HEPATITIS C

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Presenter: S Mahlasela

Outline

- Introduction
- Epidemiology
- Life Cycle
- Presentation
- Diagnosis
- Treatment

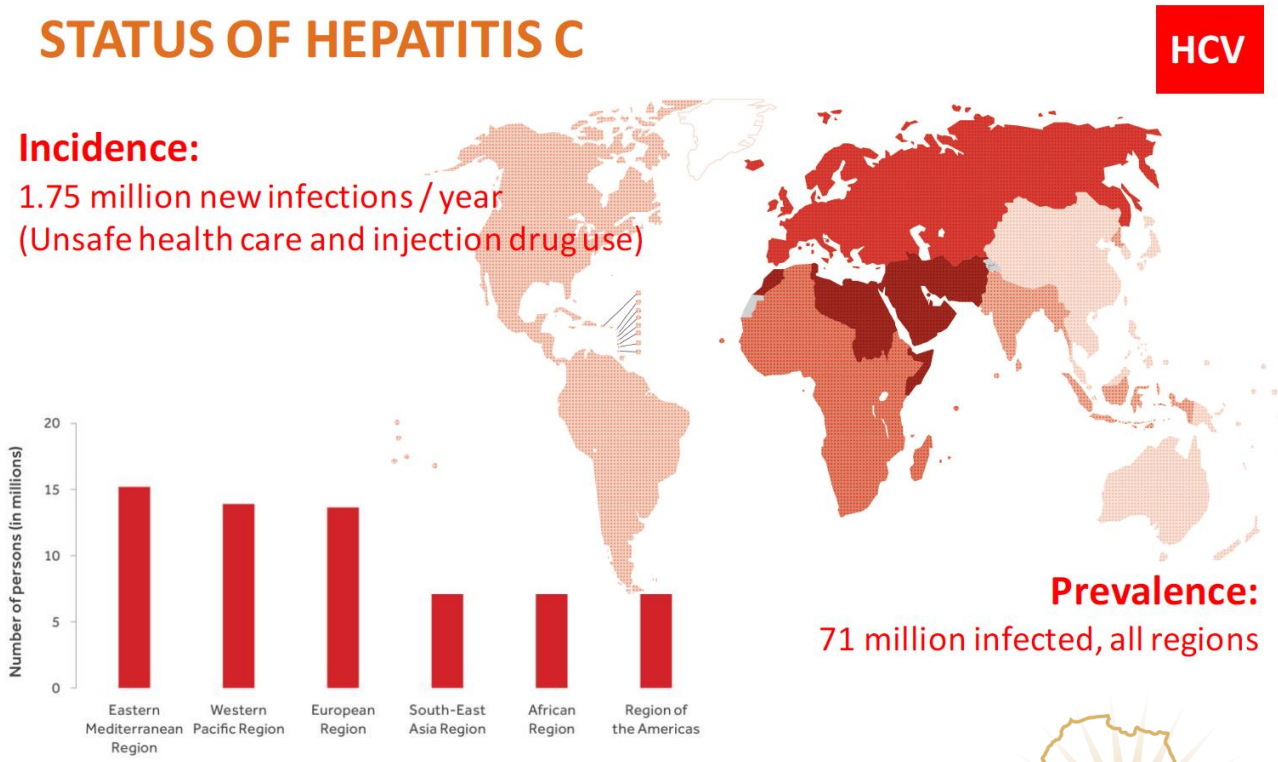
- In 2016 WHO adopted a global hepatitis strategy to eliminate viral hepatitis as a public threat by 2030.
  - 90% reduction in case incidents
  - 65% reduction in mortality
- In order to achieve these ambitiuos targets 80% of people infected would have to reach access to care
- Some African Heroes in this endeavour have emerged chief amongst which is Egypt.

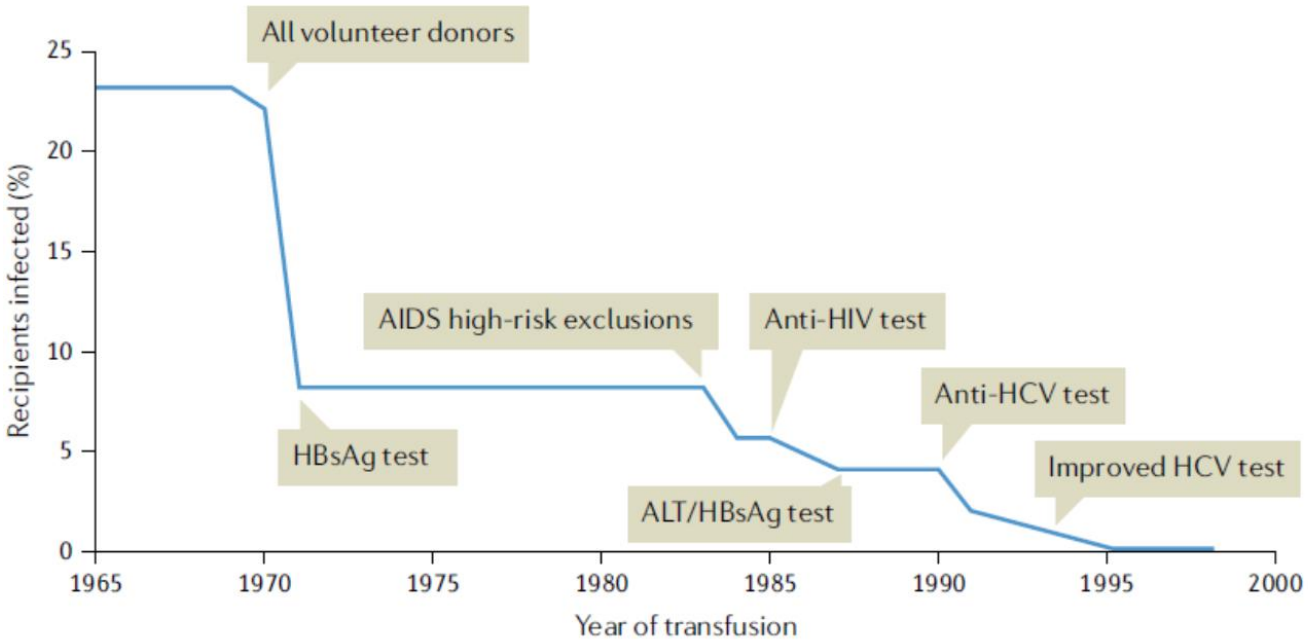
Introduction

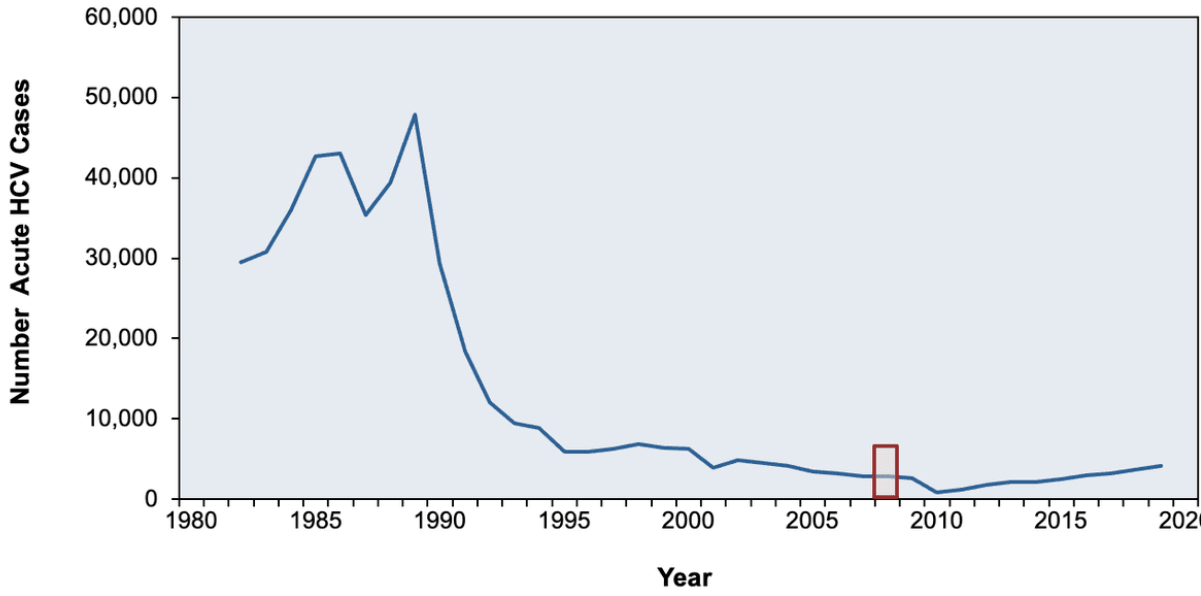
- 1970's saw a spike in hepatitis associated with blood transfusion
- This entity was called NANBH
- 1989 Virus was isolated
- 2020 Nobel Prize in Medicine

Epidemiology

- 58M infected worldwide, improvement from 71 M infected worldwide in 2015
- Accounts for majority of chronic hepatitis
- 1.5M new infections
- 290 000 people died from Hep C or related complications in 2019
- Lack of effective vaccine

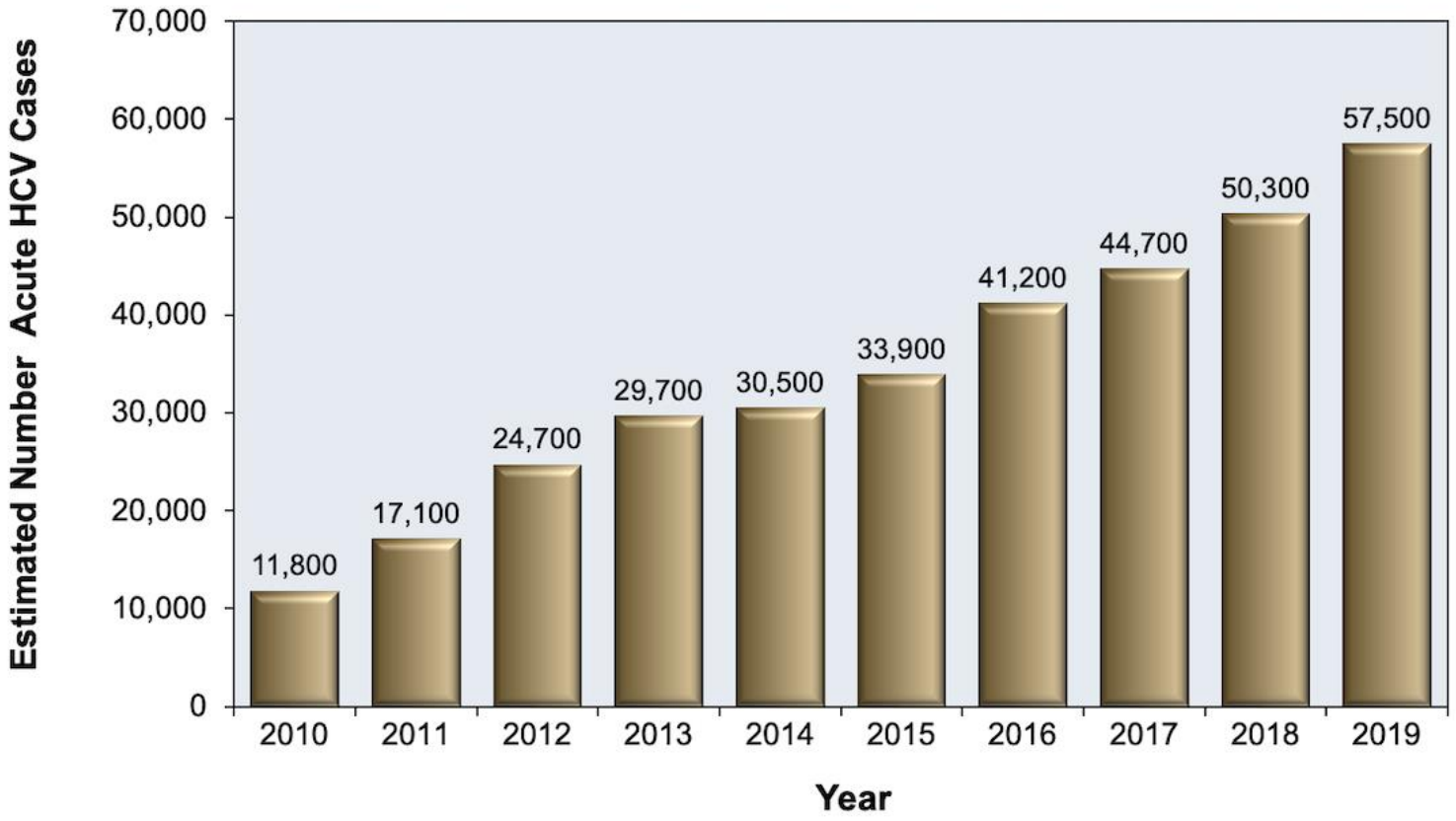






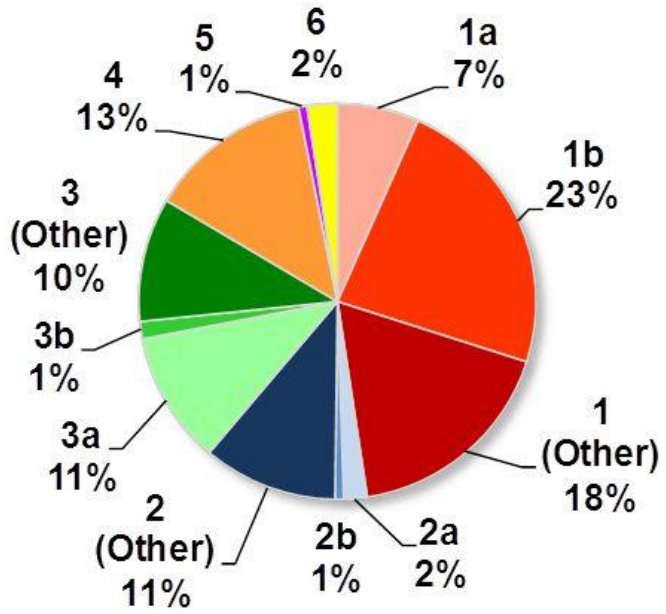
HCV Incidence: The number of people who become newly infected with HCV in a defined time period, typically reported for 1-year period.

Epidemiology Cont.



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)

In SA...

- Estimated infected population between 600 000 to 800 000

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SANBS South African National Blood Service

HCV Prevalence over 7 years						
	Collections	C	N	S	Grand Total	Prevalence %
2006	731264	30	1	7	38	0.005
2007	724280	46	2	16	64	0.009
2008	750981	49	1	24	74	0.010
2009	805087	55	1	11	67	0.008
2010	809835	63	1	8	72	0.009
2011	821780	48	2	11	61	0.007
2012	801276	31	3	16	50	0.006
Grand Total	5444503	322	11	93	426	0.008

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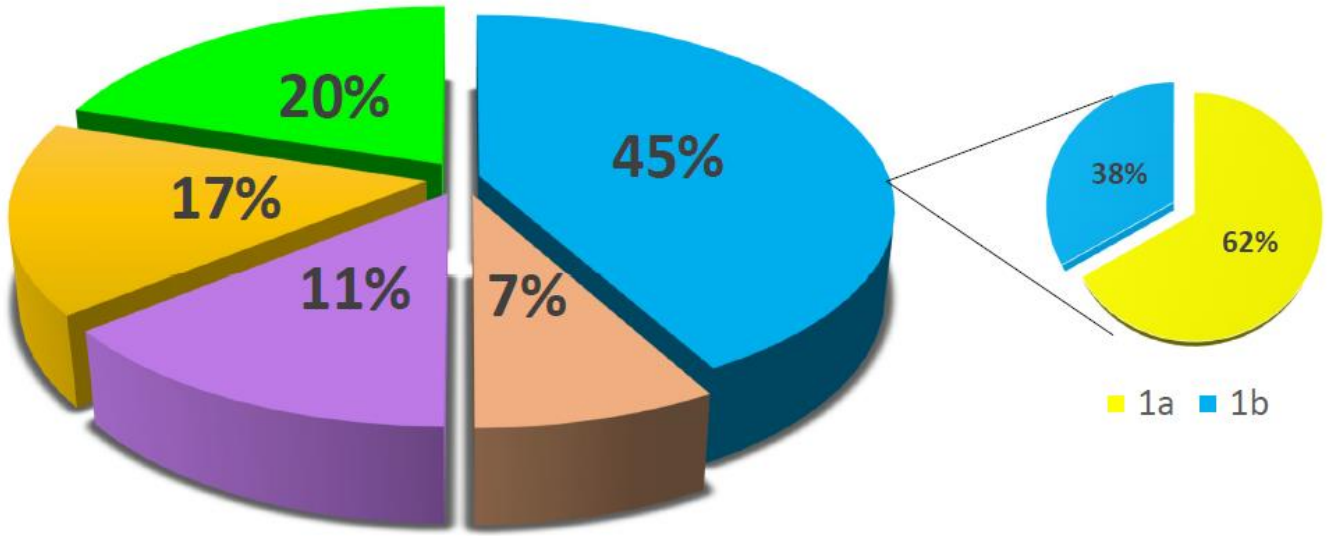
Genotype

Table 2. Viral and baseline laboratory characteristics

HCV viral load (log_{10} IU/mL), median (IQR) (N=238)	5.6 (4.7 - 6.2)
GT, n (%) (N=238)	
GT-1	83 (34.9)
GT-2	16 (6.7)
GT-3	43 (18.1)
GT-4	41 (17.2)
GT-5	38 (16.0)
Not tested	17 (7.1)
GT subtype, n (%)*	
GT-1a	42 (17.6, 62.7)
GT-1b	25 (10.5, 37.3)
GT-2a	4 (1.7, 50.0)
GT-2b	4 (1.7, 50.0)
GT-3a	36 (15.1, 97.3)
GT-3b	1 (0.4, 2.7)
GT-4a	2 (0.8, 22.2)
GT-4c	2 (0.8, 22.2)
GT-4e	5 (2.1, 55.6)
GT-5a	30 (12.6, 100)
Not tested	17 (7.1)
Serological markers	
HAV,† n (%) (N=123)	88 (71.5)
HBV,‡ n (%) (N=219)	8 (3.7)
HIV, n (%) (N=189)	31 (16.4)
Baseline CD4+ count (cells/μL), median (IQR)	395 (272 - 650)
HIV/HBV/HCV§	1 (0.4)

HCV = hepatitis C virus; IQR = interquartile range; GT = genotype; HAV = hepatitis A virus; IgG = immunoglobulin G; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen.
*Number of individuals with a genotype subtype, percentage of the total number of individuals (N=238), and percentage of the number of individuals subtyped within the genotype: GT-1 N=67, GT-2 N=8, GT-3 N=37, GT-4 N=9, GT-5 N=30.
†Hepatitis A IgG antibodies (hepatitis A immunity).
‡HBsAg (HBV co-infection).
§Triple-infected.



HCV GENOTYPE DISTRIBUTION

1 2 3 4 5

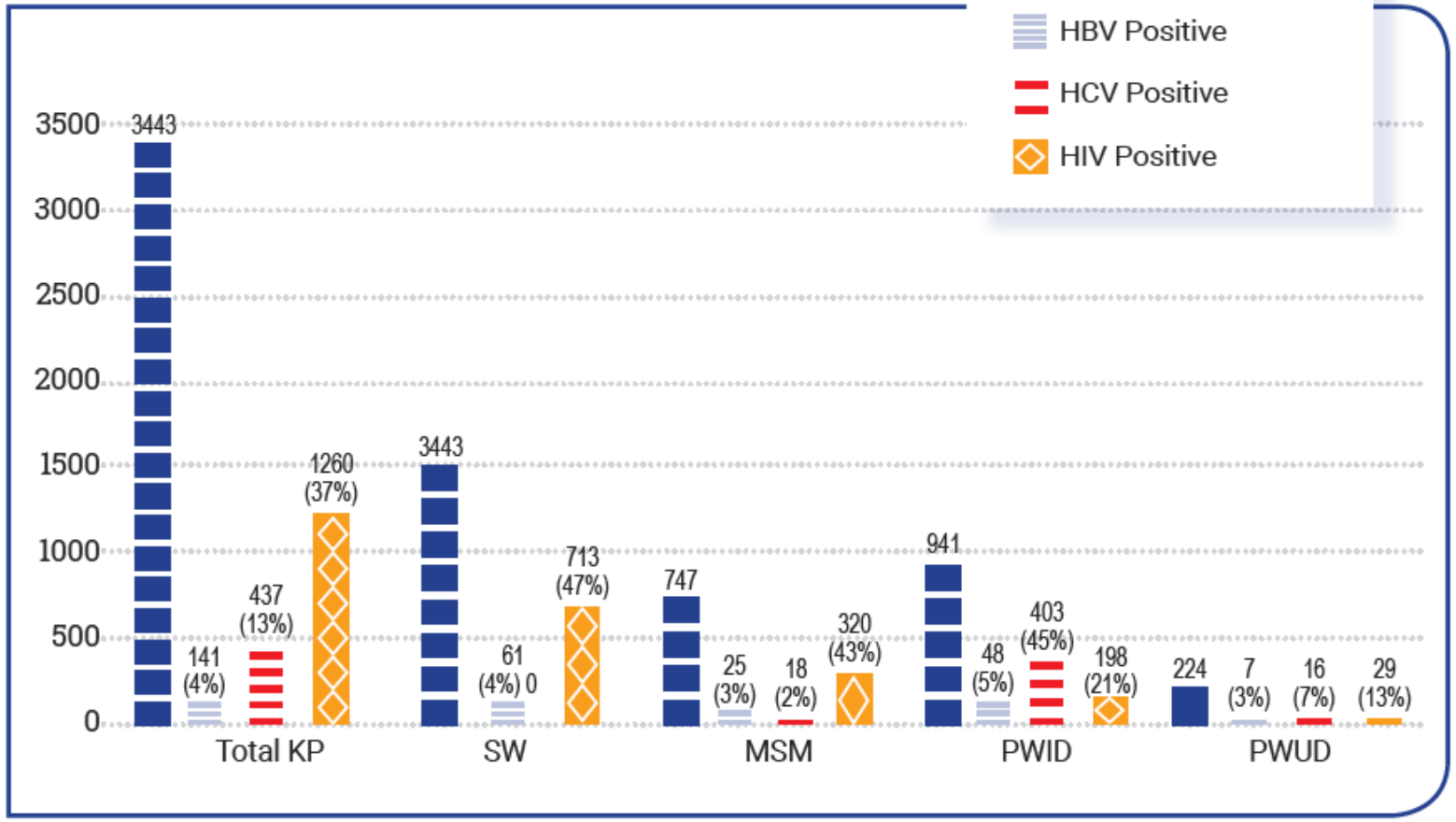
Sonderup, Gogela, Smuts, Hardie, Spearman et al. SAMJ. Feb [illegible]. 2

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

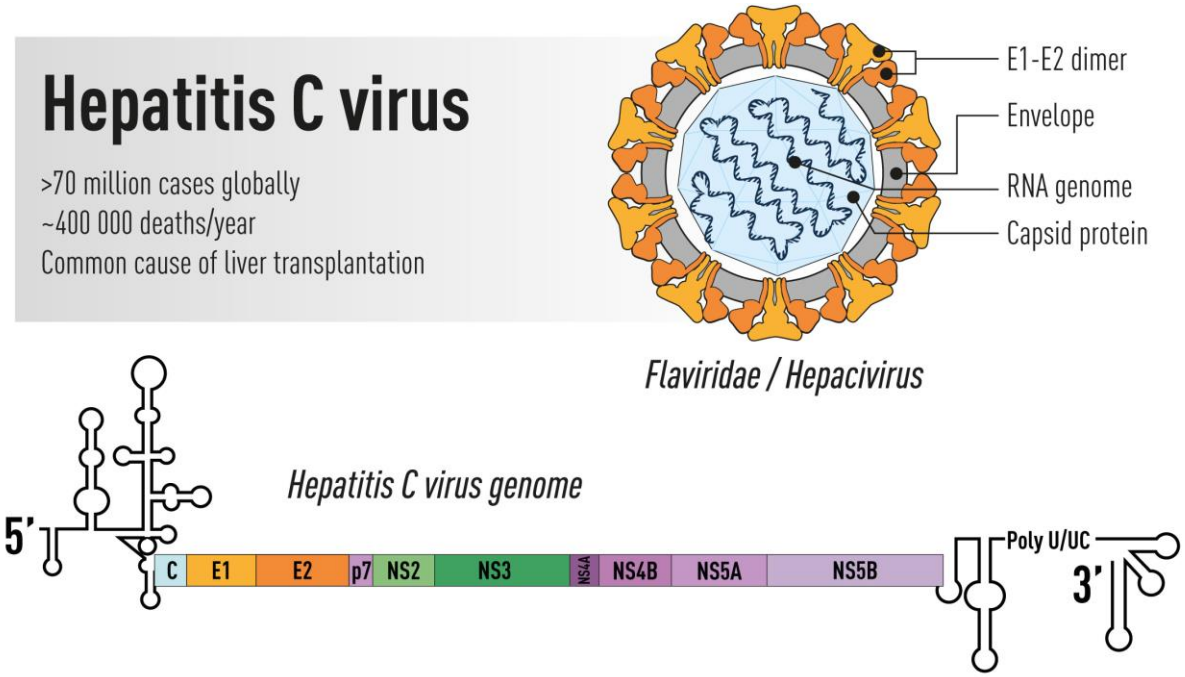
Chris Davis,[1*] George S. Mgomella ,[2,3*] Ana da Silva Filipe,[1] Eric H. Frost,[4] Genevieve Giroux,[4] Joseph Hughes,[1] Catherine Hogan,[4] Pontiano Kaleebu,[5,6] Gershim Asiki,[6] John McLauchlan,[1] Marc Niebel,[1] Ponsiano Ocama,[7] Cristina Pomila,[2] Oliver G. Pybus,[8] Jacques Pépin,[4] Peter 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**]

Key Populations in SA

Figure 2: HBV, HCV and HIV prevalence, by population



Hepatitis C

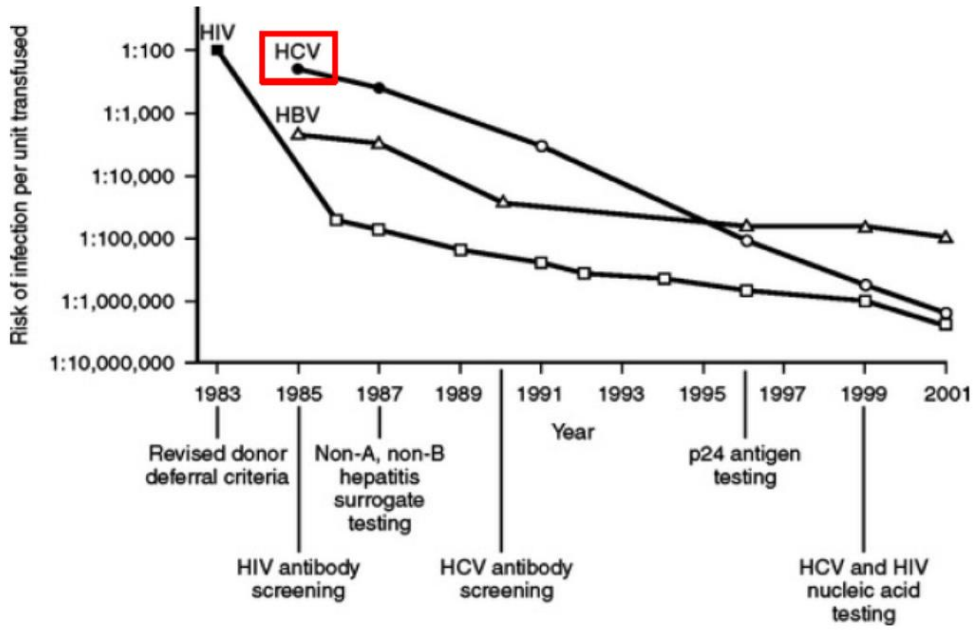


- Enveloped RNA Virus
- Single Stranded
- Half life: 2.5 hrs
- Daily production 10^{19}
- RNA Polymerase has no proofreading ability
- 8 Genotypes with more than 84 subtypes

Transmission

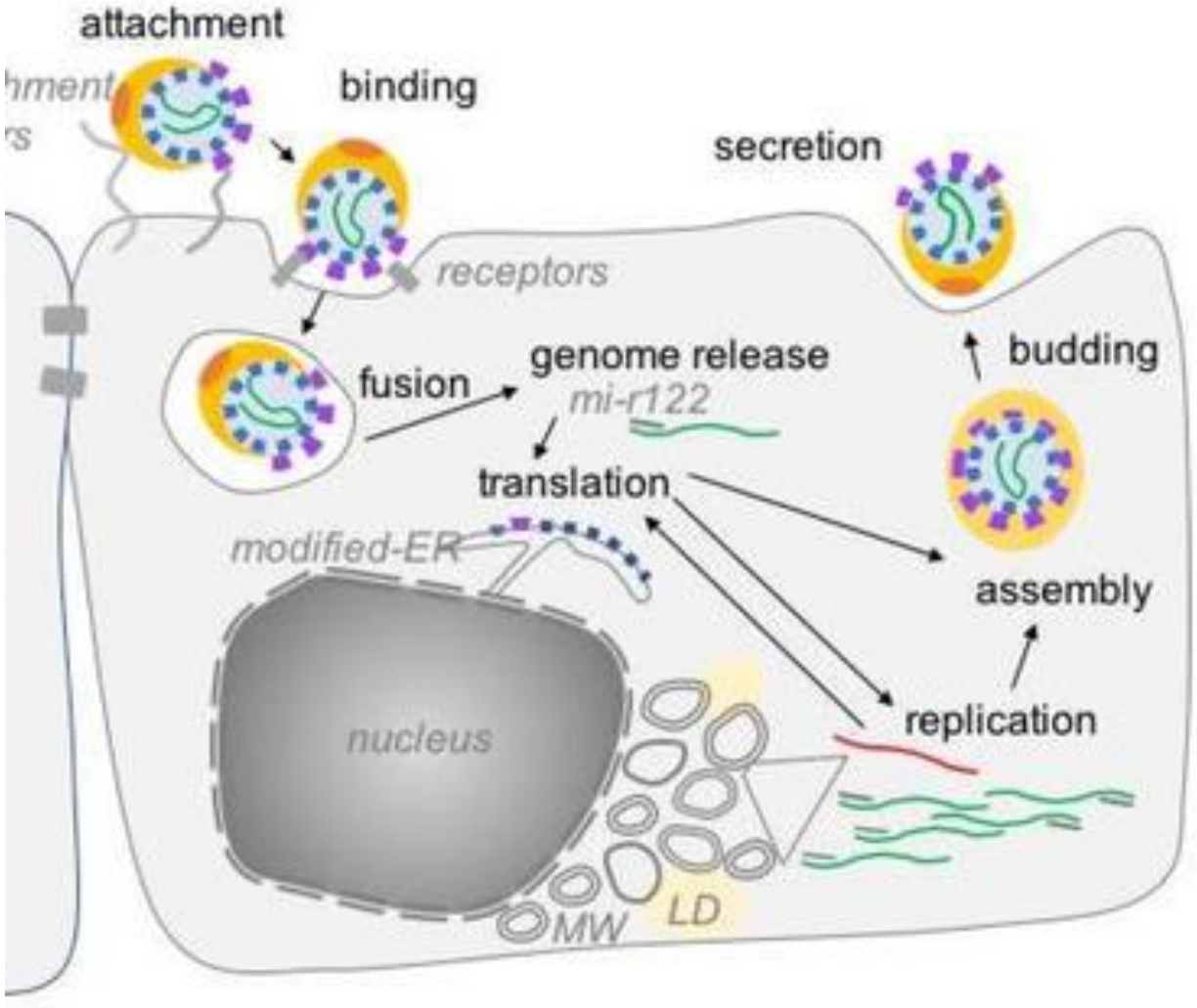
- Blood or blood products transfusion
- Unsafe injection patterns
- Hemodialysis
- Vertical
- Sexual transmission

Rapid decline in global blood transfusion related Hepatitis C



Busch MP, Kleinman SH, Nemo GJ: Current and emerging infectious risks of blood transfusions. JAMA 25; 289(2): 2003

Life Cycle

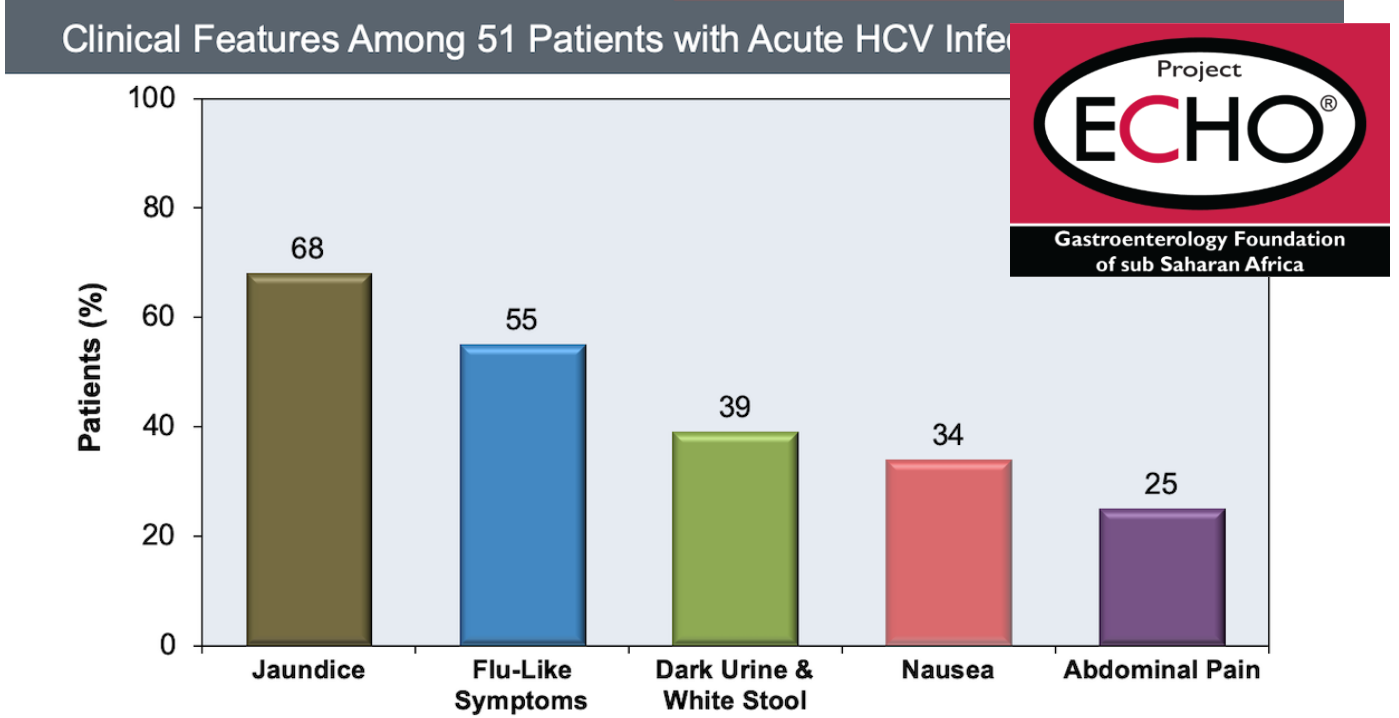

attachment
binding
secretion
receptors
fusion
genome release
mi-r122
budding
translation
modified-ER
assembly
nucleus
replication
MW
LD

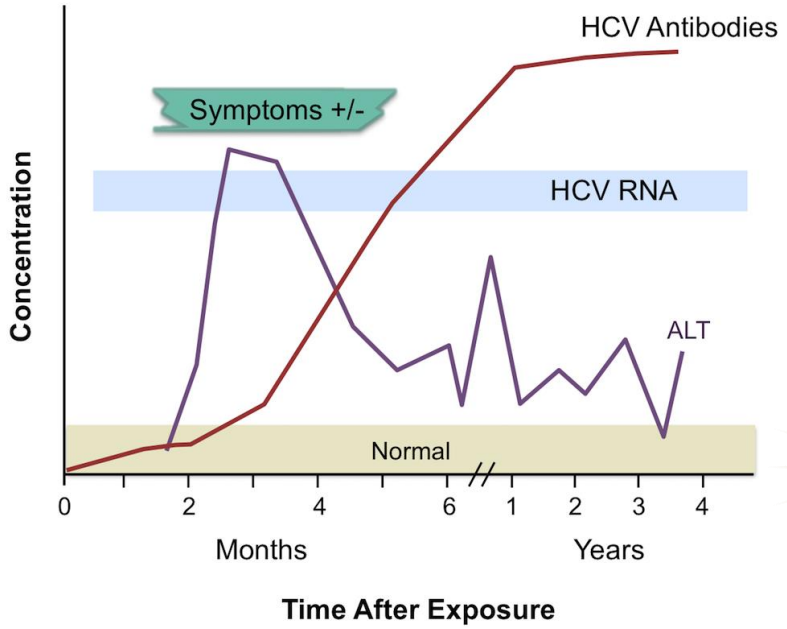
Natural Life Cycle

- 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





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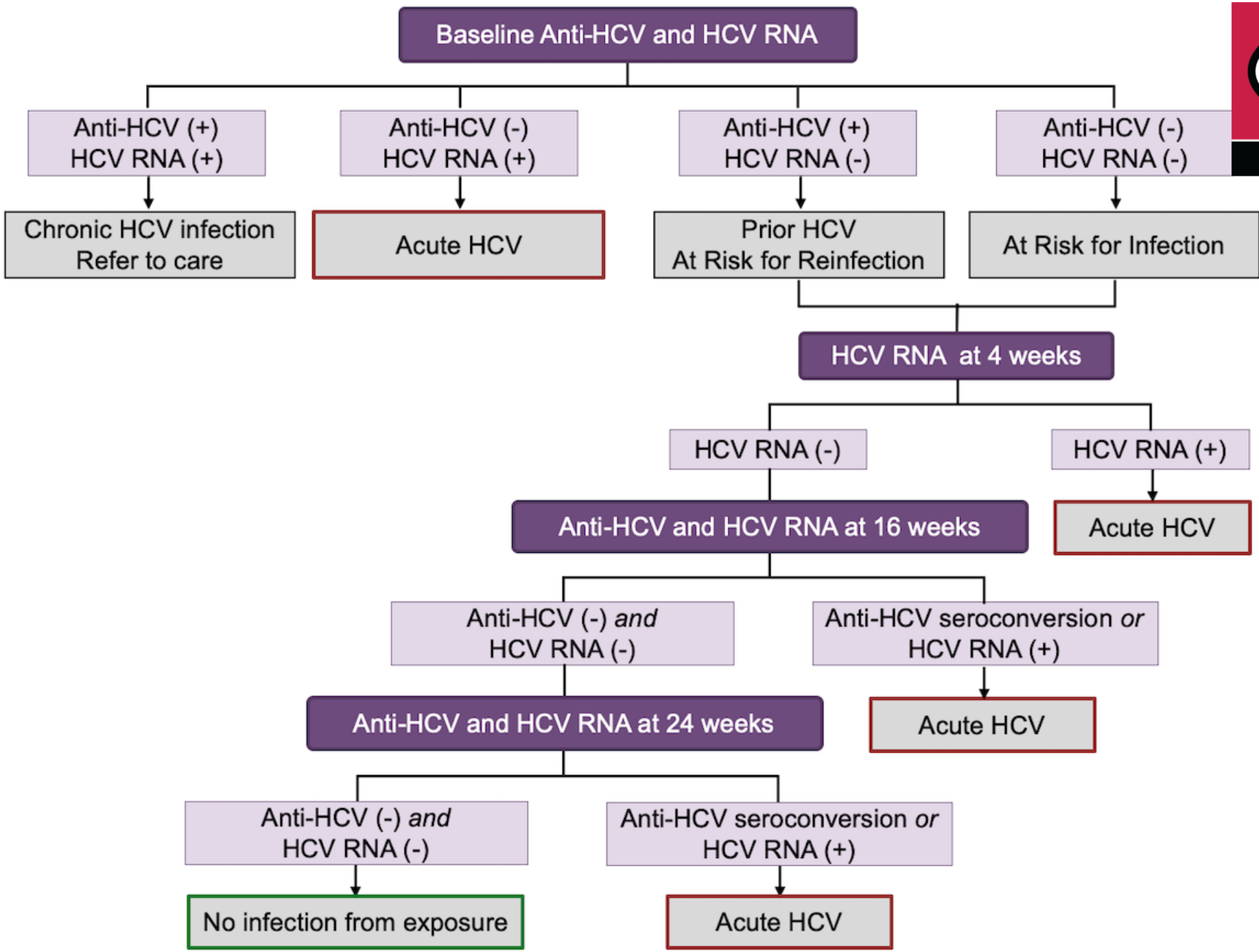

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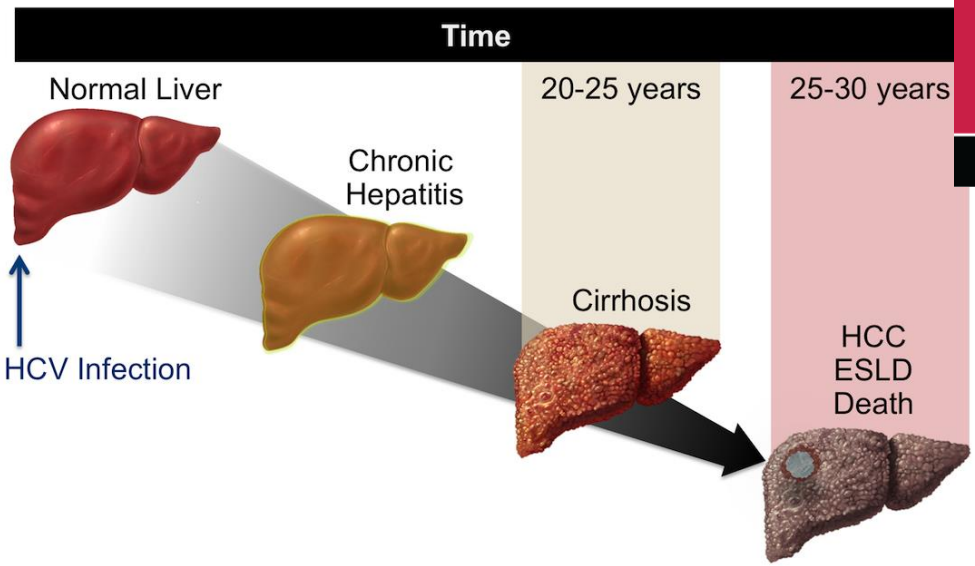
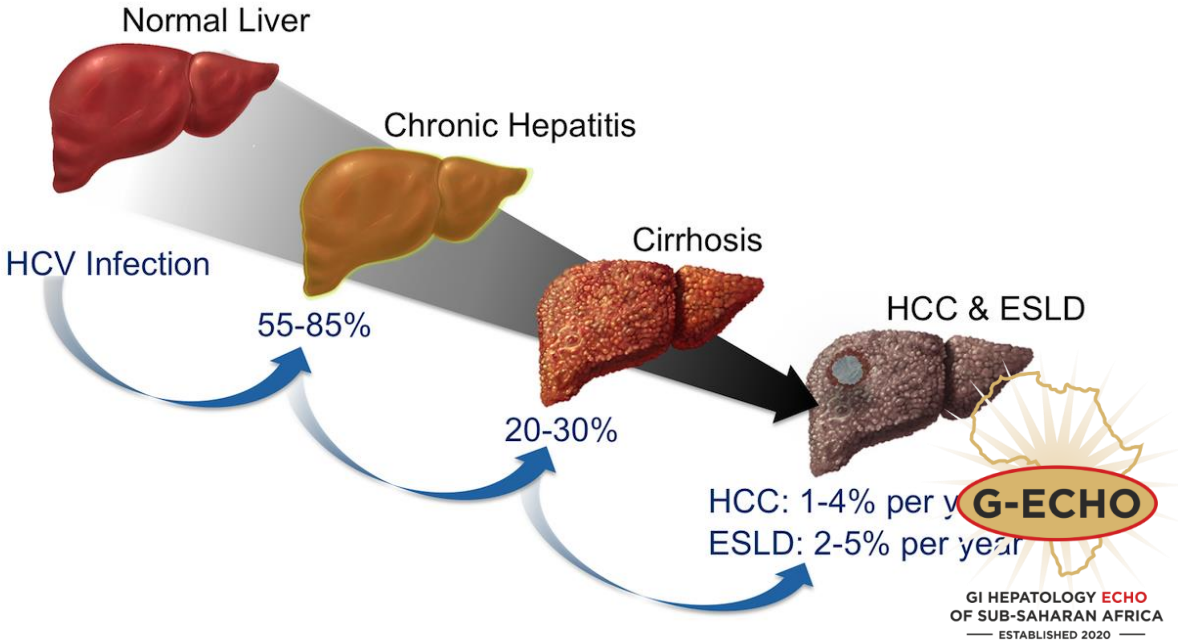
Chronic Hep C

- 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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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

Treatment

- Public Health Measures
- Aim of treatment is cure i.e. to obtain SVR (sustained virological response)
- SVR associated with:
  - Decreased liver related mortality
  - Improvement in Portal HPT
  - Improvement in fibrosis
  - Reduction in HCC
- All patients that are Hep C positive should be treated except limited lifespan.
- Urgent treatment for some patient populations e.g. pregnancy planning, etc
- Patients should be counselled about reinfection.
- Look out for:
  - Drug- drug interactions online website http://www.hep-druginteractions.org/
  - Decompensated liver disease

Public Health Measures

- Screening and Treatment
- Key populations
  - MSM, PWID, Prisoners, HIV/HCV co-infected, SW
- Self testing
- Empowering Health professionals
  - Platforms such as G-Echo
- Challenges:
  - Impact of Covid
  - Access to healthcare (specialists, testing, treatment)
  - Lack of vaccine
  - Cost of medication
  - New sporadic genotypes

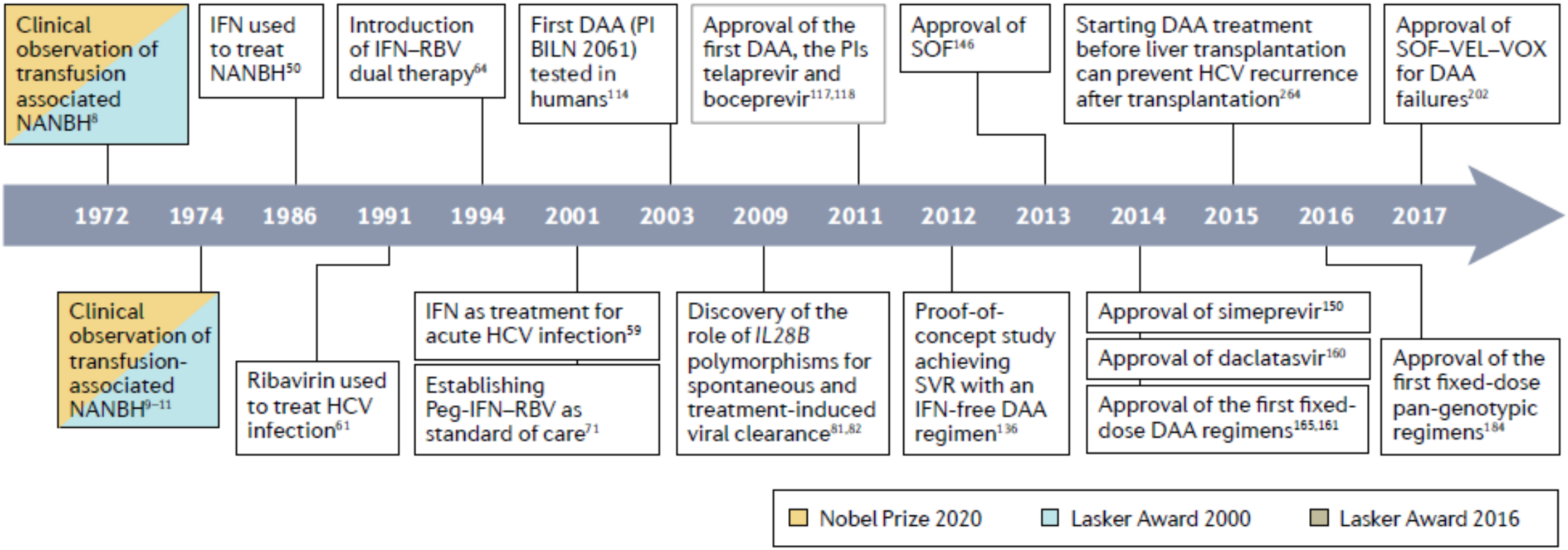
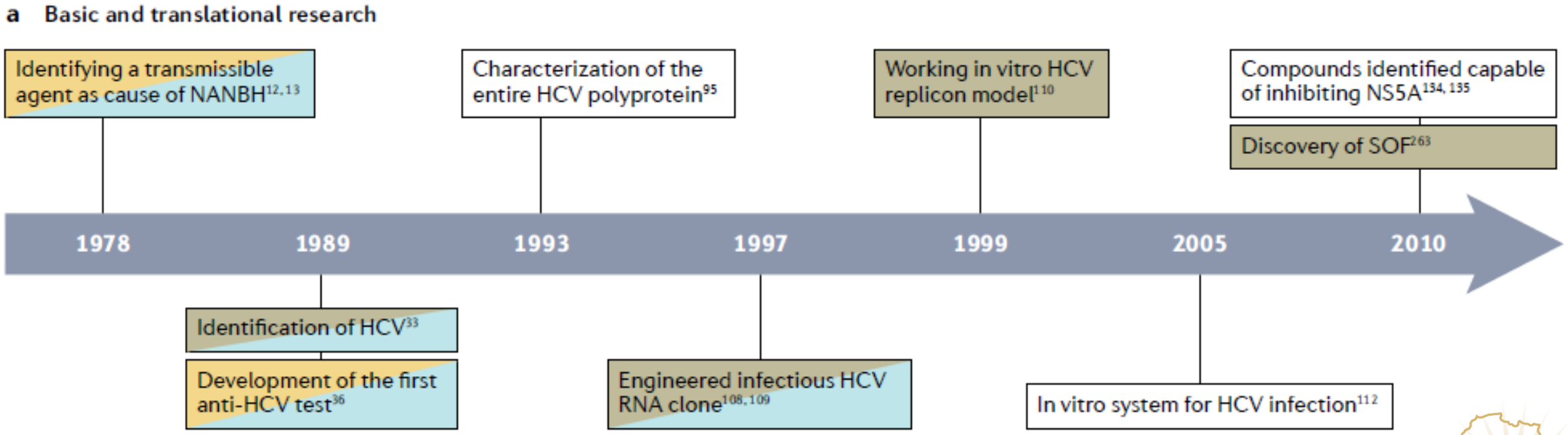
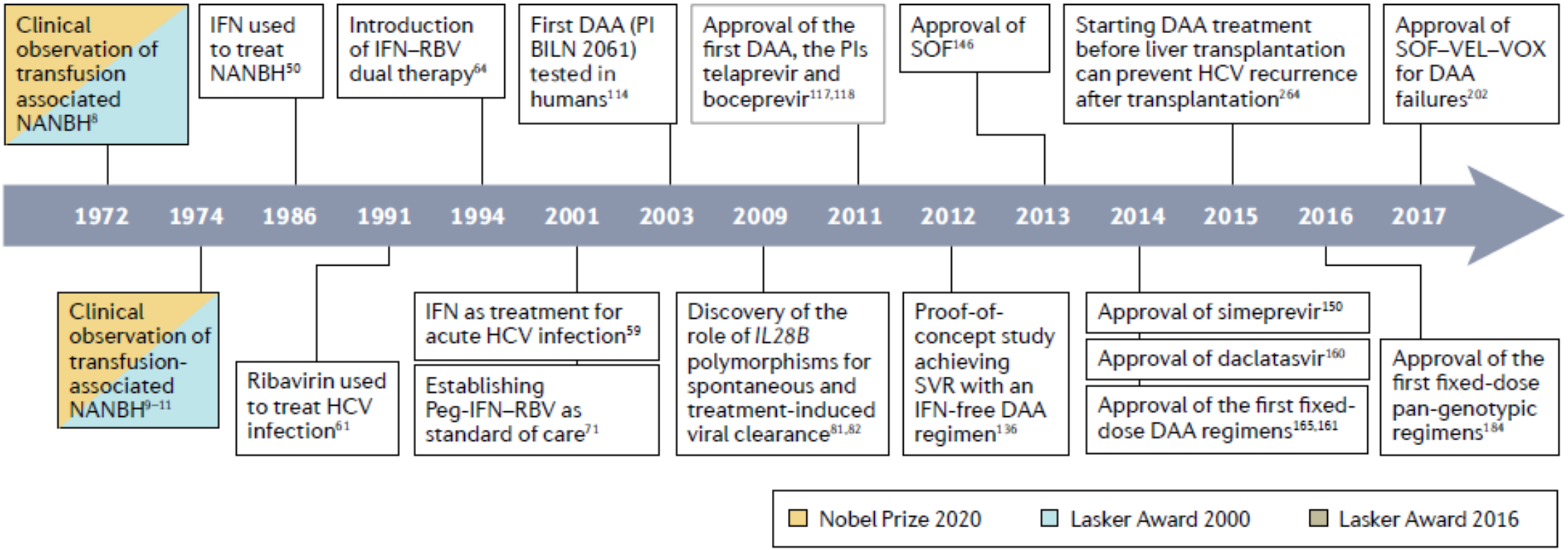


Fig. 1 | **Major breakthroughs in HCV history.** Breakthroughs are separated into basic and translational (part **a**) and clinical (part **b**) research, and research that formed part of major awards is indicated. DAA, direct-acting antiviral agent; HCV, hepatitis C virus; IFN, interferon-α; NANBH, 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].

2005/6 Heralded the HCV Replicon





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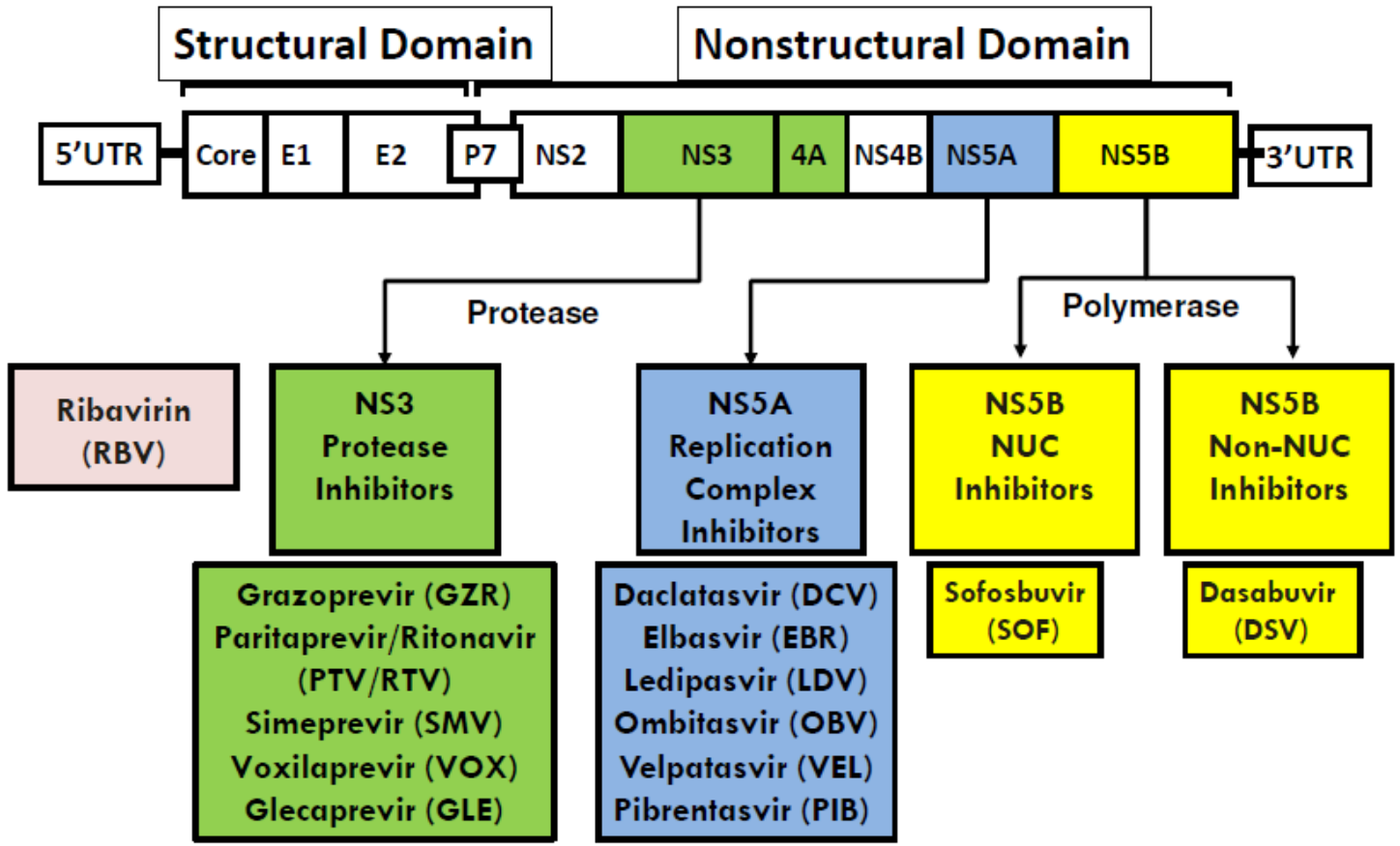
Approved DAAs From Multiple Classes: 2018



Treatment

- Treatment of patients without Cirrhosis or Child Pugh A
  - GT 1,2,4,5,6 SOF/ VEL achieved SVR of 98%
  - GT 3 SOF/VEL SVR 12 of 98% in those without RAS and 88% in those with RAS
  - GT3 with Compensated Cirrhosis lower SVR for SOF/VEL and recommendation is to use SOF/VEL/Ribavirin (polaris trial) alternative regimen with similar outcomes is SOF/VEL/VOX
  - HIV Co-infection SOF/VEL achieves SVR above 90%
  - Alternative Regimen for this population is Glecaprivir/Pibrentasvir in countries where affordability of these regimens is an issue SOF/DACL can be used
  - Despite Ribavirin efficacy in this population group in patients with Cirrhosis its use is not recommended due to the availability of regimens with fewer side effects that achieve the same SVR

Treatment

Table 6A. Recommendations for simplified, genotyping/subtyping-free treatment of HCV-monoinfected or HCV-HIV coinfected adult (≥18 years) and adolescent (12–17 years) patients with chronic hepatitis C without cirrhosis or with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients (defined as patients who have never been treated for their HCV infection) and treatment-experienced patients (defined as patients who were previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin).

Type of treatment	Genotype	Cirrhosis status	Prior treatment experience	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir	Sofosbuvir/ velpatasvir/ voxilaprevir	Grazoprevir/ elbasvir
Simplified treatment, no genotype/subtype determination[a]	All genotypes	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced		12 weeks		

IFN, interferon.
[a]Whenever HCV genotype and subtype determination is not available, not affordable and/or limits access to care.

Treatment

Table 6B. Recommendations for genotype/subtype-based treatment of HCV-monoinfected or HCV-HIV coinfected adult (≥18 years) and adolescent (12-17 years) patients with chronic hepatitis C without cirrhosis or with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients (defined as patients who have never been treated for their HCV infection) and treatment-experienced patients (defined as patients who were previously treated with pegylated IFN-α and ribavirin; pegylated IFN-α, ribavirin and sofosbuvir; or sofosbuvir and ribavirin).

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Genotype/subtype determination-based treatment	Genotype 1a, 1b, 2, 4, 5 and 6	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	12 weeks (genotype 1b only)
			Treatment-experienced		12 weeks		
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced				
	Genotype 3	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No
			Treatment-experienced		12 weeks		No
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve	12 weeks with weight-based ribavirin[a]	8-12 weeks[b]	12 weeks[a]	No
			Treatment-experienced		16 weeks		No
	Subtype 1l, 4r, 3b, 3g, 6u, 6v or any other subtype naturally harbouring one or several NS5A RASs[c]	No cirrhosis	Treatment-naïve	Unknown	Unknown	12 weeks	No
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced				

Treatment

- Child Pugh B or C with or without decompensation
  - Avoid Protease Inhibitors
  - Benefit for treatment more for B than C esp when decompensated
  - Treated at experienced centres with access to transplant
  - Close monitoring
  - Sof/Vel with weight based Ribavirin is treatment of choice if compensated
  - Sof/Vel with 600mg Ribavirin if decompensated
  - If Ribavirin contraindicated then Sof/Vel for 24 weeks
  - If transplant needed then treatment should not delay transplant

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

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
- Pregnant Women: treatment not recommended during pregnancy due to safety concerns but patients that have received treatment whilst pregnant have had no negative effects. Recommendation is to decide on a case by case basis.

Treatment

- PWID
  - Education
  - OST
  - Use of Clean Needles
  - Annual Screening
- Patients with Co-Morbid Diseases
  - Extra-Hepatic effects of Hep C improve with DAAs
  - Patients on HD if GFR >30 then no dose adjustment necessary and treat as above. If GFR <30 then Glec/Pibr are drugs of choice.
  - Renal Failure with GFR <30 and decompensated Cirrhosis Sof/VEL 12-24 weeks

Treatment Failures

- Treatment failure on DAAs is uncommon
- Best referred or discussed
- If failed:
- Check for presence of RAS and design a re-Rx regimen
- If Child Pugh A or less then treat with Sof/Vel/Vox
- If features of poor response to DAAs, e.g. failed twice, then Sof/Glec/Pibr with addition of Ribavirin

Treatment

- Last SA HCV guideline was published in 2010
- Research has been ongoing in the field. Recent Study from Cape Town wherein 210 patients were treated with DAAs shows that we can expect the same outcomes of the rest of the World.
- In this study SVR of 96% were achieved. Most of the population consisted of predominantly males (137 of 210), predominantly white (113 of 210) age range 40 – 60 yrs, 13% had previously received treatment.
- GT 1 and GT 5 were predominant 45% and 20% respectively.
- Of concern was the high fibrosis score of the patients 39% of patients being F3/F4.
- 8 patients failed therapy, of those 5 had GT 4. Emergence of Y93H RAS Mutation which is resistant to SOF/Dacl

Follow up

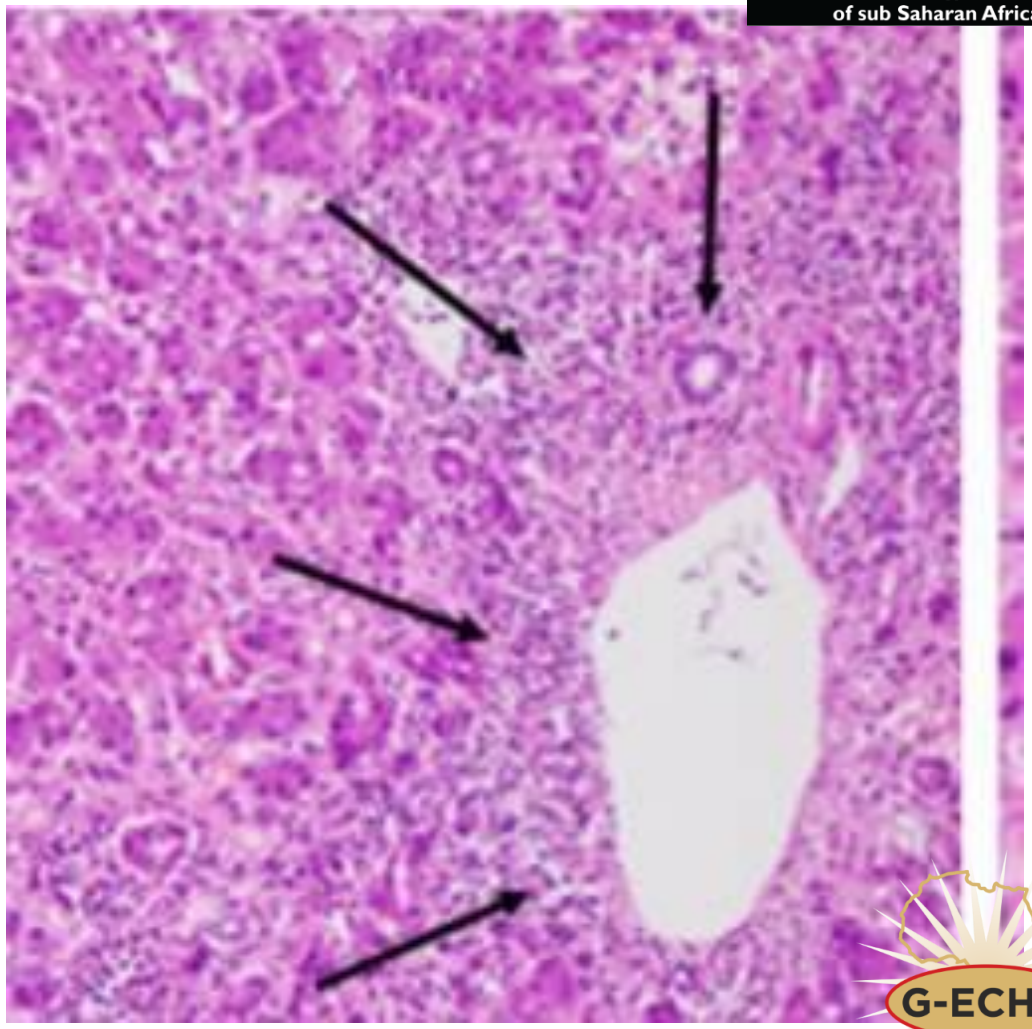
- Assess for compliance and side effects at each visit
- Screen for high risk behaviours
- Viral RNA or Hep C Antigen should be done at 12 weeks or 24 weeks post treatment
- ALT at baseline then 12 or 24 weeks post treatment
- Patients with no fibrosis or Moderate fibrosis without ongoing risky behaviour can be discharged
- Those with f3/f4 fibrosis should have hcc surveillance
- Patients with ongoing risky behaviour should have screening annually

Complications

- Classified into Hepatic:
  - Liver Failure
  - Liver Cirrhosis
  - HCC
- Extra-Hepatic

Complications

- Acute Liver Failure
- Rare
- Controversy/Diagnostic Challenge
- Occurs mostly as an acute on chronic presentation
- Risk factors include co infection with hepatitis B, Metabolic disease, HIV co-infection
- High Mortality



Complications

- Liver Cirrhosis
- Fibrosis in Hep C progresses slowly over years
- However there are factors that may lead to faster disease progression
- Initial presentation may be asymptomatic which means patients may present with advanced fibrosis
- Treatment with DAA's halts and may reverse fibrosis

- Risk of decompensation is 2 to 5% but is relevant because of those 15 to 20% die in the year after decompensation
- Risk of development of HCC
  - 5 yr risk Varies between 1% in patients without cirrhosis to 13% in those with Cirrhosis
  - Other drivers may be genetic, DM, Obesity, males, alcohol, hepB co infection, GT 3, older age, lower plts.

Extra Hepatic Complications

- Include mixed cryoglobulinemia vasculitis, vasculitis, atherosclerotic CV disease, glomerulonephritis, intestitial nephritis, DM II, lymphoma, porphyria cutanea tarda and lichen planus.
- Thyroid disease, Moorens Ulcers and Sjogrens disease

Conclusion

- WHO has set out goals towards curbing morbidity and mortality relating to viral Hepatitis
- Key to achieving this goal:
  - Identifying Key populations
  - Strengthening health care systems
  - Intensive Screening
  - Access to DAAs
  - Vaccine Development

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