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ESRD Patients Co-infected with Human Immunodeficiency Virus and Hepatitis C: Outcomes and Management Challenges

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Abstract

HIV infection is a major public health problem world-wide. Due to shared modes of acquisition, many HIV+ patients are co-infected with Hepatitis C. HIV/HCV co-infected patients have been shown to present an increased burden of chronic kidney disease and are more likely to progress to end-stage renal disease. Dialysis survival is diminished in the co-infected population, even in the contemporary era. Kidney transplantation offers a survival benefit over remaining on dialysis, however posttransplant outcomes are inferior compared to patients with HIV infection alone. Direct acting antiviral agents may offer an opportunity to improve patient survival, but there are significant drug-drug interactions involving the direct acting antiviral agents, antiretroviral therapy and immunosuppression that the clinician should be aware of.

Epidemiology

Worldwide it is estimated that >36 million people are living with HIV infection (HIV+) and 1.1 million reside in the United States¹. HIV is a recognized risk factor for the development of chronic kidney disease (CKD) and accelerates progression to end stage renal disease (ESRD). Data from 3 large, prospective cohort studies^{2–4} have demonstrated that some CKD risk factors among HIV+ patients are held in common with HIV negative patients, including African American race, diabetes, hypertension, cardiovascular disease, lower baseline GFR and older age, while others are unique to this population and related to HIV disease or its treatment: unsuppressed HIV viral loads, lower nadir CD4 count, and use of potentially nephrotoxic medications, such as tenofovir. The incidence of ESRD has decreased among HIV+ patients since the widespread adoption of highly effective anti-retroviral therapy (ART), but improvements have been uneven; in the contemporary era ESRD rates remain significantly higher among African-Americans with HIV (standardized incidence ratio [SIR] 4.5, 95% CI 3.9–5.2) than among non-African Americans with HIV (SIR 1.5, 95% CI 1.0–2.2 for Caucasians)⁴.

The prevalence of HIV in the CKD and ESRD populations is variable, but it is estimated that ~1% of ESRD patients in the United States are HIV infected⁵; this is in stark contrast to the high rates of HCV infection seen among patients with ESRD. While the prevalence of HCV

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infection in hemodialysis units varies with geography, ranging from 2–22%⁶, a generally accepted summary estimate is 7%, based upon data from the intercontinental Dialysis Outcomes and Practice Patterns Study (DOPPS)⁷. HCV has been implicated directly in the development of primary kidney disease, as with cryoglobulinemia or membranoproliferative glomerulonephritis, as well as indirectly by promoting comorbidities, such as diabetes, that increase the risk of CKD. Approximately one-third of HIV+ patients are co-infected with Hepatitis C⁸.

Available data collectively indicate that co-infection with both HIV and HCV magnifies the nephrotoxic potential of each infection alone. A systematic review and meta-analysis⁹ of studies published from 1989 through 2015 provided a summary estimate for the hazard of CKD in co-infected patients as 1.64 (95% CI 1.28–2.0). These results have been corroborated by at least 2 recent prospective cohort studies. Rossi et al.¹⁰ reported outcomes for 2595 HIV+ patients in the Canadian HIV Observational Cohort; 19% of study participants were co-infected with HCV. Co-infection with HCV was associated with a higher CKD incidence rate (26 per 1000 person years versus 10.7 per 1000 person years) and a shorter time to incident CKD (hazard ratio [HR] 1.97, 95% CI 1.33–2.90).

Lucas et al.¹¹, using data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), also found an increased incidence of CKD in patients with HIV/HCV co-infection. Nearly twenty percent of the NA-ACCORD cohort is co-infected, with only 10% having undetectable HCV viral loads. Co-infected patients had higher rates of incident advanced CKD (stage 3 CKD aHR 1.36, 95% CI 1.26–1.46; CKD stage 5 aHR 1.95, 95% CI 1.64–2.31) and clearance of HCV viremia was not protective for renal disease progression.

Dialysis Outcomes

The majority of studies reporting outcomes for patients with HIV infection on dialysis are either from the early ART era, single center series or do not specifically address the survival of patients co-infected with HCV.

A single center study¹² from San Francisco spanning the pre- and post-ART eras (1985–2002) reported dismal outcomes for HIV+ and HIV+/HCV+ patients on dialysis; two-thirds of their cohort was co-infected with HCV. Median survival was 12 months, which improved to 16 months for those in the post ART era. Higher CD4 counts and serum albumin predicted dialysis survival. Older data from the USRDS¹³, which compared outcomes for HCV mono-infected versus HIV/HCV co-infected patients all identified by ICD-9 codes, found that co-infection was associated with an increased risk of death (OR 3.2, 95% CI 2.31–4.44) but the comorbidities were different between the patient groups. Co-infected patients were less likely to have diabetes or cardiovascular disease but were more likely to have Hepatitis B infection and psychiatric disease.

The European experience^{14–16} has been better than that observed in the United States, but the population of patients with HIV (or HIV/HCV co-infection) and ESRD in Europe is different. One French study¹⁵ reported similar short-term survival for HIV+ dialysis patients

when compared to contemporary uninfected patients enrolled in the DOPPs; however, few of these patients were of African ancestry and <30% were co-infected with HCV. A multi-center study from Spain¹⁶ used dialysis center surveys to assess outcomes for HIV+ dialysis patients in their country. Of the 66 HIV+ patients about whom data was provided, the majority were co-infected with HCV (76%) and had detectable HCV viral loads (69%). Interestingly, in their univariable analysis HCV co-infection was not significantly associated with dialysis mortality (HR 0.82, 95% CI 0.30–2.28). Five-year survival on dialysis was significantly lower for HIV+ patients overall (62.7%) compared to HIV-patients (94.4%; $p<0.001$) and among HIV+ patients peritoneal dialysis was associated with an increased risk of death (OR 2.88, 95% CI 1.16–7.17). However, peritoneal dialysis patients in this cohort had a more extensive cardiovascular disease history and a greater proportion of diabetes, which may have biased these results; registry data¹⁷ from the United States has not demonstrated similar differences in HIV+ patient survival on the basis of dialysis modality.

One of the landmark studies in the field of HIV and dialysis comes from Ahuja et al.¹⁸ Using data from the USRDS they identified >6100 HIV+ patients on dialysis and demonstrated that patient survival in HIV+ patients improved significantly in those who initiated renal replacement therapy in 1999–2000 compared to those who started pre-1990 (HR 0.49, 95% CI 0.40–0.60); this dramatic reduction in mortality was attributed to the clinical implementation of ART. However, this study did not specifically address outcomes for the co-infected population. Part of the challenge of studying this group of patients using registry data is that HIV information has been removed from the CMS 2728 form when it was updated in 2005 and USRDS does not directly collect HCV information, which can only be inferred by ICD-9 diagnosis codes.

A recent publication from Sawinski et al.¹⁹ was able to address some of these limitations by using detailed clinical data from a large dialysis organization to identify a contemporary cohort of HIV+ dialysis patients through a combination of ICD-9 codes, ART prescriptions and HCV antibody testing performed as routine standard of care in dialysis units. The authors identified 5348 patients with HIV mono-infection and 1863 patients with HIV/HCV co-infection on maintenance dialysis from 2004–2014; both groups were predominantly male and African-American. Among Caucasians, HIV infection alone was not associated with an increased risk of death (HR 1.03, 95% CI 0.91–1.16, $p=0.635$) in contrast to the HIV/HCV co-infected patients (HR 1.48, 95% CI 1.18–1.87, $p=0.001$). Non-Caucasian patients experienced an increased mortality irrespective of their co-infected status (HIV+ HR 1.44, 95% CI 1.37–1.52, $p<0.001$; HIV+/HCV+ HR 1.77, 95% CI 1.60–1.84, $p<0.001$). Among all patients, the most common cause of death was cardiovascular disease. In adjusted models peritoneal dialysis was associated with a lower risk of mortality.

Kidney Transplant Outcomes

The initial kidney transplant experience for HIV+ patients transplanted in the pre ART era was poor; patient and graft survival were unacceptably low²⁰. The introduction of ART improved patient survival and viral control significantly; pilot studies^{21,22} and a multicenter trial²³ of kidney transplantation performed in the ART era demonstrated outcomes similar to those observed in the general kidney transplant population. In the NIH-sponsored multi-

center trial²³ of transplantation in HIV, 1-year patient survival was 94.6% and 1-year allograft survival was 90.4%, which was not statistically different from contemporary outcomes among HIV-older kidney transplant recipients. However, 19% of the cohort was co-infected with HCV and that subgroup had diminished survival (patient and allograft, 88% at 1-year). This study also identified acute rejection as a significant complication of renal transplantation in patients with HIV infection.

Since the publication of the NIH multi-center trial results in 2010, several groups have used national transplant registry data to examine outcomes for HIV+ kidney transplant recipients. Xia et al.²⁴ performed a “mate kidney” analysis, where one kidney was transplanted into a recipient with HIV infection (or HIV/HCV co-infection) and the other into an uninfected recipient. HIV/HCV co-infection was associated with an increased risk of death (HR 2.88, 95% CI 1.35–6.12) and death-censored graft loss (HR 2.33, 95% CI 1.06–5.12) however the number of co-infected patients in the study was small (n=36). Sawinski and colleagues²⁵ performed a retrospective study of adult kidney transplant recipients from the post-ART era (1996–2013), which included 492 HIV+ and 147 HIV+/HCV+ patients. In this study outcomes for HIV+ recipients did not differ significantly from the uninfected reference group (patient death, HR 0.90, 95% CI 0.66–1.24; all-cause graft survival HR 0.60, 95% CI 0.40–0.88), but co-infected patients had significantly worse patient (HR 2.26, 95% CI 1.45–3.52) and allograft (HR 2.59, 95% CI 1.60–4.19) survival. These results have subsequently been confirmed in other studies²⁶.

It is difficult to conclusively ascertain the driver of these differences in outcomes for patients with HIV alone versus HIV/HCV co-infection, as registry data lack important information such as CD4 counts, HCV viral load data and liver biopsies. Despite inferior long-term patient and allograft survival among HIV/HCV co-infected recipients, when compared to patients with HIV or HCV alone, kidney transplantation does provide a survival benefit over dialysis in this population, realized by as soon as 392 days posttransplant²⁷. As transplant experience with HIV and HIV/HCV co-infected patients has expanded, other risk factors for inferior outcomes have been elucidated. Locke et al.²⁸ identified >3 HLA mismatches as a potent risk factor for graft loss in co-infected kidney recipients. For HIV+ patients overall, use of protease inhibitor (PI) based ART regimens has been associated with decreased patient (aHR 1.91, 95% CI 1.02–3.59) and allograft survival (aHR 1.84, 95% CI 1.22–2.70)²⁹. In response to the challenge of achieving adequate calcineurin inhibitor (CNI) dosing in transplant recipients on PIs, many patients are now switched to integrase inhibitor-based regimens whenever possible. Raltegravir and dolutegravir are compatible with traditional CNI dosing and most DAA regimens.

The goal of HCV therapy

The goal of HCV therapy is the achievement of a sustained viral response (SVR) 12 weeks after the cessation of treatment, which is equated with HCV cure. Achievement of SVR halts the progression of liver disease and reduces patient mortality, including among co-infected patients. In a French cohort³⁰ of 313 HIV/HCV co-infected patients, SVR was associated with a stabilization or improvement in serial non-invasive measurements of liver stiffness. In an international multicenter cohort³¹ of 530 HCV mono-infected patients, achievement of

SVR was associated with a reduction in 10-year all-cause mortality (SVR 8.9% versus no SVR 26%, $p<0.001$). In this study³¹, SVR was also associated with a lower 10-year incidence of liver-related mortality or the need for liver transplantation (SVR 1.9% versus 27.4%, $p<0.001$). In a prospective cohort from France³², which enrolled 1323 patients with biopsy proven cirrhosis and followed them for a median of 58 months, achievement of SVR was associated with a reduced incidence of hepatocellular carcinoma (HR 0.29, 95% CI 0.19–0.43) and hepatic decompensation (HR 0.26, 95% CI 0.17–0.39). Since patients were recruited prior to 2012, they were treated with either pegylated interferon with ribavirin or interferon and first generation DAAs (boceprevir or telaprevir); regardless, half of the cohort achieved SVR and 5% of the cohort was co-infected with HIV. Extrahepatic complications were also decreased – cardiovascular events were reduced (HR 0.42, 95% CI 0.25–0.69), as were bacterial infections (HR 0.44, 95% CI 0.29–0.68).

The benefit of SVR on outcomes extends to the kidney transplant population, where posttransplant cure of HCV with DAAs has been shown to reduce the risk of patient death (HR 0.43, 95% CI 0.19–0.95, $p=0.04$) with a non-statistically significant trend towards reducing the risk of graft loss (HR 0.54, 95% CI 0.27–1.07, $p=0.08$)³³.

HIV/HCV co-infection and liver disease

In HCV mono-infected patients it takes several decades for liver disease to progress to cirrhosis and end-stage liver disease (ESLD), but the time course is accelerated in patients who have both HIV and HCV infection. Additionally, far fewer patients with HIV/HCV co-infection will spontaneously clear their HCV infection³⁴, in comparison to the 15–30% of mono-infected patients who are able to clear their viremia without treatment. It has been suggested that the timing of acquisition of each virus influences the progression to end-stage liver disease; Benhamou et al.³⁵ reported that patients who acquired HCV via intravenous drug use and later HIV infection had only a modest acceleration of their time to cirrhosis. In contrast, Fierer and colleagues³⁶ demonstrated that patients who acquired HIV first via sexual contact and then HCV had more rapid progression of liver fibrosis; similar results were reported in a cohort from Belgium³⁷ where nearly 60% had stage 2 fibrosis within a year of HCV infection. In long-term follow up of 4 HIV+ patients with subsequent acquisition of HCV, 100% of them progressed to decompensated cirrhosis and death within 2–8 years³⁸.

In contrast to the significant reduction in ESRD seen in HIV+ patients with the introduction of ART⁴, ART has not had as clear of an impact on the development of ESLD. A substudy³⁹ of NA-ACCORD that included patients from 1996 through 2010 with validated ESLD diagnosis demonstrated that despite increasing use of ART over the 15 years of observation, there was no decrease in the incidence rate of ESLD in HIV infected patients over time. Patients with HIV mono-infection had a low baseline rate of ESLD (1.27 per 1000 person years) and not surprisingly, the rate of ESLD was highest in patients who were triply infected with HIV, HCV and Hepatitis B (HBV) (11.57 per 1000 person years). There was a trend towards a decrease in cirrhosis rates in the contemporary era among patients with HIV and HBV infection, related to the use of ART with anti-HBV activity, but no change for patients with HIV/HCV co-infection (6.1 per 1000 person years). This difference was

attributed to a very low rate of HCV therapy, with only 1% of patients treated among cohort participants. A systematic review and meta-analysis⁴⁰ of studies published from 1990–2007 assessing the impact of ART on liver disease progression in HIV/HCV co-infected patients revealed similar findings.

In contrast, the international D:A:D study⁴¹, with >49,000 participants drawn from the United States, Europe and Australia, found a decrease in liver related deaths among HIV+ patients enrolled from 1999–2010. However, the D:A:D cohort contains a lower percentage of HIV/HCV co-infected patients than NA-ACCORD and the decline in liver-related mortality was attributed to both expanded access to ART as well as focused use of regimens with activity against both HIV and HBV. While control of HIV infection with ART is beneficial for patients, ART alone is insufficient to prevent progression to ESLD; targeted HCV therapy is required.

Liver disease assessments in co-infected patients

Planning treatment for HCV in HIV/HCV co-infected patients requires an understanding of the degree of liver fibrosis present in order to select the best regimen and appropriate duration of therapy. Liver biopsy is the gold standard for liver fibrosis assessment; however this procedure is invasive, with a risk of bleeding, and biopsy-based fibrosis scoring is subject to both sampling error and inter-observer variability. There has been great interest in non-invasive measurements of liver fibrosis, and use of these methods has gained traction in the general liver disease population. Options include transient elastography, which measures liver stiffness, and laboratory-based scoring methods such as the AST to platelet ratio index (APRI) and Fibrosis-4 index (FIB-4).

Use of transient elastography has been validated in patients with and without HIV infection. It has been studied in one cohort⁴² of 72 HIV/HCV co-infected patients with simultaneous measurement of elastography and a liver biopsy performed; 69.5% of the cohort had stage 2 fibrosis or lower. Liver stiffness was well correlated with biopsy fibrosis staging ($r=0.48$) and the AUC was 0.72 for Metavir stage 2 and 0.97 for Metavir stage 4. This is consistent with prior studies^{43,44} examining the predictive value of non-invasive measurements of liver fibrosis in HCV mono-infected populations.

Laboratory-based fibrosis measurements have also been validated in the HIV+/HCV+ population⁴⁵. Loko et al.⁴⁶ studied 200 consecutive co-infected patients in France who had a liver biopsy performed as well as the APRI score and FIB-4 index calculated; 20% of the cohort was cirrhotic. The APRI score had an AUC of 0.77 for predicting Metavir stage 2 fibrosis and an AUC of 0.79 for cirrhosis (Metavir stage F4). The FIB-4 index performed equally well, with an AUC of 0.79 for stage 2 or greater fibrosis and 0.80 for stage F4. The FIB-4 index (>3.25) has also been utilized in the VA cohort⁴⁷ to predict progression to end-stage liver disease among co-infected veterans.

HCV treatment in HIV/HCV co-infected dialysis patients – available data

Historically, treatment of HCV in co-infected dialysis patients was uncommon due to the limited efficacy and side effects associated with interferon and ribavirin based therapies,

similar to the experience of HCV mono-infected patients. The introduction of interferon-free, direct acting antiviral (DAA) based treatment has created an array of therapeutic options for patients with normal or mildly reduced renal function; options for patients with advanced CKD or dialysis are more limited. Many, but not all, DAA regimens are sofosbuvir based. The main metabolite of sofosbuvir is excreted in the urine and accumulates in patients with chronic kidney disease; therefore administration of sofosbuvir in patients with advanced CKD (GFR<30 or dialysis) is not currently recommended by society treatment guidelines⁴⁸ but this recommendation may change as more data become available.

Advanced CKD and dialysis patients with HIV and HCV co-infection currently have three available options for the treatment of HCV. Ombitasvir/paritaprevir/ritonavir/dasabuvir +/- ribavirin (3D) is approved for the treatment of genotype 1 infection⁴⁹. The RUBY-I trial⁵⁰ explored the efficacy of the 3D regimen (with ribavirin for patients with genotype 1a infection) in patients with CKD stages 4 or 5. The SVR 12 rate was 90% but HIV co-infection was an exclusion criterion for this trial. While effective, this regimen has been supplanted in current practice by two newer options, elbasvir/grazoprevir and glecaprevir/pibrentasvir.

The C-SURFER trial⁵¹ studied the use of elbasvir/grazoprevir for the cure of HCV genotype 1 infection among patients with CKD stage 4 or 5. All participants were treated for 12 weeks and the SVR 12 rate was 99%. In EXPEDITION-4, Gane et al.⁵² achieved an SVR 12 in 98% of patients after 12 weeks of therapy in an advanced CKD cohort. Together these trials demonstrate the feasibility of HCV eradication in the dialysis population, but neither C-SURFER nor EXPEDITION-4 enrolled patients with HIV/HCV co-infection.

Treatment selection and considerations in HIV/HCV co-infected dialysis patients

Society guidelines^{48,53} now recommend that HIV/HCV co-infected patients should be treated the same as HCV mono-infected patients. Drug-drug interactions are a challenge in the treatment of HCV in the HIV/HCV co-infected patient. While anti-retroviral regimen switches are permissible, they should only be undertaken by an experienced infectious disease provider and take into account HIV treatment history as well as known resistance mutations. Integrase inhibitors, which form the backbone of most contemporary ART regimens, are generally compatible with most DAAs but attention must be paid to the use of elvitegravir, which requires cobicistat boosting, and bictegravir, which is a substrate of CYP3A4 (Table 1).

The 3D regimen contains 100mg ritonavir as one of its components; therefore if this regimen is selected for a patient on a ritonavir-boosted PI (200mg/day of ritonavir) then the total daily dose of ritonavir and the timing of administration should be evaluated⁴⁸. Ritonavir boosting is held while the patient is receiving 3D and restarted once therapy is completed. Atazanavir should be taken at the same time as 3D in order to permit boosting by the 3D ritonavir component. Lopinavir, if co-formulated with ritonavir, could subject patients to excessive GI side effects and is to be avoided⁴⁸. Darunavir levels are reduced by 3D and these drugs should not be used together⁴⁹. 3D should not be prescribed to patients taking

strong inducers or inhibitors of CYP3A4 (efavirenz, etravirine, nevirapine, rilpivirine or cobicistat)⁴⁹. Concomitant administration of rilpivirine increases rilpivirine exposure and has the potential for QT prolongation⁵⁴. Elite controllers or patients not on ART for other reasons should not be prescribed the 3D regimen as they can develop HIV protease inhibitor resistance⁴⁸. While there are no studies of the 3D regimen specifically conducted in co-infected dialysis patients, the TURQUOISE-1 study⁵⁵ reported an SVR 12 rate of 93.5% after 12 weeks of therapy. This study enrolled 63 co-infected patients, randomized to 12 versus 24 weeks of 3D+ribavirin. The study cohort was predominantly male, with genotype 1a infection (89%) and 19% had compensated cirrhosis.

Elbasvir/grazoprevir is a substrate for CYP3A4 and P-glycoprotein⁵⁶; therefore it should not be co-administered with medications that interact with this metabolic pathway. Elbasvir/grazoprevir should not be given to patients on ritonavir, lopinavir, atazanavir, darunavir or any other protease inhibitor⁵⁶, as these are potent inhibitors of CYP3A4 enzymes and would lead to high levels of elbasvir/grazoprevir; Cobicistat has a similar effect. Efavirenz, etravirine or nevirapine should be avoided⁵⁶ as they induce CYP3A4 enzymes and can lead to insufficient elbasvir/grazoprevir exposure. Generally, nucleoside reverse transcriptase inhibitors, fusion inhibitors and integrase inhibitors are compatible with elbasvir/grazoprevir⁴⁸. There are no trials specifically conducted in co-infected dialysis patients, but the C-EDGE COINFECTION study⁵⁷ demonstrated a SVR 12 rate of 96% after 12 weeks of elbasvir/grazoprevir. This study enrolled 218 co-infected patients with genotype 1, 4 or 6. The study cohort was predominantly male, Caucasian and had genotype 1 (86%) with only 16% having cirrhosis; patients with a creatinine clearance <50ml/m were excluded. Naturally occurring resistance mutations can compromise elbasvir/grazoprevir efficacy; therefore patients with genotype 1a infection in whom elbasvir/grazoprevir therapy is planned should be tested for NS5a resistance mutations prior to therapy initiation.

Glecaprevir/pibrentasvir is an inhibitor of P-glycoprotein and a weak inhibitor of CYP3A4⁵⁸. It should not be administered to patients taking efavirenz, as glecaprevir/pibrentasvir levels are significantly reduced and it may be rendered ineffective⁵⁸. Atazanavir increases glecaprevir/pibrentasvir levels, and when taken together can cause elevations in ALT⁵⁸; likewise administration with ritonavir, lopinavir and darunavir should be avoided. Most non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs) and integrase inhibitors are compatible with glecaprevir/pibrentasvir, as is cobicistat⁴⁸. Data from EXPEDITION-2⁵⁹, which enrolled 153 patients, demonstrated a SVR 12 rate of 98% after 8 weeks of therapy in HIV/HCV co-infected non-cirrhotic patients; no patients with advanced kidney disease were included and similar to other DAA trials, the study population was mostly male Caucasians with genotype 1 infection (64%).

DAA-based therapy for HCV has been reported to cause Hepatitis B (HBV) reactivation in the HCV mono-infected population. Due to shared modes of acquisition, patients with HIV and/or HCV infection are at risk for HBV as well. Prior to initiating DAA therapy patients should be tested for evidence of HBV infection (surface antigen, surface antibody and core antibody) and those with a history of HBV exposure should be monitored for HBV reactivation with HBV DNA⁴⁸.

HCV treatment in co-infected transplant recipients – the published experience to date

Very limited published data exist reporting on the treatment of HCV in HIV/HCV co-infected kidney transplant recipients. There are a few studies conducted in co-infected liver transplant recipients, from which expected outcomes can be extrapolated. Campos-Varela⁶⁰ reported 20 co-infected liver transplant patients treated with a variety of sofosbuvir containing regimens; 89% achieved an SVR and HIV infection remained well controlled.

The French experience has been better – Antonini et al.⁶¹ described 29 co-infected liver transplant recipients treated with sofosbuvir/daclatasvir (n=16) or ledipasvir/sofosbuvir (n=13); the SVR 12 rate was 96.6%. Most patients were on integrase inhibitor based ART (65.5%) and no modifications in ART were required to facilitate HCV treatment. Recently the Spanish national experience⁶² with treating co-infected liver recipients was reported; Manzardo et al.⁶² described 47 HIV/HCV co-infected liver transplant recipients with recurrent HCV. These patients were predominantly treated with sofosbuvir-based regimens, with ledipasvir/sofosbuvir +/- RBV being the most common regimen selected (34% of patients). The SVR 12 rate of 95% was not statistically different from that observed in matched HCV mono-infected liver transplant controls. ART modifications were required in 11% of patients but none required dose adjustment of DAAs and DAA therapy did not impact HIV virologic control.

Sawinski et al.⁶³ described treatment of 6 co-infected kidney transplant recipients with ledipasvir-sofosbuvir; all of the patients were genotype 1. All of these patients were on an integrase inhibitor-based ART regimen with one patient on tenofovir; renal function remained stable while administered ledipasvir-sofosbuvir.

Treatment selection and considerations in HIV/HCV co-infected transplant recipients

Treatment of HCV in co-infected transplant recipients is complex. Drug-drug interactions between the DAAs, ART and immunosuppression need to be considered, in addition to DAA selection restrictions on the basis of genotype and renal function (Table 2).

The 3D regimen, which has limitations in terms of its compatibility with ART regimens, also has significant interactions with calcineurin inhibitors (CNIs), the mainstay of posttransplant immunosuppression. The ritonavir component of 3D is a potent inhibitor of CYP3A4 and can increase CNI half-life by as much as 20-fold; this leads to significant difficulties in CNI dosing and achievement of acceptable trough levels⁶⁴. This regimen would not be a preferred choice for HCV treatment in the HIV+/HCV+ kidney transplant recipient.

Sofosbuvir is a substrate of P-glycoprotein⁶⁵. It does not have significant interactions with tacrolimus or cyclosporine⁶⁵. Administration with tipranavir/ritonavir is not recommended as sofosbuvir levels are reduced, as is its efficacy⁶⁵; tipranavir is rarely used in contemporary HIV practice. There are no significant interactions with efavirenz, rilpivirine, emtricitabine or raltegravir⁴⁸.

Sofosbuvir/velpatasvir contains both a substrate of P-glycoprotein (sofosbuvir) as well as an inhibitor of P-glycoprotein and OATP1B1/3 (velpatasvir)⁶⁶. Acid reducing medications (proton pump inhibitors and H2 blockers) reduce velpatasvir levels and their administration should be separated⁶⁶. Co-administration with tipranavir/ritonavir is not recommended due to interactions with sofosbuvir; likewise efavirenz is contraindicated due to significant reductions in velpatasvir levels⁶⁶. Use of etravirine and nevirapine should also be avoided. Patients on a tenofovir-containing ART regimen can have significant increases in their tenofovir levels and therefore renal function must be closely monitored^{48,66}. Velpatasvir does not have significant effects on cyclosporine or tacrolimus levels⁶⁶.

Sofosbuvir/velpatasvir/voxilaprevir has pangenotypic activity against HCV however due to the inclusion of sofosbuvir this combination can only be recommended in transplant recipients with a GFR>30ml/m. It should not be co-administered with atazanavir or lopinavir, as voxilaprevir levels are increased⁶⁷. Use with tipranavir and ritonavir is not recommended because sofosbuvir and velpatasvir levels are reduced⁶⁷. Efavirenz significantly decreases velpatasvir and voxilaprevir levels when given together; this combination is to be avoided, as is use of etravirine or nevirapine⁶⁷. Patients who are taking tenofovir can experience an increase in tenofovir exposure and renal function should be carefully monitored⁴⁸; other regimens without the potential for nephrotoxicity should be considered. For transplant recipients specifically, cyclosporine increases voxilaprevir levels and should be avoided⁶⁷; there are no significant interactions with tacrolimus. Statins require dose reduction and monitoring for myopathy.

Daclatasvir is an inhibitor of P-glycoprotein⁶⁸; it is often used along with sofosbuvir. When daclatasvir is used in conjunction with strong inhibitors of the CYP3A4, the daclatasvir dose must be decreased to 30mg daily⁶⁸; in contrast, when given with moderate CYP3A4 inducers the dose should be increased to 90mg daily⁶⁸. The daclatasvir dose should be decreased when given with ritonavir-boosted atazanavir or the rarely used indinavir, nelfinavir or saquinavir⁶⁸; likewise a dose reduction in daclatasvir is required for use with cobicistat-boosted atazanavir or elvitegravir. No dosing changes are required for co-administration with darunavir/ritonavir, lopinavir-ritonavir or darunavir/cobicistat. The daclatasvir dose should be increased to 90mg daily when given with efavirenz, etravirine or nevirapine⁶⁸. Most azole antifungals, with the exception of fluconazole, require a daclatasvir dose reduction. Statins must be used with caution and patients monitored closely. There are no significant drug-drug interactions with cyclosporine or tacrolimus.

Ledipasvir/sofosbuvir should also be given separately from PPIs or H2 blockers⁶⁹. Most of the drug-drug interactions with ledipasvir/sofosbuvir and ART revolve around issues of tenofovir exposure; co-administration of ledipasvir/sofosbuvir and tenofovir increases tenofovir levels⁶⁹. This increase is magnified in patients on ritonavir or cobicistat-boosted protease inhibitors or fixed dose combination therapies such as elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or tenofovir alafenamide (brand names Stribild or Genvoya); administration with ledipasvir/sofosbuvir is not recommended and close renal monitoring required⁴⁸. Use of tipranavir/ritonavir is also not advised⁶⁹. No dose adjustments are required for patients on cyclosporine or tacrolimus.

Simeprevir has no effect on hepatic CYP3A4 enzyme function but does inhibit OATBP; therefore monitoring of cyclosporine or tacrolimus is advised but preemptive dose adjustment is not required⁷⁰. Due to the effect on simeprevir levels, simeprevir should not be prescribed in patients on a NNRTI or PI based ART regimen⁴⁸.

Elbasvir/grazoprevir has important interactions with both maintenance immunosuppression and ART regimens. Cyclosporine, acting via OATP1B1/3 inhibition, increases grazoprevir levels significantly; these medications should not be used together⁵⁶. Tacrolimus levels are increased by elbasvir/grazoprevir, therefore prospective level monitoring with dose adjustment as needed to remain within a therapeutic range is required. Protease inhibitors increase grazoprevir levels and can cause increases in ALT⁵⁶; this combination is to be avoided, as is cobicistat which increases both grazoprevir and elbasvir levels. Efavirenz, etravirine and nevirapine decrease grazoprevir levels⁵⁶, compromising anti-HCV efficacy; co-administration is not recommended.

Glecaprevir/pibrentasvir has similar limitations. It should not be used in patients on maintenance cyclosporine⁵⁸, but tacrolimus can be administered safely. Use of HIV protease inhibitor regimens with glecaprevir/pibrentasvir is not advised; atazanavir in specific causes increases in ALT when co-administered⁵⁸. Efavirenz and etravirine reduce glecaprevir/pibrentasvir levels significantly, negatively impacting efficacy; use together is not recommended⁵⁸.

Conclusions

HIV/HCV co-infected dialysis patients face many challenges, but renal transplantation and cure of HCV infection with DAAs can positively impact their long-term survival. There are many drug-drug interactions to consider when treating HCV in this patient population, but most patients can be cured successfully.

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Table 1.

Summary of HCV treatment regimen options for non-cirrhotic, treatment naïve HIV/HCV co-infected patients with GFR<30m/ml or on dialysis, based upon genotype.

ART regimen base	HCV Genotype				
	1a/1b	2	3	4	5/6
PI	3D	-	-	-	-
NNRTI					
<i>Rilpivirine</i>	E/G	-	-	E/G	-
	G/P	G/P	G/P	G/P	G/P
<i>All others</i>	-	-	-	-	-
NRTI	3D	-	-	-	-
	E/G	-	-	E/G	-
	G/P	G/P	G/P	G/P	G/P
Integrase Inhibitor					
<i>RAL/DTG</i>	3D	-	-	-	-
	E/G	-	-	E/G	-
	G/P	G/P	G/P	G/P	G/P
<i>EVG/COBI</i>	G/P*	G/P*	G/P*	G/P*	G/P*

*
monitor for hepatic toxicity

Abbreviations: PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI nucleoside reverse transcriptase inhibitor; RAL: raltegravir; DTG: dolutegravir; EVG/COBI: elvitegravir/cobicistat; 3D: Ombitasvir/paritaprevir/ritonavir/dasabuvir; E/G: elbasvir/grazoprevir; G/P: glecaprevir/pibrentasvir

Table 2.

Summary of HCV treatment regimen options for non-cirrhotic, treatment naïve HIV/HCV co-infected patients with a kidney transplant, based upon genotype and maintenance immunosuppression.

CNI	ART regimen base	HCV Genotype				
		1a/1b	2	3	4	5/6
Tacrolimus	PI	LDV	-	-	LDV	LDV
		VEL	VEL	VEL	VEL	VEL
		DAC ^a	-	DAC ^a	-	-
	NRTI	LDV *	-		LDV *	LDV *
		VEL *	VEL *	VEL *	VEL *	VEL *
		DAC	-	DAC	-	-
		E/G	-	-	E/G	-
		G/P	G/P	G/P	G/P	G/P
	NNRTI					
	<i>Rilpivirine</i>	SIM	-	-	-	-
		E/G	-	-	E/G	-
		G/P	G/P	G/P	G/P	G/P
	<i>All others</i>	LDV	-	-	LDV	LDV
		DAC ^b	-	DAC ^b	-	-
	Integrase					
	<i>RAL/DTG</i>	LDV	-	-	LDV	LDV
		VEL	VEL	VEL	VEL	VEL
		DAC	-	DAC	-	-
		SIM	-	-	-	-
		E/G	-	-	E/G	-
		G/P	G/P	G/P	G/P	G/P
	<i>EVG/COBI</i>	LDV	-	-	LDV	LDV
		VEL	VEL	VEL	VEL	VEL
		DAC ^a	-	DAC ^a	-	-
		G/P ^c	G/P ^c	G/P ^c	G/P ^c	G/P ^c
Cyclosporine	PI	LDV	-	-	LDV	LDV
		VEL	VEL	VEL	VEL	VEL
		DAC ^a	-	DAC ^a	-	-
	NRTI	LDV *	-		LDV *	LDV *
		VEL *	VEL *	VEL *	VEL *	VEL *
		DAC	-	DAC	-	-
	NNRTI					

		HCV Genotype				
CNI	ART regimen base	1a/1b	2	3	4	5/6
	<i>Rilpivirine</i>	SIM	-	-	-	-
	<i>All others</i>	LDV	-	-	LDV	LDV
		DAC ^b	-	DAC ^b	-	-
	Integrase					
	<i>RAL/DTG</i>	LDV	-	-	LDV	LDV
		VEL	VEL	VEL	VEL	VEL
		DAC	-	DAC	-	-
		SIM	-	-	-	-
	<i>EVG/COBI</i>	LDV	-	-	LDV	LDV
		VEL	VEL	VEL	VEL	VEL
		DAC ^a	-	DAC ^a	-	-

* requires close monitoring of renal function if NRTI is tenofovir, consider alternate agent if GFR<60ml/m

^a daclatasvir dose should be decreased to 30mg/day if ritonavir or cobicistat boosting is employed

^b daclatasvir dose should be increased to 90mg/day if NNRTI is efavirenz or etravirine.

^c monitor for hepatic toxicity

Abbreviations: PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI nucleoside reverse transcriptase inhibitor; RAL: raltegravir; DTG: dolutegravir; EVG/COBI: elvitegravir/cobicistat; 3D: Ombitasvir/paritaprevir/ritonavir/dasabuvir; E/G: elbasvir/grazoprevir; G/P: glecaprevir/pibrentasvir; LDV: ledipasvir/sofosbuvir; DAC: daclatasvir/sofosbuvir; VEL: velpatasvir/sofosbuvir; SIM: Simeprevir/sofosbuvir