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REVIEW

Challenge of hepatitis C in Egypt and hepatitis B in Mauritania

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Abstract

Egypt has one of the highest prevalence rates of hepatitis C virus (HCV) in the world, mostly with genotype 4 that is highly associated with severe fibrosis. As a consequence, hepatocellular carcinoma has become the leading cause of cancer in this country. Mauritania is a highly endemic area for hepatitis B virus (HBV). HBV and HCV could both be iatrogenically transmitted through infected blood products, infected needles, and medical equipment improperly sterilized. Adequate and efficient healthcare and public health measures with good surveillance programs, access for screening, prevention strategies, and successful treatment are needed to halt the spread of these diseases. Herein, we have reviewed the epidemiology, modes of transmission, predisposing factors, and novel treatment modalities of these viruses. We have proposed practices and interventions to decrease the risk of transmission of HCV and HBV in the affected countries, including strict adherence to standard precautions in the healthcare setting, rigorous education and training of patients and healthcare providers, universal screening of blood donors, use of safety-engineered devices, proper sterilization of medical equipment, hepatitis B vaccination, as well as effective direct-acting antiviral agents for the treatment of HCV.

Key words: Hepatitis B virus; Hepatocellular carcinoma; Hospital acquired infection; World Health Organization; Hepatitis delta virus; Hepatitis C virus

Core tip: Hepatitis C virus (HCV) and hepatitis B virus (HBV) are major public health concerns in Egypt and Mauritania. HCV and HBV can both be transmitted through medical and surgical procedures (healthcare-associated transmission) among others. Screening, prevention, and treatment strategies should be emphasized in Egypt and Mauritania to prevent the spread of these diseases. Direct-acting antivirals for the treatment of HCV are highly effective and well tolerated and should be made accessible and affordable to patients.

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HEPATITIS C VIRUS IN EGYPT

Over the last several years, Egypt continues to have one of the largest epidemics of hepatitis C virus (HCV), with an estimated prevalence of 10%. A prevalence above 4% is considered high by World Health Organization (WHO) standards[1]. A study published in the Proceeding of the National Academy of Science (PNAS) reports more than 500000 new HCV cases yearly[2]. However, others recently estimated a lower number of new cases every year, but still it remains high compared to other areas in the world[3]. Hence, viral hepatitis caused by HCV genotype 4 continues to represent the most serious public health threat currently facing Egypt[1,2].

To estimate the prevalence of HCV in Egypt, a national survey was conducted in 2015 known as the Egyptian Health Issues Survey (EHIS). This survey was a cross-sectional household survey of 16003 who were identified between the ages of 15 and 59 and had blood testing for HCV[1]. The results of this survey were compared to another cross-sectional national survey conducted in 2008 known as the Egyptian Demographic Health Survey (EDHS) in which 12008 Egyptian were interviewed[4]. The 2015 survey (EHIS) reported a prevalence of 10% for HCV antibody and 7% for HCV RNA. This reflected an estimated 29% reduction in HCV RNA prevalence compared to the 2008 national survey (EDHS). This reduction could be related to the disappearance of the highly infected group that was treated with reused syringes during the shistosomiasis treatment campaign in the 1960s and 1970s[1]. Hence, by 2015, this highly infected older age group disappeared due to differential age related migration and mortality (particularly since the survey excluded individuals that are 60 years or older). Furthermore, when a shift adjustment was made (by 7 years), the age specific prevalence of HCV RNA positivity was matched and was comparable in the 2008 surveillance (EDHS) and the 2015 surveillance (EHIS). Hence, these surveys represent an underestimate of the true prevalence of the HCV infections in Egypt, particularly since the rate of infection is among elderly patients above 60 years who acquired the infections in the 1960s and 1970s whereas these surveys were limited only to individuals with an age range of 15-59 years [1].

Based on the above and given the population of Egypt, which exceeds 95 million, we estimate that more than 6.5 million Egyptians are infected with the HCV virus, and most of those are caused by a genotype 4. Several genotypic studies have shown that genotype 4 of HCV accounts for 93.1% of HCV infections, and most (80.6%) of the Egyptians infected with HCV4 belong to subtype 4A[5-7]. It is likely that the subtype 4A was the main strain associated with antischistosomal therapy epidemic that occurred in the 1960s and 1970s and which was associated with the reuse of needles[8,9]. In fact HCV4 is the predominant HCV genotype in the Middle East and North Africa, which accounts for 59% of HCV infections in Syria, 53% in Iraq, 54% in Kuwait, and 64% in Palestine. It is also reported to be a dominant genotype in Qatar, Saudi Arabia, and Libya[5,6,10,11] and is common in other parts of the Middle East such as Lebanon, Oman, and UAE. This may possibly be related to the migration of Egyptians, who represent a major workforce in some of these Middle Eastern countries, to these areas[5,11].

Furthermore, there is evidence that HCV4 is a highly pathogenic virus. Wali *et al*[12] demonstrated that HCV4 was significantly more associated with fibrosis progression, severe fibrosis development, and confluent necrosis than other non-genotype 4 HCV infected patients. In addition, hepatocellular carcinoma (HCC) in Egypt is a leading cause of cancer and cancer mortality among men, whereby more than 84% of Egyptian patients with HCC are positive with HCV4[13,14]. Chronic infection that could lead to severe fibrosis and cirrhosis can occur in 50%-85% of HCV patients[15,16]. Given the decline in the economic and healthcare conditions, nationwide efforts to control the spread of HCV infection have been disrupted for several years.

The iatrogenic spread of HCV genotype 4 in Egypt due to the improper dental instruments sterilization has been a major concern[17]. Furthermore, between 46%-100% of hemodialysis patients and 11%-82% of patients who received multi-transfusions were found to be seropositive for HCV[18].

Despite all the effort done by the Ministry of Health and Population (MOHP) in Egypt to control infection, healthcare-associated infection (HAI) remains one of the most common cause of HCV infection in Egypt,

Table 1 Risk factors of the transmission of hepatitis C in Egypt through the healthcare system and proposed interventions

Risk factors	Proposed interventions
Needle stick injuries or other injuries	Institute infection control and occupational health programs in all healthcare facilities to reduce occupational exposure, protect against needle stick, and other healthcare related injuries Adequate education and training of healthcare providers Use of safety-engineered devices, such as needleless intravenous medication systems, blunted suture needles Use of needle disposal containers
Surgical or invasive interventions, dental procedures	Appropriate sterilization of surgical and dental instruments Good aseptic techniques practiced during invasive procedures Provide personal protective equipment, such as gloves, gowns, face/eye shields, to be used during procedures with anticipated blood exposure
Exposure to medical equipment, hemodialysis machines and procedures	Strict infection control and prevention policies Universal precautions should be used when caring for all patients
Injection and Ⅳ insertion	Use of self-sheathing needles, needleless connectors, needleless intravenous medication system, and needle disposal containers
Blood transfusion from poorly screened individuals (false negative anti-HCV)	Universal screening of all donors
Organ donation	Universal screening of all donors

HCV: Hepatitis C virus.

related to the overuse of contaminated needles and syringes[2]. In addition, healthcare workers in Egypt and many Middle Eastern countries have the highest rates of needle stick injuries worldwide[19,20]. Hence, unsafe medical and dental practices, including reuse of medical devices, inadequate sterilization of surgical and interventional equipment, poor aseptic techniques practiced during invasive procedures, circumcisions or deliveries of neonates by providers, unsafe injections, and limited testing of blood product transfusions for HCV have all contributed to high iatrogenic transmission of HCV in Egypt[21-23]. These factors play an important role in the transmission of HCV in Egypt. Table 1 outlines the risk factors for the transmission of HCV in Egypt through the healthcare system, and the proposed infection prevention interventions that could control this transmission.

To control this self-perpetuating HCV epidemic in Egypt, a health initiative was started in 2017 to screen all governorates of Egypt called "Egypt without virus C, 2020" in cooperation with Tahya Misr Fund[24]. A concerted effort should be made towards universal screening of all patients going through the healthcare system, early detection of HCV, early treatment using direct acting antiviral (DAA) regimen with simultaneous implementation of strict infection control and prevention policies within the healthcare system.

Egypt also developed a strategy for prevention and control of viral hepatitis (2008-2014) in collaboration with WHO, Centers for Disease Control (CDC), and Pasteur[25]. The National Committee for Control of Viral Hepatitis (NCCVH) in affiliation to the MOHP established a large model of care in Egypt since 2006 that aimed at elimination of HCV in Egypt and delivering DAAs for all patients at the expense of the government[25,26]. However, the limited resources, the unmet needs and suboptimal access to care, and the low rates of patients' follow-up hindered the success of the program[27,28].

Most of the individuals living with viral hepatitis caused by HCV are asymptomatic and, hence, remain unaware of their illness for decades, even though liver damage is occurring. Given the high prevalence of HCV in Egypt, universal surveillance through rapid enzyme immunoassay testing of all patients going through the healthcare system would detect a large number of asymptomatic patients. With the advent of DAA and the demonstration of high cure rates (sustained virologic response or SVR) of over 90%, including genotype 4 infected patients. The DAAs are also associated with minimal side effects and relatively short duration of treatment, when compared to interferon based treatments.

Hence, it is possible to virologically cure the majority of these patients, particularly if the patient is treated in the early phase when they are not suffering from decompensated liver disease or cirrhosis[29-32]. Curing these patients would preempt the morbidity and mortality associated with subsequent liver cirrhosis and HCC. SVR after non-interferon DAA regimens is associated with improvement in liver fibrosis and necrosis in up to 73% of patients, with reversal of cirrhosis in 49% of the cases[33]. Emerging data with DAAs show significant improvement of liver stiffness that has been reported in patients with HCV-associated advanced liver disease[34]. A recent study showed that DAA-induced SVR was associated with 71% reduction in HCC[35].

Early treatment of HCV infection, regardless of the infecting genotype, may also reduce the risk of extrahepatic complications, including mixed cryoglobulinemia, porphyria cutanea tarda, diabetes mellitus, cardiovascular disease, renal diseases, and B-cell non-Hodgkin lymphoma[36-38].

Given the availability of generic versions of DAAs

(particularly sofosbuvir at an affordable low cost), early treatment can be widely used and, hence, could effectively contribute to the elimination of HCV viral hepatitis in Egypt[3]. The WHO reported that after generic sofosbuvir became available in Egypt at a cost of $153 for a 12-wk course, approximately half a million patients with chronic HCV were treated with this drug since January 2016[3,39]. Our team conducted a large surveillance study on patients evaluated at Harpur Memorial Hospital in the Delta area of Menouf, Egypt, involving 729 adult patients (18-65 years) who were evaluated for health-related illnesses not associated with hepatitis or liver diseases between January 2012-January 2013. All patients who consented were screened by a rapid enzyme immunoassay (ELISA) to detect the presence of HCV antibodies and determine the prevalence of HCV (HCV antibodies). The reactive ELISA rapid test samples were further confirmed for HCV antibody positivity by the chemiluminescent microplate immunoassay (CIA). Subsequently, CIA HCV antibody positive samples were tested further for HCV RNA by quantitative real time polymerase chain reaction (PCR). We identified 146 patients (20%) who were positive for HCV, which was later confirmed by the ELISA antibody test and HCV-RNA levels (viral load). Interestingly, 119 (82% of the 146 patients) with a positive test had no risk factors for developing HCV, such as a surgical procedure, dental extraction, needle stick injuries, blood transfusions, and other risk factors listed in Table 1 in the prior 5 years. All of the 146 patients with positive HCV in the study were asymptomatic with no symptoms of liver disease. Therefore, this study highlights the importance of universal surveillance in the general population, as suggested by WHO, in countries with high HCV antibody seroprevalence (⩾ 2%), which will lead to the early detection of HCV in asymptomatic patients and ultimately lead to high cure rates after using DAA[29-32,40].

In addition to universal surveillance, early diagnosis, and early treatment of HCV in Egypt, promotion of infection prevention and control procedures in a healthcare setting is of paramount importance in controlling HCV transmission[40]. These infection control policies and practices should prohibit reuse of medical devices or needles, emphasize appropriate sterilization of surgical and dental instruments, promote the use of safe injectables, protect against needle stick and other healthcare related injuries, test all blood donors, and adhere to appropriate healthcare waste management. This involves a large scale training of healthcare professionals in Egypt on infection control practices and includes new safeguard technologies, such as the autodisable syringes (Table 1).

The conventional combination regimen of pegylated-interferon and ribavirin alone has demonstrated low SVR rates against genotype 4 of approximately 30% after 48 wk of treatment with poor tolerance of the regimen[41,42]. However, several DAAs have been approved in the United States and Europe that showed highly promising results; and, hence, they have changed the treatment paradigm for chronic HCV infections in general, including genotype 4 (Table 2)[43,44]. The DAA regimen should be individualized, mostly on the basis of the patient's prior antiviral therapy, presence of cirrhosis, availability, cost, and drug-drug interactions with concomitant medications[43]. In most of these regimens, the treatment duration extended between 12-24 wk[29-32,43-45].

One of the first interferon-free regimens used in treatment of genotype 4 HCV, which consisted of sofosbuvir plus ribavirin, showed that 12 wk of treatment was associated with overall lower SVR rates compared to 24 wk, and, hence, this regimen was approved for 24 wk[29].

In particular, several fixed dose combination regimens, such as ledipasvir-sofosbuvir[30,46,47], sofosbuvir-velpatasvir[31,48], and glecaprevir/pibrentasvir[49,50], have demonstrated efficacy with SVR that exceeds 90% after 8-12 wk of treatment of HCV 4. They are unique in that they achieve successful outcome with once daily dosing and without the need to administer ribavirin in the treatment of genotype 4 HCV. Only glecaprevir/pibrentasvir can be used for 8 wk in the subset of treatment-naive or peginterferon/ribavirin-experienced genotype 4 patients without cirrhosis[43,49,50].

Ledipasvir-sofosbuvir is available and widely used in the treatment of genotype 4 HCV patients in Egypt. In an open label phase 2 trial, Kohli *et al*[30] showed that ledipasvir-sofosbuvir treatment of patients with HCV genotype 4 for 12 wk resulted in 100% SVR 12 and was well tolerated with minimal mild adverse events. Crespo *et al*[47] reported on the effectiveness and safety of this once daily oral combination in the treatment of hepatitis C genotype 4 infections, showing an overall 95.4% SVR 12 response with a respective 100% SVR 12 response in patients without cirrhosis. In patients with cirrhosis, 12-wk treatment with ledipasvir-sofosbuvir without ribavirin had an equivalent successful outcome to this once daily combination with ribavirin for 12 wk or 24 wk[47]. However, many of the genotype 4 HCV patients in Egypt are elderly patients with some renal insufficiency or reflux disorder requiring proton pump inhibitors (PPIs), which might limit the activity and the use of the drug in this population[51,52].

Sofosbuvir-velpatasvir has also demonstrated high efficacy in the treatment of patients with genotype 4 HCV infections irrespective of treatment history (treatment naïve or experienced) or the presence of cirrhosis[31,48]. In a study by Feld *et al*[31], 100% of the 116 patients with genotype 4 infection achieved SVR 12 following a 12-wk treatment of sofosbuvir-velpatasvir. Similarly, this regimen was highly effective in genotype 4 HCV infections and was well tolerated, with serious adverse events occurring in only 2% of those who received this regimen[48].

The fixed dose combination of glecaprevir-pibrentasvir given once daily in three pills was uniquely effective in the treatment of HCV genotype 4 infected

Table 2 Direct-acting antiviral regimens available to treat hepatitis C virus genotype 4

[1]Combination regimen[43,44]	Duration (wk)
Sofosbuvir-ledipasvir	12
Sofosbuvir-velpatasvir	12
Glecaprevir-pibrentasvir	8 (without cirrhosis) 12 (with cirrhosis)
Sofosbuvir-velpatasvir-voxilaprevir	12
Ombitasvir-paritaprevir-ritonavir ± ribavirin	12
Elbasvir-grazoprevir ± ribavirin	12-16
Elbasvir-grazoprevir	12 (treatment naïve)
Elbasvir-grazoprevir + ribavirin	16 (treatment experienced)
Sofosbuvir + ribavirin	24
Sofosbuvir + daclatasvir ± ribavirin	12
Sofosbuvir + simeprivir ± ribavirin	12-24

[1]The information from the table is from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) hepatitis C virus guidelines.

patients when given for only 8 wk in patients without cirrhosis, resulting in an SVR 12 response rate of 93% in this patient population[49,50]. Furthermore, in 16 patients with cirrhosis who received 12 wk of this fixed combination, 100% SVR 12 was achieved. It is important to note that the HCV genotype 4 patients without cirrhosis who did not achieve SVR 12 with the 8 wk regimen were either patients who had incomplete data or discontinued therapy prematurely[50]. The advantage of this fixed dose combination regimen of glecaprevir-pibrentasvir is that it can be given in patients in any degree of renal impairment, unlike ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir[49,50].

HEPATITIS B IN MAURITANIA

Hepatitis B virus (HBV) is a major cause for liver disease worldwide, particularly in Mauritania[53]. There are approximately two billion people who have been infected with HBV, of which 400 million people are infected chronically and of whom 65 million reside in Africa. HBV infection leads to 0.5-1.2 million deaths annually due to liver cirrhosis and HCC. Sub-Saharan Africa has a high HBV prevalence rate of 16.16%[54,55]. Mauritania remains a hyper-endemic area for HBV. Studies in Mauritania on the epidemiology of HBV[56] have shown a high prevalence of HBsAg positivity in blood donors, mostly between the age of 21-30, despite HBV vaccination of children and newborns since 2000[57]. Moreover, high HBV DNA levels were shown to be associated significantly and independently with the incidence of cirrhosis and HCC.

Co-infection with hepatitis delta virus (HDV)[58] is also endemic in Mauritania[59]. There is a high prevalence of HBV (20%) and HDV (30%). HDV infection tends to occur early, affecting mainly children and young adults, leading to chronic hepatitis. The natural course of chronic HDV is rapid progression to cirrhosis and liver related complications, including HCC[60,61].

The modes of transmission in Mauritania for HBV and HDV are social close contact, sexual contact, sharing needles, and other forms of blood exchange as well as maternal-fetal transmission during delivery (Table 3). Interfamilial transmission is common and may be facilitated by poor hygiene. Thus, socially and economically disadvantaged populations, as found in Mauritania, are more affected. Children infected perinatally with HBV are asymptomatic, and 25% die in adulthood from cirrhosis complications or HCC[62].

HCC remains a major cause of mortality due to limited therapeutic options. The aim should focus on prevention. Effective vaccine for HBV is available and was recommended by WHO to be included in the national immunization program. However, not all countries have adopted and implemented this recommendation effectively, including Mauritania, which ranks among the countries with the highest mortality of HBV associated HCC[62].

Hepatitis B vaccination is the best strategy to prevent this infection and decrease its incidence in the young population[63]. Vaccination is highly recommended in high prevalence areas like Mauritania, and the vaccines should be given to all infants at the time of birth, children, and adolescents as well as adults with risk factors that are included in Table 3. In addition, booster doses of hepatitis B vaccine are recommended in hemodialysis and in the immunocompromised person. The high cost of the vaccine and the lack of the infrastructure to deliver the vaccines do impact the implementation of a universal vaccination program in Mauritania. Prevalence rates of hepatitis B and children vaccination rates in various African region have been published[64]. However, given the limited data available from the unaccounted home births, the reported vaccination rates could be inflated and the prevalence of the disease understated. Therefore, public health action is urgently needed. A multifaceted approach to improve the socioeconomic conditions, increase the awareness of the risk of transmission, aggressive vaccination campaigns, and public health intervention are strongly needed to prevent viral transmission. Also, a regional

Table 3 Risk factors of transmission of hepatitis B in Mauritania and proposed interventions

Risk factors	Proposed interventions
Direct contact with infected blood and or handling blood or body fluids (job exposure) Sharing needles or other equipment (such as cotton, spoons, and water) to inject drugs Hemodialysis	Rigorous adherence to standard precautions in healthcare settings Completely avoid sharing needles or re-using disposable devices Education of healthcare providers and patients Hepatitis B vaccinations and assessment of response to vaccine (hepatitis B surface antibody) Use of safety-engineered devices and needless infusion systems Use of sharp object disposal containers Strict infection control measures upon cleaning and reusing medical equipment Appropriate screening of blood donors Post-exposure prophylaxis Antiviral therapy
Intimate contact with a person with HBV	Hepatitis B vaccination Avoid sharing toothbrushes, razors, *etc.*
Multiple sex partners or having unprotected sex with someone who is infected with the virus	Hepatitis B vaccination Protected sexual intercourse
Mother-to-Child transmission	Screening pregnant women Antiviral therapy to pregnant women with high DNA levels Passive-active immunization of newborns of mothers with HBV Universal vaccination of newborns
Body piercings, tattoos or acupuncture	Avoid body piercing and tattoos Strict infection control and prevention policies
Ⅳ drug users	Avoid sharing syringes and needles

HBV: Hepatitis B virus.

specific clinical guideline for screening, targeting infection control measures, and using ultra-sonographic tools in the highest risk setting, such as healthcare, dentistry, and personal grooming service centers, is needed. In addition, enhanced access to health care services and providing public funds for treating HBV and HDV may help to optimize management of infected patients.

Patients with acute hepatitis B do not require antiviral medication, as most patients will recover spontaneously. Supportive care with hydration and regular follow up with their physician is recommended. However, patients with chronic hepatitis B are more likely to require antiviral medications. Its purpose is to stop any further damage to the liver by slowing the multiplication of the virus. Therapy should be given to the following patients: patients with chronic hepatitis B with HBV DNA > 20000 IU/mL and with liver alanine aminotransferase > 2 × upper limit of normal, patients with evidence of fibrosis or moderate to severe hepatitis on liver biopsy irrespective of hepatitis B DNA level, and patients with cirrhosis associated with chronic HBV irrespective of hepatitis B DNA level.

Nucleoside analogues are the preferred agents. They are very effective at viral suppression and have a high barrier to drug resistance. The current first line therapy are entecavir 0.5 mg/d × 48 wk orally, tenofovir 300 mg/d × 48 wk orally[65], and pegylated interferon in noncirrhotic HbeAg-positive patients is also an option[66]. However, most patients require lifelong therapy because relapse is common after discontinuation of therapy[67,68]. Unfortunately, most of Mauritanians with chronic HBV infection who are eligible for this therapy cannot afford it. Less than 1% of individuals eligible for antiviral therapy receive HBV treatment. In mothers with a high viral load, the antiviral treatment rate to reduce mother-to-child transmission is even lower[69]. In summary, HCV and HBV are major causes of morbidity and mortality worldwide. Both could be iatrogenically transmitted through infected blood products, infected needles and medical equipment. Egypt has one of the highest prevalence rates of hepatitis C in the world and North Africa which could be controlled by rigorous infection control measures with education of healthcare providers and patients as well as universal screening of blood donors. In addition providing the current efficacious antiviral therapy (DAA) for the Egyptians infected with HCV could also help eliminate this infection. On the other hand, Mauritania is a highly endemic area for hepatitis B and ranks among the North African countries with the highest mortality of HBV and associated HCC. Despite this impressive burden, hepatitis B in Mauritania is now considered a preventable disease with the available vaccine and the proposed implementation of several infection prevention measures. Universal surveillance programs, active infection prevention strategies particularly within the healthcare system and early detection with early treatment and precaution could be the common strategy that will halt the spread of both HCV and HBV diseases in these two countries.

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