



Published in final edited form as:

Afr J Nephrol. 2020 ; 23(1): 159–168.

Hepatitis C virus infection and global kidney health: the consensus proceedings of the International Federation of Kidney Foundations

Gamal Saadi¹, Kamyar Kalantar-Zadeh², Piero Almasio³, Gloria Ashuntantang⁴, Rashad Barsoum¹, Annette Bruchfeld⁵, Wahid Doss⁶, Hussein ElFishawy¹, Maissa El Raziky⁷, Magdy El-Serafy⁷, Fabrizio Fabrizi⁸, Hani Hafez¹, May Hassaballa¹, Mona M.R. Hammady¹, Hussein Sheishaa⁹, Tarek S. Abdelaziz¹, Ifeoma Ulasi¹⁰, Elena Zakharova¹¹, Michel Jadoul¹²

¹Department of Nephrology, Kasr Al Ainy Hospital, Cairo University, Cairo, Egypt

²Division of Nephrology, Hypertension and Kidney Transplantation, University of California, Irvine, California, USA

³University of Palermo, Palermo, Italy

⁴Department of Internal Medicine and Specialties, University of Yaoundé, Yaoundé, Cameroon

⁵Department of Renal Medicine, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden

⁶National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt

⁷Department of Tropical Medicine and Endemic Diseases, Cairo University, Cairo, Egypt

⁸Division of Nephrology, Maggiore Hospital and IRCCS Foundation, Milan, Italy

⁹Urology and Nephrology Center, Mansoura University, Mansoura, Egypt

¹⁰Renal Unit, Department of Medicine, College of Medicine, University of Nigeria, Ituku-Ozalla, Enugu, Nigeria

¹¹Department of Nephrology, City Hospital of SP Botkin, Moscow, Russia

¹²Nephrology Department, Cliniques universitaires Saint-Luc and Université catholique de Louvain, Brussels, Belgium.

Abstract

Hepatitis C virus (HCV) infection is an important cause of major morbidities including chronic liver disease, liver cancer, and acute kidney injury (AKI) as well as chronic kidney disease (CKD). HCV can affect kidney health; among CKD and AKI patients with HCV infection, the clinical outcomes are worse. The prevalence of HCV infection is exceptionally high among dialysis and kidney transplant patients throughout the globe. It is estimated that 5% to 25% or more of dialysis dependent patients are affected by chronic HCV, based on the region of the world. Almost half of

all deaths in CKD patients, including HCV-infected patients, are due to cardiovascular disease, and HCV infected patients have higher mortality. Given the importance and impact of the HCV epidemic on CKD and global kidney health, and the status of Egypt as the nation with highest prevalence of HCV infection in the world along with its leading initiatives to eradicate HCV, the International Federation of Kidney Foundations (IFKF) convened a consensus conference in Cairo in December 2017. This article reflects the opinions and recommendations of the contributing experts and reiterates that with the current availability of highly effective and well tolerated pharmacotherapy; CKD patients should be given priority for treatment of HCV, as an important step towards the elimination of viral hepatitis as a public health problem by 2030 according to World Health Organization and IFKF. Every country should have an action plan with the goal to improve kidney health and CKD patient outcomes.

Keywords

hepatitis C virus infection; Africa; chronic kidney disease

Introduction

The 69th World Health Assembly approved the Global Health Sector Strategy to eliminate viral hepatitis by 2030, with special emphasis on hepatitis C virus (HCV) infection, a goal which can become a reality with the recent launch of direct-acting antiviral (DAA) therapies [1]. There were an estimated 80 million HCV infections in 2013; the 2015 global prevalence of 1.0%, or 71 million infections, is lower, largely due to lower prevalence estimates in Africa [2]. Additionally, the mortality due to liver-related causes and an ageing population may have contributed to a reduction in the total number of HCV infections. The genotype distribution, by region, has not changed substantially since the Global Burden of Disease (GBD) study [2]. Genotype 1 accounts for most cases in Europe, North and South America as well as China and Russia, whereas genotype 3 is the most prevalent in the Indian subcontinent, and genotypes 4 and 5 are more prevalent in some African countries [3].

Viral hepatitis ranked 7th among mortality causes in the GBD analysis, much higher than in the 1990 analysis, and its global impact exceeds that of HIV infection, tuberculosis or malaria [2]. This increased burden of viral hepatitis is compatible with the long interval (generally decades) between HCV infection and serious complications such as cirrhosis, hepatocellular carcinoma or death. The GBD study may have underestimated the deleterious impact of HCV [2]. This may be due to the scarcity of reliable data from some regions of the world where estimates depend largely on extrapolation rather than surveillance of seropositivity and accurate recording of the aetiology of chronic liver disease.

Recent evidence increasingly points to the fact that, beyond the effect on liver disease, HCV infection is a systemic disease with significant cardiovascular and renal impact, not ascribed in the GBD analysis to HCV [4].

It is against this background that the International Federation of Kidney Foundations convened a conference of experts in nephrology, gastroenterology and hepatology in Cairo,

Egypt, in 2017 to review the evidence and develop recommendations for the management of HCV in patients with chronic kidney disease (CKD).

Success in the Global Eradication of HCV

HCV is an ideal target for eradication since there is no non-human reservoir of the virus and pharmacologic treatment with DAA can cure infected persons. However, re-infection is possible until the risks of transmission can be eliminated, or an effective vaccine is available. Although the biology of HCV and the availability of DAAs favour the feasibility of HCV elimination, there are serious barriers to achieve this result. This epidemiological challenge is intensified by the high prevalence of HCV infections in “difficult-to-reach” populations, such as people who inject drugs and the homeless, as well as marginalized subjects such as incarcerated people and refugees [5].

The Prevention of Nosocomial HCV Transmission within Haemodialysis Units

Patients on haemodialysis (HD) have long been known to be among the groups at highest risk for HCV infection. Recent figures from the Dialysis Outcomes and Practice Patterns Study (DOPPS) indicate that the annual incidence of seroconversion for HCV averages 1.2%, suggesting that at least 20,000 cases of HCV are acquired worldwide within HD units each year [6]. The main routes for HCV transmission in HD units are parenteral administration of drugs contaminated with traces of HCV-infected blood and the invisible contamination by blood of external surfaces and the hands of staff [7].

Thus, the application of basic hygiene precautions is crucial. These include hand hygiene before contact with patients and after removal of gloves, changing gloves between patients or dialysis stations, preparing injectable drugs in a clean area and cleaning and disinfecting surfaces of the HD environment before the next treatment session [6]. The 2018 update of the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the prevention, diagnosis, evaluation, and treatment of hepatitis C in CKD reiterates that isolation of HCV-positive patients is not required if attention is devoted to these simple precautions [8].

HCV infection is associated with higher risk of death among dialysis patients [9]. Markers of the malnutrition–inflammation–cachexia syndrome, rather than traditional cardiovascular risk factors, are among the strongest predictors of early death in these patients; the impact of HCV infection on nutritional status and inflammation may be an important cause of poor survival in this population.

Diagnosis and detection of HCV in CKD and haemodialysis patients

KDIGO recommends screening all CKD patients for HCV using immunoassay at the time of diagnosis of CKD [10]. If immunoassay is positive, then nucleic acid testing (NAT) is recommended. For patients starting hemodialysis, screening for HCV using either immunoassay or NAT is recommended. In all cases, if the immunoassay is positive, then NAT testing is recommended. The recommended interval for retesting patients on

haemodialysis is every 6 months. If a new case of HCV is diagnosed in a dialysis centre, testing of all patients is recommended [10]. The implementation of this guideline has some variability across different world regions. In the Asia Summit Conference report, most participating countries reported implementing the same guideline. However, in some countries testing for the HCV core antigen is used as an alternative due to the lower cost. The frequency of repeat testing varied from every 3 months to yearly [11].

Response to HCV Treatment and Criteria for Cure

Treating HCV infection early is the most effective way to prevent clinical complications of the infection [12]. The new drugs have made cure possible; sustained virologic response is achieved in more than 95% of patients within a relatively short period (≤ 12 weeks) and the treatment can also improve liver histology. DAA regimens have few or mild side effects. It must be noted that, although effective treatment is now available, its impact will be insignificant without implementing expanded procedures for screening, disease surveillance and appropriate management.

The goal of treatment is to reduce all-cause mortality and adverse liver-related health consequences, including end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC), by the achievement of virologic cure as evidenced by a sustained virologic response (SVR) [2]. The benefits of cure include improvements in liver inflammation, portal hypertension, extrahepatic manifestations, cryoglobulinaemia, diabetes and improved outcomes of kidney transplantation. There is also growing evidence that cardiovascular risk is reduced [1,13]. Virologic cure, defined as the absence of detectable HCV RNA at least 12 weeks after completion of therapy, is durable in more than 99% of patients followed up for ≥ 5 years. HCV RNA detection and quantification requires a sensitive assay, such as the FDA-approved quantitative NAT, which has a lower limit of detection of ≤ 15 IU/mL [14]. Sustained virologic responses at 12 months (SVR12) and 24 months (SVR24) have both been accepted as endpoints of therapy by regulators in the United States and Europe, given that their concordance is $>99\%$ [15].

Patients who achieve an SVR do not need to be retested for HCV unless they remain at risk of reinfection (e.g. haemodialysis patients and patients who inject drugs). Re-infection due to high-risk behaviour may negate the potential benefit of treatment. Reported rates of re-infection following successful HCV treatment among patients at high risk vary from 1–8% per year. Cirrhotic patients who achieve an SVR should remain under life-long surveillance for the development of HCC and for the development of oesophageal varices [2].

Hepatitis C Virus and Kidney Diseases

HCV can cause kidney disease in at least four different ways: 1) glomerular immune complex deposition, 2) direct viral invasion of renal parenchyma, 3) renal complications of chronic liver disease, and 4) complications related to the antiviral treatment. These mechanisms interact in the pathogenesis of several acute and chronic clinical renal syndromes [16].

Hepatitis C and Acute Kidney Injury

Hepatitis C (HCV) infection can cause acute kidney injury (AKI) in several ways. The best known and most common is cryoglobulinemic vasculitis. This has been reported in 1–5% of patients with chronic HCV infection[2]. Risk factors include female gender, older age, heavy alcohol consumption, longer duration of infection, type II mixed cryoglobulinemia, high cryoglobulin serum levels, low complement C4, HCV genotypes 2 or 3 and extensive liver fibrosis. Genetic and epigenetic factors appear to have a significant role in patient selection for this condition. AKI is clinically associated with oliguria, hematuria and extrarenal manifestations of cryoglobulinemia, mainly peripheral neuropathy, arthralgias, and a characteristic purpuric rash (Meltzer's triad). Renal biopsy confirms the diagnosis by the combination of vasculitic lesions, glomerular fibrinoid necrosis with cryoglobulinemic thrombi and tubular casts. Glomerular crescents are common. In 1/6 of cases the disease progresses rapidly into fatal systemic thrombotic microangiopathy (TMA) with pulmonary and cerebral vasculitis (catastrophic cryoglobulinemic vasculitis). The response to treatment has been a cure rate of 30%, a partial response rate of 50% and no response in 20% [17].

AKI may also occur in the absence of cryoglobulinemia both in native and transplanted kidneys. There is strong evidence, based on observational studies (one of which includes over 4 million hospitalized patients), that HCV infection is a significant risk factor for dialysis-requiring AKI in many settings including sepsis, myocardial infarction, HIV infection and others [18].

HCV is also a risk factor for several acute post-transplant complications including acute transplant glomerulopathy, acute vascular rejection and TMA. HCV-associated cirrhosis can cause AKI by several mechanisms including the hepatorenal syndrome, hypovolaemia and sepsis.

AKI has been reported with several therapeutic agents used for HCV. Interferon may cause acute interstitial nephritis and the first-generation DAAs are known transiently to reduce the glomerular filtration rate. They may raise serum creatinine levels by competition with its tubular secretion via the organic cation transporter-2 (OCT-2) [19]. However, true AKI has also been reported with telaprevir, and less often with boceprevir [20].

The second-generation DAAs seem to be safer, yet there have been several reports that incriminate sofosbuvir in AKI [21]. In all reported cases, AKI was reversible after discontinuation of treatment, or even without it. In our own experience, this has not always been the case; several patients needed dialysis and a few progressed to CKD [unpublished data]. Time will tell if these observations are confirmed in other series.

HCV related glomerulonephritis

HCV is associated with several types of chronic kidney involvement. The most common is membranoproliferative (mesangiocapillary) glomerulonephritis (MPGN), usually related to type II cryoglobulinaemia. MPGN may also develop in the absence of cryoglobulinaemia. Other forms of glomerular disease include IgA nephropathy (IgAN), membranous nephropathy (MN), postinfectious glomerulonephritis, TMAs, focal segmental

glomerulosclerosis (FSGS), and fibrillary and immunotactoid glomerulonephritis [22]. Overall, HCV-associated glomerular disease is infrequent and the rate of MPGN in HCV-positive patients has been reported at less than 1% [4].

The pattern of injury depends on the pathogenesis; thus, MPGN with positive staining for immunoglobulins and C3 may result either from mixed cryoglobulin (monoclonal IgM against polyclonal IgG anti-HCV antibodies) deposition, or from the deposition of anti-HCV polyclonal immunoglobulins without cryo-properties. The latter mechanism is also incriminated in HCV-associated MN and IgAN, whereas FSGS is associated with direct tissue infection [23]. The improved understanding of the mechanisms of HCV-induced glomerular disease provides the opportunity for targeted approaches to treatment: (1) non-specific immunosuppressive therapy, targeting glomerular inflammation (intravenous or oral corticosteroids and azathioprine); (2) selective immunosuppressive therapy such as rituximab, targeting B cells that synthesize cryoglobulins; and (3) antiviral therapy, since HCV infection triggers the production of immune complexes and the ensuing vasculitis. The evidence regarding the role of antiviral agents was limited until recently as the disease is infrequent and classical antiviral therapy (interferon plus ribavirin) is less effective and safe in patients with kidney disease. Preliminary data suggest that DAAs are more effective and safer than interferon-based therapies, even in patients with HCV-induced glomerular disease [24].

Patients with nephrotic syndrome, rapid loss of kidney function or an acute flare of cryoglobulinaemic disease should first be treated with immunosuppressive drugs (e.g., intravenous corticosteroids, rituximab, cyclophosphamide) and plasma exchange. Antiviral therapy (with DAAs) is recommended after the vasculitis is controlled. Patients with moderate proteinuria and slow loss of kidney function should receive DAAs first in order to achieve HCV RNA clearance [25]. Studies are in progress in order to ascertain to what extent DAAs reduce the need for immunosuppressive therapies among patients with HCV-related glomerular disease.

Hepatitis C and Progression of Chronic Kidney Disease

Chronic HCV infection has been shown to be a risk factor for CKD and its progression in several studies from different continents [26] and in a large meta-analysis. Furthermore, insulin resistance, which is specifically associated with HCV genotypes 1 and 4, is associated with chronic HCV [27]. The incidence rate for developing kidney failure was significantly higher in patients with HCV infection and diabetes compared to a control group with diabetes only, suggesting an additive effect [27]. Interestingly, an interventional study demonstrated that interferon-based anti-viral treatment for HCV infection was associated with improved renal and cardiovascular outcomes in diabetic patients [13], and more recently it was shown in patients with HCV genotype 1 infection that DAA treatment reverses insulin resistance. Preliminary data from the Kaiser-Permanente health system show that both interferon-based and DAA treatment significantly decrease the risk for kidney failure in CKD patients achieving SVR [10]. Antiviral treatment also seems to have a favourable effect on survival in patients on HD [26]. In spite of the greater risk for CKD progression with HCV infection, antiviral therapy in patients with CKD lags far behind that

of the general population. HCV treatment of CKD patients should therefore be an urgent priority in this new era, with several effective treatment options.

HCV & Kidney Transplant Outcomes

HCV infection has a significant negative impact on long-term (10 years) patient and graft survival in kidney transplant recipients. This might manifest in specific ethnic groups and be influenced by the genotype [28]. Anti-thymocyte globulin (ATG) induction therapy has long-term patient and graft survival benefits without flares of HCV infection [29]. HCV-positive recipients had better patient and graft survival when receiving grafts from HCV-negative than from HCV-positive donors; the latter option entails the risk of reinfection and/or super-infection with a different strain [28]. The recent availability of DAAs could cure HCV in transplant recipients, thus nullifying its deleterious survival impact [30].

Treating the HCV prior to transplantation is the preferred strategy, as HCV-positive recipients experience greater mortality during the post-transplant period. They may experience more hepatic and metabolic complications, infections, recurrence of the primary kidney disease and malignancies. The exception to this rule occurs where the acceptance of an HCV-positive donor markedly shortens the waiting time for kidney transplantation. The Spanish experience has shown that transplanting HCV-positive organs into HCV RNA-positive recipients is associated with good long-term outcomes [31].

Meanwhile, during the treatment of HCV in transplant recipients, one should be aware of interactions between immunosuppressive medications and DAAs, as a result of interference with the intestinal and hepatic transporter proteins as well as the liver microsomal enzymes [32]. It is important to monitor transplant patients receiving DAAs for renal complications, including proteinuria and activation of the immune system with production of allograft reactive antibodies.

Treatment of HCV in Severe CKD

The second-generation DAAs, since their introduction in 2014, were available to all patients except those with severe CKD. Indeed, sofosbuvir, the first drug to be FDA approved and the backbone of many DAA regimens, undergoes significant renal excretion (the other DAAs have minimal renal excretion) and is not approved for use below an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m² [33]. Other issues included the dialyzability of drugs and the presence or absence of autoimmune disease. With the rapid evolution of DAAs, we are now witnessing an era of interferon-free, sofosbuvir-free and even ribavirin-free regimens, which allows their use in all stages of CKD [34].

According to the AASLD (the American Association for the Study of Liver Diseases), for CKD patients stages 1–3 (eGFR > 30 mL/min/1.73 m²), any of the approved DAA combinations can be used, with no dose adjustment (evidence rating 1A; last updated September 2017) [35]. For the advanced stages of CKD, with the poor tolerability of ribavirin and the possibility of accumulation of sofosbuvir, the trend is towards non-sofosbuvir, ribavirin-free based regimens. For CKD stages 4 and 5 (eGFR < 30 mL/min/1.73 m²), genotypes 1a, 1b or 4, a daily fixed-dose combination of 50 mg elbasvir and 100 mg

grazoprevir (Zepatier) can be used for 12 weeks (rating 1B). For CKD stages 4 and 5, genotypes 1–6, 300 mg glecaprevir/120 mg pibrentasvir (Mavyret) can be used for 8–16 weeks (rating 1B). Sofosbuvir-based regimens are not mentioned in the guidelines and have shown increased risk of worsening renal function in this group of patients, though other studies demonstrated safety and efficacy at half-dose [36] as well as full-dose regimens [37]. There is no consensus on the dose of sofosbuvir in severe renal impairment and its use is off-label. However, in view of accumulating evidence on its use in this group of patients, it can be considered a third option in situations where non-sofosbuvir-based regimens are unavailable.

Summary of changes in AASLD guideline since the date of this consensus meeting

The AASLD and IDSA (Infectious Diseases Society of America) guidance has been updated for patients with severe kidney impairment and recommends no dose adjustment for any DAA regimen used, including sofosbuvir-based regimens [38].

For elbasvir/grazoprevir-based regimens, the C-SURFER trial demonstrated high efficacy in patients with advanced CKD, including patients on haemodialysis, with no significant increase in adverse events [38]. For glecaprevir/pibrentasvir, an integrated analysis of the EXPEDITION-4 and EXPEDITION-5 studies confirmed very high SVR12 in patients with genotypes 1–6 and CKD stages 3b–5, including patients on haemodialysis [38]. For sofosbuvir-based regimens, a systematic review of 717 patients with HCV and CKD stages 4–5 found high efficacy (97% SVR12 and SVR24) and good safety data (adverse event rate 4.8%). Based on these and other data, no dose adjustment for sofosbuvir-based regimens is recommended [38].

Treatment of HCV in Kidney Transplant Patients

Cure of HCV can be achieved in CKD stages 4–5, including dialysis patients and in kidney transplant recipients. The choice of DAA regimen should be based on HCV genotype, viral load, eGFR, concomitant medications, comorbidities and transplantation candidacy. The timing of the treatment (before or after transplantation) should be decided in collaboration with the transplant centre.

Multiple studies, summarized below, have shown successful HCV treatment after renal transplantation; sofosbuvir plus ledipasvir, simprevir or daclatasvir could be used with/without ribavirin. Careful attention should be devoted to the risk of interactions with immunosuppressive medications. There is still no consensus on the use of the more recent drugs Zepatier and Mavyret post-transplantation.

1. 20 HCV RNA-positive kidney transplant recipients participated in a study in which a DAA regimen was initiated an average of 888 days post-transplant. The regimen included sofosbuvir and simprevir. The patients were mostly (88%) infected by genotype 1 and 50% had advanced hepatic fibrosis. All patients had SVR12 [39].

2. 29 HCV RNA-positive kidney transplant recipients were given sofosbuvir and another drug for 12 weeks or 24 weeks; 88% of patients had viral clearance after 4 weeks and 100% at treatment end. All patients had SVR12 [40].
3. In a single-centre retrospective cohort of 31 kidney transplant recipients, patients were treated for 12 weeks by DAA (mainly sofosbuvir with ledipasvir); SVR12 was 97%. No change was observed in eGFR but 19.3% of the patients had worsening of proteinuria after starting therapy [41].
4. The transplanting hepatitis C kidneys into negative kidney recipients (THINKER) pilot trial showed that transplantation of HCV genotype 1-infected kidneys into HCV-negative recipients, followed by the use of DAAs, can provide good allograft function with a cure of HCV infection in patients after transplantation [42]

Adverse Events of Direct Acting Anti-Hepatitis C Therapy

DAAs generally have a good safety profile. The commonest adverse events (headache, fatigue, nausea, diarrhoea) are tolerable and do not require dose modification. However, in advanced cirrhosis, caution should be exercised since hepatic decompensation and life-threatening events can occur, particularly with the use of protease inhibitors. In addition, a variety of specific adverse events were reported, albeit rare. These include pulmonary hypertension, acute interstitial nephritis and hyperbilirubinaemia [43].

Pregnancy should be avoided while on DAA therapy, and strictly prevented if ribavirin has to be included, even when taken by male partner. Pregnancy can be considered a few weeks after SVR, except if ribavirin was used, when it should be avoided for 6 months [44].

HCV Co-Infection with Other Pathogens

The association of HCV infection with other viral infections may be associated with worse outcomes. Physicians should also be aware of the risk of drug–drug interactions [35].

- a. HCV–HBV. Both HBV and HCV are transmitted parenterally, and coinfection is not uncommon in Asia, sub-Saharan Africa and South America, and among subjects at high risk of parenteral transmission [45]. Few studies have investigated the mechanisms of the inhibition of HBV replication by HCV. Shih et al. reported that HBV mRNA and antigen expression was associated with a 2–4-fold reduction in the presence of HCV, and HBV particle secretion was suppressed up to 20-fold [46]. The use of interferon-free DAAs for hepatitis C infection may be complicated by reactivation of occult hepatitis B and this risk should always be considered [47]. There may also be spontaneous clearance of hepatitis C. Female gender, coinfection with hepatitis B and IL28 genetic polymorphisms are associated with higher rates of spontaneous clearance of HCV [48].
- b. HCV–HIV. Among HIV-infected individuals in 2015, an estimated 2.3 million had also been infected with HCV. Liver diseases are a major cause of morbidity

and mortality among these coinfecting patients and effective treatment of both HIV and HCV is a clear priority [49]. In a recent meta-analysis, HCV–HIV coinfection was associated with increased cardiovascular disease [50]. Moreover, HCV coinfection is associated with an increased risk of reduced GFR and/or proteinuria among HIV-infected individuals [51].

- c. HCV–schistosomiasis. Concomitant schistosomiasis and HCV infection is common in Egypt and some other developing countries. Coinfecting patients exhibit a unique clinical, virological and histological pattern with high HCV RNA titres, higher liver biopsy necro-inflammatory and fibrosis scores, and markedly accelerated disease progression once chronic HCV infection is established.

Hepatitis C in Sub-Saharan Africa: The Nigerian Experience

Continental Africa has an HCV incidence rate of 31/100,000, with most of the infections occurring in North Africa. In Nigeria, HIV and hepatitis B infections have received disproportionately more attention than HCV infection. From 1999 onwards, routine testing for HCV in blood banks started in Nigeria. Currently, there are no nationwide prevalence studies on HCV but multiple prospective cross-sectional studies in different populations, and case control studies in patients with liver diseases and HIV infection have been conducted. HCV prevalence ranges from 0.4% in a population of pregnant women [52] to 14.7% in an HIV-infected population [53]. The prevalence in patients with advanced CKD is not well known. Reports from some renal centres in Nigeria quote prevalences ranging from 0.3% to 2.5%, with genotypes 1 (85%) and 2 (15%) being the most common [54]. Few or no data exist on HCV and non-dialysis CKD in Nigeria.

Hepatitis C in North Africa: The Egyptian Experience

Egypt has one of the highest prevalences of HCV in the world. A national survey conducted in 2015 showed that about 10% of the population is chronically infected. It has been estimated that around 650,000 patients have cirrhosis, 16,000 have developed HCC and some 30,000 people die from HCV annually. A national plan of action for the management of viral hepatitis was launched in 2006, and was intensified in 2014 with the introduction of the DAAs. DAAs were introduced at 1% of the price in western countries and, later, locally manufactured generics became available at 0.1% of the price. The current focus is on the prevention of new infections and national screening to diagnose and treat patients who are unaware of their infection. The reported prevalence may thus be an under-estimate. It is hoped that HCV will be eradicated in Egypt by 2025 [55].

Conclusions

HCV infection is an important cause of morbidity and mortality in the various CKD populations. With the current availability of highly effective and well-tolerated DAA regimens, CKD patients should be a priority target for “micro-elimination” of HCV, as an important step towards the WHO target of the elimination of viral hepatitis as a public health

problem by 2030. Every country should have an action plan, and should be inspired by the impressive progress made by Egypt, where this IFKF meeting was held.

Acknowledgment

We acknowledge Roche for an unrestricted grant to IFKF to support of the consensus conference in December 2017 in Cairo, Egypt.

Disclosure of competing interests:

Dr. K. Kalantar-Zadeh has received honoraria and/or support from Abbott, Abbvie, ACI Clinical (Cara Therapeutics), Akebia, Alexion, Amgen, ASN (American Society of Nephrology), Astra-Zeneca, Aveo, BBraun, Chugai, Cytokinetics, Daiichi, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, IFKF (International Federation of Kidney Foundations), ISH (International Society of Hemodialysis), International Society of Renal Nutrition & Metabolism (ISRNM), JSDT (Japanese Society of Dialysis Therapy), Hospira, Kabi, Keryx, Kissei, Novartis, OPKO, NIH (National Institutes of Health), NKF (National Kidney Foundations), Pfizer, Regulus, Relypsa, Resverlogix, Dr Schaer, Sandoz, Sanofi, Shire, VA (Veterans' Affairs), Vifor, UpToDate, ZS-Pharma. AB received consulting fees from ChemoCentryx and Merck/MSD, and received honoraria for lectures from AbbVie, ChemoCentryx, and Merck/MSD. She also received research grant from Astra-Zeneca. MJ has been a speaker for Merck (MSD) and Abbvie, consultant for Merck and received an unrestricted educational grant from Merck. All monies paid to his institution Cliniques universitaires Saint-Luc. MJ has also co-chaired the 2018 update of the Kidney Disease: Improving Global Outcomes (KDIGO) HCV in CKD Guideline and since 2019 is KDIGO co-chair. Dr Fabrizio Fabrizi has received honoraria and/or support from Abbvie and MSD. All other authors have no disclosure.

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