Hepatitis Viral C, no longer a taboo in Family-Rural practice

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Demographics

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In the United states HCV is prevalent in 2% of people older than 20 year but this is higher in high risk population (ex. 8-9 % of those on Hemodyalisis).

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The most recent estimates of disease burden show an increase in sero-prevalence over the last 15 years to 2.8%, equating to >185 million infections worldwide.

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Persistent HCV infection is associated with the development of liver cirrhosis, hepato-cellular cancer, liver failure, and death.

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HCV genotype 1 is the most prevalent worldwide, comprising 83.4 million cases (46.2% of all HCV cases). Approximately one-third of which are in Eastern Asia

Jane Messina et al. at Oxford University (HEPATOLOGY 2014;00:000-000.

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Genotype 3 is the next most prevalent Globally (54.3 million, 30.1%) mostly South East Asia and Northern Europe.Genotype 3 infection is associated with more aggressive natural history, faster progression to cirrhosis and higher rates of hepatocellular carcinoma than other HCV genotypes.

Genotypes 2-4 and 6 are responsible for a total 22.8% of all cases.

Genotype 5 is the rarest (<1%).

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North America and Western Europe have the lowest prevalence of HCV while Africa and Eastern Europe have the highest one being mostly hospital transmitted cases.

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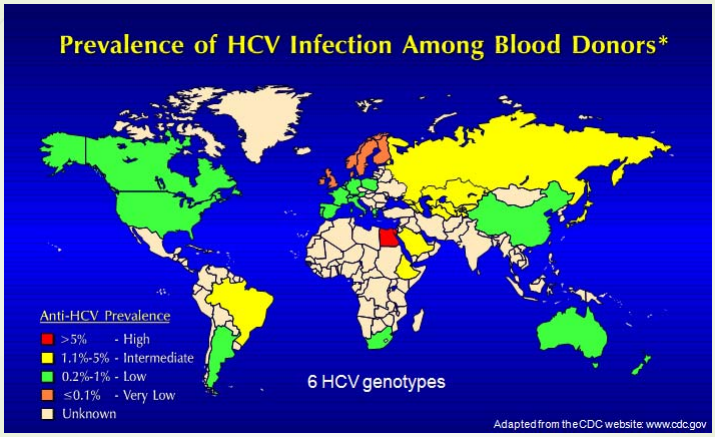

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Hepatitis C Virus

A recent modeling study suggested that about 252000 were chronically infected in 2013.

The birth cohort 1945-1975 (B.B.) has the highest prevalence of chronic HCV infection yet, it is estimated that up to 70% of this group have not been tested for HCV.

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Hepatitis C Virus

Although the overall prevalence of chronic HCV infection is declining, complications of the disease are increasing because of aging population and progression of liver fibrosis.

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Modeled hepatitis C virus (HCV) prevalence according to exposure category in Canada, 2007*

Risk group	Population	HCV prevalence %	Prevalent	Proportion of cases, n
IDU, total	268,200	52	40,000	58
Current IDU	84,400	62	52,500	22
Previous IDU	183,800	48	87,500	36
Transfusion	3,325,700	0.8	25,900	11
Hemophilia	2200	40	900	0.4
Other	27,624,300	0.27	75,800	31
Total	31,220,500	0.8	243,000	100

**Numbers rounded to the nearest 100. IDU Intravenous drug user*

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HCV is made up of a single string of RNA transmitted percutaneously by infected blood.

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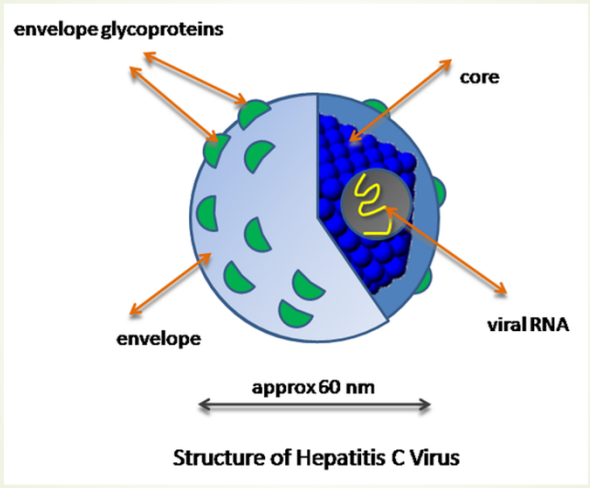

Structure of Hepatitis C Virus

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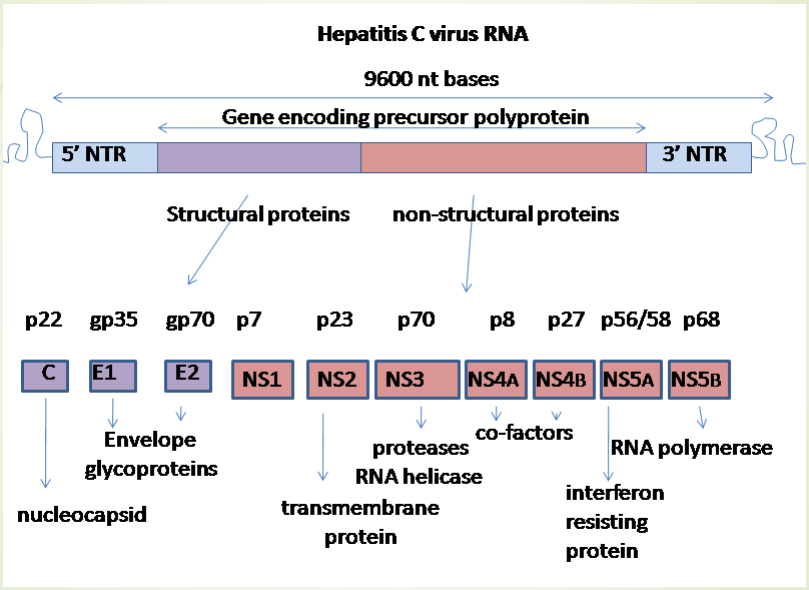

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HCV is categorized in 9 different genotypes. In North America, 72% of the patients are infected with Genotype 1. 16 to 19% by genotype 2; 8-10% by genotype 3 and 1-2% by other genotypes.

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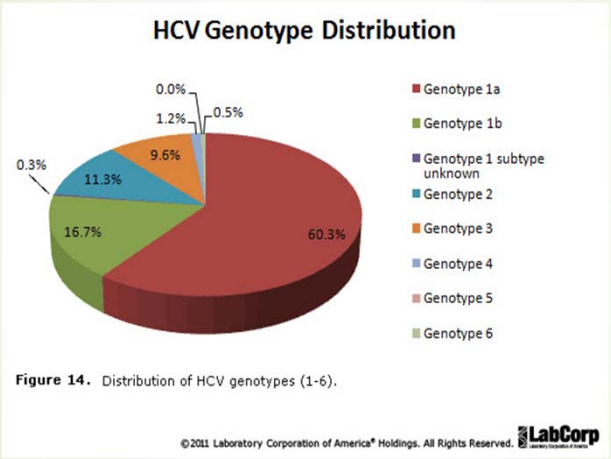
HCV Genotype Distribution
0.0%
1.2%
0.5%
9.6%
0.3%
11.3%
16.7%
60.3%
Genotype 1a
Genotype 1b
Genotype 1 subtype unknown
Genotype 2
Genotype 3
Genotype 4
Genotype 5
Genotype 6
Figure 14. Distribution of HCV genotypes (1-6).
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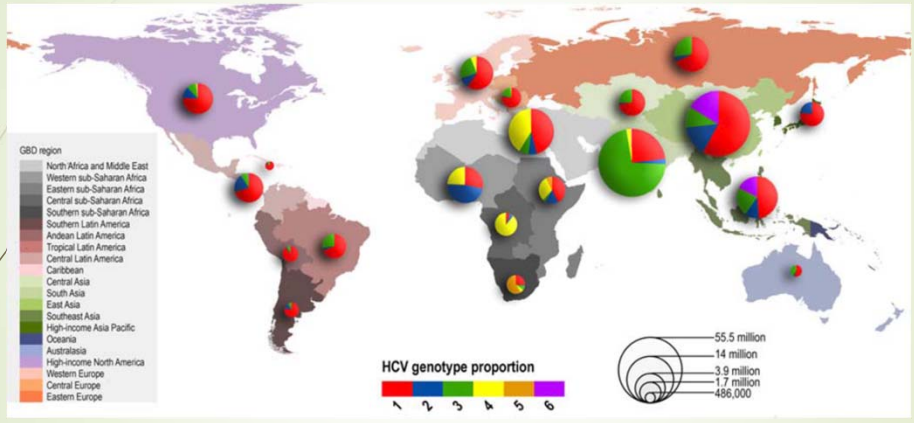
GBD region
North Africa and Middle East
Western sub-Saharan Africa
Eastern sub-Saharan Africa
Central sub-Saharan Africa
Southern sub-Saharan Africa
Southern Latin America
Andean Latin America
Tropical Latin America
Central Latin America
Caribbean
Central Asia
South Asia
East Asia
Southeast Asia
High-income Asia Pacific
Oceania
Australasia
High-income North America
Western Europe
Central Europe
Eastern Europe
HCV genotype proportion
1 2 3 4 5 6
55.5 million
14 million
3.9 million
1.7 million
486,000

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Risk factors for HCV infection

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Risk factor	*Odds ratio*
Intravenous drug use	36
Sex with intravenous drug user	17
Hemodialysis	8.3
Male sex with male (MSM)	3.1
Blood transfusion	2.3
Sex with multiple partners	2.2
Surgery	1.0
White or Hispanic race	0.9
Age 40 to 60 years	0.8
Needle stick injury	0.7
Health care occupation	0.3

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Infection diagnostic tests and test results in suspected HCV

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Initial anti-HCV test	*Confirmatory HCV tests*		
Enzyme-linked immunosorbent assay (EIA)	*Recombinant Immunoblot assay*	*HCV RNA Polymerase chain reaction*	***Test interpretation***
Negative	—	—	No infection or very early infection (repeat polymerase chain reaction if clinical suspicion of acute HCV infection)
Positive	Positive	Positive	Curent infection
Positive	Negative	Negative	False-positive antigen test
Positive	Positive	Negative	Past infection with HCV

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Anti-HCV antibody testing should be the diagnostic test of choice for initial screening. If positive, a confirmatory HCV RNA polymerase chain reaction test is required to confirm chronic infection.

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In those with previous spontaneous or treatment-induced clearance and those with suspected acute infection, HCV RNA is the screening test of choice because anti-HCV antibody tests remain positive for life, even after spontaneous or treatment-induced clearance of HCV.

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All individuals who test positive for HCV RNA should be evaluated by practitioners with experience in HCV management.

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The role of primary care physicians in providing care for hepatitis C virus (HCV) infection is increasingly emphasized, but many gaps and challenges remain.

Journal of Viral Hepatitis, 2011, 18, e332–e340

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Identification and management of HCV is increasingly occurring within primary care settings and HCV care guidelines have been disseminated to primary care physicians to advance screening efforts.

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J. Cox et al. (Journal of Viral Hepatitis, 2011, 18, e332–e340) Found important differences in correlates of HCV care among Canadian family physicians. Specifically, physicians providing basic–advanced HCV care had higher levels of familiarity and agreement with HCV care guidelines and were more likely to provide care for patients in settings where clinical follow-up care is possible and practiced in a nonurban setting.

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Physician knowledge related to HCV care

The next slide shows results of bivariate analysis of Family Physicians providing basic-advanced HCV care and not ongoing HCV care.

This analysis showed significant differences for all variables representing dimensions of HCV knowledge.

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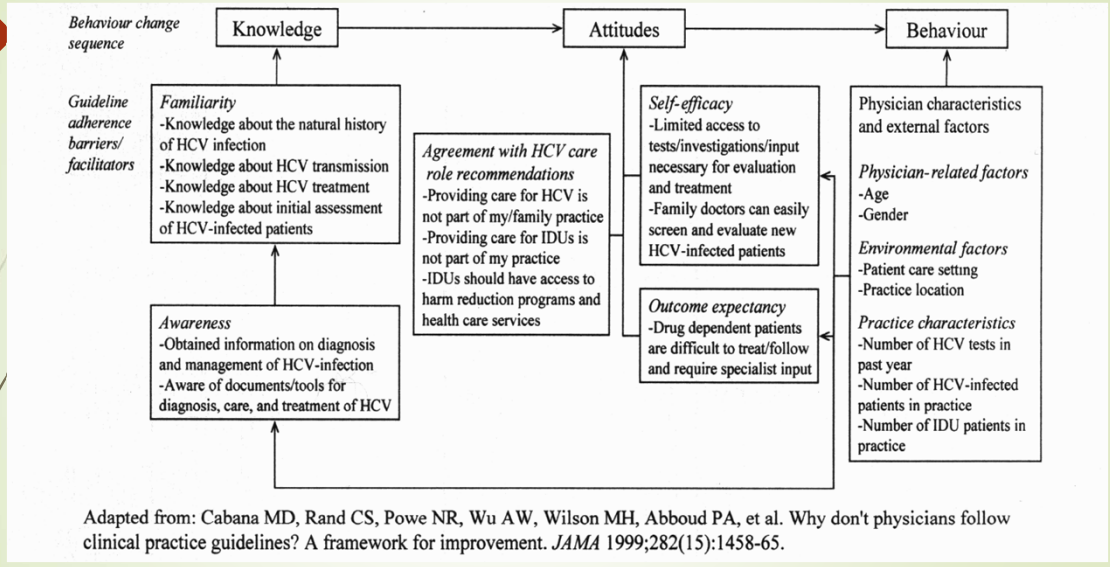

Adapted from: Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282(15):1458-65.

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Physician attitudes related to HCV care

For self-efficacy variables, most physicians, regardless of HCV care provision, reported limited access to tests, investigations or input necessary for HCV evaluation and treatment.

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Physician attitudes related to HCV care

Family doctors can easily screen and evaluate new HCV-infected patients. Scores on these two measures of self-efficacy were higher for physicians providing HCV care.

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Physician attitudes related to HCV care

Over 63% of physicians providing no ongoing HCV care reported they believed that providing HCV care was not part of their practice/family practice.

33

Family physicians providing basic-advanced HCV care were more likely to correctly identify current treatment regimens (OR = 1.74;95% CI = 1.24–2.43) as well as be familiar with the initial assessment of HCV-infected patients (OR = 1.77; 95%CI = 1.23–2.54).

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While most physicians demonstrated a high level of knowledge about HCV transmission via drug-related activities, results complement other recent findings of gaps in primary care physicians knowledge, particularly regarding the natural history of HCV infection [7] and transmission of the virus.

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Physicians providing HCV care were more likely to perceive that family doctors can easily screen and evaluate new HCV-infected patients, but that they had limited access to tests/investigations/input necessary for HCV evaluation and treatment.

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The most significant finding in relation to attitudinal factors favouring HCV care provision is the negative association with the belief that providing care for HCV is not part of the physicians/family practice.

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Physicians providing care for HCV were significantly more likely to practice in a rural or isolated setting, suggesting perhaps that family physicians take responsibility for HCV care when specialist care is less available.

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Physicians having one or more IVDUs in their practices were more likely to provide HCV care.

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Expansion of non-specialist HCV care will be required in Canada to ensure that all infected individuals receive appropriate care.

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Laboratory criteria for diagnosis:

One or more of the following criteria:
1) Anti-HCV becomes positive at 4-12 weeks post exposure
OR
2) HCV-RNA becomes positive at 2-4 weeks post exposure
AND, meets the following two criteria:
1) Anti-HAV IgM negative
AND
2) Anti-HBc IgM negative, HBSag negative, HB ADN negative

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Screening strategies for HCV infection may include screening of populations at risk of infection, birth cohort testing, and general population testing in areas of intermediate to high sero-prevalence (≥2%–5%).
Screening for HCV infection should be based on the detection of anti-HCV antibodies in serum or plasma by means of enzyme immunoassay.

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If anti-HCV antibodies are detected, the presence of HCV RNA (or alternatively HCV core antigen, if HCV RNA assays are not available) and/or not affordable) should be determined to identify patients with ongoing infection.

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Imaging techniques

Ultrasound-based transient elastography **(TE)** and Magnetic Resonance Elastography **(MRE)** are non-invasive procedures that measure liver stiffness.

Evaluations of **MRE** have shown up to 85 percent accuracy for detecting intermediate to severe fibrosis (F2–F4).

Currently only **MRE** is approved for use in the United States.

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FibroScan

Results are measured using KiloPascal's (Kpa) and range from 2 to 75

The average normal result is 5.3 Kpa

Scarring has 4 stages:

- **F0** means no scarring
- **F1** is mild fibrosis
- **F2** is moderate fibrosis
- **F3** is severe fibrosis
- **F4** is cirrhosis

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FibroScan

Condition	Fibrosis stage and approximate cutoff values			
	F0 to F1	F2	F3	F4
Hepatitis B Hepatitis C HIV (co-infection)	2 to 8	8 to 10	10 to 14	14 or higher
Cholestatic liver	2 to 7	7 to 9	9 to 17	17 or higher
NASH or NAFLD	2 to 7	7 to 10	10 to 14	14 or higher
Alcoholic Hepatitis	2 to 7	7 to 11	11 to 19	19 or higher

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Pre-therapeutic assessment

Liver disease severity must be assessed, and baseline virological parameters that will be useful for tailoring therapy should bedetermined.

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Pre-therapeutic assessment

- Fibrosis stage must be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional aetiologies.
- Renal function (creatinine/estimated glomerular filtration rate [eGFR]) should be ascertained.

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Pre-therapeutic assessment

- Extra-hepatic manifestations of HCV infection should be identified in case of symptoms (Immune related, Inflammatory related manifestations).
- HBV and HAV vaccination should be proposed to patients who are not protected (A1).

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Diagnosis of **acute HCV infection** is reason for an urgent referral to an *experienced colleague**. if viral clearance does not occur within 12 weeks of exposure, antiviral therapy should be started as there is a very high rate (>90%) of viral clearance following treatment of acute HCV with new treatments available.

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Goals and end-points of HCV therapy

The goal of therapy is to cure HCV infection, in order to:

Prevent the complications of HCV-related liver and extra-hepatic diseases, including hepatic necro-inflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extra-hepatic manifestations and death; improve quality of life and remove stigmata; and prevent onward transmission of HCV.

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Goals and end-points of HCV therapy

The endpoint of therapy is undetectable HCV RNA in serum or plasma by a sensitive assay (lower limit of detection ≤15 IU/ml) 12 weeks (SVR12) or 24 weeks (SVR24) after the end of treatment.

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Goals and end-points of HCV therapy

Undetectable HCV RNA in serum or plasma 24 weeks (SVR24) after the end of treatment, using a qualitative HCV RNA assay with a lower limit of detection ≤1,000 IU/ml (3.0 Log10 IU/ml), can be used as an alternative endpoint of therapy in areas where sensitive HCV RNA assays are not available and/or not affordable.

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Goals and end-points of HCV therapy

In patients with advanced fibrosis and cirrhosis, surveillance for HCC (AFP + abdominal U/S or better Doppler Color U/S) every 6 months must be continued because an SVR will reduce, but not abolish, the risk of HCC.

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Contraindications to Treatment for Chronic HCV Infection

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Absolute contraindications

- Active autoimmune hepatitis or other condition known to be exacerbated by interferon and ribavirin (Rebetrol).
- Known hypersensitivity to drugs used to treat HCV infection.
- Patients with co-infected HBV(Potential reactivation)
- Pregnant or unwilling to comply with adequate contraception.

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Absolute contraindications

- Renal failure (contraindicated for ribavirin only)
- Severe concurrent cardiopulmonary disease
- Uncontrolled major depressive illness, psychosis, or bipolar disorder
- Untreated hyperthyroidism.

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Relative contraindications

- Decompensated cirrhosis:
- Albumin level less than 3.4 g per dL (34.00 g per L)
- Evidence of encephalopathy or ascites
- International Normalized Ratio greater than 1.5
- Platelet count less than 75 x 103 per mm3 (75.00 X 109 per L)
- Total serum bilirubin level greater than 25.66 µmol per L.

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Relative contraindications

Alcohol use is extremely common in patients with HCV being considered for treatment

Alcohol use has a significant negative impact on treatment candidacy. Compared with non-drinkers, physicians were less inclined to offer treatment to patients with a history of alcohol use despite being abstinent for at least 6 months before therapy. (Gastroenterology, May 2006,Volume 130, Issue 6, Pages 1607–1616)

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The CAGE score, which is easy to administer in a clinical setting; a score of ≥2 is associated with a sensitivity and specificity of 74% and 91%, respectively, for alcohol abuse or dependence.

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Relative contraindications

Intra Venous Drug Use (IVDU):

- Chronic HCV is the most common infection in IDU
- Because of the allegedly poor compliance of IDUs with treatment requirements and conditions, Hepatologists recommend treatment only if former IUD is drug free for 6-12 months.

Gastroenterology, May 2006,Volume 130, Issue 6, Pages 1607–1616)

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Suggested work-up before beginning HCV therapy

Routine bloodwork

Complete blood count

Liver enzymes (alanine transaminase, aspartate transaminase, alkaline phosphatase)

Liver function (bilirubin, INR, albumin)

Creatinine

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Suggested work-up before beginning HCV therapy

Routine bloodwork

Low platelets and elevated bilirubin or INR are suggestive of cirrhosis.
Renal function is important to determine safety of some regimens

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Suggested work-up before beginning HCV therapy

Serology to exclude other infections

- HIV
- Hepatitis B (HBsAg, anti-HBc)
- If HIV-positive, treatment for HIV must take drug interactions into consideration
- If HBsAg positive or anti- HBc positive, risk of HBV reactivation).

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Suggested work-up before beginning HCV therapy

Serology to exclude other common liver diseases

- Transferrin saturation (hemochromatosis)
- IgG (Elevated immunoglobulin G may reflect cirrhosis or possibly autoimmune hepatitis).

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Suggested work-up before beginning HCV therapy

HCV specific

- HCV genotype and HCV RNA
- Resistance testing may be useful in select circumstances. Not recommended in Canada to select appropriate regime and consideration for addition of ribavirin.

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Genotype 1: Initial Treatment:

From 1998 to 2013, therapy evolved from interferon monotherapy, to **PEG interferon** monotherapy, to peg interferon plus **Ribavirin**, to triple therapy with peg interferon plus ribavirin plus a NS3A/4A protease inhibitor (**Boceprevir** or **Telaprevir**). They all are excepting Ribavirin no longer prescribed regimes.

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Recommended regimens and durations (weeks) for patients without cirrhosis who have never been treated, according to HCV genotype.

Regimen	HCV genotype						
	1a	**1b**	**2**	**3**	**4**	**5**	**6**
Ledipasvir/sofosbuvir **(Harvoni)**	8-12 wk	8-12	NR	+ Rbv 12	12	12	12
Elbasvir/grazoprevir **(Zepatier)**	12-16 wk +- Rbv	8-12	NR	+ SFV 12	12	NR	NR
Sofosbuvir + daclatasvir **(Sovaldi + Daklinza)**	12 wk	12	12	12	NR	NR	NR

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Recommended regimens and durations (weeks) for patients without cirrhosis who have never been treated, according to HCV genotype

Regimen	HCV genotype						
	1a	1b	2	3	4	5	6
Sofosbuvir/velpatasvir 12 wk **(Epclusa)**	12	12	12	12	12	12	12
Glecaprevir/pibrentasvir 8 wk **(Maviret)**	8	8	8	8	8	8	8
Sofosbuvir/velpatasvir/ voxilarevir **(Vosevi)**	NR	NR	NR	NR 12 wk (USA,GB)	NR	NR	NR

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Recommendations

Simplified, pan-genotypic anti-HCV treatment recommendations are now possible, thanks to the approval of highly efficacious, safe and well tolerated pan-genotypicanti-HCV drug regimens.

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Recommendations

Pre-treatment assessment can be limited to proof of HCV replication (presence of HCV RNA or of HCV core antigen serum or plasma) and the assessment of the presence or absence of cirrhosis by means of a simple non-invasive method.

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Recommendations

Treatment-naive and treatment-experienced patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis can be treated with either the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, or the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks without testing genotype.

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Recommendations

- A sensitive molecular method with a lower limit of detection ≤15 IU/ml should be used to monitor HCV RNA levels in serum or plasma.
- In patients treated with an IFN-free regimen, HCV RNA or HCV core antigen levels should be measured at baseline and 12 or 24 weeks after the end of therapy (to assess SVR12 or SVR24, respectively)

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Recommendations

The patients receiving Direct Acting Antivirals (DAA's) containing regimen should be assessed for clinical side effects at each visit . ALT levels should be assessed at least at baseline and at 12 or 24 weeks post-treatment, and in case of suggestive symptoms.

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Monitoring of treatment

- Asymptomatic serum ALT elevations generally occurred within the first 4 weeks of treatment, but all resolved without intervention and with continued DAA treatment, none of them being synchronous with bilirubin elevations.
- Treatment should be stopped in case of severe adverse events or in case of ALT flare >10 times the upper limit of normal values .

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CONCLUSION

The treatment of chronic HCV infection is intimidating and complex, needs a good knowledge and understanding of the infection and familiarize with different therapeutic options. However, it is very feasible for Family-Rural doctors who wish to get involved on treating this population of patients, particularly if no local specialized back up.

The new Interferon free, Ribavirin free Pan-genotypic regimes simplify by lots and provide a highly successful treatment.

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