HCV GENOTYPE 3 INFECTION

IS IT THE NEW GENOTYPE 1?

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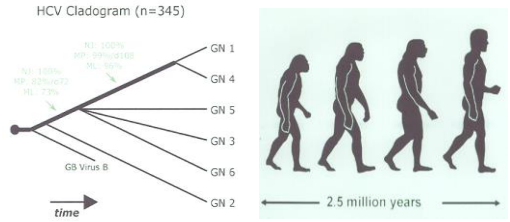
Evolution of HCV

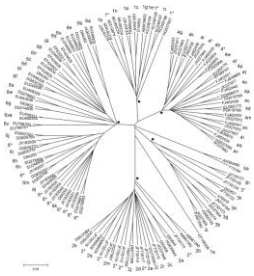


HCV may share an ancestral virus (GBV-B) with tamarins
HCV may therefore share up to 2.5 million years of evolution with man

Ref: Plosone Aug 2009 36579

Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes

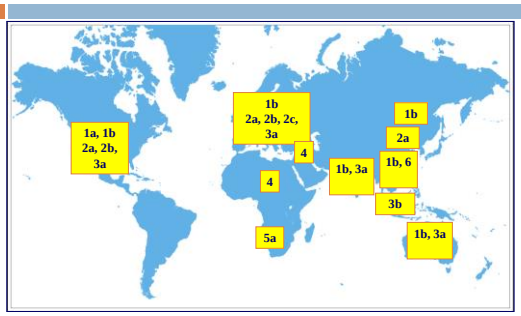
- HCV is a genetically diverse virus that is classified into seven genotypes (1–7) with an average of **35% nucleotide divergence** between strains belonging to different genotypes.
- All genotypes except 5 and 7 are subdivided into numerous subtypes (1a, 1b, 1c, 2a, 2b etc.) and the average nucleotide divergence between subtypes of the same genotype is around 25%



Hepatology
Volume 59, Issue 1, pages 318-327, 20 DEC 2013 DOI: 10.1002/hep.26744
http://onlinelibrary.wiley.com/doi/10.1002/hep.26744/full#hep26744-fig-0001

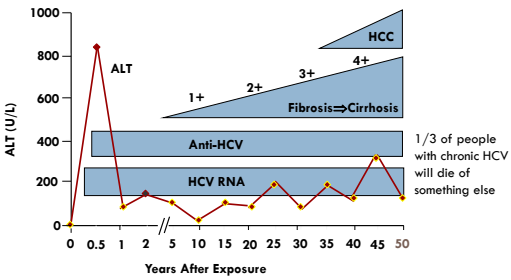
HCV Infection: Worldwide Genotype Distribution

Global infections ~ 200 million (7 million in Europe)
3-4 million individuals are newly infected each year.



Adapted from Fang J. *Clin Liver Dis.* 1997;1:503.

Progression of chronic HCV



1/3 of people with chronic HCV will die of something else

Ref: Hoofnagle JH. Hepatology. 2002;36:S21.

Effect of HCV Genotype 3 on clinical outcomes

Review: Goosens & Negro
Hepatology 2014;59:
2403-2412

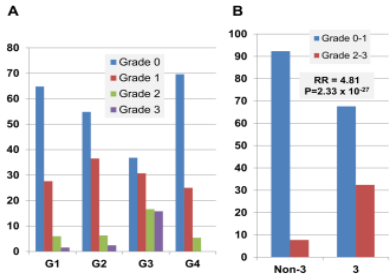
McMahon BJ et al. Gastro
2010;138:92
2-931

- Increased steatosis
- Increased liver fibrosis progression

G3 was an independent risk factors for end-stage liver disease compared to G2 (HR of 3.3).

- Increased risk of HCC
- Reduced SVR [compared to G2] after IFN alpha/ribavirin dual therapy

Association between HCV genotype and liver steatosis



Hepatology
Volume 59, Issue 6, pages 2403-2412, 14 APR 2014 DOI: 10.1002/hep.26905
http://onlinelibrary.wiley.com/doi/10.1002/hep.26905/full#hep26905-fig-0001

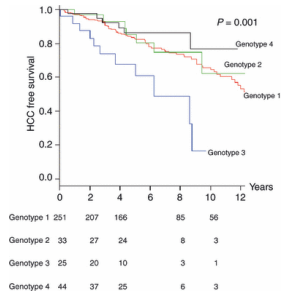
Progression of chronic HCV: summary of lipid associations

1. Increase in **liver** steatosis (more severe and frequent in genotype 3)
2. Decrease in **serum** levels of total cholesterol, LDL-C and apolipoprotein B (more marked in genotype 3)

   1 & 2 reverse after effective treatment
3. Low **serum** lipid levels correlate not only with **liver** steatosis and more advanced fibrosis but also with non-response to IFN-based therapy

Ref: Bassendine et al. Seminars in Immunopathology 2013

HCV genotype 3 is associated with a higher HCC incidence in patients with cirrhosis



Journal of Viral Hepatitis
Volume 18, Issue 10, pages e516-e522, 14 SEP 2011 DOI: 10.1111/j.1365-2893.2011.01441.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2893.2011.01441.x/full#f2

Progression of chronic HCV

- The pathogenesis of accelerated liver disease progression induced by genotype 3 of HCV remains elusive.

Are HCV-lipid interactions involved?

- Apolipoprotein E mediates attachment of clinical hepatitis C virus to hepatocytes by binding to cell surface heparan sulfate proteoglycan receptors.

PLoS One. 2013 Jul 2;8(7):e67982

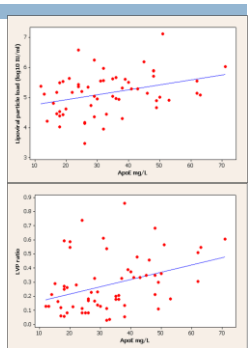
Serum apoE levels and HCV-lipoviral particles

•In HCV G1 apoE was positively associated with LVP (p=0.003) and LVP ratio (p=0.042)

•In HCV G3 apoE was inversely associated with LVP (p=0.013).

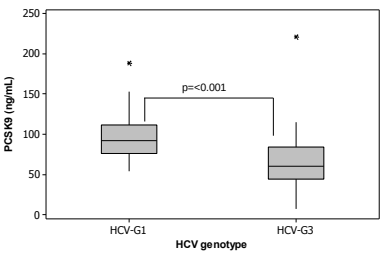
•The inverse correlation of LVP with apoE in G3 compared to the reverse on G1 suggest genotype- specific differences in viral entry.

Ref: Sheridan er al. J Hepatol 2012, 57:32-38; Bridge et al, J Hepatol [in press].



PCSK9 serum levels in HCV G1 vs G3

Bridge et al. J Hepatol. ['in press']



Lower PCSK9 = higher LDLr expression

There are HCV genotype-specific differences in lipid interaction BUT ….

The new DAAs and IFN-free regimens

'One size fits all'

EASL 2014 - the 100% meeting

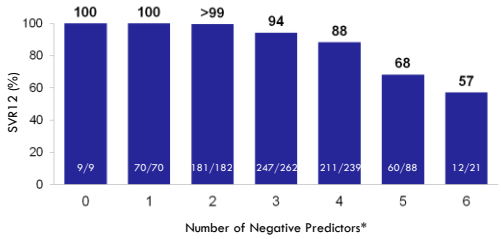
‡

Predictors of Relapse in Sofosbuvir trials
Multivariate Regression Analysis (combined dataset)

Factor	Odds Ratio	p-Value
Treatment experienced	2.3	0.001
Male	2.3	0.01
Weight ≥75 kg	2.5	0.01
IL28B non-CC	3.4	<0.001
Cirrhosis	4.0	<0.001
HCV RNA ≥800,000 IU/mL	4.7	<0.001

‡

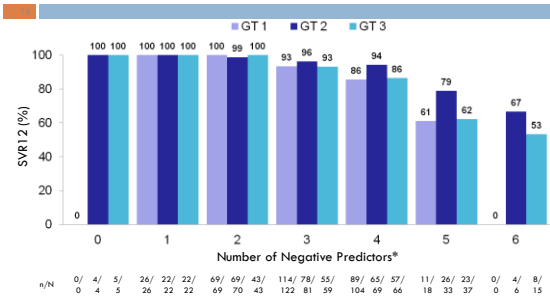
Sofosbuvir trials: SVR12 Rates by no. of negative Predictors Derived From
Multivariate Analysis (combined dataset)



Prior treatment, male, wt ≥75 kg, IL28B non-CC, cirrhosis, and high HCV RNA level.
= bad news

‡

Sofosbuvir trials: SVR12 Rates by no. of negative Predictors and genotype



Genotype 1 and 3 have similar SVR12
G2 has better SVR12 with more negative predictors

‡

Sofosbuvir trials: Conclusions

- Baseline factors significantly associated with relapse included prior treatment, male sex, weight ≥75kg, IL28B non-CC, cirrhosis, and high HCV viral load
- Sofosbuvir-based regimens were highly effective, even in patients with a combination of multiple negative factors

Most cirrhotic patients can now be cured

Sofosbuvir-based regimens according to HCV genotype and date of FDA approval

Regimen	Expected FDA approval date
HCV-1	
• IFN sparing	
– SOF + PegIFN/Rbv 12 weeks	2014
• IFN free	
– SOF + DCV 12/24 weeks	2015 (off-label)
– SOF + LDV 8/12 weeks	2015
– **SOF + SMV 12 weeks**	**2014 (off-label)**
HCV-2/3	
• IFN free	
– SOF + Rbv 12 weeks (HCV-3: 16/24 weeks)	2014
– SOF + PegIFN/Rbv 12 weeks (HCV-3 only)	2014

'Treating HCV will be easy – simply prescribe a pill for 12- 24 weeks'

The new DAAs and IFN-free regimens

The major limitation to treatment will be cost:
The current cost of a 12 week regimen of sofosbuvir alone
Is $84,000 = $1,000 per tablet.
Combination of sofosbuvir and ledipasvir in one tablet is very effective with minimal side-effects **BUT**
"treating even half the HCV-infected persons in the USA would add billions of dollars to an already over burdened medical care system"

Editorial NEJM 2014,370:16;1552-3

Remember - **HCV is a liver disease**

Long-term sequalae after cure

1. Fibrosis regression
2. Liver cancer (HCC)

Cure with PegIFN +R improves outcomes

J Hepatol 2010;52:652

- 307 patients with advanced fibrosis and cirrhosis treated with previous SOC & follow-up of 3.5 years.
- In multivariate analysis, non-SVR was an independent predictor of
  HCC (HR 3.06)
  Liver–related complications (HR 4.73)
  liver-related death (HR 3.71)

SVR has a strong positive influence on prognosis

Outcome after cure among patients with chronic HCV and advanced fibrosis (IFN-based treatment regimen)

JAMA 2012 308:2584

- Multicentre Canadian and European study of 530 patients with histological proof of advanced fibrosis/cirrhosis = Ishak score 4-6, median FU of 8.4 years

	SVR , n=192 (36%)	Non SVR, n=338 (64%)
Liver-related death/OLT	1.9%	27.4%
HCC	**5.1%**	21.8%
Liver failure	2.1%	29.9%

1 in 20 get HCC after cure = do NOT discharge

Regression of liver fibrosis after cure

J Hepatol. 2013; 59:675

- Aim of study – estimate the impact of SVR on fibrosis regression using fibrotest ± fibroscan
- 415/933 had advanced fibrosis at baseline
- At 10 years those with SVR had
  5% decrease in cirrhosis
  4.6% incidence of HCC

1 in 20 get HCC after cure = do NOT discharge

Incidence rates of HCC after cure (IFN-based treatment regimen)

J Hepatol 2013;58:495

- Japanese study of 1013 HCV patients treated with PegIFN + R & followed up for median of 3.6 years post-treatment

	Non-cirrhosis n=863	Cirrhosis n =150
HCC in SVR	**1.7%**	**18.9%**
HCC in TVR	3.2%	20.8%
HCC in NR	7.6%	39.4%

- SVR and complete viral suppression (TVR) were associated with lower risk of HCC

Clinical characteristics of HCV patients who develop HCC after cure

Intern Med. 2013;52:2701

- Cohort of 130 Japanese patients who developed HCC after SVR with IFN-based therapy
- HCC developed within 5 years in 76 (59%), at 5-10 years in 38 (29%) & 10-16.9 years in 16 (12%)
- 82% were male (82%), 71% aged ≥60 years & 71% were cirrhotic
- Independent predictors of HCC within 5 years: AFP ≥10ng/ml & albumin <39mg/dl

Does HCC screening after cure improve outcome ?

Hepatocarcinogenesis in HCV patients after cure

J Gastroenterol 2013 Dec 8

- Cohort of 562 SVR patients followed for 4.8 years
- HCC diagnosed in **5.5%**
- Cumulative incidence was 3.1%, 10.1% & 15.9% at 5,10 & 15 years after completion of therapy
- HCC diagnosed in 26% > 10 years after completion of therapy and F2 was detected in 42% of these patients.
- Predictors of HCC were:
  moderate or advanced fibrosis (HR 10.7)
  advanced age (HR 4.1)
  habitual alcohol consumption (HR 3.9)
  elevated AFP (HR 2.6)

5 year survival was 93% in those who received cancer screening vs 60% in those who had not

Predictors of HCC in non-cirrhotic HCV patients after cure

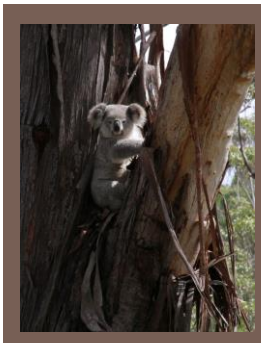
J Hepatol 2014 Mar 5

- Cohort of 642 patients with SVR followed for 53 months
- 5.1% developed HCC
- Incidence of HCC was higher in non-cirrhotic patients with high γGT vs those with low γGT (p = 0.001)
- Predictors of HCC were
  Cirrhosis (HR 5)
  age (HR 1.06)
  γGT(HR 1.008)

Incidence of HCC was NOT different between older non-cirrhotic patients with high γGT and cirrhotic patients(p=0.34)

Cancer screening in HCV patients

- Pre-treatment assess fibrosis stage and undertake cancer screening in all cirrhotics
- Try to cure patients with cirrhosis to lower HCC risk
- Consider more frequent screening in older males with lower platelets and albumin and higher AFP
- Consider cancer screening in patients with moderate fibrosis who have increased γGT, especially older males with AFP ≥10ng/ml



SUMMARY:

Try to cure all patients with the most cost-effective regimen.

Cure lowers the risk of HCC BUT follow-up still required in all patients with advanced liver disease as 1 in 20 develop HCC

[? Higher risk in G3]

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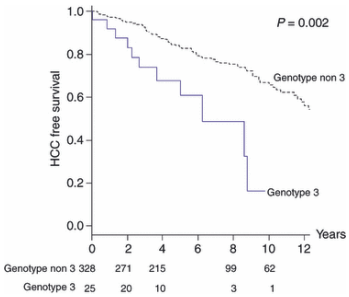
HCV infection

- Genotypes 1, 2, and 3 are widely distributed throughout the USA, Europe, Australia, and East Asia (Japan, Taiwan, Thailand, and China).
- Genotype 4 is largely confined to the Middle East, Egypt, and Central Africa.
- Genotypes 5 and 6 are found predominantly in South Africa and Southeast Asia, respectively.

- The WHO estimates that about 200 million people, or 3% of the world's population, are infected with HCV, and that 3-4 million individuals are newly infected each year.

HCV genotype 3 is associated with a higher HCC incidence in patients with cirrhosis



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