated the association of PPI users showing lower odds of achieving SVR12 compared with those with no use of PPIs

Dick TB, Lindberg LS, Ramirez DD, Charlton MR. (2016). A clinician's guide to drug-drug interactions with direct-acting antiviral agents for the treatment of hepatitis C viral infection. Hepatology. 2016;63(2):634-643. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/26033675/

- This review summarizes the available data regarding the most clinically relevant drug-drug interactions for DAAs with the goal of optimizing pharmacotherapeutic outcomes
- The potential for important drug-drug interactions increases with the complexity of the DAA regimen employed. Critical interactions exist for DAAs with many commonly prescribed and over the counter agents, e.g., greatly decreased absorption of ledipasvir in the setting of PPI therapy. The great majority of drug-drug interactions are manageable and do not present an absolute barrier to safe and effective treatment of HCV infection

Smolders EJ, et al. (2016). Pharmacokinetics, Efficacy, and Safety of Hepatitis C Virus Drugs in Patients with Liver and/or Renal Impairment. Drug Saf. 2016;39(7):589-611. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/27098247/

- All of the available drugs for the treatment of HCV can be used in patients with CP-A and in those with a GFR ≥30 mL/min. Some drugs are contraindicated in patients with advanced liver disease (CP-B or CP-C), and sofosbuvir plus ledipasvir or daclatasvir are the best options for this group. Patients with a GFR <30 mL/min can be treated with grazoprevir plus elbasvir or

paritaprevir/ritonavir and ombitasvir with or without dasabuvir. Sofosbuvir is an important part of HCV therapy, and therefore data on its use in renally impaired patients is essential information; however, data on sofosbuvir are still pending.

Smolders EJ, et al. (2016). Drug-Drug Interactions Between Direct-Acting Antivirals and Psychoactive Medications. Clin Pharmacokinet. 2016;55(12):1471-1494. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/27317413/

- Escitalopram and citalopram have been studied in combination with most direct-acting antivirals (DAAs) and either of these drugs can be safely combined with hepatitis C virus (HCV) treatment.
- No formal interaction studies between psychoactive agents and sofosbuvir or ledipasvir have been performed in humans. However, these DAAs are generally neither victims nor perpetrators of drug interactions and can therefore be safely used in combination with psychoactive drugs.
- Boceprevir, simeprevir, and the combination paritaprevir/ritonavir plus ombitasvir with dasabuvir are most likely to cause drug interactions via the inhibition of cytochrome P450 (CYP) 3A4. Therefore, caution must be exercised when CYP3A4 substrates such as midazolam and/or quetiapine are co-administered with these DAAs.

Vispo E, Barreiro P, Soriano V. (2013) Pharmacokinetics of new oral hepatitis C antiviral drugs. Expert Opin Drug Metab Toxicol. 2013;9(1):5-16. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/23094639/

- This review updates the main pharmacokinetic and pharmacodynamic characteristics of the most promising new oral direct-acting antivirals (DAA) for hepatitis C. Given that a large proportion of chronic hepatitis C patients receive other medications, drug interactions are further discussed

16.8 Management of Co-infection (HepC+ with HepB)

Chen G, et al. (2017). Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: A systematic review and meta-analysis. Hepatology. 2017;66(1):13-26. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/28195337/

- Systematic review and meta-analysis to compare the rate of HBV reactivation in chronic hepatitis C patients coinfected with overt HBV (HBsAg-positive) and occult HBV (HBsAg negative with positive HBV DNA) infection separately, treated with interferon (IFN)-based therapy to those with pan-oral DAAs. The results of the analysis showed HBV reactivation occurs earlier and is clinically more significant in chronic hepatitis C patients coinfected with overt and occult HBV who are treated with pan-oral DAAs compared with IFN-based therapy.