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Review Article

Hepatitis C Virus Infection in Egypt: Current Situation and Future Perspective

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Abstract

Hepatitis C virus (HCV) infection is the most challenging public health problem in Egypt where the prevalence is the highest in the world and its history, epidemiology, risk factors, genotype and model of care are unique. On World Hepatitis Day (July 28, 2016), the World Hepatitis Alliance (WHA) launched NO hep, the first global movement aimed at galvanizing support toward the elimination of viral hepatitis (i.e. 90% reduction in new chronic infections, 65% reduction in mortality compared with a scenario in which interventions would continue at the current level), by 2030. In the same context, Egypt has established the plan of action for the prevention, care and treatment of viral hepatitis 2014-2018. In order to achieve the elimination target in Egypt by 2030, political, community and health care system cooperation and commitments must be met. Understanding and accurately describing the magnitude of the problem, its determinants and barriers to control are crucial to achieve the target. This article reviews the problem in Egypt from a present and future perspective elucidating the current situation and future prediction adopting different scenarios.

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Global Epidemiology of Hepatitis C

Hepatitis C virus (HCV) infection is a worldwide public health problem where its seroprevalence had an estimated 2.8% increase over the last decade, corresponding to more than 185 million infections (3% of the world's population). Nearly three quarters of infected individuals are living in middle income countries.[1, 2] China, Pakistan, Nigeria, Egypt, India, and Russia together accounted for more than half of total infections.[3]

A recent estimation showed that 119 million global adult inhabitants have chronic HCV infection, with 3-4 million new infections and 350000 to 500000 deaths occurring annually as a consequence of HCV-related complications. [1, 4] HCV genotype 1 is the most prevalent worldwide (49.1%), followed by genotype 3 (17.9%), 4 (16.8%) and 2 (11%). Genotype 4 was most common (71%) in North Africa and the Middle East, but when Egypt was excluded, it accounted for 34%, while genotype 1 accounted for 46% of infections across the same region.[1, 3] Although HCV incidence seems to decrease, HCV-related mortality will continue to increase over the next couple of decades.[5]

HCV is the leading cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC). About 55%-85% of HCV infected cases become chronic active cases and pass through the way of developing fibrosis, cirrhosis, and may progress till become decompensated cirrhosis and HCC.[4]

HCV in Egypt

Since the emergence of HCV infection, it has always been a public health problem in Egypt. It took over the liver disease burden after schistosomiasis. HCV infection has a unique situation in Egypt early from its history and will continue till elimination, hopefully, in the near future.

History of the infection

Early in the twentieth century, Egypt had the greatest schistosomiasis burden in the world, and mass treatment of the parasite was introduced.[6] From the 1950s to the 1980s, community-wide mass antischistosomiasis therapy was introduced.[7-9] At that time, tartar emetic injections were the standard treatment. They were injected intravenously, unlike some other now archaic antischistosomal drugs that were injected intramuscularly. Treatment predominately targeted children and young adults. Over 2 million injections were given annually to an average of 250,000 patients, meaning over the 18 years of treatment, 36 million injections were administered.[6, 9] Each patient was supposed to have a series of injections with the average number of injections per patient being nine in the 1960s, which then dropped to six after 1975.[6]

These campaigns are hypothesized to have led to the high HCV seroprevalence rates currently observed in the Nile Delta.[6, 8, 9] There are three main causes for the transmission of HCV, as well as other blood-borne diseases in this mass treatment scheme. First, patients were exposed to multiple injections over the time period which increased the likelihood of pathogen transmission. Second, sterilization techniques were extremely poor, which led to high frequency of HCV transmission, a virus that was not known to medical science until the 1990s.[6] Finally, the mass scale of the antischistosomal eradication campaign led to widespread mistakes, including reuse of equipment, which was something not considered important until the advent of the HIV epidemic in the early to mid-1980s.[9]

To add to the danger of the campaign, symptoms are absent in about 80% of acute HCV infections.[6] This means infection spread rapidly and would go largely unnoticed. This hypothesis is further supported by the clustering effect observed between HCV infections in households with patients who received parenteral treatment for schistosomiasis.[8] Toward the end of the campaign in the 1970s, oral drugs to treat schistosomiasis were developed, including the oral agent, praziquantel, which slowly replaced the tartar emetic injections as the gold standard of treatment.[6, 7]

Risk factors of HCV infection in Egypt

Although the parenteral antischistosomal treatment (PAT) campaigns were claimed to be the main risk factor for this huge prevalence of HCV in Egypt[8, 10], recently, about 60% of the cases were thought to get infected in hospitals and clinics.[11] Also, it was estimated that 24.3% of patients were infected through blood transfusion.[12] Additionally, some social practices, such as sharing common shaving tools at barber shops, home diabetes testing equipment, or toothbrushes are considerable risk factors outside the health care settings.[11]

In a recent meta-analysis,[13] analyzing and comparing all HCV risk factors globally and in Egypt, the results are summarized as follow:

Socio-demographic risk factors

Older age is a significant risk factor all over the world. Poor education, high risk occupation and male gender carry a slightly high risk in Egypt. Residence in rural areas is a risk in Egypt, but a protective factor in other countries.

Behavior and community-acquired factors

Illicit drug users (IDUs), having an IDU partner, an HCV+ partner or household HCV index case, tattoo and alcohol abuse constitute higher risks in Egypt than other countries. Sharing either sharp or blunt objects, visiting the barber, commercial sex and having trauma or accidents are of a high risk worldwide.

Iatrogenic factors

The highest detected risk was blood transfusion, followed by receiving PAT, hospital admission, receiving any drug by injection or infusion, hemodialysis and dental care. Risk of blood transfusion decreased over the decades. Concerning the risk from being subjected to medical procedures; Caesarean section (CS) was the highest risk followed by organ transplant, then sutures, surgery, normal labor, endoscope, catheter or esophageal balloon. Risk from normal labor and major surgery increased after 2000. Acupuncture, "hijama", circumcision and ear or body piercing also carry higher risks. Acupuncture was a more significant risk factor in Egypt. Risks from "hijama", ear or body piercing and circumcision in males decreased from 1996 to 2000 to after 2000, while risk from acupuncture increased along the three time intervals.

Current burden of HCV infection in Egypt during the last decade

Prevalence

Egypt had the highest HCV prevalence in the world; in 2008, according to the Egyptian Demographic Health Survey (EDHS), that was conducted on a large nationally representative sample, HCV prevalence was 14.7% in 15-59 year age group, 10% chronic infection, 90% genotype 4.(14) In Egyptian Health Issues Survey (EHIS) 2015, a significant reduction of 32% and 29% in HCV antibodies and HCV RNA positive individuals was reported respectively reaching 10% HCV seroprevalence and 7% viremia, in the same age group. EHIS included younger age group and a seroprevalence of 6.3% in 0-59 years age group was detected.(15) Table 1 summarizes the most important and recent surveys done in Egypt over the last decade.

Table (1): Egypt HCV prevalence results in recent surveys

Year	Prevalence (Ab)	Prevalence (RNA)	Sample size	Sample type	Age group (years)	Reference
2008	14.7%	9.9%	11 126	Multistage probability	15-59	EDHS [14]
2015	0.4% (95% CI 0.3-0.5)	0.2% (95% CI 0.1-0.3)	10 878	Multistage probability	1-14	EHIS 2015 [15]
	10% (95% CI 9.5-10.5)	7.0% (95% CI 6.6-7.4)	16 003		15-59	
2016	14.8% (95% CI 14.1-15.4)	8.8% (95% CI 8.3-9.3)	12 169	Governorate-based using probability proportionate to size	≥15	El-Ghitany et al. (In preparation)

In terms of numbers, nearly 5.3 million persons aged 1-59 years have HCV antibodies, of whom, approximately 3.7 million individuals (69.5%) have chronic HCV infection in 2015. This is an underestimation of the total human HCV reservoir in Egypt because older age groups (>59 years) were not included in the 2015 EHIS. Hence, unpublished results are included in table 1 that included all the Egyptians above 15 years that show a higher prevalence level than the 2015 EHIS. Lower Egypt governorates showed a prevalence ranging from 14.4% to 18.5%.[16, 17] The phenomena of increasing prevalence with age was evident in both surveys (2008, 2015), because of the continuing exposure with age. This clearly demonstrates the cumulative incidence over time till HCV-related morbidity and mortality becomes manifest; the rate of progression to cirrhosis was estimated at 7% after two decades of infection and the proportion of chronic HCV infected patients who progress to develop severe disease and die of it remains low until 30 years after infection.[18]

The significant reduction in prevalence between 2008 and 2015 surveys is apparent in all age groups, but is more profound, reaching 75% relative risk reduction, in the youngest (15-19 years). Considering the prevalence in this age group reflects the cumulative incidence over the past 20 years, there was a profound incidence reduction. The frontier governorates did not show any significant change, however, this is possibly owing to the fact that the sample size was very low (n < 200), in both surveys.[19]

Reasons beyond reduction may be related to ageing of the reservoir group, better infection control strategies, the directly acting antiviral drugs (DAAs) evolution. Finally, differential migration and mortality of persons infected with HCV could have contributed to the reduced prevalence of both HCV antibody and HCV RNA-positive persons in 2015, as long as these rates are higher than infection incidence[20, 21]; these topics needs to be explored further.[19]

Prevalence among high-risk groups

They include, but not limited to schistosomiasis patients, patients on hemodialysis, multi-transfused patients, IDUs, healthcare workers and barbers. Most of these groups are usually neglected when the HCV problem magnitude is estimated and future is predicted. High HCV prevalence rates were observed with averages of about 42% among multi-transfused children and about 58% among children with thalassemia. Regarding the prevalence among hemodialysis patients, 94.1% of them had HCV according to a study conducted in Mansoura Dakahlia, Lower Egypt[22], while the prevalence decreased to 70% in Cairo.[23] The burden of disease among healthcare workers is also high where HCV prevalence was about 17% in average.[22] Also it was found that the prevalence among barbers reached 12.3%.[24]

Incidence

Few studies in Egypt have addressed the estimation of incidence rate. They were done either through a long time follow up of a cohort of Egyptian regarding seroconversion of HCV antibodies or by mathematical modelling methods. The incidence rates among populations were; 6.8/1,000, 2.4/1000 and 0.8/1,000 person-years in rural villages in Qaliubyia[25], Menoufia[26] (lower Egypt) and Assiut[25] (upper Egypt) respectively. The incidence rates in specific groups such as children and pregnant women were 2.7/1000 and 5.2/1000 PY respectively.[27]

Another two studies built mathematical models to estimate the incidence of HCV in Egypt. In 2010, Miller and Abu-Raddad [28] built their model using age-specific prevalence extracted from a population based survey, EDHS 2008. The estimated incidence was 6.9/1,000 (95% CI, 5.5-7.4) PY. On the other hand, in 2013, another model was conducted to address the assumption of time-independent epidemiology to reach more realistic estimate. This model estimated the incidence of HCV nationwide at around 2.0/1000 PY.[29]

There is a considerable difference in the estimated incidence among different studies ranging from 0.8 to 6.9/1000 annually. In terms of numbers, it would correspond to a wide range from 100 000 - according to figures of the Egyptian Ministry of Health and Population (MOHP)- to more than 500,000 Egyptians –according to one modelling study- getting infected annually.[11, 28-30] The large number of incidence cases makes the problem ongoing and requires special attention.

Morbidity and mortality

Among patients with chronic HCV, 35%-45% will develop some level of progressive liver disease, and without treatment approximately 5%-10% will develop cirrhosis (10%-20% lifetime risk) and 1%-3% develop HCC.[31, 32] According to EHIS 2015, the prevalence of active hepatitis ranged from less than 1% in age groups below 20 and reached 22.1% among age group 55-59 years.[15] In 2013, the estimated HCV disease burden was 626,000 compensated cirrhosis, 137,000 decompensated cirrhosis, 16,100 HCC cases and 33,000 liver related mortality.[12]

Chronic HCV infection is also associated with several extrahepatic manifestations. Patients with HCV may develop mixed cryoglobulinemia and its sequelae, ranging from cutaneous and visceral vasculitis to glomerulonephritis and B-cell non-Hodgkin lymphoma. HCV-infected patients have increased rates of insulin resistance, diabetes, and atherosclerosis, which may lead to increased cardiovascular morbidity and mortality. Neurological

manifestations of HCV infection include fatigue and cognitive impairment. The mechanisms causing the extrahepatic effects of HCV infection are likely multifactorial and may include endocrine effects, HCV replication in extrahepatic cells, or a heightened immune reaction with systemic effects. Successful eradication of HCV was shown to improve some of these extrahepatic effects.[33] In one study, the estimated prevalence of extrahepatic manifestations among chronic HCV patients were; rheumatologic manifestations 16.4%, chronic fatigue syndrome 9.5%, sicca symptoms 8.8%, arthralgia 6.5%, fibromyalgia 1.9%, myalgia 1.3%, arthritis 0.7%, cryoglobulinemic vasculitis 0.7%, autoimmune hemolytic anemia 0.7% and thrombocytopenia 0.7%. Xerophthalmia was significantly present in male population, whereas fibromyalgia, cryoglobulinemic vasculitis, arthritis, and autoimmune hemolytic anemia were significantly present in female population.[34]

In rural Egypt, among 18,111 survey participants enrolled in 1997–2003, mortality rate ratios (MRR) of males with chronic HCV infection aged <35, 35–44, and 45–54 years were 2.35 (95% CI 1.00–5.49), 2.87 (1.46–5.63), and 2.22 (1.29–3.81), respectively. No difference in mortality rate was seen in older males or in females. The all-cause mortality rate attributable to chronic HCV infection was 5.7% (95% CI: 1.0–10.1%), while liver-related mortality was 45.5% (11.3–66.4%).[35]

Economic burden

Although the problem of HCV in Egypt is huge and ongoing, limited data regarding the economic and in-depth epidemiological burden of disease were found. Even with this limitation, the data available regarding the economic burden of disease in Egypt became outdated especially after the dramatic changes in the key inputs of the previously published models. The main changes were in the baseline data of the prevalence of HCV among the different age groups where the previous two published models used data from DHS 2008, however, a new DHS report was published recently in 2015. Also, new protocols of treatment were approved by MOHP which lead to dramatic changes in drug efficacy rather than that used in the previously published models, in addition to the most recent dramatic decrease in the drugs prices as well.[36]

During the past 2 years and since the introduction of DAAs to the hepatitis treatment protocol in Egypt, the Egyptian government spent around 2.8 billion L.E. (350 million US dollars) for HCV national treatment program. Almost 88% of treated patients were totally sponsored by the government (29% through the Heath Insurance Organization (HIO) and 56% through governmental support funds). The remaining 12% of patients were treated out of pocket at the reduced prices.[37]

Other types of disease burden:

Lack of awareness, stigma and inadequate counselling following diagnosis

Lack of awareness about hepatitis C in the community often leads to misinformation, missing of opportunities for prevention and treatment, and stigmatization of infected populations.[38] Patients with HCV face significant discrimination within the community, and that can occur also within the healthcare settings.[37] Level of support that someone with chronic hepatitis C might receive was less when compared to someone with a chronic illness that does not carry a stigma which might affect self-esteem and cause decrease in the quality of life [38] This stigma of the disease push 30.9% of the patients to conceal the nature of their illness and 24.4% of them even conceal this information from their families, according to a study conducted in Elghar village, Zagazig governorate.[39]

Corrections of malpractices following diagnosis were documented in Egypt, but also unnecessary restrictions were adopted which indicates inadequate counselling.[40]

Control efforts adopted by the Egyptian government during the last decade and their implications

HCV Model of Care (MOC) in Egypt

Although the magnitude of the HCV problem was known for many years, the HCV MOC only came into being in 2006 with the establishment of the National Committee for Control of Viral Hepatitis (NCCVH) to set up and implement a national control strategy for the disease and other causes of viral hepatitis. The strategy outlines best practices for patient care delivery by applying a set of service principles through identified clinical streams and patient flow continuums. The Egyptian national viral hepatitis treatment program is considered one of the most successful and effective public health programs. More than one million patients were evaluated and more than 850,000 received treatment under the umbrella of the program since 2006.

The NCCVH has been successful in establishing a strong infrastructure for controlling viral hepatitis in Egypt. It established a nationwide network of digitally connected viral hepatitis-specialized treatment centers covering the country map to enhance treatment access. Practice guidelines suiting local circumstances were issued and regularly updated and are applied in all affiliated centers.[37]

Milestones of developing the HCV MOC in Egypt[37]

In 2001, improvements in infection control practices over the years resulted in a decrease in the annual incidence of new HCV infection among dialysis patients from 28% to 6% in 2008.[41]

In 2006, NCCVH advisory board members are volunteering Hepatology and Public Health Professors in Egyptian Universities, a Ministry of Health representative, and included initially ad hoc experts from Pasteur Institute in Paris, France, and the University of California in San Francisco, U.S.A.

The initial target was to provide antiviral treatment for HCV-infected.

In 2007, the NCCVH established its first specialized centers for treatment of viral hepatitis within MOHP healthcare facilities. More than 54 centers were established between 2007 and 2016 providing care and treatment to nearly 800,000 chronic HCV-infected persons.

In 2010, a closed virtual private network (VPN), the National Network of Treatment Centers (NNTC), was founded to connect the viral hepatitis treatment centers to the head office.

The first strategy was developed for 2008-2012, with an annual budget of $80 million. Treatment was based on pegylated interferon (PEG-INF) in combination with ribavirin (RBV) for 48 weeks.[42] The strategy aimed to treat 20% of patients by 2012 under subsidized schemes; however, only patients with relatively higher chances of cure had access to treatment, and advanced liver care was not financially feasible.[43] Also, children were excluded from this strategy.[44]

In 2014, availability of DAAs at the reduced price of $300 per bottle (a reduction from $28,000 per bottle in the U.S.A. market) was ensured.

The Ministry of State for Administrative Development developed a web-based online registration system (www.nccvh.org.eg) once the DAA was registered in Egypt. By the end of November 2016, around 1,500,000 patients registered and received appointments through the web-based system. Helplines are available to answer patients' queries and receive complaints, if any.

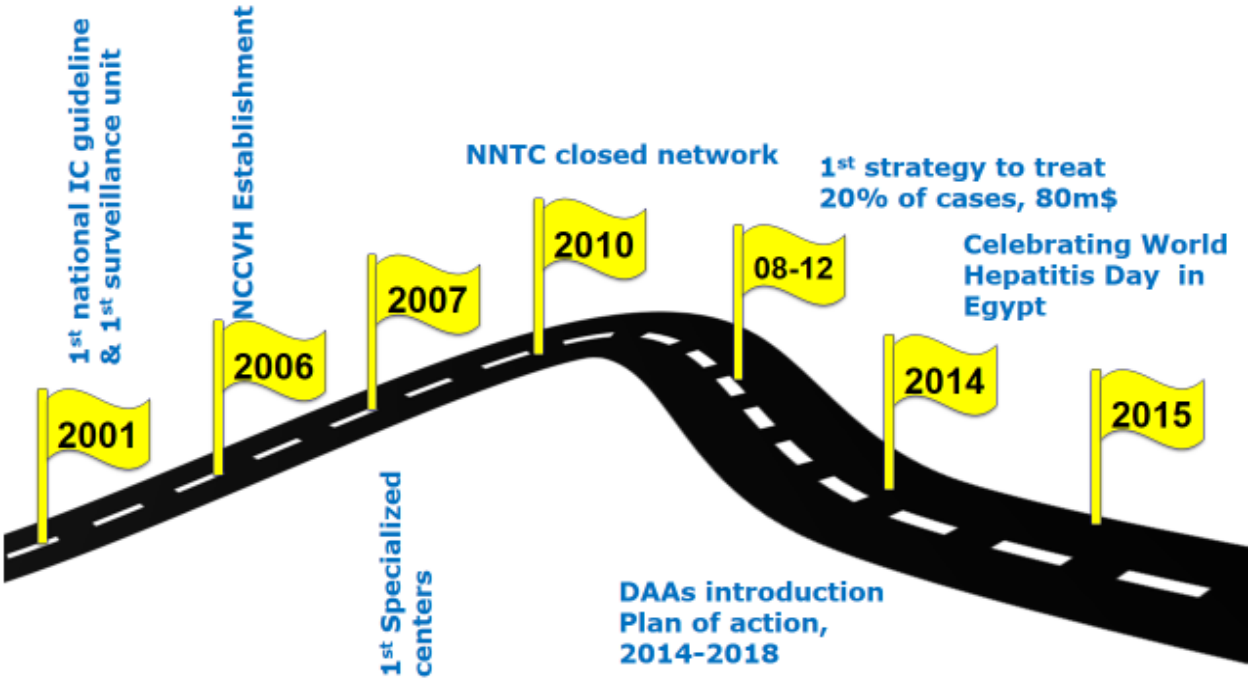

Figure 1: Milestones for developing HCV MOC in Egypt

Efficacy of oral DAA combinations

Using DAAs for treatment HCV-G4 has showed significant increase in cure rate where sustained virologic response (SVR) has reached nineties in some combinations. For example, in Doss et al. 2015, using sofosbuvir (SOF) + RBV among Egyptian patients with G4 for 24 weeks showed 92% and 89% SVR among naïve and experienced patients respectively; and SVR among cirrhotic and non-cirrhotic were78% and 93% respectively, with an average SVR 90%.[45]

Prevention

Various public health interventions were implemented by the MOHP and its partners since 2008 till 2011.[19,37] Efforts have been limited to;

- Promote and expand the infection prevention and control programs beyond MOHP hospitals, particularly to the university hospitals.
- Auto disabled syringes were introduced to the routine immunization sector in 2008 in order to promote safe injection practices among children.

- Safe blood transfusion activities, including policies and guidelines, have been intensified since 2009.
- Raising the awareness of the public, by targeting universities and schools to improve their understanding on the epidemiology and prevention of viral hepatitis, was also carried out (that reached close to 100,000 university undergraduates in different areas).
- Pre-service education targeting healthcare staff has been carried out since 2008 to enforce the concepts of safe healthcare and prevention of blood-borne pathogens.
- A vaccination campaign for hepatitis B was carried out that reached 30000 persons, and
- Limited media awareness campaigns.

"Plan of Action for the Prevention, Care and Treatment of Viral Hepatitis, Egypt, 2014-2018" (MOHP, 2014) was established and supported by World Health Organization (WHO), Center of Disease Control and Prevention (CDC) in U.S, NAMRU-3, and Institut Pasteur/Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS) for building a comprehensive national strategy for prevention and control of HCV.

This was followed by the WHO selecting Egypt as one of the three countries to be supported for the global injection safety program and celebrating the global world hepatitis day in 2015 in Egypt.

The plan of action is composed of seven pillars to ensure efficient prevention and control of viral hepatitis.

The first pillar aimed to strengthen national surveillance system for viral hepatitis. **The second pillar** is focused on infection control to decrease transmission. **The third pillar** focused on blood safety. **The fourth pillar** is focused on vaccination against hepatitis B. **The fifth pillar** is concerned with raising community awareness. **The sixth pillar** is ensuring availability and accessibility of effective drugs for treatment of viral hepatitis. **The seventh pillar** is concerned with scientific research.[46]

Future of HCV infection in Egypt

Few studies predicted the future of HCV infection in Egypt based on different scenarios. Using Markov simulation modelling techniques, HCV infection was projected to yield 750,210 PY of decompensated cirrhosis, 132,894 PY of hepatocellular carcinoma producing 127,821 deaths from cirrhosis and 117,556 deaths from HCC from 2009 to 2028, prematurely ending 32.86 million years of life compared to a non-infected cohort.[30]

Looking forward for the best scenario, assuming increasing the drug efficacy (90%) and treatment eligibility (90%), in addition to increasing the treatment rate to reach 325,000 patient by 2018, the total number of infection, compensated and decompensated cirrhosis, HCC and HCV related mortality would be 280000, 76000, 17000, 2400 and 7500 respectively.

The second study developed Markov model to model the transition of HCV infected cohort among different age groups using Egyptian DHS 2008 through following them up over time. The results showed that while treating 300,000 - 450,000 patients, the expected total viremic HCV cases will reach 1,000,000 cases by 2030, number of liver related deaths will be lower than 15,000 deaths, and the number of patients with cirrhosis will decline by 87 % to reach about 100,000 cases by 2030.[47]

Regarding the economic burden, it is predicted in one study that the cumulative total costs, including direct and indirect costs, would be US $ 57,562,482,460 in 2030, decreasing by 35.4% compared to 2013.[48]

In another study that used a Markov model, under the management strategy of 125,000 patients/ year, it was estimated that chronic active HCV patients will show minimal decrease to reach about 4.1 million cases, with high economic burden of this strategy where the direct costs are estimated $23.3 billion, and the total costs are $48.3 billion between 2015 and 2025. While increasing the treatment rate to reach one million patient annually for 5 years in addition to decreasing the annual incidence in the coming 10 years will drop HCV cases to about 636 thousands by 2025, and with only $16.2 billion as a direct costs, and total costs $34.2 billion between 2015-2025 which is 29.2% lower than the current management scenario.[36]

Challenges facing HCV infection elimination in Egypt

HCV infection is thought to be eliminated globally in the next 15–20 years.[49] Although it is an achievable target in Egypt, it has to be focused on three strategies; prevention of new infections, screening and cure current infection. The potential challenges have to be understood and promptly managed.

✓ ***Social and community challenges***

HCV is a social disease in Egypt that is impacted by the social determinants of health (SDH). HCV prevalence was found higher in illiterate people (14.5%) while it was much lower among people who have completed secondary education and higher (4.1%).[14] Illiteracy was also associated with poor knowledge, attitude and practice (KAP).[40, 50] There is a poor KAP of the community and inadequate counselling by health care workers. The knowledge has shown evidence of improvement during the last few years. It was described as poor in a KAP study done in 2012 that measured all aspects of HCV infection.[40] Another study in 2016 described the knowledge as satisfactory, but it only measured the

knowledge regarding the mode of transmission, and yet one third of participants did not know how HCV is transmitted.[50] Both studies showed negative attitude towards infection. While counselling improved knowledge dramatically, it failed to show an effect on attitude.[40] This suggests that efforts beyond providing knowledge should be sought for to improve people's attitude towards HCV infection.

Calling for a legalization that prohibits discrimination against HCV-infected patients was addressed by the NCCVH in the National Council. It invited discussions to consider it illegal to discriminate against people on the basis of disability caused by an infectious disease, except where discrimination is necessary to protect public health. Similar laws exist in the U.K. and U.S.A. People with hepatitis C are entitled to receive the same level of access to medical treatment as other members of the community.[37]

✓ ***Prevention challenges***

- Absence of post-infection immunity makes a possibility of reinfection after treatment or spontaneous cure.
- Unavailability of vaccine; the development of an effective HCV vaccine is hampered by several factors. First, HCV is characterized by an extraordinary genetic variability resulting from the lack of proofreading activity of the NS5B RNA-dependent polymerase.[51] This determines an impressive error rate per replication cycle that, in combination with the short viral half-life and the rapid turnover, leads to the generation of multiple distinct but closely related HCV variants, known as "quasispecies," in one infected subject. Mutated viruses have the ability to persist in infected people by escaping immune control of cytotoxic T lymphocytes (CTL) and antibodies against different regions of the viral envelope.[52, 53] On the basis of some promising data obtained in phase I clinical trials, different types of prophylactic HCV vaccines are approaching phase II and phase III clinical trials.[54]
- Some high risk groups are neglected in terms of screening and treatment. This underestimates the problem magnitude and ignores a considerable reservoir. They include IDUs, HIV patients, homosexuals, homeless children, prisoners, etc.
- Provision of adequate public health infrastructure.
- Sustainability of political and societal will, and national and international organizations support.
- Strengthening and maintenance of strict infection control measures.
- Training and awareness of health staff.

✓ ***Diagnostic challenges***

- Diagnosis of HCV infection in Egypt is usually accidental (49% of diagnosed cases) or after symptoms due to liver insult appear (47.6%). Only 3.4% of patients are diagnosed actively [50] Globally, 15% of chronic HCV patients are unaware of their infection.[55]

Providing a strong scientifically based cost-effective screening strategy is a challenge. According to a television interview with Professor Wahid Doss in July, 30, 2017, he stated that till that time, 1,600,000 patients have been treated, but approximately 3000,000 are still looked for. Together with the incidence rate we mentioned earlier, and the estimated basic reproduction number (R_0) of 3·54 (95% CI 1·28–6·18)[56]— which corresponds to the number of new infections that an index case generates in an uninfected population, efforts to prevent HCV from being self-sustained are mandatory. Therefore, one important thing is that effective screening strategy must be adopted. Recently, the state has paid attention to this issue and started screening efforts through "Tahya Misr Fund" in conjunction with private sectors funds. There are many campaigns in some organizations, villages, healthcare workers, etc. From the author's perspective, these efforts are random and lack a clear scientific basis. Unless there is the ability and feasibility to screen every citizen, a risk-based approach has to be followed. This strategy is well followed by both wealthy and less privileged countries in many infections including HCV. If every Egyptian citizen > 15 years old is screened with a minimal cost L.E. 20/test, the total budget would exceed L.E. 1.2 billion. In U.S.A., CDC recommends HCV screening for baby boomers, persons who were born during 1945-1965 because they are 5 times more likely to have hepatitis C than other adults.[57]

An effective risk-based HCV screening tool tailored to Egyptians (EGCRISC) has been developed, validated and showed a good performance.[58-60] The cost analysis of EGCRISC use as a screening tool versus mass screening showed that, applying EGCRISC would save LE 0.44 billion accounting for about 21 646 227 unnecessary tests and would only miss about 69 660 cases. This estimation is based on a minimal cost of 20 L.E./test and the population census in January 2015 and did take into account the population growth.[61]

- Using an accurate and feasible test for HCV diagnosis.

✓ ***Therapeutic challenges***

Despite the very successful and unique Egyptian MOC through which a highly effective treatment is readily provided to HCV patients, on the state expense, upon request, there are still barriers that must be met;

- Cost; despite the massive reduction in cost relative to the global price particularly after the local production of directly acting antivirals (DAAs), there is still a question of the continuity of the free of charge care for the patients.

- Drug resistance; the efficacy of DAAs is very high in terms of SVR; nonetheless 10–15% of therapeutic failure is observed in clinical practice, mainly associated with the selection of DAAs-resistant viral variants, resulting from mutations produced by amino acid substitutions in the target virus protein that reduce viral sensitivity to DAAs. Resistance-associated variants (RAVs) may be present, despite being usually at low levels even before the beginning of DAAs treatment due to the great genetic variability of HCV.[62]
- New drugs development and therapeutic vaccines; research efforts for the development of alternative therapeutic options have been made contextually to the development of DAAs and the research on preventive vaccines. To date, several approaches have been adopted in the development and production of HCV therapeutic vaccines including peptide vaccines, recombinant protein vaccines, DNA vaccines with different carriers, and virally vectored vaccines.[63]
- Application of DAAs in children.

The coming wave of HCV-related liver disease

For some years, HCV-related morbidity will continue even after virus elimination as can be predicted from its natural history.[55]

Conflict of Interest: None to declare.

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