Genotype 4, finally cured?

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Paris, January 12, 2015

Disclosures

- Investigator, speaker, and advisory board member for: Roche, MSD, BMS, Gilead, Janssen, Abbvie

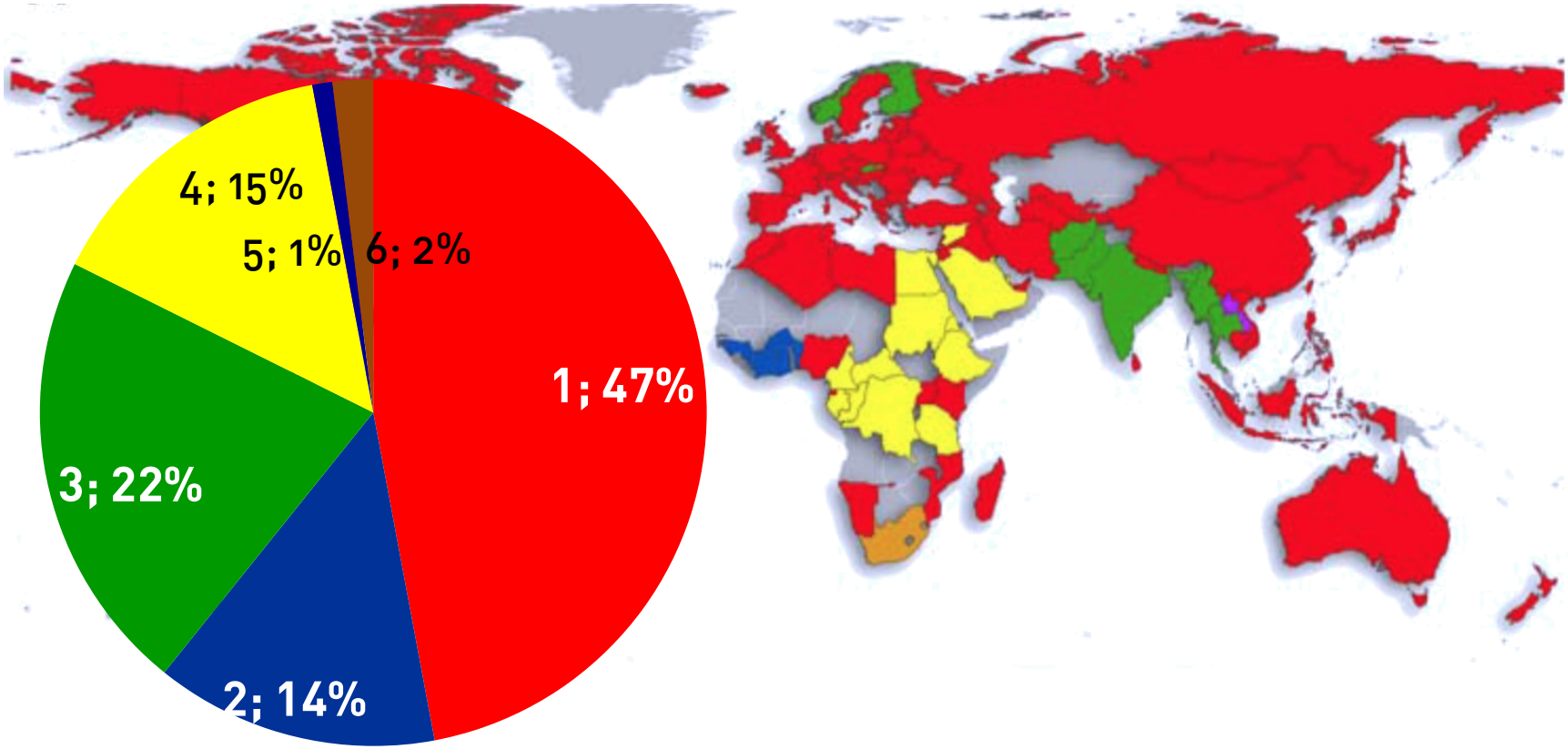
- Presentation includes use of unlicensed drugs

Genotype 4, finally cured?
Outline

- Epidemiology
- Therapy
  - Historical: PEG-RBV
  - Current:
    - PEG-RBV Triple therapy
    - IFN Free therapy
    - IFN and RBV Free therapy
- Subtypes
- The Final Cure?

HCV Genotype Distribution Globally

- HCV a global health challenge with ~150-180 Million chronic HCV infections
- Genotype 1 is the most prevalent in most countries

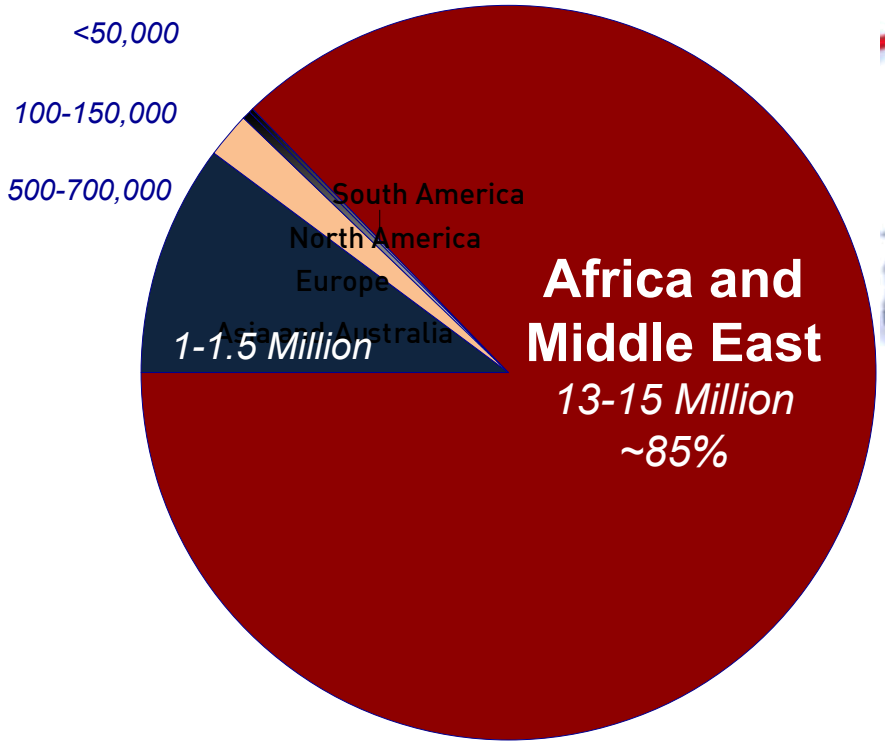


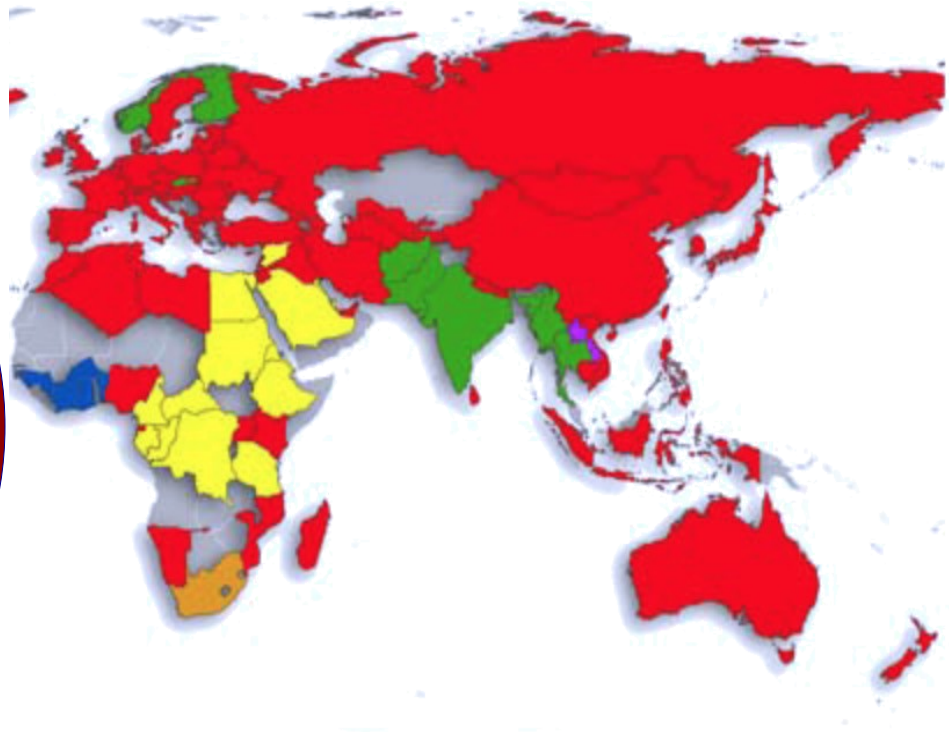
- Genotype 4: 12%-15% (15-18 Million) of total global HCV infection

1. Gower, E., et al., J Hepatol 2014; 61:S45–S57; 2. Messina J. et al. Hepatology, 2015;61:77-87

HCV Genotype Distribution Globally

Global Total ~15-18 Million



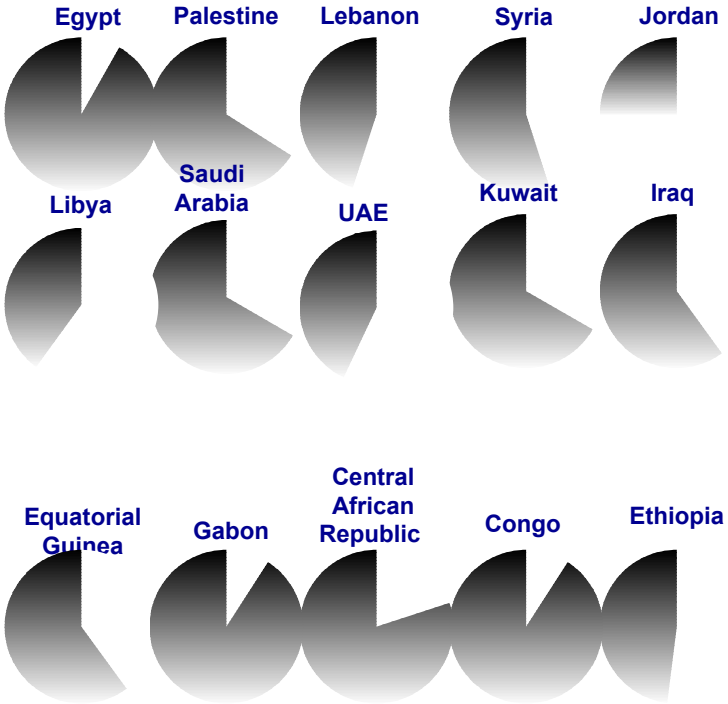


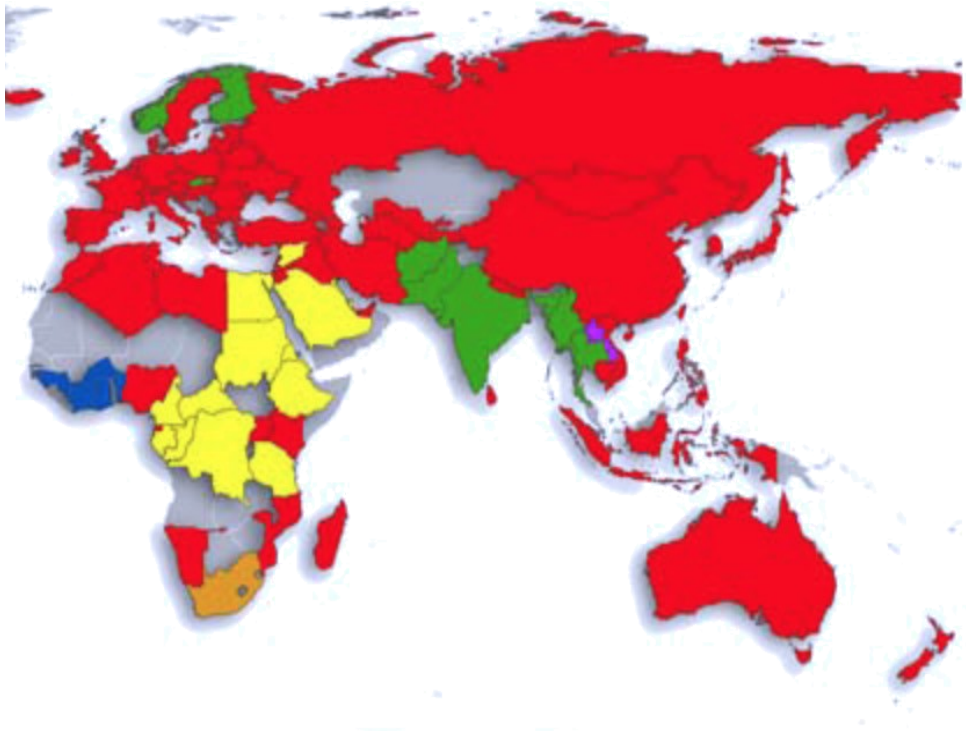
- G-4 distribution restricted to regions: in Egypt, Central Africa, and the Middle East

1. Gower, E., et al., J Hepatol 2014; 61:S45–S57;

2. Messina J. et al. Hepatology, 2015;61:77-87

Genotype 4 Distribution by Country
Africa & Middle East

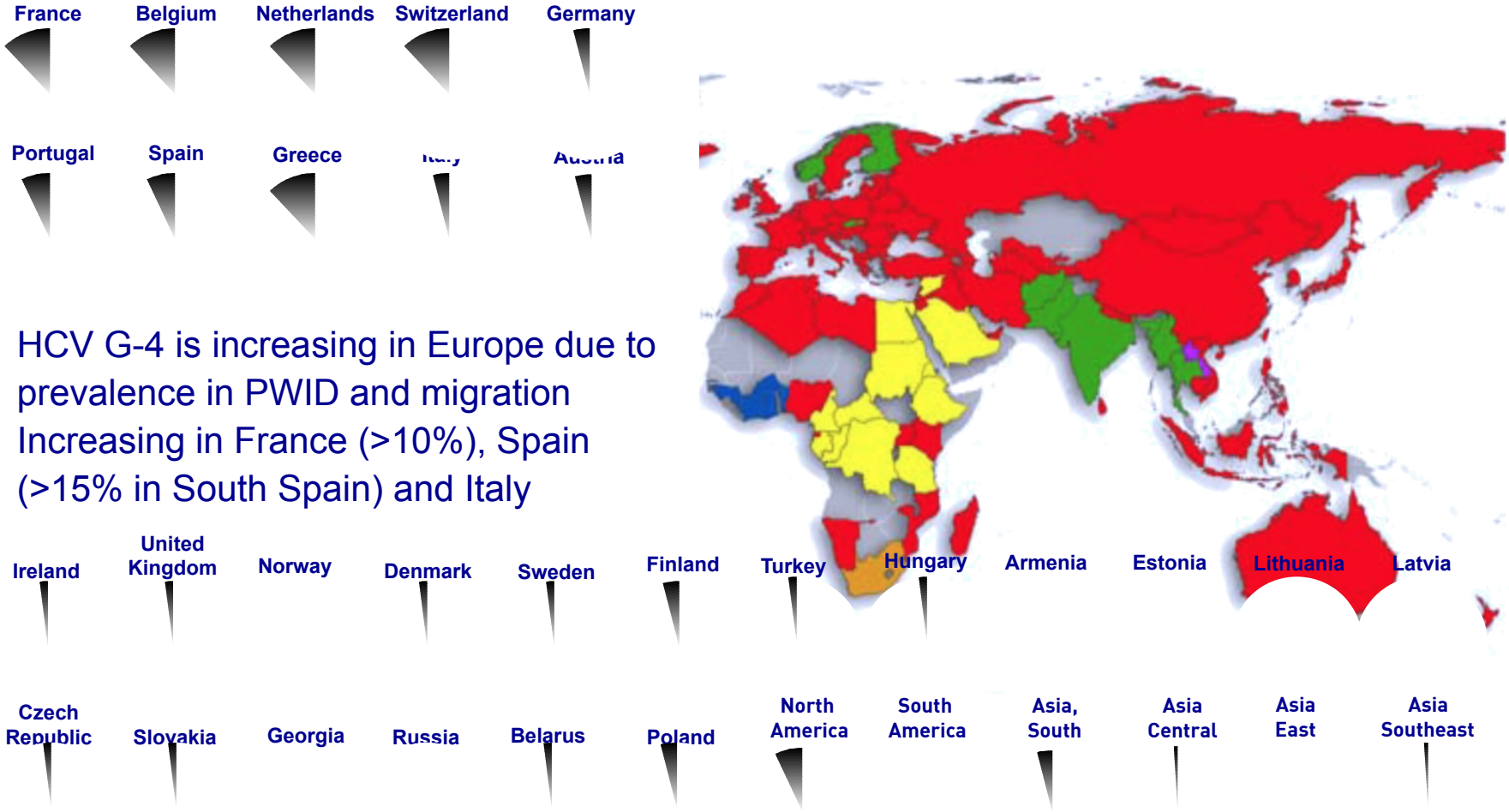




- G-4 is considered “endemic”, circulated for generations in restricted regions

1. Gower, E., et al., J Hepatol 2014; 61:S45–S57; 2. Messina J. et al. Hepatology, 2015;61:77-87

Genotype 4 Distribution by Country
Europe, Asia, North and South America



- HCV G-4 is increasing in Europe due to prevalence in PWID and migration
- Increasing in France (>10%), Spain (>15% in South Spain) and Italy

1. Gower, E., et al., J Hepatol 2014; 61:S45–S57; 2. Messina J. et al. Hepatology, 2015;61:77-87
3. Asselah et al. J Hepatol. 2012; 56:527-32; 4. Cifuentes C Et al. Enferm Infecc Microbiol Clin 2012; 30:452-7;
5. Sariguzel et al. Clin Lab. 2013; 59:1403-8

Genotype 4, finally cured?

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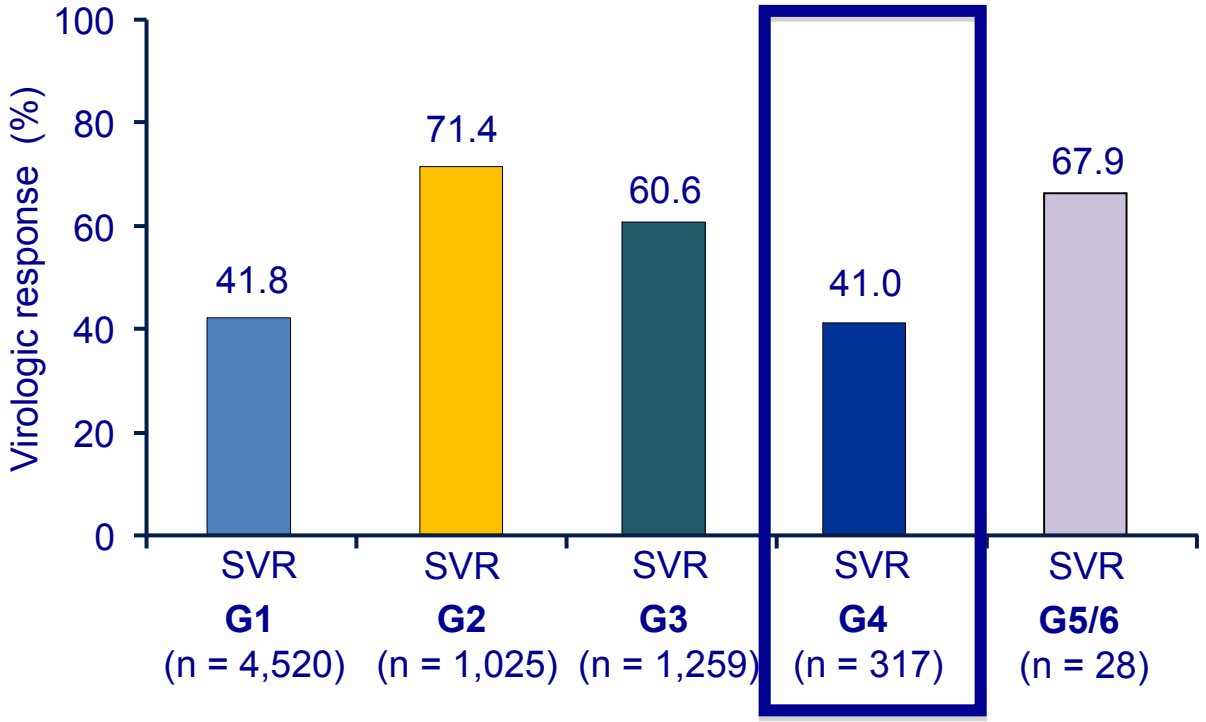
Genotype 4 PEG-RBV Therapy

Real-World Experience for naive HCV patients (PROPHESYS cohort study, n=7,163)

- Historically, HCV-G4 was considered to respond to PEG-RBV better than G1 but lower than G2 and G3



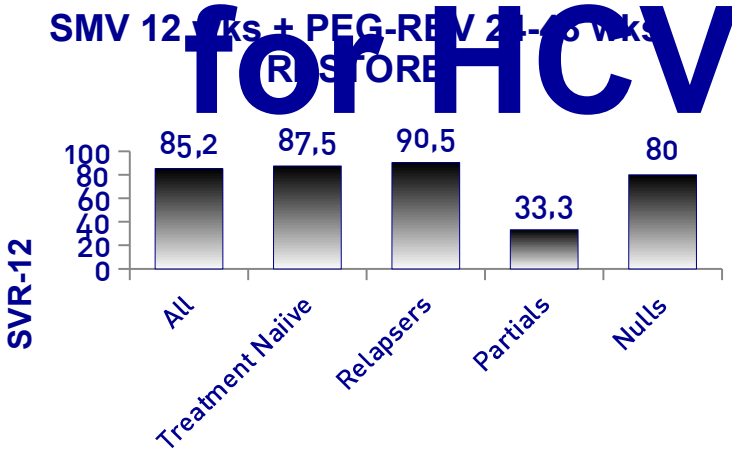
Pts with HCV GT4 treated with PegIFNα + RBV for 48 wks

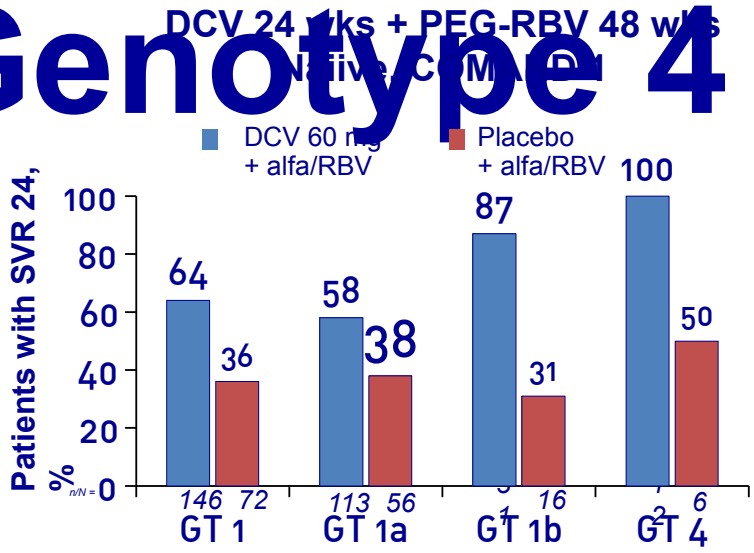
Marcellin P, et al. Hepatology 2012; 56:2039–2050.

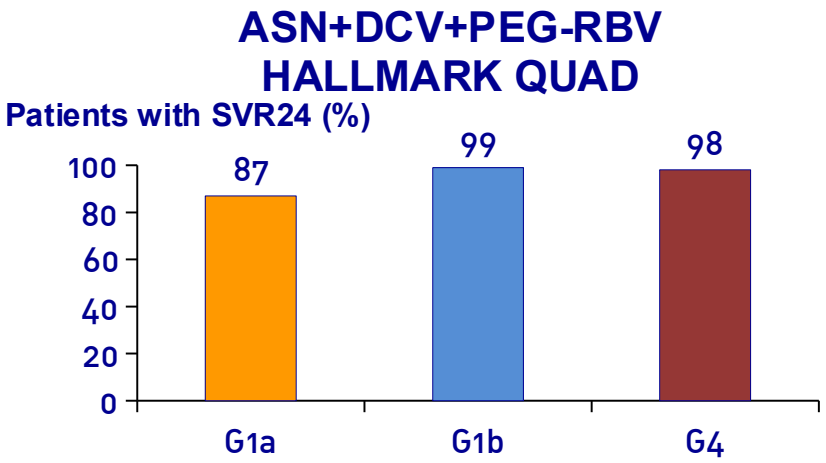
DAAs with Efficacy Data for HCV-G4

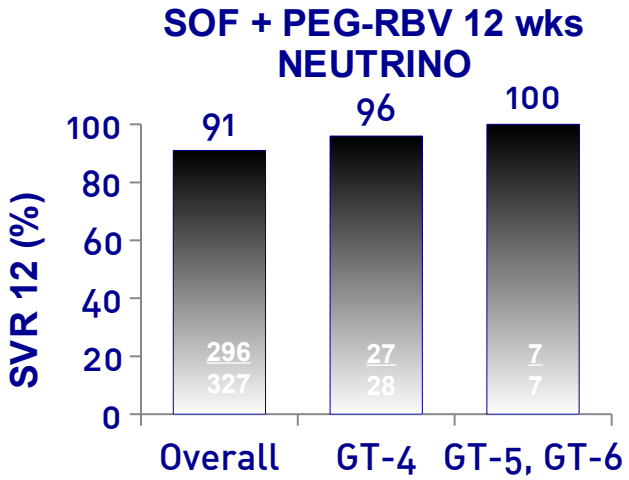
Drug Target		Drugs		
		G4 Approved	Approved for other genotype Effective in G4	Phase II and III Effective in G4
Protease		**Simeprevir**	**Asunaprevir** **Paritaprevir**	**Danoprevir**
NS5A		**Daclatasvir**	**Ledipasvir** **Ombitasvir**	**PPI-668** **GS-5816**
NS5B	Non-nucleoside			**Beclabuvir**
	Nucleoside	**Sofosbuvir**		

PEG-RBV + DAA Triple Therapy for HCV-Genotype 4





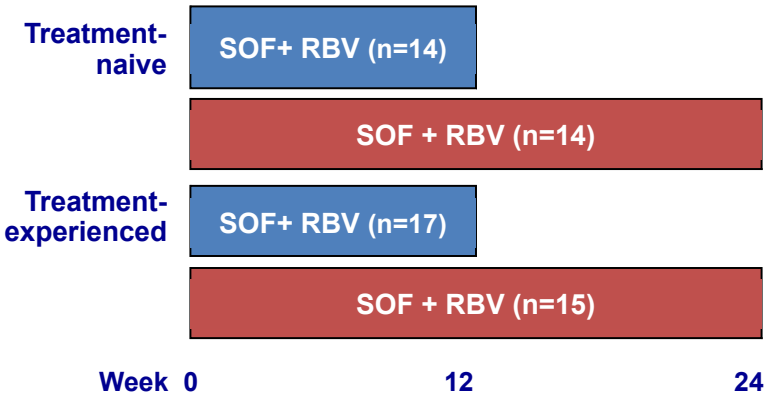


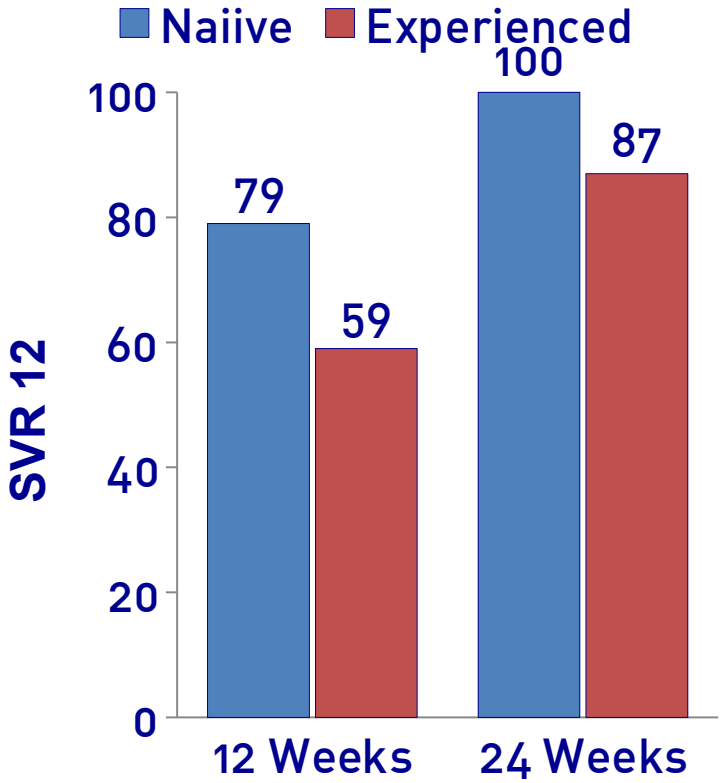


1. Moreno, C., et al. J Hepatol, 2014.
2 Hézode C, et al. Gut, 2014.
3. Jenssen D et al. Liver Intl. 2015.
4. Lawitz, E., et al. N Engl J Med, 2013.

IFN-Free Therapy in Genotype 4
SOF + RBV in Treatment-Naïve and Experienced US Patients of Egyptian Ancestry

- Randomized, open-label, single-center study conducted in the US of the safety and efficacy of all-oral SOF + RBV in patients of Egyptian ancestry with HCV GT 4, 60 patients





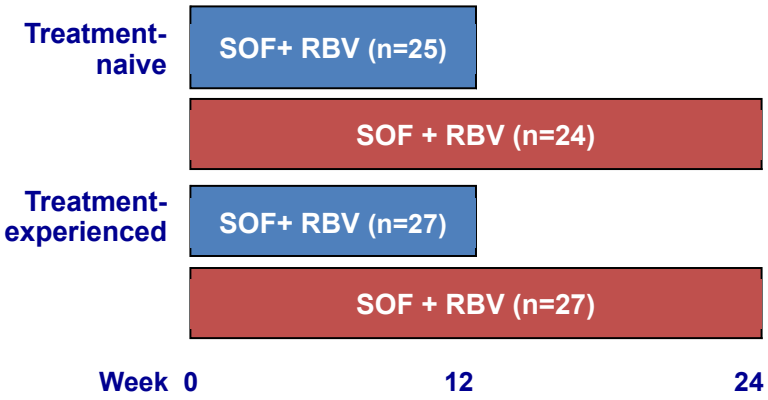
- SOF 400 mg + Weight-based RBV dosing (1000-1200 mg).
- Male (68%), cirrhosis (23%), HCV RNA (5.7 to 6.1 log10 IU/mL), IL28B non-CC (83%).

- SOF+RBV well-tolerated for up to 24 weeks of treatment
  - No discontinuation due to AEs
  - No Grade 4 AEs or lab abnormalities were reported
- No SOF resistance mutation S282T was found in any patient with virologic failure

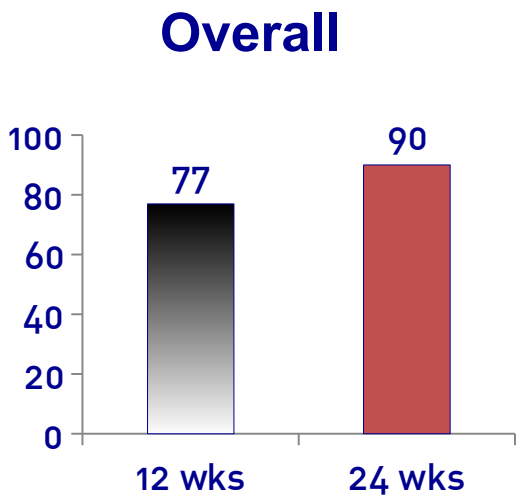
Ruane P, EASL, 2014, P1243

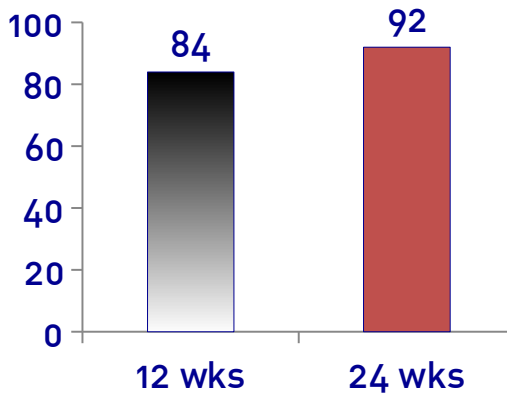
IFN-Free Therapy in Genotype 4
SOF + RBV in Treatment-Naïve and Experienced Egyptian Patients

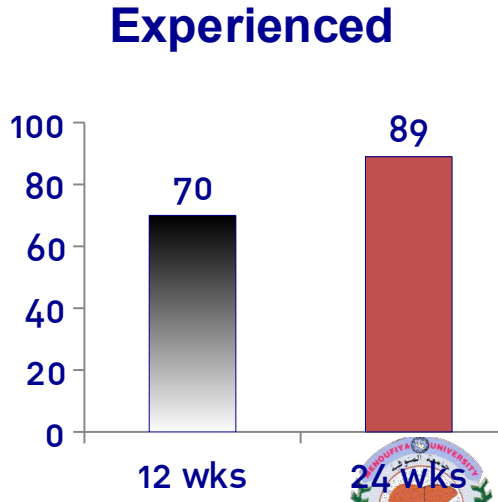
- Randomized, open-label, multi-center study conducted in Egypt of the safety and efficacy of all-oral SOF + RBV in Egyptian patients with HCV GT 4, 103 patients



- SOF 400 mg + Weight-based RBV dosing (1000-1200 mg).
- Male (67%), cirrhosis (17%), 52% high viral load (>800,000 IU/ml), IL28B non-CC (81%).







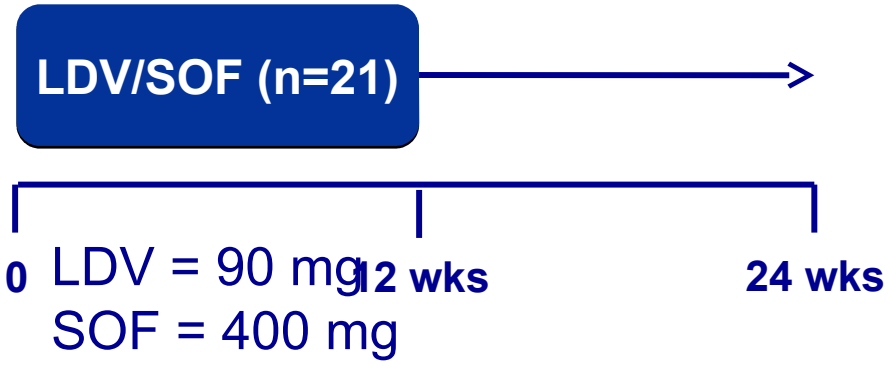
Naïve patients, with <=F2 Fibrosis, low viral load (<600,000 IU): **100% SVR** with 12 wks treatment

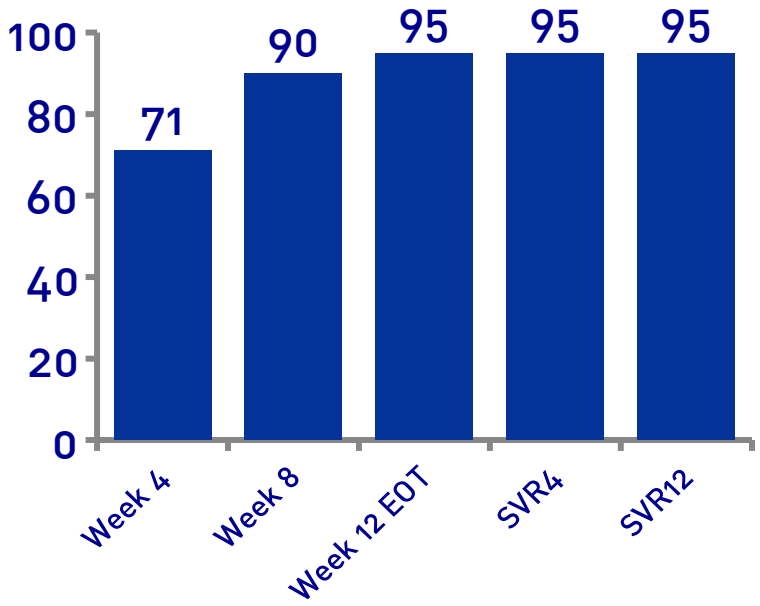
Esmat G. et al. AASLD 2014

IFN- & RBV-Free Therapy in Genotype 4

LED + SOF in Treatment-Naïve and Experienced Patients (SYNERGY)

Phase II trial of LDV/SOF for 12 weeks in GT4-infected patients, including 43% with advanced fibrosis





- 38% Treatment experienced
- 10% advanced fibrosis
- 33% compensated cirrhosis

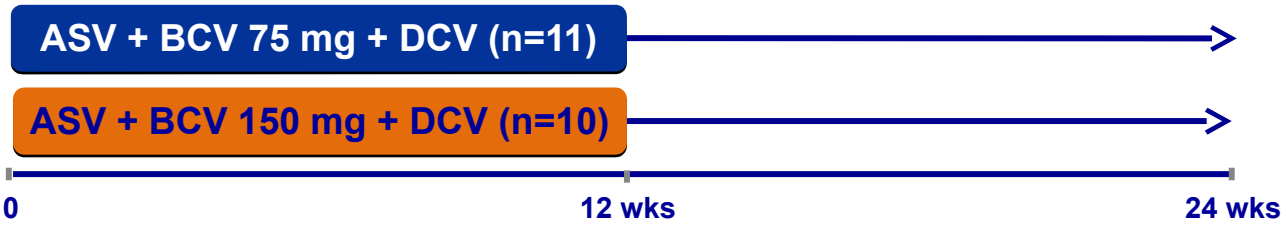
- One person stopped treatment after the first dose.
- Regimen safe and well tolerated, no deaths, SAEs or grade 4 laboratory abnormalities.
- Most common AEs: fatigue, diarrhea and nausea.

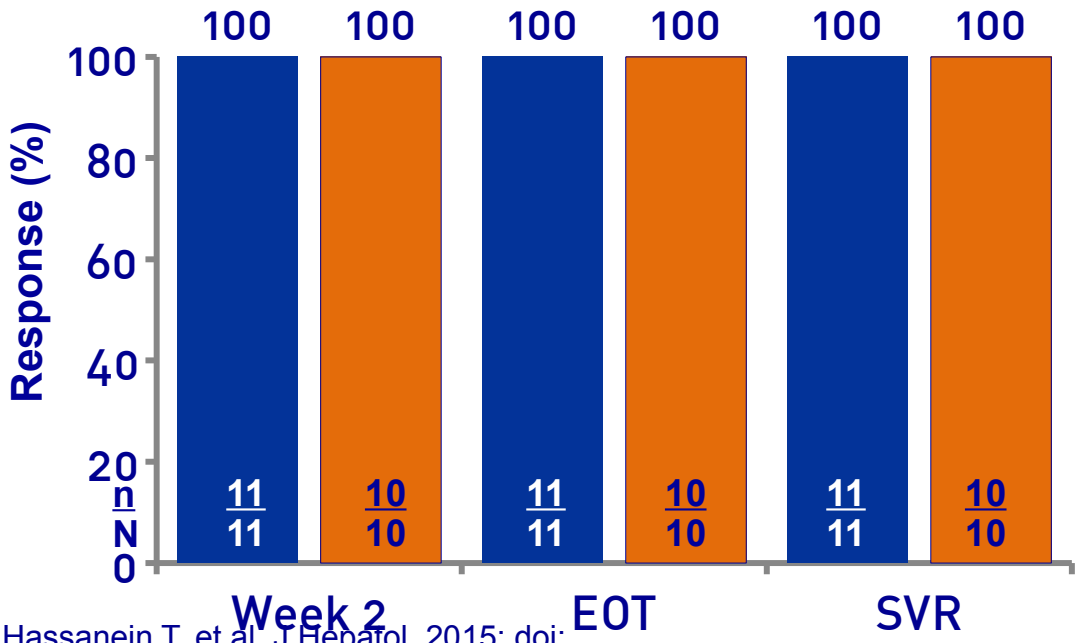
Kapoor R, et al. Hepatology 2014;60(Suppl):91A.

IFN- & RBV-Free Therapy in Genotype 4

ASV + BCV + DCV in Treatment-Naïve Patients

HCV GT4 treatment-naive adults, including those with compensated cirrhosis received triple therapy of ASV, BCV, and DCV for 12 weeks





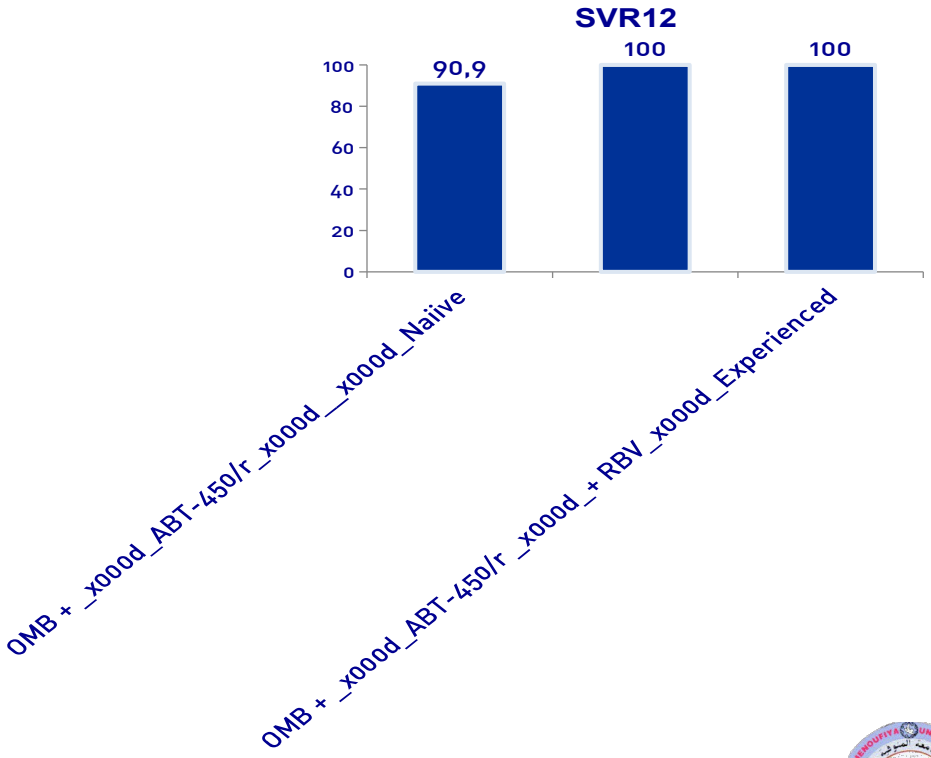
- Two patients had missing data at post-treatment Week 12 but subsequently achieved SVR
- No patient had on-treatment virologic failure or experienced relapse

Hassanein T, et al. J Hepatol. 2015; doi: http://dx.doi.org/10.1016/j.jhep.2014.12.025

IFN- & RBV-Free Therapy in Genotype 4
OMB + PAR/r +/- RBV in Treatment-Naive Patients (PEARL-I)

- An open-label Phase 2b study (PEARL-I) evaluated the safety and efficacy of 2DAAs with or without RBV for 12 weeks for the treatment of HCV GT4-infected patients

Group I N=44 G4	PAR/r + OMB Naiive
Group 2 N=44 G1b	PAR/r + OMB Naiive
Group 3 N=40 G1b	PAR/r + OMB Null Responders
Group 4 N=42 G4	PAR/r + OMB + RBV Naiive
Group 5 N=44 G4	PAR/r + OMB Partial/Null Responders, Relapsers
Group 6 N=49 G4	PAR/r + OMB + RBV Partial/Null Responders, Relapsers



Pol S, et al. Hepatology 2014; 60: 1129A

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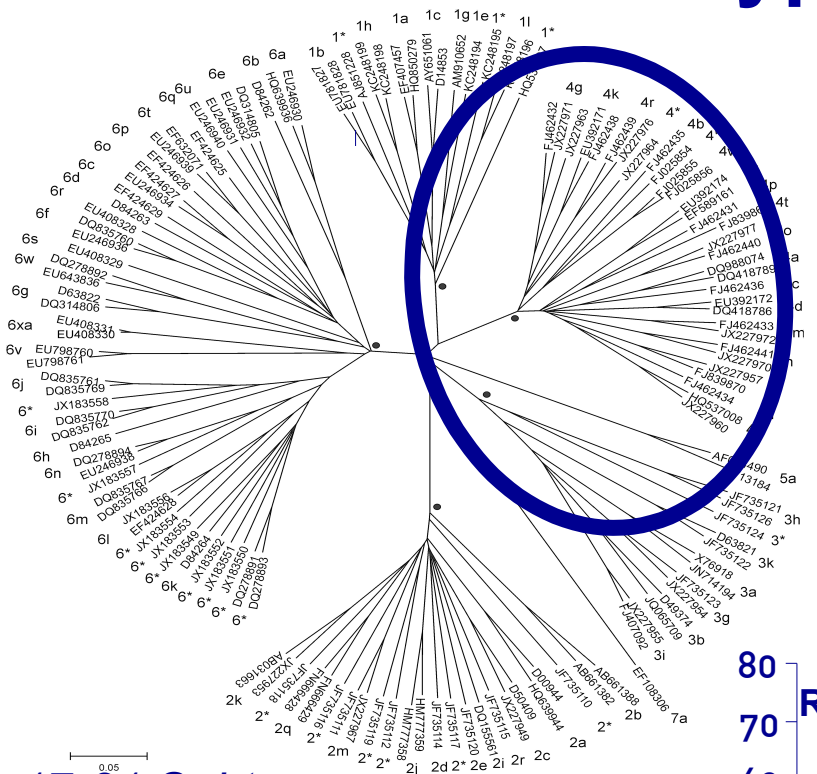
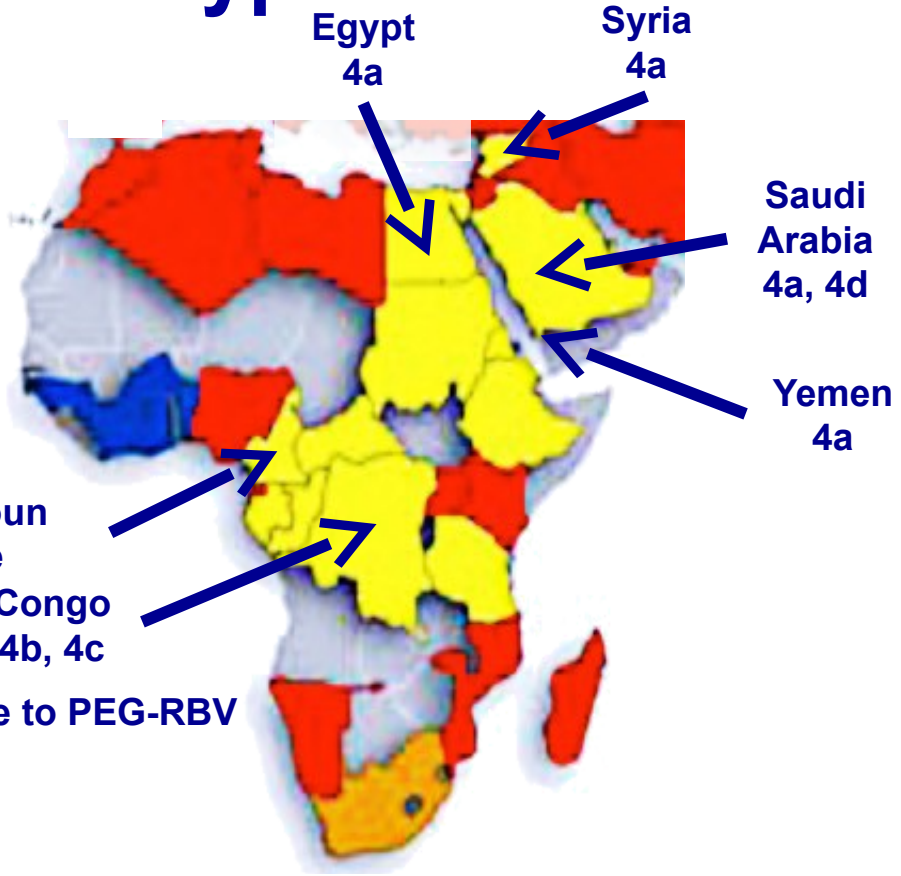
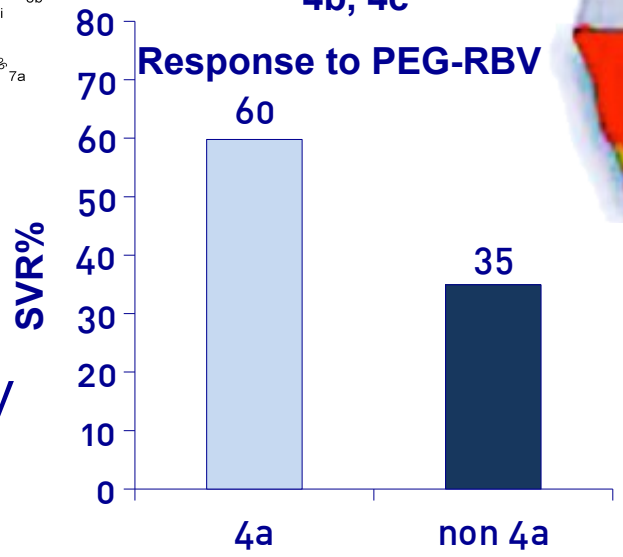
Genotype 4 Subtypes



17-21 Subtypes (4a-4w)





- Subtypes responded differently to PEG-RBV therapy

- Impact of G4 subtype on response to DAA still not known

1. Smith DB. et al. Hepatology. 2014;59:318-27. 2. Gower, E., et al., J Hepatol 2014; 61:S45–S57;
3. Messina J. et al. Hepatology, 2015;61:77-87 4. Roulot D et al. J Viral Hepat 2007 5. Moucari R et al. Gut 2009

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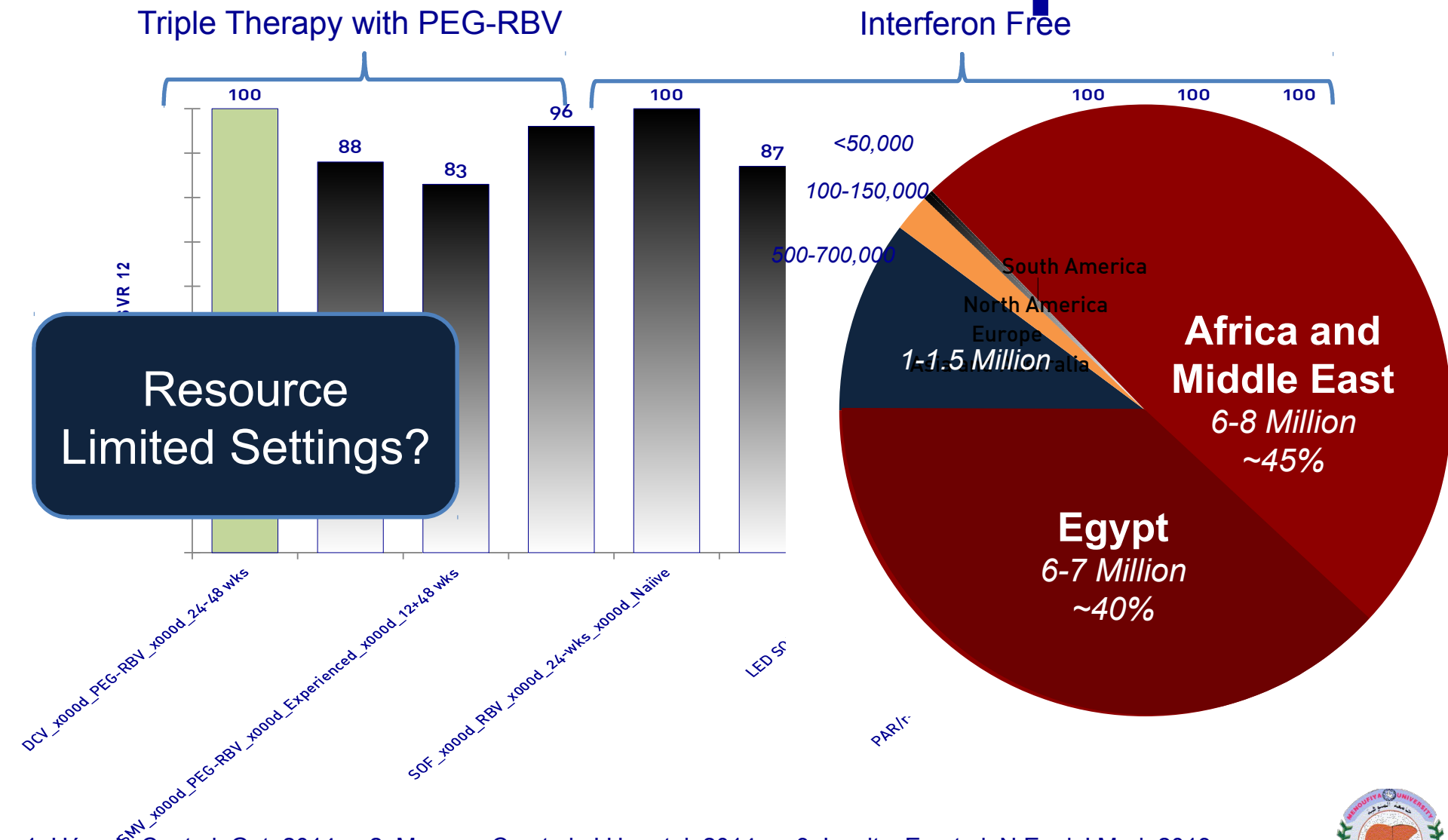
Summary of Currently Available Therapies

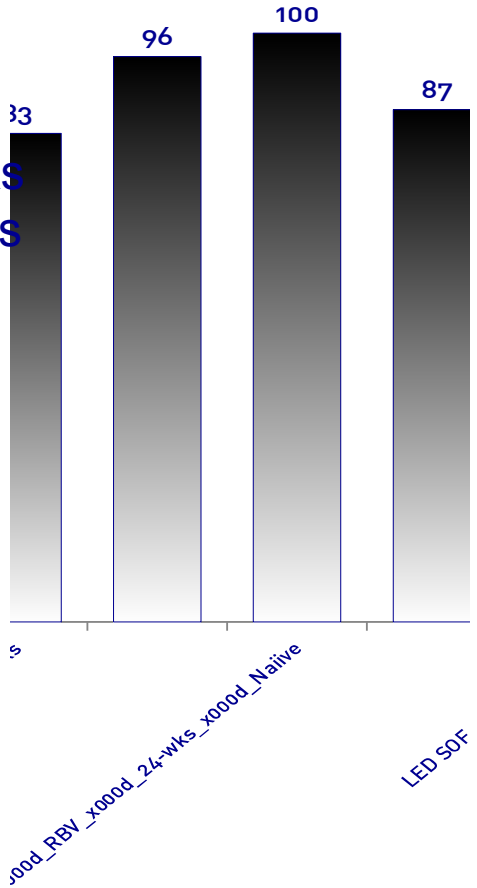


1. Hézodé C, et al. Gut, 2014 2. Moreno, C., et al. J Hepatol, 2014, 3. Lawitz, E., et al. N Engl J Med, 2013.
4. Ruane P et al. EASL 2014, 5. Esmat G el al. AASLD 2014, 6. Kapoor et al. AASLD 2014, 7. Pol S. et al. Hepatology 2014

The Final Cure?
Resource Limited Settings?
The Egypt Example

- Currently: SOF based therapy
  - SOF-PEG-RBV 12 wks for IFN eligible patients
  - SOF-RBV 24 wks for IFN ineligible patients
- Total estimate 6-7 Mill
  95% G4

  - Gilead access program reduced cost drastically
  - National treatment program started October 2014



- 738,000 registered for evaluation
- 40,000 F3 and F4 selected for treatment
- 15,000 started treatment,
  33% SOF+PEG-RBV
  67% SOF+RBV

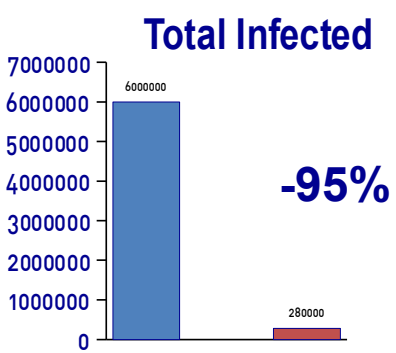
  - Of those who reached wk4,
    - 99% >2 log10 reduction in viral load
    - 82% RNA <LLQ (<15 IU/ml)

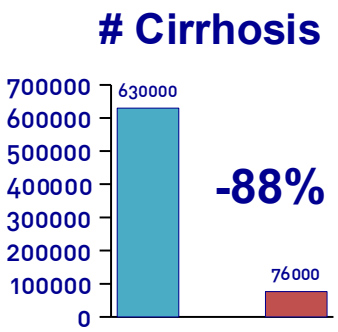
81.3% SOF-RBV
83.3% SOF-PEG-RBV

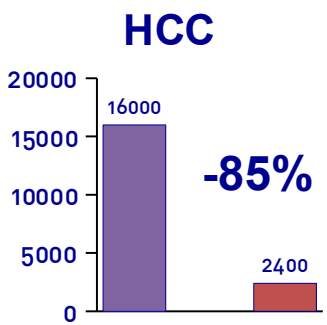
NCCVH Egypt, Data on file

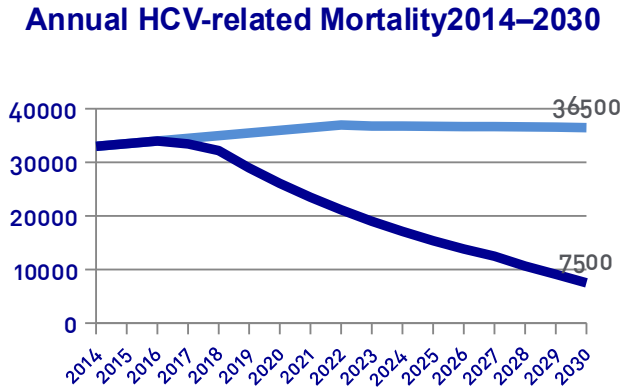
The Final Cure?
Resource Limited Settings?
The Egypt Example

- Negotiating and evaluating IFN & RBV free therapies for G4:
  LED-SOF, SIM-SOF, DCV-SOF, OMB-PAR/r
- National HCV Control Target:
  Treat 300-350,000 a year, 90% SVR, 10-15 yrs









- **HCC: 170,000 cases Prevented between 2015 and 2030**
- **Mortality: 260,000 cases prevented between 2015 and 2030**

1. NCCVH data 2. Waked I, et al. Arab J Gastro. 2014

Summary

- HCV G4 is common, mainly in resource limited settings in Africa and the Middle East
- Increasing in Western Europe
- Egypt has 40% of global HCV-G4 patients
- Current therapies have high cure rates
- All oral therapies with > 95% SVR and short duration becoming available, promising complete cure
- With affordable prices, HCV-G4 will be cured, even in the resource limited settings where it is most prevalent

Merci

Thank You

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