Utility of Virological Assays at the DAA Era

Prof. Jean-Michel Pawlotsky, MD, PhD

National Reference Center for Viral Hepatitis B, C and delta
Department of Virology & INSERM U955

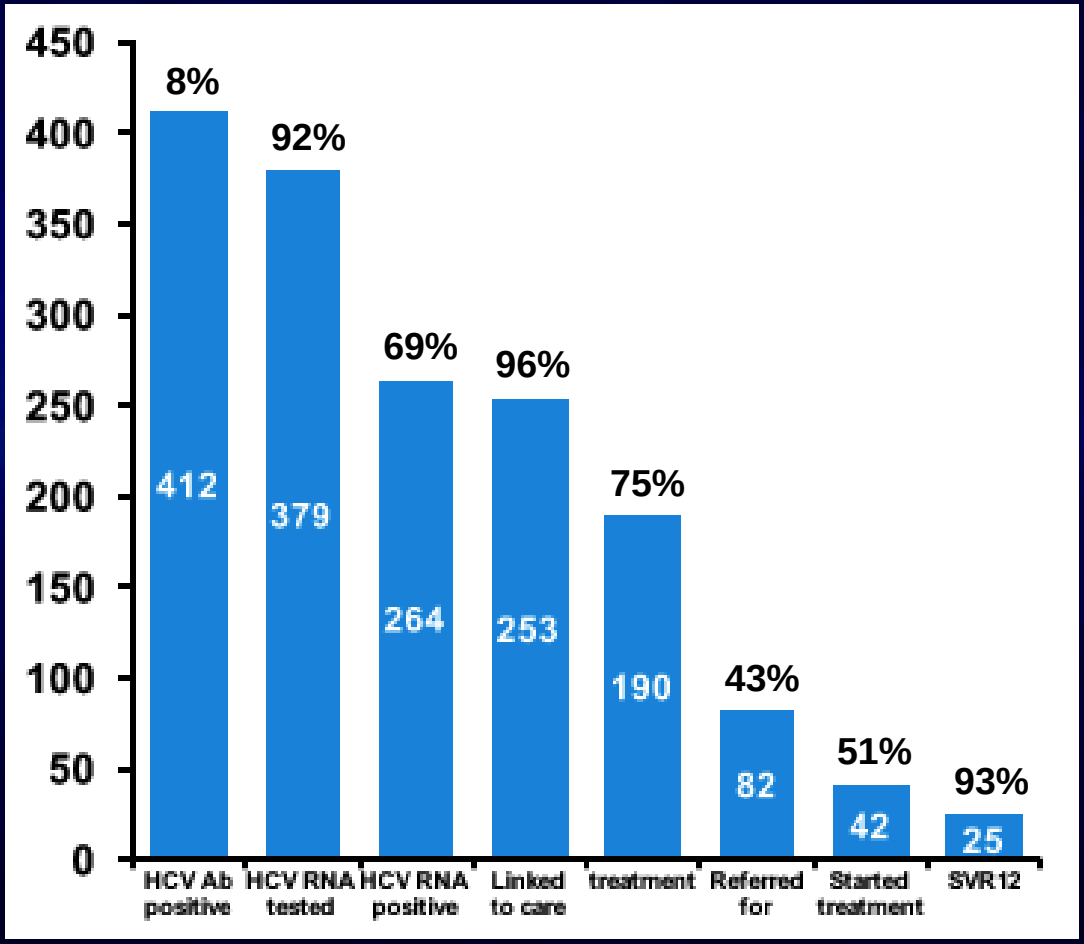
Henri Mondor Hospital
University of Paris-Est
Créteil, France

Conflict of Interest Disclosure

- I have received research grants from Gilead and Abbvie
- I have served as an advisor for Abbvie, Bristol-Myers Squibb, Gilead, Janssen and Merck

Cascade of Care for 5239 Baby Boomers Screened for HCV Ab 2012-2014

Grady Memorial Hospital, Atlanta



(Miller et al., AASLD 2016)

Screening

EASL Recommendations 2016

- Screening for HCV infection is presently based on the detection of **anti-HCV antibodies**
- **Rapid diagnostic tests (RDTs)** using serum, plasma, fingerstick whole blood or crevicular fluid (saliva) as matrices can be used instead of classical enzyme immunoassays to facilitate anti-HCV antibody screening and improve access to care
- Whole blood sampled on **dried blood spots** can be used as an alternative to serum or plasma obtained by venipuncture

(EASL Recommendations on Treatment of Hepatitis C 2016)

Principle of an RDT

Example of the Oraquick Test

HCV Antibody RDTs

Assay	Manufacturer	Specimen	Volume	Duration
Oraquick® HCV	*Orasure*	Serum, plasma Whole blood Oral fluid	20-40 µL	20-40 min
Toyo® HCV	*Turklab*	Serum, plasma Whole blood	10-30 µL	5-15 min
Labmen® HCV	*Turklab*	Serum, plasma Whole blood	10 µL	15 min
Multisure HCV	*MP Biomedicals*	Serum, plasma Whole blood	25 µL	15 min
Assure® HCV Rapid Test	*MP Biomedicals*	Serum, plasma Whole blood	5-50 µL	15 min
Signal HCV v2.0	*Span Diagnostics*	Serum, plasma	100 µL	10 min
First Response HCV Card Test	*Premier Medical Corp. Ltd.*	Serum, plasma Whole blood	35 µL	20-30 min
SD Bioline HCV	*Standard Diagnostics*	Serum, plasma Whole blood	10 µL	5-20 min

Performance of HCV Antibody RDTs
Fingerstick whole blood

318 HCV-positive, 171 HCV-negative

	Specificity	Sensitivity	PPV	NPV
OraQuick® HCV Rapid Ab Test	100%	99.4%	100%	98.4%
TOYO® anti-HCV test	98.2%	96.2%	99.0%	93.1%
Labmen® HCV test	100%	62.7%	100%	49.6%

(Chevaliez et al., Clin Microbiol Infect 2016;22:459.e1-6)

Performance of HCV Antibody RDTs

Crevicular fluid (Oraquick test)

318 HCV-positive, 171 HCV-negative

	Specificity	Sensitivity	PPV	NPV
OraQuick® HCV Rapid Ab Test	**100%**	**98.2%**	**100%**	**96.6%**

(Chevaliez et al., Clin Microbiol Infect 2016;22:459.e1-6)

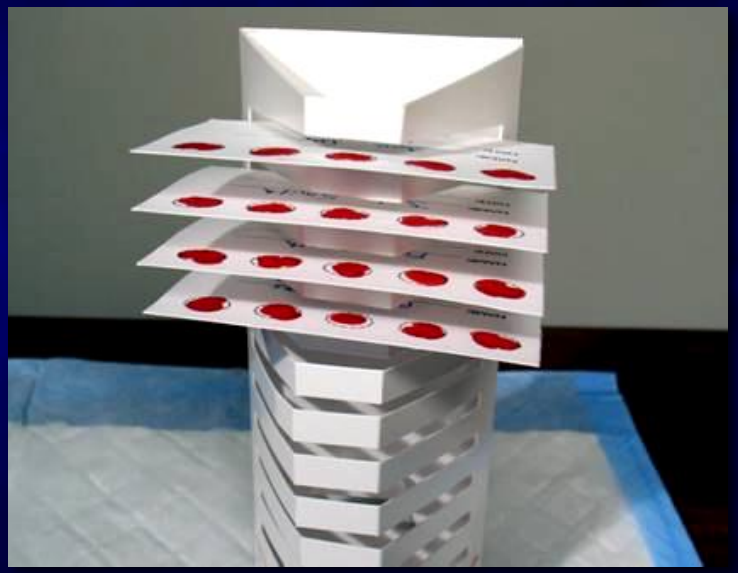
Performance of HCV RDTs
Meta-analysis 2012

- **>13,000 individuals included in 18 studies between 1994 and 2001**
  - **Whole blood (venous and capillary): 4,259 specimens**
  - **Saliva: 3,994 specimens**

Specimen	Specificity	Sensitivity
Whole blood	**99.5%**	**98.9%**
Saliva	**98.2%**	**97.1%**

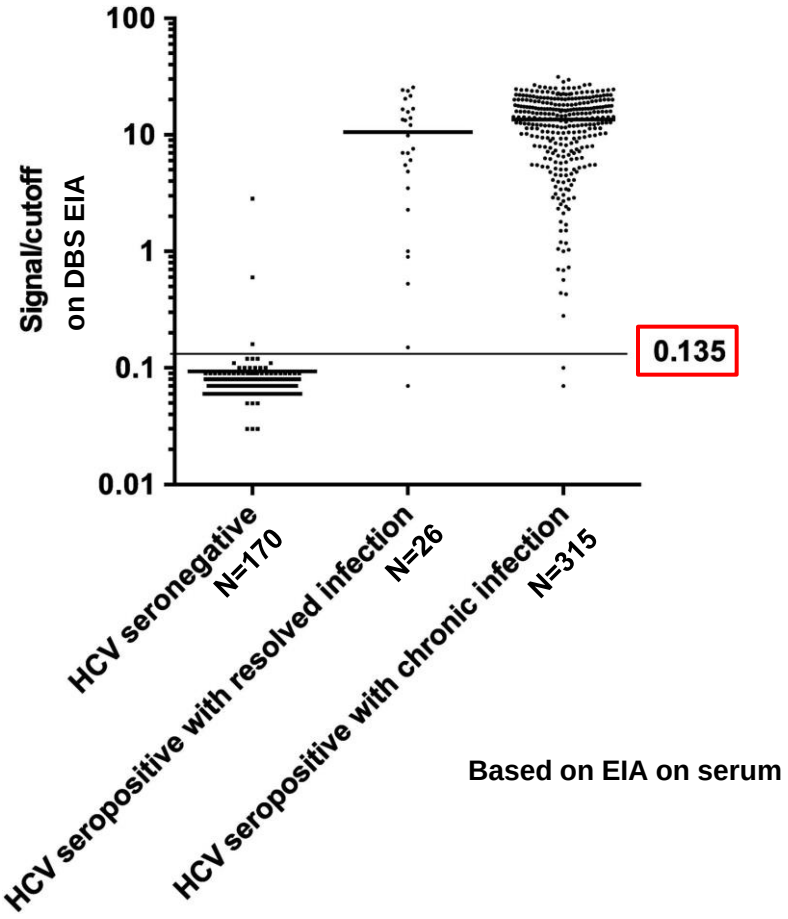
(Shivkumar et al., Ann Intern Med 2012;157:558-66)

Dried Blood Spots



HCV Antibodies by 3rd-Gen EIA in DBS

Sensitivity = 99.1%
Specificity = 98.2%



(Soulier et al., J Infect Dis 2016;213:1087-95)

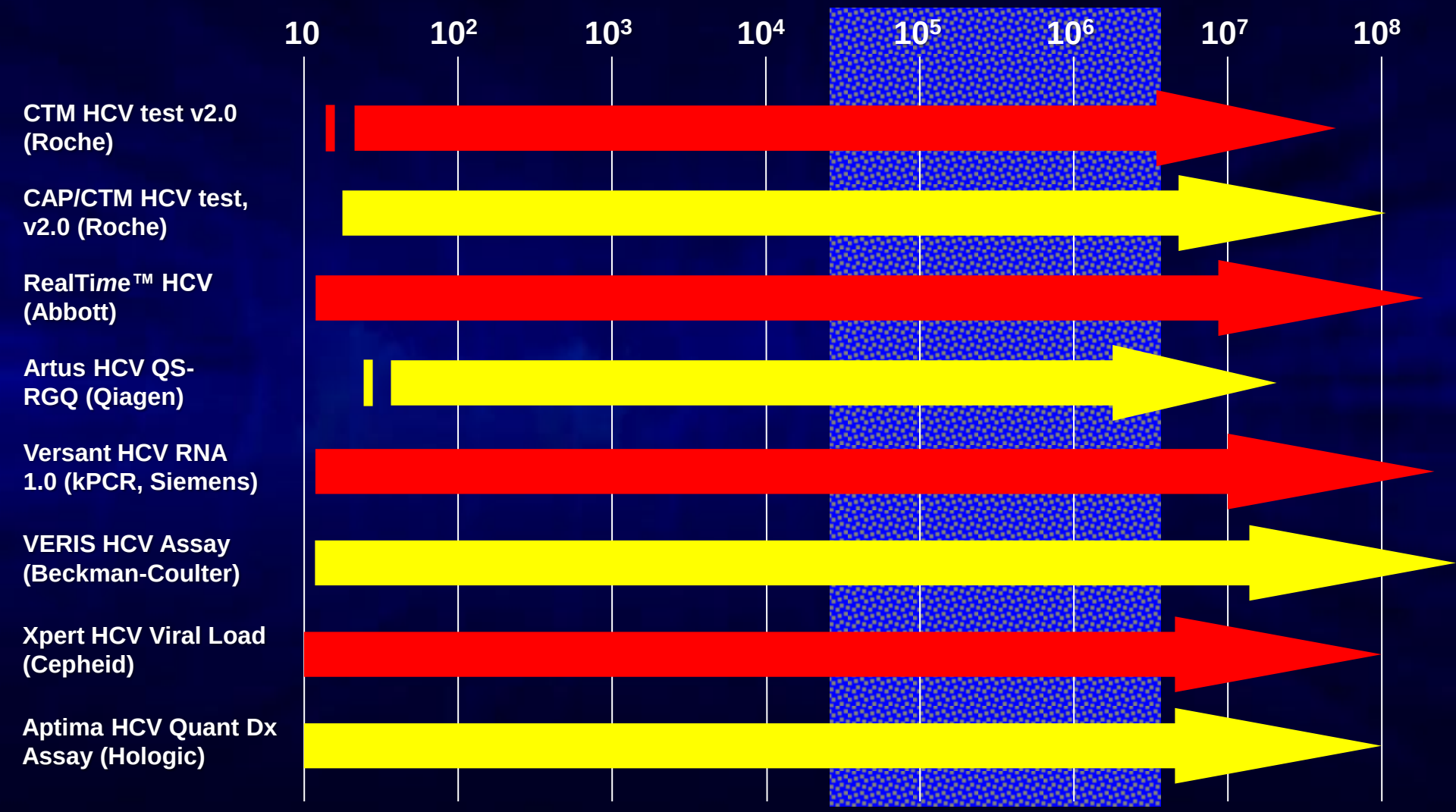
Confirmation of Diagnosis and Decision to Treat

EASL Recommendations 2016

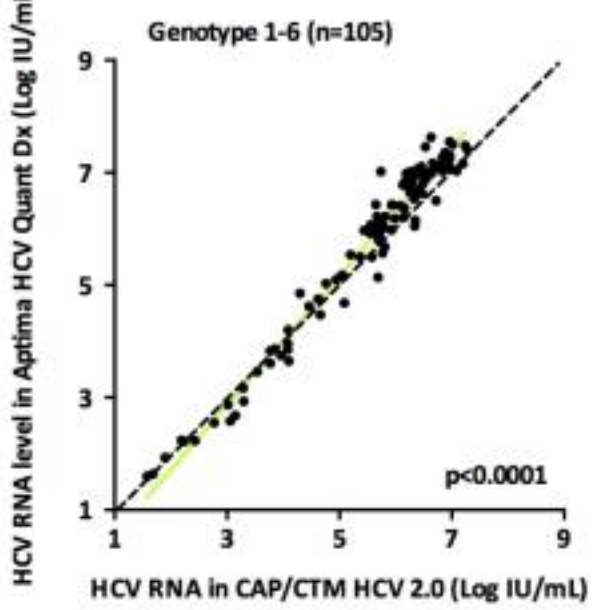
- If anti-HCV antibodies are detected, **HCV RNA** should be determined by a sensitive molecular method
- **HCV RNA detection and quantification** should be made by a sensitive assay with a lower limit of detection of ≤15 IU/mL
- If HCV RNA testing is not available or not affordable, **HCV core antigen detection and quantification** by EIA can be used as a surrogate marker of HCV replication
- The **HCV genotype and genotype 1 subtype** (1a or 1b) must be assessed prior to treatment initiation and will determine the choice of therapy, among other parameters

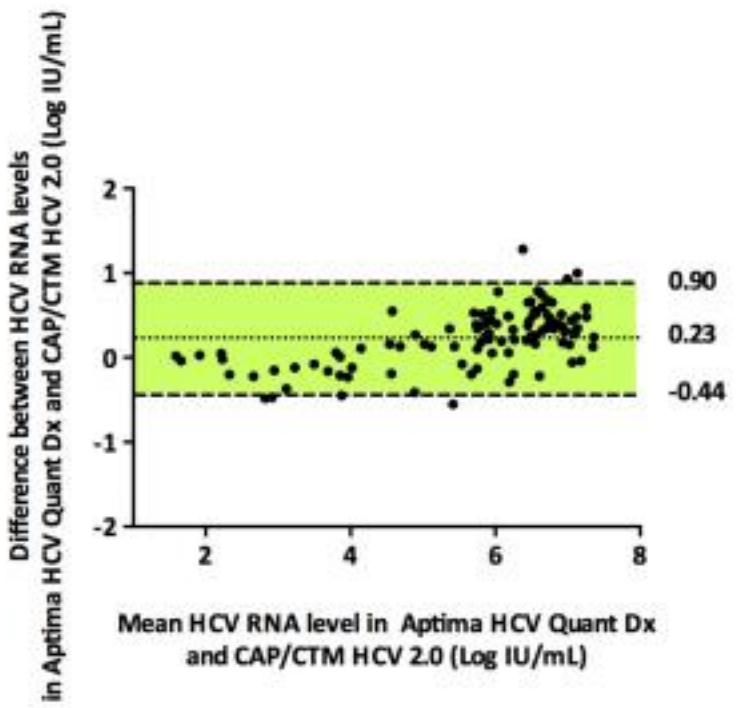
(EASL Recommendations on Treatment of Hepatitis C 2016)

HCV RNA Assays (rtPCR or TMA)



Aptima Real-Time TMA Assay (Hologic)

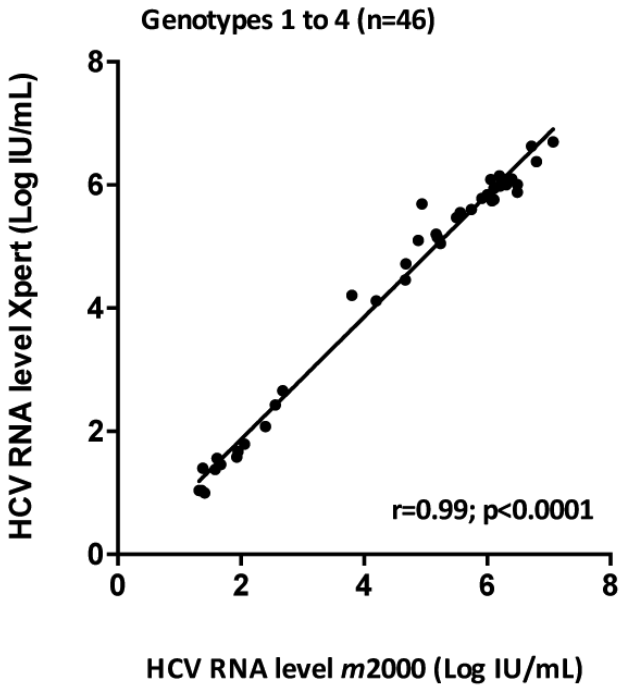




(Chevaliez et al., J Clin Virol 2017;91:5-11)

Xpert HCV Viral Load (Cepheid)

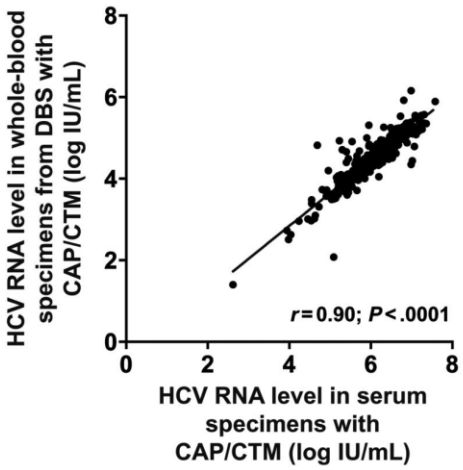
Point-of-care HCV RNA test

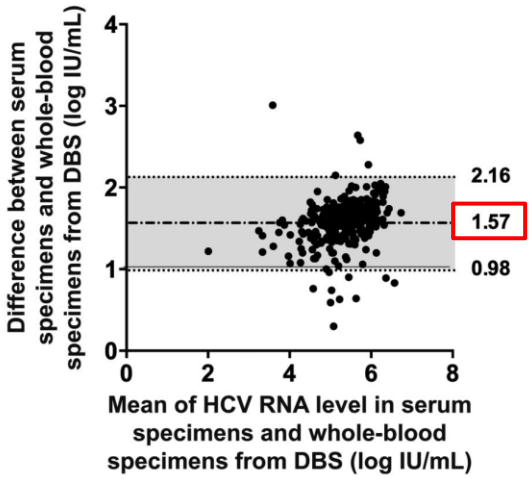


(Chevaliez S, Pawlotsky JM, unpublished data)

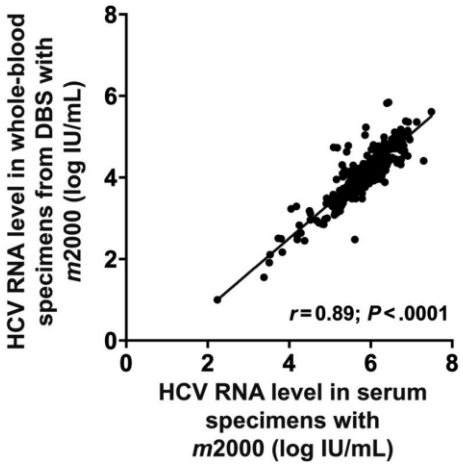
HCV RNA from DBS

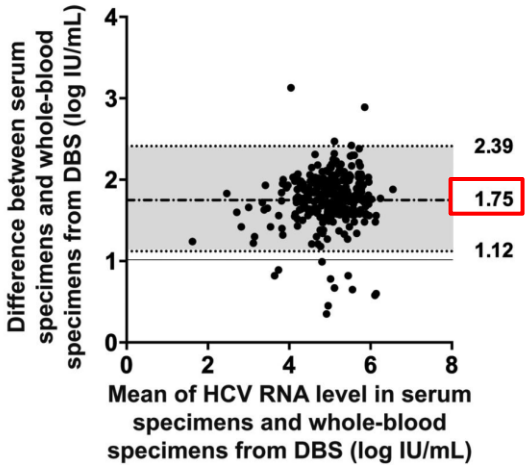
CAP/CTM (Roche)





***m*2000 (Abbott)**

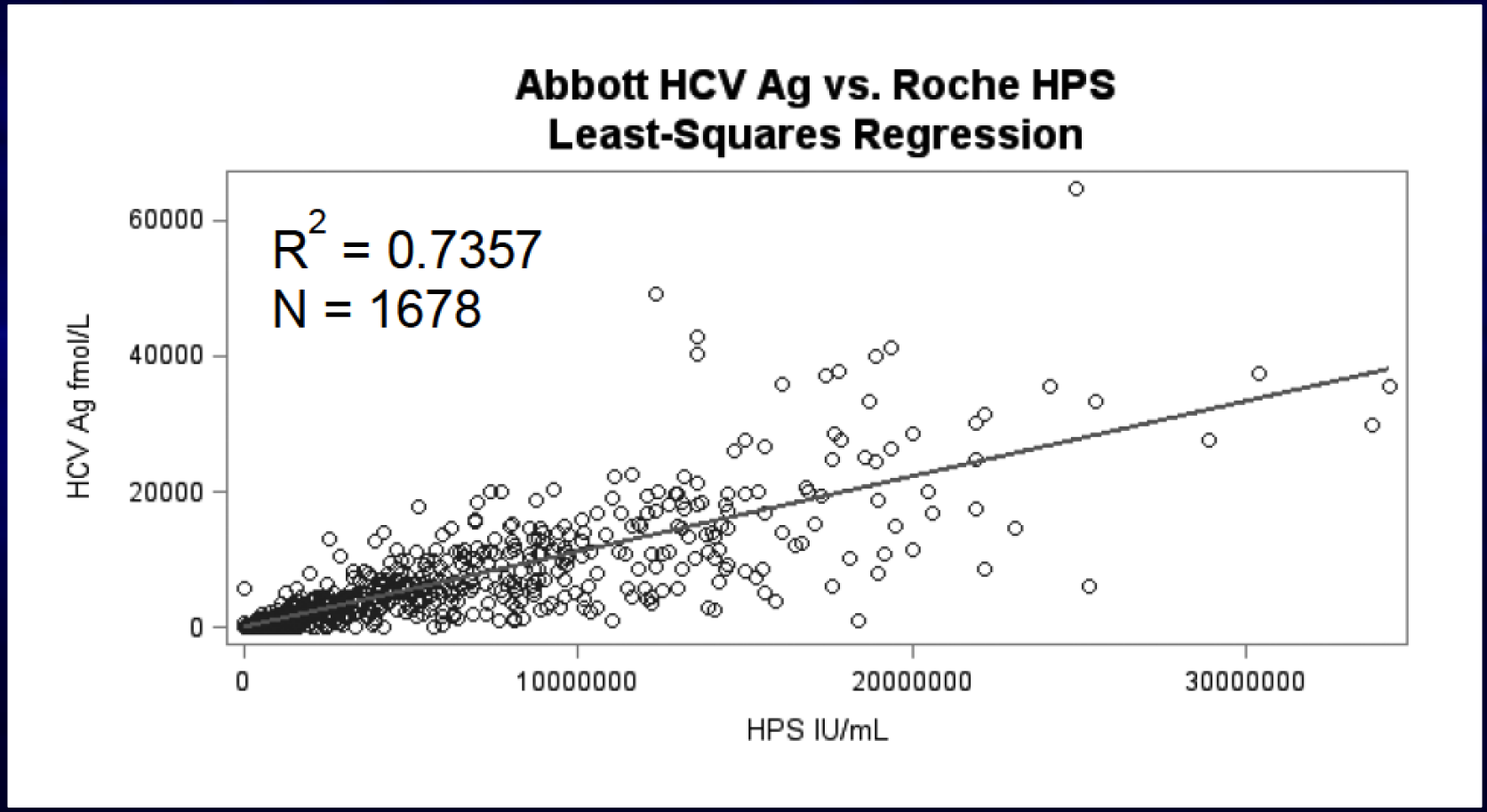




(Soulier et al., J Infect Dis 2016;213:1087-95)

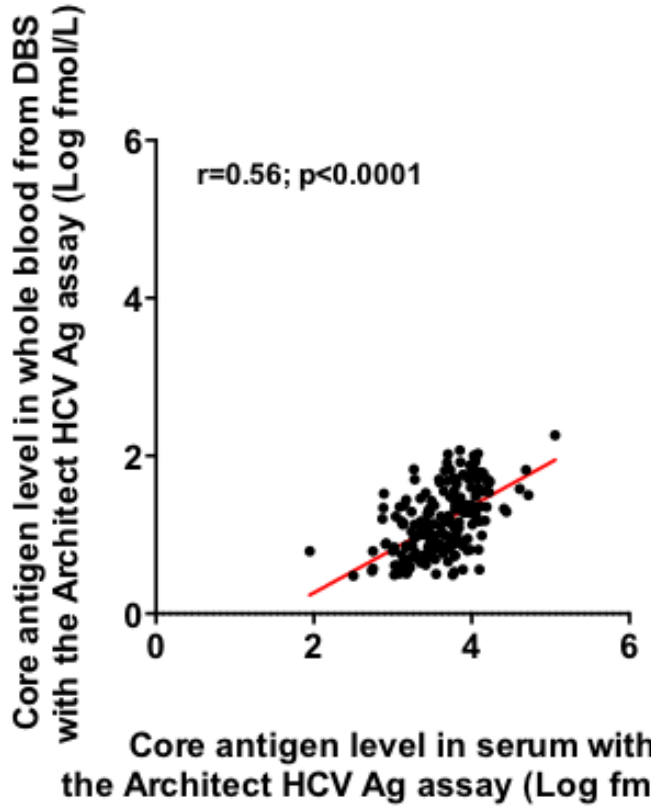
Baseline and On-Treatment HCV Core Ag *vs* HCV RNA in SAPPHIRE-I trial

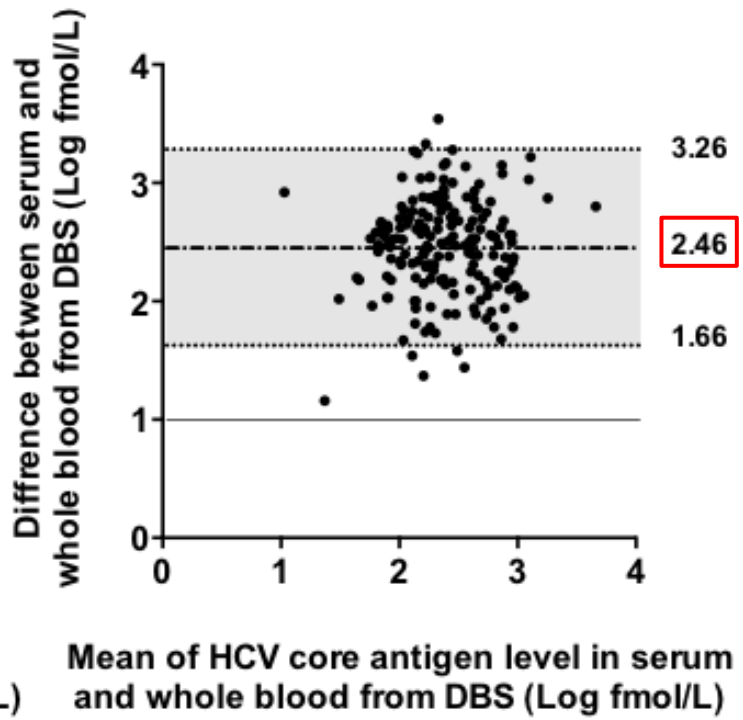
Baseline and on-treatment samples



(Chevaliez et al., Antivir Ther 2016; epub ahead of print)

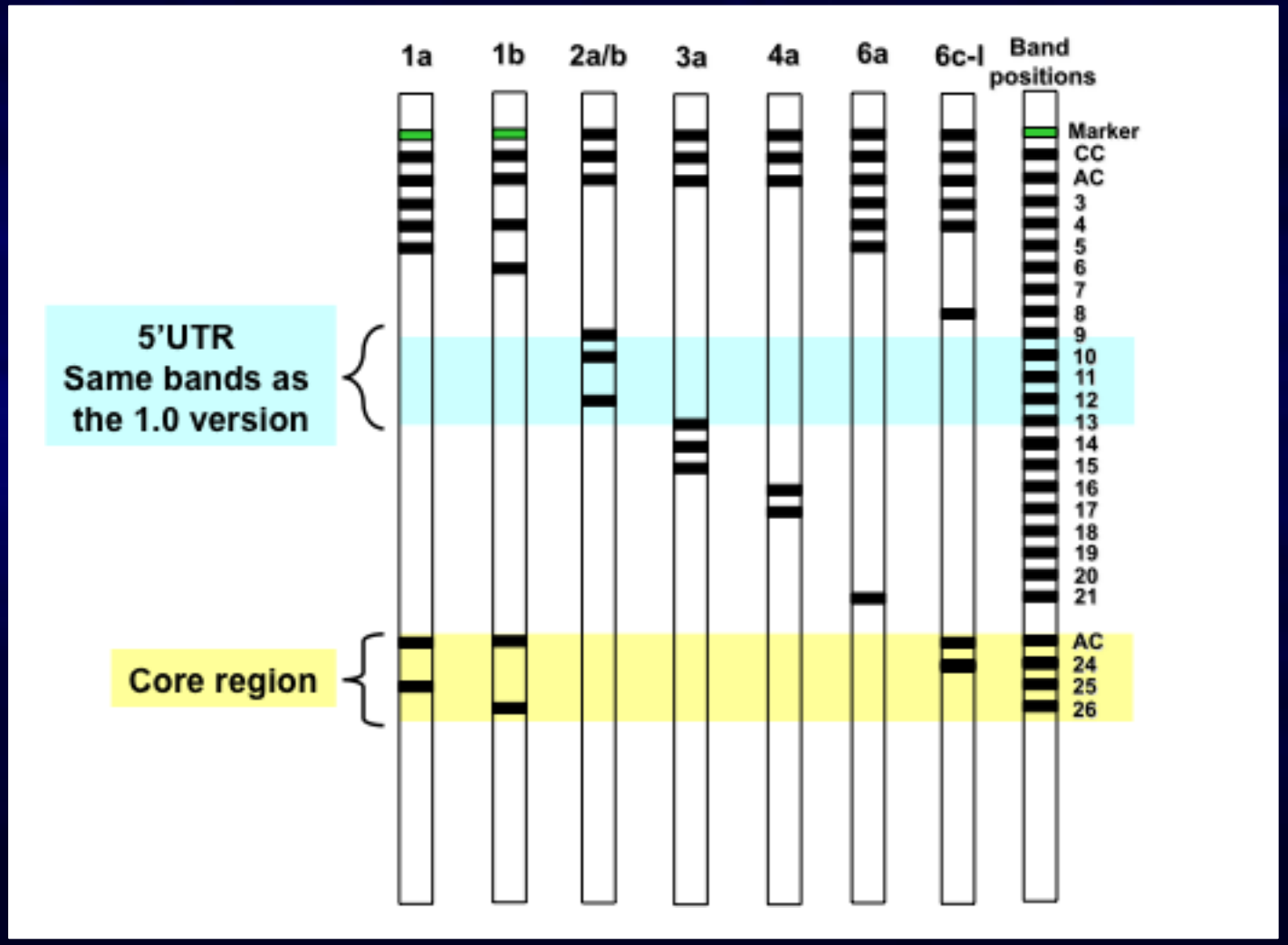
HCV Core Antigen from DBS





(Soulier et al., J Infect Dis 2016;213:1087-95)

Versant® HCV Genotype 2.0 Assay (INNO-LiPA)



HCV Genotype from DBS

- HCV genotype determination from DBS (N=263)
  - 100% concordance at the genotype level
  - Subtyping failed in 16 cases and was erroneous in one case

(Soulier et al., J Infect Dis 2016;213:1087-95)

HCV resistance testing prior to first-line therapy

EASL Recommendations 2016

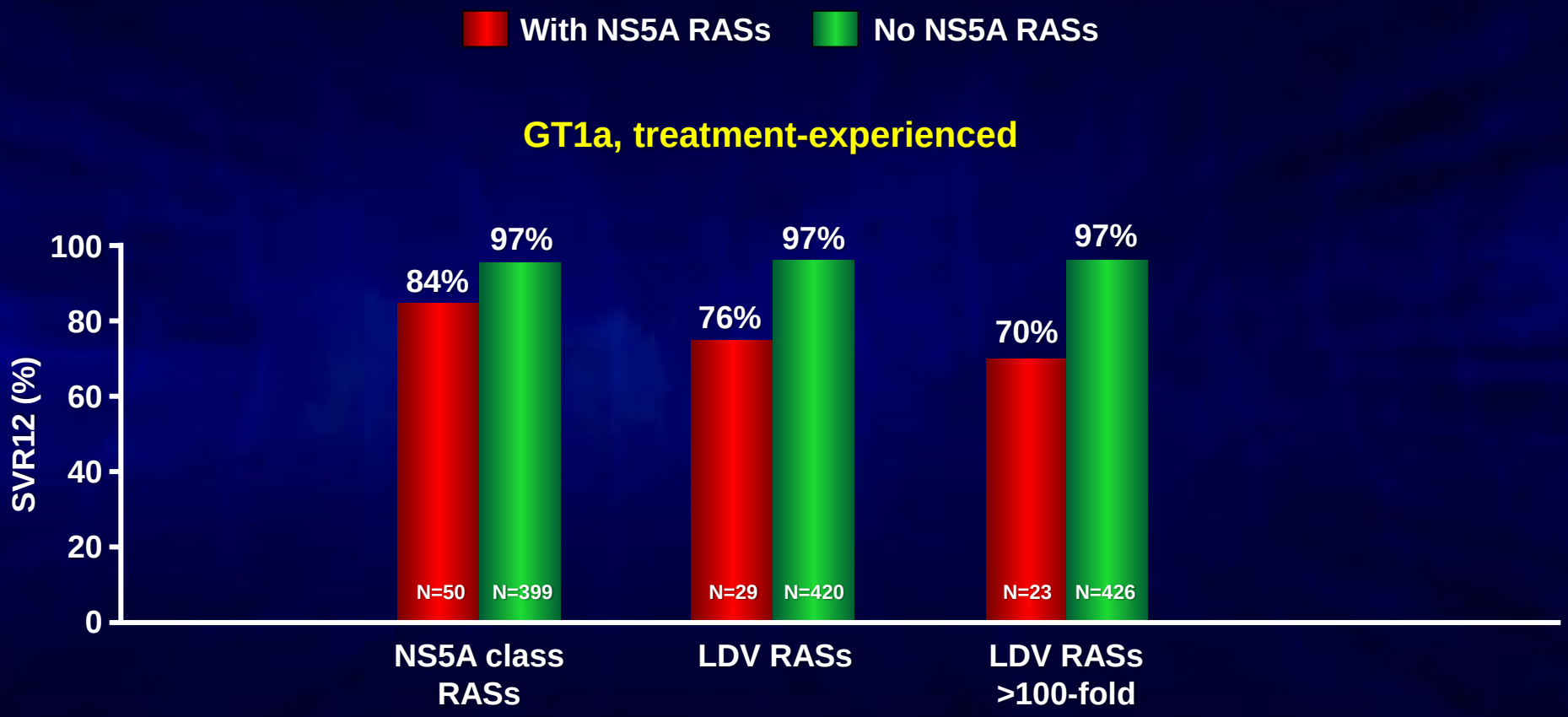
- Systematic **testing for HCV resistance** prior to treatment is **NOT recommended**. Indeed, this obligation would seriously limit access to care and treatment regimens can be optimized without this information

- Physicians who have **easy access** to a **reliable** test assessing HCV resistance to NS5A inhibitors (spanning amino acids 24 to 93) can use these results to guide their decisions

(EASL Recommendations on Treatment of Hepatitis C 2016)

SVR According to Baseline NS5A RASs

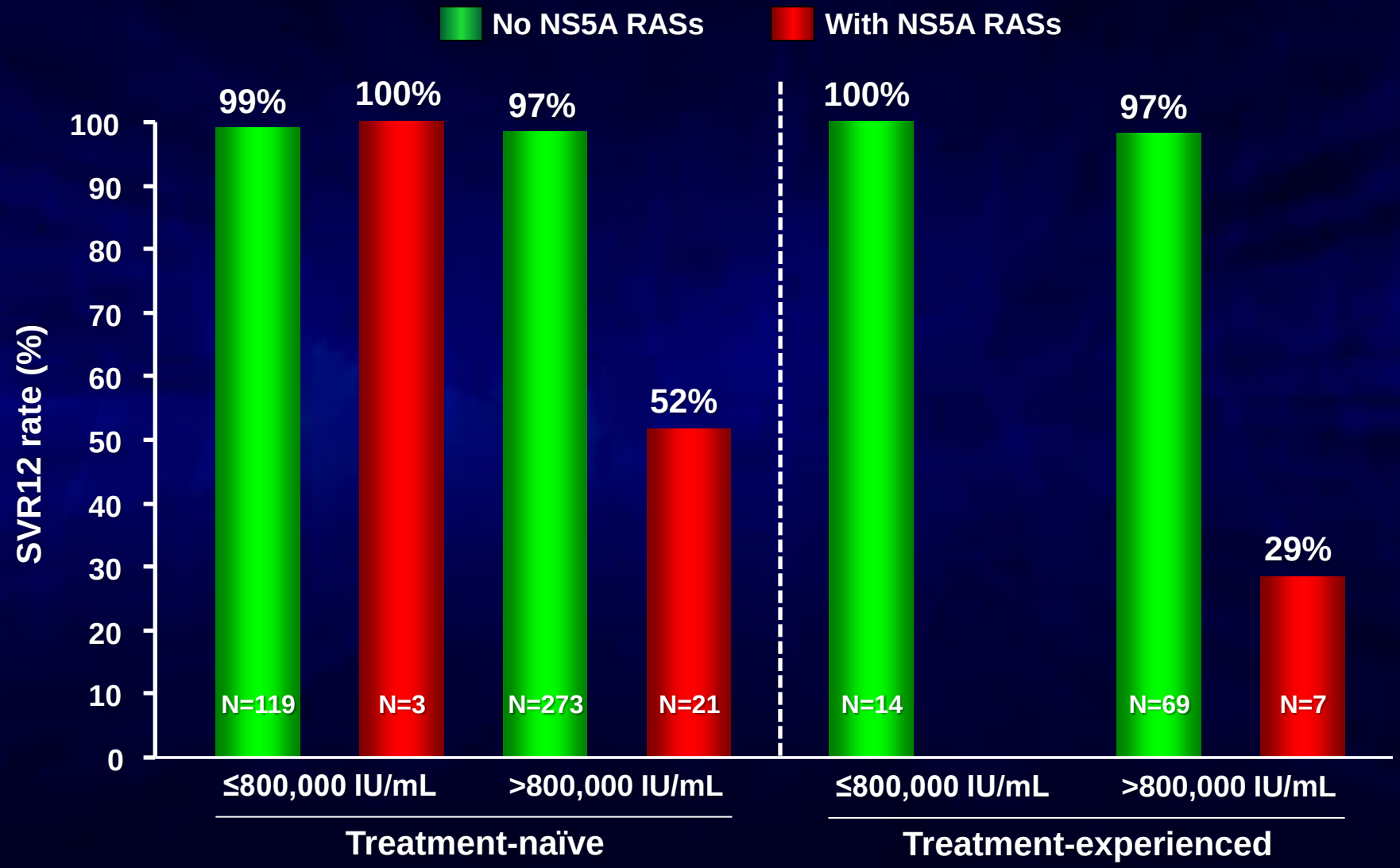
GT1a, SOF/LDV, guidelines-recommended



(Zeuzem et al., J Hepatol 2017; epub ahead of print)

Grazoprevir/Elbasvir

Pooled efficacy population-Phase II and III trials, GT1a, 12 weeks, no RBV

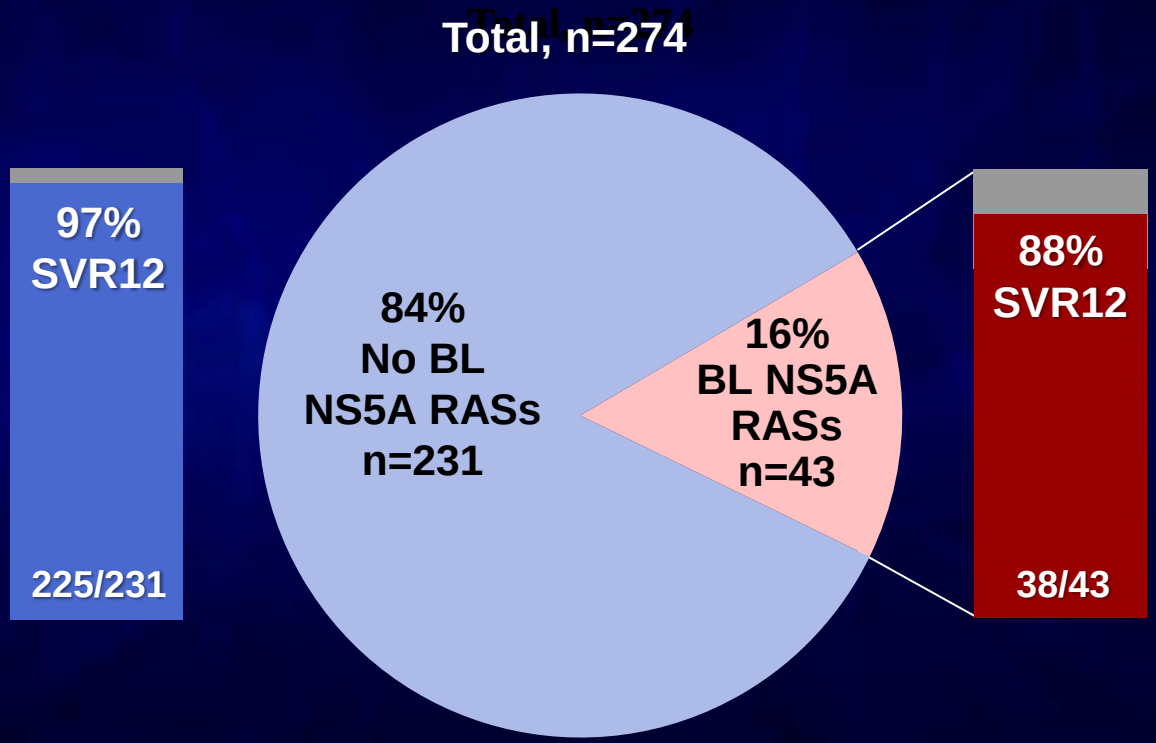


(EASL Recommendations on Treatment of Hepatitis C 2016: Merck unpublished data)

Sofosbuvir + Velpatasvir

ASTRAL-3– Phase III, TN and TE (26%), Gt 3, 30% cirrhosis, 12 weeks

Resistance analysis (1% cutoff, deep sequencing)



- **SVR12 was 84% (21/25) in patients with Y93H**

(Foster et al., N Engl J Med 2015;373:2608-17)

HCV Resistance Testing Prior to First-Line DAA Therapy

Not available

↓

Optimize therapy to avoid treatment failure

↓

- **SOF/LDV, SOF/DCV, SOF/SIM: Add RBV in G1a-4-5-6 TE**
- **SOF/VEL: Add RBV in G3 TE patients and cirrhotics**
- **GZR/EBR: use 16 weeks with RBV in GT1a**

Available, reliable, interpretable, understandable*

***recommended for GZR/EBR for US patients with GT1a**

↓

Presence of NS5As RASs conferring high-level resistance (pop seq or >15%)

↓

Add ribavirin and/or increase treatment duration in patients with NS5A RASs

Monitoring of treatment efficacy

EASL Recommendations 2016

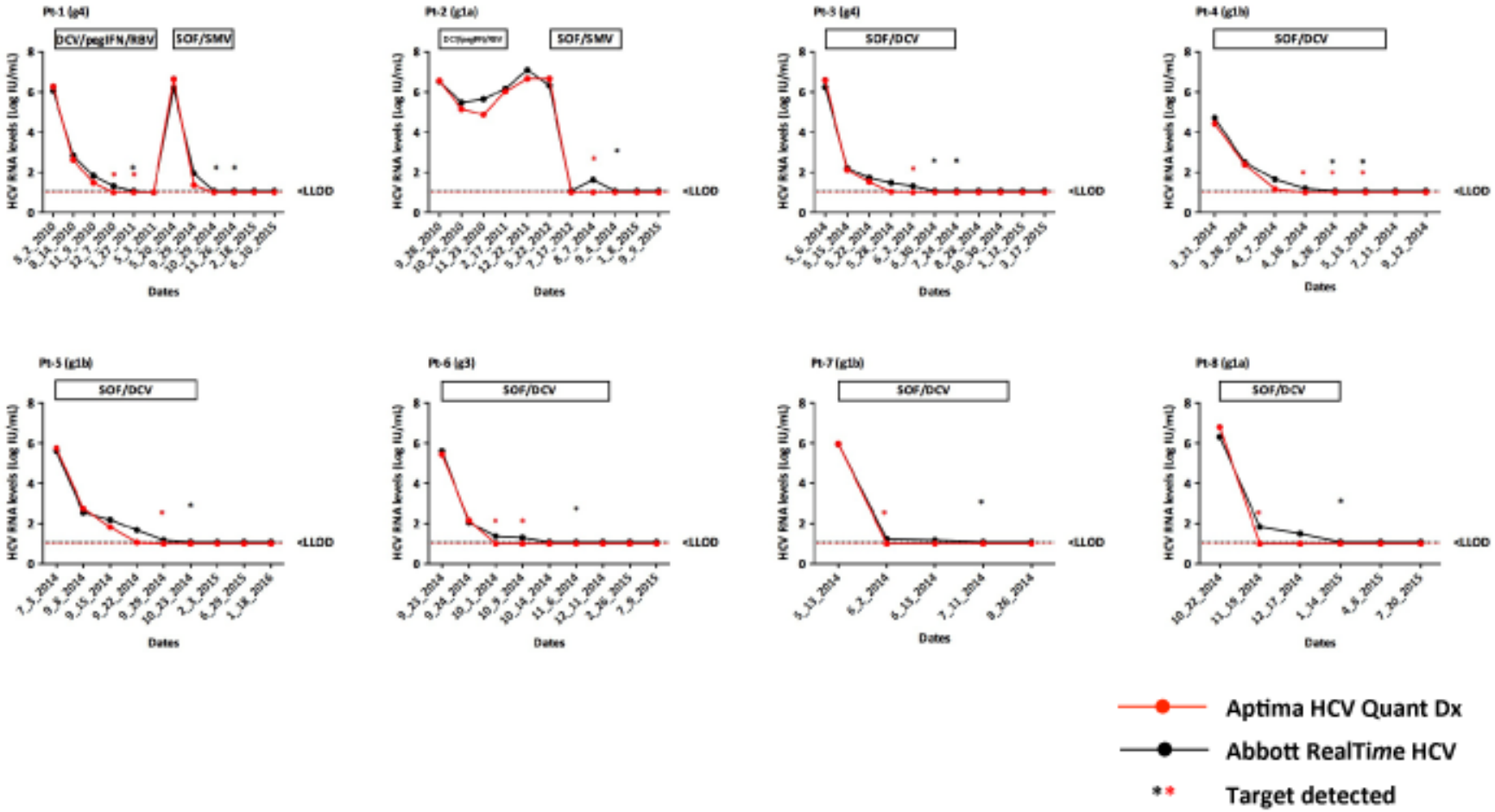
- A **real-time PCR-based assay** with a lower limit of detection of ≤15 IU/mL should be used to monitor HCV RNA levels during and after therapy

- Measurement of **HCV core antigen levels** by EIA can be used as an alternative to HCV RNA level measurement to monitor treatment efficacy during and after therapy when HCV RNA assays are not available or not affordable

(EASL Recommendations on Treatment of Hepatitis C 2016)

Monitoring HCV DAA Therapy

Abbott Real-Time (PCR) vs Aptima (TMA)



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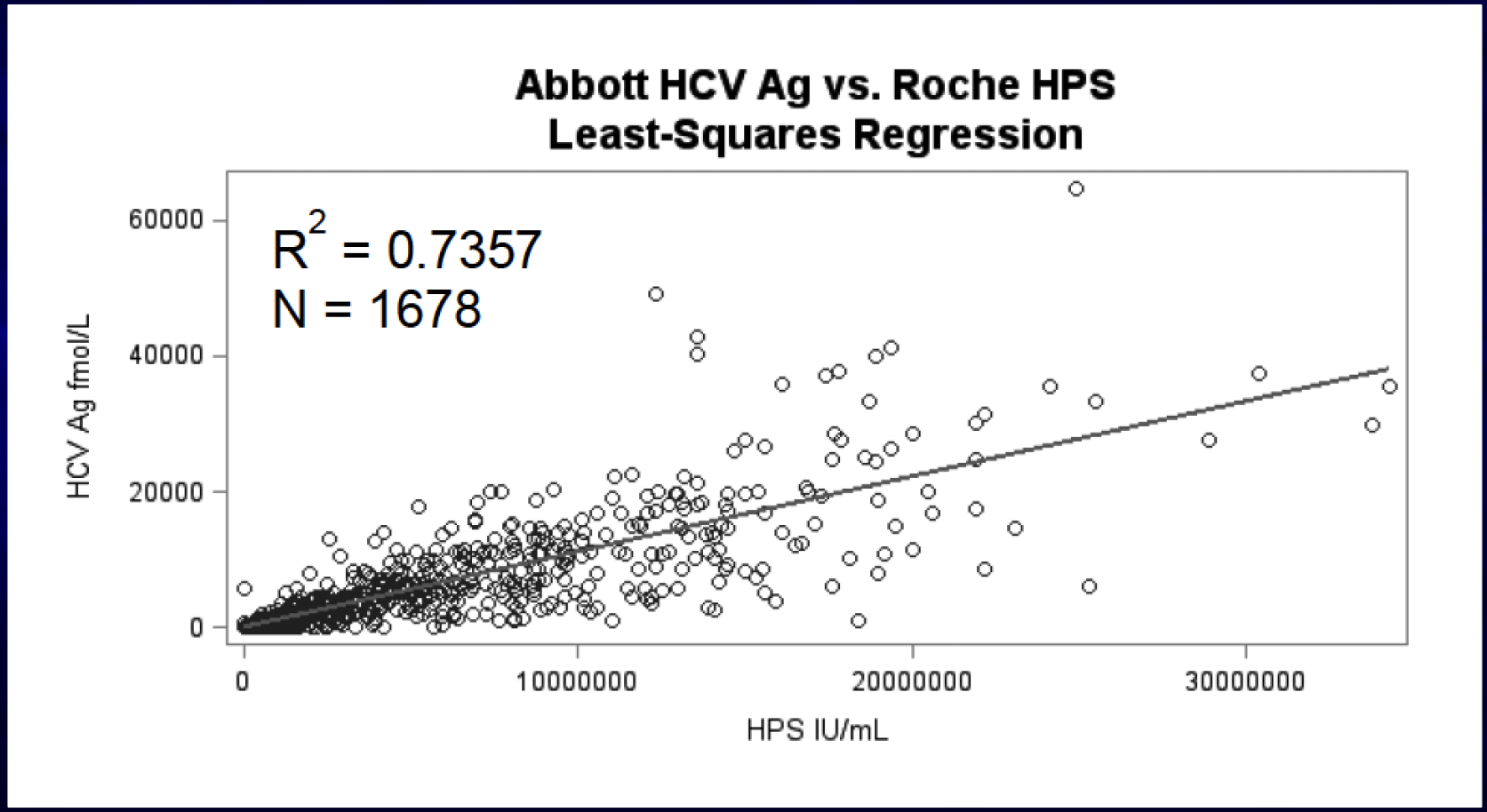


(Chevaliez et al., Antivir Ther 2016; epub ahead of print)

HCV resistance testing prior to retreatment

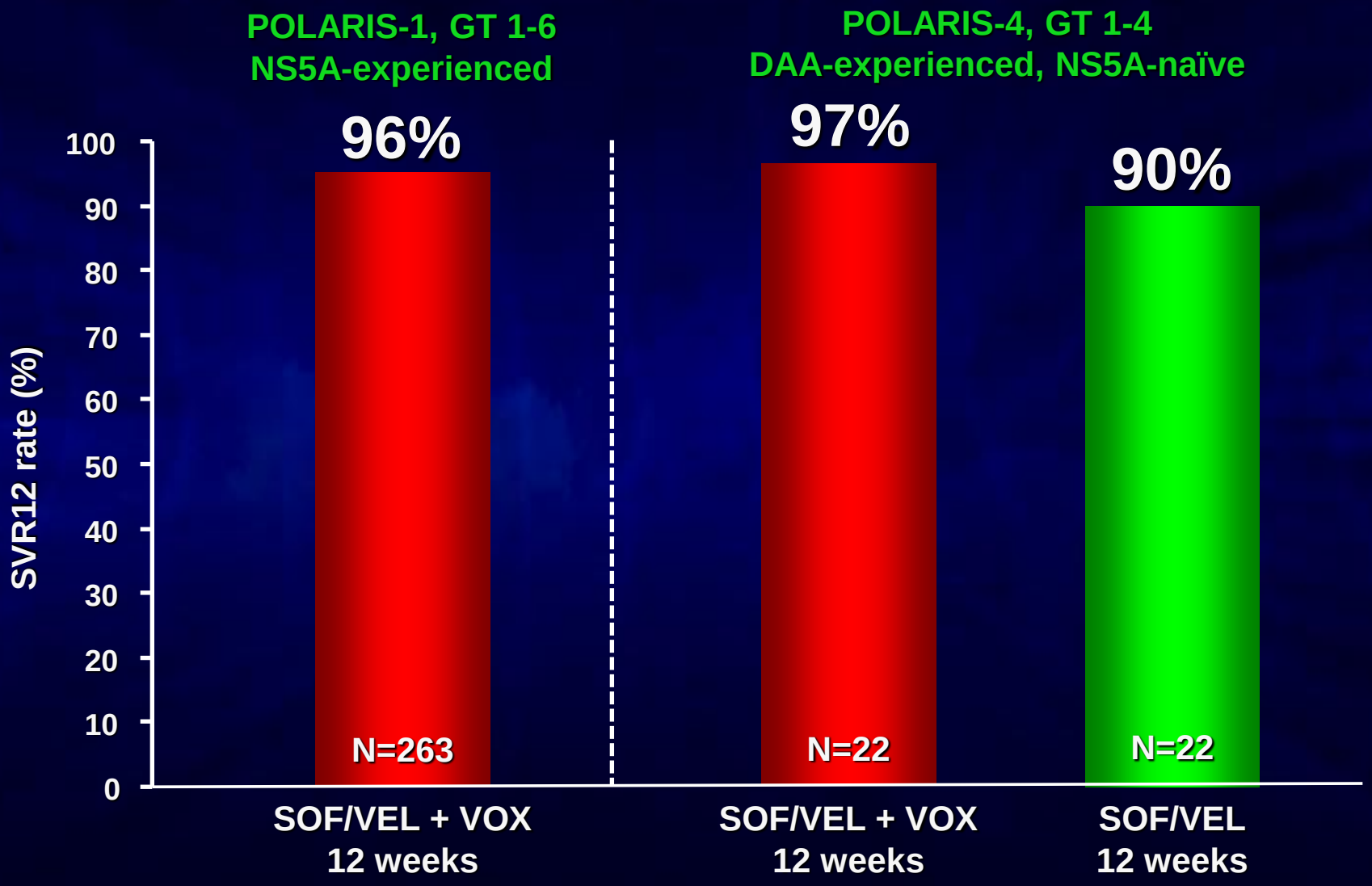
HCV Resistance Testing Prior to Retreating NS5A Inhibitor Failures

- Not absolutely necessary, useful to guide retreatment decision
- Particularly useful in patients with advanced liver disease who need to rapidly cure infection
- Still empirical in the absence of trial data and guidelines

(Pawlotsky JM, Gastroenterology 2016;151:70-86)

Sofosbuvir + Velpatasvir + Voxilaprevir

POLARIS-1 and -4- Phase III, GT 1-6, DAA-experienced, ~40-45% cirrhosis, 12 wk



(Bourlière et al., AASLD 2016; Zeuzem et al., AASLD 2016)

Conclusion

- A number of assays and tests exist to diagnose HCV infection and help clinicians to make appropriate therapeutic decisions
- Novel assays are or will soon be available
- They will allow HCV treaters to simplify diagnosis, assessment of severity, treatment decision and monitoring, in order to optimize access and linkage to care worldwide

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