Working Luncheon:
How to optimize treatment in G4 patients?
Treatment

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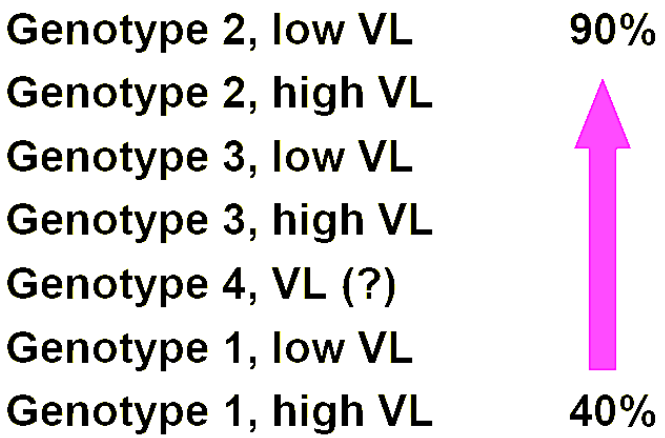
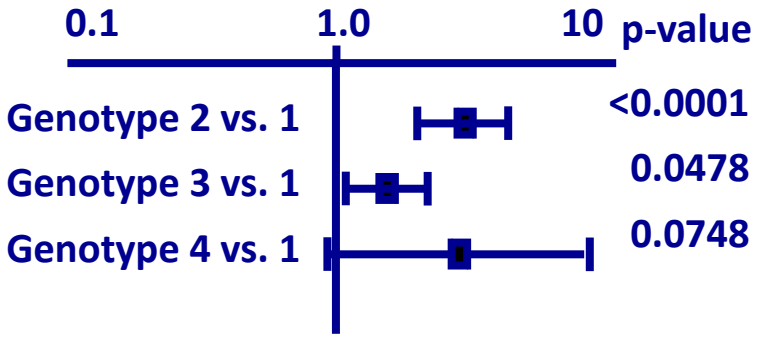
Background

- G4 considered *"difficult to treat"* with PEG-RBV
- Response was better than G1, less than G2&3
- With G1 effective DAAs, G4 became the *"most difficult to treat"*
- SOF approval for G4 changing outcome





Fried MW et al. J Hepatol. 2008;48:S5

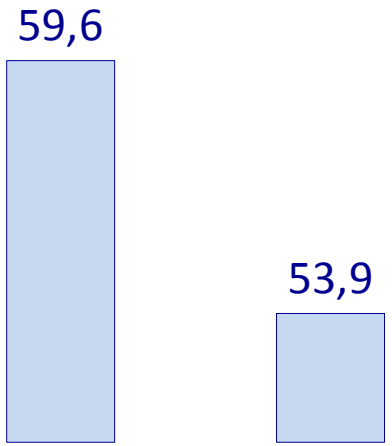
Outline

- Current status of therapy and predictors of response to PEG-RBV
- Response guided therapy?
- Can we improve outcome of PEG-RBV therapy? NTX, Vit D
- Direct acting antivirals

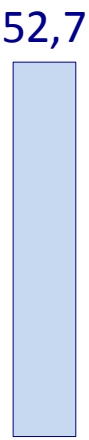
G4 Real Life Response to PEG-RBV

Egypt treatment program:

- MOH: 50-60,000/year since 2006
- HIO: ~5,000/ year since 2009
- ~350,000 treated patients in 6 years



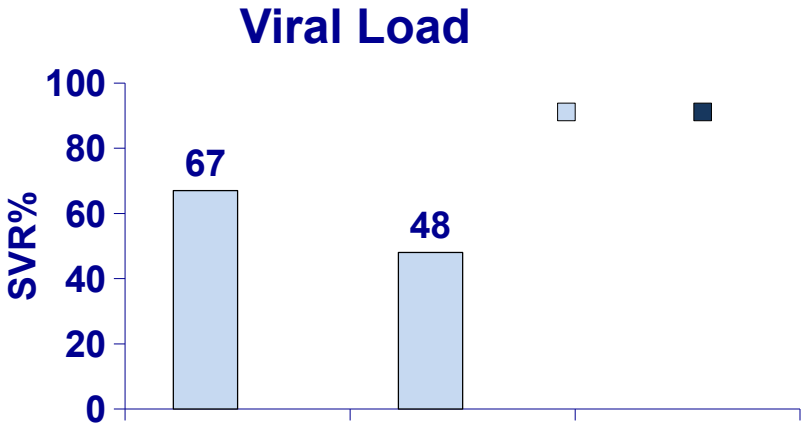
3,718 chronic HCV patients
1,985 PEG-IFN alfa-2a+RBV
1,733 PEG-IFN alfa-2b+RBV

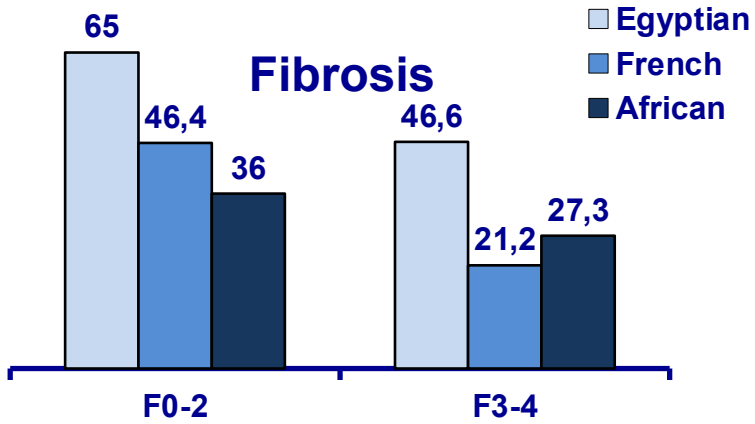


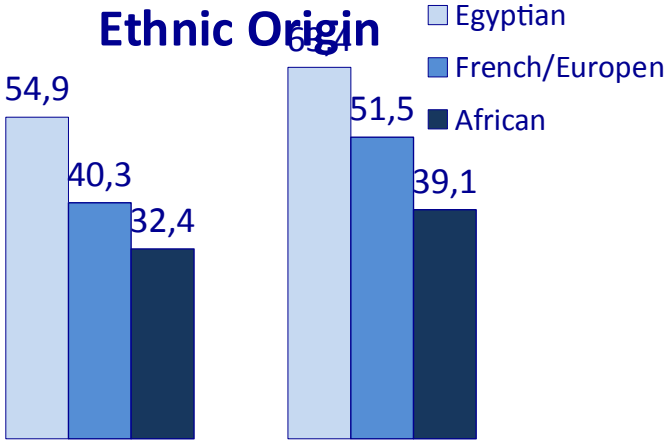
2,200 chronic HCV patients.
PEG-IFN alfa-2a (bio-similar 160 mcg) + RBV

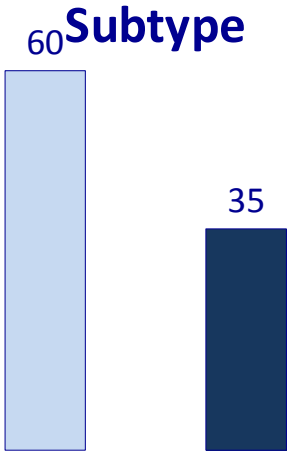
El Raziky et al, Hepatitis Mon, 2013
Esmat et al. HIO, unpublished

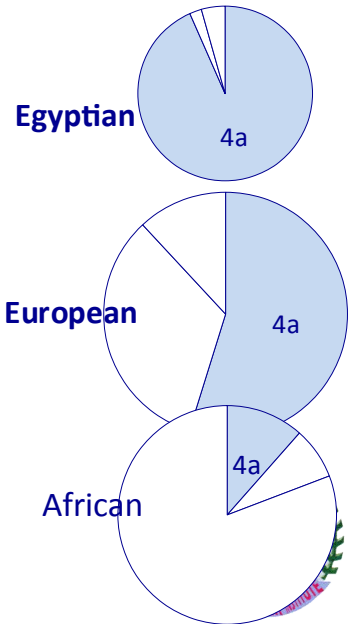
G4 Predictors of Response to PEG-RBV





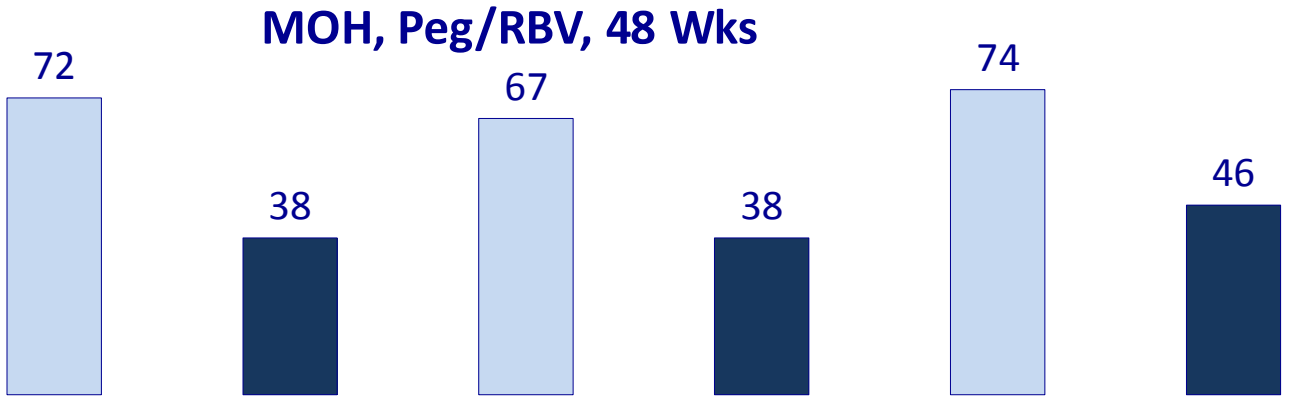


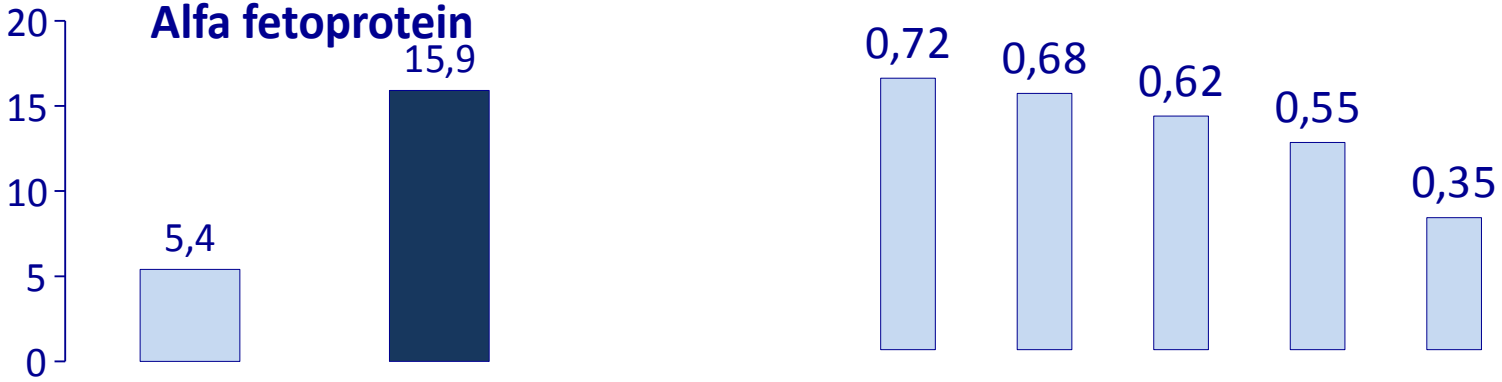




Huepper et al, AASLD 2007; Roulot D et al. J Viral Hepat 2007
Moucari R et al. Gut 2009

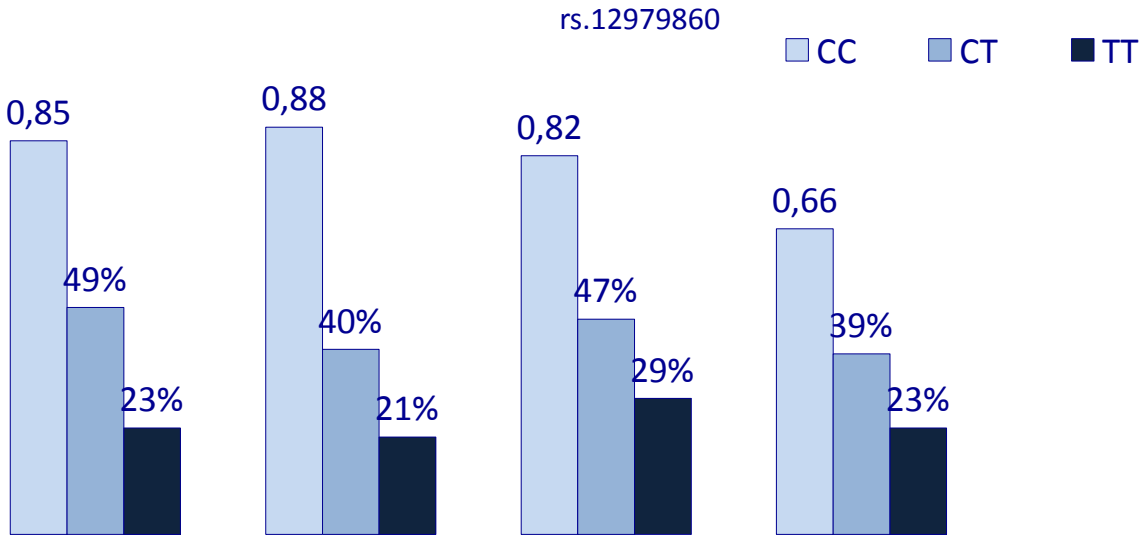
G4 Predictors of Response to PEG-RBV





Gad et al. Liver Intl. 2008; Abdoul H, et al. PLoS ONE. 2008
Barbesh et al., MOH, 2013 in Press; El Raziky et al., MOH, 2013, In Press

G4 Predictors of Response to PEG-RBV
IL28B genotype



Stättermayer et al, Clin Gastro and Hepatol, 2011. De Nicola et al. Hepatology 2011.
Assellah et al. J Hepatol 2011,. Antaki et al. Journal of Viral Hepatitis, 2013

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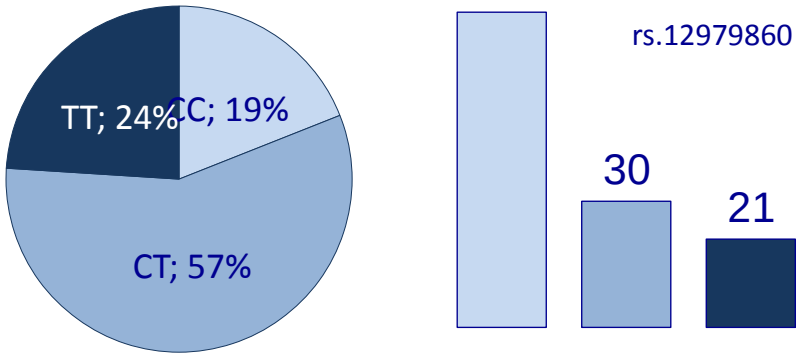
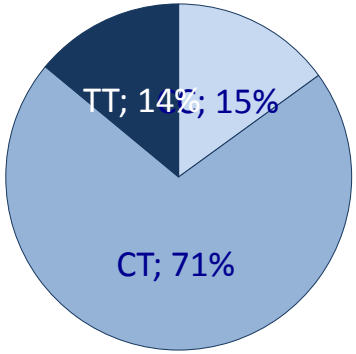
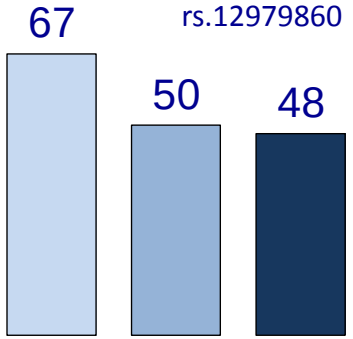
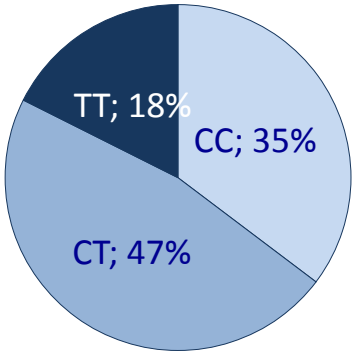
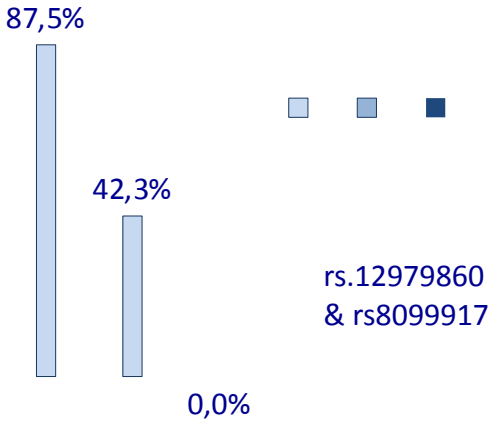






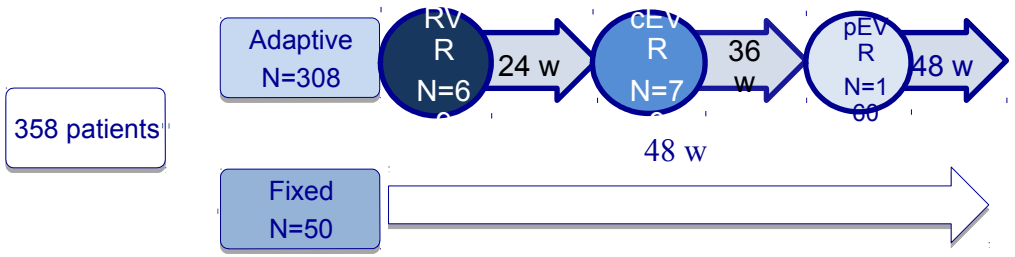


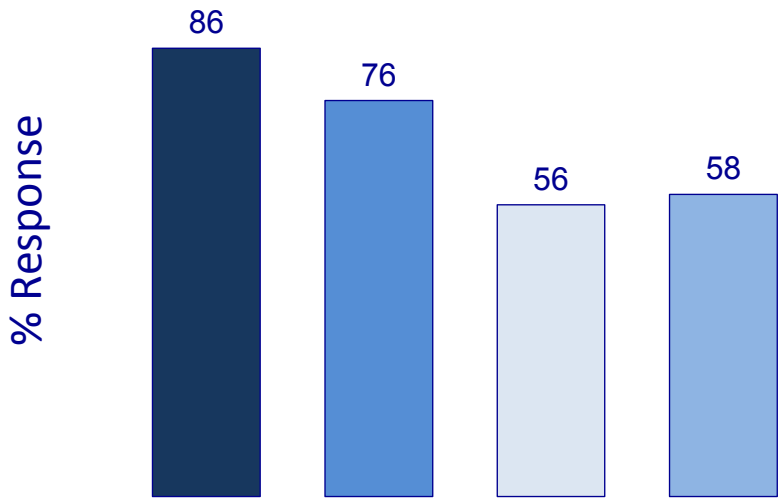


Shaaban et al. MOH, NLI, in press; El-Awady M, et al.World J Gastroenterol 2013
Ragheb et al. Liver Intl. 2013

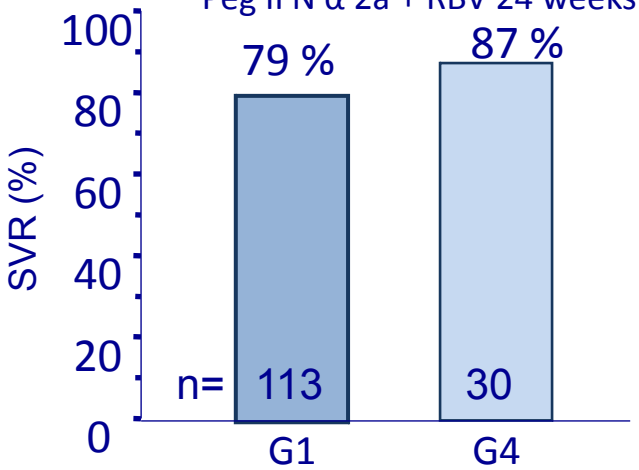
Response Guided Therapy in G4 treated with PEG-RBV

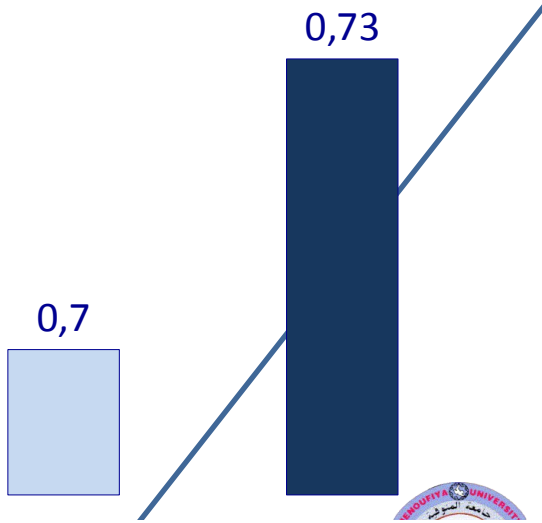
RVR, EVR guide for length of therapy





SVR in RVR (45%)
Peg IFN α 2a + RBV 24 weeks

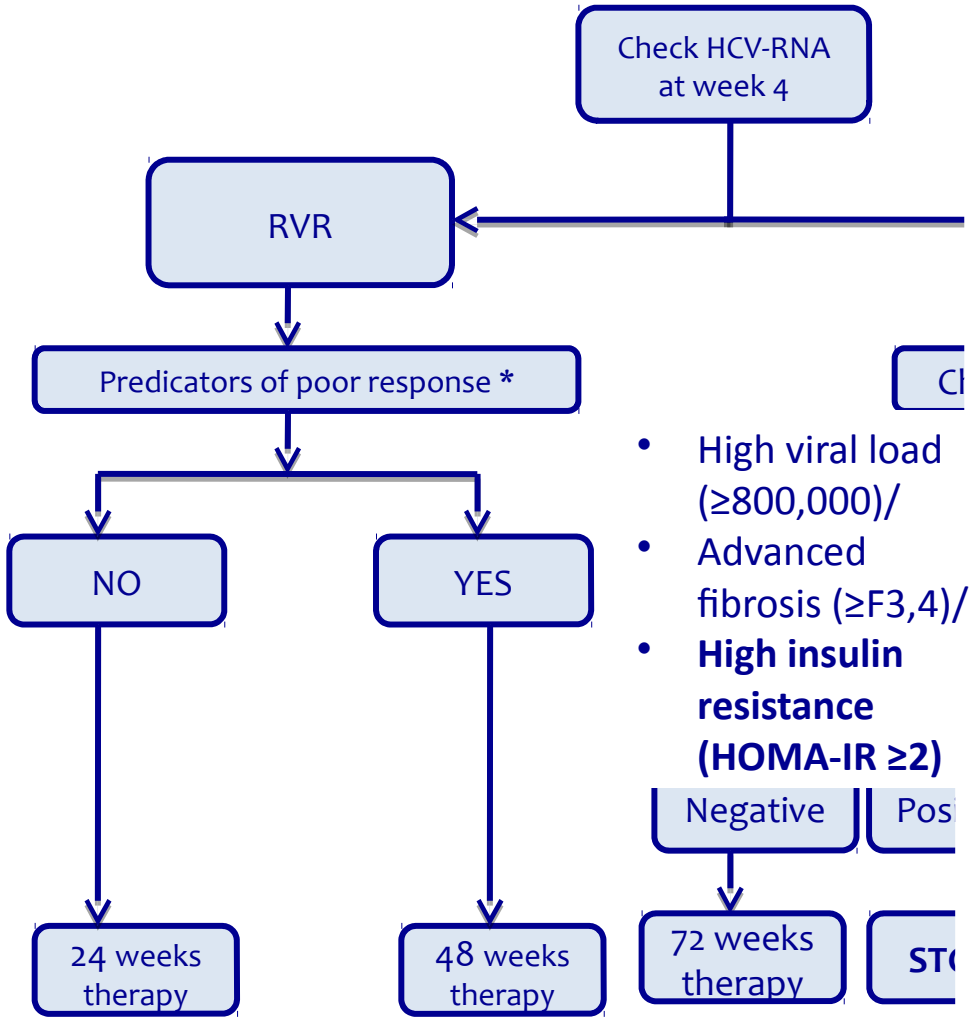


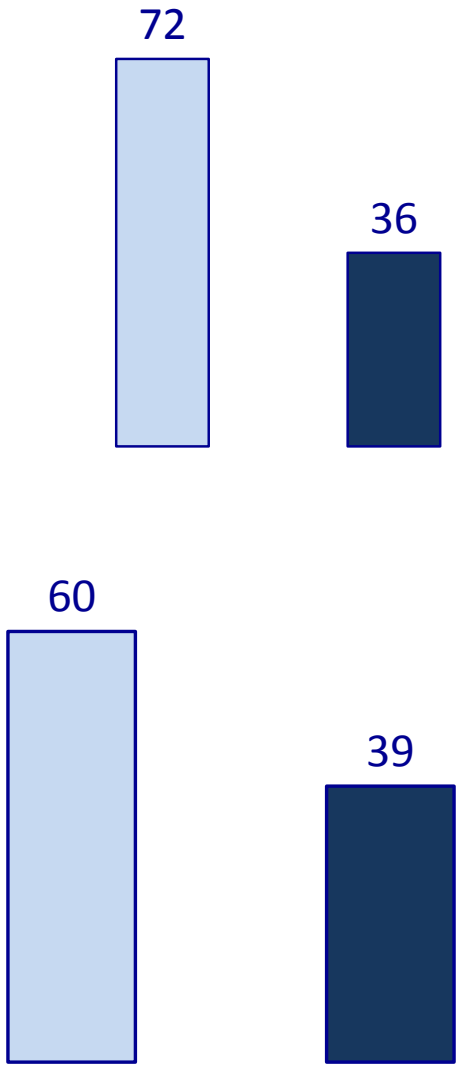


Kamal et al, Hepatology. 2007
Ferenci P, et al. Gastroenterology 2008
El-Khayat H, et al. Tropical Gastroenterology 2012

Pts with low viral load (<600,000 IU/ml), no cirrhosis, RVR: 85%, 24 vs 48 wks

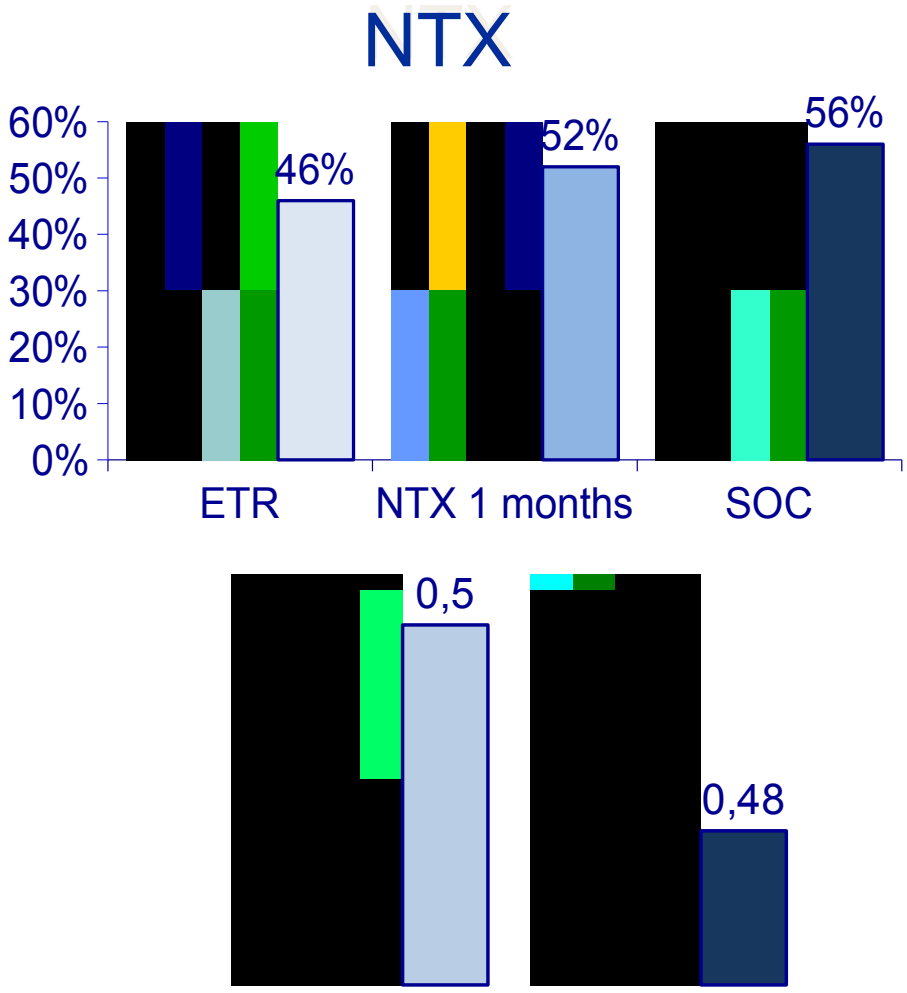
International Expert Panel Algorithm

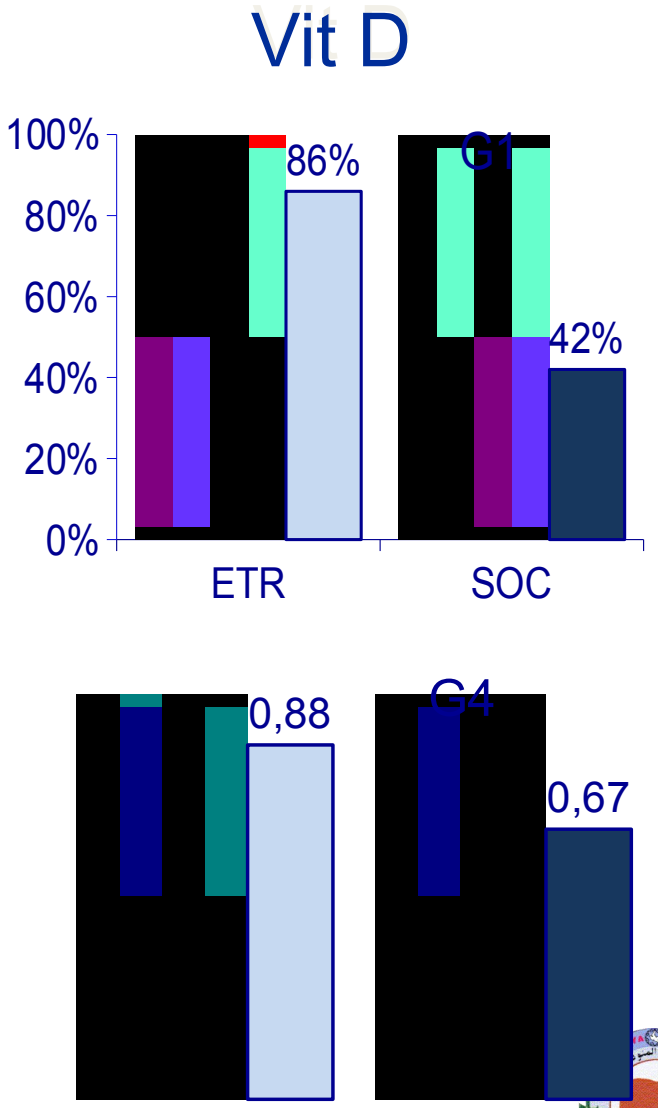




Khattab et al. J. Hepatology 2011
Moucari R et al. Gut 2009; Khattab M et al. Liver Int. 2010

Improving on Current Therapy

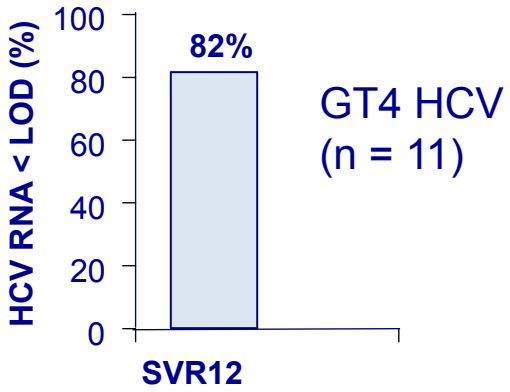




Abu-Mouch S, et al. World J Gastroenterol 2011
Shehab, H et al. Liver International. 2013
El-Deeb et al. MOH data, In Press

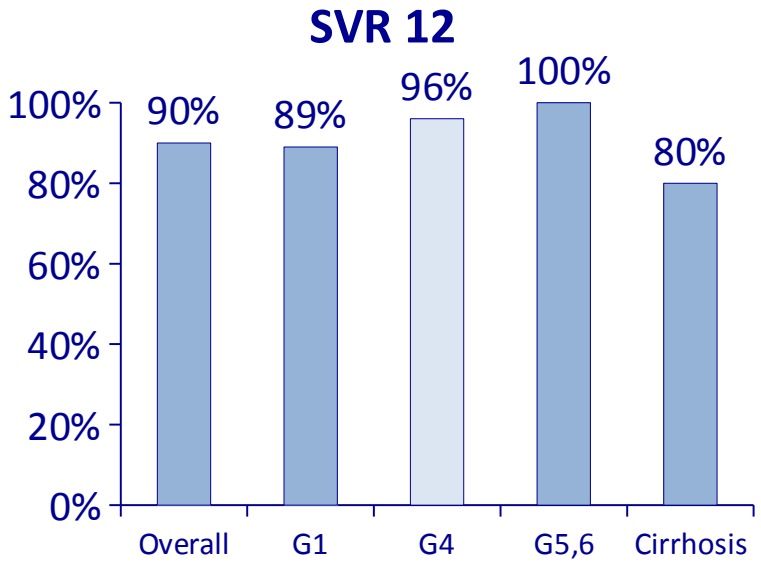
Direct Acting Antivirals for G4 2nd Generation: Triple Therapy Sofosbuvir (Sovaldi) + Peg/RBV

Phase II, ATOMIC



- 11/11 patients with genotype 4 HCV achieved RVR and EOT response
  - 2 LTFU without posttreatment data
- No relapse after SVR12 in either group

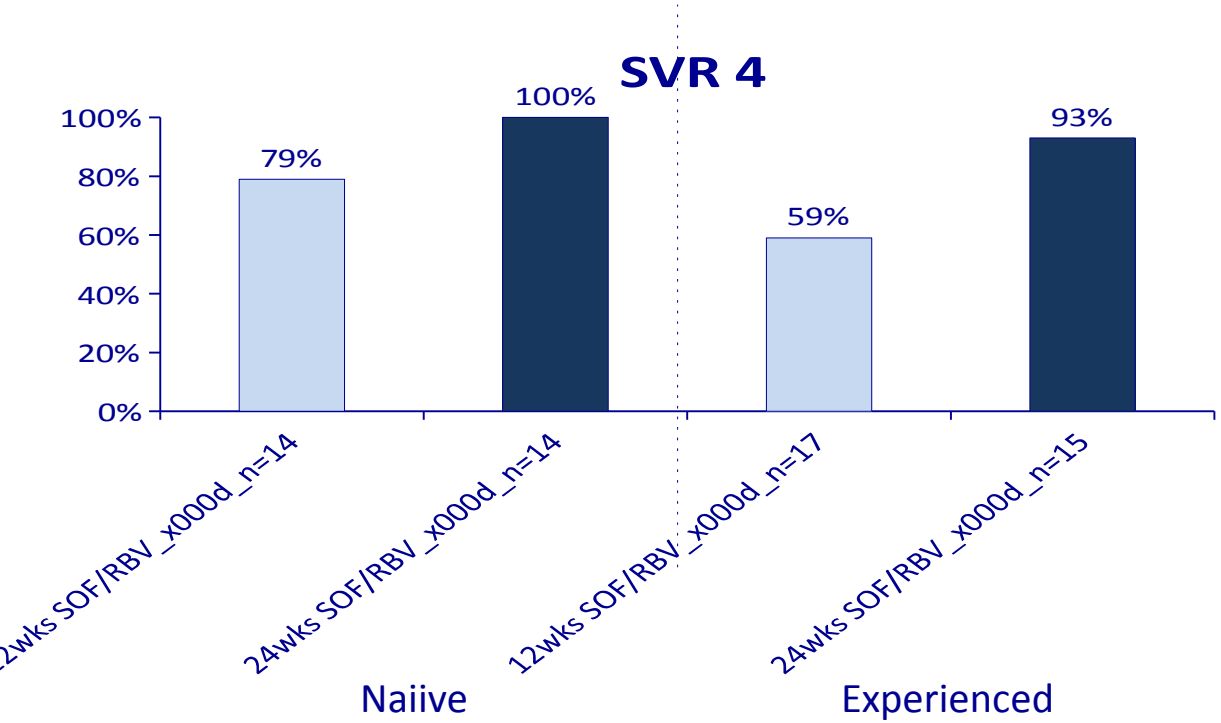
Phase III, NEUTRINO



- 12 wks SOF 400 mg QD+ PEG-RBV
- 291 (89%) genotype 1
- 28 (7%) G4, 7 (2%) G5,or6

Kowdley C, et al.Lancet 2013
Lawitz et al. N Engl J Med. 2013

Direct Acting Antivirals for G4 2nd Generation: Interferon Free Sofosbuvir (Sovaldi) + RBV



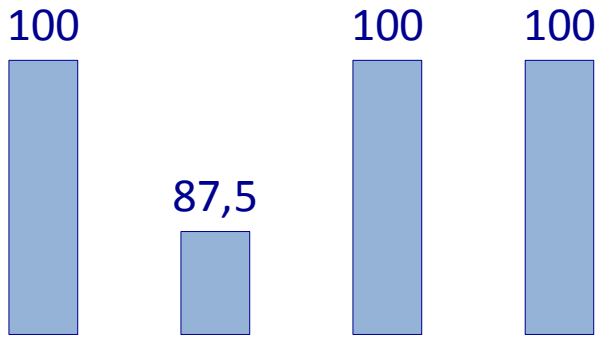
IFN Free study in Egypt:

- 12 vs 24 wks SOF+RBV
- Naiive and experienced
- LPLD in 2/2014
- SVR 12 expected in 5/2014

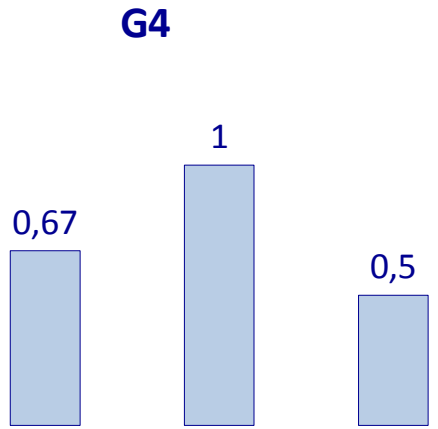
Ruane P et al. AASLD 2013

Direct Acting Antivirals for G4
2nd Generation: Phase II

Danoprevir/ritonavir + Peg/RBV
Naiive, Phase II, DAUPHINE



Daclatasvir + Peg/RBV
Naiive, Phase II, Command 1



- **ABT 450/r + ABT267 ± RBV: Pearl I: G4**
- **SMV + PRG/RBV (RESTORE) SVR4~90% in Naiive & Relapsers**
- **SMV + Samatasvir (IDX719) + RBV (Helix) ~80% in G1 and 4**

Hézode C, el al. AASLD 2012. Hézode C, et al, AASLD 2012. Moreno et al., EACS 2013

Conclusions

- Patient selection can identify G4 patients with high possibility of cure (~80%)
  - Low viremia, low fibrosis
  - IL-28B CC
  - Low HOMA score
- RVR can select patients for shorter therapy
- Vit D can further increase response?
- DAA effective, will not be immediately available for all G4 patients everywhere

- In Egypt: cost of treatment for with PEG-IFN-RBV
  - <€1,500 per patient
- MOH budget for HCV: €70Million
  - 50,000 patients with IFN-RBV, 60% completing therapy
  - 50-55% SVR (25,000 SVR)
  - 2nd Generation DAAs: 3 months therapy: €50-70,000
  - ~1,000 patients with 2nd generation DAAs

Case 1

- 26 Y male, HCV+ve on pre-employment
- Transfused at age 3 for hemolysis due to G6PD deficiency
    - ALT normal
    - RNA 2,500,000 IU/ml
    - G4d
    - Fibroscan 5 KPa
    - Bx A1F1
    - IL-28 TT

Case 1

- Decision:
  - Treat Now?
  - FU and Wait for 2nd generation DAA
- What are his chances of achieving SVR with PEG/RBV therapy?
  - 15%
  - 25%
  - 40%
- Treated PEG/RBV 48 wks, EVR, ETR, relapsed
- What will be his chances of SVR with all oral combo:
  - 50%
  - 85%
  - 100%
- What is his risk of progressing to advanced fibrosis or cirrhosis (F3-4) in the next 5 years?

Case 2

- 32 Y female, HCV+ve on travel check-up
- Transfused for PP-Hge 5 years earlier
  - ALT normal
  - RNA 400,000 IU/ml
  - G4a
  - Fibroscan 6 KPa
  - Bx A0F1
  - IL-28 CC

Case 2

- Decision:
  - Treat Now?
  - FU and Wait for 2nd generation DAA
- What are her chances of achieving SVR with PEG/RBV therapy?
  - 25%
  - 55%
  - 80%
- Treated PEG/RBV
  - RVR
  - Continue 24 wks or 48 wks?
- Continued for 48 wks, RBV dose reduction, EPO, SVR
- What would have been her chances of achieving SVR with G4 effective all oral combo therapy?

شُكْراً

Thank You