¿Qué aporta el laboratorio a la terapia del VHC en 2015?

Eva Poveda

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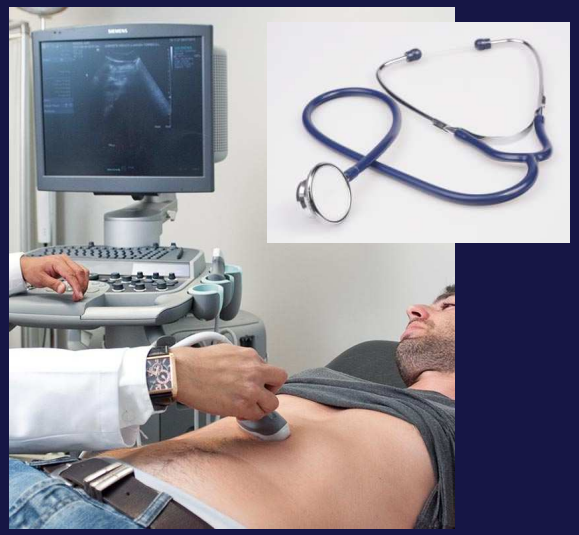
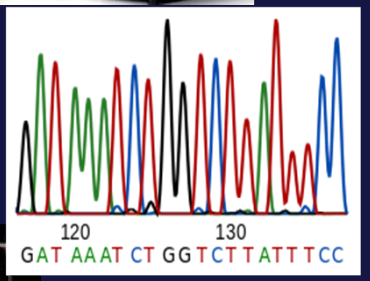
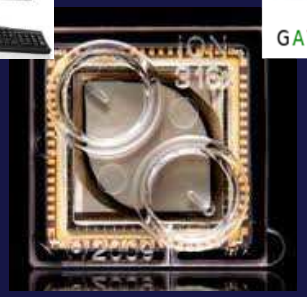
INIBIC-Complexo Hospitalario Universitario de A Coruña

HCV Medicine in 2015







Liver function & fibrosis

Molecular Tests

Molecular Diagnosis Tools in the Management of HCV infection

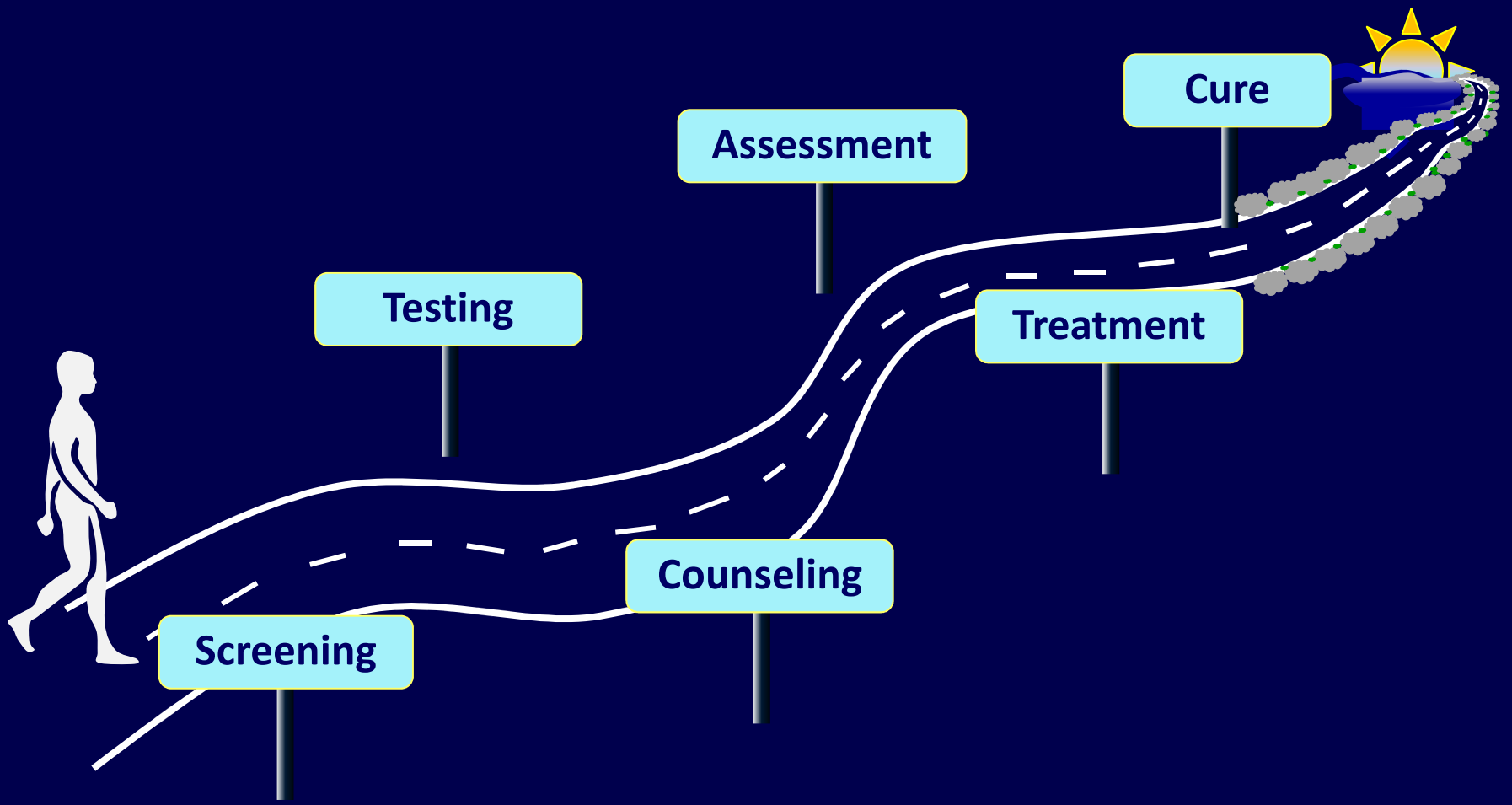
- HCV Diagnosis
- Design & Optimization of HCV therapies
- Monitoring HCV treatment response

New Era for the treatment of HCV infection:

With the advent of new therapeutics options for HCV treatment with minimal side effects, shortened courses of therapy and cure rates > 90 %

… new challenges come to advance towards HCV eradication

HCV Screening Is the First Step on the Road to a Cure



Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 61 / No. 4
August 17, 2012

Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965

Limited effectiveness of current testing strategies

- Of the estimated 2.7-3.9 million persons living with HCV infection in the United States, 45%-85% are unaware of their infection status and do not receive care.

- Barriers to testing include inadequate health insurance coverage and limited access to regular health.

- 41,7 % of primary care physicians reported being unfamiliar with the guidelines on HCV testing from the American Association for the study of Liver Disease (AASLD).

Seroprevalence of HCV and HIV Infections by Year of Birth in Spain: Impact of US CDC and USPSTF Recommendations for HCV and HIV Testing

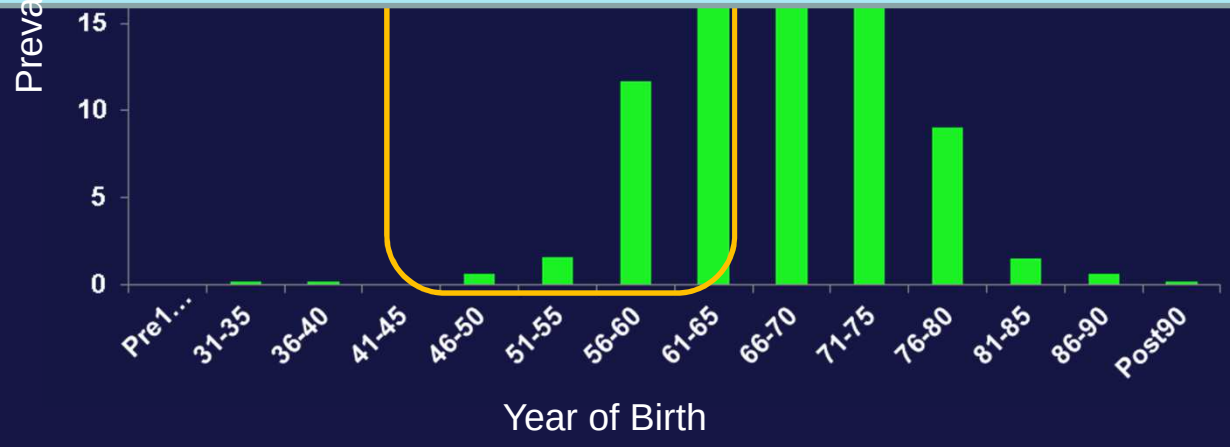
PLOS ONE | December 1, 2014

Alvaro Mena[1*], Luz Moldes[2], Héctor Meijide[1,3], Angelina Cañizares[2], Ángeles Castro-Iglesias[1], Manuel Delgado[1,4], Sonia Pértega[5], José Pedreira[1], Germán Bou[2], Eva Poveda[1]

- 108,159 anti-HCV-Ab results between 2008-2012.
- Prevalence of anti-HCV-Ab+ by year of birth

Conclusions:

- **The recomendations made by the US CDC of HCV testing (1945-1965) are not aplicable to our population.**
- **In Spain, once in a lifetime HCV testing might be especially considered in persons aged 38-58.**



Promote HCV Diagnosis & Link to Clinical Expert

There is a need to promote HCV screening strategies and improve the link between HCV diagnosis & subspecialty care. Undiagnosed persons cannot take advantage of the great advances in treatment.

- Project: Screening for HCV infection in Northem Spain – Towards HCV Eradication.
  Division of Clinical Virology, INIBIC-XXIAC & Public Health Department of Galicia

Objectives:

- To unmask HCV infection in our population promoting HCV screening (OraQuick®HCV test) in centers of *primary care* in *A Coruña*.

- To identify *epidemiological, clinical and virological characteristics* of HCV-infected patients who unaware they are infected

- To develop an *educational program* of training lectures for primary care physicians (update last date regard HCV diagnosis and new HCV therapies).

Target population: persons born between 1960-1969 (n=3,000) (*Mena et al, Plos One 2014).*

Factors Influencing the Clinical Responses to Anti-HCV Therapies

Virological	Host
HCV genotypes/subtypes	IL-28 B (CC vs. CT/TT)
HCV Viral load	Fibrosis
Genetic polymorphisms	PegIFN/RBV exposure
Resistance	Age
HIV-coinfection	Gender

Monitoring HCV Treatment Responses

- HCV Viral Load
- HCV Genotypes/subtypes
- Host genetics
- HCV polymorphisms/resistance

- To Whom…
- When…
- How…

HCV Viral Load

- To whom: patients undergo antiviral therapy.

- When: At different time points to monitor treatment efficacy and eventually guide decisions on treatment duration:

  - patient adherence to therapy (week 2 determination).

  - treatment should be abandoned (futility rules).

  - treatment can be abbreviated (response guided therapy -RGT).

  - treatment has been succesful (end of treatment & post-treatment SVR)

Monitoring of Treatment Efficacy, RGT & Stopping Rules

Regimen	HCV RNA quantification	Recommendation
SMV+PR	Baseline, weeks 4, 12, 24 or 48 (end of treatment) & 12 and/or 24 after end of treatment.	Treatment should be stopped if HCV-RNA ≥ 25 IU/mL at 4, 12 or 24 ARN-VHC
DCV+PR	Baseline, week 4, 10, 24 (end of treatment) & 12 or 24 after the end of treatment	Patients who achieve an HCV RNA < 25 UI/mL at week 4 & and <15 IU/mL at week 10 should stop daclatasvir at week 12 and continue with PR alone until week 24.
SOF+PR	Baseline, week 4, 12 or 24 (end of treatment)	There is no RGT/Futility rules
SOF + DCV	Baseline, week 2 (check adherence), 4, 12 or 24 (end of treatment) & 12 or 24 after the end of treatment.	There is no RGT/Futility rules

Recommendations:

- A RT-PCR assay with a ***LLOD of < 15IU/mL*** should be used to monitor HCV RNA levels.
- Futility Rules have been defined only with **SMV+PR**.
- RGT is used only for **DCV+PR**.

Quantitative Real-Time PCR-based RNA assays

Assay (*manufacter*)	Technology (target region)	Dynamic Range (UI/mL)	LLOQ (IU/mL)	LLOD (IU/mL)	IVD Approval Status
COBAS Ampliprep/COBAS Taqman v2.0 Test (*Roche Molecular Systems*)	RT-PCR (5' UTR)	15-1x10^8	15	15	FDA, CE
COBAS Taqman for use with the High Pure System Test, v2.0 (*Roche Molecular Systems*)	RT-PCR (5' UTR)	25x3,91x10^8	25	20	FDA, CE
Abbott Real Time HCV Test (*Abbott RealTime HCV Test*)	RT-PCR (5' UTR)	12-1x10^8	12	12	FDA, CE
VERSANT™ HCV-RNA Test V1.0 (kPCR) (*Siemens*)	RT- PCR (5' UTR)	15-1x10^8	15	15	CE
Quiagen Hepatitis C Test (QS-RGQ)	RT-PCR (target propietary)	65-1x10^6	35	21	CE

HCV Genotypes/subtypes

- To whom: All patients with chronic HCV infection.
- When: HCV genotype and genotype 1 subtype (1a/1b) must be assessed prior to treatment initiation and will determine the choice of therapy:

	AASLD (January 2015)	EASL (April 2014)
G1a	SOF+LPV SOF+SMV PTV/r+OBV+DAS	SOF+Peg/RBV (O.1) SMV+Peg/RBV (O.2) DCV+Peg/RBV(O.3) SOF+RBV 24w(O.4) SOF+SMV(O.5) SOF+DCV (O.6)
G1b	SOF+LPV SOF+SMV PTV/r+OBV+DAS	
G2	SOF/RBV 12w	SOF/RBV 12w
G3	SOF/RBV 24w	SOF/Peg/RBV 12w (O.1) SOF/RBV 24w (O.2)
G4	SOF/LPV PTV/r+OBV+DAS SOF/RBV 24w	SOF+Peg/RBV (O.1) SMV+Peg/RBV (O.2) DCV+Peg/RBV(O.3) SOF+RBV 24w(O.4) SOF+SMV(O.5) SOF+DCV (O.6)
G5 **G6**	Peg/RBV/SOF 12w SOF+LPV 12 w	Peg/RBV/SOF 12w

HCV Genotyping Assays

Assay (*manufacter*)	Technology (target region)	Genotypes/ subtypes detected	LLOD (Volume)	IVD Approval Status
INNO-LiPA HCV II Genotype Test (Siemens)	RT-PCR & Line probe assay (5'UTR & Core)	1a, 1b, 2a, 2b, 2c, 3a, 4, 5, & 6	2000 IU/mL (0.5-1mL)	CE
Abbott HCV Genotype Test	RT-PCR (5' UTR & NS5B)	1a, 1b, 2, 3, 4, 5, & 6	500 IU/mL (0.5mL)	FDA, CE
Linear Array HCV Genotyping Test for use with COBAS AMPLICOR HCV Tests, v2.0	RT-PCR & Line probe assay (5' UTR)	1-6	500 IU/mL 0.2mL	CE

Host Genetics (*IL28B*)

- IL28B genotyping has lost predictive value with the new *highly efficacious IFN-free treatment regimens*.

- To whom: Only in settings where only PR can be used or to select cost-effective treatment options in settings with economical restrictions.

- When: Prior to treatment initiation.

- How: RT-PCR Allelic Discrimination Assays analysis on DNA using fluorescent probes specific for the C and T alleles of the SNP (rs12979860, chromosome 19q13).
  The SNP genotype CC, CT, or TT is reported.

HCV Polymorphims/resistance

■ Natural changes at different positions at the NS3 protease, NS5B polymerase, and NS5A protein have been associated with loss of susceptibility to DAAs.

Table 3
Prevalence of key polymorphisms at NS3/4A, NS5B polymerase and NS5A protein sequences associated with resistance to DAA agents.

Drug family	Mutation	Fold-change in EC50	1a	1b	2	3	4	DAA agents potentially affected by specific polymorphisms
NS3/4A protease inhibitors	Q80K	10.9	19–48%	0	0	0	0	Simeprevir WHO (2013) Asunaprevir European Association for the Study of the Liver (2011) Sovaprevir WHO (2013)
	D168Q	>700	0	0	0	99.2%	0	Second PI generation McHutchison et al. (2009)
NS5B non-nucleoside analogs inhibitors	C316N	>30*		13.3%				Setrobuvir Pawlotsky et al. (2007) (NNI-site 3 inhibitors) ABT-072 Pawlotsky et al. (2007) (NNI-site 3 inhibitors) ABT-333Pawlotsky et al. (2007) (NNI-site 3 inhibitors)
	L419V	<4			13%			Filibuvir Soriano et al. (2011) (NNI-site 2 inhibitors) VX-222 Poordad et al. (2011) (NNI-site 2 inhibitors) GS-9669 Poordad et al. (2011) (NNI-site 2 inhibitors)
NS5A inhibitors	L31M	3–341		7%				Daclatasvir Bacon et al. (2011) Ledipasvir Jacobson et al. (2011)
	Y93H	5.4–24		6–12.5%				Daclatasvir Bacon et al. (2011) Ledipasvir Jacobson et al. (2011)

Poveda E et al. Antivir Res 2014

Impact of Q80K in HCV G1a infected patients

- To whom: All patients with HCV genotype 1a when therapy with simeprevir is considered.

- OLYSIO (Simeprevir)-Indications and usage

La eficacia de simeprevir en combinación con peginterferón alfa y ribavirina se reduce sustancialmente en los pacientes infectados con hepatitis C genotipo 1a que presentan polimorfismo basal Q80K en NS3 en comparación con los pacientes con hepatitis C genotipo 1a sin polimorfismo Q80K en NS3 (ver sección 5.1). Es altamente recomendable realizar el test de detección de la presencia del polimorfismo Q80K en los pacientes con VHC genotipo 1a cuando se valore iniciar un tratamiento con OLYSIO en combinación con peginterferón alfa y ribavirina. Se debe considerar una terapia alternativa en los pacientes infectados con el VHC genotipo 1a con polimorfismo Q80K o en los casos donde el test no esté accesible.

- HCV Treatment Guidelines

This combination is not recommended in patients

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Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection.

9th, January 2015

baseline Q80K testing for all HCV genotype 1a–infected patients prior to the use of simeprevir with PEG-IFN and RBV. In contrast, the presence of the Q80K polymorphism does not preclude treatment with simeprevir and sofosbuvir, because the SVR rate was high in patients with HCV genotype 1a and the Q80K polymorphism (88%; 51/58). (Lawitz, 2014b) Given the low but finite failure

Rating

Review

Update on hepatitis C virus resistance to direct-acting antiviral agents ☆

Eva Poveda [a,*], David L. Wyles [b], Álvaro Mena [a], José D. Pedreira [a], Ángeles Castro-Iglesias [a], Edward Cachay [b]

[a] Grupo de Virología Clínica, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, Spain
[b] Department of Medicine, Owen Clinic and Division of Infectious Diseases, UC San Diego, USA

Table 2
Main characteristics of the genotype activity and resistance of DAA classes.

	Genotype activity	Cross-resistance	Key resistance mutations
NS3 protease inhibitors	First PI generation: genotypes 1 (1b > 1a) Second PI generation: across all but genotype 3 (D168Q) Pawlotsky (2013)	High	First PI generation WHO (2013), European Association for the Study of the Liver (2011), McHutchison et al. (2009), Pawlotsky et al. (2007), Soriano et al. (2011), Poordad et al. (2011), Bacon et al. (2011), Jacobson et al. (2011) and Zeuzem et al. (2011): G1a: R155K, V36M G1b: V36M, T54A/S, A156T Second wave and second PI generation Pawlotsky (2013), Asselah and Marcelin (2013) and Neumann et al. (1998): F43S, Q80K, R155K, D168A/E/H/T/V
NS5 nucleos(ti)de analogs inhibitors	Across all genotypes Sofosbuvir displays less antiviral activity againts genotypes 3 and requires 24 weeks of sofosbuvir + RBV therapy Kieffer et al. (2012) and Kuntzen et al. (2008)	High	Sofosbuvir* Martell et al. (1992): G1a: S282T+(I434M) G1b: S282T G2a: S282T+(T179A, M289L, I293L, M434T, and H479P) Mericitabine* Soriano et al. (2008) and Soriano et al. (2011): S282T+(K81R,S84S/P, I239L, A300F/L/C, A421V, and Y586C)
NS5B non-nucleoside analogs inhibitors	Genotypes 1 (1b > 1a)	Low Overlapping resistance profile for NNI-site 3 and NNI-site 5 inhibitors (C316Y/N and Y448H)	NNI-site 1 Kieffer et al. (2010): A421V, P495L/S, V499A NNI-site 2 Vermehren and Sarrazin (2012) and WHO (2013): L419S, R422K, M423I/L/T NNI-site 3 Kieffer et al. (2012): C316Y/NS368T, Y448C/H, S556G NNI-site 5 Barnard et al. (2012): C316Y/N, Y448C/H
NS5A inhibitors	Across all genotypes (1b > 1a)	High	G1a Ogert et al. (2013) and Osinusi et al. (2013): M28T, Q30E/R, L31F/M/V, Y93C/H/N G1b Ogert et al. (2013) and Osinusi et al. (2013): L31F/M/V, Y93C/H/N

HCV resistance prior to retreatment after failure

■ To whom: Testing for RAVs before repeat antiviral treatment is not routinely recommended. The presence of RAVs does not preclude achieving and SVR with a combination of DAAs. Subsequent retreatment with SOF (high genetic barrier for resistance) may overcome the presence of resistance to 1 or more antivirals.

Failing regimen	Retreatment regimen
TVR/BOC+PR SMV+PR	SOF+DCV SOF+LPV
SOF+PR	SOF+SMV SOF+DCV SOF+LPV
SOF+SMV	SOF+DCV SOF+LPV
SOF+DCV SOF+LPV	SOF+SMV
SOF, SMV, DCV, LPV	Wait new treatment combinations

Summary (2015)

Prior to Starting	During&End	Lack of efficacy
HCV Genotype/subtype	Just in case of reinfection	
HCV RNA Quantification	Week 4, 12, end of treatment and 12 or 24 after the end If HCV-RNA is < 15IU/mL at the end and 12/24 week after the patient is cured.	If HCV-RNA is detectable at w4, 12, or 24 stop SMV+PR If HCV-RNA is detectable at w4, repeat at w6, if HCV-RNA >1log IU/mL, discontinuation is recommended. If HCV-RNA is detectable at w4 if HCV-RNA remain positive at w6 or w8, but lower, there is no recommendation to stop or extend therapy at this time.
IL28B		
Q80K polymorphism if SMV+PR is considered		
RAVs not preclude SVR in DAA combinations	Not Recommended	Not Recommended

In the Future…

- The approval of *pan-genotypic DAA combinations* with equally efficacy against all genotypes will be able to treat without the need to identify genotypes.

- With the new *IFN free DAA therapies,* viral kinetics likely are no longer predictive of the virologic outcome, therefore viral load quantification as a tool for response guided therapy is going to disappear.

- *HCV viral load quantification* will be still *necesary at the end of treatment and 12 weeks later* (if negative the patient has achieved SVR and is cured).

- With rates of cure up to 95%, *no room for HCV resistance tests*.

- Identification of *molecular markers* (i.e. PNPLA-3) to follow-up those patients who eliminate the virus to evaluate the risk for the development or liver-related diseases (i.e. fibrosis, hepatocarcinoma).