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Case Review

Eliminating Hepatitis C Viral Infection in India

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Abstract

Viral hepatitis causes nearly as many deaths as tuberculosis and more deaths than those caused by malaria and HIV/AIDS. Viral hepatitis needs to be therefore considered as one of the four major infectious diseases of this century. Although many viruses (from Hepatitis A virus through G) cause the clinical syndrome of viral hepatitis, it is Hepatitis C virus, a RNA virus first detected in 1989 which appears to be ripe for special attention and eradication efforts. An estimated 185 million people have been infected with HCV (80% of those infected reside in lower middle income countries) and are at risk of cirrhosis of liver and/or hepatocellular carcinoma.

The recent discovery and subsequent availability at subsidised prices of a number of directly acting antiviral drugs which are pan genotypic active as well as the improvement of diagnostics tests (both viral load and point of care testing for HCV antibodies) should make an attempt to eliminate morbidity and mortality by Hepatitis C virus a distinct possibility.

Keywords: Hepatitis C; RNA; HCV

Viral hepatitis is not an emerging infectious disease, but the cause of a silent epidemic of serious and often fatal liver disease, including liver cancer; the causative agents (hepatitis A, B, C, D, and E viruses) have been circulating in the human population for millennia. This liver disease burden is increasingly recognised as a global health threat. Viral hepatitis caused 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis and higher than those caused by HIV or Malaria. However, the number of deaths due to viral hepatitis is increasing over time, while mortality caused by tuberculosis and HIV is declining Viral hepatitis needs to be tackled as one of the "big four" infectious diseases of our age.

Across the world, about 400 million people are living with chronic hepatitis. Countries in the Asia Pacific region are the epicentre of the epidemic. In this region, about 1 million people die each year from hepatitis and its complications a figure three times as high as that for HIV/AIDS. If not diagnosed, treated, or managed, viral hepatitis B and C infections can lead to chronic liver diseases, including cirrhosis and liver cancer. Chronic hepatitis B and C infections are the main cause of liver cancer, and account for 78% of all liver cancer cases globally.

The global response to viral hepatitis entered a new phase in 2015, when the UN General Assembly adopted the 2030 Agenda for Sustainable Development, which called on the international community to combat hepatitis. The following year, the World Health Assembly adopted WHO's first "Global Health Sector Strategy on viral hepatitis" with elimination as its overarching vision. An early win in the global response to viral hepatitis was achieved through the effective scaling up of hepatitis B vaccine. In 2015, global coverage with the three doses of hepatitis B vaccine in infancy reached 84%. This has substantially reduced HBV transmission in the first five years of life, as reflected by the reduction in HBV prevalence among children to 1.3%. However, coverage with the initial birth

dose vaccination is still low at 39%. Other prevention interventions are available but insufficiently implemented.

Although injection drug use is the major route of HCV transmission in some regions, the provision of effective harm reduction services has been inadequate. Globally, 5% of health-care-related injections remained unsafe. As a result, an estimated 1.75 million new HCV infections occurred worldwide in 2015.

Eradication of Hepatitis C

Hepatitis C was first detected in 1989 using molecular biology techniques after extensive testing of serum from experimentally infected animals. It was later characterized to be an RNA virus that belongs to the Flaviviridae family and genus Hepacivirus. An estimated 185 million people have been infected with HCV and over 80% live in Lower Middle Income countries (LMIC). Untreated HCV infection leads to liver cirrhosis in up to a third of those who are chronically infected and these individuals are at risk for complications such as hepatocellular carcinoma (HCC) and hepatitis decompensation. Upto 500,000 people die each year from complications secondary to HCV infections : most in LMIC. It is now widely recognized as one of the common aetiological agents for cirrhosis of the liver. It is the leading cause of liver transplantation and the most common chronic blood borne infection in developed countries like the USA. The impact of this infection is just emerging in India. India's blood-banking system has serious shortcomings. Professional blood donation continues to flourish because of paucity of genuine voluntary blood donors. Another malaise in our health system is the reuse of improperly sterilized needles. Both these factors are potential sources for the spread of hepatitis C in India.

Improving the rate of diagnosis is the crucial first step so that people who need treatment and care can be identified and hepatitis transmission and liver cancer can be prevented. The science for viral hepatitis treatment is ready. HCV is a curable disease. Not only can patients live without symptoms after successful treatment but their risk of developing hepatocellular carcinoma is also reduced by 75%. The new generation of direct-acting antiviral treatments, including sofosbuvir, semiprevir, ledipasvir, and daclatasvir, have a high cure rate of well over 90% and are effective against the difficult-to-treat genotypes. They have better safety profiles, minimum drug interactions, and treatment courses of shorter duration. One great advantage is that these drugs are orally administered. Drug combinations (sofosbuvir with ledipasvir or daclatasvir) achieve higher cure rates even for patients with cirrhosis. Eradicating infection with hepatitis C is the most effective way to reduce the incidence of liver decompensation and hepatocellular carcinoma. Centres for Disease Control, Atlanta, USA estimates that one premature death in prevented for every three virological cures. Few medical interventions against chronic diseases can match this number needed to treat rate. In addition, reducing the pool of infected people could significantly decrease new infections and the overall prevalence of HCV infection in a community. Major challenges include diagnosing infected individuals, linking them into care and ensuring access to treatment with DAAs.

Epidemiology of HCV in India

Currently India harbours an estimated 10 -15 million chronic carriers of HCV, which is a major cause of liver related mortality and morbidity of the country. The prevalence of HCV infection in the general population is estimated to be around 0.5% to 1.5%. However, the prevalence of HCV is variable in different high risk populations according to various studies and there is still a paucity of data from large multi-centric studies. Studies on voluntary or mixed donors have reported a prevalence of HCV below 2%. In a large community based systematic study from the Indian state of West Bengal the prevalence was documented to be around 0.71%. On the contrary, a comparatively smaller study from the north eastern state of Arunachal Pradesh showed a much higher prevalence of HCV of 7.89%. A recent study done in Mizoram, another state in the north east of the country, showed HCV prevalence of 71.2% among the active injection drug addicts. There continues to be variations in reporting the HCV prevalence, depending upon the geographical region population sub-groups included in these studies. Overall, genotype 3 is the predominant genotype (63.85%) followed by genotype 1 (25.72%) in India. However there is a genotypic difference in different geographical regions of India, with genotype 3 being the commonest in northern, eastern and western India while genotype 1 is the commonest in the southern states of India (Figure 1). Besides the widespread prevalence of genotypes 3 and 1, there is also a trend of increased prevalence of genotypes 4 and 6 in certain regions of the country. Genotype 4 is found mostly in south Indian patients from the states of Andhra Pradesh and Tamil Nadu. Genotype 6 is found to be prevalent exclusively in patients from north eastern parts of the India. It is also to be noted that there is also increased prevalence of genotype 6 in various parts of the neighbouring country of Myanmar which shares its boundaries with the north-eastern states of India thus showing an ecological niche for HCV genotype 6 in north-eastern India and adjacent geographical areas. Genotype 2 has rarely been reported from India where-

as genotype 5 is yet to be reported. Such epidemiological studies and trend analysis are important in the wake of licensure of the newer generation DAAs which may revolutionize the management of HCV. However, it must be stressed that the reported distribution of the various genotypes can be expected to change with increasing migration of population and changes in high risk behaviour and lifestyle.

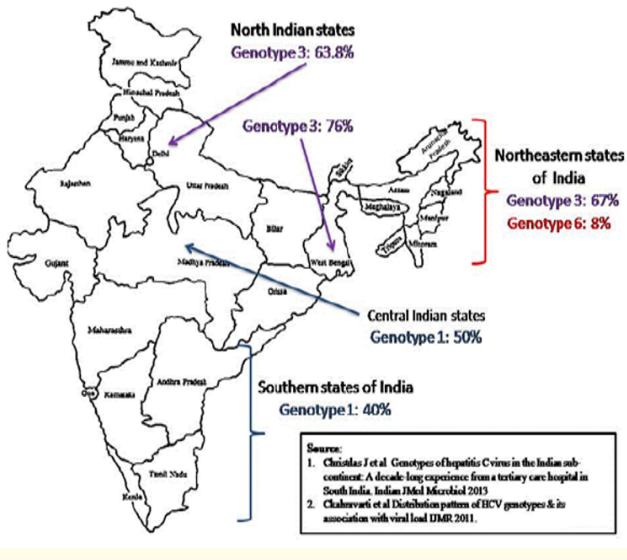

Figure 1

Strategies to eradicate Hepatitis C in India:

Spread of viruses causing hepatitis has three components, an infectious source, a susceptible host and an established route of transmission. Various strategies for control of viruses causing hepatitis would include control of infectious source, immunization of the host (susceptible subjects) and interruption of all routes of transmission. There is no vaccine to prevent HCV infection. In India three to six billion injections are given every year, of which two third are unsafely administered. Improving safe injections would help decrease transmission. But the real game changer has been the recent availability of a number of DAAs which have been licenced to Indian companies by Gilead, the original patent holder, so that Indian patients can receive the drugs at a fraction of the cost in USA, makes this strategy possible. A 12 week treatment costing Rs 30,000 can lead to complete cure in over 95% of patients.

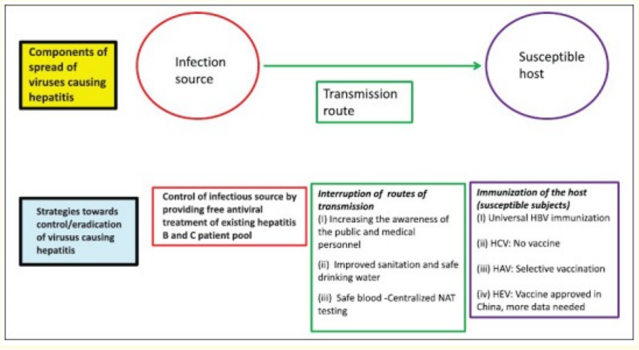

Figure 2

Diagnosis of hepatitis C infection

Who should be screened for HCV infection

One of the biggest challenge is how to diagnose the person. HCV is a silent killer. The virus lives in the body for decades, without showing any symptoms. When symptoms finally appear, they signal that the liver itself has been severely affected, making reversal from cirrhosis difficult. There are two approaches to screening: Risk based screening and Population based screening.

Risk based testing performs poorly as a strategy to identify people who have been exposed to HCV, as evidenced by up to 85% of people in USA who are unaware of their diagnosis in spite of recommendations in place since 1998 to test people with well characterized risk factors. CDC recently recognized that people with HCV infection were born from 1945 through 1965 because of the dynamics of peak transmission during 1960s to 1980s. This has led to a recommendation to test everyone in this birth cohort once. To identify those most at risk for development of severe complications of HCV infection, a global age based HCV testing program, adjusted for local epidemiology, would be the first step, to identifying those people with most advanced liver disease who are most likely to benefit immediately from diagnosis and treatment.

Populations for whom testing for hepatitis C virus (HCV) is recommended by CDC

Risk factor–based screening

- History of current or past (even once) injection drug use*

- Received health care or personal services where there is a lack of infection prevention and control practices
- Received a blood transfusion, blood products or organ transplant before 1992 in Canada
- History of or current incarceration
- Born or resided in a region where hepatitis C prevalence is > 3%,
- Born to a mother who is HCV-infected
- History of sexual contact or sharing of personal care items with someone who is HCV-infected*
- HIV infection, particularly men who have sex with men*
- Received chronic hemodialysis treatment
- Elevated alanine aminotransferase

Population-based screening

Born between the years 1945 and 1975.

*Retesting should be performed at least once per year in those individuals who are engaged in ongoing high-risk activities and must be done with HCV RNA, as anti-HCV antibody test will remain positive even after achievement of sustained virologic response.

Diagnosis of HCV infection is based on two categories of laboratory tests

A reliable culture method for HCV is not currently available. Laboratory assays currently available to diagnose and manage HCV infection include serological tests to detect HCV antibodies and core antigen, molecular tests to detect and quantify HCV RNA, and genotyping techniques. Currently, third-generation EIAs are the principal laboratory tests used to detect HCV exposure. Seropositivity by these tests occurs as early as 8 to 10 weeks after exposure to the virus and the tests remain positive for 6 months to a lifetime after infection. The specificity of EIA-3 is 99% or greater and sensitivity 97%, in high-prevalence population

- Indirect tests : Serological assays detecting specific antibodies to HCV
- Direct test: assays that can detect and quantify HCV viral RNA or core antigen.

Type of test [ELISA / CLIA]	Antigenic targets for HCV diagnosis			
	Core	NS3	NS4a	NS5b
ELISA 1st generation	--	--	+	--
ELISA 2nd generation	+	+	+	--
ELISA 3rd generation / CLIA	+	+	+	+

Table 1

All patients with a positive HCV EIA or CLIA result, and high-risk patients with negative EIA or CLIA results and unexplained elevated ALT levels should be further tested via nucleic acid tests (NAT) to detect the presence of HCV RNA. Detection of HCV RNA is helpful in certain situations; for example, the presence of HCV RNA in the absence of anti-HCV antibodies indicates acute infection, which can be confirmed by seroconversion a few days to a few weeks later. If HCV RNA is positive in a patient with a positive screening test result, HCV RNA detection has the advantage of detecting the presence of active HCV infection as well as verifying the presence of anti-HCV antibodies. CDC recommends that initial testing for HCV infection needs to be performed by a rapid or laboratory-conducted assay to detect the presence of HCV antibodies. A nonreactive HCV antibody result indicates no HCV detected. A reactive result indicates one of the following: 1) current HCV infection, 2) past HCV infection that has resolved, or 3) false positivity. A reactive result should be followed by NAT for HCV RNA. If HCV RNA is detected, that indicates current HCV infection. If HCV is not detected, that indicates either past, resolved HCV infection, or false HCV antibody positivity.

Nucleic acid-based RT-PCR is necessary to detect and quantify HCV RNA and to confirm positive results on EIA and CIA testing of patient samples. HCV RNA measurement by nucleic acid amplification is also essential for determining past chronic and resolved HCV infection.

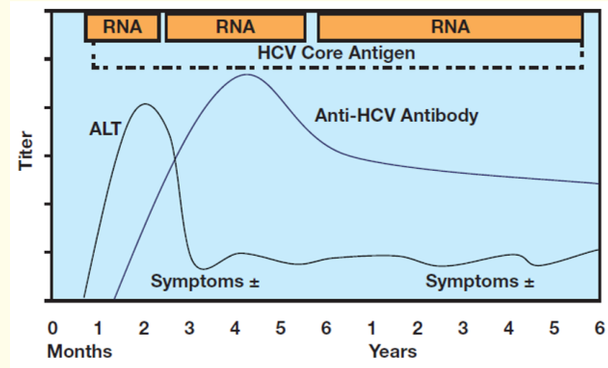

Figure 3

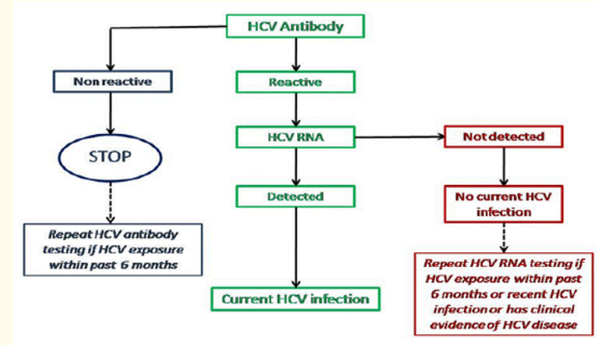

Figure 4

An alternative to nucleic acid tests is determination of the HCV core antigen via serological methods. The HCV core antigen is detectable 1 to 2 days after HCV RNA becomes detectable. HCV core antigen kinetics parallel HCV RNA and thus can be used as a marker of HCV replication. The HCV core antigen assay is independent of genotype and has a specificity of 99.5%. The limit of detection is 1.5 pg/ mL, which corresponds to an HCV RNA concentration of approximately 10,000 to 50,000 IU/mL. Commercially available assays include the Architect HCV Ag assay (Abbott Laboratories), which comprises 5 different antibodies to detect HCV core antigen, is highly specific (ie, 99.8%), and has sensitivity for determination of chronic hepatitis C equivalent to that of HCV RNA measurement. The detection limit of the HCV antigen assay corresponds to HCV RNA concentrations of 600 to 1000 IU/mL. The clinical usefulness of this test has been in question, given the availability of sensitive nucleic acid amplification tests and the fact that most HCV treatment algorithms are guided by qualitative and quantitative HCV RNA PCR results.

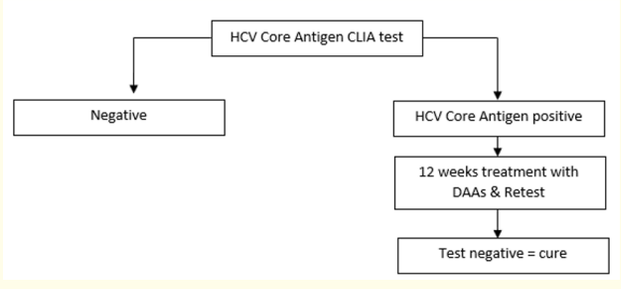

Figure 5

In the past, HCV genotypes and subtypes played an important role in treatment response and patient outcome. Patients infected with genotypes 2 and 3 are more likely to respond to therapy, compared with genotype 1 infection. Until recently, the conventional treatment of chronic HCV infection was pegylated interferon alpha in combination with ribavirin for 24 weeks in patients with HCV genotypes 2 or 3, and for 48 weeks in patients with genotype 1.

New directly-acting antivirals (DAAs) for HCV treatment are highly effective, with DAA based regimens providing rates of sustained virological response (SVR) exceeding 95% against virus belonging to all genotypes. These regimens are also very safe and convenient, needing administration of oral drugs once or twice daily for 12 ± 24 weeks. Thus, these drugs offer a hope of reducing the burden of HCV. In India, three DAAs (sofosbuvir, ledipasvir and daclatasvir) are available from several generic manufacturers at a low price.

Suggested workup before staring therapy

Category	Investigations	Considerations
Routine bloodwork	• Complete blood count • Liver enzymes (alanine transaminase, aspartate transaminase, alkaline phosphatase) • Liver function (bilirubin, INR, albumin) • Creatinine	• Low platelets and elevated bilirubin or INR are suggestive of cirrhosis • Renal function is important to determine safety of some regimens
Serology to exclude other infections	• HIV • Hepatitis B (HBsAg, anti-HBs, anti-HBc)	• If HIV-positive, treatment for HIV must take drug interactions into consideration • If HBsAg-positive or anti-HBc-positive consider risk of HBV reactivation)
Serology to exclude other common liver diseases	• Transferrin saturation (hemochromatosis) • IgG	• Elevated immunoglobulin G may reflect cirrhosis or possibly autoimmune hepatitis
Staging of liver disease	• APRI [Aspartate Aminotransferase to platelet ratio index] • FibroTest (serum panel) • Ultrasound • Transient elastography	• All persons with HCV must have evaluation of fibrosis to exclude cirrhosis. • Normal ultrasound does not exclude cirrhosis. • APRI < 0.7 has a very high negative predictive value to exclude cirrhosis
HCV-specific	• HCV genotype and HCV RNA • Resistance testing (may be useful in select circumstances)	• To select appropriate regimen, and consideration for addition of ribavirin.

Table 2

Treatment of HCV infection

Who should be treated

Treatment may be prioritized in certain patients who have high risk of progression like those with significant fibrosis or cirrhosis especially, ones with decompensated cirrhosis, HBV or HIV co-infection, HCV recurrence after liver transplantation, presence of clinically significant extra-hepatic manifestations and individuals who are at the risk of transmitting HCV. Counselling to stop alcohol consumption needs to be emphasized.

Goal of treatment

The goal of therapy is to cure HCV infection in order to prevent the complications of HCV-related liver fibrosis and cirrhosis which can result in decompensation, HCC and death. The endpoint of therapy is a Sustained Virus Response, defined by undetectable HCV RNA 12-24 weeks after end of treatment. Once the virus is undetectable 12-24 weeks after end of treatment (SVR 12/24) the chances of recurrence are <1% and can be termed a cure in more than 99% of cases. In patients with advanced fibrosis and cirrhosis, HCV eradication reduces the rate of decompensation and may reduce however not abolish the risk of HCC surveillance for HCC by six monthly ultrasound will need to be continued even after viral clearance. Anti HCV tests remains positive in the majority despite successful viral clearance and should not raise concern of persistent or recurrent infection.

Polymerase Inhibitors		NS 5 A inhibitors	Available in India
Nucleotide	Non Nucleotide		
Sofosbuvir		Ledipasvir	Yes
Sofosbuvir		Velpatasvir	Yes
Sofosbuvir		Daclatasvir	Yes

Table 3

Regimen: A. Sofosbuvir 400 mg + Ledipasvir (90 mg) [Harvoni] I tablet PO OD for 8 weeks (if patient is HIV -ve, non-cirrhotic and HCV RNA viral load is < 6 million copies/ml) or for 12 weeks (if patient has HIV coinfection, compensated cirrhosis or HCV RNA > 6 million copies/ml).

B. Sofosbuvir 400 mg + Velpatasvir (100 mg) 1 tablet PO OD for 12 weeks with or withour compensated cirrhosis C. Sofosbuvir 400 mg + Daclatasvir (60 mg) 1 tablet PO OD for 12 weeks in non-cirrhotic patients only [1-14].

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