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Review Article: Egyptian Efforts to Control Hepatitis C Virus in Egypt

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ABSTRACT

Worldwide, hepatitis C virus (HCV) represents a great risk to public health and is associated with life-threatening outcomes. Since Egypt historically has the highest HCV incidence rates in the world, this virus is providing serious social and economic issues to millions of Egyptians. For HCV combating, the Egyptian nationwide HCV elimination program considered as achievement prime example, having cured over 90% of HCV Egyptian infected patients. Thus, it is markedly reducing the disease's prevalence and incidence. Other African countries with similar HCV prevalence and incidence rates might greatly benefit from Egypt's program, which give flexible frameworks and important insights. The aim of this review is to shed the light on the Egyptian program challenges and successes in combating the great HCV public health problem.

Keywords: HCV, Egypt, Direct acting anti-viral agents, NCCVH.

1. INTRODUCTION

Hepatitis C virus (HCV) is a kind of positive-sense RNA tiny enveloped (55-65 nm in size) virus that is a member of the genus Hepacivirus and the Flaviviridae family [1, 2]. According to the World Health Organization (WHO), more than 350000 individuals are estimated to be dying each year from diseases and complications related to HCV, and more than 58 million persons have a chronic HCV (CHC) infection [2, 3]. In Egypt, hepatic disorders have been a serious health issue for thousands of years [4, 5]. With HCV discovery and serological methods availability, it became apparent that Egypt has the highest prevalence levels in the world and HCV was causing most liver disease in the country [5, 6]. Egyptian epidemiological reports in 2008 and 2015 demonstrated high HCV incidence rates, with about 10-15% of

the national population being HCV seropositive and 10% chronically infected and accounting for 7.6% of the country's mortality [5]. HCV prevalence in rural Egypt (reaching 24%) was very high which compared to other global areas like the United States (about 10-20 fold) [5]. From Egyptian patients, HCV-genotype 4 (G4) represented >90% of HCV isolates [5, 7].

Parenteral national anti-schistosomal therapy during 1950s-1980s, primarily using reusable glass syringes that were not properly sterilized, was the primary cause of HCV high prevalence in Egypt. Even when oral schistosomal therapy took its place in the 1980s, the disease continued to spread because of inadequate blood safety protocols, equipment sterilization, and infection control practices in the healthcare system at the time [8, 9].

2. The NCCVH establishment

In response to the increasing prevalence of viral hepatitis in Egypt, the Egyptian Ministry of Health and Population (MOHP) founded the National Committee for the Control of Viral Hepatitis (NCCVH) in 2006 with the responsibility of creating and carrying out a national strategy to battle HCV [10-12]. The board of NCCVH is composed of volunteer stakeholders and experts from several majors, involving policy-makers, pharmaceuticals, epidemiologists, infectious disease specialists and gastroenterologists /hepatologists. In order to raise public awareness, improve treatment outcomes and decrease hepatitis prevalence, the NCCVH set the required plans for viral hepatitis management. After accurate epidemiological data collection, they set guidelines of HCV treatment and recommendations for the best infection control and disease management [5, 13]. Of the population, 65% were paying out-of-pocket, 30% received coverage by the national health insurance and only 5% were covered by private insurers. Thus, regardless of their financial ability, the Egyptian government agreed to treat, at the state expense, all uninsured HCV cases so that all cases will have access to HCV treatment [5].

3. Interferon (INF) treatment national program

Since 1986, CHC patients have been treated with IFN-α monotherapy. The sustained response rate (SVR), however, is only roughly 8-9% [14]. In the CHC treatment, ribavirin (RBV) subsequent introduction in combination with IFN-α has significantly improved the treatment SVR [14, 15]. For decades, the HCV standard of care is consisting of a combination of pegylated IFN-α (PEG-IFN) with RBV as this strategy showed more efficacy over both standard IFN and PEG-INF monotherapy [15, 16].

At first and during IFN treatment era (before 2014), Egyptian HCV patients were treated by qualified gastroenterologists and hepatologists with experience in IFN therapy and its related side effects at specialized IFN treatment centers that established by the NCCVH. By 2014, there were 26 centers, up from just one in 2007 [5, 12]. In Egypt, in patients with HCV, dual therapy with PEG-INF/RBV for 48 weeks had been the standard of care before the advent of direct acting anti-viral agents (DAAs) [17]. The SVR rates for such treated patients ranged from 40-50% [18], depending on insulin resistance [19], IL-28B genotype [20], baseline viral load, HCV genotype [21], adherence to the treatment regimen [22] and patient's fibrosis scores [18] were the primary variables that predicted response [5]. In patients without liver fibrosis or cirrhosis, a worldwide study with real-life data reported higher SVR rate (41.5%) compared to patients with cirrhotic liver (27%) [18]. In Egyptian HCV patients HCV G4, similar SVR rates were obtained [23].

Because of the extremely low SVR rate (27–41%), the NCCVH chose to solely treat cases with with biopsy-confirmed F2-3 fibrosis stages only. When better treatment alternatives became available, HCV cases with F1 fibrosis or no fibrosis were postponed. At this time, cases with high body mass index (BMI), aged over 60, with a history of treatment failures, and with fibrosis stages F4 were not eligible for treatment [24]. Between 2007 and 2014, the Egyptian government's HCV treatment strategy treated almost 350000 patients with low SVR (45-55% as revealed in actual data from Egypt) [12, 24].

PEG/RBV dual treatment was related to notably side effects that often cause early discontinuation and poor adherence of therapy, including anemia, depression, fatigue, flu-like symptoms and some hematological abnormalities [25]. Furthermore, PEG/RBV therapy had several contraindications, such as decompensated cirrhosis [26]. During the period 2007-2017, there were >200000 PEG/RBV treatment failures and 300000 were postponed owing to the presence of cirrhosis or absence of fibrosis. This caused a pool of >700000 untreated HCV cases waiting introduction of novel antiviral therapy [5, 12].

4. DAAs combination with PEG/RBV

Both telaprevir (TVR) and boceprevir (BOC), 1st generation NS3/4A protease inhibitors, were approved in 2011 for HCV-G1 treatment in combination with PEG/RBV, but these treatments were not effective in HCV-G4 [17, 27]. The first Food and Drug Administration (FDA) approved oral DAAs in 2013 that effectively treat HCV genotype 4 were sofosbuvir (SOF) and simeprevir (SMV). They are inhibitors for nucleotide polymerase and protease, respectively [28, 29]. After that the FDA approved, in 2015, an NS5A inhibitor [daclatasvir (DCV)] [30]. Owing to its high barrier to resistance, SOF was launched in a new era of genotype 4 treatment as a powerful polymerase pangenotypic inhibitor [31]. In treatment-naive HCV-G4 cases, the combination of PEG/RBV treatment with SOF for 12 weeks leads to SVR rate of almost 96% [32]. Another American study that involved Egyptian HCV cases with genotype 4 revealed favorable findings after SOF/RBV therapy (SVR of 59 and 79% in treatment-experienced and treatment-naıve cases, respectively) [33]. In Egypt, other studies after that evaluated the RBV or SOF+PEG/RBV treatment efficacy for HCV-G4. The SVR improved to 40% in prior non-responders, to 86% in prior relapsers and to 83% in HCV-G4 treatment-naive cases after using SMV (once a day for 12 weeks) with PEG/RBV for 24-48 weeks [34]. In HCV-G4 cases, in contrast to standard PEG/RBV treatment for 48-weeks (SVR of 50%), adding oral daily DCV of dose 20 and 60 mg for 24weeks to PEG/RBV therapy enhanced SVR rates to 67 and 100%, respectively [35]. Owing to such findings, the Egyptian NCCVH introduced SOF-based therapy to the national treatment program (Table 1) by the 2014 end, followed by DCV and SMV treatment regimens [36].

Table 1. Approved HCV-G4 treatment regimens before INF free DAAs regimens [25, 32, 37, 38].

Year	Treatment regimen	SVR%
2001	PEG/RBV×48 weeks	42-46
2013	PEG/SOF×12 weeks	96

5. IFN-Free DAAs

The limited PEG/RBV tolerability and efficacy have prompted the development of several DAAs that target HCV replication certain proteins. For all HCV genotypes, liver disease stages and comorbidities, IFN-free regimens became available with additional approved DAAs (Table 2) [39]. For HCV-G4 treatment, 25 mg ombitasvir (OBV), 100 mg ritonavir (r) and 150 mg paritaprevir (PTV) were used [40]. Ritonavir is CYP2D6 and CYP3A4 inhibitor, which is used to reduce paritaprevir breakdown allowing lower dose use [41]. Ombitasvir had pan-genotypic antiviral activity and it is an NS5A inhibitor [42]. Paritaprevir is NS3/4A serine protease inhibitor [43].

Compared to the US market (28000 USD), and owing to their efforts with Gilead Sciences, the NCCVH succeeded in a significant 99% SOF price reduction (300 USD for a 28 pills bottle enough for a dose of four-week). Negotiations with other manufacturers of DAAs caused comparable price decrease; a 4-week supply cost of SOF/ledipasvir (LDV) and PTV/OBV to 400 and USD 300, respectively and DCV and SMV was decreased to USD 250 each [5, 12].

The government in Egypt, in 2016, urged domestic pharmaceutical businesses to generate generic DAAs at a price fraction of those produced abroad. The 12-week SOF-DCV therapy cost for the National program reduced from original 900 USD to <100 in 2018 compared to 300 in 2016. The widespread usage of generic DAAs made the therapy accessible and affordable, resulting in a markedly decrease in the HCV burden [5, 12].

Table 2. DAAs general features [25].

DAAs	Antiviral efficacy	Genotypic coverage	Resistance barrier	Drug interactions	Side effects
Inhibitor of NS3/4A protease (1st generation)	++	Genotype 1	+	+++	+++
Inhibitor of NS3/4A protease (2nd generation)	+++	Multiple genotypes	++	++	+
Inhibitor of NS5A replication complex	+++	Multiple genotypes	++	++	+
Inhibitor of NS5B nucleotide polymerase	+++	All genotypes	+++	+	+
Inhibitor of NS5B non-nucleoside polymerase	++	Genotype 1	+	++	++

NS: nonstructural protein; +++: significant; ++: intermediate; +: minimal

6. The NCCVH national DAA treatment program

The international health organizations, regional pharmaceutical companies and the Egyptian government worked together to create the DAA national treatment program [44]. Because it was successful in addressing a significant health concern, this national HCV treatment program in Egypt, launched in October 2014, has gathered international recognition [44, 45]. After IFN-based treatment, there were >1000000 HCV cases waiting for the new antiviral drugs. These included >200000 previous treatment failures, patients with severe obesity, with decompensated cirrhosis, patients with F4 fibrosis and without significant fibrosis (F0-1) who were not considered for IFN therapy [5]. The developed NCCVH's comprehensive strategy [13] included the following:

Education and public awareness: increasing public knowledge about HCV prevention and transmission. To educate the public about the disease, how it spreads, the screening value, safe medical procedures, and accessible treatments, awareness-raising educational initiatives were started.

Diagnosis and screening: Putting in place extensive screening programs by starting nationwide mass screening campaigns that aim to identify HCV in high-risk groups, such as those engaging in high-risk behaviors and those over 18 years old.

Treatment Access: By negotiating the production of generic DAAs with local pharmaceutical companies, Egypt was able to drastically lower treatment costs. The illness burden was significantly reduced as a result of therapy's affordability and accessibility being ensured by the generic DAAs use.

Healthcare infrastructure: Improving the healthcare system to facilitate diagnosis, treatment, and aftercare. Specialized treatment facilities with the required infrastructure and qualified medical staff were set up all around the nation. To track patients' development and guarantee the effectiveness of treatment, a strong monitoring and assessment system was implemented.

The Egyptian patients were evaluated for treatment at facilities supervised by the Health Insurance Organization (HIO) or the NCCVH. The daily schedule and workload were modified in accordance with the capability of each center. Appointment confirmations were sent to patients by text message and the web site. A total of 103000 cases were signed up for therapy on the first day of the portal's opening.

Within the first month, this figure increased to over 500000, and by the end of November 2016, it had reached almost 1500000 [5].

All cases underwent an abdominal ultrasound, viral load testing, blood counts, biochemical tests and clinical examinations. To confirm efficacy in HCV-G4, local clinical studies were carried out before any new generic DAA was included to the national HCV treatment program [46-50]. As a part of the first treatment protocol, treatment-naive cases without liver cirrhosis got a 12-week course of SOF+PEG/RBV, whereas cases with earlier failed PEG/RBV therapy or cases with liver cirrhosis were received a SOF/RBV 24-week course. SVR12 rates were 78.7 and 94%, respectively, in cases got SOF/RBV and SOF+PEG/RBV, according to real-world data [51]. By the middle of 2016, all patients had been assessed and started therapy within a week of enrolling on the portal thanks to an expanded supply of medications, locally produced generics, and more treatment facilities [5, 52].

More than 150,000 Egyptians started therapy with SOF based programs, which were the only DAA accessible till 3-2015. For cases without cirrhosis, a 12-week SOF/SMV program replaced the standard (SOF+PEG/RBV) after SMV registration. Before DCV was launched, the SOF/RBV 24-week course for cirrhosis patients stayed the same. Since the DCV cost was lower than SMV, its supply was designated for individuals with renal impairment once it became available [5, 12].

Locally made DCV and SOF subsequent availability guaranteed a sufficient and steady supply of these important drugs. Cases who had failed prior treatments or had a FIB-4 > 3.25 were classified as "difficult to treat" and received a 12-week course of SOF+DCV/RBV (or SOF/DCV for 24 weeks if they were RBV-intolerant or had decompensated cirrhosis to improve efficacy), whereas cases without cirrhosis who were new to treatment were classified as "easy to treat" and received 12 weeks of SOF+DCV [53, 54]. For SOF-containing regimens, the real-world SVR rates were 98.5, 97, 83 and 94% with SOF+DCV, SOF+SMV, SOF+RBV and SOF+PEG/RBV, respectively [50, 55]. Patients who experienced failure to DAA regimens were retreated with SOF+SMV+DCV or SOF-paritaprevir-ritonavir-ombitasvir treatments with RBV unless they had heart problems or anemia and were RBV-intolerant [5].

Although more than two million HCV cases had initiated treatment by 2018, the monthly new cases registration dropped to <10000, which is far less than what is required to treat roughly 350000 cases annually to reach the eradication aim [56].

7. The 2018 Egyptian national program

The Egyptian government was encouraged to change its approach from the disease control to HCV eradication because of the national treatment strategy (2014-2018) success [44]. Within one year, and to screen every Egyptian one aged ≥18 year old (about 62.5 million persons), the Ministry of Health and the NCCVH established a thorough nationwide screening campaign and set their goals and provide treatment for all patients with HCV viremia. In May 2018, planning started and the nation was divided into 3 screening phases (2-3 months/each, 7 to 11 states/each, population of 17.9-23.3 million/each). Additionally, they sought to detect and treat undiagnosed hepatitis C in 12 million adolescent students enrolled in high and middle schools [44].

In a blood-drop, to detect anti-HCV in initial screening, a low cost rapid test for HCV antibody (about 0.56 USD) with immediate results was used. Immediately, findings were registered electronically to a central database and cases with positive HCV results were registered for additional assessment at the nearest treatment centre. This involved an abdominal ultrasound, low cost HCV-RNA testing (< 5 USD), blood counts, biochemical tests (including liver tests) and clinical examinations. Among 50 million cases screened for antibodies, about 2.4 million were seropositive and 1.6 million from them were diagnosed as viremic cases and treated against HCV. Over a period of 7 months, HCV cases received a course of 12 weeks SOF/DCV with or without RBV (SVR was >98%) [5, 12, 44].

Regarding the teenage population, the results were not communicated to the school staff or students to prevent stigmatization. Instead of this, results were mailed to parents. At health insurance clinics, children with positive HCV results were scheduled for evaluation and treatment. Among 7 million registered teenagers, about 20000 were identified as seropositive. The SVR rate was 100% among these children. Around the world, this effort was the 1st teenager treatment and screening program for HCV [12].

8. The national program outcomes

After national DAA program (initiated in 2014) and the national treatment and screening program (during 2018-2019), almost > 4 million HCV cases were treated using SOF-based therapy, with SVR rates around 95-98% [12, 13]. The Egyptian treatment timeline, patient inclusion criteria, and different approved treatments from beginning the national PEG/RBV program in 2007 till reaching the WHO "gold-tier" grant of near HCV eradication in 2023 were outlines in Figure 1. Of the Egyptian population HCV incidence is estimated to reduce to <0.5% (<400000 patients) in 2021 compared to 6% (5 million patients) in 2015. Egypt reached all WHO elimination aims: diagnosis of >90% of all HCV cases, offering treatment for >90% of them and a treat for >95% of these cases [5]. Furthermore, the total number of HCV positive cases is expected to reduce by 86% in 2030, leading to the prevention of 250000 new infected persons during 2020-2030, and the national program would result in preventing >150000 new cases of hepatocellular carcinoma (HCC) and about 250000 HCV-related mortalities and consequently averting > one million disability-adjusted life years (DALYs) [57, 58].

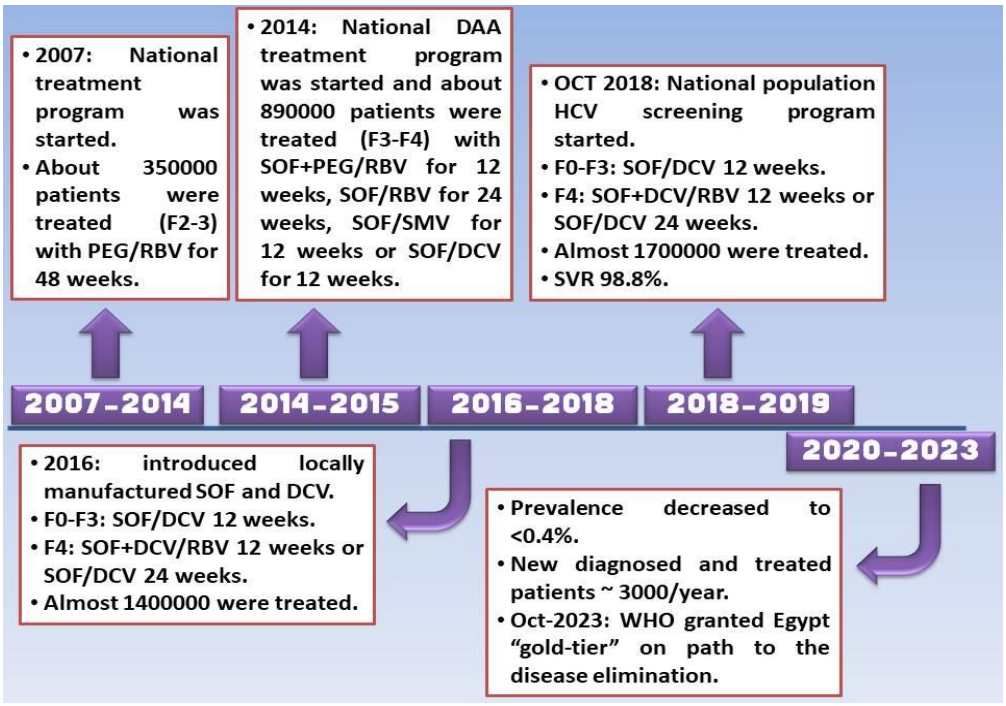

Figure 1. Egyptian HCV treatment programs timeline (2007-2023) [5].

A survey with a nationally representative sample (20881 individuals) was conducted in 2022 by The MOH to verify the National Screening and Treatment program effectiveness. Compared to 2015, they reported that the HCV incidence had decreased by 93% as only 0.4% (only 92 cases) was HCV-infected [59].

9. CONCLUSION

Significant improvements in public health can be obtained and millions of fatalities can be prevented if HCV infections are eliminated by 2030. To achieve these aims, much of what's needed are already exists. Despite the difficulties involved, the Egyptian national HCV program is an example of a successful method to achieve this aim. To decrease related-death numbers and HCV associated morbidity, it is very important to take lessons from Egypt's historic achievement. The HCV prevalence in our nation has reduced to 0.4% in 2021 compared to 7% in 2015 with very significant economic effect.

10. CONFLICT OF INTEREST

There is no conflict of interest.

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