HEPATITIS C

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Presenter: Dr G Shamhuyashe

Outline

- Introduction
- Epidemiology
- Life Cycle
- Presentation
- Diagnosis
- Treatment
- Follow up after HCV Cure

INTRODUCTION

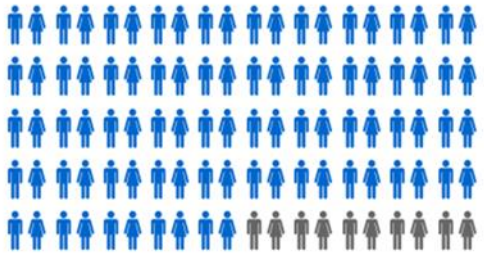
- Worldwide 71 million people infected chronically

- Highly variable long term natural history
- Necro-inflammatory to extensive fibrosis and cirrhosis, HCC
- WHO goal is to eliminate HCV infection by 2030

Primary goal of therapy – cure HCV infection (SVR12 or SVR24)

- Achieve Sustained Viral Response (SVR) - undetectable HCV RNA. SVR→ with cure.
- Generally normalization of liver enzymes & regression of inflammation and fibrosis.
  - Reduced decompensation
  - Decreased risk of HCC and Complications.
  - Extrahepatic manifestations
  - Improve QOL

- Prevent onward transmission
- *HCC- still risk in those who are cirrhotic*



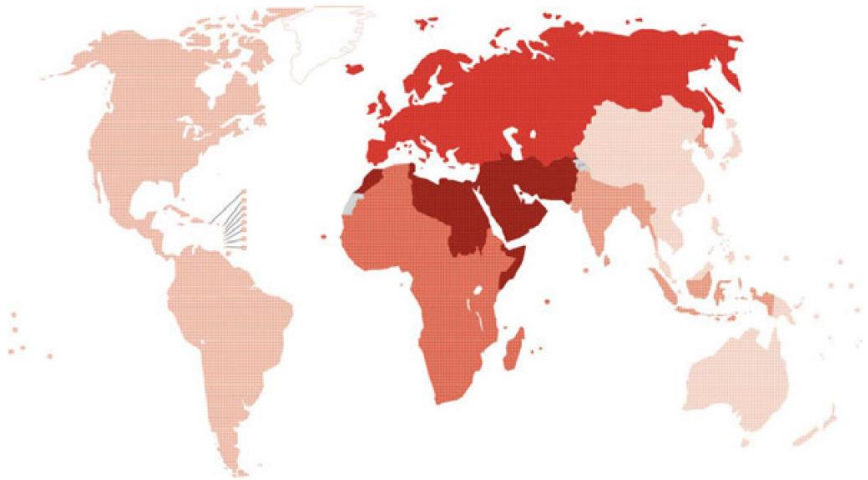
90% reduction in new cases of chronic hepatitis B and C by 2030

65% reduction in hepatitis B and C by 2030

80% of treatment eligible persons with chronic hepatitis B and C infections treated by 2030

Epidemiology

- Estimated global prevalence of HCV in 2015: 1.0% (95% uncertainty interval 0.8–1.1)[1]
- Corresponds to **71.1 million** (62.5–79.4) viraemic infections[1,2]
- ~**399,000** deaths each year, mostly from cirrhosis and HCC[2]
- GT 1 and 3 are the most common causes of infection (44% and 25%, respectively)[1]



WHO region	Map key	HCV incidence rate per 100,000: Best estimate (uncertainty level)	New HCV infections (x 1,000): Best estimate (uncertainty level)
African		31.0 (22.5–54.4)	309 (222–544)
Americas		6.4 (5.9–7.0)	63 (59–69)
Eastern Mediterranean		62.5 (55.6–65.2)	409 (363–426)
European		61.8 (50.3–66.0)	565 (460–603)
South-East Asia		14.8 (12.5–26.9)	287 (243–524)
Western Pacific		6.0 (5.6–6.6)	111 (104–124)
Global		**23.7 (21.3–28.7)**	**1,751 (1,572–2,120)**

1. Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol 2017;2:161–76; 2. World Health Organization. Global Hepatitis Report 2017. Available at: http://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf?sequence=1; EASL CPG HCV. J Hepatol 2018;69:461–511.

HCV Epidemiology

LOCAL DATA:

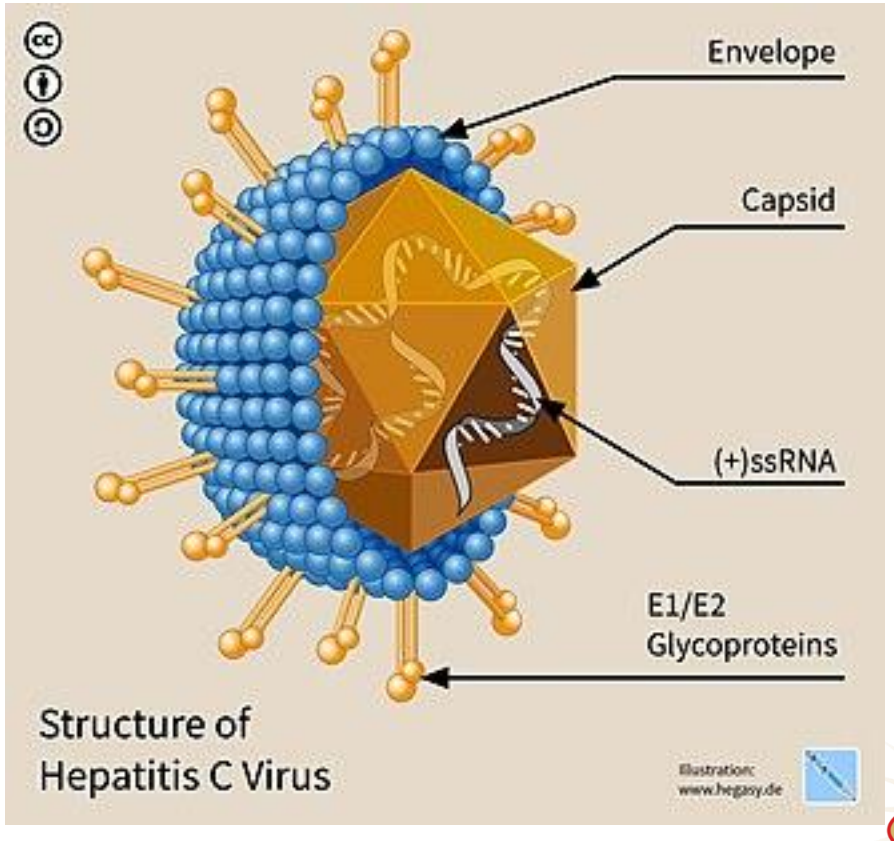
- In South Africa data is poorly understood and characterised
- Estimated 600 000 South Africans chronically infected.

- Seroprevalence:
  - Urban blood donors (low risk) of 0.01 - 2.6 %
  - Higher rates in the rural population (3.8 %)
  - High-risk groups →50% of PWID & 3-6% MSM (especially if HIV positive)
  - PWID, there is significant regional variation in viraemic prevalence
    - Highest in Pretoria (~75 %) and between 30 and 40 %in Durban and Cape Town 5,6%

https://sahivsoc.org/Files/SA NDOH Viral Hepatitis guidelines 2020

Hepatitis C

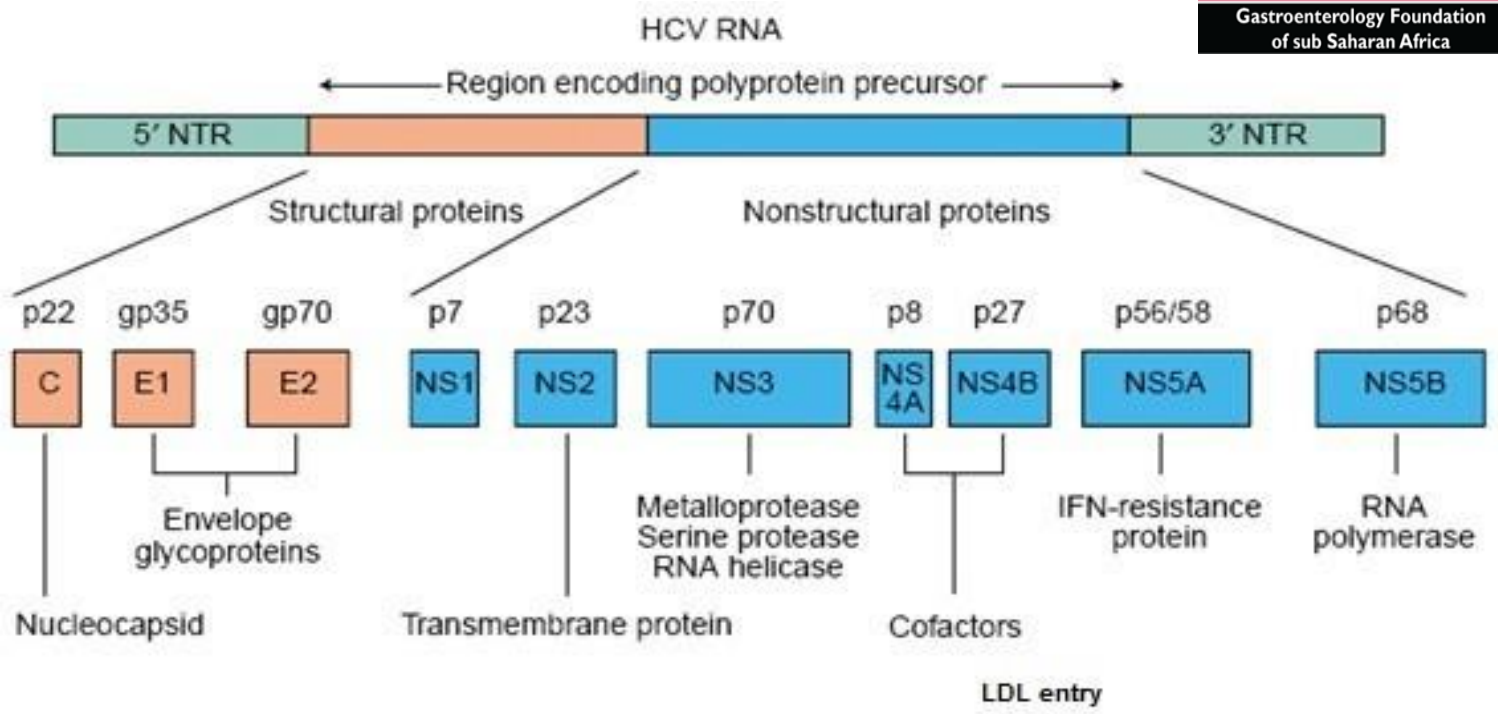
- Enveloped RNA virus. 50nm in diameter. 2 envelope proteins: E1 and E2
- Single stranded. Half life-2.5hrs
- Envelope proteins anchor onto host-cell derived lipid bilayer that surrounds the nucleocapsid→ composed of multiple copies of core protein
- Internal icosahedral coat that encapsulates the genomic RNA
- Circulates in various forms in serum→ bound to VLDL/ LDL→ infectious fraction
- bound to Immunoglobulins or as free virons



Genomic organization of HCV

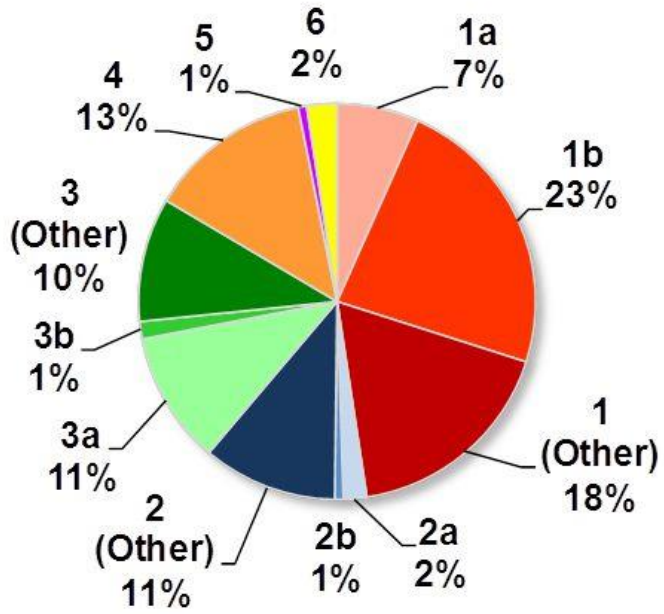
- Single stranded positive-sense RNA virus
- Flaviviridae family
- No polymerase proofreading ability therefore produces heterogenous viral populations
- 8 Genotypes with more than 84 subtypes

- 9600 nucleotides in genome
- Encodes 3000 amino acids



Global Epidemiology

HCV Genotype Distribution Globally



Genotype 1	48%
Genotype 2	14%
Genotype 3	22%
Genotype 4	13%
Genotype 5	1%
Genotype 6	2%

Gower, E., Estes C., Hindman, S., Razavi-Shearer, K., Razavi, H., Global epidemiology and genotype distribution of the hepatitis C virus, *Journal of Hepatology* (2014)

South Africa – HCV Genotypes

- Pan-genotypic country →genotypes 1 to 5
- Predominantly **genotype 1 and 5**
- **genotype 4** detected increasing frequency.
- **Genotype 5a**→ first identified in South Africa
  - unique to South Africa.
- In **PWID**
  - genotype 1a (73 %) & 3a (15%.)

https://sahivsoc.org/Files/SA NDOH_Viral Hepatitis guidelines 2020

HEPATOLOGY

HEPATOLOGY, VOL. 69, NO. 4, 2019

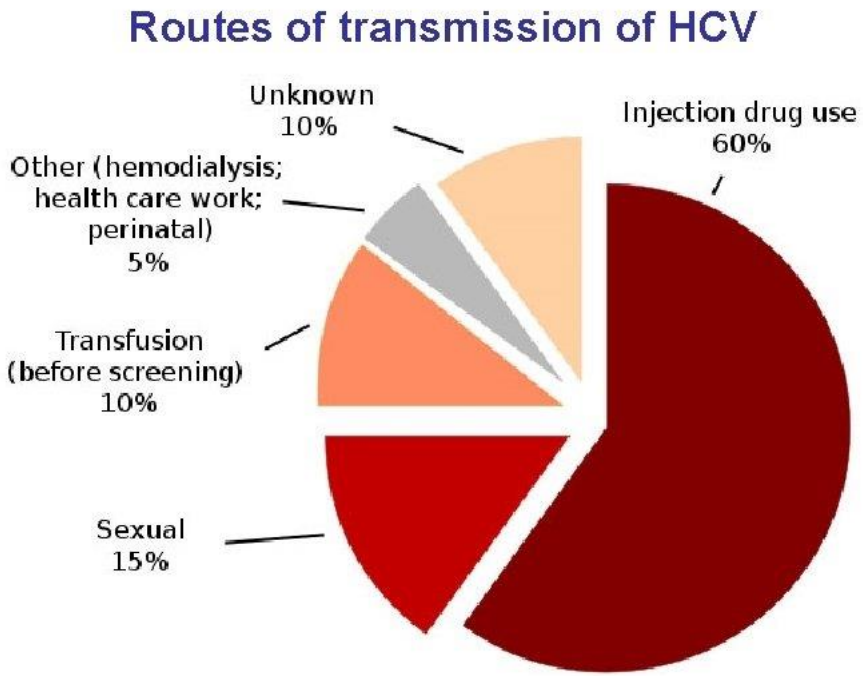
Highly Diverse Hepatitis C Strains Detected in Sub-Saharan Africa Have Unknown Susceptibility to Direct-Acting Antiviral Treatments

Chris Davis,[1*] George S. Mgomella ,[2,3*] Ana da Silva Filipe,[1] Eric H. Frost,[4] Genevieve Giroux,[4] Joseph Hughes,[1] Catherine Hogan,[4] Pontiano Kaleebu,[5,6] Gershim Asiki,[6] John McLauchlan,[1] Marc Niebel,[1] Ponsiano Ocama,[7] Cristina Pomila,[2] Oliver G. Pybus,[8] Jacques Pépin,[4] Peter Simmonds,[9] Joshua B. Singer,[1] Vattipally B. Sreenu,[1] Clara Wekesa,[6] Elizabeth H. Young,[2,3] Donald G. Murphy,[10**] Manj Sandhu,[2,3**] and Emma C. Thomson [1**]

HCV Transmission

Percutaneous

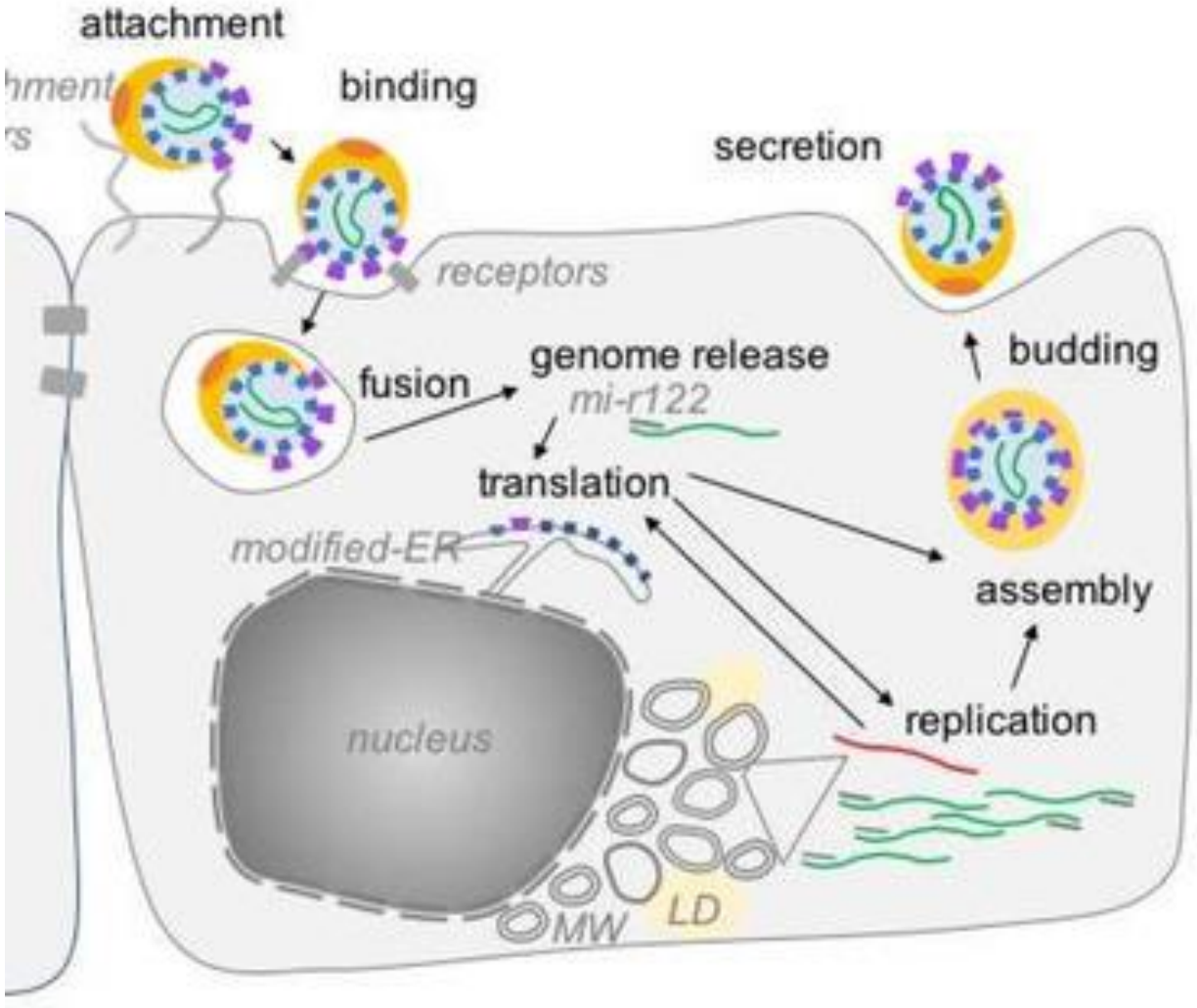
- **Blood transfusion**
  - Prior to introduction of screening.
  - 1990-1992
- **IV drug use**
  - PWID
  - HBV/HIV overlap
- **Chronic hemodialysis**
- **Occupational exposure**
  - HCW Eg. Needlestick injury
  - No post exposure prophylaxis



Nonpercutaneous

- **Sexual practices**
- **MTCT**
  - Perinatal transmission HBV>2-3x higher in HIV coinfected.
  - Mother with high HCV RNA
  - Use of HAART decreased both –hiv & hcv
  - ?NVD vs C/section
  - Breastfeeding

Life Cycle

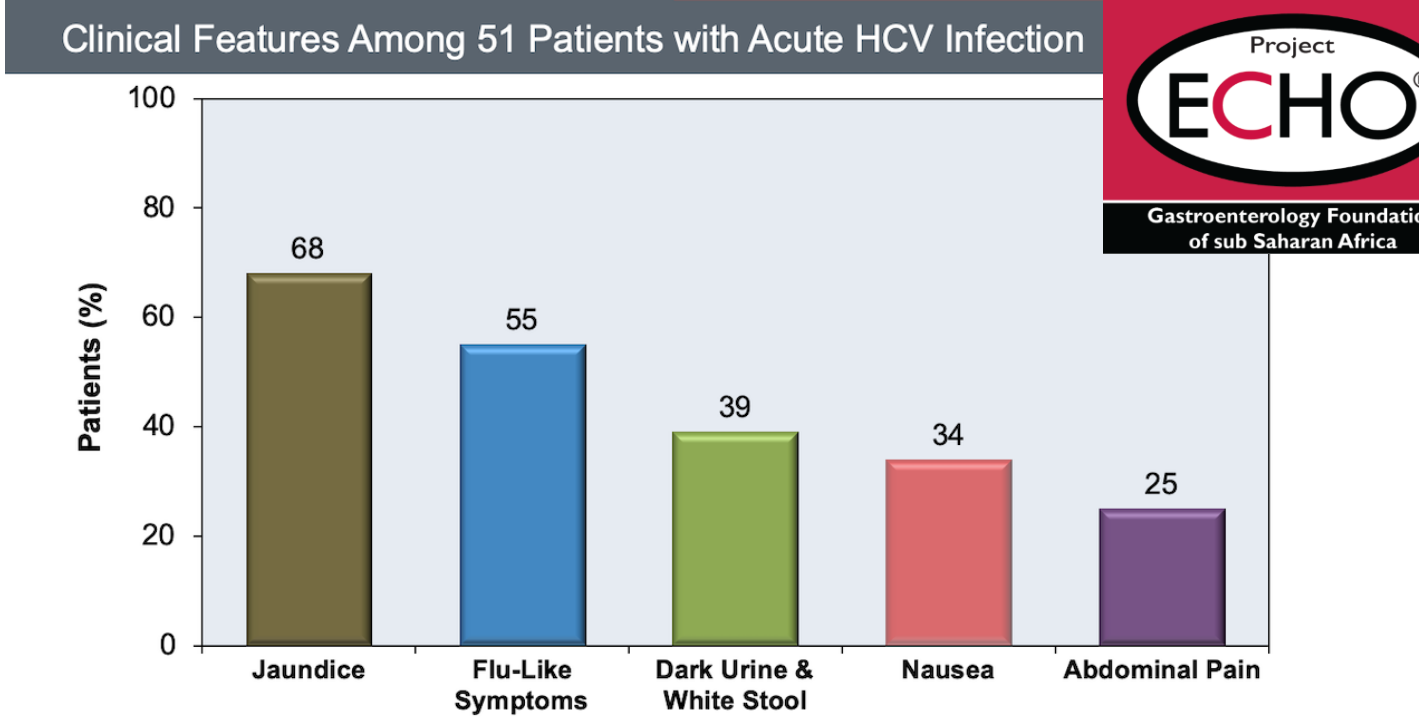

attachment
binding
secretion
receptors
fusion
genome release
mi-r122
budding
translation
modified-ER
assembly
nucleus
replication
MW
LD

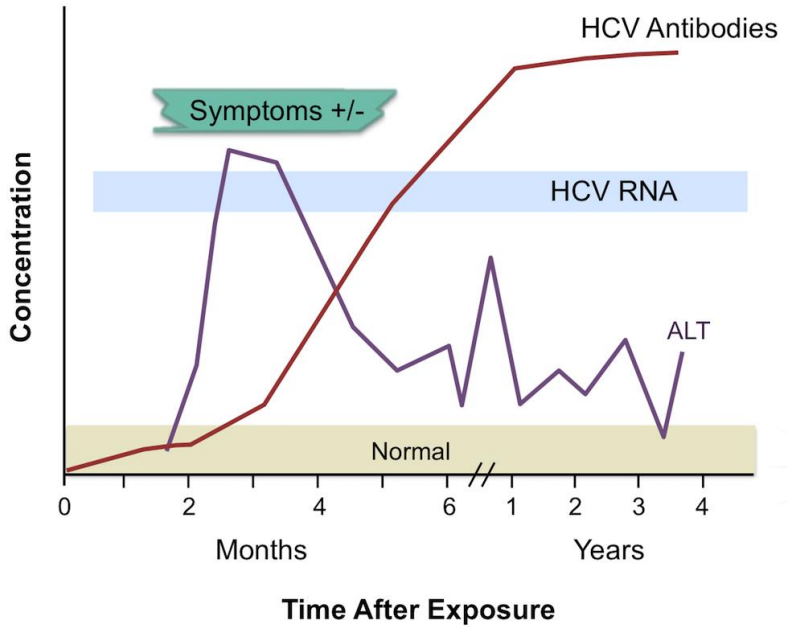
Natural Life Cycle

- Acute Hep C
- Chronic Hep C

Acute Hep C

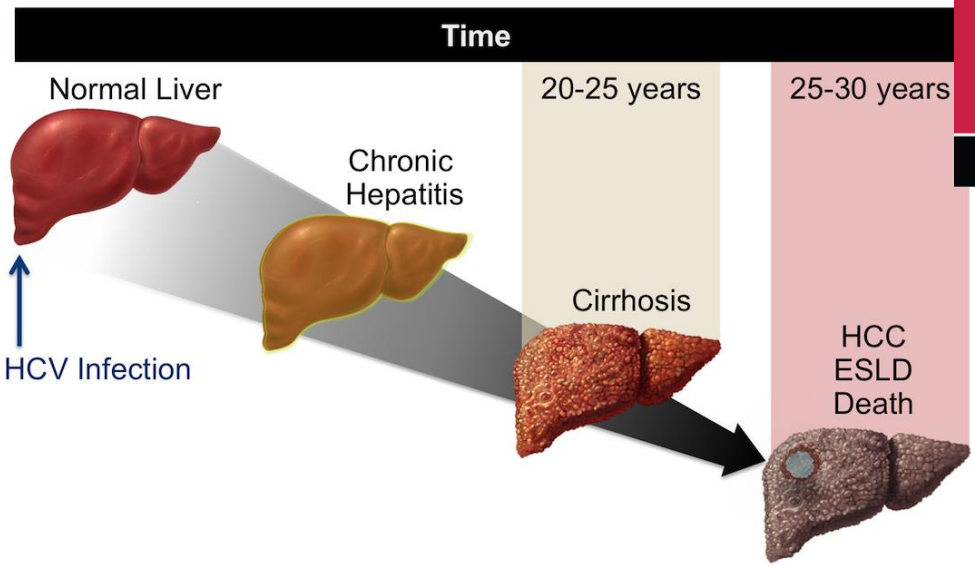
- Usually Mild,
- Usually is undiagnosed, so incidence of 1.5m most likely an underestimate
- 15 to 40% of patients will clear the acute episode
- Positive viral RNA at 12 weeks predicts chronicity
- Treatment should be instituted at 12 weeks if still RNA positive
- Short duration of treatment during acute episode may reduce risk of spreading infection
- No lasting immunity

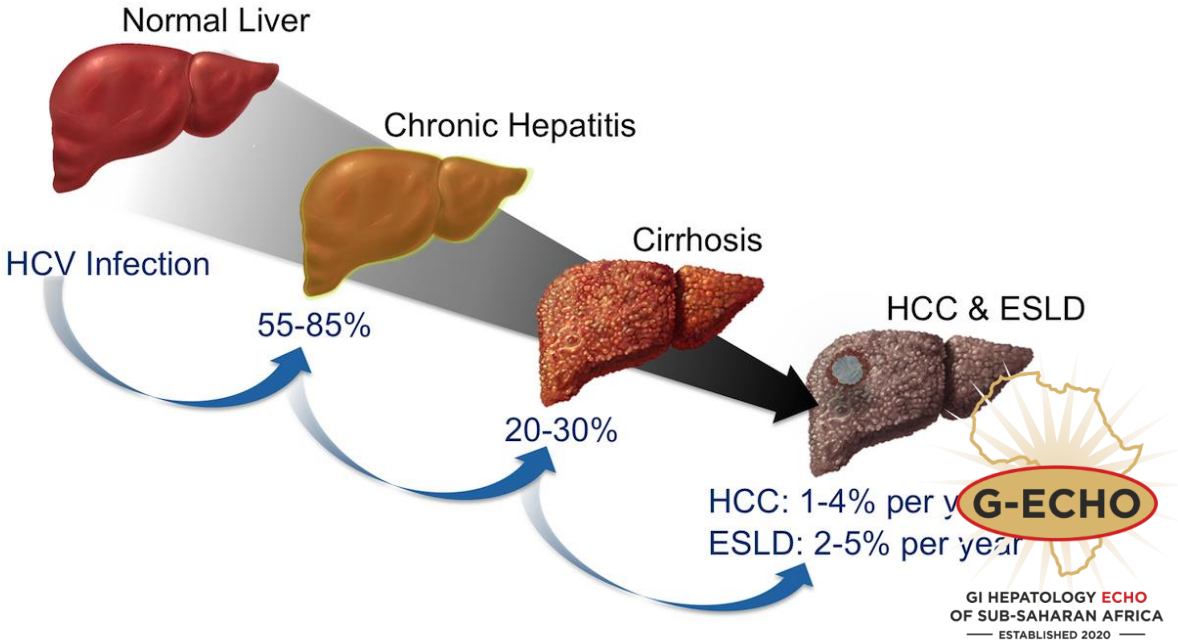




Chronic Hep C

- Chronic Hep C is the most common complication of acute hep C infection
- Factors that drive progression to cirrhosis include:
  - Host Factors
  - Viral factors
  - Environmental Factors





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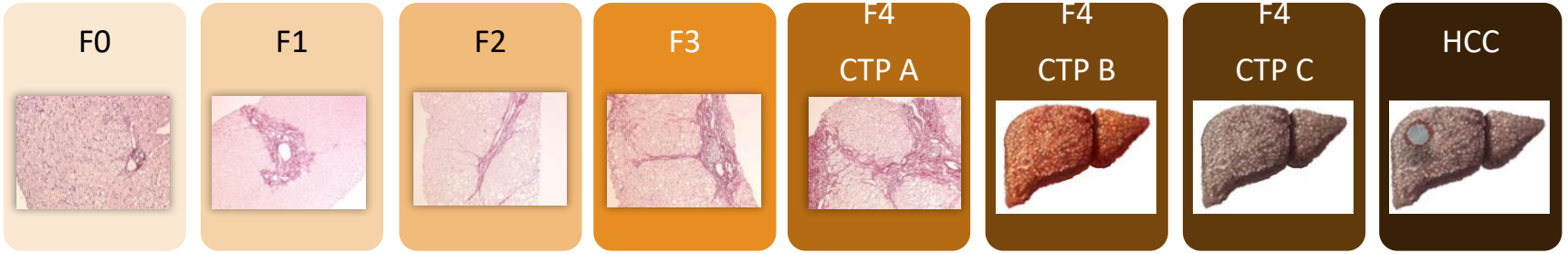
Natural history/disease burden

- Long-term natural history of HCV infection is highly variable
- Chronic HCV infection is accompanied by
  - Extrahepatic manifestations reported in up to 75% of patients, including:[1]
    - Mixed cryoglobulinaemia vasculitis, renal disease (elevated creatinine), type 2 diabetes, cardiovascular disease (vasculitis, arterial hypertension), porphyria cutanea tarda, lichen planus and lymphoproliferative disorders
    - Non-specific symptoms: fatigue, nausea, abdominal pain, weight loss
  - Rapid development of hepatic fibrosis and accelerated time to cirrhosis[2]



  - Increased risk for liver failure, HCC and liver-related mortality
    - Overall estimated annual risk for liver failure of 2.9%, HCC 3.2% and liver-related death 2.7% in patients with advanced fibrosis[1,3]

Figure adapted from Asselah T, et al. J Hepatol 2014;61:193–5

1. van der Meer AJ, et al. J Hepatol 2016;65:S95–S108; 2. Butt AA, et al. JAMA Intern Med 2015;175:178–85;
3. Singh AG, et al. Clin Gastroenterol Hepatol 2010;8:280–8;
EASL CPG HCV. J Hepatol 2018;69:461–511.

Chronic Hep C

AASLD/IDSA: HCV Guidance

Factors Associated with Accelerated Fibrosis Progression

Host	Viral
▪ **Non Modifiable** Fibrosis stage Inflammation grade Older age at time of infection Male sex Organ transplant	Genotype 3 Coinfection with HBV or HIV • **Genotype 3- higher mortality** • **Flares more frequent in genotype 2**
▪ **Modifiable** Alcohol consumption Nonalcoholic fatty liver disease Obesity Insulin resistance	

Caffeine beneficial

- Several studies have linked caffeine with lower degree of fibrosis and inflammation in the liver.
- Less steatosis, lower ALT and insulin resistance
- Regular basis

ORIGINAL ARTICLES: HEPATITIS

Impact of caffeine in hepatitis C virus infection: a systematic review and meta-analysis

Wijarnpreecha, Karn[a]; Thongprayoon, Charat[a]; Ungprasert, Patompong[b,c]

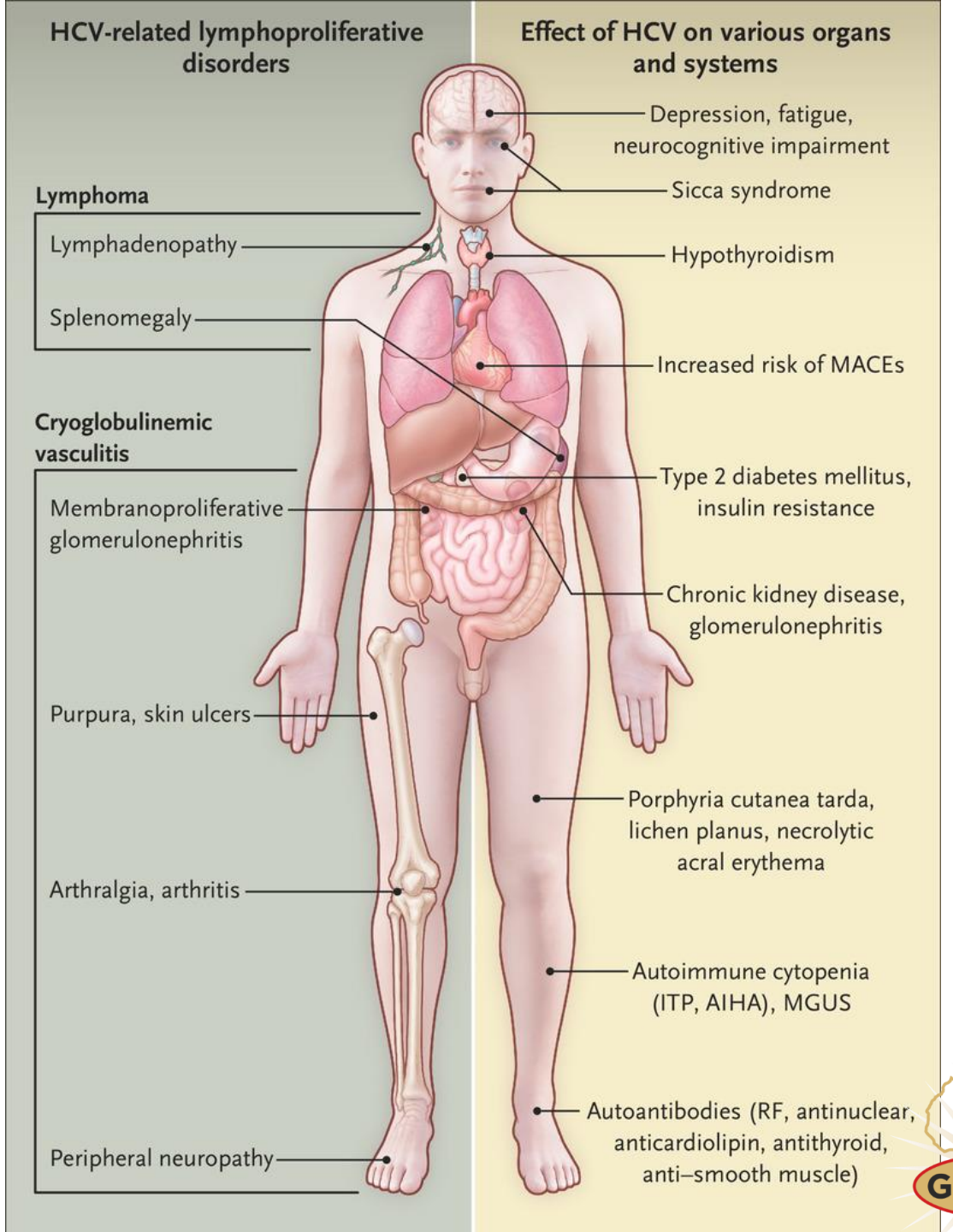
Author Information

European Journal of Gastroenterology & Hepatology: January 2017 - Volume 29 - Issue 1 - p 17-22
doi: 10.1097/MEG.0000000000000757

HCV Extrahepatic manifestations:

- **Type 2 and 3 cryoglobinemia**
  - 2-polyclonal IgG &monoclonal IgM
  - 3- polyclonal IgG & polyclonal IgM
  - 5% clinical manifestation
  - 19-50% cryoglobulins in serum
  - Fatigue/arthritis/ purpura/ raynaulds phenomena/ vasculitis/peri neuropathy/nephropathy
  - RF+/C3&C4 low

- **Glomerular disease**
  - Cryoglobulinemic (20%type 2; 15%ESRD/HD req)
  - Membranoproliferative GN
  - Membranous



Screening

1.One-time, routine, out-pt HCV screening is recommended for all individuals aged 18 years or older.

Risk -Based HCV testing

Recommendations

2. One-time HCV testing should be performed for all persons younger than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV infection.
3. Periodic repeat HCV testing should be offered to all persons with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV exposure.
4. Annual HCV testing is recommended for all PWID and for men with HIV infection who have unprotected sex with men

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HCV Diagnosis

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- **Anti-HCV ab ELISA** detectable in serum may be undetectable in early phase
- OR in profoundly immunosuppressed
- Spontaneous or Rx induced clearance – persist +
- Reinfection +

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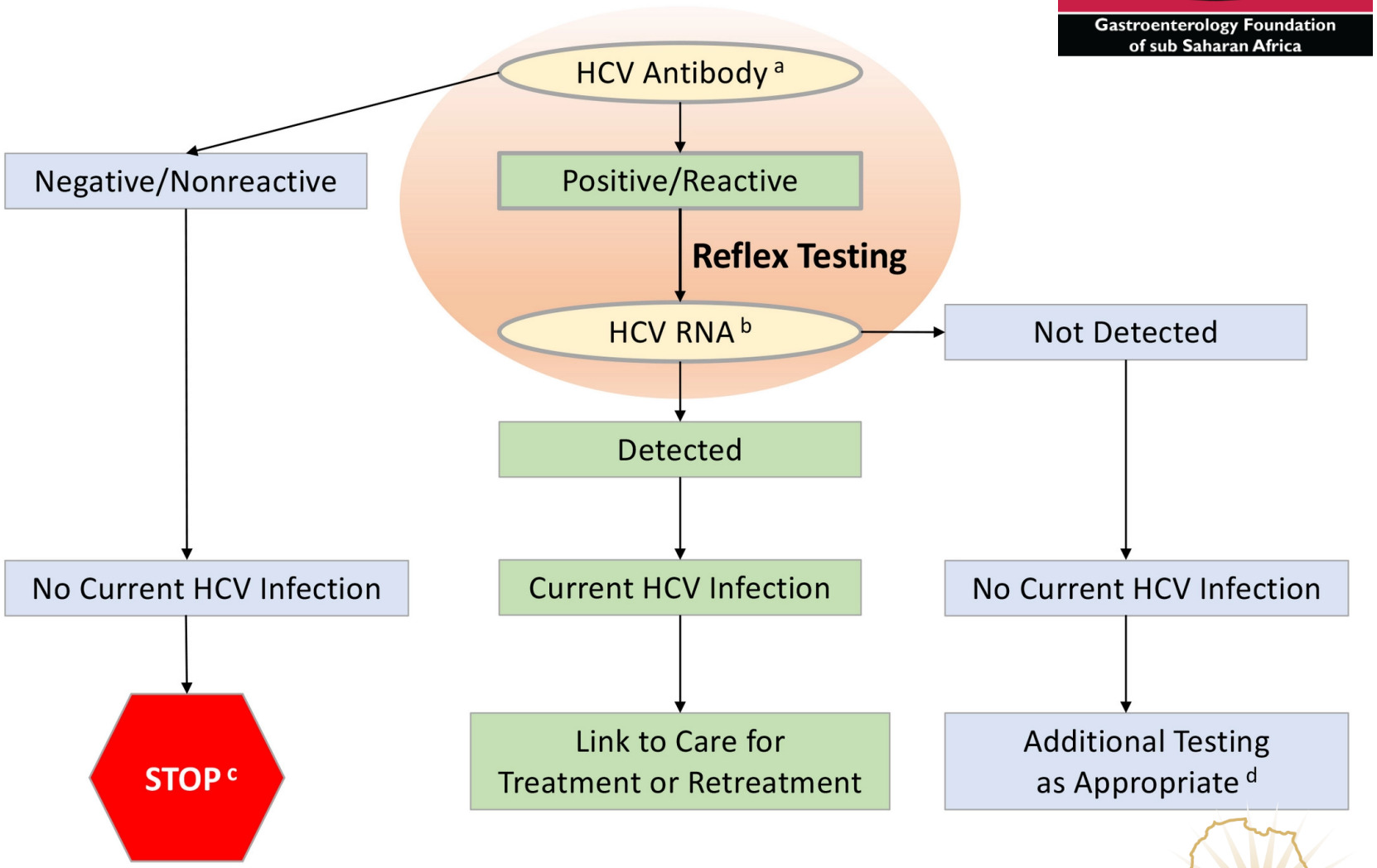
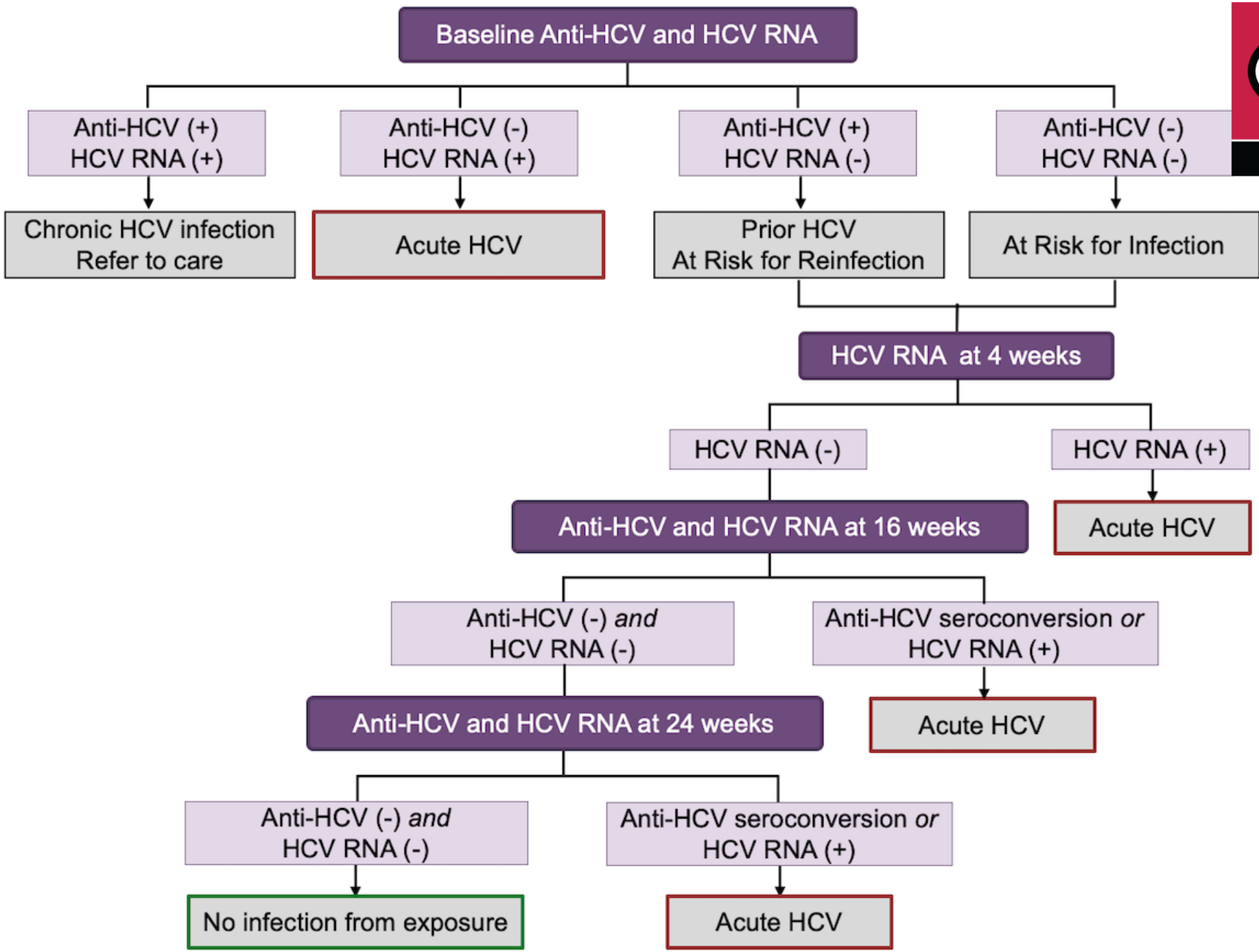
- **HCV antibody testing with reflex HCV RNA PCR for initial testing.**
- Negative- ab→ exposed within 6months→ then do HCV RNA or FFU antibody 6months
- Risk of reinfection→ HCV RNA

- **HCV Genotype testing** → if it will alter treatment recommendations





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Initial Consultation

- Identify risk factors for acquiring hep C
- Alcohol history and metabolic diseases
- Prior stage of liver fibrosis or cirrhosis if patient has been in the health care system as well as prior GT
- Prior treatment regimens for Hep C
- Extra-Hepatic Manifestations
- Initial testing should include:
  - FBC, TFT, LFT, EUCr, Hep C viral Load, Hep C Genotype, HIV, Hep B, Fibro-Scan or FIB-4 or APRI score

PRETREATMENT ASSESSMENT*

- **Calculate FIB-4 score.**
- **Cirrhosis assessment**: Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 **or** any of the following findings from a previously performed test.
  - Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
  - Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
  - Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3, etc)
  - Prior liver biopsy showing cirrhosis
- **Medication reconciliation:** Record current medications, including over-the-counter drugs, and herbal/dietary supplements.
- **Potential drug-drug interaction assessment:** Drug-drug interactions can be assessed using the AASLD/IDSA guidance or the University of Liverpool drug interaction checker.
- **Education:** Educate the patient about proper administration of medications, adherence, and prevention of reinfection.

- **Pretreatment laboratory testing**

Within 6 months of initiating treatment:

  - Complete blood count (CBC)
  - Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], and aspartate aminotransferase [AST])
  - Calculated glomerular filtration rate (eGFR)

INR

Any time prior to starting antiviral therapy:

  - Quantitative HCV RNA (HCV viral load)
  - HIV antigen/antibody test
  - Hepatitis B surface antigen

Before initiating antiviral therapy:

  - Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

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Counseling and clinical care for persons with active HCV infection

- Education and interventions aimed at reducing liver disease progression and preventing HCV transmission.
- Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection
- Evaluation for advanced fibrosis using noninvasive markers (or liver biopsy, if required)is recommended for all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for cirrhosis management (e.g., hepatocellular carcinoma [HCC] screening).
- Evaluation for other conditions that may accelerate liver fibrosis, including hepatitis B virus [HBV] and HIV infections, is recommended for all persons with active HCV infection.
- Vaccination against hepatitis A and hepatitis B is recommended for all susceptible persons with HCV infection.
- Vaccination against pneumococcal infection is recommended for all persons with cirrhosis
- All persons with HCV infection should be provided education about how to prevent HCV transmission to others.

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TREATMENT: The goal of therapy

- Is to cure HCV infection, in order to

1.Prevent the complications of HCV-related liver and extrahepatic diseases, including hepatic necroiflammation ,fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and Death .

2.Improve quality of life and remove stigma

3.Prevent onward transmission of HCV .

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Who should be treated ?

All treatment-naïve and treatment-experienced patients with recently acquired or chronic HCV infection must be offered treatment without delay.

Treatment is generally not recommended in patients with limited life expectancy due to non-liver related comorbidities

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Urgent treatment should be considered in patients with

- Significant fibrosis or cirrhosis (METAVIR score F2, F3 orF4), including compensated (Child-Pugh A) and decompensated (Child-Pugh B or C) cirrhosis

- Clinically significant extrahepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma)

- HCV recurrence after liver transplantation

- Risk of a rapid evolution of liver disease because of concurrent comorbidities (non-liver solid organ or stem cell transplant recipients, HBV and HIV coinfections, diabetes)

- In individuals at risk of transmitting HCV (PWIDs, MSM ,women of childbearing age who wish to get pregnant, patients on haemodialysis , incarcerated individuals) .

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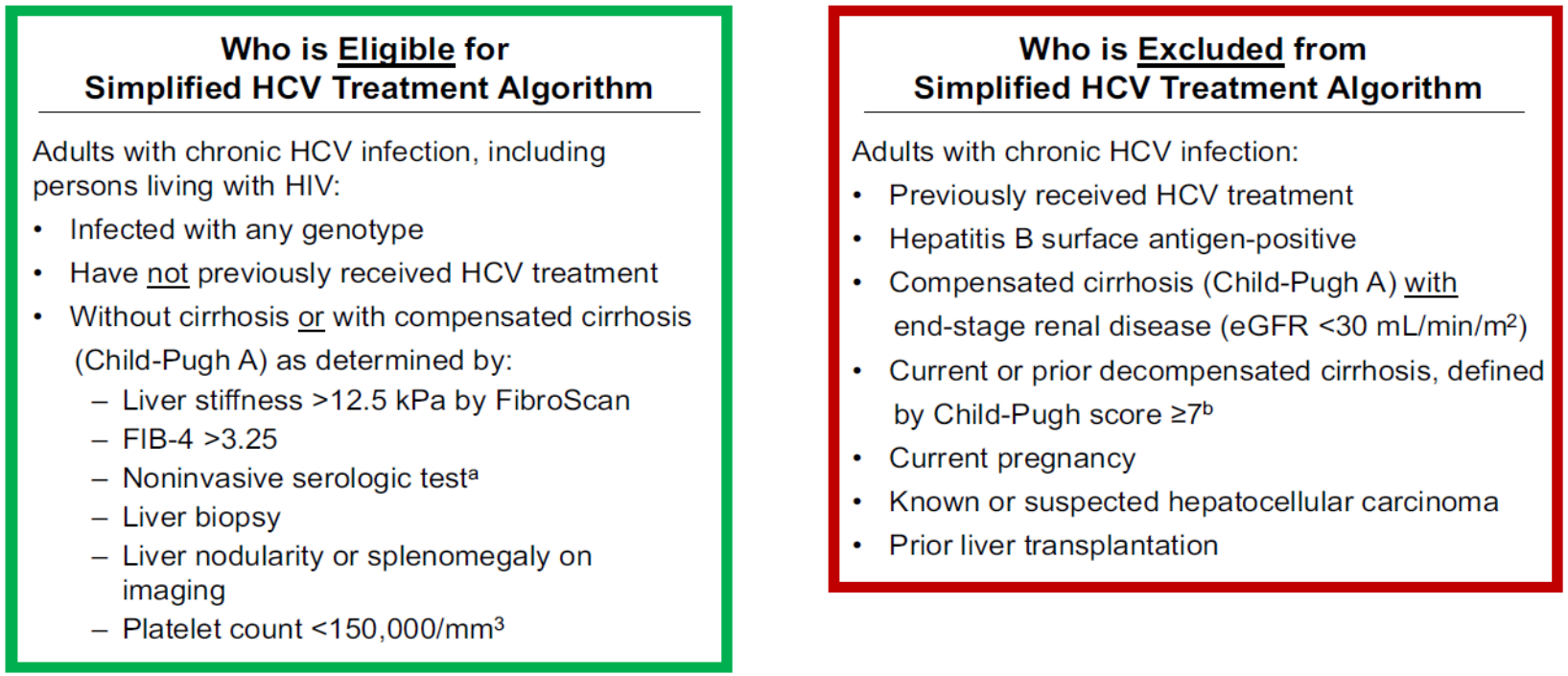

Figure 3. Inclusion and exclusion criteria for simplified HCV treatment algorithm. Abbreviations: eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index for liver fibrosis; HCV, hepatitis C virus. [a]Noninvasive serologic tests include HCV FibroSure or enhanced liver fibrosis test. [b]Child–Pugh score based on presence of ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, or international normalized ratio ≥1.7.

AASLD 2023

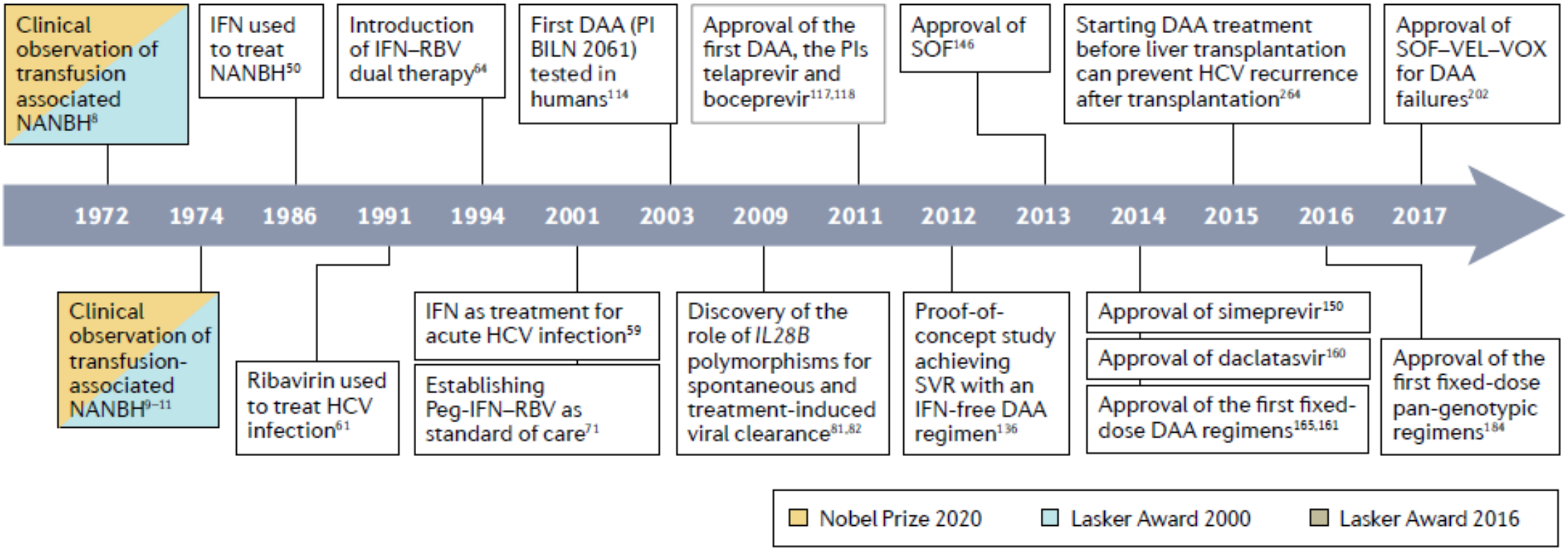

Fig. 1 | **Major breakthroughs in HCV history.** Breakthroughs are separated into basic and translational (part **a**) and clinical (part **b**) research, and research that formed part of major awards is indicated. DAA, direct-acting antiviral agent; HCV, hepatitis C virus; IFN, interferon-α; NANBH, non-A, non-B hepatitis; NS5A, nonstructural protein 5A; Peg-IFN, pegylated interferon-α; PI, protease inhibitor; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir; VOX, voxilaprevir. Additional REFS[263,264].

HCV Drugs

- IFN-free DAA regimens
- **Ribavirin**: still in use→ oral guanosine analog with activity against DNA and RNA viruses
  - Hemoglobin monitor
  - **Dose dependent haemolytic anaemia**
    - Hx of cardioresp disease caution or in any patient that won't tolerate a drop in SUDDEN FALL IN HB
  - **Teratogenic**→ in women and men. Contraception and 6 months after end of Rx
  - Renal adjustment
  - Used in difficult to Rx cases

Direct acting antiviral agents

3 main classes:

1. ***NS3/4A Protease Inhibitors (PI):***
   Simeprevir, Grazoprevir, Voxilaprevir, Glecaprevir
   • PIs have a high potency, but a low barrier to resistance.
   Voxilaprevir and Glecaprevir are pangenotypic

2. ***NS5Ainhibitors:***
   Daclatasvir,Iedipasvir, Elbasvir, Velpatasvir, Pibrentasvir
   •High potency, a low barrier to resistance
   Active against all genotypes, except Elbasvir and Iedipasvir

3. ***NS5B polymerase inhibitors:***
   - **Nucleoside NS5B polymerase inhibitor**
   - ***Sofosbuvir, Dasabuvir***
   - Sofosbuvir is the first in this class→ intermediate potency →pangenotypic activity and a high barrier for resistance

   Non-nucleoside polymerase inhibitors
   - Dasabuvir have intermediate potency, a more limited genotypic activity and a low barrier to resistance

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Approved DAAs From Multiple Classes: 2018

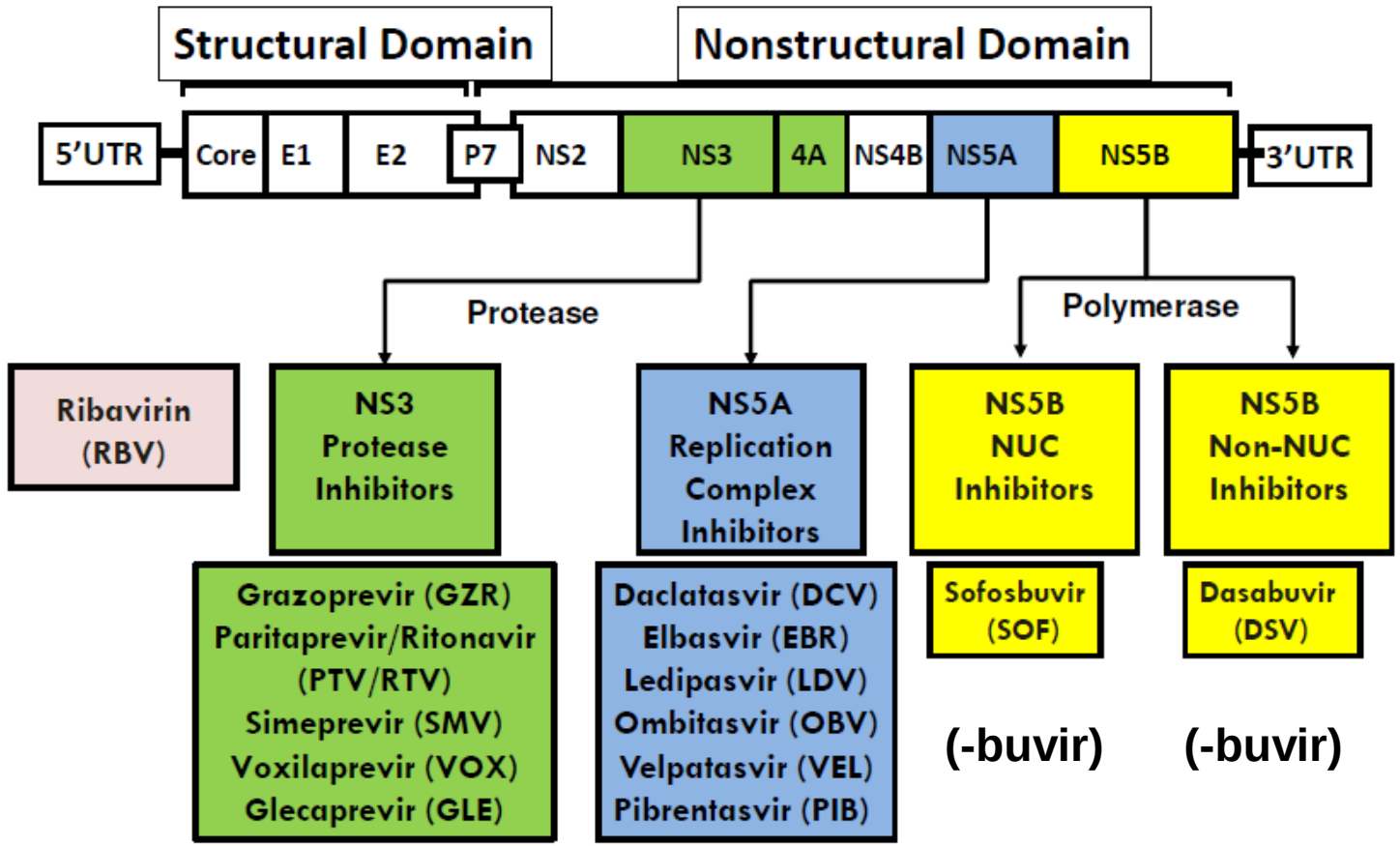

Table 1: Drug–drug interactions: Medications not recommended to be taken concurrently with DAAs

Concurrent drugs	SOF/DCV	SOF/VEL	SOF/VEL/VOX	GLE/PIB
Antiarrhythmics				
Amiodarone	Avoid	Avoid	Avoid	Use with caution and consider monitoring for amiodarone toxicity
Dronedarone	Avoid	Avoid	Avoid	
Anticoagulant and antiplatelet agents				
Dabigatran	Close monitoring for bleeding signs (↑ dabigatran concentration)	Close monitoring for bleeding signs (↑ dabigatran concentration)	Avoid	Avoid
Edoxaban	Close monitoring for bleeding signs (↑ edoxaban concentration)	Close monitoring for bleeding signs (↑ edoxaban concentration)	Avoid	Close monitoring for bleeding signs (↑ edoxaban concentration)
Anticonvulsants and barbiturates				
Phenytoin	Avoid	Avoid	Avoid	Avoid
Phenobarbital	Avoid	Avoid	Avoid	Avoid
Amobarbital	Avoid	Avoid	Avoid	Avoid
Carbamazepine	Avoid	Avoid	Avoid	Avoid
Oxcarbazepine	Avoid	Avoid	Avoid	Avoid
Eslicarbazine	Avoid	Avoid	Avoid	Avoid
Primidone	Avoid	Avoid	Avoid	Avoid
Anti-hypertensives				
Aliskiren	Safe	Safe	Monitor for side effects of Aliskiren	Avoid
Anti-mycobacterials				
Rifampicin	Avoid	Avoid	Avoid	Avoid
Rifabutin	Avoid	Avoid	Avoid	Avoid
Rifapentine	Avoid	Avoid	Avoid	Avoid
HIV antiretrovirals				
Protease Inhibitors				
Atazanavir/ritonavir	↓DCV to 30 mg	Safe	Avoid	Avoid
Atazanavir/cobicistat	↓DCV to 30 mg		Avoid	Avoid
Darunavir/ritonavir	Safe		Monitor if twice daily dose is administered	Avoid
Darunavir/cobicistat	Safe		Safe	Avoid
Lopinavir/ritonavir	Safe		Avoid	Avoid
Non-nucleoside reverse transcriptase inhibitors				
Efavirenz	↑DCV to 90 mg	Avoid	Avoid	Avoid
Etravirine	↑DCV to 90 mg	Avoid	Avoid	Avoid
Nevirapine	↑DCV to 90 mg	Avoid	Avoid	Avoid
Calcineurin inhibitors				
Cyclosporine	Safe	Safe, monitoring cyclosporin levels is recommended	Avoid	Safe, but avoid in patients requiring cyclosporin doses >100 mg/day (↑GLE/PIB concentration)

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Table 1: Contd...

Concurrent drugs	SOF/DCV	SOF/VEL	SOF/VEL/VOX	GLE/PIB
Contraception products				
Ethinyl estradiol containing contraception products	Safe	Safe	Avoid	Avoid
Heart failure agents				
Bosentan	Avoid	Avoid	Avoid	Avoid
Herbals				
St. John's wort	Avoid	Avoid	Avoid	Avoid
Macrolide antimicrobials				
Troleandomycin	↓DCV to 30 mg	Caution. May increase concentration of velpatasvir	Avoid	Avoid

SOF: Sofosbuvir, DCV: Daclatasvir, VEL: Velpatasvir, VOX: Voxilaprevir, GLE: Glecaprevir, PIB: Pibrentasvir

Cancer Therapies				
Vinblastine	Safe	Monitor for side effects of cancer therapy /doses may require alteration	Avoid	Avoid
Vincristine			Avoid	Avoid
Methotrexate			Avoid	
Imatinib			Avoid	
Lapatinib			Avoid	
Nilotinib			Avoid	
Mitoxantrone			Avoid	
Irinotecan			Avoid	
Cholesterol-lowering agents				
Atorvastatin	Use with caution. Monitor for statins adverse events/ dose reduction may be required	Use with caution. Monitor for statins adverse events/dose reduction may be required	Avoid	Avoid
Simvastatin			Avoid	Avoid
Lovastatin			Avoid	Avoid
Rosuvastatin			Avoid	
Fluvastatin			Avoid	
Pitavastatin			Avoid	
COVID-19 antivirals				
Nirmatrelvir/ritonavir	Safe	Safe	Check ALT levels during and post treatment	Avoid

Contd...

Table 1. Recommendations for Initial Treatment of Hepatitis C Virus–Infected Adults

Regimen	Genotype	Classification	Duration	Rating	Caveats and Other Considerations
Treatment-naive without cirrhosis or with compensated cirrhosis Glecaprevir/pibrentasvir	1–6	Recommended	8 wk	I, A[a]	
Sofosbuvir/velpatasvir	1–6	Recommended	12 wk	I, A[b]	For genotype 3 infection with compensated cirrhosis, NS5A RAS testing is recommended. If baseline NS5A RAS Y93H is present, add weight-based ribavirin or choose another recommended regimen.
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	12 wk	I, A[c]	Not recommended for genotype 6e infection if subtype is known.
	1 without cirrhosis	Recommended	8 wk	I, B	Applicable to patients without cirrhosis who are not living with human immunodeficiency virus and whose HCV RNA is <6 million IU/mL.
Elbasvir/grazoprevir	1b, 4	Recommended	12 wk	I, A[d]	
	1a	Alternative	12 wk	I, A	For genotype 1a infection, NS5A RAS testing is recommended. If baseline RASs are present (ie, substitutions at amino acid positions 28, 30, 31, or 93), another recommended regimen should be used.
Sofosbuvir/velpatasvir + weight-based ribavirin	3	Alternative	12 wk	IIa, A	Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.
Sofosbuvir/velpatasvir/ voxilaprevir		Alternative	12 wk	IIa, B	Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.
Treatment-naive with decompensated cirrhosis					
Sofosbuvir/velpatasvir + weight-based ribavirin	1–6	Recommended	12 wk	I, A[e]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
Sofosbuvir/velpatasvir	1–6	Recommended	24 wk	I, A[e]	Applicable to patients who are ribavirin ineligible.
Ledipasvir/sofosbuvir + weight-based ribavirin	1, 4, 5, 6	Recommended	12 wk	I, A[f]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	24 wk	I, A[f]	Applicable to patients who are ribavirin ineligible.

Recommendations are listed by recommended vs alternative and by genotypic activity, evidence level, and alphabetically.

Abbreviations: CTP, Child–Turcotte–Pugh score; HCV, hepatitis C virus; NS5A, hepatitis C virus nonstructural protein 5A; RAS, resistance-associated substitution.

[a]The level of evidence rating is I, B for persons with compensated cirrhosis.

[b]The level of evidence rating is I, B for persons with genotype 5 or 6 infection.

[c]The level of evidence rating is IIa, B for persons with genotype 5 or 6 infection and those with genotype 4 infection and compensated cirrhosis.

[d]The level of evidence rating is IIa, B for persons with genotype 4 infection and compensated cirrhosis.

[e]Only available data for genotype 6 infection are in persons with compensated cirrhosis.

[f]Only available data for genotypes 5 or 6 infection are in a small number of persons with compensated cirrhosis.

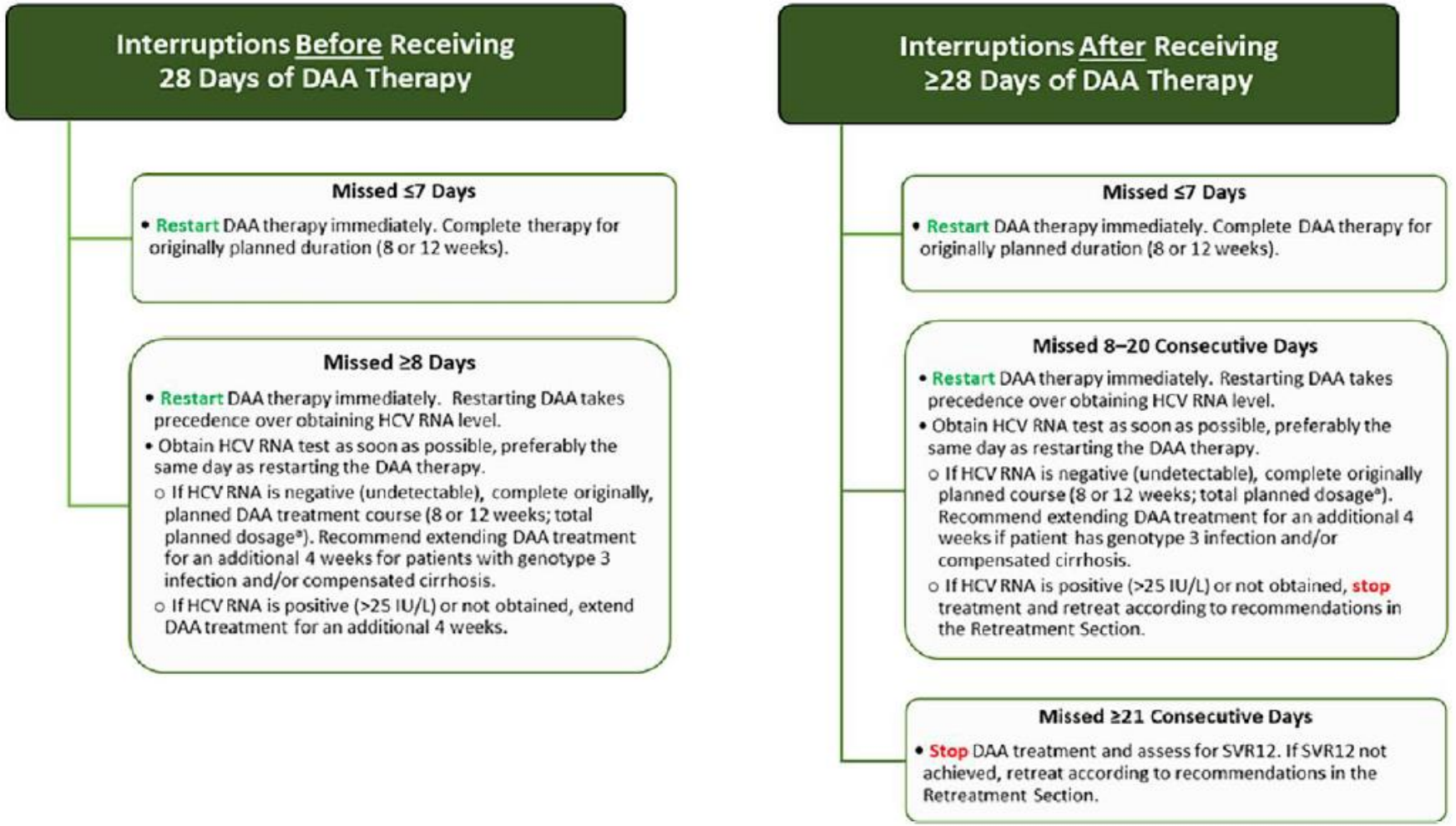

Figure 2. Recommended management of DAA treatment interruptions for treatment-naive patients without cirrhosis or with compensated cirrhosis receiving glecaprevir/pibrentasvir or sofosbuvir/velpatasvir. Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; SVR12, sustained virologic response 12 weeks after completion of therapy. [a]Extend duration of therapy such that the patient receives the total planned dosage (ie, the total number of daily pills). For example, if a patient missed 10 days of a planned 8-week course of therapy, treatment would be extended to 8 weeks plus 10 days.

Table 2. Recommendations for Retreatment of Hepatitis C Virus–Infected Adults by Prior Exposure

Regimen	Genotype	Classification	Duration	Rating	Caveats and Other Considerations
Sofosbuvir-based treatment failure without cirrhosis or with compensated cirrhosis					
Sofosbuvir/velpatasvir/ voxilaprevir	1–6	Recommended	12 wk	I, A	For genotype 3 infection with compensated cirrhosis, add weight-based ribavirin if there are no contraindications.
Glecaprevir/pibrentasvir	1, 2, 4, 5, 6	Alternative	16 wk	I, A	Not recommended for patients with prior exposure to an NS5A inhibitor plus NS3/4A protease inhibitor regimen (eg, elbasvir/grazoprevir).
Glecaprevir/pibrentasvir treatment failure without cirrhosis or with compensated cirrhosis					
Glecaprevir/pibrentasvir + sofosbuvir + weight-based ribavirin	1–6	Recommended	16 wk	IIa, B	
Sofosbuvir/velpatasvir/ voxilaprevir	1–6	Recommended	12 wk	IIa, B	For patients with compensated cirrhosis, addition of weight-based ribavirin is recommended (rating IIa, C).
Sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir + glecaprevir/pibrentasvir treatment failure without cirrhosis or with compensated cirrhosis					
Glecaprevir/pibrentasvir + sofosbuvir + weight-based ribavirin	1–6	Recommended	16 wk	IIa, B	Extension to 24 wk should be considered in extremely difficult cases (eg, genotype 3 infection with compensated cirrhosis) or failure following sofosbuvir + glecaprevir/pibrentasvir therapy.
Sofosbuvir/velpatasvir/ voxilaprevir + weight-based ribavirin	1–6	Recommended	24 wk	IIa, B	
Sofosbuvir- or NS5A inhibitor–based treatment failure with decompensated cirrhosis					
Sofosbuvir/velpatasvir + weight-based ribavirin	1–6	Recommended	24 wk	II, C[a]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
Ledipasvir/sofosbuvir + weight-based ribavirin	1, 4, 5, 6	Recommended	24 wk	II, C[b]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.

Recommendations are listed by recommended vs alternative and by genotypic activity, evidence level, and alphabetically.

Abbreviations: CTP, Child–Turcotte–Pugh score; NS3/4A, hepatitis C virus nonstructural protein 3–4A; NS5A, hepatitis C virus nonstructural protein 5A.

[a]Only available data for genotypes 5 or 6 infection are in a small number of persons with compensated cirrhosis.

[b]Only available data for genotype 6 infection are in persons with compensated cirrhosis.

AASLD 2023

HCV & Pregnancy

- HCV infection may influence the outcome of pregnancy,

  -Higher incidence of preterm births and a higher incidence of IUFD, preterm delivery and small-for-gestational age.

  - Higher rates of antepartum and post-partum haemorrhage, gestational diabetes, or premature rupture of membranes have been reported.

- Chronic HCV infection has also been linked with higher rates of intrahepatic cholestasis of pregnancy.
- **Treatment during pregnancy is not recommended .**
- Treatment may be considered during pregnancy on a case-by case basis after a discussion of potential risks and benefits
- Breast feeding is not contraindicated except when the mother has

  * Cracked ,damaged or bleeding nipples .

  *If she has HIV co-infection .

AASLD 2023

HCV and HBV Coinfection

- HCV is usually the dominant virus and may suppress levels of HBV DNA
- High risk of developing HCC- infiltrating and aggressive form
- Treatment of both viruses required
- Moderate risk of HBV reactivation among HBsAg-positive people receiving DAA
- Monitor serum ALT and HBV DNA during HCV infection

WHO Guidelines for the prevention, diagnosis, care and treatment people with chronic hepatitis B infection. 2024

HCV & renal insufficiency

- Severe renal impairment (eGFR <30 ml/min/1.73 m2)
- ESRD on haemodialysis → should be treated in expert centres, with close on- and post-treatment monitoring by a multidisciplinary team(B1).

Mild to moderate (eGFR>–30 ml/min/1.73 m2) or severe (eGFR <30 ml/min/1.73m2) renal impairment (including those with ESRD on haemodialysis):

- Should be treated according to the general recommendations
- With no need for dose adjustments of HCV DAAs (A1).

Patients with decompensated (Child-Pugh B or C) cirrhosis :

- Mild to moderate renal impairment (eGFR >–30 ml/min/1.73 m2: SOF/VEL (all genotypes) + RBV* for 12 weeks.
- Severe renal impairment (eGFR <30 ml/min/ 1.73 m2) : SOF/VEL for 24 weeks.

EASL 2020

Treatment:

- Solid Organ Transplants
  - Hep C more aggressive in liver transplants and may progress to cirrhosis in 5 yrs in the graft.
  - Recurs if patients are RNA positive at time of transplant
  - Prior to treatment transplant rejection was 30% higher for HCV positive patients receiving liver transplants
  - Sof/ Vel or GLE/PIB used
  - Recommendation for treatment remains the same for other organ transplants
  - Organ donation from HCV positive donors feasible

AASLD recommends initiating therapy at least within 2 weeks after transplantation but preferably within 1 week when the patient is clinically stable.

Post transplant recurrence of HCV

- All patients with post-transplant recurrence of HCV infection must be treated.

- Treatment should be initiated early after liver transplantation, ideally as early as possible when the patient is stabilised (generally after the first 3 months post-transplant), because the SVR12 rates diminish in patients with advanced post-transplant liver disease.

AASLD 2019

Treatment

- Patient with HCC
  - Those with Child Pugh A or less with potential for curative treatment should receive treatment for HCC first then Sof/ Vel.
- Children born to Mothers that are Hep C pos should be tested at 18 months
- Adolescents with Hep C and Child Pugh A or less should be treated as adults with Sof/Vel or Sof/LDV
- PWID
  - Education
  - OST
  - Use of Clean Needles
  - Annual Screening

Follow up after HCV cure

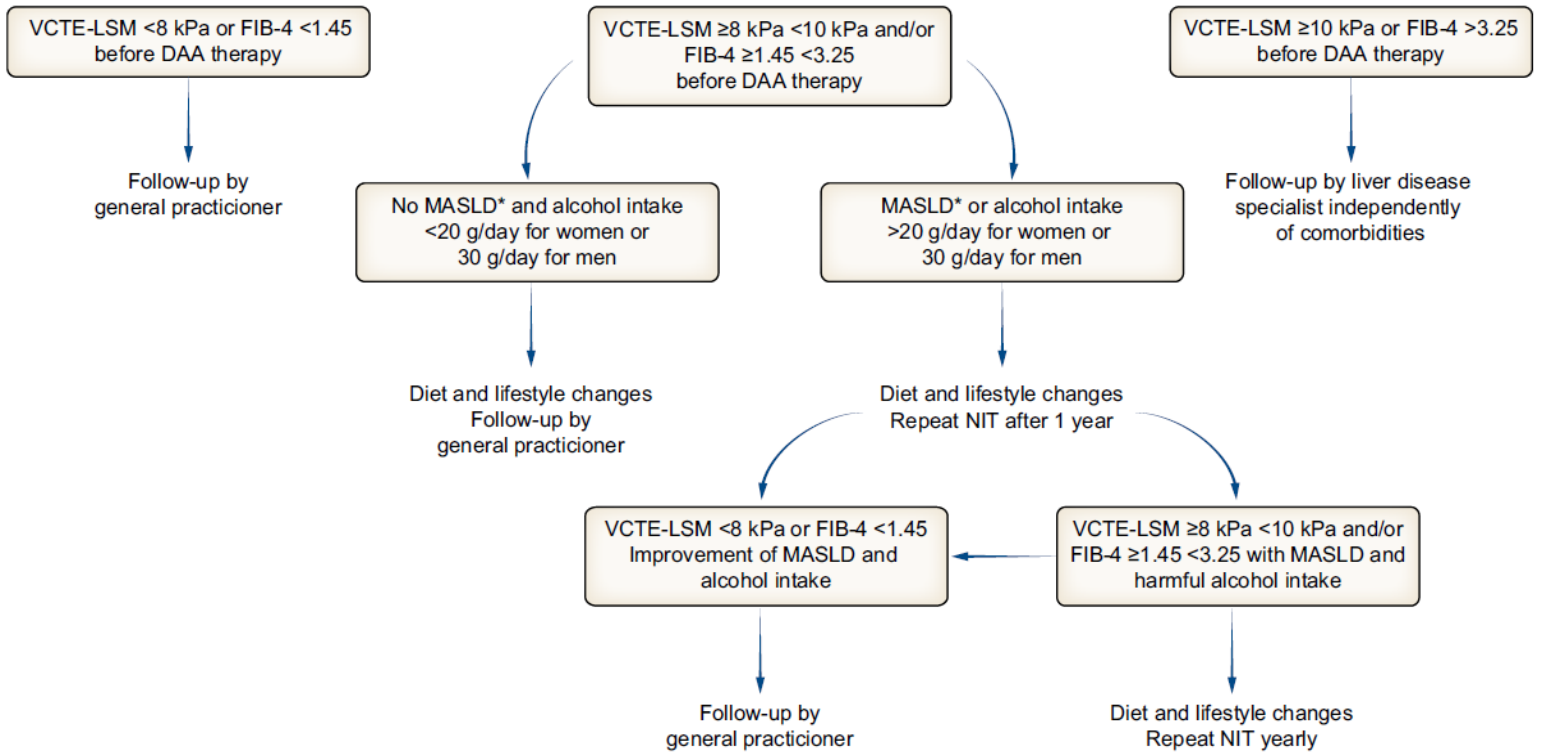

Fig. 1. Proposed algorithm to select patients who can be discharged from specialised care after SVR. *MASLD: hepatic steatosis and at least one cardiometabolic risk factor (overweight, pre/diabetes mellitus, arterial hypertension, dyslipidemia).[34] DAAs, direct-acting antivirals; FU, follow-up; MASLD, metabolic dysfunction-associated steatotic liver disease; NITs, non-invasive tests; VCTE-LSM, vibration-controlled transient elastography-liver stiffness measurement (Fibroscan (R)).

Journal of Hepatology, August 2024. vol. 81 j 326–344

Patients with clinically significant portal HPT(CSPH)

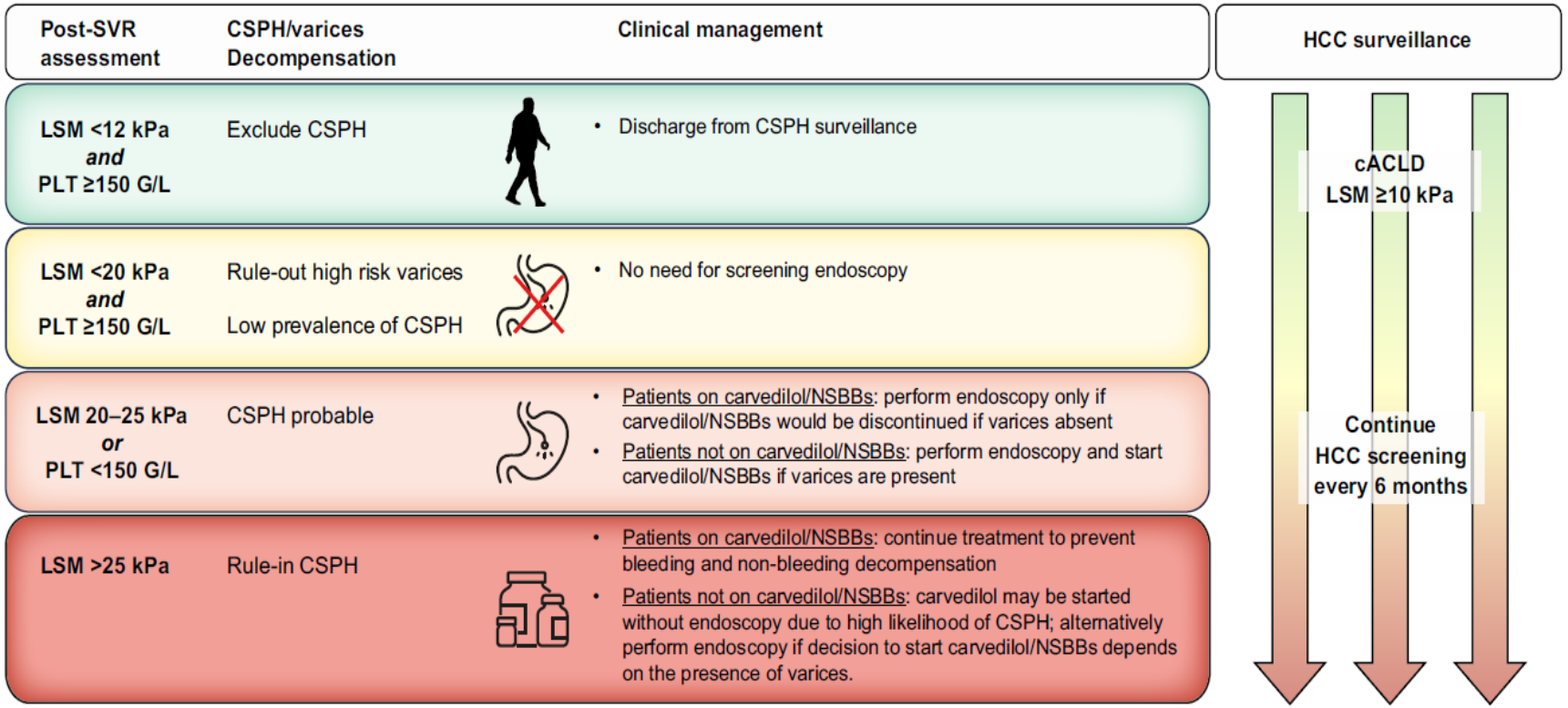

Fig. 2. CSPH risk stratification according to post-SVR VCTE-LSM (and PLT) categories and recommendation in terms of clinical management. CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement, NSBBs, non-selective beta-blockers; PLT, platelet count. Adapted from Jia, J., Lens, S., Yoshiji, H., Francque, S., Tsochatzis, E.A., Mandorfer, M. (2022). Management of ACLD After HBV-Suppression and HCV-Cure. In: de Franchis, R. (eds) Portal Hypertension VII. Springer, Cham. https://doi.org/10.1007/978-3-031-08552-9_20.

Journal of Hepatology, August 2024. vol. 81 j 326–344

SVR in HCV-related decompensated cirrhosis

- Cirrhosis recompensation requires resolution of ascites(off diuretics), encephalopathy(off lactulose/rifaximin) and absence of variceal bleeding for ≥ 1 year in the absence of TIPS
- Needs to be assessed at each follow –up visit
- Reduction or discontinuation of diuretics and/or lactulose/rifaximin is encouraged particularly if clinical and laboratory improvements are documented
- Improvement in portal hypertension may take a long period of time
- It is reasonable to wait at least 2 years to allow for clinical improvement and before assuming a patient will not recompernsate

HCC risk assessment post -SVR

- All patients with pre-SVR ACLD(F3 or F4 METAVIR) who achieve SVR with DAA therapy should undergo lifelong HCC surveillance with ultrasound screening every six months.
- Global annual HCC incidence in patients achieving SVR in the case of ACLD ranges from 0.2 to 2.5%.

HCC risk assessment

Table 1. Predictors of higher or lower risk of HCC post-SVR.

Study	Cohort	Factors	Risk of HCC
Calvaruso V, *et al.*[77]	N = 2,249	Albumin, platelets and no-SVR	Higher risk
Mariño Z *et al.*[78]	N = 1,123	Baseline liver function, alcohol intake, hepatic decompensation and non-characterised nodules	Higher risk
Kim NJ, *et al.*[79]	N = 29,003	Cirrhosis and FIB-4 >3.25	Higher risk
Semmler G, *et al.*[80]	N = 527 (derivation) N = 1,500 (validation)	Alcohol, albumin, AFP and LSM	Identifies a low-risk population <1%/year
Alonso-Lopez *et al.*[81]	N = 1,046	Albumin, LSM and dynamic changes (1-year Delta LSM and 1-year FIB-4 score)	Identifies a low-risk population <1%/year
Innes H, *et al.*[82]	N = 2,139	Age-male sex-ALBI-platelet count score (aMAP)	Higher risk
Audureau E, *et al.*[83]	N = 836	Elevated AST, low platelet count and shorter prothrombin time	Higher risk

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; AST, aspartate aminotransferase; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; SVR, sustained virological response.

Journal of Hepatology, August 2024. vol. 81 j 326–344

Management of Extrahepatic manifestations of HCV infection after SRV

- Patients with cryoglobulinemic vasculitis(CV) usually have a good and persistent clinical and immunological response after SRV
- High risk of recurrence after SVR in: cirrhosis, high RF values post-SVR, respiratory infections, cancer, and vaccinations(very rarely)
- Complete response (clinical and immunological/laboratory response) should be evaluated 1 year after SVR, and when confirmed, patients may be discharged from CV follow-up.
- Be aware of potential clinical relapse, especially after certain triggering events (such as cancer, infections, or vaccinations).

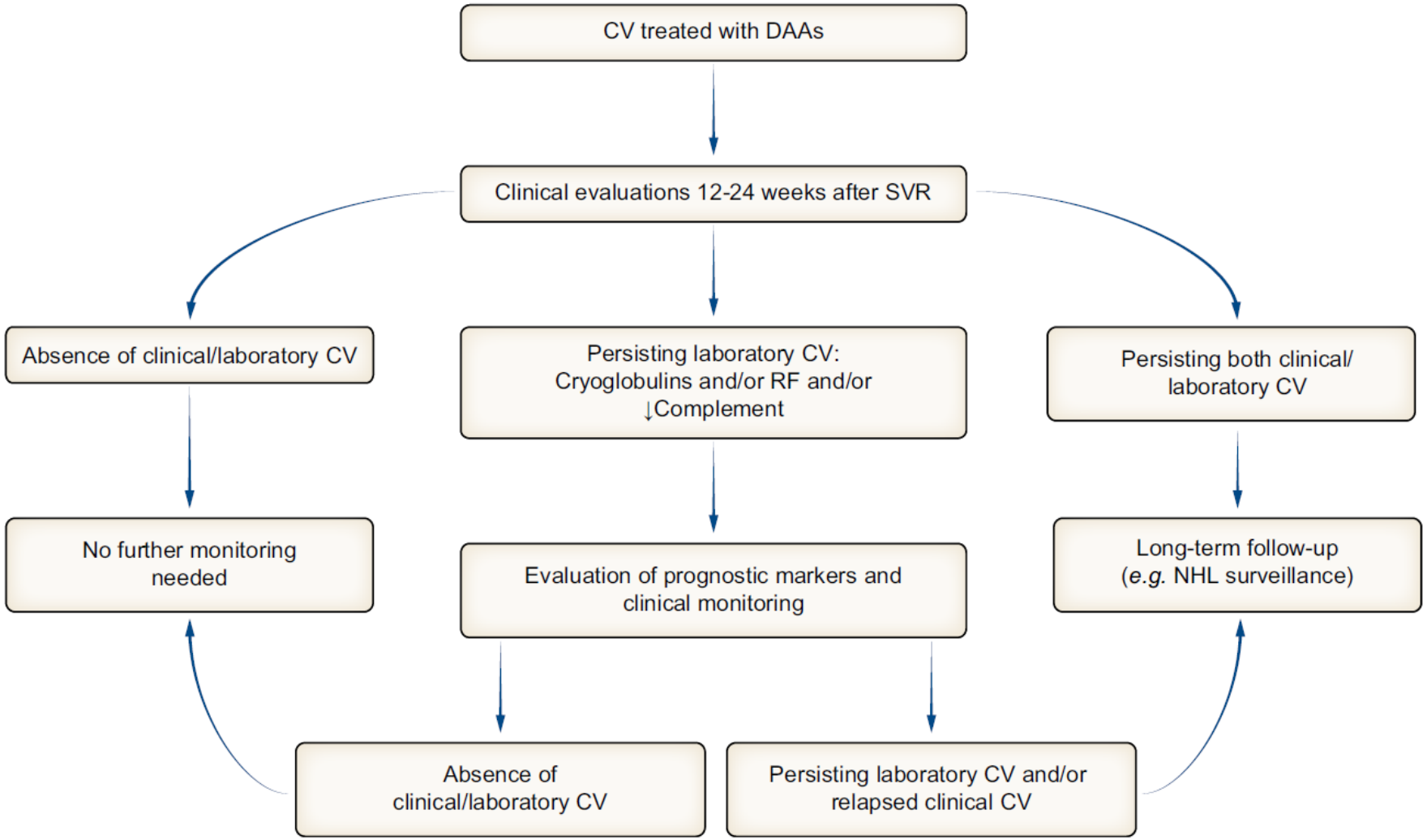

Fig. 3. Proposed follow-up of HCV MC patients after SVR. CV, cryoglobulinemic vasculitis; DAAs, direct-acting antivirals; MC, mixed cryoglobulinemia; NHL, non-Hodgkin lymphoma; RF, rheumatoid factor; SVR, sustained virological response.

HCV reinfection after achieving SVR

- Main risk populations for reinfection are: PWID and MSM with high-risk practices, including those residing in prisons, nosocomial acquisition (i.e. in patients undergoing haemodialysis or with multiple hospital admissions).
- In individuals with ongoing risk behaviour and/or elevated ALT levels, HCV RNA or HCV antigen should be tested at least every 6 months.
- Point of care or dried blood spot testing are useful alternatives for monitoring HCV reinfection.
- When reinfection is documented, therapy with DAAs should be initiated to achieve SVR at the individual level and to prevent onward transmission of HCV.

References

- EASL 2020 Guideline- recommendations on treatment of hepatitis C
- EASL 2024 Position paper on clinical follow-up care after HCV cure
- AASLD- Hepatitis C 2023 Guidance update
- South African Viral Hepatitis Guidelines 2020
- WHO's vision to eliminate Hep C
- SASLT guidelines: Update in treatment of Hepatitis C Virus infection, 2024

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Thank you

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