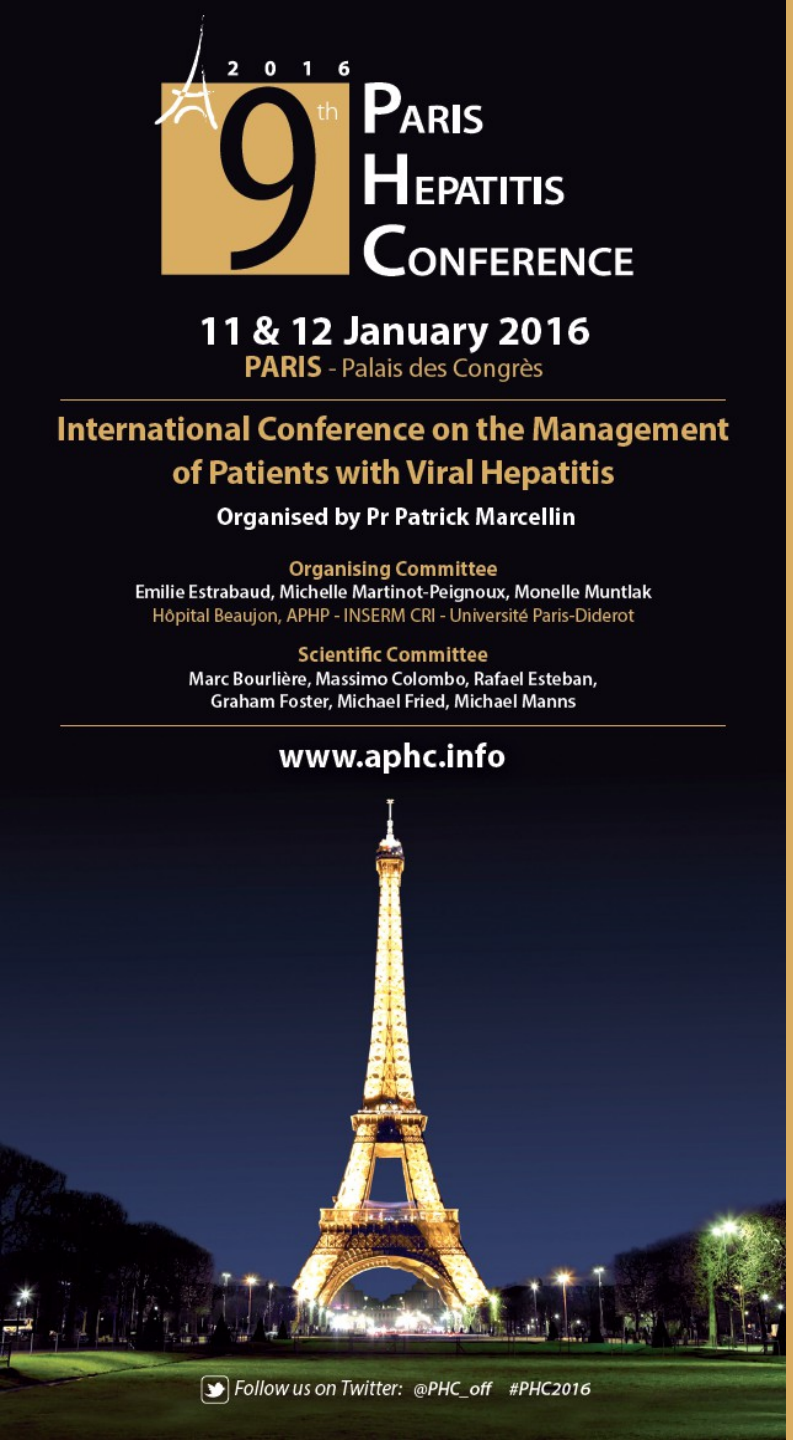


HCV eradication with direct acting antivirals (DAAs)?

Why is viral cure possible in HCV?

Emilie Estrabaud

Service d'Hépatologie et INSERM UMR1149,
AP-HP Hôpital Beaujon, Paris, France.
emilie.estrabaud@inserm.fr

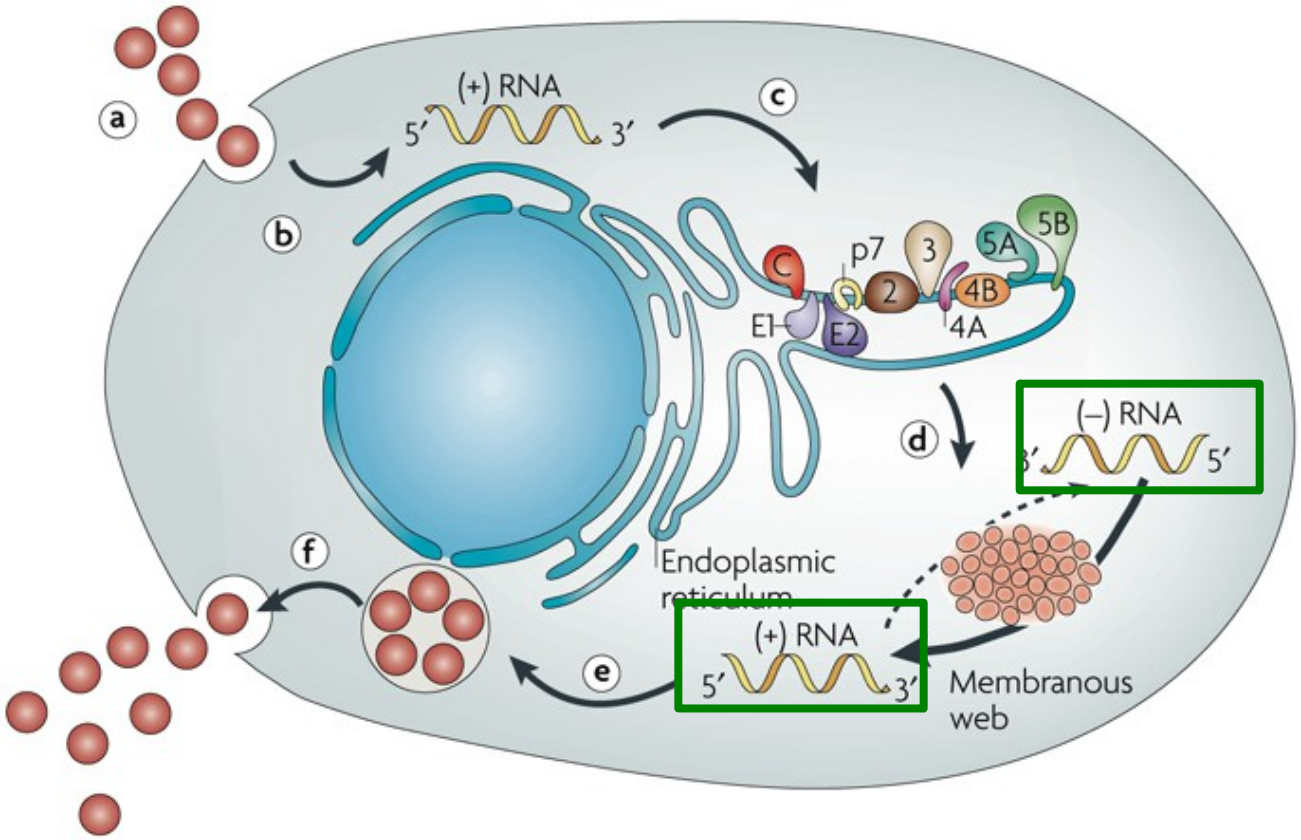
Plan

1. Virological cure: virus characteristics allowing eradication

2. Interaction with immune system and risks of reinfection

3. Functionnal cure: improvements after viral cure

HCV life cycle



Nature Reviews | Microbiology

Absence of persitence in HCV:

1- Only cytoplasmic

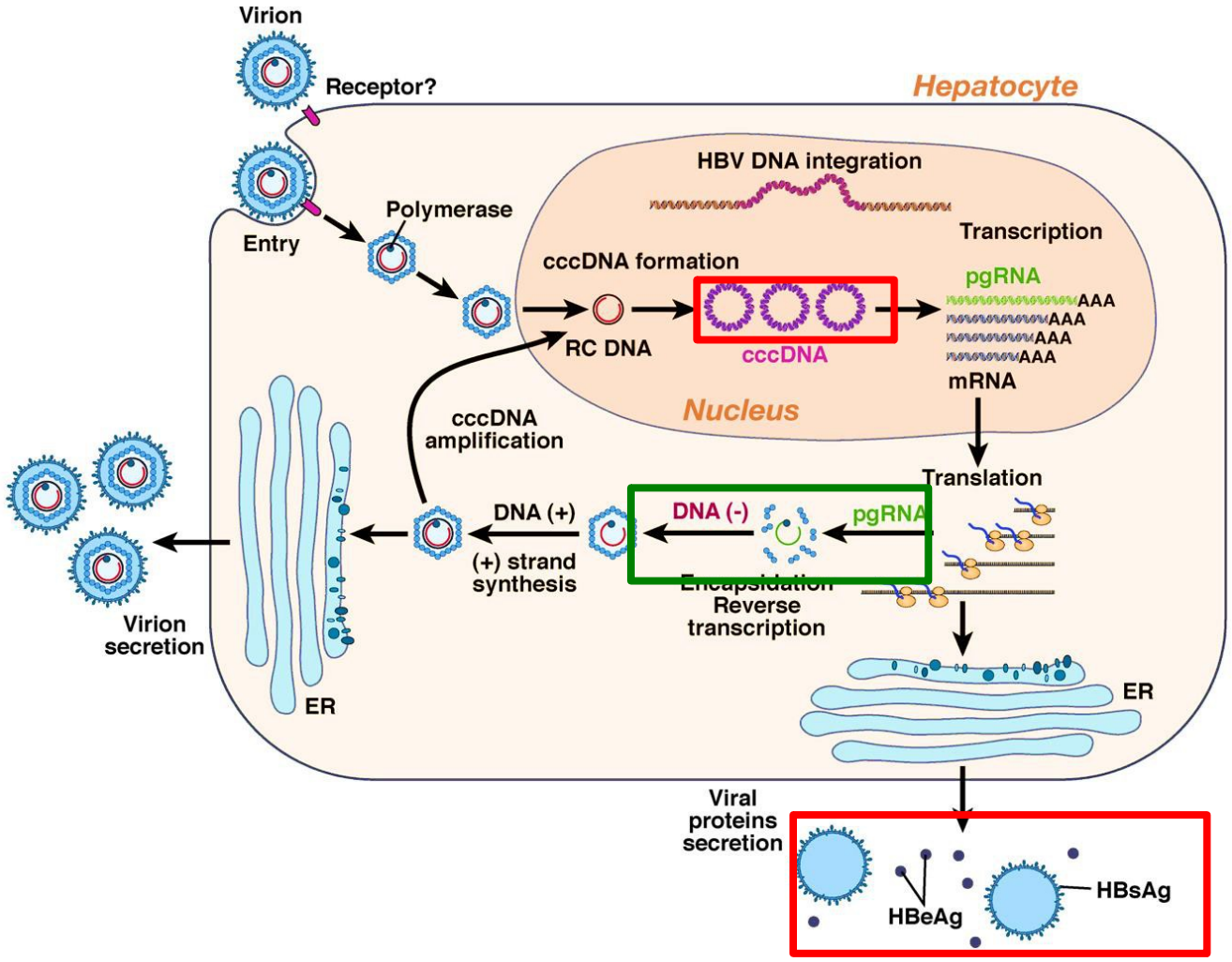
2-No cellular reservoir

Viral polymerase:

2 steps

Moradpour et al. 2007 *Nature Reviews Microbiology* **5**, 453–463.

HBV life cycle



cccDNA: closed circular covalent DNA;
RC: relaxed circular; pgRNA: pregenomic RNA;
ER: endoplasmic reticulum

HBV persistence:

1-Cytoplasmic and nuclear replicative forms

2- HBV cccDNA

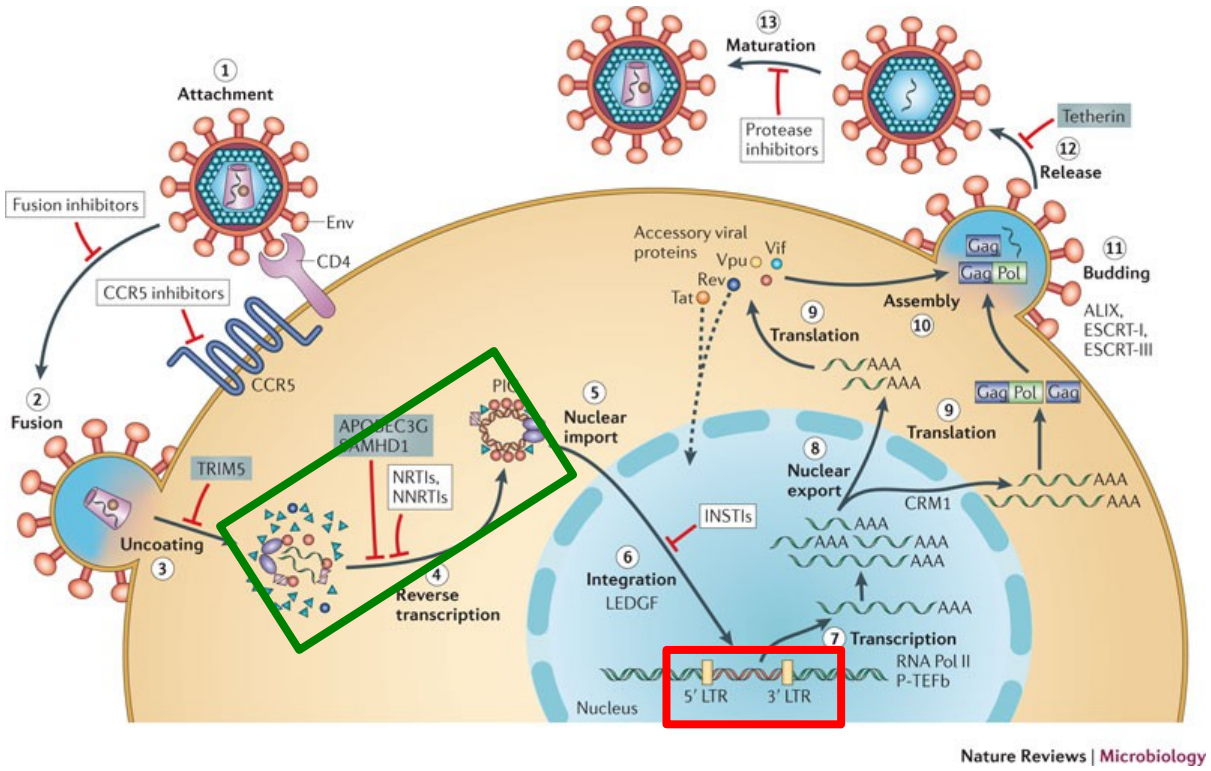
3- Empty particules to stimulate the immune system

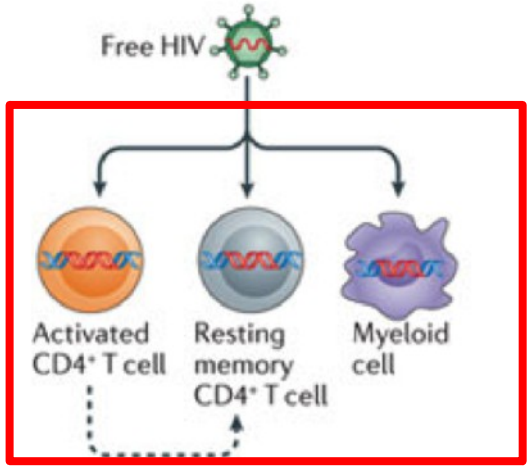
Viral polymerase:

1 step

Fletcher SP, Delaney WE. Semin Liver Dis 2013;33:130–7.

HIV-1 life cycle





HIV persitence:

1-Cytoplasm and nucleus replication

2- proviral insertion

3- Multiple cell targets

Viral polymerase: 1 step

Engelman et al. 2012. Nature Reviews Microbiology **10**, 279-290

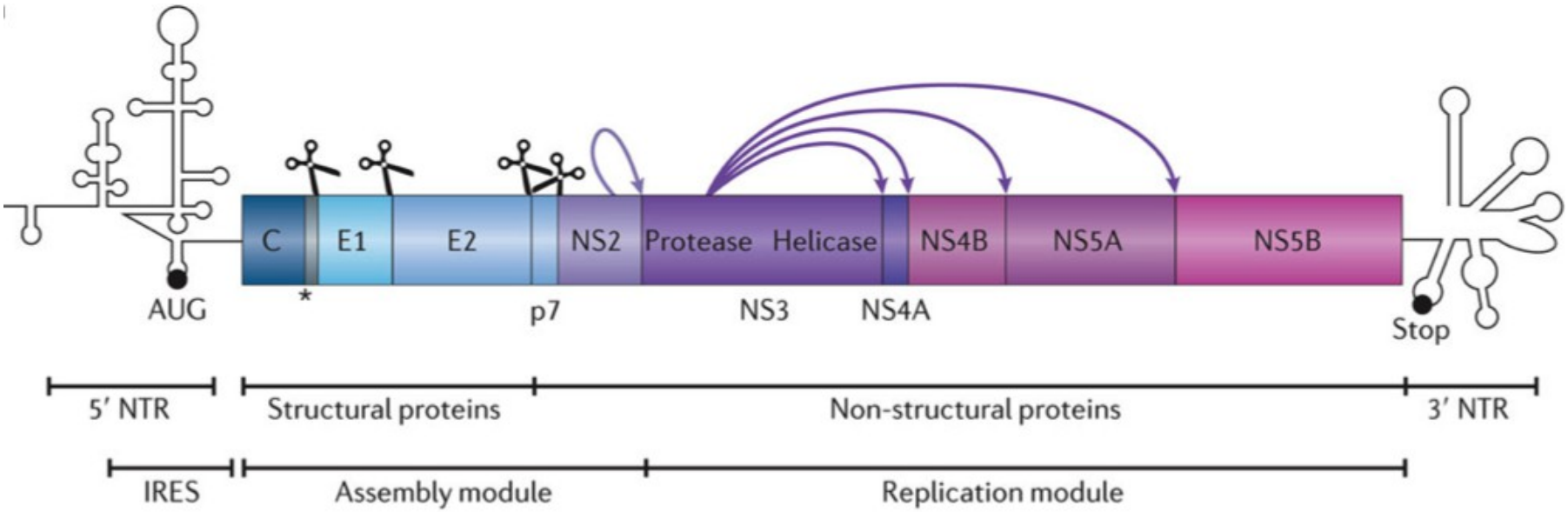
Deeks et al 2012. *Nature Reviews Immunology* **12**, 607-614.

HCV, HBV and HIV: different dynamics of selection of mutations

	HCV	HBV	HIV
Daily production of virion per day	1012	1012-1013	1010
Half life free virions (hours)	2-3	3-24	1
Mutation rate	Very high	high	Very high
Constraints due to ORFs	none	high	moderate

Soriano et al. J Antimicrob Chemother. 2008;62:1-4.

HCV: only 1 ORF

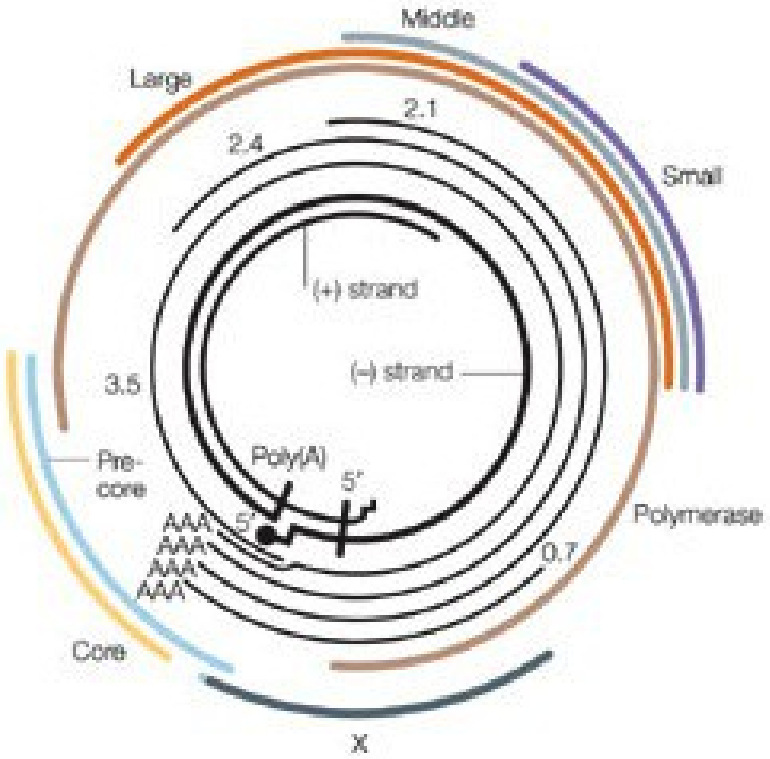


No ORFs constraints for the selection of mutations

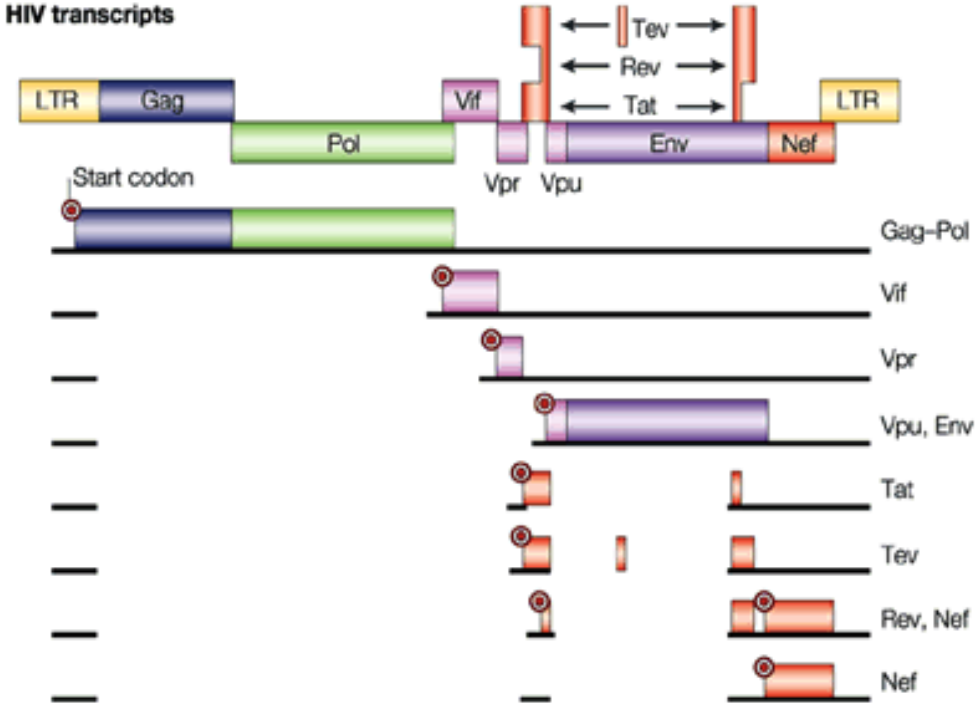
Bartenschalger et al. 2013, Nature Reviews Microbiology **11**, 482–496.

Viral Genome: multiple ORF and splicing constraint the selection of mutations

HBV: multiples overlapping ORFs



HIV: fewer overlapping ORFs



Rehermann et al. Nat Rev Immunol 2005 5: 215-229.

Peterlin et al. Nat Rev Immunol 2003. 3 (2): 97-107.

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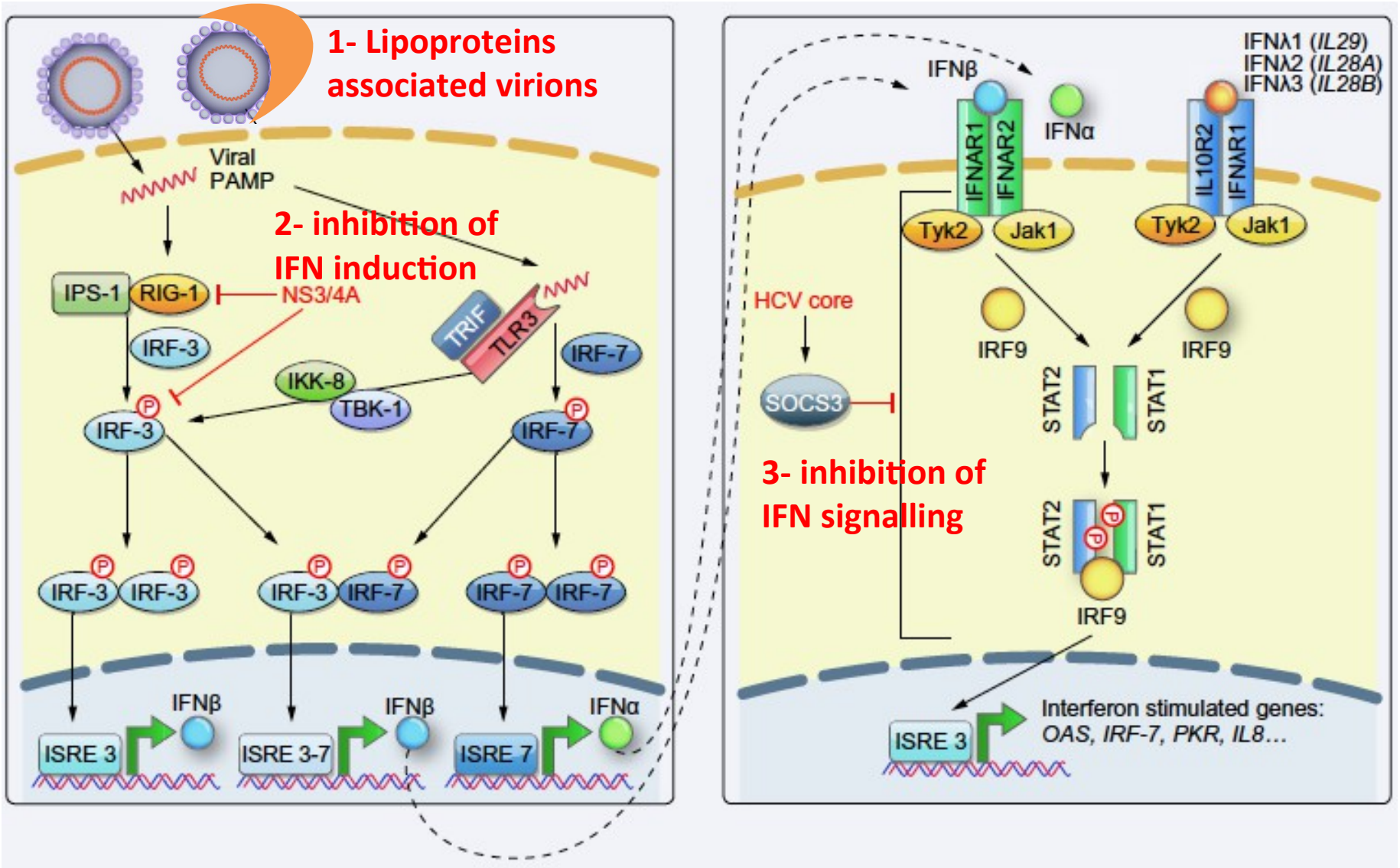
HCV strategies to escape immune response



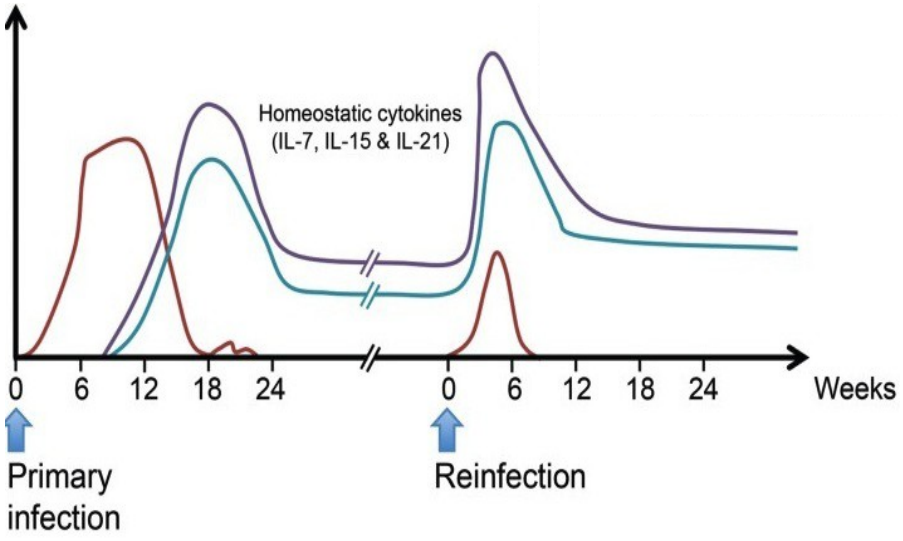
Viral strategies to escape immune response

HCV	HBV	HIV
Association of virions with lipoproteins	Production of empty particles	Reduction of antigen presentation by MCH I (Nef)
Inhibition of IFNs induction (NS3/4A, NS5A)	Inhibition of IFNs induction (HBV polymerase, HBx)	Reduction of antiviral factors APOBEC (Vif)
Inhibition of IFNs signalling (NS5A/Core)	Inhibition of IFNs signaling :RIG-I /MDA5/TLRs (HBx)	Reduction of CD4 and Tetherin (Vpu): increased viral production

Busca et al. J virol 2014. 11:22
Cook et al. Plos Path 2013 (9)
Li et al. Semin Immunopathol 1013 (1) 53-72

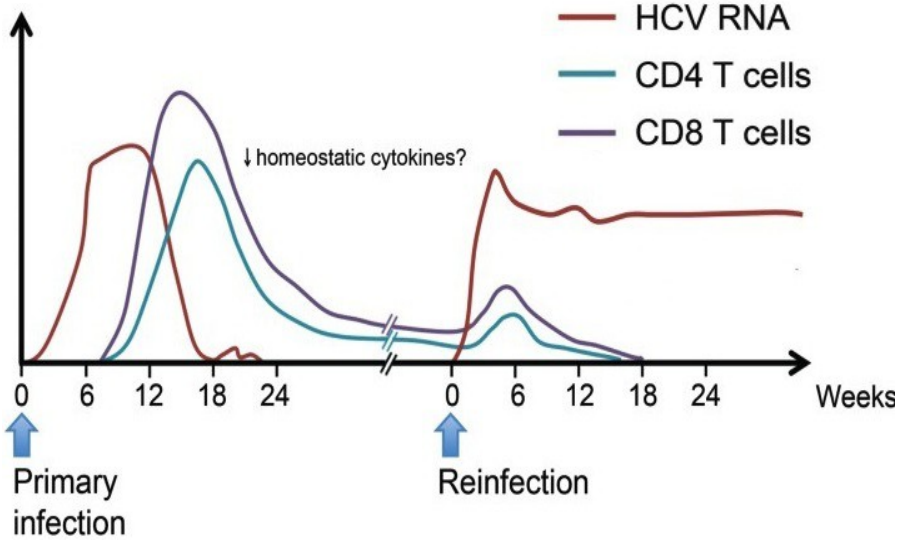
HCV: limited memory immune response and the risk of re-infection

Protection



CD4 an CD8 T cell detected (up to 20 years), in patients with spontaneous viral clearence.

No protection



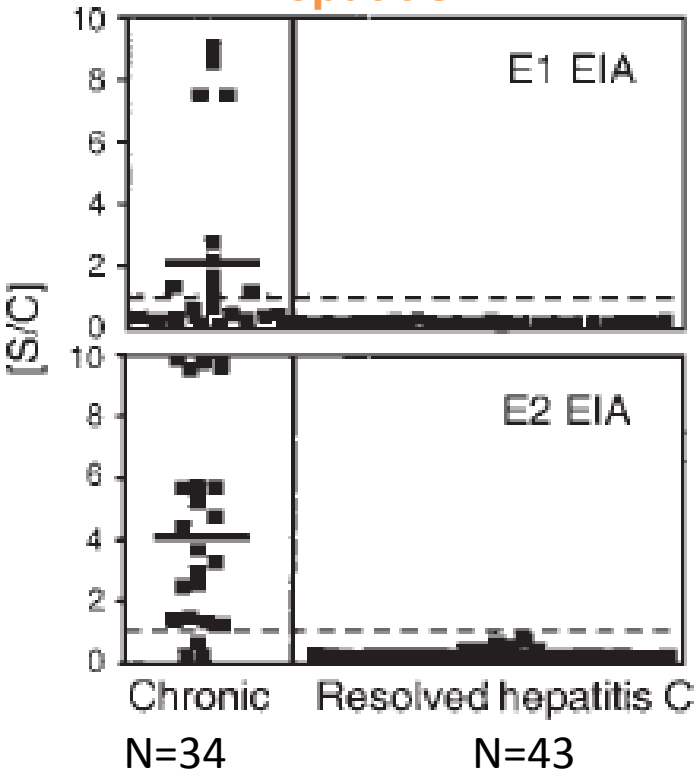
Treatment-induced viral clearance

Cellular protection after HCV spontaneous clearance.

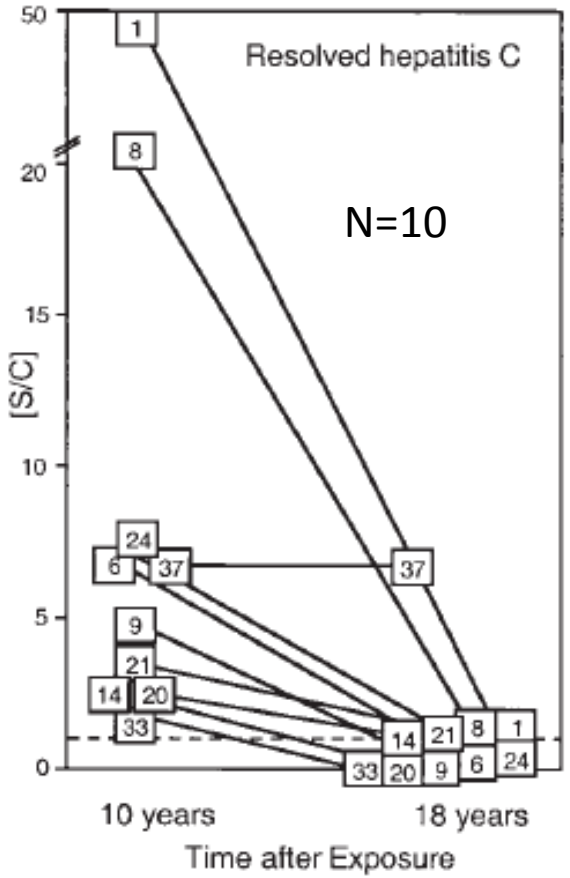
Abdel-Hakkem et al. Front Immunol. 2014; 5: 274

Reduction of anti-HCV antibodies after HCV recovery

No HCV epitopes in resolved hepatitis C



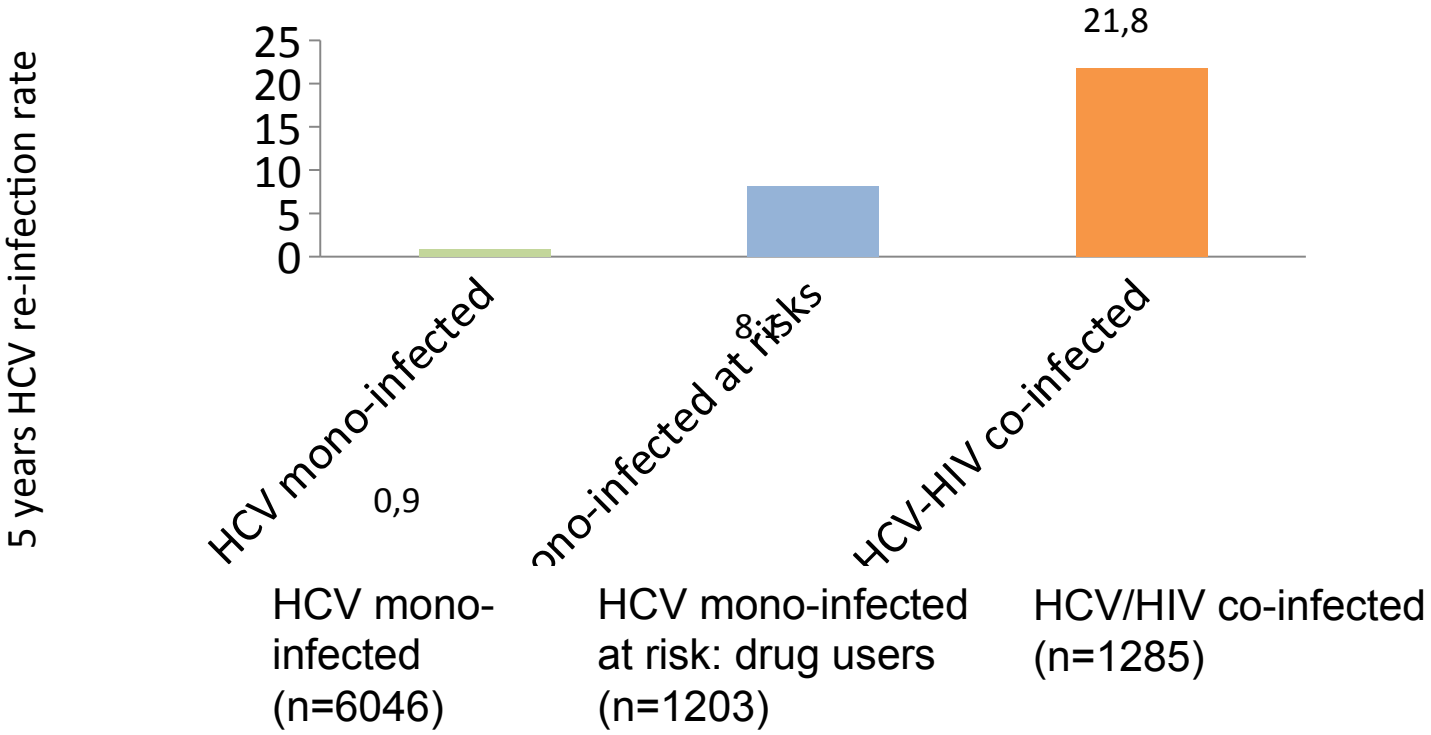
Gradual decrease of HCV antibodies after HCV recovery



No humoral immunity after HCV spontaneous clearance.

Takaki et al. Nat Med (2000) 6:578-8210

HCV: populations at risks of re-infection



Hill et al. CROI 2015; February 23-26, 2015. Seattle, Washington. Abstract 654.

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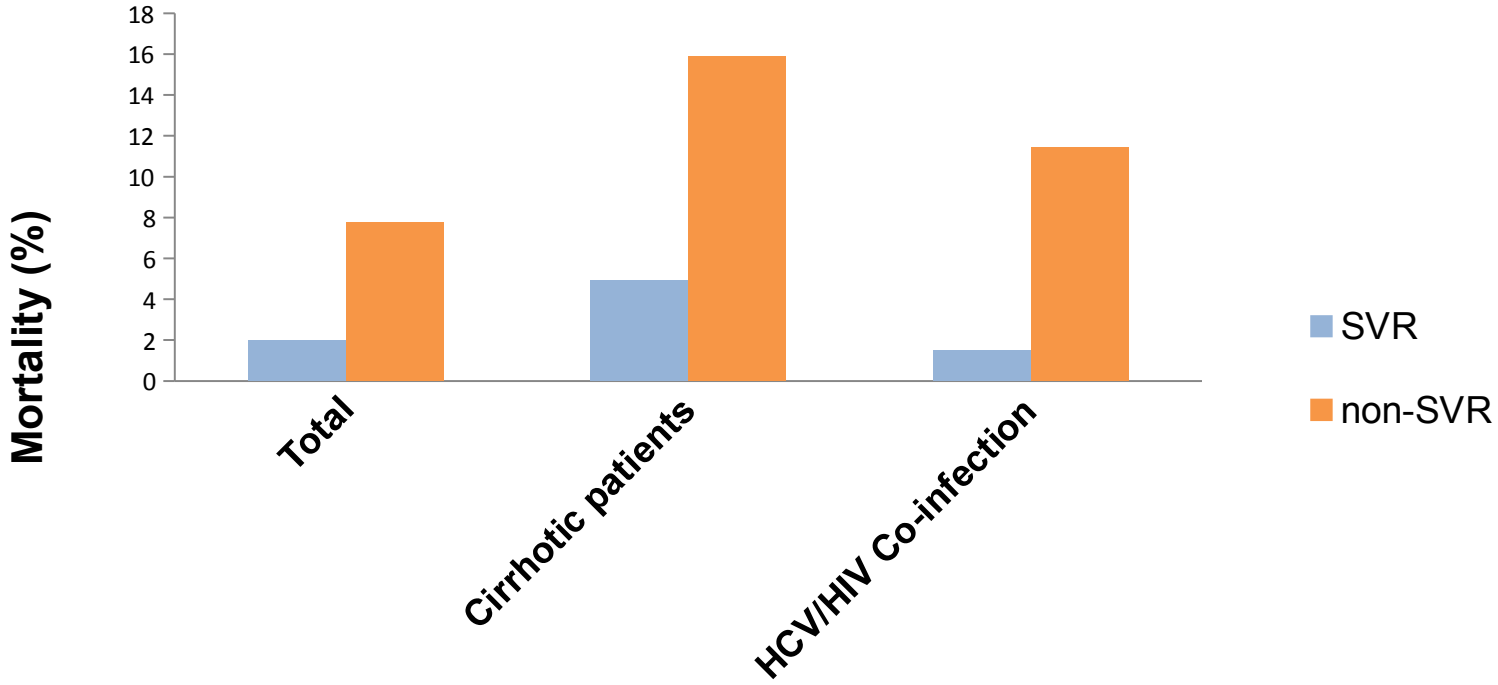
Increased survival in patients with SVR

Meta-analysis (n=33,360 patients)



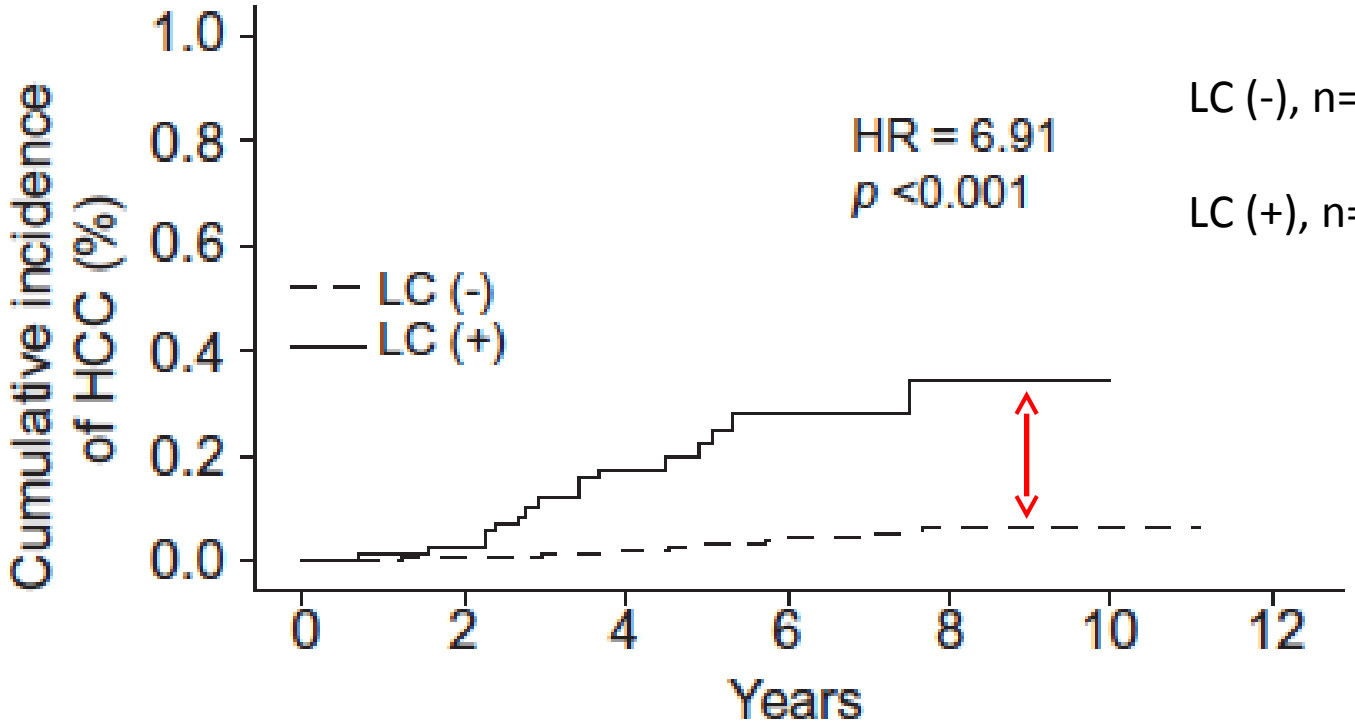
After SVR, patients cirrhotic patients have still higher risk of mortality than the total population.

HCV eradication greatly improves mortality risk in HIV/HCV co-infected patients.

Simmons et al. Clin Infect Dis 2015; 61: 730–40.

HCC risk remains, after viral eradication in cirrhotic patients

Patients with SVRs to PEG-IFN+RBV (n=642)



LC (-), n=556 patients

LC (+), n=86 patients

HCC risk increases over the time even after SVR, in patients with LC.

Huang et al. J Hepatol 2014; 61: 67–74.

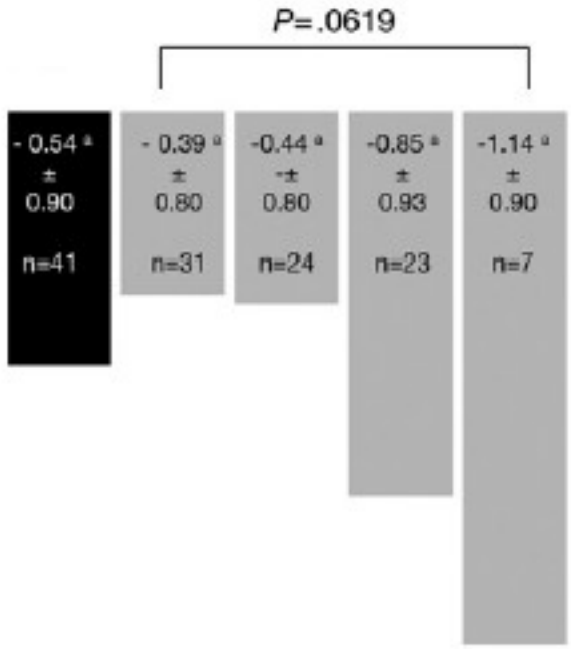
Slow fibrosis regression after SVR

Reduction of F3-F4 after SVR

	Post-treatment					
Pretreatment	F0	F1	F2	F3	F4	
F0	1	2	0	0	0	
F1	14	16	7	0	0	
F2	7	23	12	2	0	
F3	0	5	12	7	4	27
F4	0	1	2	6	5	14
				15	9	

The shade area indicates the number of patients with fibrosis stage that remained stable or improved.

Improvement of liver fibrosis after the EOT



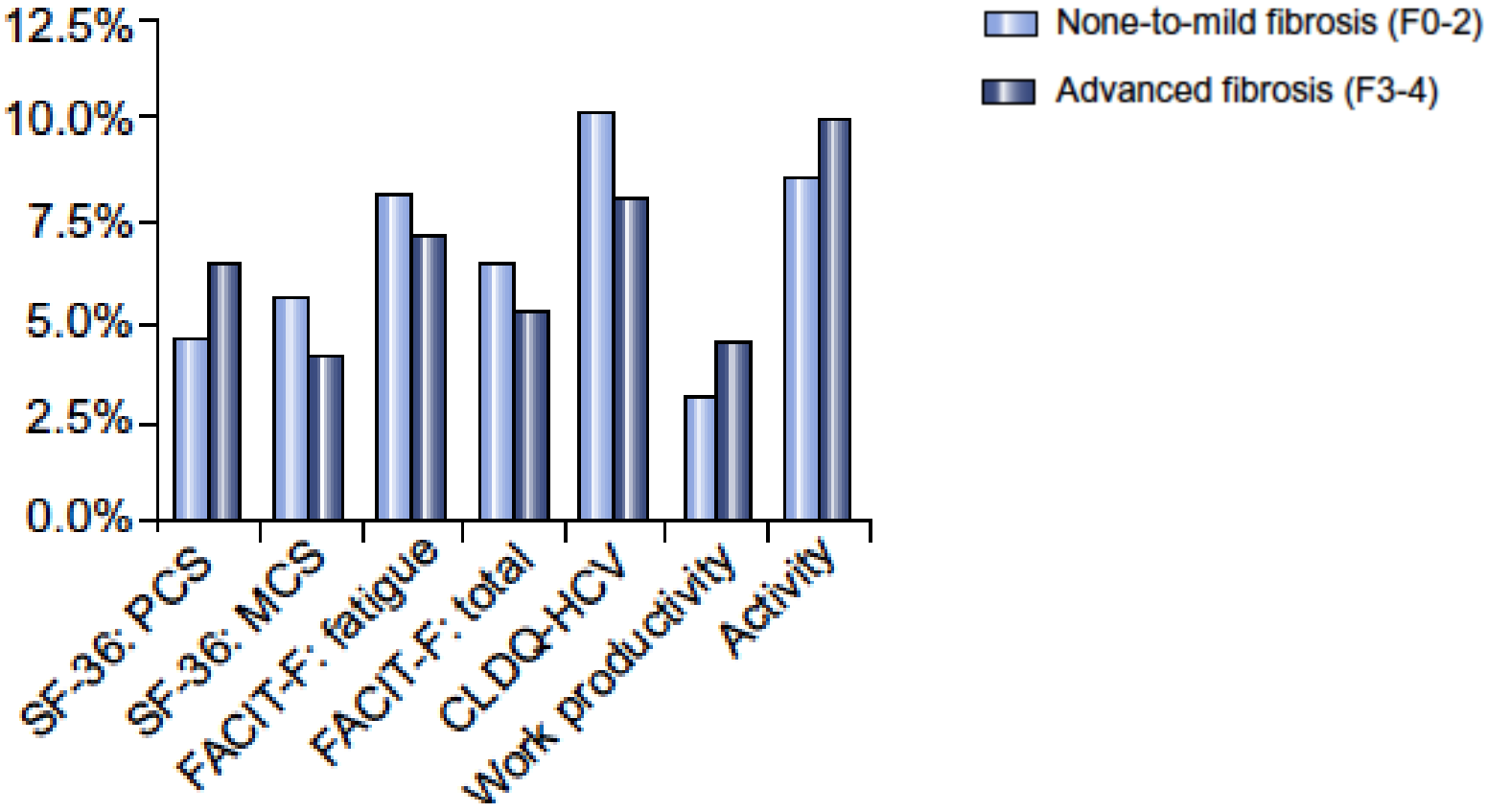
EOT 0,5y 1y 3 to 5y >6y

Maylin et al. Gastroenterology. 2008 Sep;135(3):821-9.

DAAs improve quality of life during the treatment

ION 1, 2 and 3 studies

Improvements at SVR12 LDV/SOF



Improvements even during the course of DAAs treatment.

Younossi et al. 2015 J Hepatol. Aug;63(2):337-45.

Conclusions

- HCV has no cellular reservoir.
- HCV develops several mechanisms to counteract the immune response.
- In treatment induced HCV clearance there is no protection against reinfection.
- Drugs users and HCV/HIV co-infected had higher risks for reinfection.
- SVR is associated with reduction of mortality risks and HCC.
- Risk of HCC remains important in cirrhotic patients after SVR.
- Studies on benefits after SVR induced by DAAs combinations, will be needed.