

Hepatitis C Virus Infection: A Brief Review

Hisham Qadri, Saleem Kamili

Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Hepatitis C, caused by hepatitis C virus (HCV) was originally described as parenterally transmitted non-A non-B hepatitis. The field of HCV research is a shining example of successful translation of basic research wherein in a short of span of 30 years the virus was discovered, highly sensitive and specific diagnostic assays were developed, epidemiology and clinical characteristics of the disease were well defined and with the availability of these highly efficacious antiviral therapies many countries are already on their way to achieving World Health Organization's (WHO) elimination targets of hepatitis C by 2030. However, much work needs to be done to eliminate hepatitis C especially in resource poor countries. An estimated 71 million people are currently infected with HCV worldwide and approximately 400,000 people die each year from causes related to HCV. Of these estimates, more than 13 million HCV infected persons are in India and Pakistan (Figure 1). Despite the availability of a cure for hepatitis C, only 20% of those infected patients have been diagnosed¹. In order to achieve the WHO targets of hepatitis C elimination, concerted efforts are needed to make affordable and reliable diagnostics available worldwide.

The Virus

HCV, a member of the Flaviviridae family and the genus Hepacivirus, is an enveloped virus with a single-stranded positive-sense RNA genome of approximately 9.6 kb^{2,3}. The RNA genome, flanked on its 5' and 3' ends by an untranslated region, encodes a single open reading frame which encodes a polyprotein of approximately 3000 amino acids (Figure 2). The polyprotein is cleaved into 10 separate

proteins by virally and cellularly encoded proteases. The structural proteins which form the viral particle, include the core protein and the envelope glycoproteins E1 and E2. The non-structural proteins include p7, NS2, NS3, NS4A, NS5A, and NS5B proteins. During an active infection, HCV is capable of producing an estimated 10 trillion viral particles per day⁴. HCV isolates are classified into eight genotypes [Table 1] that differ in their nucleotide sequence by 30%-35% and into multiple subtypes that differ in their nucleotide sequence by 20%-25%⁵. HCV genotypes 1 is the most prevalent genotype in the United States and western Europe; genotype 2 is prevalent in some regions of South America and Africa; genotype 3 is the predominant genotype in India and Pakistan; genotype 4 is common in Egypt, genotypes 5 and 6 are prevalent in South Africa and Southeast Asia, respectively. The actual prevalence of genotypes 7 and 8 is currently unknown and only a few cases have been reported thus far.

Natural History of HCV infection

HCV causes both acute and chronic infection but is seldom diagnosed during the acute phase due to mostly an asymptomatic nature of infection in the majority of the infected persons. Among symptomatic patients, clinical manifestations, which may include jaundice, malaise and nausea, can occur within 7-8 weeks (range 2-26) after

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Correspondence:

Dr. Saleem Kamili
Division of Viral Hepatitis
Centers for Disease Control & Prevention Atlanta, GA 30329
Email: skamili@cdc.gov

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Table 1. HCV genotypes and subtypes

Genotype (subtypes)	Over all Prevalence	Geographic distribution	Remarks
1 [a, b, c, e, g, h, l, m, n, o]	46%	Worldwide US	1a: IDU 1b: Iatrogenic
2 [a, b, c, d, e, i, j, k, l, m, q, r, t, u]	9%	Worldwide Western Africa	2a; 2b: Iatrogenic
3 [a, b, d, e, g, h, i, k]	30%	Worldwide Northern Europe South Asia	3a: IDU
4 [a, b, c, d, f, g, k, l, m, n, o, p, q, r, s, t, v, w]	8%	Middle East North & Central Africa	4a: Iatrogenic (Egypt) 4d: IDU (Europe)
5 (a)	1%	South Africa	
6 [a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, xa, xb, xc, xd, xe, xf, xg, xh]	6%	Southeast Asia	6a: IDU (Hong Kong; Vietnam)
7 (a, b)	-	Central Africa (only few cases)	
8 (a)	-	Punjab, India (only few cases)	

Table 2. Interpretation of HCV markers of infection

Anti-HCV	HCV RNA	Interpretation
Negative	Negative	No infection
Positive	Positive	Acute or chronic HCV infection
Negative	Positive	Window Phase infection Delayed Seroconversion (immunosuppressed)
Positive	Negative	Resolved infection Treated infection False-positive anti-HCV test Intermittent viremia

exposure⁶. The rates of acute infection with spontaneous resolution within approximately six months fall between 15-45%⁷. For patients with acute infection, serum alanine aminotransferase (ALT) levels start to rise 2 to 8 weeks after exposure whereas HCV RNA can be detected as early as 1 to 2 weeks after exposure (Figure 3). HCV RNA levels usually rise and then disappear before the appearance of any symptoms or before any changes in ALT levels can be observed^{8,9}. The majority of the chronically infected patients, remain asymptomatic, however, infection can lead to liver fibrosis, cirrhosis or hepatocellular carcinoma. Chronic infection is characterized by the presence of detectable levels of HCV RNA for more than 6 months after acute infection. A side from causing hepatitis, HCV can lead to various extrahepatic manifestation impacting a patient's renal, musculoskeletal, integumentary, or nervous systems, the prominent comorbidities being depression, diabetes mellitus and chronic kidney disease. It is estimated that 1% to 2% of all HCV infected patients will develop at least one extra-hepatic manifestation with the most common being mixed-cryoglobulinemia¹⁰.

Transmission routes

HCV is primarily transmitted through parenteral exposures to infectious blood or body fluids that contain blood (Box 1). Health-care settings remain a major source of HCV transmissions especially in resource poor countries. Transmission of HCV can occur through unscreened or inadequately screened blood transfusions, unsafe injections and invasive medical procedures including surgeries, dental procedures, dialysis, endoscopy, or other procedures when lapses in infection control protocols occur^{7,11}. Unsafe injections and overuse of healthcare injections remain one of the major contributors of HCV transmission in developing countries. An estimated 315,000 new HCV infections are attributed to unsafe injections⁷. Improving blood safety by implementing screening of blood transfusion in a quality assured manner and introducing use of reuse-prevention syringes and a reduction in unnecessary healthcare injections are necessary for preventing HCV transmissions in healthcare settings. Another major risk factor for HCV transmission globally, accounting for 23% of new HCV infections, is injection drug use⁷. Mother-to-child transmission of HCV occurs among 4-8% of children born to HCV infected mother, the risk increases more than

twice if the mother is coinfectd with HIV/HCV¹². While HCV is not commonly spread through sexual contact in heterosexual couples, men who have sex with men have a higher risk of HCV infection¹³.

Laboratory Diagnostics

The diagnostic landscape of HCV infection is limited to a nucleic acid test (NAT) for detection of HCV RNA and an antibody test for the detection of IgG anti-HCV, commonly referred to as anti-HCV¹⁴. A third test, the HCV core antigen test, is not yet widely used in clinical practice because of its availability in only an automated platform by a single manufacturer. HCV RNA is detectable within 1-2 weeks after exposure to HCV while anti-HCV, the primary screening marker for hepatitis C, appears after an average of 8-11 weeks (Figure 4). During the period between the appearance of HCV RNA and anti-HCV, known as "window period", early infections can be missed if only anti-HCV test is performed. HCV RNA remains detectable during acute and chronic phases of infection. Absence of HCV RNA in the blood of infected persons is indicative of resolution of infection spontaneously or as result of anti-viral therapy. Anti-HCV is detectable in all phases of HCV infection including acute, chronic and resolved stages and is therefore not a marker of current HCV infection (Table 2).

Assays for detection of anti-HCV are available in various formats which include enzyme Immunoassays (EIA), enhanced chemiluminescence immuno assays (CIA) and immuno chromatographic assays (ICA) or lateral flow assays also known as Rapid Diagnostic Assay (RDT). Anti-HCV assay assays approved by regulatory authorities in various countries or assays that are WHO-prequalified generally have excellent performance characteristics with sensitivity and specificity above 95%. False positivity of any approved anti-HCV assay is observed when the tests are used in low-risk settings and is related to the correlation of prevalence of an infection in a population with positive predictive value of an assay. The US Centers for Disease Control and Prevention updated its HCV testing guidelines in 2013 recommending all anti-HCV reactive samples should be tested for HCV RNA for the diagnosis of current HCV infection (Figure 5)¹⁵.

RDTs variously known as immunochromatographic strip tests, Lateral flow assays, Lateral flow devices, Dipstick Assays, Card Tests, Strip Tests or simply "Rapids" are being

Table 3. Seroprevalence of hepatitis C in various clinical settings in Kashmir

Population (Setting)	Number of subjects	Anti-HCV positive (%)	Reference
Blood donors (SKIMS, Srinagar)	94,427	194 (0.2%)	29
Persons with dental procedures (Government Dental College and Hospital, Srinagar)	2000	86 (4.3%)	30
End-stage renal disease patients (SKIMS, Srinagar)	459	46 (10.0%)	30
Psoriatic patients (SMHS Dermatology Clinic, Srinagar)	50	1 (2.0%)	32
Chronic liver disease patients (SKIMS, Srinagar)	25	2 (8.0%)	33
Acute Liver Failure patients (SKIMS, Srinagar)	180	13 (7.2%)	34
Jaundiced children (Pediatrics and Transfusion medicine departments, Govt. Medical College Srinagar)	100	2 (2.0%)	35
Leprosy patients (Leprosarium, Srinagar)	79	36 (45.5%)	36

SKIMS = Sheri-Kashmir Institute of Medical Sciences; SMHS = Shri Maharaja Hari Singh Hospital

Table 4. Community-associated hepatitis C outbreaks in Kashmir adapted from reference 36

Characteristics	Anantnag district (January 2013)	Kulgam district (July 2014)	Srinagar (May 2015)
Suspected cases	2051	187	187
Anti-HCV positive (%)	767 (37.39%)	6 (3.20%)	39 (20.85%)
HCV RNA positive/number tested (%)	53/79 (67.08%)	2/6 (33.33%)	22/30 (70.33%)
Median age (range) years	33 (25-34)	23 (25-34)	33 (25-34)
Male	29	2	17
Female	50	4	13

increasingly used for anti-HCV screening in resource-poor countries. RDTs though more expensive than conventional EIAs have the advantage of producing results in less than an hour and can be used with fingerstick whole blood in addition to serum and plasma samples. However, the majority of these assays are generally unregulated and have variable performance characteristics¹⁶. It is therefore imperative that only quality assured assays with validated analytic and diagnostic performance be used for detection of anti-HCV¹⁷.

Detection of HCV RNA remains the gold standard for diagnosing current HCV infection. Qualitative and quantitative NAT methodologies for HCV RNA detection are based on polymerase chain reaction, endpoint and real-time, branched-DNA signal amplification, and transcription-mediated amplification techniques. These assays can detect HCV RNA levels as low as 5 IU/mL and have a broad dynamic range¹⁴. All NATs for HCV RNA have high specificities of 99% and above. In addition to commercially available HCV RNA assays that are well-regulated and approved for clinical use, in-house assays mostly in research laboratories are also used for detection of HCV RNA in clinical samples. However, NATs require specialized equipment, trained staff, expensive reagents and supplies and are therefore performed in well-equipped and sophisticated laboratories. HCV RNA positive samples can be further subjected to sequencing for the determination of viral genotype and for outbreak investigations using various bioinformatics approaches and computational technologies. One such cloud-based technology and a public health tool, the Global Hepatitis Outbreak and Surveillance Technology (GHOST) developed at the US Centers for Disease Control and Prevention, is available online for users who can generate HCV sequences using Next Generation Sequencing method for determination of molecular epidemiology of HCV infections¹⁸.

A potential alternate test to HCV RNA, the HCV core antigen is detectable in blood of HCV infected person in the acute and chronic phases of infection. The test, though not as sensitive as NATs for HCV RNA, presents a reliable and cost-effective alternative for diagnosing current HCV infections¹⁹. However, the test is currently available from one manufacturer (Abbott Diagnostics) and can be only performed on an automated immunoassay platform, the ARCHITECT machine

Prevention and Treatment

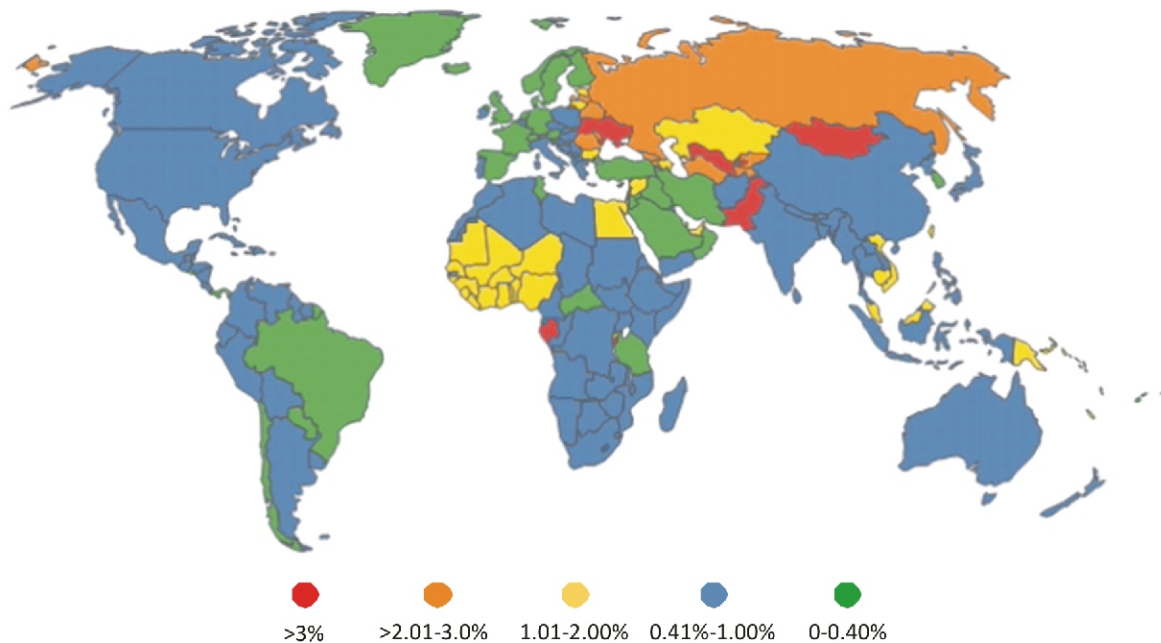
Attempts to develop a vaccine against HCV have not been successful. The prevention of HCV infection therefore depends on primary prevention measures which include reducing or eliminating transmission of HCV through unsafe blood and its products, unsafe and unnecessary injections, drug use, improving infection control practices in healthcare settings and avoiding high risk sexual activities. Robust screening for HCV infections and linkage to care of HCV infected persons are keys to secondary prevention of HCV.

With the advent of direct-acting antiviral (DAA) regimens, genotype-specific as well as pangenotypic regimens and real-world data on their use becoming regularly available, WHO (Figure 6), American Association for the Study of Liver Diseases, European Association for the Study of Liver Diseases and Asian Pacific Association for the Study of Liver Diseases have recently updated their guidelines^{7,20,21,22} for treatment of hepatitis C patients.

Hepatitis C in Kashmir

There is limited data on the seroprevalence of hepatitis C from various regions/states in India. A systemic review of available data, mostly based on blood donors and pregnant women, estimates prevalence rates likely between 0.4% and 1.0%²³. A comprehensive study, conducted in the Punjab state, found an overall weighted prevalence of anti-HCV of 3.6% and HCV RNA of 2.6%²⁴. In this study, males, persons aged 40-59 years and persons living in rural areas had the greatest odds of being infected with HCV. Among other risk factors associated with having been infected with HCV were, lack of education, history of having blood transfusion, and having received their most recent injection by a nurse or other medical practitioner as compared to a medical doctor. Data on the seroprevalence of hepatitis C and associated risk factors in the general population in Kashmir are lacking²⁵⁻²⁷ and only a few studies have reported on the prevalence of hepatitis C in various clinical settings in Kashmir [Table 3]. These include blood donors²⁸, persons attending dental clinics²⁹, patients with end-stage renal disease³⁰, patients with psoriasis³¹, patients with acute, chronic and fulminant liver diseases^{32,33}, jaundiced children³⁴ and patients with leprosy³⁵. Overall, the prevalence reported in these studies, using a wide variety of anti-HCV assays with unknown performance characteristics, ranges from

Figure 1. Global distribution of HCV viremic prevalence 2020

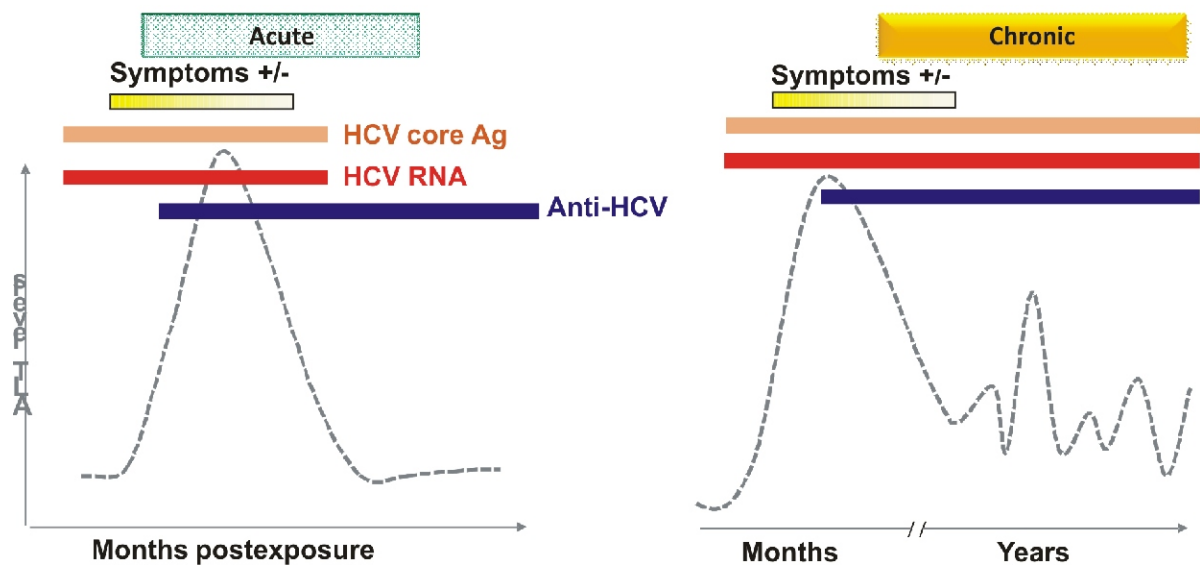


CDA Foundation's Polaris Observatory; 2020. Available from <https://cdafound.org/polaris/> (Accessed 30 May 2020)

Figure 2. Genomic Organization of HCV



Figure 3. Clinical and serologic course of HCV infection



0.2% to 45.5%. Studies utilizing well characterized diagnostic assays are warranted to gauge the actual burden of disease in the general population as well as various high-risk patient populations in Kashmir. Virologic characterization of HCV isolates detected in chronic hepatitis C patients have shown the circulation of HCV genotype 3 in Kashmir³⁶⁻⁴¹, the predominant genotype reported from other regions in India and Pakistan.

Kashmir, a place otherwise known for the discovery of hepatitis E and numerous large and small outbreaks associated with it⁴², has also witnessed unprecedented back-to-back community-based outbreaks of hepatitis C over a period of three years^{36, 43}. The first outbreak in a remote village Takya Magam, in south Kashmir, was detected in January 2013 when the Chief Medical Officer of Anantnag district promptly informed the Directorate of Health Services Kashmir about an unusual cluster of seven anti-HCV positive cases identified during their routine pre-operative screening for various surgical procedures. Subsequent survey of the contacts of the seven cases followed by screening of the entire population of 2600 persons dwelling in 538 households showed an unexpectedly high prevalence of 38% (787/2051) of anti-HCV positivity in the village. HCV RNA was detected in 86% (43/50) samples based on testing a subset of anti-HCV positive samples. Of the 43 HCV RNA positive samples, 16 were sequenced which showed HCV genotype 3a in all the samples⁴³. Epidemiologic investigation, which was expanded to three nearby villages as controls, found injection use given by local chemists was quite widespread - more than 80% of subjects had a history of injection use. The association of dental procedures was significantly associated with HCV infection among cases. Other risk factors, though not statistically significant between cases and controls, included ear and nose piercing among women and sharing of razors among men. The other two outbreaks occurred in June 2014 in the village Checkpora, district Kulgam and in May 2015 among a colony of leprosy patients in Srinagar city (Table 4, Figure 7). Whether these outbreaks represent only the tip of an iceberg or are isolated cases in Kashmir remains to be determined and will require well designed serosurveys in the general population as well as in high-risk settings.

Conclusion

A major challenge in the prevention of hepatitis C virus infection in Kashmir is the use of unsafe medical injections. This challenge can be greatly addressed by following WHO's new injection safety guidelines launched in 2015 which includes the recommendation of using safety engineered injection devices. Success stories about the improvement in knowledge and practice of safe medical injections have been reported from rural Pakistan as well as from the state of Punjab in India¹¹. The potential transmission of HCV in healthcare settings, through blood transfusions, unsafe injections and various medical procedures, remains another area of concern in Kashmir. Improving blood safety by ensuring appropriate screening of blood donations using quality assured diagnostics will further prevent transmission of HCV through blood transfusions. In the hepatitis C outbreaks in rural areas of Kashmir, dental procedures were noted as significant risk factor among HCV infected patients. Special attention needs to be paid to implementing and strengthening infection control practices in dental clinics. With concerted efforts, which include development and implementation of a robust infection prevention

and control program across the healthcare system, making diagnostic assays readily available and affordable and linking infected individuals to care and treatment, it is quite possible to achieve the WHO targets of elimination of hepatitis C especially when highly efficacious anti-viral therapies for hepatitis C are readily available at affordable costs in India.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the United States Centers for Disease Control and Prevention

Box 1. Transmission routes of HCV

- ♦ **Percutaneous**
 - ♦ Injecting drug use
 - ♦ Clotting factors before viral inactivation*
 - ♦ Transfusion, transplant from infected donor*
 - ♦ Therapeutic (contaminated equipment, unsafe injection practices)
 - ♦ Occupational (needle stick)
- ♦ **Permucosal**
 - ♦ **Perinatal**
 - ♦ 4-8% risk; more than twice if mother HCV/HIV co-infected
 - ♦ **Sexual**
 - ♦ Heterosexual transmission is rare
 - ♦ HIV+ Men Who Have Sex with Men are at highest risk

** before 1992 when screening test became available*

Figure 4. Markers of HCV infection

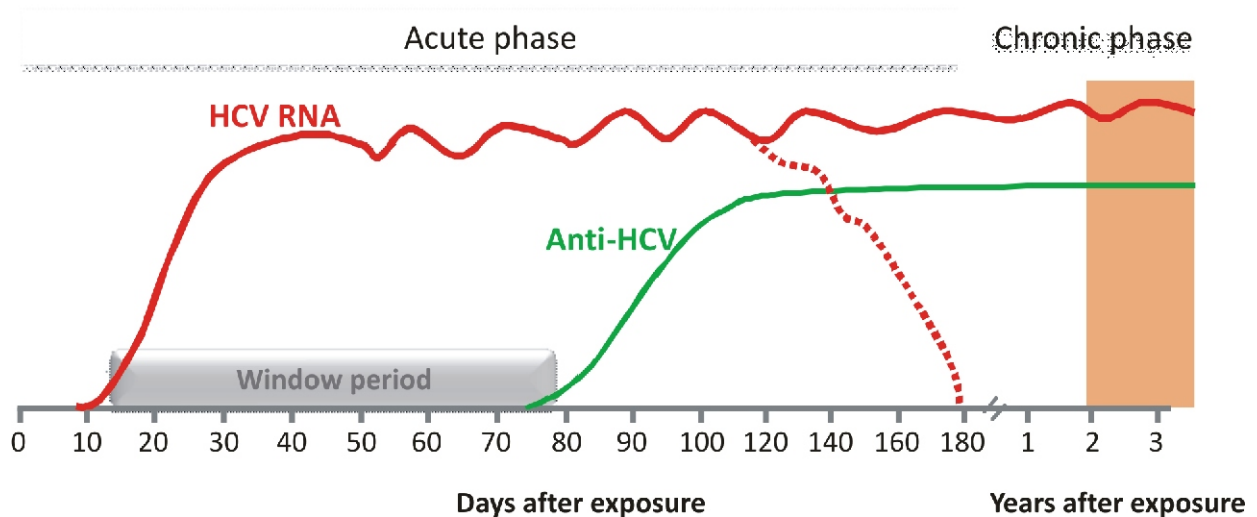


Figure 5. US Centers for Disease Control and Prevention recommended testing guidelines for hepatitis C

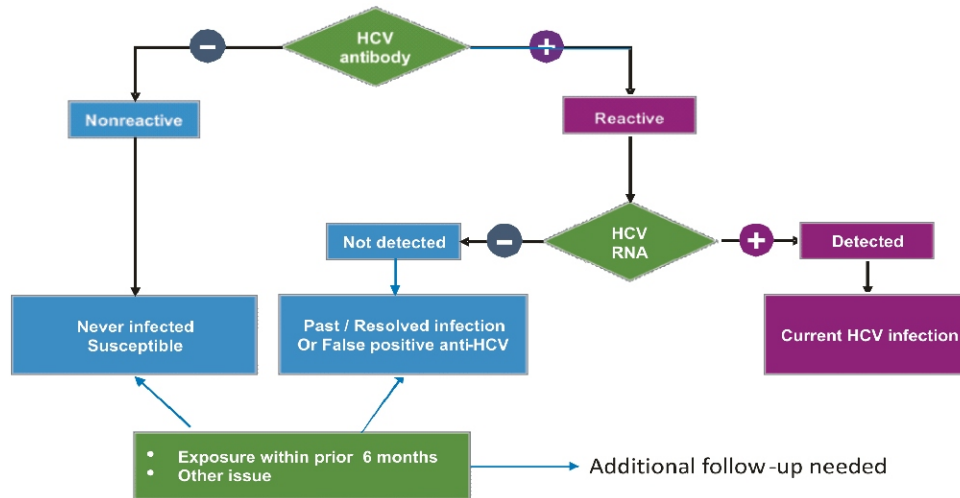
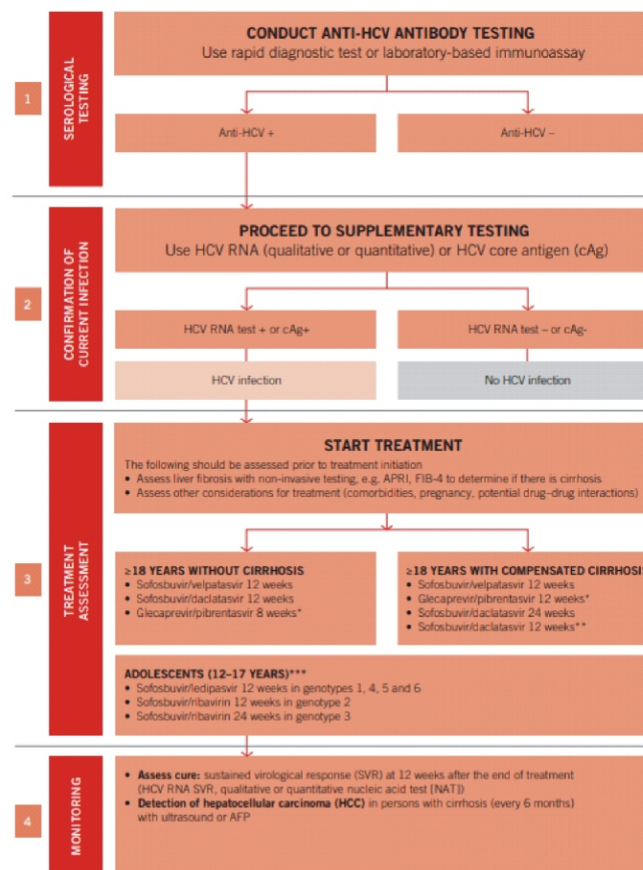
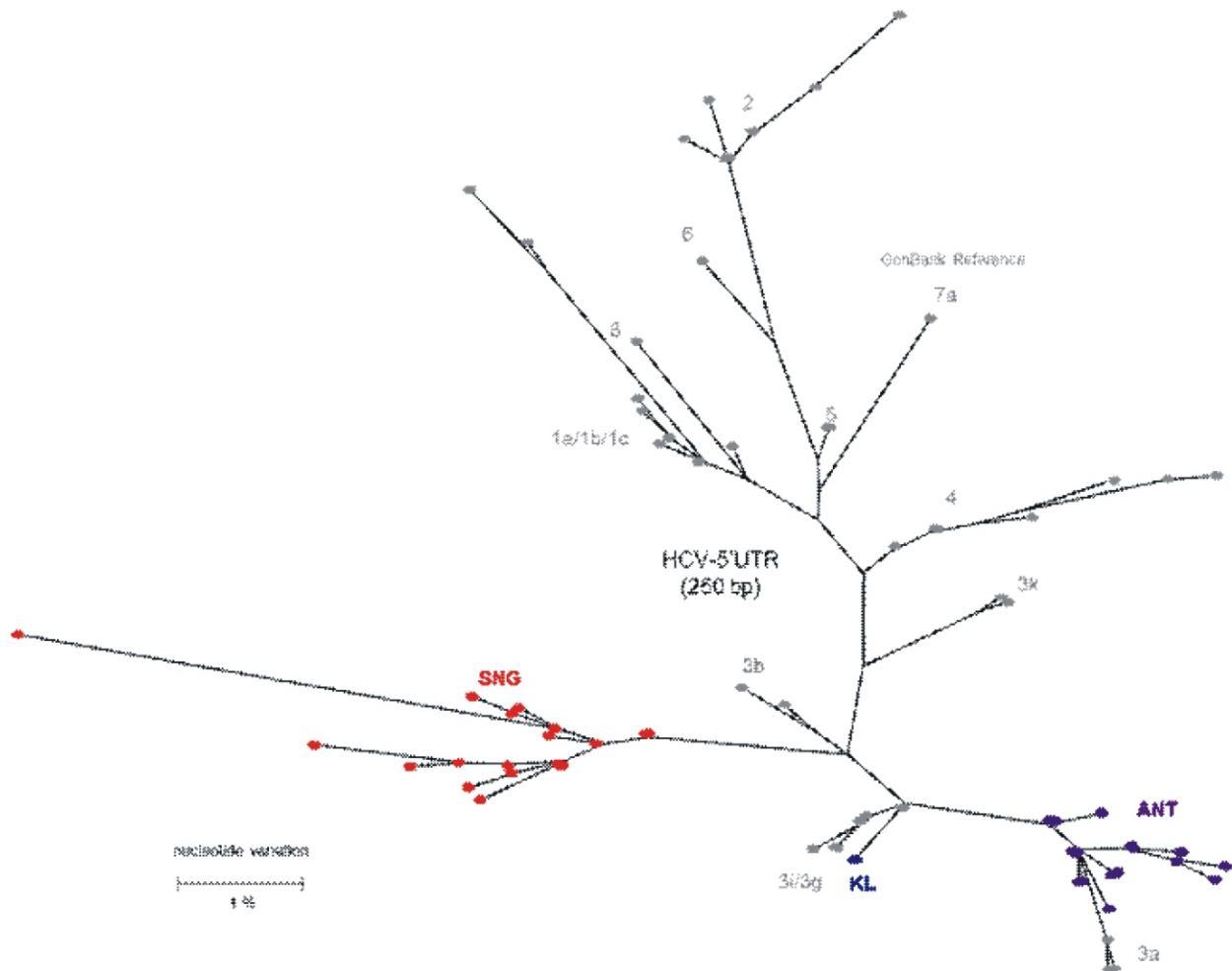


Figure 6. WHO recommended summary algorithm for the diagnosis, treatment and monitoring of chronic HCV infection in adults and adolescents



* Persons with HCV genotype 3 infection who have received interferon and/or ribavirin in the past should be treated for 16 weeks.
 ** May be considered in countries where genotype distribution is known and genotype 3 prevalence is <5%.
 *** Treatment in adolescents at this time still requires genotyping to identify the appropriate regimen.
 AFP: alpha fetoprotein, APRI: aspartate-to-platelet ratio index, FIB-4: fibrosis stage

Figure 7. Unrooted phylogenetic tree generated by Maximum Likelihood method using MEGA software (version 10.1.8), on the basis of sequencing a 250base pair segment of the HCV 5'-UTR genomic region from Kulgam (KL), Anantnag (ANT) and Srinagar (SNG) outbreaks. Reference sequences of different HCV genotypes from GenBank are shown in gray filled circles, while samples sequences of Kashmir HCV outbreaks are shown in color filled circles. Please note that 5'UTR of HCV genome is not suitable for genotype/subtype determination or for establishing relatedness among isolates because of its conserved nature among HCV isolates.



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