High Institute of Public Health
Department of Tropical Health

Screening for Hepatitis C among High Risk Groups in Egypt. Validation of a Developed Short Risk Assessment Screening Tool

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AASLD	**:**	American association for the study of liver disease
ART	**:**	Antiretroviral therapy
AUC	**:**	Area under the curve
CDC	**:**	Centers for disease control and prevention
DAAs	**:**	Direct acting antiviral agents
EDHS	**:**	Egypt demographic health survey
EGCRISC	**:**	Egyptian HCV risk screening tool
EHIS	**:**	Egypt health issues survey
EIA	**:**	Enzyme immunoassay
ELISA	**:**	Enzyme linked immunosorbent assay
EMA	**:**	European medicines agency
FSWs	**:**	Female sex workers
G	**:**	Genotype
HCC	**:**	Hepatocellular carcinoma
HCV	**:**	Hepatitis C virus
HCW	**:**	Health care worker
HIPH	**:**	High Institute of Public Health
HIV	**:**	Human immunodeficiency virus
IDSA	**:**	Infectious diseases society of America
IDUs	**:**	Illicit drug users
MSM	**:**	Men who have sex with men
NA	**:**	Narcotic anonymous
NIDUs	**:**	Non-injecting drug users
NIH	**:**	National institutes of health
NPV	**:**	Negative predictive value
NS5A	**:**	Non-structural 5A
NSI	**:**	Needle-stick injuries
PCPs	**:**	Primary care physicians
PCR	**:**	Polymerase chain reaction
PEG-IFN	**:**	Pegylated interferon
PLWHA	**:**	People living with HIV/AIDS

PPV	**:**	Positive predictive value
PWIDs	**:**	People who inject drugs
RBV	**:**	Ribavirin
ROC	**:**	Receiver operation coefficient curve
SE	**:**	Sensitivity
SHWs	**:**	Slaughter house workers
SP	**:**	Specificity
SPSS	**:**	Statistical package for the social sciences
STIs	**:**	Sexually transmitted infections
SVR	**:**	Sustained virological response
UNAIDS	**:**	United nations programme on HIV/AIDS
US	**:**	United States
USPSTF	**:**	US preventive services task force
WHO	**:**	World Health Organization

INTRODUCTION

Hepatitis C virus (HCV) is one of the most common blood-borne pathogens which constitutes a major public health problem and represents a leading cause of death and morbidity worldwide.[1]

Most HCV cases (80%) develop chronic infection; of them 3%–11% will develop liver cirrhosis within 20 years with the probability of progression to liver failure, hepatocellular carcinoma (HCC) and death.[2-4]

Factors that may be associated with a more progressive course include older age at acquisition, male gender, comorbid medical conditions such as heavy alcohol use, human immunodeficiency virus (HIV) infection, other associated chronic liver disease and longer duration of infection.[5]

HCV infection can also cause fatigue and decreased quality of life in the absence of cirrhosis or other complications.[6-8] Hepatitis C related end-stage liver disease is the most common indication for liver transplantation among adults in the United States (US) corresponding to more than 30% of cases.[9]

The recent estimates of global prevalence of HCV-Ab was estimated to be 2 % (1.7% –2.3%) corresponding to 104 (87–124) million among adults and 1.6% (1.3% –2.1%) corresponding to 115 (92–149) million infections for all ages. Regarding the viraemic prevalence it was 1.4% (1.2% –1.7%) and 1.1% (0.9% –1.4%) among adults and all ages which accounted for 75(62–89) million and 80 million (64–103) respectively. [10]

Thirty-one countries accounted for 80% of total viraemic infections; of them: China, Pakistan, Nigeria, Egypt, India and Russia accounted for more than half of total infections.[10]

The most prevalent genotype worldwide is genotype G1 (49.1%), followed by G 3 (17.9%), G 4 (16.8%) and G 2 (11.0%). G 5 and 6 are responsible for the remaining < 5%. G 4 and 5 mainly present in lower-income countries. [11]

North Africa/Middle East has an estimated prevalence in the general population of 2.7%, corresponding to 12.7 million of cases. The countries with the highest prevalence include Egypt (14.7%), Iraq (3.2%) and Yemen (2.2%). On the other hand, the countries with the lowest prevalence include Qatar (0.9%) and Turkey (1 %).The most predominant genotype in North Africa/Middle East is the G 4 (65.3%), followed by 1 (27.3%) and 3 (6.3%). Most of G 4 cases (93.1%) are derived from Egypt.[11]

In response to the increasing medical and economic burden of HCV on the health, the landscape of HCV antiviral therapy has changed rapidly in the past three years. Between 2001 and 2011, the standard treatment for chronic HCV infection was a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) with a sustained virological response (SVR) of up to 40% to 50% in G 1 and up to 70% to 80% in G 2 and 3. However, it was associated with constitutional, neuropsychiatric, autoimmune and hematological side effects. [12]

This resulted in the development of new therapeutic strategies (direct acting antiviral agents (DAAs) that target specific proteins involved in HCV replication. In May 2011, boceprevir and telaprevir, two first-generation protease inhibitors, were approved in combination with PEG-IFN and RBV (triple therapy) for 24 to 48 weeks in HCV G1 infections. Although triple therapy, improved the SVR to 60% - 75% in G1 treatment-naive patients, it remained suboptimal (30% to 40%) in patients with cirrhosis and was associated with additional side effects. Nevertheless, the use of triple therapy is associated with a heavy pill burden, complex dosing schedule and numerous drug interactions, even though the treatment duration could be shortened.[12]

In December 2013, simeprevir, a second-generation protease inhibitor, was approved for use with PEG-IFN and RBV for 12 weeks in G 1, while sofosbuvir, a nucleotide polymerase inhibitor, was approved for use with PEG-IFN and RBV for 12 weeks in G 1 and 4, as well as with RBV alone for 12 weeks in G 2 and for 24 weeks in G 3. Sofosbuvir combined with simeprevir or an NS5A replication complex inhibitor (ledipasvir or daclatasvir) with or without RBV for 12 weeks in G 1 resulted in a SVR >90%, irrespective of previous treatment history or presence of cirrhosis.[12]

In 2014/2015, seven new DAAs obtained the approval of the European Medicines Agency (EMA), and interferon-free treatments became available.[13] Three classes of DAAs exist: protease inhibitors (anti-NS3/4A), RNA-dependent polymerase inhibitors (anti-NS5B) and NS5A inhibitors, which are characterized by different antiviral potency and barrier to resistance and therefore are usually combined in different treatment schedules. Treatment regimens are determined according to HCV genotype and stage of liver disease, with duration ranging between 12 - 24 weeks, with excellent efficacy and safety that reach up to 95% in most patient groups. Finally, these IFN-free regimens can be safely used among subjects who were formerly contraindicated to antiviral therapy, such as decompensated cirrhosis and solid organ transplant recipients.[14]

The World Health Organization (WHO) has recently formulated the "Global Health Sector Strategy on Viral Hepatitis, 2016-2021" a strategy that contributes to the achievement of the 2030 agenda for sustainable development. The strategy addresses all five hepatitis viruses (A, B, C, D and E), with a particular focus on hepatitis B and C, owing to their relative public health importance. This new strategy targets to eliminate HCV as a public health threat by 2030. [15]

Risk factors for HCV infection include past or current injection drug abuse, long-term hemodialysis, receipt of blood transfusion before 1992, being born to an HCV-infected mother, tattooing, high risk sexual behavior (multiple sex partners, unprotected sex, sex with an HCV-infected person or injection drug user), incarceration, healthcare professionals dealing with blood and blood products via needle stick injury, organ transplants from HCV-positive donors as well as the use of blood contaminated straws for cocaine snorting.[16, 17]

There is no vaccine or post-exposure prophylactic drugs for HCV. Therefore, primary prevention of HCV infection remains the main pillar to prevent HCV transmission and complications.[18, 19] However, due to the asymptomatic nature of infection making patients unaware of their infection status HCV infection is usually diagnosed at a late stage particularly in the absence of robust screening strategies.[20]

In 1998, the Centers for Disease Control and Prevention (CDC) issued recommendations for risk based hepatitis C testing as part of an overall strategy to prevent and control HCV infection. These recommendations categorize groups of persons who should undergo routine testing for HCV infection based on their risk for infection and based on a recognized exposure.[21]

According to their risk for infection; persons who ever injected illegal drugs, including those who injected once or a few times many years ago and do not consider themselves as drug users, persons with selected medical conditions, including (persons who received clotting factor concentrates produced before 1987, persons who were ever on chronic (long-term) hemodialysis and persons with persistently abnormal alanine aminotransferase levels), prior recipients of transfusions or organ transplants, including (persons who were notified that they received blood from a donor who later tested positive for HCV infection, persons who received a transfusion of blood, blood components or an organ transplant before July 1992) should be routinely tested. [21]

Additionally, HCV testing based on a recognized exposure is also recommended for: healthcare, emergency medical and public safety workers (after needle sticks, sharps, or mucosal exposures to HCV-positive blood) and children born to HCV-positive women. [21]

In 2002, the National Institutes of Health (NIH) recommended testing for HCV in persons considered at high risk of acquiring HCV infection: people who had transfusion of blood or blood products before routine blood screening began, people who received dialysis, people who might had intimate contact with any one infected with HCV, healthcare workers exposed to infected people, current or former injection drug users, people with abnormal liver tests and people who are HIV positive.[22]

Despite the previous CDC and NIH recommendations for risk-based screening, about 50% of HCV infected persons remain undiagnosed. Moreover, surveys of primary care medical providers revealed that more than 40% were not familiar with the 1998 CDC recommendations for risk-based HCV screening. [23]

The prevalence of HCV-Ab in the United States is about 1.6%. According to data from 1999 to 2008, about three fourth of those were born between 1945 and 1965 possibly because they have received blood transfusions before the introduction of blood screening in 1992 or have a history of other risk factors for exposure decades earlier.[24] As a result, the US Preventive Services Task Force (USPSTF) recommended offering 1-time screening for HCV infection in the birth cohort (adults born between 1945 and 1965) which may identify infected patients at earlier stages of disease. Nevertheless, the USPSTF concluded that the benefit of screening for HCV infection in persons in the birth cohort is probably similar to that in persons at higher risk for infection.[17]

In 2012, the CDC recommended the same standard risk-based screening in addition to initiation to one-time screening for HCV infection in all persons born during 1945 to 1965 "baby boomers". The prevalence of anti-HCV in this birth cohort is approximately 3.5%. [25]

In 2014, the American Association for the study of liver disease (AASLD) and Infectious diseases society of America (IDSA) issued guidance for testing, managing, and treating hepatitis C.[26] The guidance recommended performing hepatitis C testing at least

once for all persons born between 1945 and 1965 as well as testing based on risk behaviors, risk exposures, and medical conditions associated with acquisition of HCV as (injection drug use, illicit intranasal drug use, long term hemodialysis, tattoo at unregulated setting, after needle stick, sharp, mucosal exposure to HCV infected blood, children born to HCV infected mother, prior recipients of transfusions or organ transplants, persons who were ever incarcerated, HIV patients, unexplained liver disease and solid organ donors).[26]

In low- and middle-income countries, the WHO recommends one-time screening of individuals who are at high risk of HCV, defined broadly to include people at risk of healthcare associated transmission, individuals with HIV, injection drug users, etc.[27]

Universal HCV antibody testing, regardless of risk factors, is neither cost-effective nor practical.[5] Therefore, risk based screening could be a critical tool for primary care providers to identify patients appropriate for antibody testing, particularly in settings with a high prevalence and low resources.[28]

There are many benefits for screening persons at increased risk; identification of HCV-infected people at earlier stages of disease before they develop serious or irreversible liver damage, persons who are diagnosed as HCV positive through targeted testing could seek medical advice to determine the disease stage, to start earlier treatment to enhance virologic suppression that is associated with higher treatment success rate, better clinical outcomes and acceptable cost per quality-adjusted life years estimates.[27, 29-32]

Moreover, early diagnosis coupled with patient education and subsequent lifestyle modifications would reduce disease complications as well as reduction of transmission to others by avoiding risky behaviors and elimination of the source.[33] Furthermore, routine screening will lead to more accurate determination of HCV prevalence. Improved understanding of prevalence rates in particular communities will allow resources to be directed where they are needed. [34-36]

Nevertheless, targeted screening strategies in high-risk persons were reported to be associated with high sensitivity (> 90%) and smaller numbers needed to screen to identify one case of HCV infection.[17]

A study from Japan indicated that national screening programs for HCV in the general population and high risk groups could be cost-effective in comparison to non-screening.[37] Moreover, a study from United States concluded that targeted screening with a high estimated prevalence is cost-effective.[38] Another study from United States highlighted the importance of risk factor screening and identification by physicians to increase the rate of identification of individuals who might have been exposed to HCV in the past as well as appropriate testing.[39]

Although primary care physicians (PCPs) are responsible for screening for multiple health problems during a routine visit, the benefits of identifying HCV risk factors and infection must not be ignored.[39] Only 59% of PCPs reported asking patients about HCV risk factors.[40] Another study from New Haven Country found that 46% of PCPs routinely asked about history of blood transfusion and 62% asked about a history of injection drug use.[41]

Several studies have developed screening tools to assist in identifying persons who could be targeted for blood testing; a prediction tool was validated in New York to be used in the primary care which comprised 27-item questionnaire assessing five HCV risk factor domains: work, medical, exposure, personal care, and social history to help in identifying patients at high risk of HCV who might benefit from serologic screening.[36]

Another self-administered 72-item questionnaire about demographic, social and clinical risk factors for HCV infection was developed in Philadelphia to help in targeted HCV screening.[42] Nevertheless, other HCV risk assessment questionnaire was developed and evaluated to be used online as a selection tool for HCV blood screening in the general population.[43]

Potential HCV infection risk groups that are included in the current study

Illicit drug users (IDUs)

As HCV main mode of transmission is direct contact with human blood; high risks for HCV infection include intravenous and percutaneous drug use.[44] People who inject drugs (PWIDs) are at an especially high risk of contracting HCV infection which has been identified as the most common viral infection affecting PWIDs making it to be endemic among them. [45, 46]

According to World Drug Report 2016, it is estimated that 1 in 20 adults, or a quarter of a billion people between the ages 15 -64 years, used at least one drug in 2014. Of them, 12 million are PWIDs.[47] In Egypt, an estimated number of 100,000 were PWIDs in 2011.[48]

Factors influencing HCV transmission among PWIDs include high viral infectivity, efficient parenteral transmission, size of the susceptible population, probability of contact with infectious individuals and frequency of risky behaviors.[49]

PWIDs may experience any of the most severe health-related harms associated with unsafe drug use, overall poor health outcomes including a high risk of non-fatal and fatal overdoses and a greater chance of premature death. Additionally, they are a key at-risk population for HIV and hepatitis as 1.6 million are living with HIV and 6 million are living with hepatitis C. In other words; one in seven is living with HIV and one in two is living with hepatitis C, with an estimated 207,400 drug-related deaths in 2014, corresponding to 43.5 deaths per million people aged 15-64 years .[47]

HCV is estimated to be about 10 times more infectious than HIV, per unit of blood required and therefore, requires less exposure than HIV to reach high prevalence.[45]

A review of global HCV prevalence among PWIDs in 2011 found that 17 Western European countries reported prevalence rates exceeding 50% in this population group with estimated 10 million (range 6 –15.2 million) PWIDs globally that might be anti-HCV positive. [50]

The largest HCV-positive PWIDs populations were estimated to be living in Eastern Europe (2.3 million; range 1.2–3.9 million) and East and South-East Asia (2.6 million;