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

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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

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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.

INTRODUCTION

With a global prevalence rate of 2.8%, equating to over 185 million infections, and more than 350,000 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[2,12]. 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[5,10].

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 cutanea 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[1,22,27,28]. 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[2,22]. 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[11,22,31,33]. 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
inhibit the function of viral proteins that are essential for viral replication\cite{3,37,38}. These DAAs include NS3/4A protease inhibitors, NS5A replication complex inhibitors, nucleoside NS5B polymerase inhibitors, and non-nucleoside NS5B polymerase inhibitors (Table 1)\cite{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\cite{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\cite{45,47}.

Telaprevir and boceprevir are not recommended by WHO due to the frequent adverse effects and low cure rates\cite{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\cite{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\cite{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\cite{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\cite{84,85}. Since, despite having undetectable level of HCV RNA, blood and blood products are potentially infectious\cite{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\cite{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\cite{88,89}. Several vaccine candidates against HCV have been developed so far, including recombinant protein vaccine, peptide-based vaccine,
| 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 | Vicrelis | 1 | BOC + IFN ± RBV |
|  | Faldaprevir (FDV) | BI-201335 | Olysio | 1 and 4 | FV + IFN + RBV |
|  | Asunaprevir (ASV) | BMS-650322 | 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-1425 | - | 1 | Sovaprevir + ODV + RBV |
|  | Grazoprevir (GZP) | MK-5172 | - | 1a, 1b, 4 and 6 | Zepatier (GZP + EVB) |
|  | Danoprevir (DNV) | RG-7227 | ITMN-191 | 1 and 4 | DNV + PEG-IFN + RBV |
|  | Delprevir (DDV) | ACH-2684 | - | 1 | DDV + ODV |
|  | Narlaprevir (NVR) | SCH-900518 | Arlansa | 1 | NVR + R + PEG-IFN ± RBV |
|  | Vedoprevir (VDR) | GS-9451 | - | 1 | VDR + LDV + Sof |
|  | Glevaprevir (GLE) | ABT-493 | - | Pan-genotypic antiviral activity | GLE + PIB ± RBV |
|  | - | GS-9256 | - | 1 | GS-9256 + PEG-IFN + RBV |
|  | - | - | - | - | - |
|  | NS5A replication complex inhibitors (-Asvir) | Daclatasvir (DCV) | BMS-790052 | Daklinza | 1, 2 and 3 | Sovodak (DCV + SOF) ± RBV |
|  | Ledipasvir (LDV) | GS-5885 | - | 1, 3, 4, 5 and 6 | Harvoni (LDV + SOF) ± RBV |
|  | Ombitasvir (OBV) | ABT-267 | - | 1 and 4 | Viekira Pak (OBV + PTV + R + DSV) ± RBV |
|  | Elbasvir (EBV) | MK-8742 | - | 1a, 1b, 4 and 6 | Technivie (OBV + PTV + R) |
|  | Velpatasvir (VPR) | GS-5816 | - | Pan-genotypic antiviral activity | Zepatier (EBV + GZP) ± RBV |
|  | Odalasvir (ODV) | ACH-3102 | - | 1 | Epclusa (VPR + SOF) ± RBV |
|  | Ravidasvir (RVD) | PFI-668 | - | 4 | RVD + Sof ± RBV |
|  | - | PFI-461 | - | 1 | - |
|  | Samatasvir | IDX-18719; IDX-719 | - | 1, 2, 3 and 4 | Samatasvir + SIM ± RBV |
|  | - | MK-1894 | - | - | - |
|  | - | BMS-824393 | - | 1 | BMS-824393 + PEG-IFN + RBV |
|  | - | ABT-530 | - | Pan-genotypic antiviral activity | PIB + GLE ± RBV |
|  | - | MK-8408 | - | Pan-genotypic antiviral activity | RZR + UPR + GZP |
|  | Nucleoside NS5B polymerase inhibitors (-Buvir) | Sofosbuvir (SOF) | PSI-7977; Sovaldi; Sofooral | Pan-genotypic antiviral activity | SOF + IFN ± RBV |
|  | - | GS-7977 | - | - | Sovodak (DCV + SOF) ± RBV |
|  | Mericitabine (MCB) | RC-7128 | - | 1 and 4 | MCB + PEG-IFN + RBV |
|  | - | RO324048 | - | - | MCB + DNV |
|  | - | VX-135 | - | 1 | VX-135 + GSK2336805 + SIM |
|  | - | ALS-2200 | - | Pan-genotypic antiviral activity | VX-135 + TVR ± RBV |
|  | Valopicitabine | NM283 | - | 1 | Valopicitabine + Peg-IFN |
|  | Non-nucleoside NS5B polymerase inhibitors (-Buvir) | Beclabuvir (BCV) | BMS-791325 | - | BCC + ASV + DCV |
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. Introduction of IFN-free DAAAs 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. 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-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.

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. 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. 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.
### 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 E2-vaccinated animals; clear HCV infection in only E1-vaccinated animals (neutralizing antibodies) | Therapeutic vaccine | BPRC | 2011 | Published | [102] |
| | Recombinant E1/Alum | Phase I | 20 healthy volunteers | 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 / II | 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**
  - Phase I | 54 healthy volunteers | Induce HCV-specific cellular immune responses; viral clearance | Prophylactic vaccine | NIH | 2007 | Published [117] |

- **Recombinant baculovirus containing core, E1 and E2**
  - 4 chimpanzees | Induce HCV-specific cellular immune responses; viral clearance | Prophylactic vaccine | NIH | 2001 | Published [118] |

**Bacterial-vector vaccine**

- **Attenuated Salmonella typhimurium containing NS3 gene**
  - Mice | Induce long-lasting T-cell responses | Therapeutic vaccine | NIH | 2001 | Published [119] |

**Viral-vector vaccine**

- **Recombinant adenoviral vectors and plasmid DNA expressing NS3-NS5B**
  - Phase I | 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 | 15 patients with chronic HCV infection | Induce T-cell responses | Therapeutic 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 | Phase I | 2 chimpanzees | Induce humoral and cellular immune responses; resolve the infection; prevent progression to chronicity | Prophylactic vaccine | NIAID/NIH | 2000 | Published [128] |
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\cite{119,143}. 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 the growing number of IDUs and the relatively young lac�� of awareness among young drug takers. As the core activity of any harm reduction intervention, as the 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\cite{119,141,146}. 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\cite{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 unnoticed 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%)\cite{35,137,139,147}. 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\cite{148,149}.

Blood transfusion before 1990 was the most im-}

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**Table: Vaccine Trials for HCV Prevention**

| Vaccine | 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] |
|---|---|---|---|---|---|---|---|---|
| ChronVac-C: Plasmid expressing NS3 and NS4A delivered by in vivo electroporation | 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] |

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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.
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.

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