How to optimize treatment for HCV Genotype 4

Paris Hepatitis Conference

Pr Tarik Asselah

14 janvier 2014

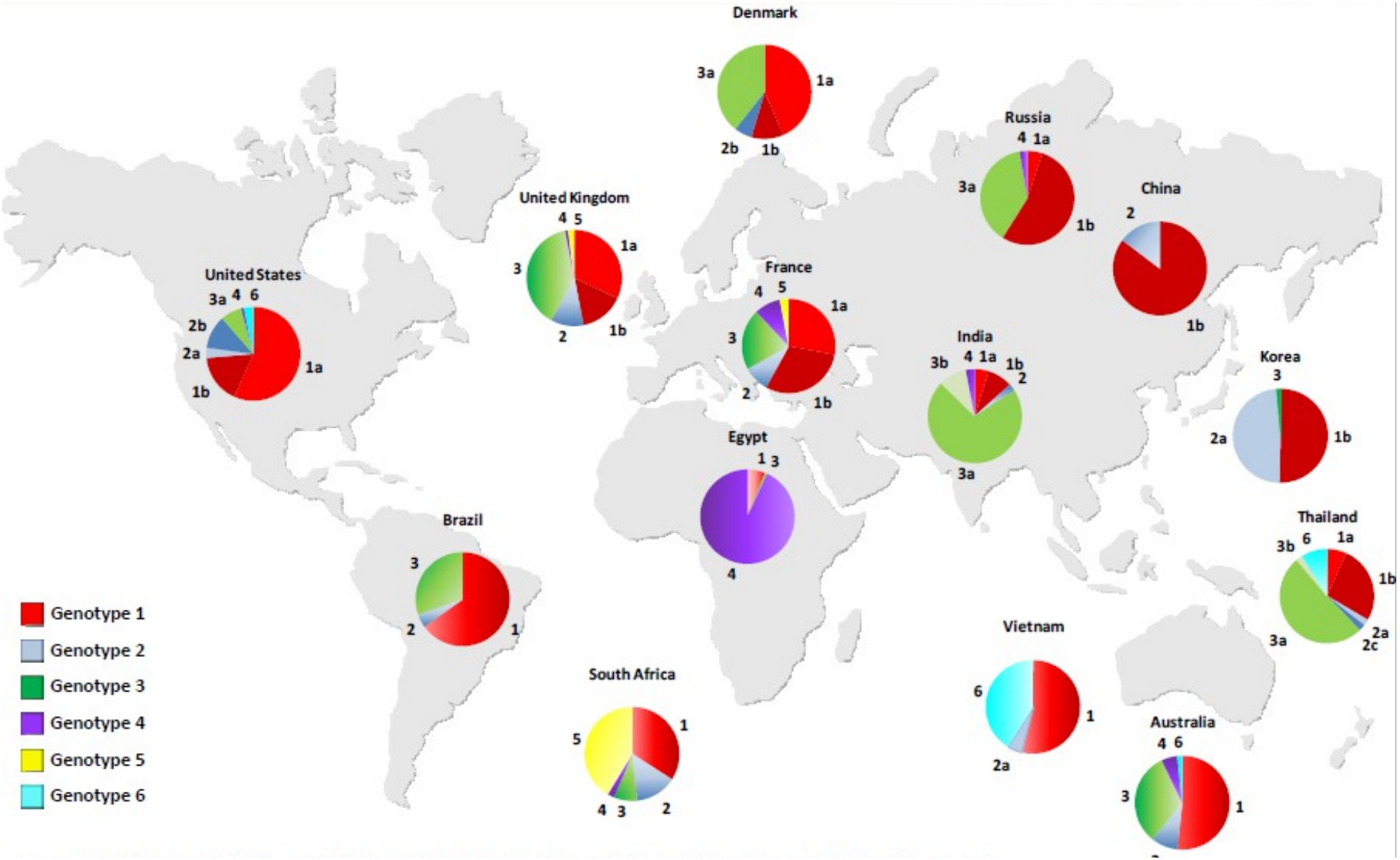
MD, PhD
Service d'Hépatologie & INSERM U773
University Paris Diderot
Hôpital Beaujon, Clichy
tarik.asselah@bjn.aphp.fr

How to optimize treatment for HCV Genotype 4

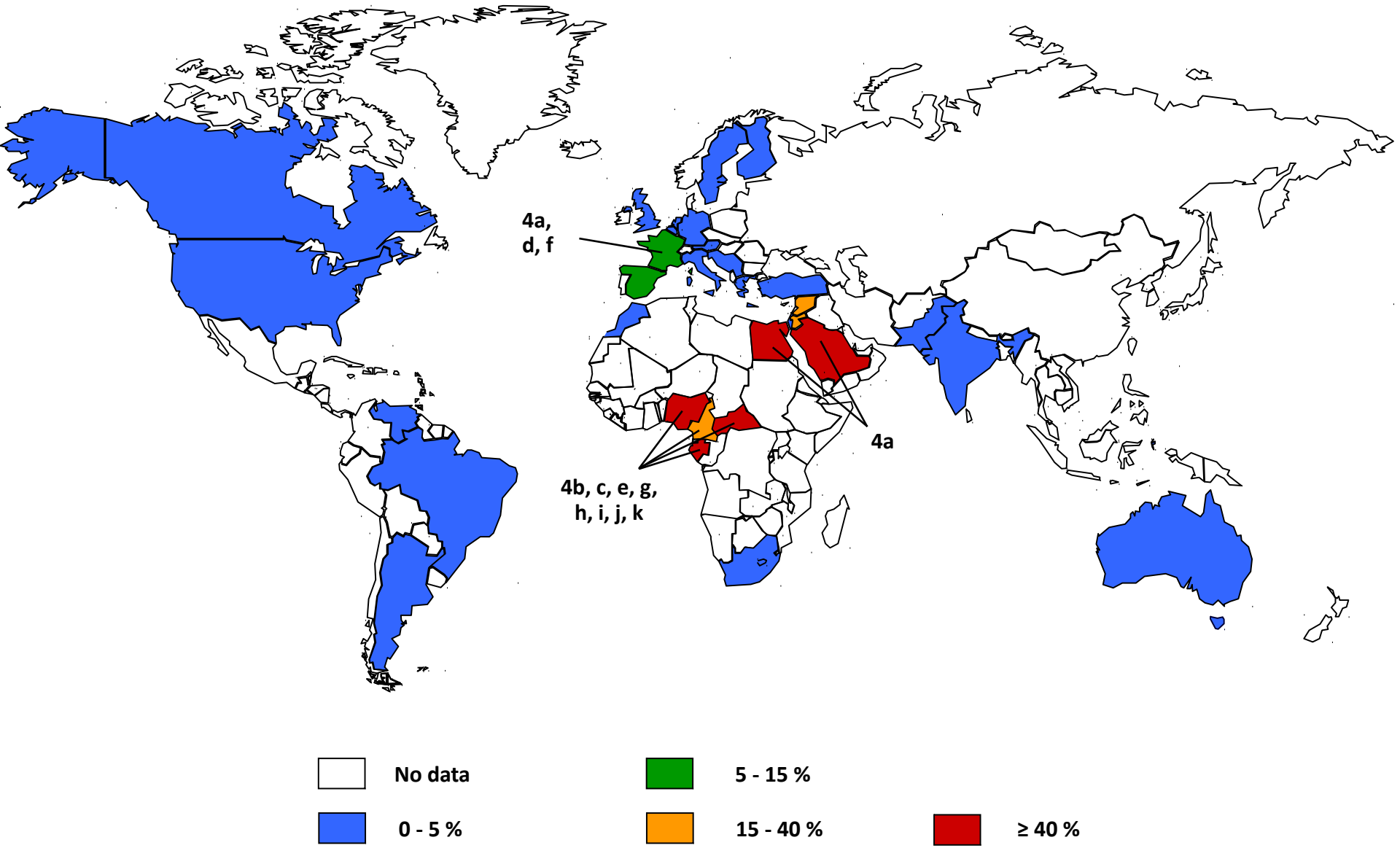
- **Epidemiology and natural history**
- Current PEG-IFN plus RBV therapy
- Direct-acting antivirals (DDAs)
- Conclusion

Between 50 to 70 millions individuals are infected by non-1 genotype

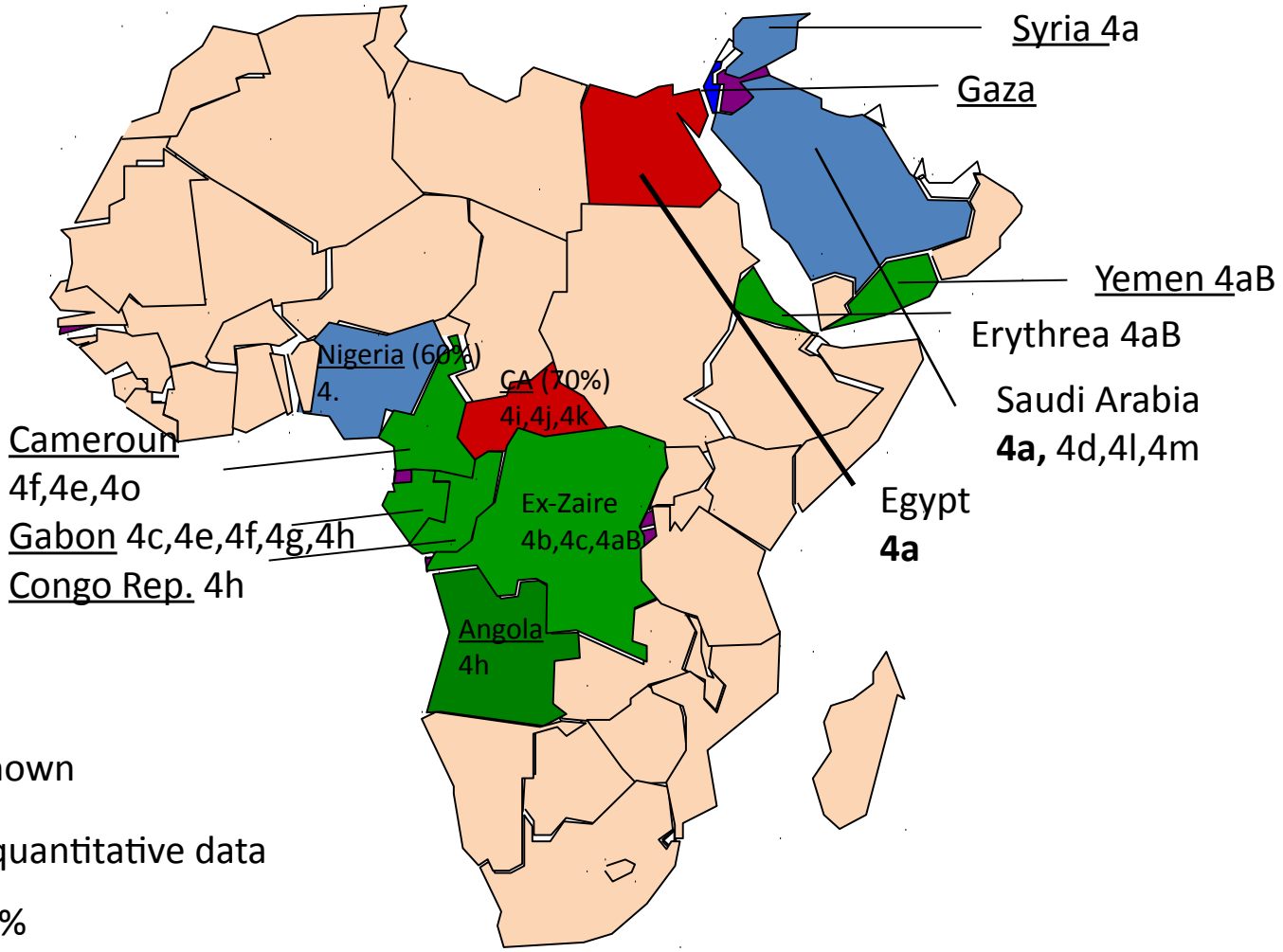
Genotype 4 : (20% of 170 millions) approximately 34 millions



Geographical distribution of HCV-4 infection



HCV-G4 in Africa and Middle East



From Y.Morice (personal comm.)

HCV in Egypt

- Highest prevalence of HCV worldwide: 15%
  - 80 millions inhabitants, 15 % (12 millions) patients

- blood donors: 15-20%

- major cause of chronic hepatitis (67%)

- Highest prevalence of HCV-4 :

- 91% of total VHC

- 70%-82% VHC4a

Kamel, Lancet 1992, Zekri, Infection 2001
Ray, J Infect Dis 2000
Angelico, J Hepatol 1997
Kamal SM, Hepatology 2008

Epidemiological data in Europe (2011)

	Belgium	France	Germany	Italy	Spain	UK
Prevalence	0.87%	0.84%	0.6%	4%	1.9%	0.7%
	73,000	360,000	460,000	2,000,000	690,000	340,000
Screening	50%	64%	48%	46%	35%	34%
Genotype (%)						
G1	61%	56%	56%	62%	82%	44%
G2-3	26%	32%	32%	37%	14%	53%
G4-5-6	13%	12%	12%	1%	4%	3%

*Thierfelder et al. Eur J Epidemiol 2001; Rossol, Gesundheitswesen 2007; Zehnter et al. Hepatology 2005; Beutels et al. Eur J Epidemiol 1997; Carsauw et al. Acta Gastroenterol Belg 2003; Dominguez et al. J Med Virol 2001; Meffre et al. J Med Virol 2010; Mariano et al. Dig Liver Dis 2009; Ansaldi et al, J Med Virol 2005; Gungabissoon et al., Epidemiol Infect 2007
†Poynard et al, Lancet 1997; Roudot-Thoraval et al, Hepatology 1997; Martinot-Peignoux et al, J Viral Hepatitis 1999; Gerard et al, J Med Virol 2005; De Maeght et al, Acta Gastroenterol Belg 2008; Delwaide et al, Eur J Gastroenterol Hepatol 2005; Serra et al, J Viral Hepatitis 2003 ; Mohsen et al, Gut 2001; Mariano et al, Scand J Infect Dis 2009

HCV-4 patients characteristics according to the geographical origin of infection (1532 patients)

n=1532	France n=1056 (69%)	Egypt n=227 (15%)	Africa n=249 (16%)	*P*-value
Age (yrs)	44 ± 10	45 ± 10	50 ± 11	0.0001
Gender: male %	64.7	93.4	47.8	0.0001
Infection duration	20 ± 6.5	27 ± 9.8	21 ± 9	0.0001
BMI (kg/m2)	**23.5 ± 4.0**	**26.8 ± 3.3**	**26.4 ± 4.3**	**0.0001**
Diabetes %	**3.2**	**9.2**	**10.2**	**0.0001**
HIV infection %	10.6	0.8	5.3	0.0002
HBV infection %	1.9	2.5	4.8	0.05

Roulot et al, J Viral Hepat 2007;14:460

Beaujon : Patients Profiles

(HCV, n=500 – HBV, n=100)

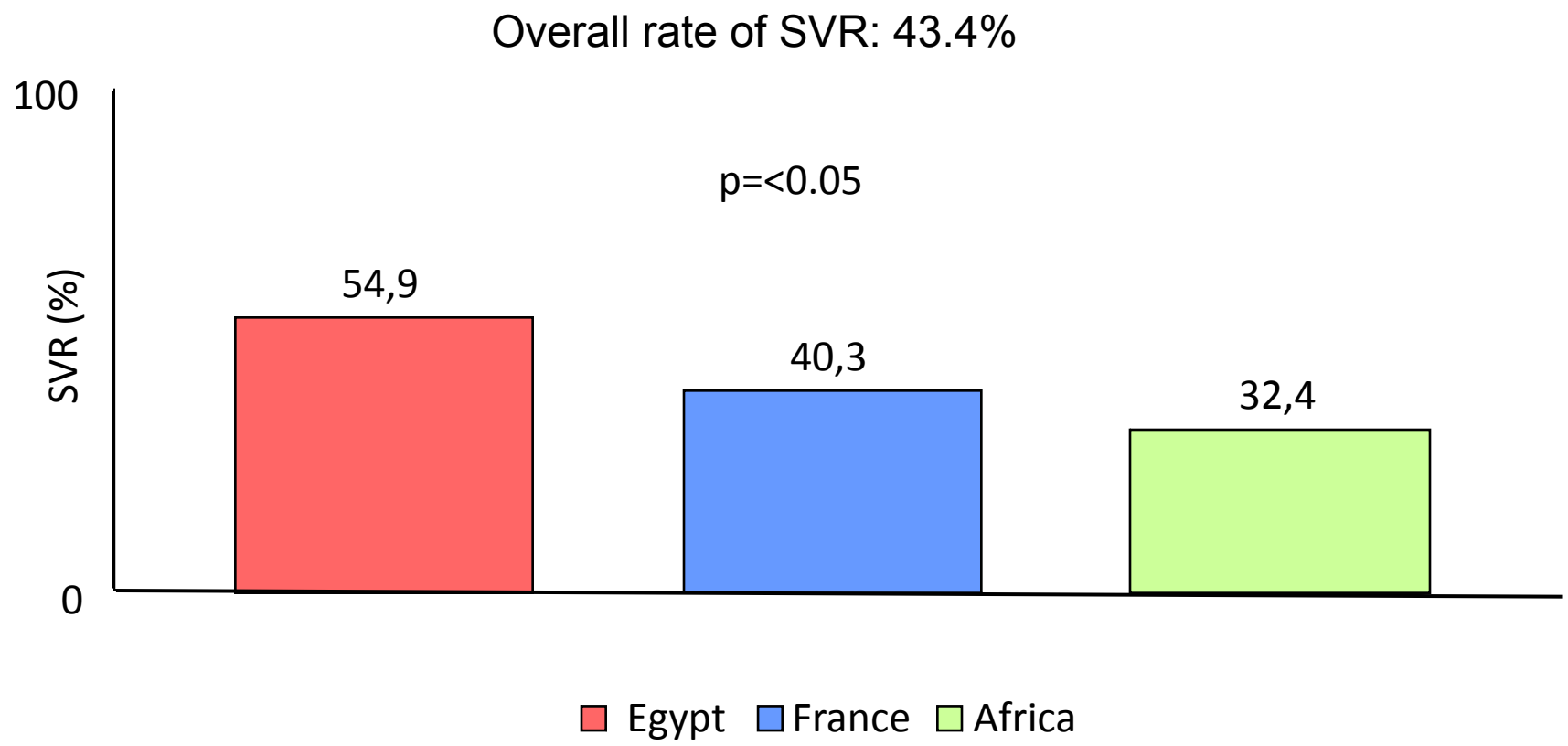
Characteristics	
Gender (M, %)	57
Age (> 40 ans, %)	77
Metabolic syndrome (%)	12
Obesity (%)	10
Diabetes (Glucose > 126 mg/dl, %)	7
Insuline Resistance (HOMA-IR > 3, %)	36
Genotype distribution (n, %)	
•1	285 (55)
•2	30 (6)
•3	78 (16)
•4	96 (19)
•5 & 6	11 (2)

Moucari et al. Gastroenterology, 2008

How to optimize treatment for HCV Genotype 4

- Epidemiology and natural history
- **Current PEG-IFN plus RBV therapy**
- Direct-acting antivirals (DDAs)
- Conclusion

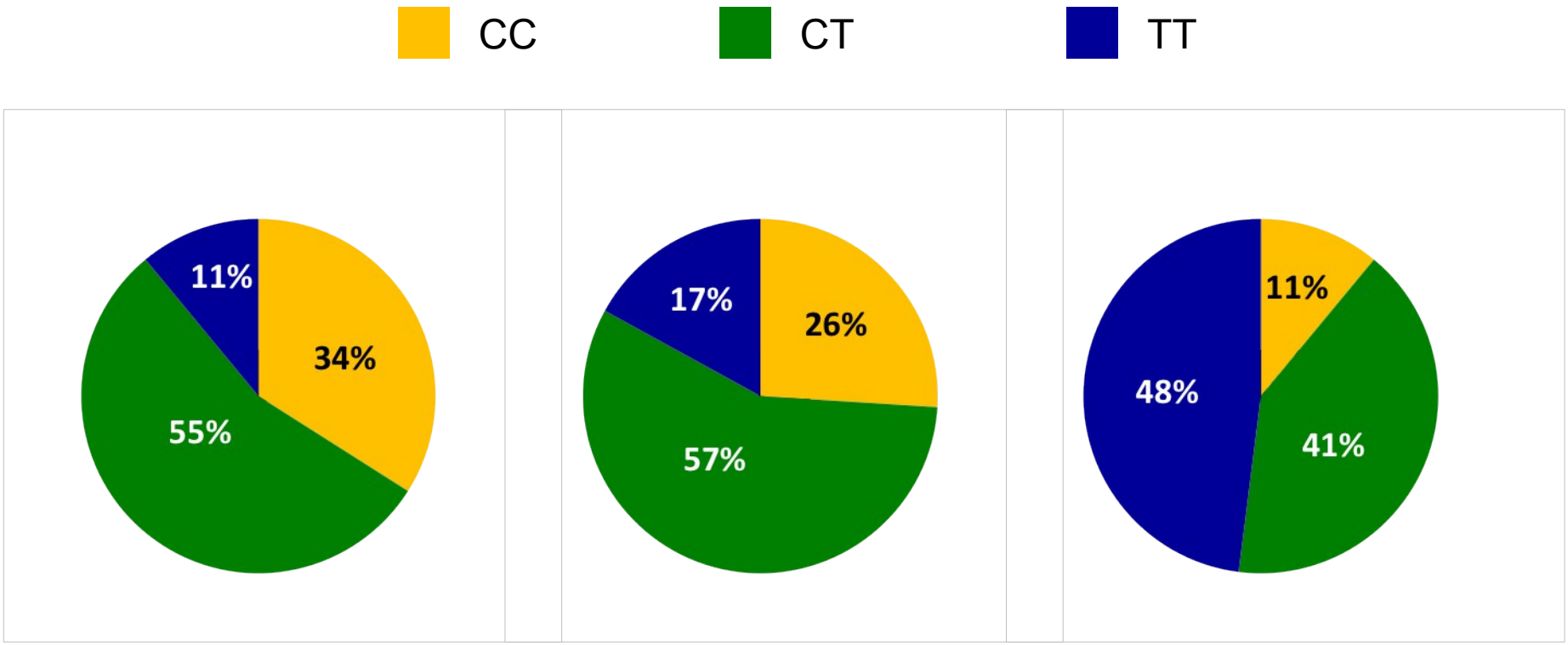
SVR rate according to geographical origin



PegIFNα2b (1.5 mg/kg/wk) + RBV(1000-1200 mg/d) for 48 weeks

Roulot et al, J Viral Hepat 2007; 14: 460

Beaujon: HCV genotype 4 and IFNL3 (IL28B)



N = 70 **Egyptian**

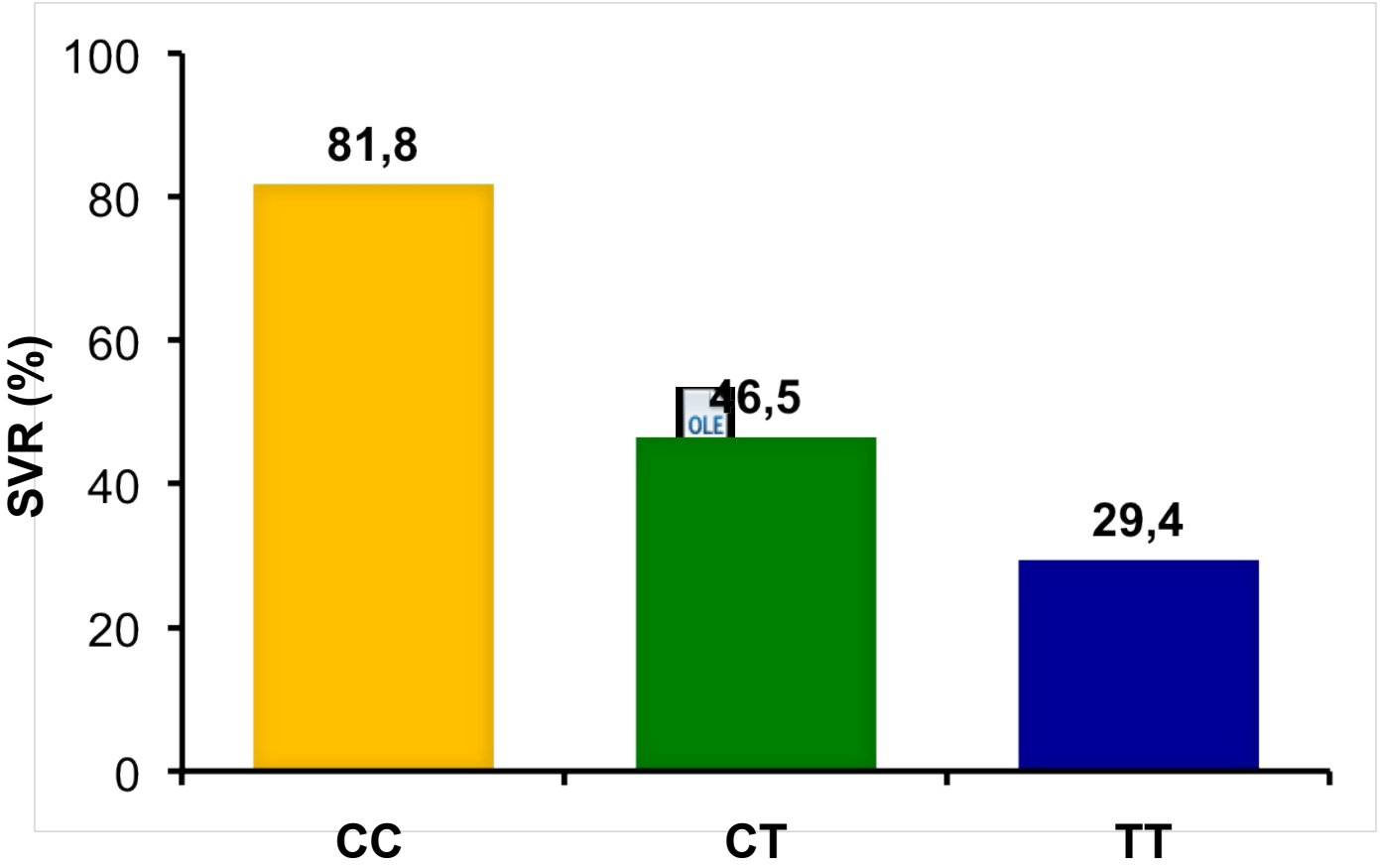
N = 53 **European**

N = 37 **Sub-Saharan African**

Asselah T, et al. J Hepatol 2012

Unmet need : G4; IFNL3 (IL28B) non CC

Current SOC : PEG-IFN plus ribavirin 48w



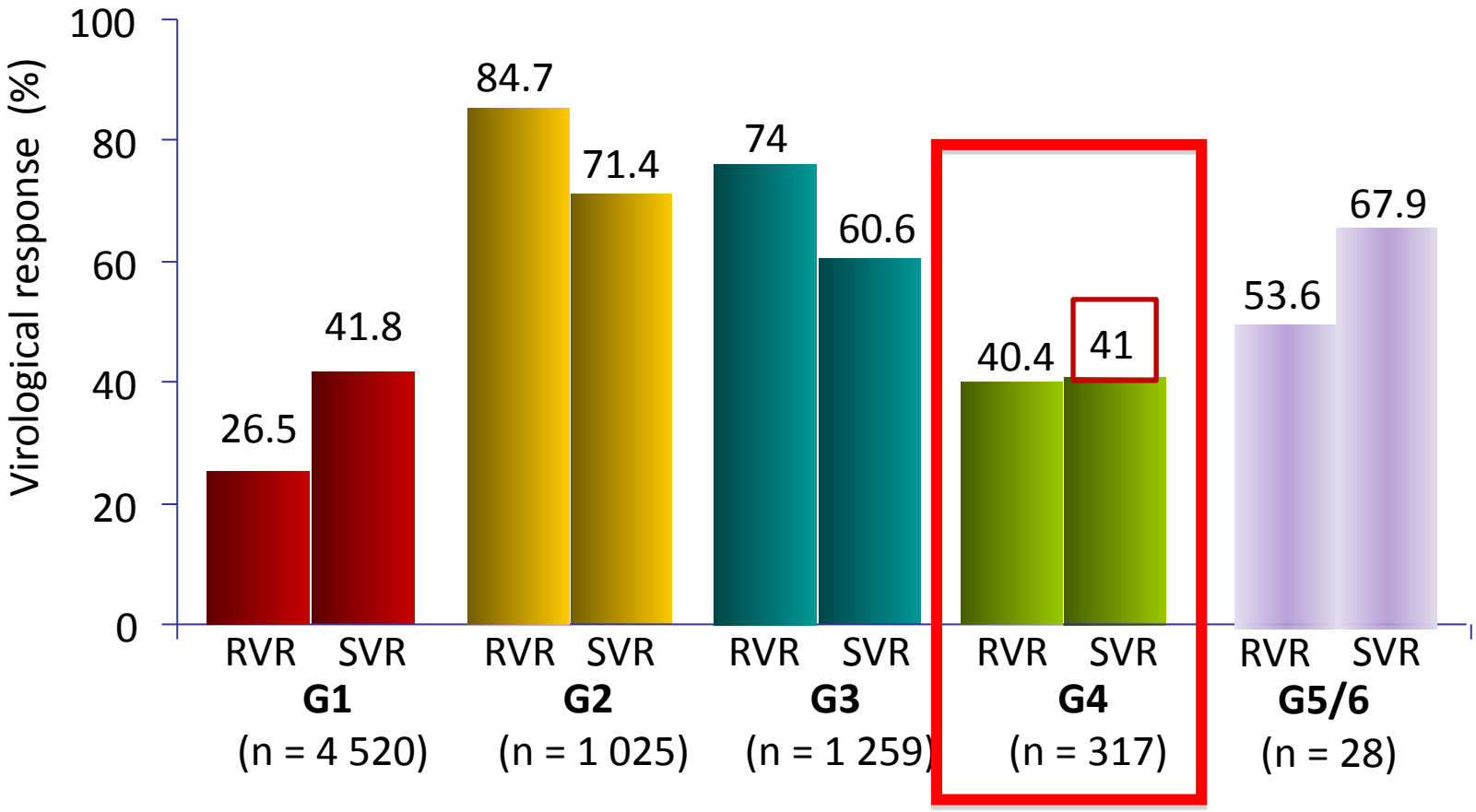
HCV-4 subtypes according to geographical origin

n=156	France n=84	Egypt n=46	Africa n=26
4a	54.8 %	93.5%	11.5 %
4d	33.3 %	2.2 %	7.7 %
4f,4h,4j,4k,4r	11.9 %	4.4 %	80.8 %

Roulot et al, J Viral Hepat 2007;14:460

Worldwide experience of SOC among 7163 naive HCV patients: PROPHESYS cohort study

- 63.1 % patients were G1, 28.5 % had advance disease (F3, F4)
- Patients were treated with PEG-IFNα-2a (92.5 %) or α-2b (7.5%) + RBV



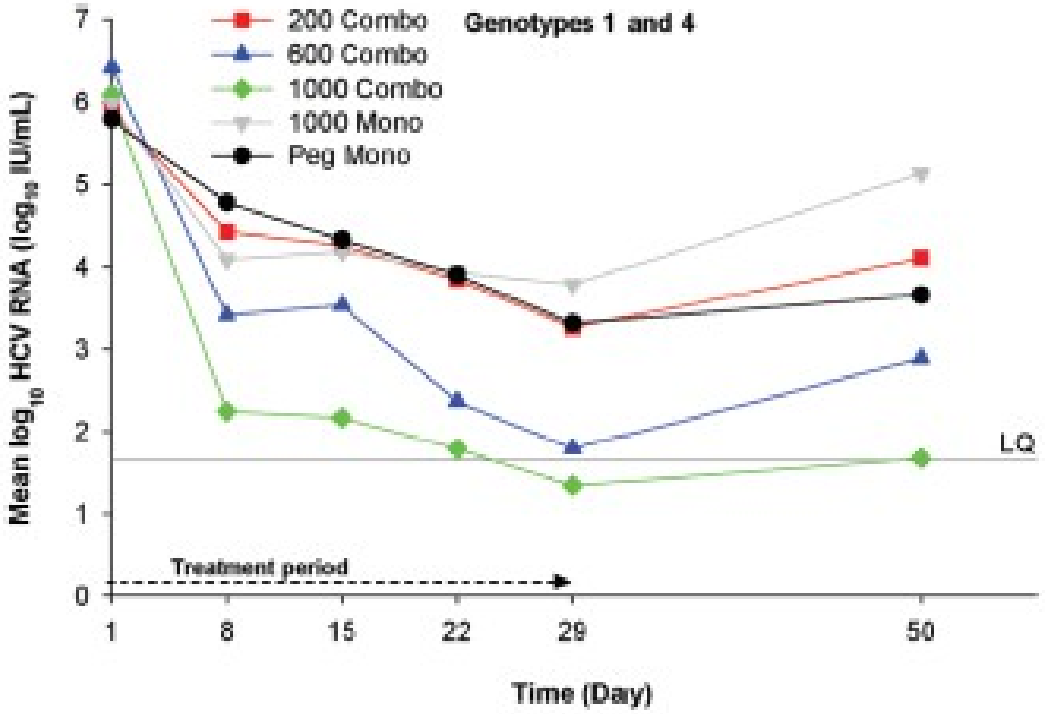
Marcellin P et al . Hepatology 2011: 54 (suppl), AASLD 2011, Abs. 984

How to optimize treatment for HCV Genotype 4

- Epidemiology and natural history
- Current PEG-IFN plus RBV therapy
- **Direct-acting antivirals (DDAs)**
- Conclusion

Debio 025 (Alisporivir) in Naive GT 4 patients

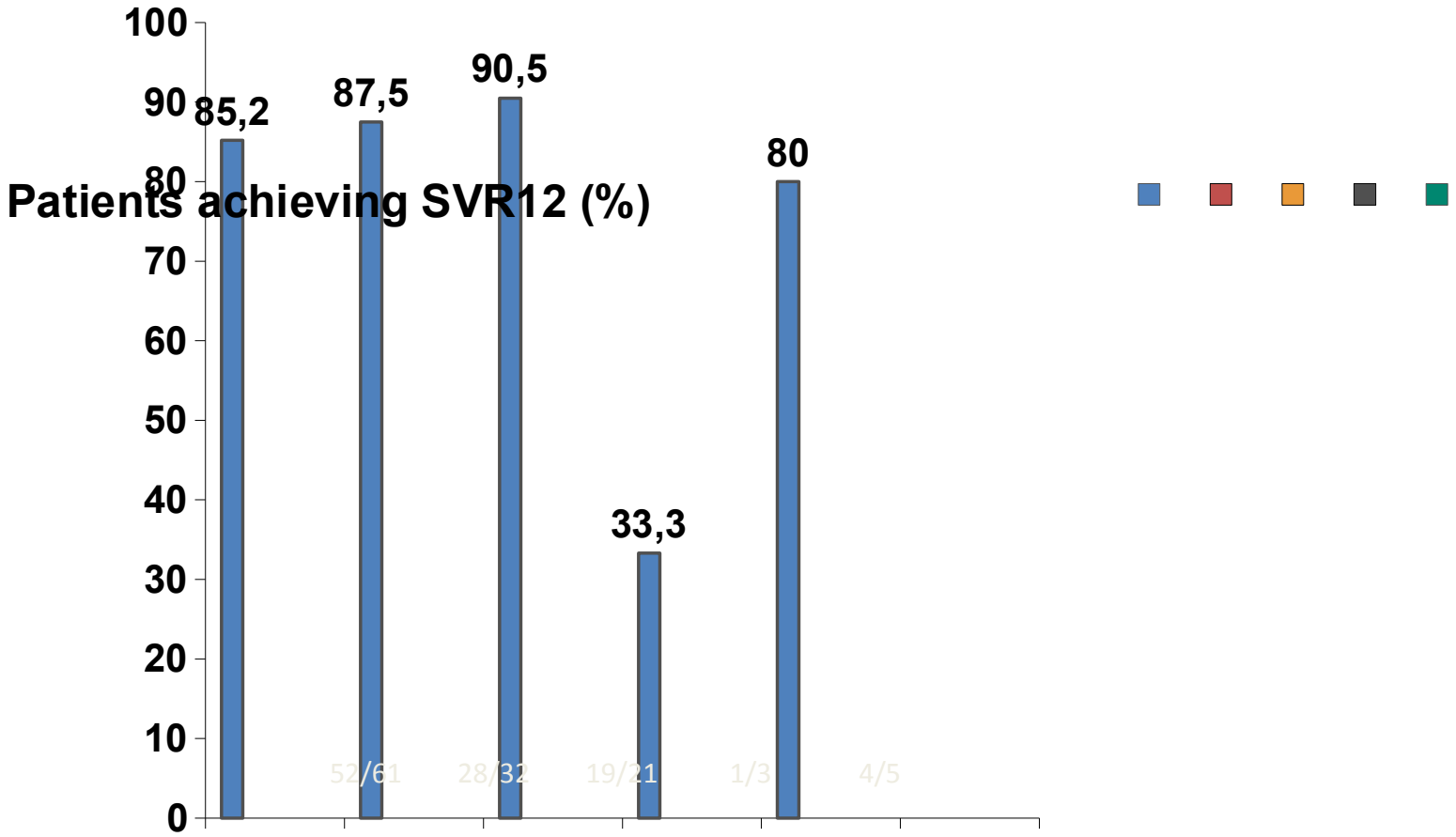
- Phase 2a, dose ranging study, 29 days treatment



4 GT4 patients :
VL > 2 log10 decrease at W4
In monotherapy

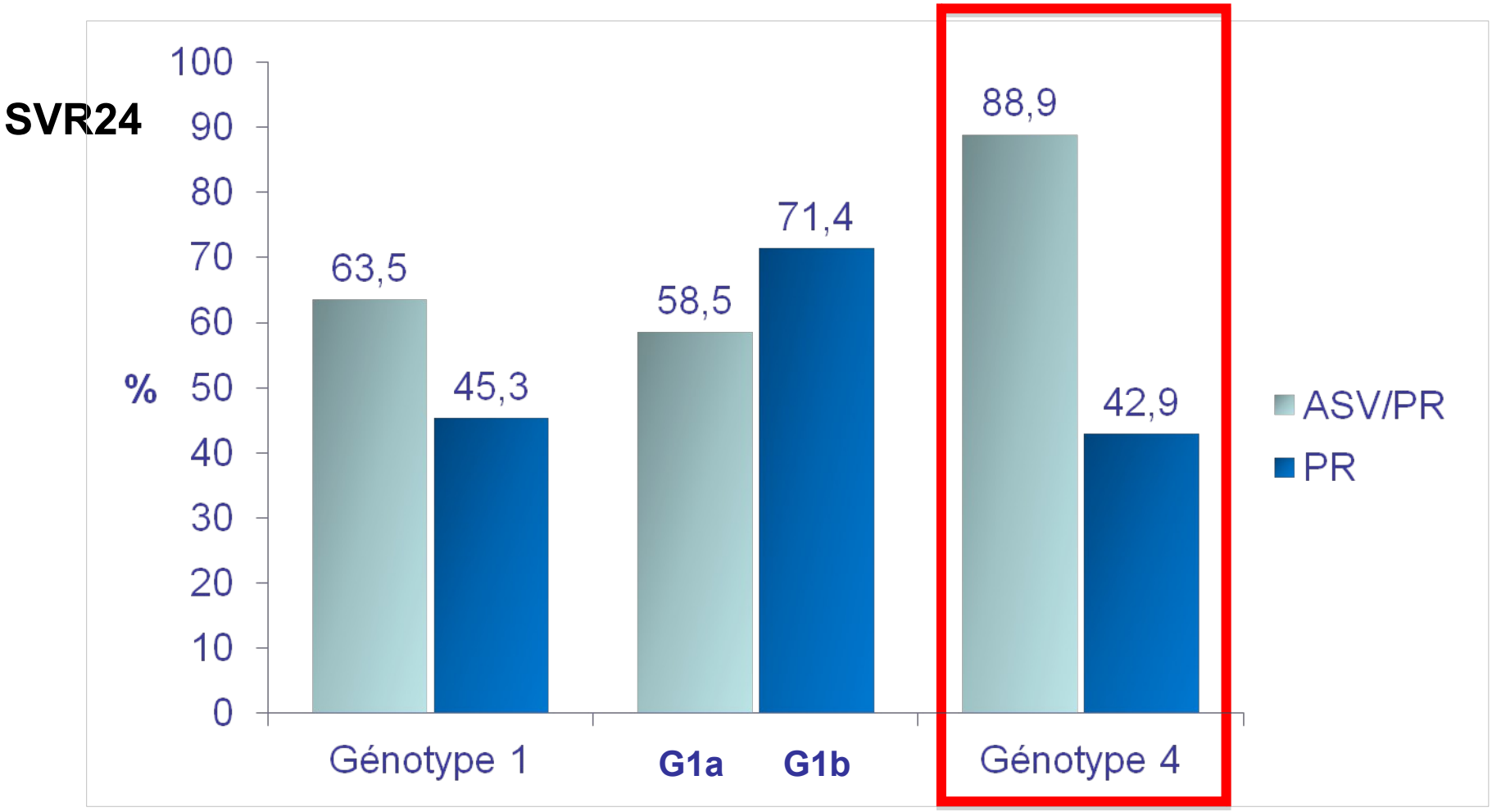
Flisiak R et al. Hepatology 2009; 49: 1460-1468

Simeprevir (PI) and G4: Patients achieving SVR12



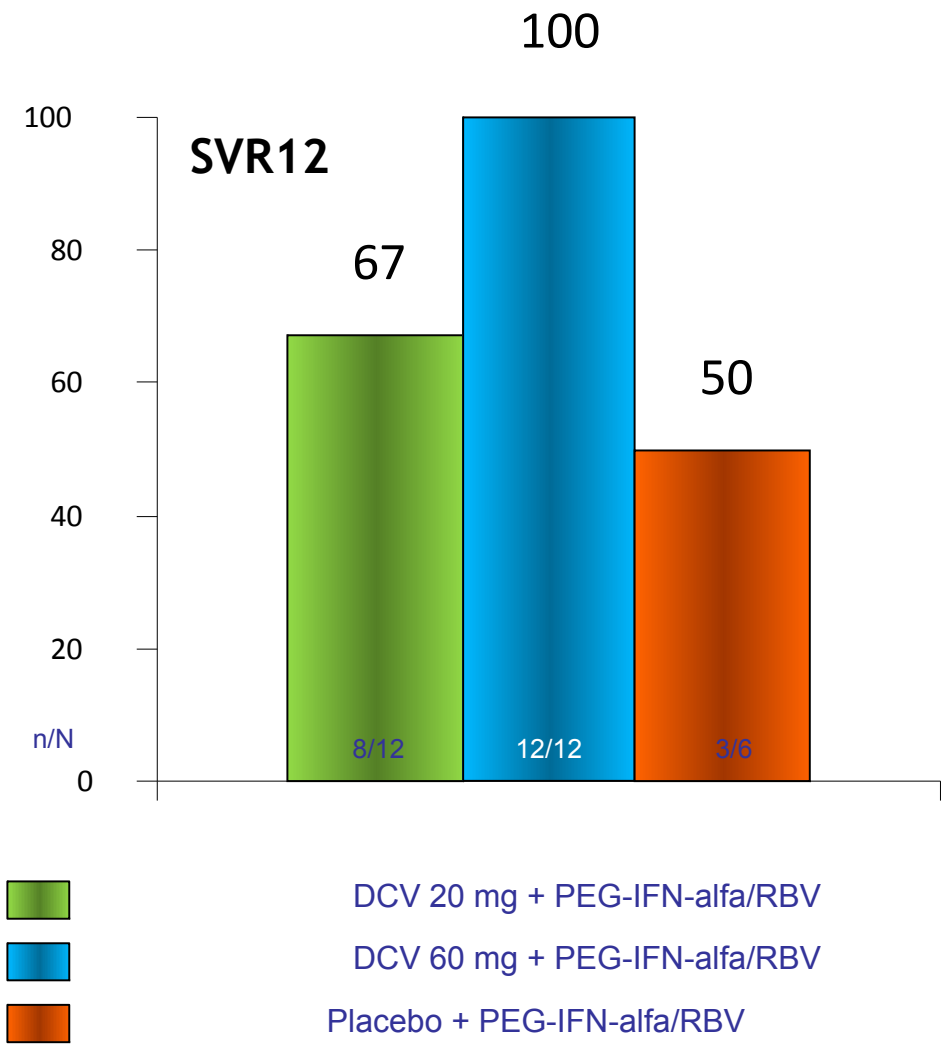
Moreno C et al. HepDart 2013

Asunaprevir (PI) + PEG-IFN/RBV : HCV-G4



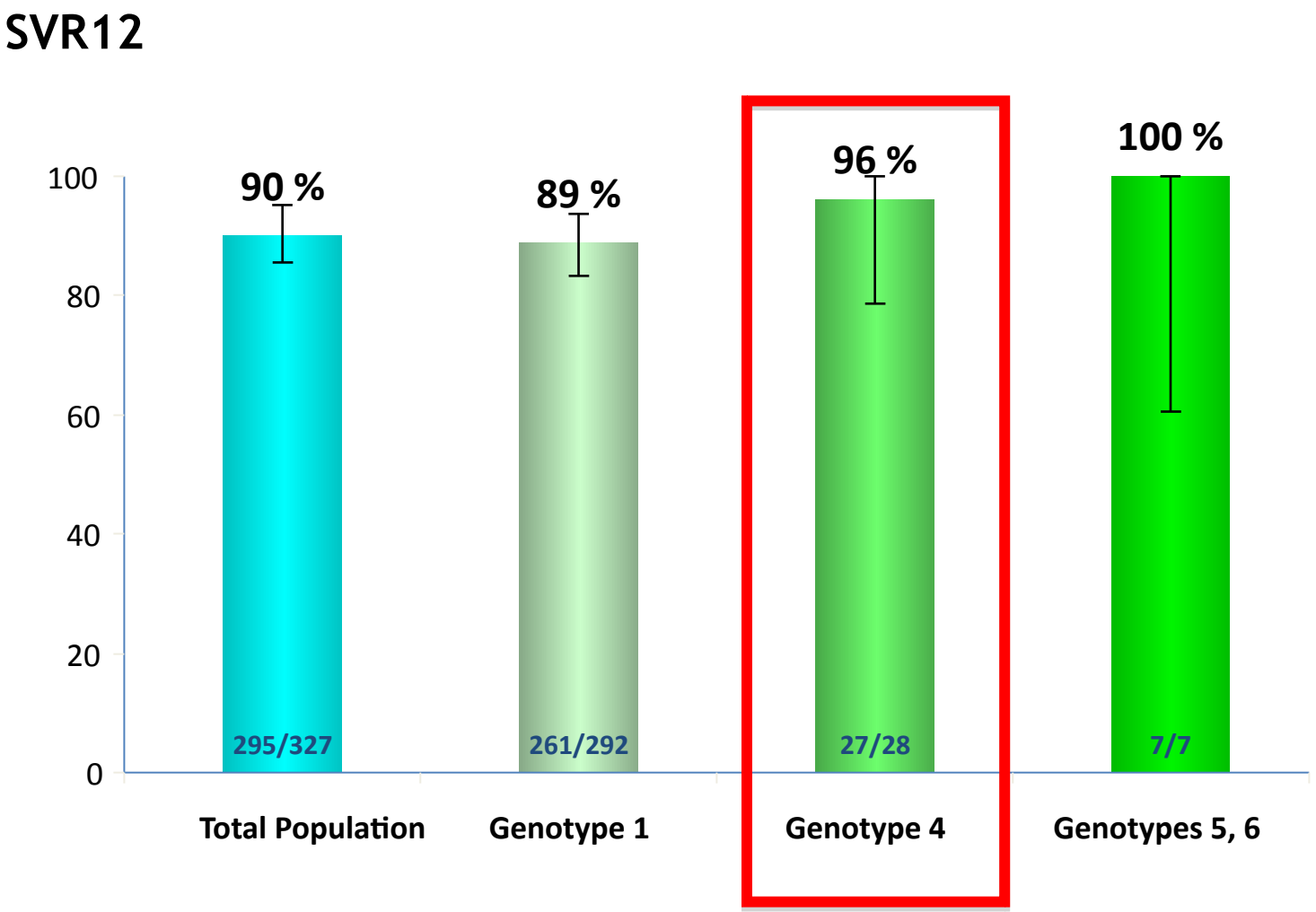
Bronowicki et al. EASL 2013, A 1420

Daclatasvir (NS5A I)+ PR : HCV G4



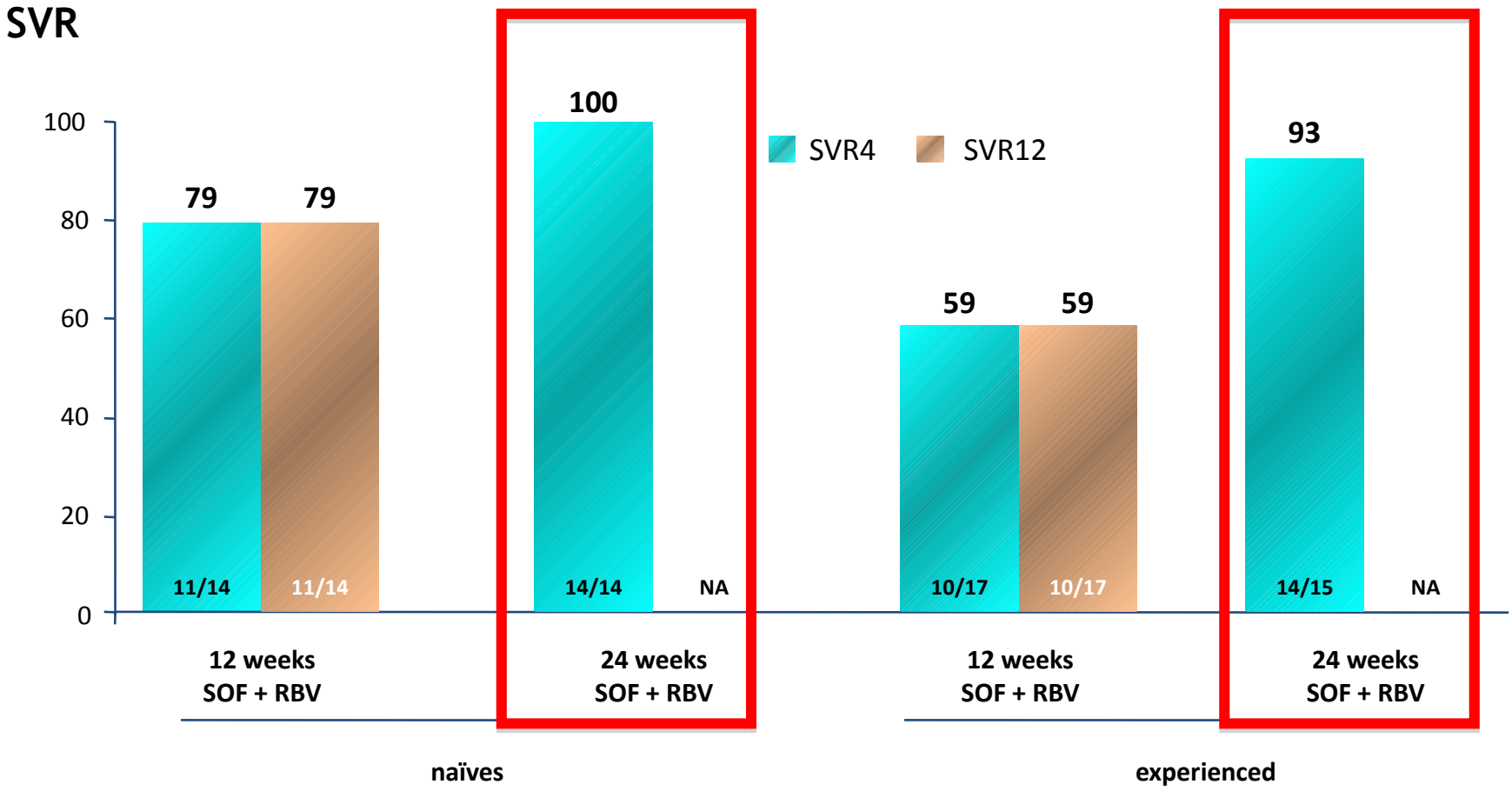
Hezode et al. AASLD 2012, A755

Sofosbuvir (NS5B I) + PR for 12W (Neutrino)



Lawitz et al. NEJM 2014

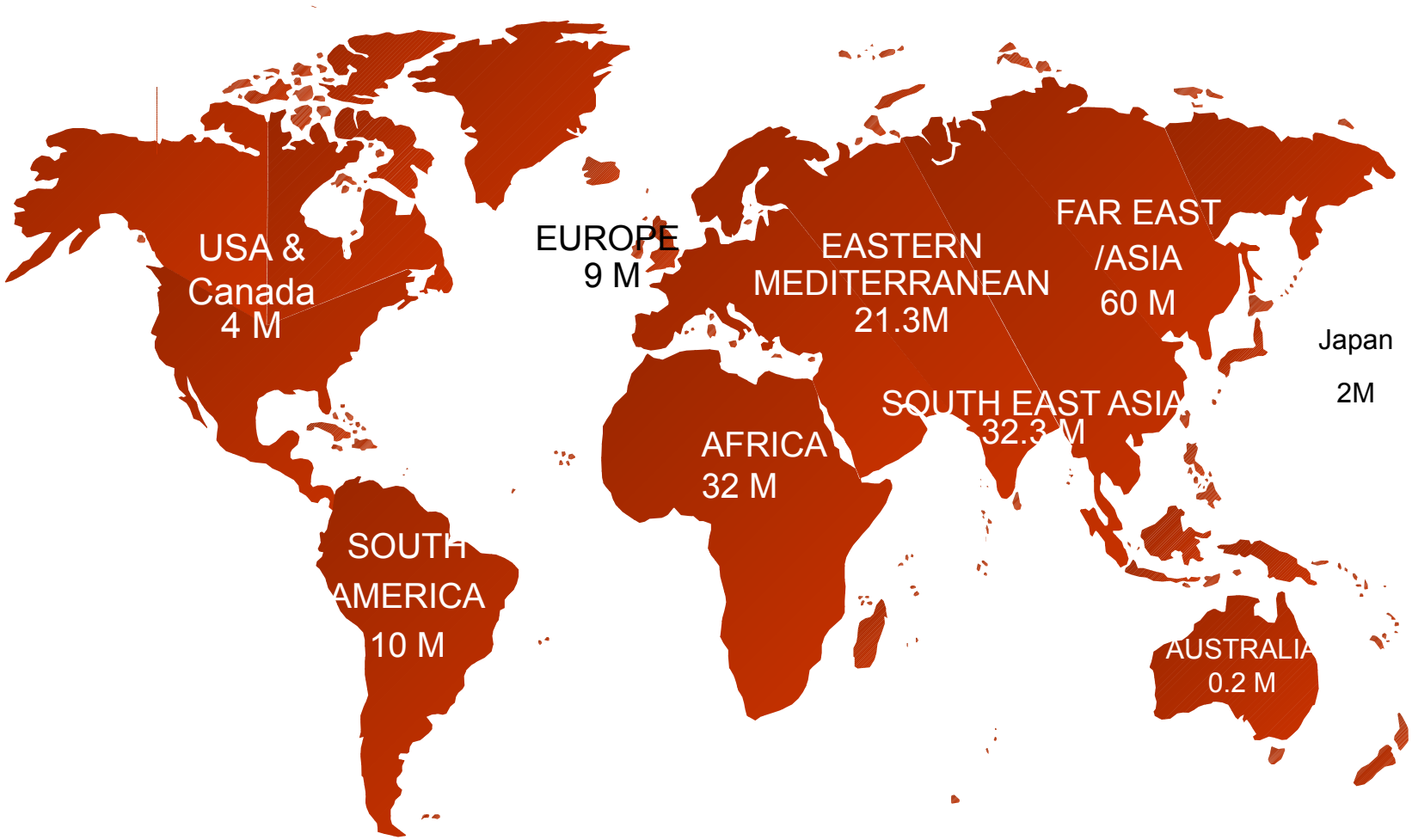
Sofosbuvir + ribavirine : G4 Egyptian origin



NA : non applicable

Ruane PJ, Etats-Unis, AASLD 2013, Abs. 1090, actualisé

HCV worldwide: Limited access to new treatment options in countries with the highest HCV prevalence



Majority of the World
No treatment or
Dual | PegIFN/RBV

170 Millions worldwide

WHO, 1999

Conclusions

- Better knowldege of virology: HCV-4: significant genetic divergence and many subtypes.
- Heterogeneity of HCV-4 disease: Mostly related to the geographical origin of the patients (Europe, Egypt, Africa).
- SVR rates for with PEG-IFN & RBV for HCV-4 around 40 to 50%, mainly related to IFNL3 polymorphism, and cirrhosis
- There is a need for studies with DAAs.
- Finally we need to explore cost effectiveness of DAA treatment strategies.