

Management of Hepatitis C Infection in Kidney Transplantation Candidates and Recipients

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ABSTRACT

Hepatitis C virus (HCV) infection remains a global major health problem. HCV related liver and kidney diseases constitute a worldwide significant burden on countries' economy. Liver disease progresses rapidly in HCV positive patients with end stage renal disease (ESRD). Allograft and patients' survival are reduced in post kidney transplant patients with HCV. Screening and infection control measures have aided in decreasing the prevalence of HCV in dialysis units and subsequently in post kidney transplant patients. The management of HCV in patients with renal disease continues to be challenging. Until recently, treatment of HCV relies mainly on pegylated interferon and ribavirin. However, this treatment was associated with low sustained virological response (SVR) and was poorly tolerated in patients with ESRD. Further, it has the potential for rejection in post renal transplant setting. The discovery of the direct-acting antiviral agents (DAAs) has made a revolution in the treatment of HCV. Several pan-genotypic DAA are available to treat HCV in ESRD and in post renal transplant with high SVR and low adverse events. In post renal transplant patients, the drug-drug interaction between DAA and immunosuppressant remain a concern and carries the risk of potential rejection. In this chapter, we performed an updated comprehensive review on the impact of HCV on patients with ESRD and in post kidney

transplant. We emphasize on the development in the treatment of HCV with DAA in pre and post renal transplant patients. We also addressed the immunosuppression effect in these settings.

INTRODUCTION

Hepatitis C virus (**HCV**) is a systemic infection, which primarily affects the liver. About 60-80% of infected individuals will develop chronic HCV infection. Liver cirrhosis will affect 15-30% within 20 years [1]. Globally, an estimated 71 million people have chronic hepatitis C (**CHC**). A substantial number of CHC will develop cirrhosis, liver failure or liver cancer [1-3]. Approximately 400,000 people die each year from complications of HCV, mostly from cirrhosis and hepatocellular carcinoma [1]. There is a rising international concern from HCV due to the extensive influence on morbidity and mortality [4-7]. Recently, The World Health Assembly adopted the first “Global Health Sector Strategy on Viral Hepatitis, 2016-2021” to eliminate viral hepatitis and implement global targets to decrease new viral hepatitis infections by 90% and reducing deaths due to viral hepatitis by 65% by 2030 [8, 9].

Enormous health and economic burden are constantly imposed on countries worldwide from HCV hepatic as well as extra-hepatic effects [10-12]. Nearly 40% of CHC patients exhibit some extra-hepatic manifestations during their illness [13]. The identification, diagnosis and management of extra-hepatic HCV manifestation are crucial [14]. The prevalence of HCV in patients with CKD is more than that in the general population, further, HCV is an additional factor for the increased morbidity and mortality rates in end-stage renal disease (**ESRD**) patients [15]. Presently, HCV infection is the main cause of chronic liver disease in kidney transplant recipients [15,16].

In Western countries, the prevalence of HCV in hemodialysis patients is highly variable (2.6-22.9%), therefore the prevalence in renal transplant recipients is high and quite variable (1.8% - 8%) compared to the general population [17-20]. The most common cause of HCV in renal transplant recipients is multiple previous hemodialyses and not the organ transplant [21].

EFFECT OF HEPATITIS C ON THE KIDNEY

The effect of HCV on the kidney is a well-known phenomenon. The most frequent kidney manifestations of HCV infection are; membranoproliferative and membranous glomerulonephritis secondary to mixed cryoglobulinemia with high potential for chronic kidney disease (**CKD**) and end-stage renal disease (**ESRD**) [22,23-28]. Similarly, there is a high risk for patients with ESRD to get infected with HCV due to the repeated exposure to hemodialysis [29-31]. Furthermore, hemodialysis patients who are positive for HCV have more liver-related complications than general population [32, 33]. Recently, it was observed that the prevalence of HCV in HD patients is declining to 2- 8% due to the strict precautions and infection control strategies in most of dialysis centers [34].

KIDNEY TRANSPLANTATION IN PATIENTS WITH HCV

A significant number of dialysis patients will ultimately proceed to renal transplantation, and this will accordingly increase the prevalence of HCV infection after renal transplantation more than in the general population [35,36]. There is a variable prevalence of HCV in renal allograft recipients ranging from 6% and 40% in most centers but has reached up to 75% in others [37-42].

HCV infection that was acquired during the hemodialysis period or after unscreened blood transfusion and renal impairment were attributed as the main causes for the high prevalence of HCV in renal transplant recipient compared to general population [43,44]. For this reason, Kidney Disease: Improving Global Outcomes (**KDIGO**) clinical practice guideline has recommended all CKD and kidney transplant candidates be tested for HCV infection and to be evaluated for possible antiviral therapy [15]. The guidelines emphasized that early detection and treatment of HCV-related renal disease post renal transplantation could improve the outcomes in these patients [15]. HCV is associated with an increased morbidity and mortality in patients on the waiting list for renal transplant and in post transplant setting [37,45]. Graft and patient survival in HCV-positive kidney transplant recipients are worse than those who are HCV-negative [37,46-53]. Moreover, HCV-positive renal transplantation recipients have higher risks of cardiovascular disease, sepsis, and liver disease [37,46,47,51,54]. The existing liver disease in these patients typically progresses rapidly to liver cirrhosis with its subsequent complications including hepatocellular carcinoma, liver failure and death [15,55-61].

Extra-hepatic manifestations of HCV that include recurrent or de novo glomerulonephritis, new onset diabetes mellitus may develop after renal transplant. Other complications that may develop post-renal transplant include; chronic allograft nephropathy and immunosuppression induced nephrotoxicity and malignancy particularly the lymphoproliferative disorder [17,62-70]. Fabrizi et al in a recent meta-analysis to study the impact of HCV infection on all-cause mortality and graft loss after RT showed that the summary estimate for adjusted relative risk (**RR**) of all-cause mortality to be 1.85; 95% confidence interval (**CI**) = 1.49 - 2.31, ($P < 0.0001$) and the overall estimate for adjusted RR of all-cause graft loss was 1.76; 95% CI = 1.46 - 2.11), ($P < 0.0001$) [51].

Despite all of the potential lethal effect of HCV on renal transplant clinical course, kidney transplantation is highly recommended for these patients due to its cost-effectiveness and improvement in survival compared to long-term hemodialysis [45,71,72].

TREATMENT OF HEPATITIS C IN CHRONIC RENAL DISEASE

It is of paramount clinical importance to practice every effort to treat HCV early and prevent its liver and renal complications after renal transplant. In the past, treatment of HCV patients includes a combination of conventional interferon and ribavirin. This was followed by the use of pegylated interferon (**PEG-IFN**) with or without ribavirin. Ribavirin alone found to be contraindicated in

dialysis patients due to its intolerance and anemia worsening caused by hemolysis [73]. The use of regular interferon or PEG-IFN either alone or in combination with ribavirin in hemodialysis patients showed some response and it was suggested that it prolongs the durability of response post kidney transplantation [74-83]. Combination of PEG-IFN and ribavirin is still the mainstay and the standard of care therapy of HCV in ESRD in some centers. However, this combination is commonly accompanied with significant side effects that frequently lead to its discontinuation [15,84-87].

The first-generation direct acting antiviral (DAA) agents include the protease inhibitors, telaprevir and boceprevir, which have inhibitory activity against NS3/4A protease of the HCV virus. Although they do not need dose modification in ESRD patient, they are unfortunately requiring combination with PEG-IFN and ribavirin, which brings the same dilemma of the use of the later in ESRD. Further, viral resistant may develop if they were used as a mono therapy [63].

The recent discovery of the all-oral, interferon-free DAA has made a revolution in the treatment of chronic HCV infection. They directly inhibit the viral proteins at different locations of the nonstructural part of HCV including NS3, NS4A, NS4B, NS5A, and NS5B [85,86,88]. Figure 1 shows the HCV virus structure and the target locations of DAA action on its specific parts.

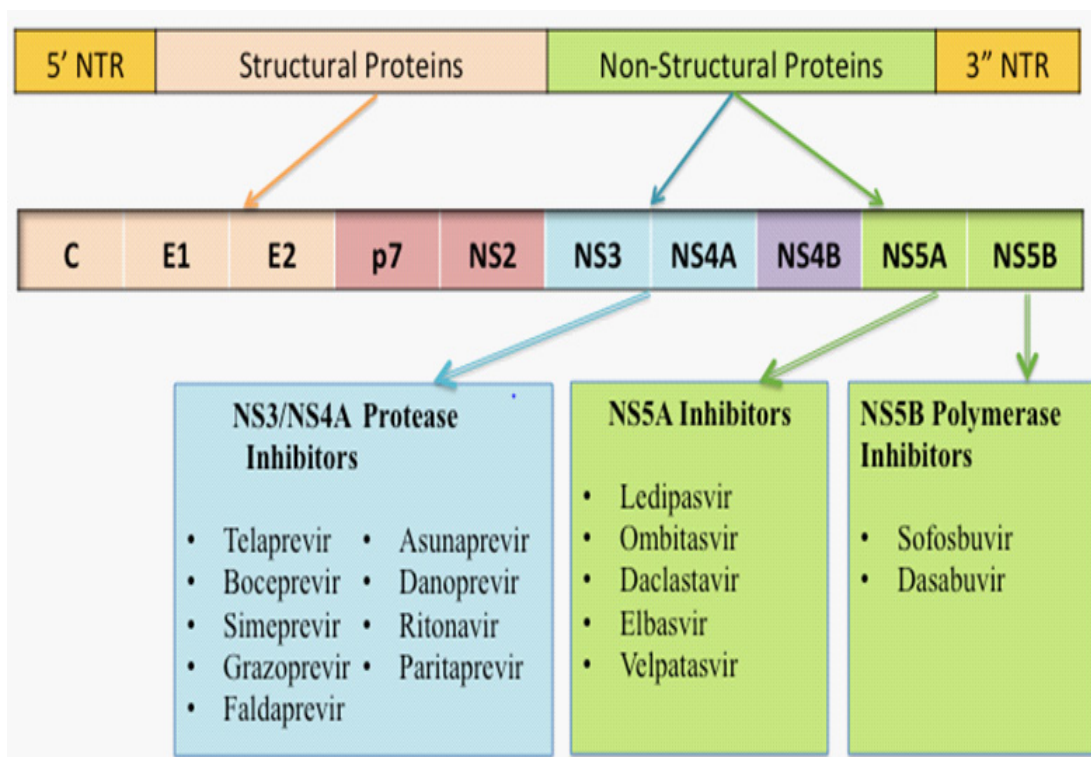


Figure 1: Hepatitis C virus Structure and Targets for Direct-Acting Antiviral Drugs.

C: Core, E: Envelope, NS: Non-Structural, NTR: Non-Translated Region.

Sofosbuvir, NS5B polymerase inhibitor, whether alone or in combination with ledipasvir (NS5A inhibitor) or simeprevir (NS3/4A protease inhibitor) does require dose adjustment in ESRD because the sofosbuvir component is excreted through the kidney [63]. The Safety and efficacy of sofosbuvir-based therapy has not been established with estimated GFR \leq 30 mL/min [85,88].

In a recent study by Saxena et al, evaluating the safety and efficacy of sofosbuvir-based therapy in HCV patients with GFR \leq 45 ml/min, although achieved a high SVR at 83%, this was associated with serious adverse effects including a decline in renal function and severe anemia [89].

Several other DAA that are not excreted by the kidney, can be used for the treatment of HCV in patients with stage 4-5 CKD, such as grazoprevir (NS3/4A protease inhibitor) and elbasvir (NS5A replication complex inhibitor), daclatasvir (NS5A replication complex inhibitor) and asunaprevir (NS3/4A protease inhibitor) [63,90-92]. Zepatier (A combination of grazoprevir and elbasvir), is a pan-genotypic DAA which does not need dosage adjustment for patients with any degree of renal impairment including patients on hemodialysis is highly effective and has a low rate of adverse events in these settings [93,94]. In RUBY-1 study, assessing the efficacy and safety of paritaprevir/ritonavir/ombitasvir and dasabuvir (3D) with or without ribavirin in HCV patients with CKD stage 4 or 5, including those who were on hemodialysis, has revealed a 90% virological response rate and only a few and manageable adverse effects [95]. Most recently, Surendra et al evaluated therapy with alternate days DAA in hemodialysis patients in an open-label observational study utilizing ledipasvir and sofosbuvir. They treated 21 patients with ledipasvir and sofosbuvir combination on alternate days for a period of 12 weeks. SVR was achieved in the 19 patients who were available for analysis. None of the patients discontinued the therapy and no major adverse effects were reported [96]. Roth et al in a randomized study to assess an all-oral, ribavirin-free DAA treatment in patients with HCV genotype 1 infection and stage 4-5 chronic kidney disease, 122 received grazoprevir and Elbasvir once daily for 12 weeks. SVR was achieved in 99% of patients and none of the patients in the treatment arms has developed significant adverse effects that necessitated discontinuation of therapy [92]. Currently, there are ongoing studies to evaluate the efficacy and safety of different DAA in patients with ESRD.

TREATMENT OF HCV POST RENAL TRANSPLANTATION

Regular and Pegylated Interferon

Post-renal transplant Treatment of HCV presents difficulties and challenges. Multiple studies reported a very low efficacy rate of the combination of regular interferon and ribavirin. Furthermore, it was associated with severe side effects including allograft rejection and intolerance [97-101]. The use of PEG-IFN and ribavirin in post kidney transplanted was reported by different investigators and revealed very good response rate however it has multiple limiting adverse effects [102-104]. We previously reported our experience of treating HCV patient in the

post renal transplant settings and have shown a virological response rate of 42.1% and only 5% adverse effects that were mild and manageable [105].

Direct Acting Antiviral Agents

The use of direct acting antiviral agents in such patients presents an opportunity for better response rates and less adverse effects, particularly in interferon-free treatment regimens. The choice of the treatment of HCV post renal transplant is similar, to some extent, to HCV treatment in non-transplant setting. It depends on several factors that make the antiviral more effective and with minimal adverse effects. This include; previous history of antiviral treatment intake, presence or absence of liver cirrhosis and its complications, the HCV genotype and drug-drug interaction. However, post renal transplant patients although, in the post-transplantation setting patients are typically have a normal renal function, they still need to be evaluated for the extent of their kidney function and avoidance for the potential but harmful interaction between DAA and immunosuppression medications. Multiple DAA protocols for treatment of HCV in kidney transplant recipients are evolving which support a high SVR and they are well tolerated. In contrast to interferon, host immune system does not get stimulated by DAA, hence the allograft rejection would not be expected with the use of DAA for the treatment of HCV infection post renal transplant [37, 106]. Sawinski et al. recently reported successful treatment of 20 HCV, genotype 1 and 2 in post renal transplant patients using interferon-free, sofosbuvir-based, DAA regimens. They achieved 100% SVR and treatment was well tolerated with preservation of allograft function [107]. Similarly, Kamar et al. in a pilot study treated 25 HCV positive kidney transplant patients with sofosbuvir plus daclatasvir or simeprevir or ledipasvir or pegylated-interferon with and without ribavirin. All developed SVR at 4 and 12 weeks after completing DAA therapy. Patients tolerated therapy well without any adverse events [108]. In a study evaluating the efficacy and safety of DAA in kidney transplant recipients with HCV Infection, Lin et al. treated 24 patients with sofosbuvir-based therapy. It revealed an overall SVR at 91% and adverse events in 46%, the later were managed clinically without discontinuation of therapy. All patients received sofosbuvir either with simeprevir with or without ribavirin, or ledipasvir with or without ribavirin [106]. In a more recent study by Lubetzky et al., a total of 31 patients were treated with different regimens of DAA, most of them were by sofosbuvir and ledipasvir. SVR was achieved in 97% and graft and patient survivals were 100%. There was no significant change in GFR before or immediately after therapy, however, 3 patients later developed GFR less than 20. Worsening proteinuria developed in 6 of 31 patients towards the end therapy. Proteinuria with more than 500 mg/g at the start of treatment was a predictor for the development of worsening proteinuria ($P < 0.001$). They retrospectively reviewed another 20 untreated HCV patients and found no worsening allograft function or proteinuria during a median follow-up time [109]. Taneja et al. treated 47 HCV infected renal transplant recipients with sofosbuvir-based regimen. Fourteen received sofosbuvir and ribavirin for 24 weeks, 22 received sofosbuvir and ledipasvir and 12 received sofosbuvir and daclatasvir with or without Ribavirin for 12 or 24 weeks depending on genotype and underlying

cirrhosis. The SVR12 rates were 100% in all groups except in the sofosbuvir and ribavirin group (86%). Anemia was the only serious adverse effect and was observed in 8 patients treated with sofosbuvir and ribavirin [110].

Eisenberger et al reported treating 15 renal transplant recipients with therapy-naïve HCV with the combination of sofosbuvir and ledipasvir without ribavirin for 8 or 12 weeks. All patients showed SVR. There were only little adverse events; renal function and proteinuria remained stable. A dose adjustment for tacrolimus was required to maintain sufficient trough levels [111]. Colombo et al., in a recent multicounty, randomized, phase 2, open-label study, Patients were randomly assigned 1:1 to receive either 12 or 24 weeks of treatment with a fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) once daily. Total of 114 patients were treated (57 in each group), SVR was achieved in all patients [112]. DAAs were also proposed to be useful in improving kidney graft survival. Goetsch et al., in a retrospective study, treated 19 kidney transplant patients with HCV with DAAs. Glomerular functions were assessed using average urinary protein/creatinine (P/C) ratios tested pre-and post-treatment. Their results revealed that the post-treatment P/C ratios were significantly lower than pre-treatment ratios ($P=0.01$). In 14 of 19 patients, the P/C ratios were reduced (74%).The estimated GFR post-treatment was not significantly different than the pre-treatment values ($P=0.82$). Further, SVR was achieved in all patients [113].

There are no clear strategies on the proper and ideal timing for commencement of DAA in HCV post renal transplant. Singh et al., have adopted a local policy of treating such patients with ledipasvir-sofosbuvir in the first 3 months post-transplant. They recently reported their results of treating 11 patients, in all of them, SVR were achieved. All this approach may reduce the HCV-related post transplant complications; they warned against a potential for increased risks of interaction between DAA and calcineurin inhibitors [114].

IMPACT OF IMMUNOSUPPRESSION ON HCV AFTER KIDNEY TRANSPLANT PATIENTS

The impact of immunosuppression type on HCV in kidney transplant patients is not well studied. Most of the reported studies on the relation between immunosuppression and HCV have come from liver transplant experience. It is not clear that what has been applied on liver transplant is necessarily applicable in HCV-infected kidney transplant setting. However, it is a challenging task and needs large-scale clinical studies for proper evaluation of the patients and graft outcome.

Earlier studies have suggested that immunosuppression increase the HCV viremia level particularly in the immediate period after liver and kidney transplant compared to pre-transplantation [115,116]. However, this increase in the HCV viremia was not found to correlate with the clinical outcome or the progression of the HCV related liver fibrosis [117-122].

Kahraman et al reported their experience of a cohort of 71 HCV positive, post kidney transplant patients who were put on immunosuppression with either cyclosporine A (**CsA**) or tacrolimus (**Tac**). Although they found that the HCV viral level in the early course after kidney transplantation was less in patients treated with Tac compared to CsA, this difference was not appreciated after 3 months post transplant and the degree of liver fibrosis in both groups was found to be comparable [123]. Aljumah et al. in a study on treatment of HCV post renal transplant with Peg-IFN and ribavirin, they found no relation between the response rate or the development of renal dysfunction and the type of immunosuppression used [105]. Cyclosporine was suggested to have anti- HCV activity that may be inhibiting viral replication, but its clinical significance was not confirmed [124]. While tacrolimus was linked to increasing the risk for diabetes mellitus in HCV- infected kidney transplant recipients [125]. Luan et al. reported the finding from a large kidney transplant registry that there was no survival benefit in HCV- infected renal transplant patients who have used either tacrolimus or cyclosporine [126]. Steroids are commonly used immunosuppressant agent especially in the early post transplant period, however, there was no statistically significant difference between patients who received steroids and those who did not in term of mortality [126]. Furthermore, Patient and graft survival were not affected by rapid steroid withdrawal [127]. Mycophenolate mofetil (**MMF**) is currently used in combination with CNI and steroids as a standard immunosuppressive therapy. There are conflicting reports on its benefit in HCV infected transplant candidate. Some studies have suggested that it increase the HCV viral level without a clearly document lethal effect on the clinical outcome [128]. On the other hand, MMF was found to decrease the risk of mortality by one third in HCV- infected kidney transplant patients [126].

Sirolimus is an mTOR inhibitor, which was claimed to have a broad antiviral activity and anti-proliferative effects [129]. It was shown that sirolimus was associated with reduced liver fibrosis and cell proliferation *in vitro* [130]. From studies on HCV in liver transplant patients, mTOR inhibitors were reported to decrease the HCV viral level and fibrosis [131,132].

The relationship between the uses of certain type of immunosuppression in HCV- infected renal transplant patients and the clinical outcome is not properly established.

The use of DAA in treating HCV post transplant has opened a wide door to treat patients who were historically difficult to treat in the interferon era. DAA does not cause robust immune triggering effect and so has less effect on immunosuppression modification in such patients.

Recent studies showed that IFN free, all oral DAA, are effective and safe in the treatment of HCV post renal transplant [108,133-135]. However, it is still necessary to observe for any possible drug-to-drug interaction and the need for dose adjustment if required. The drug-drug interaction between DAA and immunosuppression post transplantation is a challenging subject. Most of DAA can be used safely after transplant. However, it is always advisable to monitor the immunosuppressant level and closely observe for any adverse events [85,136,137]. Two DAA

needs special attention as they are contraindicated to use post transplant due to drug-drug interaction. First is the concomitant use of elbasvir/grazoprevir with cyclosporine may increase the risk of ALT elevations due to several folds increase in grazoprevir plasma level caused by OATP1B1/3 inhibition [139]. Second is the concomitant use of simeprevir and cyclosporine will lead to significant increase in the level of both drugs [140]. The potential interactions between DAA and commonly used immunosuppression are shown in table 1.

Table 1: Drug Interactions between DAAs and commonly used Immunosuppressants.

Anti-Viral	Immunosuppression					
	Cyclosporine	Tacrolimus	Mycophenolate	Sirolimus	Methylprednisolone	Prednisone
Simeprevir	Confirmed Interaction. Its use is Contraindicated.	Potential Interaction. Its use needs observation and Monitoring.	No known Interaction	Potential Interaction. Its use needs observation and Monitoring.	Potential Interaction. Its use needs observation and Monitoring.	Potential Interaction. Its use needs observation and Monitoring.
Sofosbuvir	No known Interaction	No known Interaction	No known Interaction	No known Interaction	No known Interaction	No known Interaction
Daclatasvir	No known Interaction	No known Interaction	No known Interaction	No known Interaction	No known Interaction	No known Interaction
Ledipasvir/ Sofosbuvir	No known Interaction	No known Interaction	No known Interaction	No known Interaction	No known Interaction	No known Interaction
Sofosbuvir/ Velpatasvir	No known Interaction	No known Interaction	No known Interaction	No known Interaction	No known Interaction	No known Interaction
Elbasvir/ Grazoprevir	Confirmed Interaction. Its use is Contraindicated.	Potential Interaction. Its use needs observation and Monitoring.	No known Interaction	Potential Interaction. Its use needs observation and Monitoring.	No known Interaction	No known Interaction
Ombitasvir/ Paritaprevir/ Rritonavir	Potential Interaction. Its use needs observation and Monitoring.	Potential Interaction. Its use needs observation and Monitoring.	Potential Interaction Its use needs observation and Monitoring	Potential Interaction. Its use needs observation and Monitoring.	Potential Interaction Its use needs observation and Monitoring	Potential Interaction. Its use needs observation and Monitoring.
Ombitasvir/ Paritaprevir/ Rritonavir + Dasabuvir	Potential Interaction. Its use needs observation and Monitoring.	Potential Interaction. Its use needs observation and Monitoring.	Potential Interaction Its use needs observation and Monitoring	Potential Interaction. Its use needs observation and Monitoring.	Potential Interaction. Its use needs observation and Monitoring.	Potential Interaction. Its use needs observation and Monitoring.

Adapted with modification from: [85,136,137].

However, the ideal timing for HCV treatment after kidney transplantation is still unclear. Although earlier cure of HCV in the immediate post-transplantation period will lead eventually to decrease in the hepatic or extra-hepatic complications attributed to HCV, it carries a higher risk for kidney rejection due to the interactions with immunosuppression medications.

RECOMMENDATIONS FROM INTERNATIONAL GUIDELINES

There are multiple international guidelines for the management of HCV infection. The European Association for the Study of the Liver (**EASL**) that was updated recently and the American Association for the Study of Liver Diseases (**AASLD**) jointly with the Infectious Diseases Society of America (**IDSA**) has detailed guidelines that are on continuous update [85,86].

CONCLUSION

Treatment of HCV in general population with DAA along with screening programs is expected to eradicate this infection with subsequent improvement in the health status of renal disease patients in the pre and post transplant. Several effective, pan-genotypic DAA are available and could be given to ESRD and in post renal transplant patients with high SVR and low adverse events rates. DAAs, like; simeprevir, daclatasvir, and the combination of ritonavir, paritaprevir, ombitasvir, and dasabuvir, are the current choice for patients with ESRD. The use of DAA in HCV-positive kidney transplant patients have changed the long-term outcomes and improved survival. Sofosbuvir-based therapy is currently the most studied DAA in the post renal transplant setting and appears to be very effective and has a wide safety margins. Other DAA can also be used but require a close monitoring and observation to avoid the drug-drug interaction between them and immunosuppressant.

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