ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2017 November 28; 9(33): 1239-1260

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

Contents

Three issues per month Volume 9 Number 33 November 28, 2017

Contents

World Journal of Hepatology
Volume 9 Number 33 November 28, 2017

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Fatemeh Farshadpour, PhD, the Persian Gulf Tropical Medicine Research Center, Bushehr University of Medical Sciences, Bushehr 7514633341, Iran

AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Hepatology is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, and Scopus.

FLYLEAF

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
36 Issues/Year (8th, 18th, and 28th of each month)

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Hepatology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
November 28, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Hepatology

Submit a Manuscript: http://www.f6publishing.com

World J Hepatol 2017 November 28; 9(33): 1239-1252

DOI: 10.4254/wjh.v9.i33.1239

ISSN 1948-5182 (online)

REVIEW

Global elimination of hepatitis C virus infection: Progresses and the remaining challenges

Reza Taherkhani, Fatemeh Farshadpour

Reza Taherkhani, Fatemeh Farshadpour, the Persian Gulf Tropical Medicine Research Center, Bushehr University of Medical Sciences, Bushehr 7514633341, Iran

ORCID number: Reza Taherkhani (0000-0001-6499-0531); Fatemeh Farshadpour (0000-0002-8317-9573).

Author contributions: Farshadpour F designed the study and wrote the manuscript; Taherkhani R provided the literature review and edited the manuscript and was also involved in designing the study.

Conflict-of-interest statement: The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Manuscript source: Invited manuscript

Correspondence to: Fatemeh Farshadpour, PhD, the Persian Gulf Tropical Medicine Research Center, Bushehr University of Medical Sciences, Moallem Street, Bushehr 7514633341, Iran. f.farshadpour@bpums.ac.ir
Telephone: +98-917-1712653

Received: July 15, 2017
Peer-review started: July 19, 2017
First decision: August 15, 2017
Revised: September 1, 2017
Accepted: September 16, 2017
Article in press: September 16, 2017
Published online: November 28, 2017

Abstract

Today, with the introduction of interferon-free direct-acting antivirals and outstanding progresses in the prevention, diagnosis and treatment of hepatitis C virus (HCV) infection, the elimination of HCV infection seems more achievable. A further challenge is continued transmission of HCV infection in high-risk population specially injecting drug users (IDUs) as the major reservoir of HCV infection. Considering the fact that most of these infections remain undiagnosed, unidentified HCV-infected IDUs are potential sources for the rapid spread of HCV in the community. The continuous increase in the number of IDUs along with the rising prevalence of HCV infection among young IDUs is harbinger of a forthcoming public health dilemma, presenting a serious challenge to control transmission of HCV infection. Even the changes in HCV genotype distribution attributed to injecting drug use confirm this issue. These circumstances create a strong demand for timely diagnosis and proper treatment of HCV-infected patients through risk-based screening to mitigate the risk of HCV transmission in the IDUs community and, consequently, in the society. Meanwhile, raising general awareness of HCV infection, diagnosis and treatment through public education should be the core activity of any harm reduction intervention, as the root cause of failure in control of HCV infection has been lack of awareness among young drug takers. In addition, effective prevention, comprehensive screening programs with a specific focus on high-risk population, accessibility to the new anti-HCV treatment regimens and public education should be considered as the top priorities of any health policy decision to eliminate HCV infection.

Key words: Hepatitis C virus; Epidemiology; Elimination; Injecting drug user; Prevention; Vaccine; Diagnosis; Treatment

Core tip: Despite the outstanding progresses in the management of hepatitis C virus (HCV) infection, the elimination of HCV would be difficult due to the emergence of injection drug use as the main source of HCV transmission. Asymptomatic nature of HCV infection,

restricted accessibility to diagnostic approaches and appropriate antiviral treatments in the injecting drug users (IDUs) community are the root cause of failure in control of HCV infection among IDUs. These circumstances create a strong demand for timely diagnosis and proper treatment of HCV-infected patients as well as raising general awareness of HCV infection through public education to mitigate the risk of HCV transmission.

Taherkhani R, Farshadpour F. Global elimination of hepatitis C virus infection: Progresses and the remaining challenges. *World J Hepatol* 2017; 9(33): 1239-1252 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i33/1239.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i33.1239

INTRODUCTION

With a global prevalence rate of 2.8%, equating to over 185 million infections, and more than 350000 deaths annually, hepatitis C virus (HCV) infection is undoubtedly considered a major public health problem[1]. Globally, an estimated 3 million to 4 million new cases of HCV infection emerge every year[1]. Furthermore, the HCV-related mortality is increasing and HCV infection is projected to be the most important leading cause of viral hepatitis-related mortality in the near future[1,2]. Apparently, the management of HCV infection faces several challenges. These challenges merit further attention if elimination of HCV infection is aimed to be achieved.

HCV

HCV is a member of the family *Flaviviridae* and the genus *Hepacivirus*. The HCV genome is a positive-stranded RNA, which encodes a core protein (C), two envelope glycoproteins (E1 and E2), and several non-structural proteins (NS1, NS2, NS3, NS4A, NS4B, NS5A and NS5B)[3,4]. This enveloped positive-stranded RNA virus is usually acquired through exposure to infected blood. This might happen through transfusion of blood and blood products, surgery, organ transplantation, intravenous drug use, tattooing, hemodialysis, unsafe injection practices, mother to fetus, and sexual intercourse[5-8]. However, sexual transmission of HCV is less common and most often observed among men who have sex with men and HIV-infected patients[9,10].

HCV is the causative agents of hepatitis C infection. This infection is characterized by an acute or chronic course in the host. The complications are preliminary asymptomatic, mild or severe, which spontaneously clear or slowly progress to chronic liver disease, cirrhosis and finally hepatocellular carcinoma (HCC) within about 20 years[11,12]. The clinical symptoms of acute HCV infection might include fever, fatigue, malaise, and gastrointestinal symptoms such as anorexia, nausea, vomiting, right upper quadrant pain, dark urine, grey-colored stool, and yellow skin and sclera of the eyes, the well-characterized symptoms of jaundice. These symptoms might appear from 3 to 12 wk after being infected. The clinical symptoms of chronic HCV infection might take decades to develop, and they are usually indicative of an advanced liver disease[13-15].

The long-term chronic HCV infection is capable of causing some extra hepatic manifestations with serious consequences, such as glomerulonephritis, diabetes mellitus, thyroid disorders, porphyria cutaneous tarda, mixed cryoglobulinemia, lichen planus, and B cell lymphoproliferative disorders[16-21]. These extrahepatic complications might outshine the hepatic manifestations of HCV infection, and the presence of HCV infection might be overlooked, paving the way for the silent development of advanced liver disease. Therefore, the possible role of HCV in the development of extrahepatic manifestations merits further attention.

Due to genomic heterogeneity, there are 7 major genotypes and over 67 subtypes of HCV[1,22,23]. HCV genotype distribution varies by the route of transmission and geographical location[24,25]. In addition, pathogenicity, response to antiviral therapy and the duration of treatment can be influenced by different HCV genotypes[5,24,26]. The genotypes 1, 2 and 3 show a widespread distribution in almost all parts of the world. HCV genotype 4 has been traditionally restricted to a few countries in the Middle East and Africa and is more prevalent in Saudi Arabia, Bahrain, Jordan, Egypt and Ethiopia[1,27,28]. HCV genotype 5, 6 and 7 have been reported in South Africa, South East Asia and Central Africa, respectively[11,29,30] (Figure 1).

Genotype 1 is more prevalent among patients with history of blood and blood products transfusion, surgery, and dental procedure[24,25,27]. Infection with HCV genotype 2 is mainly associated with nosocomial transmission and prior dental treatment[1,22]. Genotype 3 is frequently found in the intravenous drug user communities and in those with history of tattooing and piercing[24,31,32]. Genotype 4 is mainly transmitted through high-risk sexual practices, especially among homosexual males, and intravenous drug use[1,22].

Infection with HCV genotype 3 is associated with a more rapid progression of fibrosis, a higher degree of steatosis, and a higher incidence of cirrhosis and hepatocellular carcinoma[1,22,31,33]. Spontaneous clearance is more often observed in infection with HCV genotype 1, while if patients remain HCV RNA positive, the disease progresses in a more aggressive manner than the other genotypes[11]. Genotypes 1 and 4 are associated with lower response rates and higher treatment duration in response to interferon (IFN) and ribavirin (RBV) combination therapy as compared to genotypes 2 and 3[6,24,34].

PROGRESSES IN THE MANAGEMENT OF HCV INFECTION

In addition to IFN-based therapies, the direct-acting antivirals (DAAs) have been developed, which specifically

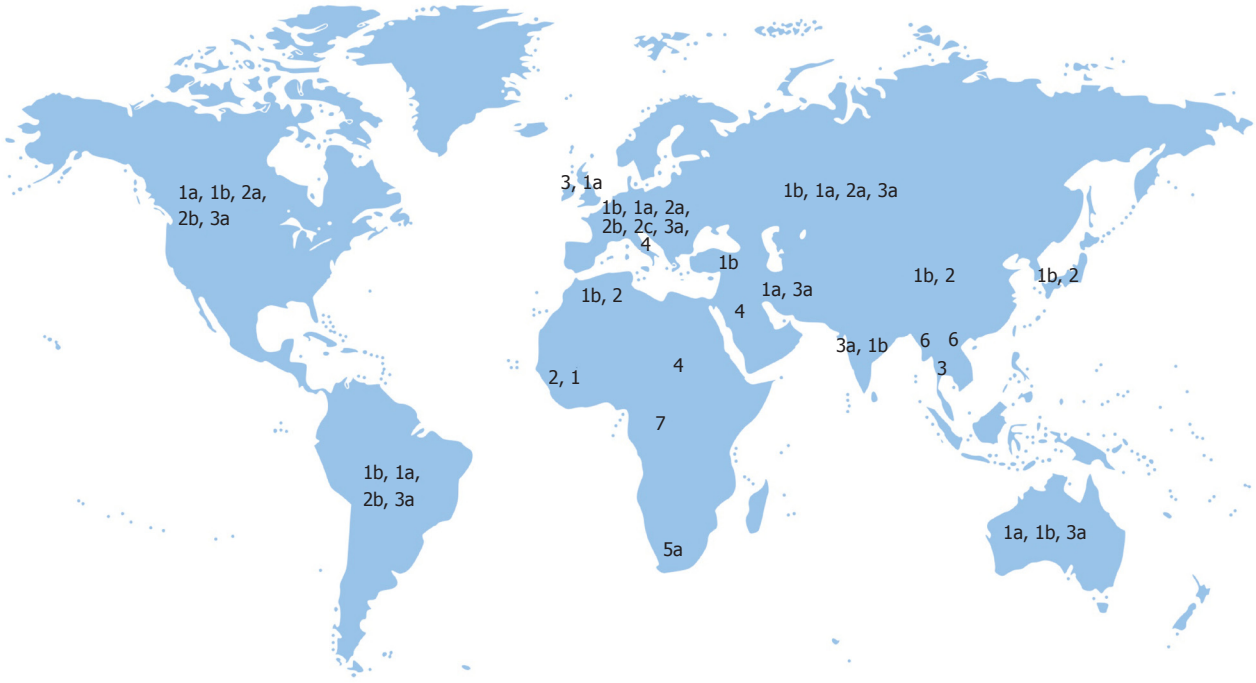

Figure 1 Geographical distribution of hepatitis C virus genotypes. Hepatitis C virus (HCV) genotypes 1, 2 and 3 show a widespread distribution in almost all parts of the world. HCV genotype 4 has been restricted to a few countries in the Middle East and Africa. HCV genotype 5, 6 and 7 have been reported in South Africa, South East Asia and Central Africa, respectively[1,11,30,35,36].

inhibit the function of viral proteins that are essential for viral replication[4,37,38]. These DAAs include NS3/4A protease inhibitors, NS5A replication complex inhibitors, nucleoside NS5B polymerase inhibitors, and non-nucleoside NS5B polymerase inhibitors (Table 1)[39-43]. These novel antiviral drugs, despite having considerable advantages over conventional IFN-based therapy, suffer from the resistance-associated mutations, which occur naturally during the replication of the virus and select under the pressure of DAAs. The emergence of HCV resistance-associated variants (RAVs) decreases the susceptibility to DAAs and finally results in treatment failure[38,44-46]. Assessment of resistance substitutions at pretreatment baseline in patients candidate for DAA therapy seems to be the best option to optimize first-line therapeutic strategies, to avoid the fitness of resistant variants as the predominant viral population and to prevent DAA failure due to baseline resistant variants. In addition, failing DAA-based therapy should be discontinued as soon as possible to avoid an increase in the frequency of RAVs, to preserve HCV re-treatment options. Finally, development of next-generation DAAs with higher resistance barrier is strongly recommended[45,47].

Telaprevir and boceprevir are not recommended by WHO due to the frequent adverse effects and low cure rates[79].

Prior to the treatment, the infected individuals need to be identified. HCV infection is described by the presence of anti-HCV antibodies and HCV-RNA in plasma or serum with either elevated or normal levels of liver enzymes[29]. Anti-HCV antibodies are detected by using serological screening tests, including enzyme linked immunosorbent assay and recombinant immunoblot assay. Detection of anti-HCV antibodies indicates current or past HCV infection. An additional test called HCV RNA test or reverse transcriptase polymerase chain reaction assay (RT-PCR) is needed to determine if a person is currently infected with HCV[17,80-82].

However, those infected individuals with undetectable levels of HCV-RNA in serum or plasma might remain undiagnosed. In this condition, HCV-RNA can be detected in peripheral blood mononuclear cells (PBMCs) specimens, liver biopsies, and ultracentrifugated serum samples[81,83]. Serological screening tests might be negative or positive in these patients. This kind of infection is defined as occult HCV infection, which is a serious threat to blood safety[84,85]. Since, despite having undetectable level of HCV RNA, blood and blood products are potentially infectious[84,86]. In fact, the presence of blood donors with occult HCV infection can increase the risk of HCV transmission through blood transfusion and therefore is a potential source of HCV transmission in the society[87].

Despite having appropriate antiviral treatments and diagnostic approaches, diagnosis rate and access to treatment is considerably low especially in resource-limited settings. Perhaps the most promising strategy to control HCV infection is the development of a prophylactic vaccine[88,89]. Several vaccine candidates against HCV have been developed so far, including recombinant protein vaccine, peptide-based vaccine,

Table 1 Profile of direct-acting antiviral agents[4,37,40,42,44,48-78]

Direct-acting antiviral agent	Generic name (abbreviation)	Code name	Trade name	Active against HCV genotype (based on clinical trial outcomes)	Combination therapy
NS3/4A protease inhibitors (-previr)	Telaprevir (TVR)	VX-950	Incivek/ Incivo	1	TVR + IFN ± RBV
	Boceprevir (BOC)	SCH-503034 EBP-520	Victrelis	1	BOC + IFN ± RBV
	Faldaprevir (FDV)	BI-201335	-	1	FDV + Peg-IFN + RBV
	Simeprevir (SIM)	TMC-435	Olysio	1 and 4	SIM + SOF ± RBV
	Vaniprevir (VNV)	MK-7009	Vanihep	1	VNV + IFN ± RBV
	Asunaprevir (ASV)	BMS-650032	Sunvepra	1 and 4	ASV + DCV
	Paritaprevir (PTV)	ABT-450	Veruprevir	1 and 4	PTV+R+OBV+DAV ± RBV
	Voxilaprevir (VOX)	GS-9857	-	Pan-genotypic antiviral activity	VOX + SOF + VPR
	Sovaprevir	ACH-1625	-	1	Sovaprevir + ODV + RBV
	Grazoprevir (GZP)	MK-5172	-	1a, 1b, 4 and 6	Zepatier (GZP + EBV)
	Danoprevir (DNV)	RG-7227 ITMN-191 ASC08	-	1 and 4	DNV + PEG-IFN + RBV DNV + R + PEG-IFN + RBV
	Deldeprevir (DDV)	ACH-2684	-	1	DDV + ODV
	Neceprevir	ACH-0142684			
	Narlaprevir (NVR)	SCH-900518	Arlansa	1	NVR + R + PEG-IFN ± RBV
	Vedroprevir (VDV)	GS-9451	-	1	VDV + LDV + SOF VDV + LDV + TGV + RBV
	Glecaprevir (GLE)	ABT-493	-	Pan-genotypic antiviral activity	GLE + PIB ± RBV
	-	GS-9256	-	1	GS-9256 + PEG-IFN + RBV GS-9256 + TGV + Peg-IFN ± RBV
NS5A replication complex inhibitors (-Asvir)	Daclatasvir (DCV)	BMS-790052	Daklinza	1, 2 and 3	Sovodak (DCV + SOF) ± RBV DCV + VX-135
	Ledipasvir (LDV)	GS-5885	-	1, 3, 4, 5 and 6	Harvoni (LDV + SOF) ± RBV LDV + SOF ± (VDV or Radalbuvir)
	Ombitasvir (OBV)	ABT-267	-	1 and 4	Viekira Pak (OBV + PTV + R + DSV) ± RBV Technivie (OBV + PTV + R)
	Elbasvir (EBV)	MK-8742	-	1a, 1b, 4 and 6	Zepatier (EBV + GZP) ± RBV
	Velpatasvir (VPR)	GS-5816	-	Pan-genotypic antiviral activity	Epclusa (VPR + SOF) ± RBV
	Odalasvir (ODV)	ACH-3102	-	1	ODV + Sovaprevir + RBV
	Ravidasvir (RVD)	PPI-668 ASC16	-	4	RVD + SOF ± RBV
	-	PPI-461	-	1	-
	-	JNJ-56914845 GSK2336805	-	1	GSK2336805 + PEG-IFN + RBV GSK2336805 + VX-135 + SIM
	Samatasvir	IDX-18719 IDX-719 MK-1894	-	1, 2, 3 and 4	Samatasvir + SIM + RBV
	-	BMS-824393	-	1	BMS-824393 + PEG-IFN + RBV
	Pibrentasvir (PIB)	ABT-530	-	Pan-genotypic antiviral activity	PIB + GLE ± RBV
	Ruzasvir (RZR)	MK-8408	-	Pan-genotypic antiviral activity	RZR + UPR + GZP
Nucleoside NS5B polymerase inhibitors (-Buvir)	Sofosbuvir (SOF)	PSI-7977; GS-7977	Sovaldi; Soforal	Pan-genotypic antiviral activity	SOF + IFN ± RBV Sovodak (DCV + SOF) ± RBV
	Mericitabine (MCB)	RG-7128 RO5024048	-	1 and 4	MCB + PEG-IFN + RBV MCB + DNV MCB + R + DNV ± RBV
	-	VX-135 ALS-2200	-	1	VX-135 + GSK2336805 + SIM VX-135 + TVR + RBV VX-135 + DCV VX-135 + RBV VX-135 + SIM
	Valopicitabine	NM283	-	1	Valopicitabine + Peg-IFN
Non-nucleoside NS5B polymerase inhibitors (-Buvir)	Beclabuvir (BCV)	BMS-791325	-	1	BCV+ ASV+ DCV

	Dasabuvir (DAV)	ABT-333	Exviera	1	DAV + OBV+ PTV + R ± RBV
	Lomibuvir	VX-222 VCH-222	-	1	VX-222 + TVR + RBV VX-222 + Filibuvir
	Filibuvir	PF-00868554, PF-868554	-	1	Filibuvir + Peg-IFN + RBV Filibuvir + VX-222
	Setrobuvir (STV)	ANA-598 RO-5466731 RG-7790	-	1	STV + IFN + RBV STV + R + DNV + RBV ± MCB
	Nesbuvir (NBV)	HCV-796 VB-19796	-	1	NBV +Peg-IFN + RBV
	Tegobuvir (TGV)	GS-9190	-	1	TGV + GS-9256 +Peg-IFN ± RBV TGV + LDV + VDV + RBV
	Deleobuvir (DBV)	BI-207127	-	1	DBV + PEG-IFN + RBV DBV + FDV DBV + FDV + RBV
	Uprifosbuvir (UPR)	MK-3682	-	Pan-genotypic antiviral activity	UPR + RZR UPR + RZR + GZP
	Radalbuvir	GS-9669	-	1	Radalbuvir + LDV + SOF
	AL-335	ALS-335	-	1	AL-335 + ODV + SIM

IFN: Interferon; RBV: Ribavirin; R: Ritonavir; PEG-IFN: Pegylated interferon.

virus-like particles, bacterial-vectored vaccine, viral-vectored vaccine, and DNA vaccine (Table 2)[29,88,90-96]. The currently developed vaccines against HCV, despite inducing strong humoral and cellular immune responses in preclinical animal models or clinical trials in humans, have not been approved for use in human beings[89,90,97]. The reason is high genomic diversity of HCV and viral escape from immune responses[88,90,93,98,99]. Targeting the conserved regions within HCV proteins might help to overcome this genetic variability[100].

In the absence of an approved prophylactic vaccine for hepatitis C, reducing exposure to HCV through prevention seems to be the best option. This can be achieved through routine screening of donated blood for HCV markers, providing safe medical procedures, promoting risk-reduction counseling and services for at risk population, increasing public awareness and offering regular HCV testing to high-risk populations with the goal of breaking the cycle of HCV transmission in the society[7,9,82,133]. Despite the so-called improvements in the management of HCV infection, still a long way is ahead to achieve a world free of HCV infection. Here, the remaining challenges to eliminating HCV infection will be discussed.

REMAINING CHALLENGES TO ELIMINATING HCV INFECTION

For many years, IFN-based therapy, despite having frequent side effects, poor tolerability, suboptimal efficacy and prolonged treatment course, was recommended as the standard treatment for HCV infection[134,135]. Introduction of IFN-free DAAs has solved most of these problems in the treatment course of HCV infection. Switch the HCV treatment regimens from IFN-based therapy to DAA therapy is a desirable approach, yet encounter practical barriers such as high price and the restricted accessibility of DAAs[135-138]. Most of the time, the cost of antivirals rather than their effectiveness is the main driver in the treatment decisions. The use of these DAAs is far beyond the financial means of the most-in-need patients especially those who are IFN-intolerant or non-responder. While, equity in health demands that all patients with every socioeconomic status have equitable access to these treatment regimens. Currently, reducing treatment costs and providing DAAs with a relatively high health insurance coverage seem to be best options to improve access to DAA therapy[139].

Accessibility to DAAs, though, by itself is a superb health achievement, still alone might not be sufficient to mitigate the burden of HCV infection. A further challenge is continued transmission of HCV infection in high-risk population specially injecting drug users (IDUs) as the major reservoir of HCV infection[133,137,139]. Considering the fact that most of these infections remain undiagnosed, unidentified HCV-infected IDUs are potential sources for the spread of HCV infection in the society[133,139-141]. While, silent introduction of HCV infection into the community is a serious threat to the national effort to eliminate HCV infection, a threat that will increase with time. Therefore, timely diagnosis of HCV-infected patients through risk-based screening is of the greatest importance[126,133,137]. Screening of blood donations for hepatitis C initiated in the early 1990s has remarkably reduced the risk of HCV transmission through blood transfusion since then. Blood transfusion before the early 1990s was a major contributor to the HCV transmission, but today this risk has become minute[142]. However, it is far, far more difficult to screen IDUs, those who most need risk assessment. Despite the remarkable advantages, the cultural objections hinder screening progress, resulting in low diagnosis rate and, consequently, persistent silent spread of infection. On the other hand, the stigma of injecting drug use makes recognition of all HCV-infected IDUs impossible or logistically difficult at best[133]. In addition, establishment of HCV screening system with a specific

Table 2 Vaccine candidates against hepatitis C virus in preclinical and clinical trials

Type of vaccine	Vaccine structure/ adjuvant	Stage of development	Outcome	Application	Developer	Year	Current status	Ref.
Recombinant protein vaccine	Recombinant E1 or E2/MF59	7 chimpanzees	Induce strong humoral immune response; complete protection in 5 chimpanzees	Prophylactic vaccine	Chiron/ Novartis	1994	Completed	[101]
	Recombinant E1 or E2/Alum	4 Chimpanzees	Induce antigen-specific T-helper cytokines in either E1 or	Therapeutic vaccine	BPRC	2011	Published	[102]
	Recombinant E1/Alum	Phase Ⅰ 20 healthy volunteers	E2-vaccinated animals; clear HCV infection in only E1-vaccinated animals (neutralizing antibodies) Induce strong cellular and humoral anti-E1 responses	Therapeutic vaccine	Fujirebio Europe	2004	Published	[103]
	Recombinant E1 and E2/MF59	Phase Ⅰ 60 healthy volunteers	Induce humoral and cellular immune responses	Prophylactic vaccine	Novartis	2010	Completed	[104]
	Recombinant E1/Alum	Phase Ⅰ/Ⅱ 20 healthy volunteers and 35 patients with chronic HCV infection/122 HCV-infected patients	Induce HCV specific humoral and cellular immune responses (Th1 type); no change in HCV viral load	Therapeutic vaccine	Innogenetics/ GenImmune	2003/2008	Published	[103,105,106]
	HCV core protein/ ISCOMATRIX	Phase Ⅰ/Ⅱa 30 healthy volunteers	Induce strong humoral immune responses in all except one patients; induce CD8+ T cell responses in 2 of 8 patients receiving the highest dose	Prophylactic vaccine	CSL Ltd	2009	Published	[107]
	GI5005: Inactivated recombinant Saccharomyces cerevisiae expressing NS3-core fusion protein/ GI-5005 plus SOC	Phase Ⅰ/Ⅱ 66 patients with chronic HCV infection/	Improve SVR	Therapeutic vaccine	GlobeImmune	2009/2010	Completed	[108,109]
Peptide-based vaccine	Peptide from core protein (C35-C44)/ ISA51	Phase Ⅰ 26 patients with chronic HCV infection	Induce peptide-specific cellular and humoral immune responses in 15 of 25 patients; decline HCV viral load in 2 of 25 patients	Therapeutic vaccine	Karume University	2009	Published	[110]
	Four peptides from E1, E2, NS3 and NS5A/Freund's adjuvant	Phase Ⅰ 12 nonresponder patients with chronic HCV infection	Induce peptide-specific cellular and humoral immune responses; decline HCV viral load in 3 patients	Therapeutic vaccine	Karume University	2007	Published	[111]
	Autologous dendritic cell delivered six CD8+ T cell epitope peptides from core, NS3 and NS4B	Phase Ⅰ 6 nonresponder patients with chronic HCV infection	Induce transient T-cell response	Therapeutic vaccine	Burnet Institute + others	2010	Completed	[112]

	IC41: Five peptides from core, NS3, and NS4/Poly-L-arginine	Phase Ⅰ / Ⅱ 128 volunteers/60 non-responders with chronic HCV infection	Induce HCV-specific T-cell responses	Therapeutic vaccine	Intercell AG	2006/2008	Published	[113,114]
	IC41/Poly-L-arginine + imiquimod	Phase Ⅰ 54 healthy volunteers	Induce significant T cell responses; low immunogenicity of topical imiquimod	Therapeutic vaccine	Intercell AG	2010	Published	[115]
	IC41 + imiquimod	Phase Ⅱ 50 HCV-infected patients	Decline viral load; induce T cell responses	Therapeutic vaccine	Intercell AG	2012	Completed	[116]
Virus-like particles	Recombinant HCV-like particles (HCV-LPs) containing core, E1, and E2/AS01B	4 chimpanzees	Induce HCV-specific cellular immune responses; viral clearance	Prophylactic vaccine	NIH	2007	Published	[117]
	Recombinant baculovirus containing core, E1 and E2	Mice	Induce high titers of anti-E2 antibodies and strong HCV-specific cellular immune responses (CD8+ T and Th1 cells)	Prophylactic vaccine	NIH	2001	Published	[118]
Bacterial-vectored vaccine	Attenuated Salmonella typhimurium containing *NS3* gene	Mice	Induce long-lasting T-cell responses	Therapeutic vaccine	NIH	2001	Published	[119]
Viral-vectored vaccine	Recombinant adenoviral vectors and plasmid DNA expressing NS3-NS5B	5 chimpanzees	Induce memory HCV-specific T cells; control of viremia	Prophylactic vaccine	NIH/Okairos	2012	Completed	[120]
	Multiple adenoviral vectors (Ad5, Ad6, Ad24, ChAd32 and ChAd33) expressing NS3-NS5B proteins	Mice and rhesus macaque	Induce strong cellular immune responses; long-term maintenance of memory cells	Prophylactic vaccine	Okairos	2006	Published	[121]
	Recombinant vaccinia viruses (rVV) expressing core, E1, E2, P7, NS2 and NS3	4 chimpanzees	Induce cellular immune responses; reduce viral load; resolve HCV infection	Prophylactic vaccine	NYC Blood Center	2008	Published	[122]
	Recombinant adenoviral vectors (Ad6 and ChAd3) expressing NS3-NS5B proteins	Phase Ⅰ 40 healthy volunteers	Induce sustained HCV-specific T cell responses	Prophylactic vaccine	Okairos	2012	Completed	[123]
	Adenovirus vector (Ad6 and ChAd3) expressing NS3-NS5B proteins	Phase Ⅰ 36 healthy volunteers	Highly immunogenic; induce HCV specific T cell responses	Prophylactic vaccine	Okairos and Oxford University	2009	Published	[124]
	TG4040: MVA vector expressing NS3, NS4 and NS5B proteins	Phase Ⅰ 15 patients with chronic HCV infection	Decline HCV viral load in 7 of 15 patients associated with T-cell response	Therapeutic vaccine	Transgene	2009	Withdrawn	[125]
	MVA and ChAd3 vectors expressing NS3, NS4, NS5A and NS5B proteins	Phase Ⅰ / Ⅱ Healthy at risk population (68/472 IDU)	July 28, 2018: Final data collection date	Prophylactic vaccine	NIAID	2017	Ongoing	[126]
	TG4040 + SOC	Phase Ⅱ 153 patients with chronic HCV infection	Induce HCV- and MVA-specific T-cell responses; develop anti-MVA antibodies; increase rate of early virologic response	Therapeutic vaccine	-	2014	Published	[127]
DNA vaccine	Recombinant DNA plasmid encoding E2	2 chimpanzees	Induce humoral and cellular immune responses; resolve the infection; prevent progression to chronicity	Prophylactic vaccine	NIAID/NIH	2000	Published	[128]

Recombinant DNA plasmid and adenovirus vector expressing core, E1, E2 and NS3-5	8 chimpanzees	Induce HCV-specific T-cell and long-lasting E2-specific antibody responses; reduce viral load	Prophylactic vaccine	NIH	2005	Published	[129]
Recombinant DNA plasmids and MVA vector expressing core, E1, E2 and NS3	6 chimpanzees	Induce HCV-specific immune responses; reduce viral load; early control of acute HCV infection; fail to impact on chronicity	Prophylactic vaccine	Transgene	2007	Published	[130]
CIGB-230: Plasmid expressing core/E1/E2 plus recombinant core protein	Phase Ⅰ 15 non-responder patients with chronic HCV infection	Induce humoral and cellular immune responses; no viral clearance	Therapeutic vaccine	University of Montreal + others	2009	Published	[131]
ChronVac-C: Plasmid expressing NS3 and NS4A delivered by in vivo electroporation	Phase Ⅰ / Ⅱa 12 HCV-infected patients	Decline HCV viral load in 4 of 6 patients receiving the highest dose with corresponding HCV-specific T-cell response in 3 patients	Therapeutic vaccine	Tripep AB	2009	Recruiting	[132]

HCV: Hepatitis C virus; SOC: Standard-of-care (PEGylated-IFNalpha and ribavirin); Imiquimod: An activator of the toll-like receptor (TLR) 7; Ad: Human Adenovirus; ChAd: Chimpanzee Adenovirus; MVA: Modified vaccinia Ankara virus; IDU: Injecting drug user.

focus on IDUs imposes high financial burden on the health system. Given the treatment expenses and dependence of these expenses on the stage of liver disease, screening of all at-risk populations seems much more affordable in a long run. Overall, in addition to interrupting unrecognized transmission of HCV, a part of costs expended in the treatment sector will also be saved with the prompt diagnosis and timely treatment of infected but asymptomatic patients[133,143]. While this process would demand allocation of adequate budgets and resources to integrate routine screening of high-risk population into national health programs.

As another solution, the coverage of needle and syringe exchange program should be expanded to increase the daily access to fresh needles and syringes among IDUs[144]. However, this program has not been very successful to control HCV transmission thus far, as the prevalence of HCV infection among IDUs is on the rise[139]. In fact, the overall focus on syringe sharing as the main vehicle for HCV spread has taken focus away from the other risk behaviors of IDUs such as the shared use of drug ampoules or the other injecting paraphernalia, engagement in high-risk sexual practices and the other drug-related harms[145]. These circumstances create a strong demand for precise surveillance of IDUs to obtain a reliable insight into risk behaviors of IDUs community, and subsequently harm reduction interventions should be tailored to the common risk behaviors among IDUs to mitigate the risk of HCV transmission. In addition, raising general awareness of HCV infection, diagnosis and treatment through public education should be the core activity of any harm reduction intervention, as the root cause of failure in control of HCV infection has been lack of awareness among young drug takers[133,141,146]. The growing number of IDUs and the relatively young age distribution of HCV-infected IDUs have evoke huge attention and provided a good opportunity to drive down the increasing trend of HCV-related mortality in near future through timely interventions and appropriate treatment[139,147].

The changes in HCV genotype distribution attributed to injecting drug use is another challenge in eliminating HCV infection. The changes in genotype distribution are so slight as to be unnoticeable but can have a deep impact on the epidemiology of HCV infection in a long run. These changes merit further attention if we want to properly manage the future burden of HCV infection. Globally, the most prevalent genotype is 1 (46%), followed by 3 (22%), 2 (13%) and 4 (13%)[35,137]. Over the last decade, however, a gradual decrease in the prevalence of genotype 1 and an increase in genotype 3 have been reported due to some changes in the route of transmission, risk factors, source of infection, human migration flow, and age distribution[148,149].

Blood transfusion before 1990 was the most important contributor to the spread of HCV, which has been reflected in the predominance of genotype 1 among older individuals[149,150]. In fact, screening for hepatitis C made blood transfusion remarkably safe since 1990s, paving the way for a gradual increase in the prevalence of genotype 3, which is mostly transmitted by IDU[148-150]. In recent years, IDU has become the main source of HCV transmission[35,137,144,145]. Globally, the estimated number of HCV-infected IDUs is up to 10.0 million (6.0-15.2 million), most of whom are young[35,139,144,147,151]. Meanwhile, the most common risk behavior of IDUs, syringe sharing, is more frequent among young drug injectors than in experienced and long-term injectors[152], amplifying the transmission of HCV among young IDUs population and favoring the continuous increase of HCV genotype 3. In

addition to the change in the route of HCV transmission, the ongoing civil strife in the Middle East and the active migration flow from India, Afghanistan and Pakistan, where subtype 3a is endemic, have fuelled the increasing prevalence of genotype 3[148]. On the other hand, death of elderly HCV carriers is slowly driving down the prevalence of HCV genotype 1.

These changes in genotype distribution have profound effects on the prevalence of HCV infection, response to antiviral therapy, cost and duration of treatment, and future burden of HCV infection. Given the higher rates of sustained virological response (SVR) to IFN-based therapy, the first-line therapy in low- and middle-income countries, in patients with HCV genotype 3 as compared to genotype 1[149], an increase in the prevalence of genotype 3 beneficially affects the treatment course both in terms of duration and in terms of cost and brings high benefits on an individual level. However, this increase would impose a greater risk on a population level. In reality the rising prevalence of HCV infection along with the continuous increase in the number of IDUs outweigh this benefit. The disastrous interacting epidemics of HCV infection and IDU are harbinger of a forthcoming public health dilemma, presenting a serious challenge to control transmission of HCV infection. On the other hand, high prevalence of HCV infection among young IDUs is a cause for concern, paving the way for rapid spread of HCV in the community. The old story of hepatitis C has gotten a new scenario. The emergence of IDU as the main risk factor for transmission of HCV is a surrogate in this new scenario. If this scenario is to continue, the emergence of an uncontrollable epidemic of hepatitis C will be expected in the near future.

CONCLUSION

The global community has always been concerned about the future burden of HCV infection. Although action on this concern has started many years ago with great hopes to eliminate HCV infection, the success remains elusive and will become even more elusive if the current HCV management paradigm is to be continued. We believe that it is now time to reconsider the wisdom of the current management strategies, admit failure, and act with all the strength. If we want to succeed in eliminating HCV infection, a more integrated international effort will be required, involving health policy makers, healthcare practitioners, public health organizations, antiviral drug manufacturers, health insurance companies, and all major stakeholders. In addition, effective prevention, comprehensive screening programs with a specific focus on high-risk population, accessibility to the new anti-HCV treatment regimens and public education should be considered as the top priorities of any health policy decision to eliminate HCV infection. While waiting for a solution, prevalence of HCV infection continues to increase. If we do not want to encounter another uncontrollable public health dilemma, the time to act is now, tomorrow will be very late.

REFERENCES

1 **Petruzziello A**, Marigliano S, Loquercio G, Cacciapuoti C. Hepatitis C virus (HCV) genotypes distribution: an epidemiological up-date in Europe. *Infect Agent Cancer* 2016; **11**: 53 [PMID: 27752280 DOI: 10.1186/s13027-016-0099-0]

2 **Morgan RL**, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med* 2013; **158**: 329-337 [PMID: 23460056 DOI: 10.7326/0003-4819-158-5-201303050-00005]

3 **Falcón V**, Acosta-Rivero N, González S, Dueñas-Carrera S, Martinez-Donato G, Menéndez I, Garateix R, Silva JA, Acosta E, Kourı J. Ultrastructural and biochemical basis for hepatitis C virus morphogenesis. *Virus Genes* 2017; **53**: 151-164 [PMID: 28233195 DOI: 10.1007/s11262-017-1426-2]

4 **Yang CHT**, Yoo ER, Ahmed A. The Role of Direct-acting Antivirals in the Treatment of Children with Chronic Hepatitis C. *J Clin Transl Hepatol* 2017; **5**: 59-66 [PMID: 28507928 DOI: 10.14218/JCTH.2016.00053]

5 **Rehan HS**, Manak S, Yadav M; Deepinder, Chopra D, Wardhan N. Diversity of genotype and mode of spread of Hepatitis C virus in Northern India. *Saudi J Gastroenterol* 2011; **17**: 241-244 [PMID: 21727729 DOI: 10.4103/1319-3767.82576]

6 **Farahat MA**, Bahnasy KA, Abdo A, Kamal SM, Kassim SK, Eldin AS. Response Prediction for Chronic HCV Genotype 4 Patients to DAAs. *IJACSA* 2016; **1**: 173-178

7 **Ferreira PM**, Guimarães RA, Souza CM, Guimarães LC, Barros CV, Caetano KA, Rezza G, Spadoni L, Brunini SM. Exposure to hepatitis C virus in homeless men in Central Brazil: a cross-sectional study. *BMC Public Health* 2017; **17**: 90 [PMID: 28100196 DOI: 10.1186/s12889-016-3952-6]

8 **Alter MJ**. HCV routes of transmission: what goes around comes around. *Semin Liver Dis* 2011; **31**: 340-346 [PMID: 22189974 DOI: 10.1055/s-0031-1297923]

9 **Omata M**, Kanda T, Wei L, Yu ML, Chuang WL, Ibrahim A, Lesmana CR, Sollano J, Kumar M, Jindal A, Sharma BC, Hamid SS, Dokmeci AK, Al-Mahtab M, McCaughan GW, Wasim J, Crawford DH, Kao JH, Yokosuka O, Lau GK, Sarin SK. APASL consensus statements and recommendations for hepatitis C prevention, epidemiology, and laboratory testing. *Hepatol Int* 2016; **10**: 681-701 [PMID: 27229718 DOI: 10.1007/s12072-016-9736-3]

10 **Li Q**, Yao Y, Shen Y, Cao D, Li Y, Zhang S, Cun W, Sun M, Yu J, Shi L, Dong S. Assessment of HCV genotypes in Yunnan Province of Southwest China. *Virus Genes* 2017; **53**: 190-196 [PMID: 28012010 DOI: 10.1007/s11262-016-1420-0]

11 **Seto WK**, Lai CL, Fung J, Hung I, Yuen J, Young J, Wong DK, Yuen MF. Natural history of chronic hepatitis C: genotype 1 versus genotype 6. *J Hepatol* 2010; **53**: 444-448 [PMID: 20554340 DOI: 10.1016/j.jhep.2010.04.009]

12 **Umumararungu E**, Ntaganda F, Kagira J, Maina N. Prevalence of Hepatitis C Virus Infection and Its Risk Factors among Patients Attending Rwanda Military Hospital, Rwanda. *Biomed Res Int* 2017; **2017**: 5841272 [PMID: 28246598 DOI: 10.1155/2017/5841272]

13 **Nepal A**, Kunwar B. Evidence of Hepatitis C Virus Infection and Associated Treatment in Nepal. *J Mol Biomark Diagn* 2016; **7**: 1000270 [DOI: 10.4172/2155-9929.1000270]

14 **Chen SL**, Morgan TR. The natural history of hepatitis C virus (HCV) infection. *Int J Med Sci* 2006; **3**: 47-52 [PMID: 16614742 DOI: 10.7150/ijms.3.47]

15 **Hoofnagle JH**. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997; **26**: 15S-20S [PMID: 9305658 DOI: 10.1002/hep.510260703]

16 **Farshadpour F**, Raherkhani R. Hepatitis C-related diabetes mellitus: A health dilemma too necessary to consider. *Virol Research J* 2016; **1**: 1-2

17 **Taherkhani R**, Farshadpour F. Epidemiology of hepatitis C virus in Iran. *World J Gastroenterol* 2015; **21**: 10790-10810 [PMID:

26478671 DOI: 10.3748/wjg.v21.i38.10790]
18 **Hwang SJ**, Chen LK. Chronic hepatitis C and diabetes mellitus. *J Chin Med Assoc* 2006; **69**: 143-145 [PMID: 16689193 DOI: 10.1016/S1726-4901(09)70194-7]
19 **Rouabhia S**, Malek R, Bounecer H, Dekaken A, Bendali Amor F, Sadelaoud M, Benouar A. Prevalence of type 2 diabetes in Algerian patients with hepatitis C virus infection. *World J Gastroenterol* 2010; **16**: 3427-3431 [PMID: 20632447 DOI: 10.3748/wjg.v16.i27.3427]
20 **Jadoon NA**, Shahzad MA, Yaqoob R, Hussain M, Ali N. Seroprevalence of hepatitis C in type 2 diabetes: evidence for a positive association. *Virol J* 2010; **7**: 304 [PMID: 21054842 DOI: 10.1186/1743-422X-7-304]
21 **Galossi A**, Guarisco R, Bellis L, Puoti C. Extrahepatic manifestations of chronic HCV infection. *J Gastrointestin Liver Dis* 2007; **16**: 65-73 [PMID: 17410291]
22 **Kartashev V**, Döring M, Nieto L, Coletta E, Kaiser R, Sierra S; HCV EuResist Study group. New findings in HCV genotype distribution in selected West European, Russian and Israeli regions. *J Clin Virol* 2016; **81**: 82-89 [PMID: 27367545 DOI: 10.1016/j.jcv.2016.05.010]
23 **Smith DB**, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, Simmonds P. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. *Hepatology* 2014; **59**: 318-327 [PMID: 24115039 DOI: 10.1002/hep.26744]
24 **Roman F**, Hawotte K, Struck D, Ternes AM, Servais JY, Arendt V, Hoffman P, Hemmer R, Staub T, Seguin-Devaux C, Schmit JC. Hepatitis C virus genotypes distribution and transmission risk factors in Luxembourg from 1991 to 2006. *World J Gastroenterol* 2008; **14**: 1237-1243 [PMID: 18300350 DOI: 10.3748/wjg.14.1237]
25 **Keskın F**, Çıftçı S, Türkoğlu S, Badur S. Transmission routes of chronic hepatitis C and their relation to HCV genotypes. *Turk J Gastroenterol* 2010; **21**: 396-400 [PMID: 21331993 DOI: 10.4318/tjg.2010.0126]
26 **Farshadpour F**, Makvandi M, Samarbafzadeh AR, Jalalifar MA. Determination of hepatitis C virus genotypes among blood donors in Ahvaz, Iran. *Indian J Med Microbiol* 2010; **28**: 54-56 [PMID: 20061766 DOI: 10.4103/0255-0857.58731]
27 **Al-Kubaisy W**, Al-Naggar RA, Ibrahim NSN, Bobryshev YV, Al-Kubaisy MW. Is dental extraction a risk factor for contracting HCV infection: Abs, RNA and genotype detection. *Oral Biol Dentist* 2014; **2**: 7 [DOI: 10.7243/2053-5775-2-7]
28 **Albenmousa A**, Al Obary E, Bzeizi K. Treatment Options for HCV Genotype-4. *J Infect Dis Ther* 2016; **4**: 1000266 [DOI: 10.4172/2332-0877.1000266]
29 **Nouroz F**, Shaheen S, Mujtaba G, Noreen S. An overview on hepatitis C virus genotypes and its control. *EJMHG* 2015; **16**: 291-298 [DOI: 10.1016/j.ejmhg.2015.05.003]
30 **Murphy DG**, Sablon E, Chamberland J, Fournier E, Dandavino R, Tremblay CL. Hepatitis C virus genotype 7, a new genotype originating from central Africa. *J Clin Microbiol* 2015; **53**: 967-972 [PMID: 25520447 DOI: 10.1128/JCM.02831-14]
31 **Ampuero J**, Romero-Gómez M, Reddy KR. Review article: HCV genotype 3 - the new treatment challenge. *Aliment Pharmacol Ther* 2014; **39**: 686-698 [PMID: 24612116 DOI: 10.1111/apt.12646]
32 **Salemovic D**, Pesic-Pavlovic I, Jevtovic D, Bojovic K, Ranin J, Brmbolic B, Stanojevic M. Intravenous drug use - an independent predictor for HCV genotypes 3 and 4 infection among HIV/HCV co-infected patients. *Arch Med Sci* 2017; **13**: 652-658 [PMID: 28507583 DOI: 10.5114/aoms.2017.66022]
33 **Chan A**, Patel K, Naggie S. Genotype 3 Infection: The Last Stand of Hepatitis C Virus. *Drugs* 2017; **77**: 131-144 [PMID: 28074358 DOI: 10.1007/s40265-016-0685-x]
34 **Yee BE**, Nguyen NH, Zhang B, Lin D, Vutien P, Wong CR, Lutchman GA, Nguyen MH. Sustained virological response and its treatment predictors in hepatitis C virus genotype 4 compared to genotypes 1, 2, and 3: a meta-analysis. *BMJ Open Gastroenterol* 2015; **2**: e000049 [PMID: 26462288 DOI: 10.1136/bmjgast-2015-000049]
35 **Gower E**, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol* 2014; **61**: S45-S57 [PMID: 25086286 DOI: 10.1016/j.jhep.2014.07.027]
36 **Ramia S**, Eid-Fares J. Distribution of hepatitis C virus genotypes in the Middle East. *Int J Infect Dis* 2006; **10**: 272-277 [PMID: 16564719 DOI: 10.1016/j.ijid.2005.07.008]
37 **Kanda T**, Nakamoto S, Nakamura M, Jiang X, Miyamura T, Wu S, Yokosuka O. Direct-acting Antiviral Agents for the Treatment of Chronic Hepatitis C Virus Infection. *J Clin Transl Hepatol* 2014; **2**: 1-6 [PMID: 26356295 DOI: 10.14218/JCTH.2013.00025]
38 **Bartels DJ**, Sullivan JC, Zhang EZ, Tigges AM, Dorrian JL, De Meyer S, Takemoto D, Dondero E, Kwong AD, Picchio G, Kieffer TL. Hepatitis C virus variants with decreased sensitivity to direct-acting antivirals (DAAs) were rarely observed in DAA-naive patients prior to treatment. *J Virol* 2013; **87**: 1544-1553 [PMID: 23152524 DOI: 10.1128/JVI.02294-12]
39 **Asselah T**. A revolution in HCV treatment with direct-acting antivirals: from non-response to eradication. *J Hepatol* 2012; **57**: 455-457 [PMID: 22465738 DOI: 10.1016/j.jhep.2012.03.005]
40 **Tamori A**, Enomoto M, Kawada N. Recent Advances in Antiviral Therapy for Chronic Hepatitis C. *Mediators Inflamm* 2016; **2016**: 6841628 [PMID: 27022210 DOI: 10.1155/2016/6841628]
41 **Wyles D**, Dvory-Sobol H, Svarovskaia ES, Doehle BP, Martin R, Afdhal NH, Kowdley KV, Lawitz E, Brainard DM, Miller MD, Mo H, Gane EJ. Post-treatment resistance analysis of hepatitis C virus from phase II and III clinical trials of ledipasvir/sofosbuvir. *J Hepatol* 2017; **66**: 703-710 [PMID: 27923693 DOI: 10.1016/j.jhep.2016.11.022]
42 **Falade-Nwulia O**, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. *Ann Intern Med* 2017; **166**: 637-648 [PMID: 28319996 DOI: 10.7326/M16-2575]
43 **Wang S**, Wang Y, Wang J, Sato T, Izawa K, Soloshonok VA, Liu H. The second-generation of highly potent hepatitis C virus (HCV) NS3/4A protease inhibitors: Evolutionary design based on tailor-made amino acids, synthesis and major features of bio-activity. *Curr Pharm Des* 2017; Epub ahead of print [PMID: 28530544 DOI: 10.2174/1381612823666170522122424]
44 **Alavian SM**, Hajarizadeh B, Bagheri Lankarani K, Sharafi H, Ebrahimi Daryani N, Merat S, Mohraz M, Mardani M, Fattahi MR, Poustchi H, Nikbin M, Nabavi M, Adibi P, Ziaee M, Behnava B, Rezaee-Zavareh MS, Colombo M, Massoumi H, Bizri AR, Eghtesad B, Amiri M, Namvar A, Hesamizadeh K, Malekzadeh R. Recommendations for the Clinical Management of Hepatitis C in Iran: A Consensus-Based National Guideline. *Hepat Mon* 2016; **16**: e40959 [PMID: 27799966 DOI: 10.5812/hepatmon.guideline]
45 **Esposito I**, Trinks J, Soriano V. Hepatitis C virus resistance to the new direct-acting antivirals. *Expert Opin Drug Metab Toxicol* 2016; **12**: 1197-1209 [PMID: 27384079 DOI: 10.1080/17425255.2016.1209484]
46 **Karbalaie Niya MH**, Salman-Tabar S, Bokharaei-Salim F, Behmanesh M, Keyvani H. Prevalence of resistant associated variants (RAVs) in the naïve HCV patient candidate for direct acting antiviral (DAA) therapy. *Microb Pathog* 2017; **105**: 166-170 [PMID: 28161357 DOI: 10.1016/j.micpath.2017.01.060]
47 **Ghany MG**, Nelson DR, Strader DB, Thomas DL, Seeff LB; American Association for Study of Liver Diseases. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; **54**: 1433-1444 [PMID: 21898493 DOI: 10.1002/hep.24641]
48 **Deutsch M**, Papatheodoridis GV. Danoprevir, a small-molecule NS3/4A protease inhibitor for the potential oral treatment of HCV infection. *Curr Opin Investig Drugs* 2010; **11**: 951-963 [PMID: 20721837]
49 **Guedj J**, Dahari H, Shudo E, Smith P, Perelson AS. Hepatitis C viral kinetics with the nucleoside polymerase inhibitor mericitabine (RG7128). *Hepatology* 2012; **55**: 1030-1037 [PMID: 22095398 DOI: 10.1002/hep.24788]
50 **Greig SL**. Sofosbuvir/Velpatasvir: A Review in Chronic Hepatitis C. *Drugs* 2016; **76**: 1567-1578 [PMID: 27730529 DOI: 10.1007/s40265-016-0648-2]
51 **Tong L**, Yu W, Chen L, Selyutin O, Dwyer MP, Nair AG, Mazzola

R, Kim JH, Sha D, Yin J, Ruck RT, Davies IW, Hu B, Zhong B, Hao J, Ji T, Zan S, Liu R, Agrawal S, Xia E, Curry S, McMonagle P, Bystol K, Lahser F, Carr D, Rokosz L, Ingravallo P, Chen S, Feng KI, Cartwright M, Asante-Appiah E, Kozlowski JA. Discovery of Ruzasvir (MK-8408): A Potent, Pan-Genotype HCV NS5A Inhibitor with Optimized Activity against Common Resistance-Associated Polymorphisms. *J Med Chem*2017; **60**: 290-306 [PMID: 27808515 DOI: 10.1021/acs.jmedchem.6b01310]

52 **Walker J**, Crosby R, Wang A, Woldu E, Vamathevan J, Voitenleitner C, You S, Remlinger K, Duan M, Kazmierski W, Hamatake R. Preclinical characterization of GSK2336805, a novel inhibitor of hepatitis C virus replication that selects for resistance in NS5A. *Antimicrob Agents Chemother* 2014; **58**: 38-47 [PMID: 24126581 DOI: 10.1128/AAC.01363-13]

53 **Adkison KK**, Gan J, Elko-Simms L, Gardner S, Dumont E, Jones LS, Saunders J, Marbury T, Smith W, Berg J, Galloway C, Stump PJ. Pharmacokinetics of hepatitis C virus NS5A inhibitor JNJ-56914845 (GSK2336805) in subjects with hepatic impairment. *J Clin Pharmacol* 2015; **55**: 1042-1050 [PMID: 25857714 DOI: 10.1002/jcph.512]

54 **Rodriguez-Torres M**, Stoehr A, Gane EJ, Serfaty L, Lawitz E, Zhou A, Bourque M, Bhanja S, Strizki J, Barnard RJ, Hwang PM, DiNubile MJ, Mobashery N. Combination of vaniprevir with peginterferon and ribavirin significantly increases the rate of SVR in treatment-experienced patients with chronic HCV genotype 1 infection and cirrhosis. *Clin Gastroenterol Hepatol* 2014; **12**: 1029-37.e5 [PMID: 24120953 DOI: 10.1016/j.cgh.2013.09.067]

55 **Gane EJ**, Rouzier R, Wiercinska-Drapalo A, Larrey DG, Morcos PN, Brennan BJ, Le Pogam S, Nájera I, Petric R, Tran JQ, Kulkarni R, Zhang Y, Smith P, Yetzer ES, Shulman NS. Efficacy and safety of danoprevir-ritonavir plus peginterferon alfa-2a-ribavirin in hepatitis C virus genotype 1 prior null responders. *Antimicrob Agents Chemother* 2014; **58**: 1136-1145 [PMID: 24295986 DOI: 10.1128/AAC.01515-13]

56 **Sarrazin C**, Castelli F, Andreone P, Buti M, Colombo M, Pol S, Calinas F, Puoti M, Olveira A, Shiffman M, Stern JO, Kukolj G, Roehrle M, Aslanyan S, Deng Q, Vinisko R, Mensa FJ, Nelson DR. HCVerso1 and 2: faldaprevir with deleobuvir (BI 207127) and ribavirin for treatment-naïve patients with chronic hepatitis C virus genotype-1b infection. *Clin Exp Gastroenterol* 2016; **9**: 351-363 [PMID: 27920566 DOI: 10.2147/CEG.S111116]

57 **Tao T**, Jiang X, Chen Y, Song Y. Efficacy and Safety of Ledipasvir/Sofosbuvir with and without Ribavirin in Patients with Chronic Hepatitis C Virus Genotype 1 Infection: a meta-analysis. *Int J Infect Dis* 2017; **55**: 56-71 [PMID: 28040553 DOI: 10.1016/j.ijid.2016.12.023]

58 **Jensen CM**, Holle LM. Ledipasvir-Sofosbuvir: A Once-Daily Oral Treatment Option for Chronic Hepatitis C Virus Genotype 1 Infection. *Pharmacotherapy* 2016; **36**: 562-574 [PMID: 27027412 DOI: 10.1002/phar.1748]

59 **Sato K**, Hosonuma K, Yamazaki Y, Kobayashi T, Takakusagi S, Horiguchi N, Kakizaki S, Kusano M, Ohnishi H, Okamoto H, Yamada M. Combination Therapy with Ombitasvir/Paritaprevir/Ritonavir for Dialysis Patients Infected with Hepatitis C Virus: A Prospective Multi-Institutional Study. *Tohoku J Exp Med* 2017; **241**: 45-53 [PMID: 28090038 DOI: 10.1620/tjem.241.45]

60 **Flisiak R**, Janczewska E, Wawrzynowicz-Syczewska M, Jaroszewicz J, Zarębska-Michaluk D, Nazzal K, Bolewska B, Bialkowska J, Berak H, Fleischer-Stępniewska K, Tomasiewicz K, Karwowska K, Rostkowska K, Piekarska A, Tronina O, Madej G, Garlicki A, Lucejko M, Pisula A, Karpińska E, Kryczka W, Wiercińska-Drapało A, Mozer-Lisewska I, Jabłkowski M, Horban A, Knysz B, Tudrujek M, Halota W, Simon K. Real-world effectiveness and safety of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in hepatitis C: AMBER study. *Aliment Pharmacol Ther* 2016; **44**: 946-956 [PMID: 27611776 DOI: 10.1111/apt.13790]

61 **Calleja JL**, Crespo J, Rincón D, Ruiz-Antorán B, Fernandez I, Perelló C, Gea F, Lens S, García-Samaniego J, Sacristán B, García-Eliz M, Llerena S, Pascasio JM, Turnes J, Torras X, Morillas RM, Llaneras J, Serra MA, Diago M, Rodriguez CF, Ampuero J, Jorquera F, Simon MA, Arenas J, Navascues CA, Bañares R, Muñoz R, Albillos A, Mariño Z; Spanish Group for the Study of the Use of Direct-acting Drugs Hepatitis C Collaborating Group. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: Results from a Spanish real-world cohort. *J Hepatol* 2017; **66**: 1138-1148 [PMID: 28189751 DOI: 10.1016/j.jhep.2017.01.028]

62 **Crespo J**, Calleja JL, Fernández I, Sacristan B, Ruiz-Antorán B, Ampuero J, Hernández-Conde M, García-Samaniego J, Gea F, Buti M, Cabezas J, Lens S, Morillas RM, Salcines JR, Pascasio JM, Turnes J, Sáez-Royuela F, Arenas J, Rincón D, Prieto M, Jorquera F, Sanchez Ruano JJ, Navascués CA, Molina E, Moya AG, Moreno-Planas JM; Spanish Group for the Study of the Use of Direct-acting Drugs Hepatitis C Collaborating Group. Real-World Effectiveness and Safety of Oral Combination Antiviral Therapy for Hepatitis C Virus Genotype 4 Infection. *Clin Gastroenterol Hepatol* 2017; **15**: 945-949.e1 [PMID: 28238958 DOI: 10.1016/j.cgh.2017.02.020]

63 **Wilfret DA**, Walker J, Adkison KK, Jones LA, Lou Y, Gan J, Castellino S, Moseley CL, Horton J, de Serres M, Culp A, Goljer I, Spreen W. Safety, tolerability, pharmacokinetics, and antiviral activity of GSK2336805, an inhibitor of hepatitis C virus (HCV) NS5A, in healthy subjects and subjects chronically infected with HCV genotype 1. *Antimicrob Agents Chemother* 2013; **57**: 5037-5044 [PMID: 23896477 DOI: 10.1128/AAC.00910-13]

64 **Cho BW**, Kim SB, Song IH, Lee SH, Kim HS, Lee TH, Kang YW, Kim SH, Lee BS, Chae HB. Efficacy and safety of daclatasvir plus asunaprevir for Korean patients with HCV genotype Ib infection: a retrospective multi-institutional study. *Clin Mol Hepatol* 2017; **23**: 51-56 [PMID: 28297836 DOI: 10.3350/cmh.2016.0053]

65 **Poordad F**, Felizarta F, Asatryan A, Sulkowski MS, Reindollar RW, Landis CS, Gordon SC, Flamm SL, Fried MW, Bernstein DE, Lin CW, Liu R, Lovell SS, Ng TI, Kort J, Mensa FJ. Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment. *Hepatology* 2017; **66**: 389-397 [PMID: 28128852 DOI: 10.1002/hep.29081]

66 **Brieva T**, Rivero A, Rivero-Juarez A. Pharmacokinetic drug evaluation of velpatasvir plus sofosbuvir for the treatment of hepatitis C virus infection. *Expert Opin Drug Metab Toxicol* 2017; **13**: 483-490 [PMID: 28165830 DOI: 10.1080/17425255.2017.1292253]

67 **Feld JJ**, Ramji A, Shafran SD, Willems B, Marotta P, Huchet E, Vachon ML, Svarovskaia ES, Huang KC, Hyland RH, Yun C, Massetto B, Brainard DM, McHutchison JG, Tam E, Bailey R, Cooper C, Yoshida EM, Greenbloom S, Elkhashab M, Borgia S, Swain MG. Ledipasvir-Sofosbuvir Plus Ribavirin in Treatment-Naive Patients With Hepatitis C Virus Genotype 3 Infection: An Open-Label Study. *Clin Infect Dis* 2017; Epub ahead of print [PMID: 28535298 DOI: 10.1093/cid/cix289]

68 **Ramos H**, Linares P, Badia E, Martín I, Gómez J, Almohalla C, Jorquera F, Calvo S, García I, Conde P, Álvarez B, Karpman G, Lorenzo S, Gozalo V, Vásquez M, Joao D, de Benito M, Ruiz L, Jiménez F, Sáez-Royuela F, Asociación Castellano Y Leonesa de Hepatología ACyLHE. Interferon-free treatments in patients with hepatitis C genotype 1-4 infections in a real-world setting. *World J Gastrointest Pharmacol Ther* 2017; **8**: 137-146 [PMID: 28533924 DOI: 10.4292/wjgpt.v8.i2.137]

69 **Wyles DL**, Rodriguez-Torres M, Lawitz E, Shiffman ML, Pol S, Herring RW, Massetto B, Kanwar B, Trenkle JD, Pang PS, Zhu Y, Mo H, Brainard DM, Subramanian GM, McHutchison JG, Habersetzer F, Sulkowski MS. All-oral combination of ledipasvir, vedroprevir, tegobuvir, and ribavirin in treatment-naïve patients with genotype 1 HCV infection. *Hepatology* 2014; **60**: 56-64 [PMID: 24501005 DOI: 10.1002/hep.27053]

70 **Kanda T**, Yokosuka O, Omata M. Faldaprevir for the treatment of hepatitis C. *Int J Mol Sci* 2015; **16**: 4985-4996 [PMID: 25749475 DOI: 10.3390/ijms16034985]

71 **Zeuzem S**, Soriano V, Asselah T, Bronowicki JP, Lohse AW, Müllhaupt B, Schuchmann M, Bourlière M, Buti M, Roberts SK, Gane EJ, Stern JO, Vinisko R, Kukolj G, Gallivan JP, Böcher WO, Mensa FJ. Faldaprevir and deleobuvir for HCV genotype 1 infection. *N Engl J Med* 2013; **369**: 630-639 [PMID: 23944300 DOI: 10.1056/

NEJMoa1213557]
72 **Jensen DM**, Brunda M, Elston R, Gane EJ, George J, Glavini K, Hammond JM, Le Pogam S, Nájera I, Passe S, Piekarska A, Rodriguez I, Zeuzem S, Chu T; ANNAPURNA study investigators. Interferon-free regimens containing setrobuvir for patients with genotype 1 chronic hepatitis C: a randomized, multicenter study. *Liver Int* 2016; **36**: 505-514 [PMID: 26519669 DOI: 10.1111/liv.12997]
73 **Jiang M**, Zhang EZ, Ardzinski A, Tigges A, Davis A, Sullivan JC, Nelson M, Spanks J, Dorrian J, Nicolas O, Bartels DJ, Rao BG, Rijnbrand R, Kieffer TL. Genotypic and phenotypic analyses of hepatitis C virus variants observed in clinical studies of VX-222, a nonnucleoside NS5B polymerase inhibitor. *Antimicrob Agents Chemother* 2014; **58**: 5456-5465 [PMID: 24982088 DOI: 10.1128/AAC.03052-14]
74 **Yi G**, Deval J, Fan B, Cai H, Soulard C, Ranjith-Kumar CT, Smith DB, Blatt L, Beigelman L, Kao CC. Biochemical study of the comparative inhibition of hepatitis C virus RNA polymerase by VX-222 and filibuvir. *Antimicrob Agents Chemother* 2012; **56**: 830-837 [PMID: 22143520 DOI: 10.1128/AAC.05438-11]
75 **Vince B**, Hill JM, Lawitz EJ, O'Riordan W, Webster LR, Gruener DM, Mofsen RS, Murillo A, Donovan E, Chen J, McCarville JF, Sullivan-Bólyai JZ, Mayers D, Zhou XJ. A randomized, double-blind, multiple-dose study of the pan-genotypic NS5A inhibitor samatasvir in patients infected with hepatitis C virus genotype 1, 2, 3 or 4. *J Hepatol* 2014; **60**: 920-927 [PMID: 24434503 DOI: 10.1016/j.jhep.2014.01.003]
76 **de Bruijne J**, Bergmann JF, Reesink HW, Weegink CJ, Molenkamp R, Schinkel J, Tong X, Li J, Treitel MA, Hughes EA, van Lier JJ, van Vliet AA, Janssen HL, de Knegt RJ. Antiviral activity of narlaprevir combined with ritonavir and pegylated interferon in chronic hepatitis C patients. *Hepatology* 2010; **52**: 1590-1599 [PMID: 20938912 DOI: 10.1002/hep.23899]
77 **Lawitz E**, Poordad F, Wells J, Hyland RH, Yang Y, Dvory-Sobol H, Stamm LM, Brainard DM, McHutchison JG, Landaverde C, Gutierrez J. Sofosbuvir-velpatasvir-voxilaprevir with or without ribavirin in direct-acting antiviral-experienced patients with genotype 1 hepatitis C virus. *Hepatology* 2017; **65**: 1803-1809 [PMID: 28220512 DOI: 10.1002/hep.29130]
78 **Bourlière M**, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, Ravendhran N, Vierling JM, Tran TT, Pianko S, Bansal MB, de Lédinghen V, Hyland RH, Stamm LM, Dvory-Sobol H, Svarovskaia E, Zhang J, Huang KC, Subramanian GM, Brainard DM, McHutchison JG, Verna EC, Buggisch P, Landis CS, Younes ZH, Curry MP, Strasser SI, Schiff ER, Reddy KR, Manns MP, Kowdley KV, Zeuzem S; POLARIS-1 and POLARIS-4 Investigators. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med* 2017; **376**: 2134-2146 [PMID: 28564569 DOI: 10.1056/NEJMoa1613512]
79 **World Health Organization**. Hepatitis C, WHO fact sheet; No. 164, updated April 2017. Available from: URL: http://www.who.int/mediacentre/factsheets/fs164/en/
80 **Shaheen MA**, Idrees M. Evidence-based consensus on the diagnosis, prevention and management of hepatitis C virus disease. *World J Hepatol* 2015; **7**: 616-627 [PMID: 25848486 DOI: 10.4254/wjh.v7.i3.616]
81 **Helaly GF**, Elsheredy AG, El Basset Mousa AA, Ahmed HK, Oluyemi AE. Seronegative and occult hepatitis C virus infections in patients with hematological disorders. *Arch Virol* 2017; **162**: 63-69 [PMID: 27665588 DOI: 10.1007/s00705-016-3049-7]
82 **Easterbrook PJ**, Roberts T, Sands A, Peeling R. Diagnosis of viral hepatitis. *Curr Opin HIV AIDS* 2017; **12**: 302-314 [PMID: 28306597 DOI: 10.1097/COH.0000000000000370]
83 **Carreño V**. Seronegative occult hepatitis C virus infection: clinical implications. *J Clin Virol* 2014; **61**: 315-320 [PMID: 25304062 DOI: 10.1016/j.jcv.2014.09.007]
84 **De Marco L**, Manzini P, Trevisan M, Gillio-Tos A, Danielle F, Balloco C, Pizzi A, De Filippo E, D'Antico S, Violante B, Valfrè A, Curti F, Merletti F, Richiardi L. Prevalence and follow-up of occult HCV infection in an Italian population free of clinically detectable infectious liver disease. *PLoS One* 2012; **7**: e43541 [PMID: 22927986 DOI: 10.1371/journal.pone.0043541]
85 **Jain P**, Nijhawan S. Occult hepatitis C virus infection is more common than hepatitis B infection in maintenance hemodialysis patients. *World J Gastroenterol* 2008; **14**: 2288-2289 [PMID: 18407613 DOI: 10.3748/wjg.14.2288]
86 **Carreño V**, Bartolomé J, Castillo I, Quiroga JA. New perspectives in occult hepatitis C virus infection. *World J Gastroenterol* 2012; **18**: 2887-2894 [PMID: 22736911 DOI: 10.3748/wjg.v18.i23.2887]
87 **Farshadpour F**, Taherkhani R, Tajbakhsh S, Gholizadeh Tangestani M, Hajiani G, Sharifi N, Taherkhani S, Nejadbolkheyr A. Prevalence and Trends of Transfusion-Transmissible Viral Infections among Blood Donors in South of Iran: An Eleven-Year Retrospective Study. *PLoS One* 2016; **11**: e0157615 [PMID: 27309959 DOI: 10.1371/journal.pone.0157615]
88 **Baumert TF**, Fauvelle C, Chen DY, Lauer GM. A prophylactic hepatitis C virus vaccine: a distant peak still worth climbing. *J Hepatol* 2014; **61**: S34-S44 [PMID: 25443345 DOI: 10.1016/j.jhep.2014.09.009]
89 **Abdelwahab KS**, Ahmed Said ZN. Status of hepatitis C virus vaccination: Recent update. *World J Gastroenterol* 2016; **22**: 862-873 [PMID: 26811632 DOI: 10.3748/wjg.v22.i2.862]
90 **Zingaretti C**, De Francesco R, Abrignani S. Why is it so difficult to develop a hepatitis C virus preventive vaccine? *Clin Microbiol Infect* 2014; **20** Suppl 5: 103-109 [PMID: 24829939 DOI: 10.1111/1469-0691.12493]
91 **Forns X**, Bukh J, Purcell RH. The challenge of developing a vaccine against hepatitis C virus. *J Hepatol* 2002; **37**: 684-695 [PMID: 12399239 DOI: 10.1016/S0168-8278(02)00308-2]
92 **Man John Law L**, Landi A, Magee WC, Lorne Tyrrell D, Houghton M. Progress towards a hepatitis C virus vaccine. *Emerg Microbes Infect* 2013; **2**: e79 [PMID: 26038445 DOI: 10.1038/emi.2013.79]
93 **Ghasemi F**, Rostami S, Meshkat Z. Progress in the development of vaccines for hepatitis C virus infection. *World J Gastroenterol* 2015; **21**: 11984-12002 [PMID: 26576087 DOI: 10.3748/wjg.v21.i42.11984]
94 **Dunlop J**, Owsianka A, Cowton V, Patel A. Current and future prophylactic vaccines for hepatitis C virus. *Vaccine: Development and Therapy* 2015; **2015**: 31-44
95 **Yu CI**, Chiang BL. A new insight into hepatitis C vaccine development. *J Biomed Biotechnol* 2010; **2010**: 548280 [PMID: 20625493 DOI: 10.1155/2010/548280]
96 **Halliday J**, Klenerman P, Barnes E. Vaccination for hepatitis C virus: closing in on an evasive target. *Expert Rev Vaccines* 2011; **10**: 659-672 [PMID: 21604986 DOI: 10.1586/erv.11.55]
97 **Naderi M**, Gholipour N, Zolfaghari MR, Moradi Binabaj M, Yegane Moghadam A, Motalleb G. Hepatitis C virus and vaccine development. *Int J Mol Cell Med* 2014; **3**: 207-215 [PMID: 25635247]
98 **Ogholikhan S**, Schwarz KB. Hepatitis Vaccines. *Vaccines* (Basel) 2016; **4**: E6 [PMID: 26978406 DOI: 10.3390/vaccines4010006]
99 **Balasco N**, Barone D, Sandomenico A, Ruggiero A, Doti N, Berisio R, Ruvo M, Vitagliano L. Structural versatility of hepatitis C virus proteins: implications for the design of novel anti-HCV intervention strategies. *Curr Med Chem* 2017; Epub ahead of print [PMID: 28482787 DOI: 10.2174/0929867324666170508105544]
100 **Li S**, Plebanski M, Smooker P, Gowans EJ. Editorial: Why Vaccines to HIV, HCV, and Malaria Have So Far Failed-Challenges to Developing Vaccines Against Immunoregulating Pathogens. *Front Microbiol* 2015; **6**: 1318 [PMID: 26640461 DOI: 10.3389/fmicb.2015.01318]
101 **Choo QL**, Kuo G, Ralston R, Weiner A, Chien D, Van Nest G, Han J, Berger K, Thudium K, Kuo C. Vaccination of chimpanzees against infection by the hepatitis C virus. *Proc Natl Acad Sci USA* 1994; **91**: 1294-1298 [PMID: 7509068 DOI: 10.1073/pnas.91.4.1294]
102 **Verstrepen BE**, Depla E, Rollier CS, Mares G, Drexhage JA, Priem S, Verschoor EJ, Koopman G, Granier C, Dreux M, Cosset FL, Maertens G, Heeney JL. Clearance of genotype 1b hepatitis C virus in chimpanzees in the presence of vaccine-induced E1-neutralizing antibodies. *J Infect Dis* 2011; **204**: 837-844 [PMID: 21849281 DOI: 10.1093/infdis/jir423]

103 **Leroux-Roels G**, Depla E, Hulstaert F, Tobback L, Dincq S, Desmet J, Desombere I, Maertens G. A candidate vaccine based on the hepatitis C E1 protein: tolerability and immunogenicity in healthy volunteers. *Vaccine* 2004; **22**: 3080-3086 [PMID: 15297058 DOI: 10.1016/j.vaccine.2004.02.002]

104 **Frey SE**, Houghton M, Coates S, Abrignani S, Chien D, Rosa D, Pileri P, Ray R, Di Bisceglie AM, Rinella P, Hill H, Wolff MC, Schultze V, Han JH, Scharschmidt B, Belshe RB. Safety and immunogenicity of HCV E1E2 vaccine adjuvanted with MF59 administered to healthy adults. *Vaccine* 2010; **28**: 6367-6373 [PMID: 20619382 DOI: 10.1016/j.vaccine.2010.06.084]

105 **Nevens F**, Roskams T, Van Vlierberghe H, Horsmans Y, Sprengers D, Elewaut A, Desmet V, Leroux-Roels G, Quinaux E, Depla E, Dincq S, Vander Stichele C, Maertens G, Hulstaert F. A pilot study of therapeutic vaccination with envelope protein E1 in 35 patients with chronic hepatitis C. *Hepatology* 2003; **38**: 1289-1296 [PMID: 14578869 DOI: 10.1053/jhep.2003.50474]

106 **Wedemeyer H,** Mazur W, Nevens F, Horsmans Y, Adler M, Blum H, Inglot M, Gerken G, Janczewska E, Roskams T. Factors influencing progression of liver fibrosis in patients with chronic hepatitis C: results of the 3-year T2S-918-HCV study with HCVE1 therapeutic vaccine. *J Hepatol* 2008; **48**: S27-S28 [DOI: 10.1016/S0168-8278(08)60063-X]

107 **Drane D**, Maraskovsky E, Gibson R, Mitchell S, Barnden M, Moskwa A, Shaw D, Gervase B, Coates S, Houghton M, Basser R. Priming of CD4+ and CD8+ T cell responses using a HCV core ISCOMATRIX vaccine: a phase I study in healthy volunteers. *Hum Vaccin* 2009; **5**: 151-157 [PMID: 19246990 DOI: 10.4161/hv.5.3.6614]

108 **Habersetzer F**, Baumert TF, Stoll-Keller F. GI-5005, a yeast vector vaccine expressing an NS3-core fusion protein for chronic HCV infection. *Curr Opin Mol Ther* 2009; **11**: 456-462 [PMID: 19649991]

109 **Pockros P**, Jacobson I, Boyer TD, Schiff ER, Everson GT, Lee WM, Vierling JM, Lawitz E, Kugelmas M, Tsai N. GI-5005 Therapeutic vaccine plus Peg-IFN/Ribavirin improves sustained virologic response versus Peg-IFN/Ribavirin in prior non-responders with genotype 1 chronic HCV infection. *Hepatology* 2010; **52**: 404A-405A

110 **Yutani S**, Komatsu N, Shichijo S, Yoshida K, Takedatsu H, Itou M, Kuromatu R, Ide T, Tanaka M, Sata M, Yamada A, Itoh K. Phase I clinical study of a peptide vaccination for hepatitis C virus-infected patients with different human leukocyte antigen-class I-A alleles. *Cancer Sci* 2009; **100**: 1935-1942 [PMID: 19604246 DOI: 10.1111/j.1349-7006.2009.01256.x]

111 **Yutani S**, Yamada A, Yoshida K, Takao Y, Tamura M, Komatsu N, Ide T, Tanaka M, Sata M, Itoh K. Phase I clinical study of a personalized peptide vaccination for patients infected with hepatitis C virus (HCV) 1b who failed to respond to interferon-based therapy. *Vaccine* 2007; **25**: 7429-7435 [PMID: 17845828 DOI: 10.1016/j.vaccine.2007.08.005]

112 **Gowans EJ**, Roberts S, Jones K, Dinatale I, Latour PA, Chua B, Eriksson EM, Chin R, Li S, Wall DM, Sparrow RL, Moloney J, Loudovaris M, Ffrench R, Prince HM, Hart D, Zeng W, Torresi J, Brown LE, Jackson DC. A phase I clinical trial of dendritic cell immunotherapy in HCV-infected individuals. *J Hepatol* 2010; **53**: 599-607 [PMID: 20667615 DOI: 10.1016/j.jhep.2010.05.007]

113 **Firbas C**, Jilma B, Tauber E, Buerger V, Jelovcan S, Lingnau K, Buschle M, Frisch J, Klade CS. Immunogenicity and safety of a novel therapeutic hepatitis C virus (HCV) peptide vaccine: a randomized, placebo controlled trial for dose optimization in 128 healthy subjects. *Vaccine* 2006; **24**: 4343-4353 [PMID: 16581161 DOI: 10.1016/j.vaccine.2006.03.009]

114 **Klade CS**, Wedemeyer H, Berg T, Hinrichsen H, Cholewinska G, Zeuzem S, Blum H, Buschle M, Jelovcan S, Buerger V, Tauber E, Frisch J, Manns MP. Therapeutic vaccination of chronic hepatitis C nonresponder patients with the peptide vaccine IC41. *Gastroenterology* 2008; **134**: 1385-1395 [PMID: 18471515 DOI: 10.1053/j.gastro.2008.02.058]

115 **Firbas C**, Boehm T, Buerger V, Schuller E, Sabarth N, Jilma B, Klade CS. Immunogenicity and safety of different injection routes and schedules of IC41, a Hepatitis C virus (HCV) peptide vaccine. *Vaccine* 2010; **28**: 2397-2407 [PMID: 20060945 DOI: 10.1016/j.vaccine.2009.12.072]

116 **Klade CS**, Schuller E, Boehm T, von Gabain A, Manns MP. Sustained viral load reduction in treatment-naive HCV genotype 1 infected patients after therapeutic peptide vaccination. *Vaccine* 2012; **30**: 2943-2950 [PMID: 22401867 DOI: 10.1016/j.vaccine.2012.02.070]

117 **Elmowalid GA**, Qiao M, Jeong SH, Borg BB, Baumert TF, Sapp RK, Hu Z, Murthy K, Liang TJ. Immunization with hepatitis C virus-like particles results in control of hepatitis C virus infection in chimpanzees. *Proc Natl Acad Sci USA* 2007;**104**: 8427-8432 [PMID: 17485666 DOI: 10.1073/pnas.0702162104]

118 **Lechmann M**, Murata K, Satoi J, Vergalla J, Baumert TF, Liang TJ. Hepatitis C virus-like particles induce virus-specific humoral and cellular immune responses in mice. *Hepatology* 2001; **34**: 417-423 [PMID: 11481628 DOI: 10.1053/jhep.2001.26523]

119 **Wedemeyer H**, Gagneten S, Davis A, Bartenschlager R, Feinstone S, Rehermann B. Oral immunization with HCV-NS3-transformed Salmonella: induction of HCV-specific CTL in a transgenic mouse model. *Gastroenterology* 2001; **121**: 1158-1166 [PMID: 11677208 DOI: 10.1053/gast.2001.29311]

120 **Park SH**, Shin EC, Capone S, Caggiari L, De Re V, Nicosia A, Folgori A, Rehermann B. Successful vaccination induces multifunctional memory T-cell precursors associated with early control of hepatitis C virus. *Gastroenterology* 2012; **143**: 1048-60.e4 [PMID: 22705008 DOI: 10.1053/j.gastro.2012.06.005]

121 **Fattori E**, Zampaglione I, Arcuri M, Meola A, Ercole BB, Cirillo A, Folgori A, Bett A, Cappelletti M, Sporeno E, Cortese R, Nicosia A, Colloca S. Efficient immunization of rhesus macaques with an HCV candidate vaccine by heterologous priming-boosting with novel adenoviral vectors based on different serotypes. *Gene Ther* 2006; **13**: 1088-1096 [PMID: 16554842 DOI: 10.1038/sj.gt.3302754]

122 **Youn JW**, Hu YW, Tricoche N, Pfahler W, Shata MT, Dreux M, Cosset FL, Folgori A, Lee DH, Brotman B, Prince AM. Evidence for protection against chronic hepatitis C virus infection in chimpanzees by immunization with replicating recombinant vaccinia virus. *J Virol* 2008; **82**: 10896-10905 [PMID: 18753204 DOI: 10.1128/JVI.01179-08]

123 **Barnes E**, Folgori A, Capone S, Swadling L, Aston S, Kurioka A, Meyer J, Huddart R, Smith K, Townsend R, Brown A, Antrobus R, Ammendola V, Naddeo M, O'Hara G, Willberg C, Harrison A, Grazioli F, Esposito ML, Siani L, Traboni C, Oo Y, Adams D, Hill A, Colloca S, Nicosia A, Cortese R, Klenerman P. Novel adenovirus-based vaccines induce broad and sustained T cell responses to HCV in man. *Sci Transl Med* 2012; **4**: 115ra1 [PMID: 22218690 DOI: 10.1126/scitranslmed.3003155]

124 **Barnes E**, Antonella F, Aston S, Smith K, Brown AC, Capone S, Ambrosio M, Ammendola V, Bartiromo M, Traboni C. Phase I trial of a highly immunogenic T-cell vaccine for hepatitis C virus based on novel adenoviral vectors from rare serotypes. *Hepatology* 2009; **50**: 397A-398A

125 **Habersetzer F**, Zarski J-P, Leroy V, Maynard-Muet M, Bronowicki J-P, Feray C, Hezode C, Fournillier A, Bain C, Inchauspe G, Honnet G, Trepo C. A novel vectorized HCV therapeutic vaccine (TG4040): results of a Phase I study in naive patients chronically infected by HCV. 44th Annual Meeting of the European Association for the Study of the Liver; 2009 April 23-26; Copenhagen, Denmark

126 **Page K**, Yu M, Cohen J, Evans J, Shumway M, Riley ED. HCV screening in a cohort of HIV infected and uninfected homeless and marginally housed women in San Francisco, California. *BMC Public Health* 2017; **17**: 171 [PMID: 28173785 DOI: 10.1186/s12889-017-4102-5]

127 **Di Bisceglie AM**, Janczweska-Kazek E, Habersetzer F, Mazur W, Stanciu C, Carreno V, Tanasescu C, Flisiak R, Romero-Gomez M, Fich A, Bataille V, Toh ML, Hennequi M, Zerr P, Honnet G, Inchauspé G, Agathon D, Limacher JM, Wedemeyer H. Efficacy of immunotherapy with TG4040, peg-interferon, and ribavirin in a Phase 2 study of patients with chronic HCV infection. *Gastroenterology* 2014; **147**: 119-131.e3 [PMID: 24657484 DOI: 10.1053/j.gastro.2014.03.007]

128 **Forns X**, Payette PJ, Ma X, Satterfield W, Eder G, Mushahwar

IK, Govindarajan S, Davis HL, Emerson SU, Purcell RH, Bukh J. Vaccination of chimpanzees with plasmid DNA encoding the hepatitis C virus (HCV) envelope E2 protein modified the infection after challenge with homologous monoclonal HCV. *Hepatology* 2000; **32**: 618-625 [PMID: 10960458 DOI: 10.1053/jhep.2000.9877]

129 **Youn JW**, Park SH, Lavillette D, Cosset FL, Yang SH, Lee CG, Jin HT, Kim CM, Shata MT, Lee DH, Pfahler W, Prince AM, Sung YC. Sustained E2 antibody response correlates with reduced peak viremia after hepatitis C virus infection in the chimpanzee. *Hepatology* 2005; **42**: 1429-1436 [PMID: 16317673 DOI: 10.1002/hep.20934]

130 **Rollier CS**, Paranhos-Baccala G, Verschoor EJ, Verstrepen BE, Drexhage JA, Fagrouch Z, Berland JL, Komurian-Pradel F, Duverger B, Himoudi N, Staib C, Meyr M, Whelan M, Whelan JA, Adams VC, Larrea E, Riezu JI, Lasarte JJ, Bartosch B, Cosset FL, Spaan WJ, Diepolder HM, Pape GR, Sutter G, Inchauspe G, Heeney JL. Vaccine-induced early control of hepatitis C virus infection in chimpanzees fails to impact on hepatic PD-1 and chronicity. *Hepatology* 2007; **45**: 602-613 [PMID: 17326154 DOI: 10.1002/hep.21573]

131 **Alvarez-Lajonchere L**, Shoukry NH, Grá B, Amador-Cañizares Y, Helle F, Bédard N, Guerra I, Drouin C, Dubuisson J, González-Horta EE, Martínez G, Marante J, Cinza Z, Castellanos M, Dueñas-Carrera S. Immunogenicity of CIGB-230, a therapeutic DNA vaccine preparation, in HCV-chronically infected individuals in a Phase I clinical trial. *J Viral Hepat* 2009; **16**: 156-167 [PMID: 19017255 DOI: 10.1111/j.1365-2893.2008.01058.x]

132 **Sallberg M**, Frelin L, Diepolder H, Jung MC, Mathiesen I, Fons M, Hultcrantz R, Carlsson T, Weiland O. A first clinical trial of therapeutic vaccination using naked DNA delivered by in vivo electroporation shows antiviral effects in patients with chronic hepatitis C. 44th Annual Meeting of the European Association for the Study of the Liver; 2009 April 23-26; Copenhagen, Denmark.

133 **Dillon JF**, Lazarus JV, Razavi HA. Urgent action to fight hepatitis C in people who inject drugs in Europe. *Hepatol Med Policy* 2016; **1**: 2 [DOI: 10.1186/s41124-016-0011-y]

134 **Kottilil S**, Wright M, Polis MA, Masur H. Treatment of hepatitis C virus infection: is it time for the internist to take the reins? *Ann Intern Med* 2014; **161**: 443-444 [PMID: 25222390 DOI: 10.7326/M14-0741]

135 **Seo KI**, Yun BC, Li WJ, Lee SU, Han BH, Park ET. Barriers to treatment of failed or interferon ineligible patients in the era of DAA: single center study. *Clin Mol Hepatol* 2017; **23**: 74-79 [PMID: 28259115 DOI: 10.3350/cmh.2016.0052]

136 **McCance-Katz EF**, Valdiserri RO. Hepatitis C Virus Treatment and Injection Drug Users: It Is Time to Separate Fact From Fiction. *Ann Intern Med* 2015; **163**: 224-225 [PMID: 26120801 DOI: 10.7326/M15-0007]

137 **Robaeys G**, Bielen R, Azar DG, Razavi H, Nevens F. Global genotype distribution of hepatitis C viral infection among people who inject drugs. *J Hepatol* 2016; **65**: 1094-1103 [PMID: 27520879 DOI: 10.1016/j.jhep.2016.07.042]

138 **Lim SG**, Aghemo A, Chen PJ, Dan YY, Gane E, Gani R, Gish RG, Guan R, Jia JD, Lim K, Piratvisuth T, Shah S, Shiffman ML, Tacke F, Tan SS, Tanwandee T, Win KM, Yurdaydin C. Management of hepatitis C virus infection in the Asia-Pacific region: an update. *Lancet Gastroenterol Hepatol* 2017; **2**: 52-62 [PMID: 28404015 DOI: 10.1016/S2468-1253(16)30080-2]

139 **Moradpour D**, Grakoui A, Manns MP. Future landscape of hepatitis C research - Basic, translational and clinical perspectives. *J Hepatol* 2016; **65**: S143-S155 [PMID: 27641984 DOI: 10.1016/j.jhep.2016.07.026]

140 **Grebely J**, Bruggmann P, Treloar C, Byrne J, Rhodes T, Dore GJ; International Network for Hepatitis in Substance Users. Expanding access to prevention, care and treatment for hepatitis C virus infection among people who inject drugs. *Int J Drug Policy* 2015; **26**: 893-898 [PMID: 26254497 DOI: 10.1016/j.drugpo.2015.07.007]

141 **Taherkhani R**, Farshadpour F. Lurking epidemic of hepatitis C virus infection in Iran: A call to action. *World J Hepatol* 2017; **9**: 1040-1042 [PMID: 28932350 DOI: 10.4254/wjh.v9.i24.1040]

142 **Moyer VA**; U.S. Preventive Services Task Force. Screening for hepatitis C virus infection in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2013; **159**: 349-357 [PMID: 23798026 DOI: 10.7326/0003-4819-159-5-201309030-00672]

143 **Aggarwal R**, Chen Q, Goel A, Seguy N, Pendse R, Ayer T, Chhatwal J. Cost-effectiveness of hepatitis C treatment using generic direct-acting antivirals available in India. *PLoS One* 2017; **12**: e0176503 [PMID: 28520728 DOI: 10.1371/journal.pone.0176503]

144 **Davis SM**, Daily S, Kristjansson AL, Kelley GA, Zullig K, Baus A, Davidov D, Fisher M. Needle exchange programs for the prevention of hepatitis C virus infection in people who inject drugs: a systematic review with meta-analysis. *Harm Reduct J* 2017; **14**: 25 [PMID: 28514954 DOI: 10.1186/s12954-017-0156-z]

145 **Midgard H**, Weir A, Palmateer N, Lo Re V 3rd, Pineda JA, Macías J, Dalgard O. HCV epidemiology in high-risk groups and the risk of reinfection. *J Hepatol* 2016; **65**: S33-S45 [PMID: 27641987 DOI: 10.1016/j.jhep.2016.07.012]

146 **U.S. Department of Health and Human Services**. Combating the Silent Epidemic of Viral Hepatitis: Action Plan for the Prevention, Care, and Treatment of Viral Hepatitis. Technical consultation: hepatitis C virus infection in young persons who inject drugs. 2013; Available from: URL: https://hepfree.nyc/wp-content/uploads/2014/04/hcv-and-young-pwid-consultation-report.pdf?x77964

147 **Grebely J**, Dore GJ. Prevention of hepatitis C virus in injecting drug users: a narrow window of opportunity. *J Infect Dis* 2011; **203**: 571-574 [PMID: 21282190 DOI: 10.1093/infdis/jiq111]

148 **Messina JP**, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* 2015; **61**: 77-87 [PMID: 25069599 DOI: 10.1002/hep.27259]

149 **Dias PT**, Hahn JA, Delwart E, Edlin B, Martin J, Lum P, Evans J, Kral A, Deeks S, Busch MP, Page K. Temporal changes in HCV genotype distribution in three different high risk populations in San Francisco, California. *BMC Infect Dis* 2011; **11**: 208 [PMID: 21810243 DOI: 10.1186/1471-2334-11-208]

150 **Yan Z**, Fan K, Wang Y, Fan Y, Tan Z, Deng G. Changing pattern of clinical epidemiology on hepatitis C virus infection in southwest china. *Hepat Mon* 2012; **12**: 196-204 [PMID: 22550528 DOI: 10.5812/hepatmon.857]

151 **Morris MD**, Shiboski S, Bruneau J, Hahn JA, Hellard M, Prins M, Cox AL, Dore G, Grebely J, Kim AY, Lauer GM, Lloyd A, Rice T, Shoukry N, Maher L, Page K; International Collaboration of Incident HIV and HCV in Injecting Cohorts (InC3). Geographic Differences in Temporal Incidence Trends of Hepatitis C Virus Infection Among People Who Inject Drugs: The InC3 Collaboration. *Clin Infect Dis* 2017; **64**: 860-869 [PMID: 28362947 DOI: 10.1093/cid/ciw869]

152 **Oliveira ML**, Yoshida CF, Telles PR, Hacker MA, Oliveira SA, Miguel JC, do O KM, Bastos FI. **Trends in HCV prevalence,** risk factors and distribution of viral genotypes in injecting drug users: findings from two cross-sectional studies. *Epidemiol Infect* 2009; **137**: 970-979 [PMID: 19144250 DOI: 10.1017/S0950268808001970]

P- Reviewer: Dang SS, El-Shabrawi M, Sanal MG, Takahashi T
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com