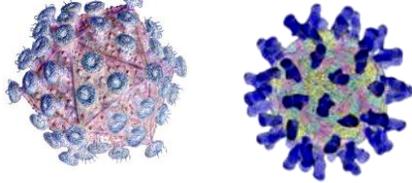


## Future HCV Therapy for non-1 Genotype Infection



Ed Gane  
NZ Liver Transplant Unit

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## Disclosures

- I have the following financial relationships to disclose within the past 12 months:
  - Advisory board committees or speaking for Gilead Sciences, Janssen, MSD, Roche, Achillion, Idenix, AbbVie, Novartis

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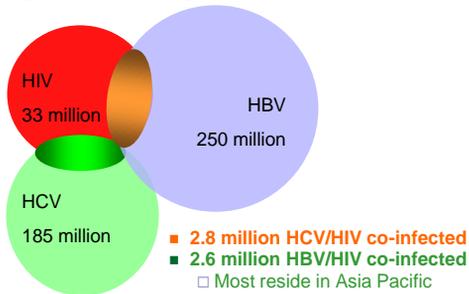
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## Worldwide Prevalence of Chronic Hepatitis B, Hepatitis C and HIV



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### Triple Therapy cannot meet the unmet medical need in patients with HCV?

**1. Poor tolerability**

- Still requires Pegylated Interferon and ribavirin
- Added toxicities of the PIs
- Poor safety in advanced liver disease

**2. Complex dosing regimen**

- High pill burden - 8 hourly, with high-fat meal
- Frequent on-treatment monitoring required
- Multiple drug interactions with ART

**3. Limited Efficacy**

- Null responders
- Subtype 1a and Q80K RAV
- HCV genotypes other than 1

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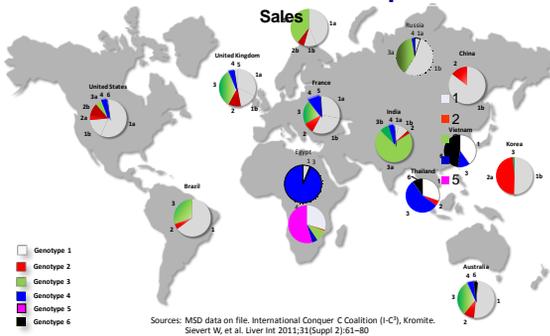
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### HCV Non-1 Genotype: Almost 50% Global HCV Population




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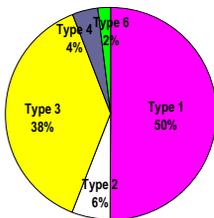
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### HIV/HCV Co-infection in Auckland Hospital HCV Genotype Distribution (n=86)




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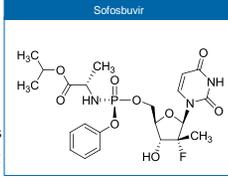
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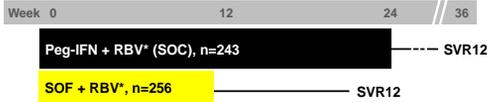
## Sofosbuvir (SOF; GS-7977)

- ◆ Potent HCV-specific nucleotide analog (chain terminator)
- ◆ Pan-genotypic antiviral effect
- ◆ High barrier to resistance
- ◆ Safe and well tolerated in >5000 patients in Phase 2 and Phase 3 studies
  - 400 mg once daily, no food effect
  - No significant drug interactions
  - No safety signals in preclinical/clinical studies



16

## FISSION: Sofosbuvir for previously untreated HCV Genotype 2 or 3

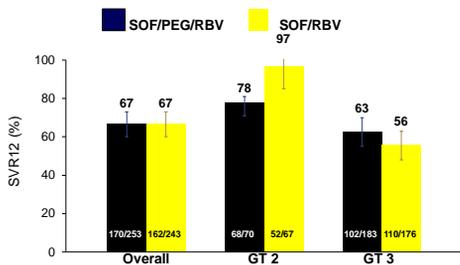


\*RBV dose 1000-1200 mg/day for SOF + RBV and 600 mg/day for Peg-IFN + RBV.

- Treatment-naïve, genotype 2 or 3 HCV-infected patients
  - Targeted 3:1 genotype 3:genotype 2 patients
  - ~20% with cirrhosis
- Expanded inclusion criteria
  - No upper limit to age or BMI; methadone allowed
  - Platelet count >75,000/mm<sup>3</sup>
- Randomization 1:1; stratified by genotype, HCV RNA, cirrhosis

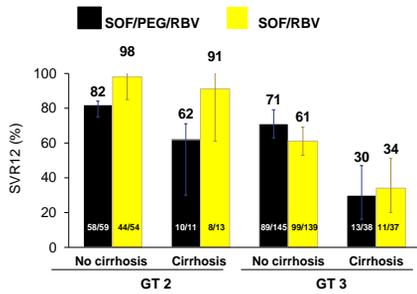
Lawitz et al NEJM 2013; 368:20:1878-86

## FISSION Results: SVR rates by HCV Genotype



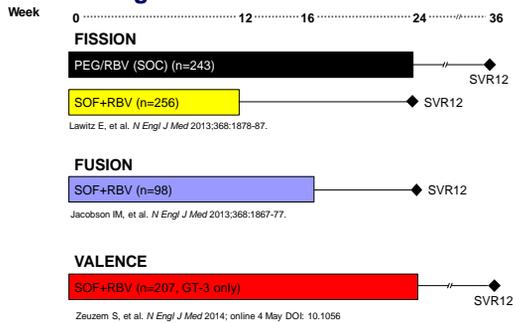
<sup>18</sup> Lawitz et al NEJM 2013; 368:20:1878-86

## FISSION Results: SVR rates by Genotype and Cirrhosis

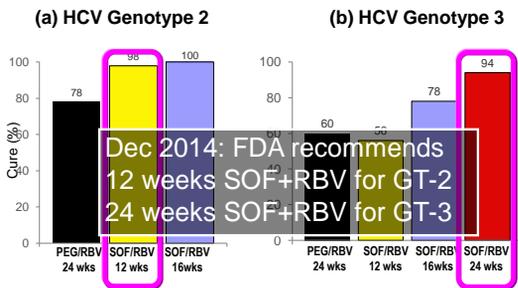


Lawitz et al NEJM 2013; 368:20:1878-86 <sup>19</sup>

## Sofosbuvir plus RBV in HCV GT2/3 Phase 3 Programme



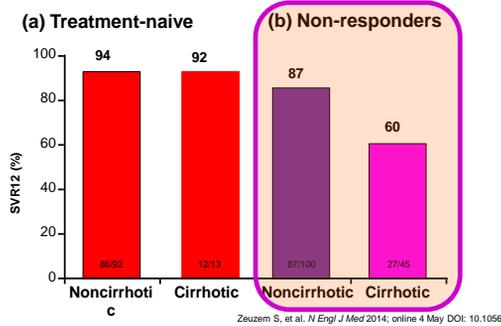
## Sofosbuvir plus RBV in HCV GT3 Phase 3 Programme



Lawitz E, et al. N Engl J Med 2013;368:1878-87.  
Jacobson IM, et al. N Engl J Med 2013;368:1867-77.

Zeuzem S, et al. N Engl J Med 2014; online 4 May DOI: 10.1056

**Sofosbuvir plus RBV for 24 weeks  
GT-3 Results**




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**Possible reasons for difference in HCV RNA decline between GT2 and GT3**

- 1) Small difference in susceptibility to SOF
  - Too small to account for differences.
- 2) Intrinsic differences in stability of replication complex between different genotypes
  - lower SVR in GT3 than GT2 in response to PEG/RBV
  - GT3 is more associated with lipid than GT2
- 3) No difference in barrier to resistance
- 4) Difference in response to immune response?

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**SOF/RBV in Genotype 2 and 3  
Conclusions**

**Genotype 2:**

- SOF/RBV for 12 weeks highly effective (98% SVR), including prior IFN-non-responders, cirrhotics

**Genotype 3:**

- In treatment naïve, extending SOF/RBV for 24 weeks is highly effective (94% SVR)
- In IFN non-responders, need to add 2<sup>nd</sup> agent

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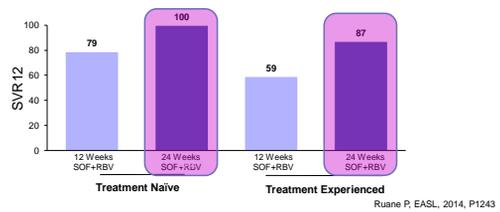
# IFN-free DAA in HCV GT-4, 5, 6



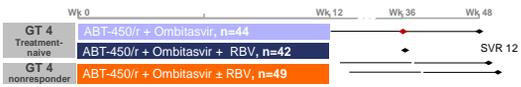
## HCV GT-4: SOF/RBV



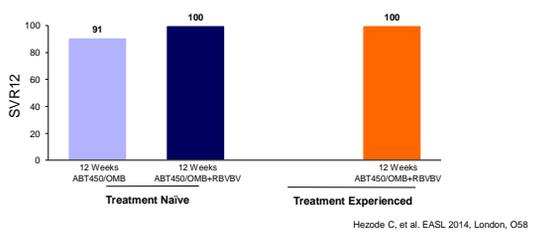
- Phase II open-label RCT in 60 Egyptian GT-4
  - 24% cirrhotic; 55% treatment-experienced



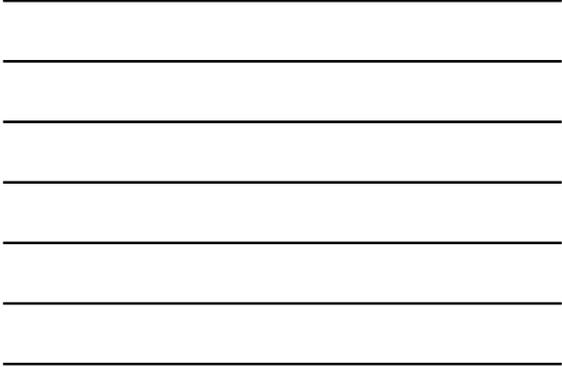
## HCV GT-4: ABT-450/r + Ombitasvir ± RBV



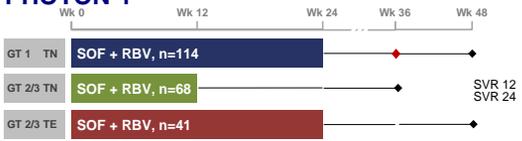
- Phase II open-label RCT in 135 French GT-4



# IFN-free DAA in HIV/HCV coinfection



## SOF/RBV in HIV/HCV co-infection PHOTON-1

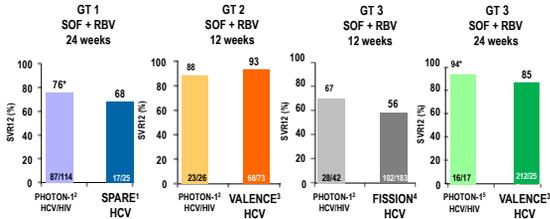


- Phase III open-label study (N = 223)
  - HCV treatment-naïve or -experienced HIV+ patients
  - 76% on wide range of ART regimens
  - Cirrhotics allowed, no platelet cut-off
  - Methadone allowed

Sulkowski M, et al; AASLD 2013 Abstract 212  
Naggi S, et al. CROI 2014 Abstract 26



## SOF/RBV in HIV/HCV co-infection PHOTON-1: Efficacy



- Efficacy of SOF in co-infection similar to that in HCV mono-infection

Sulkowski M, et al; AASLD 2013 Abstract 212  
Naggi S, et al. CROI 2014 Abstract 26



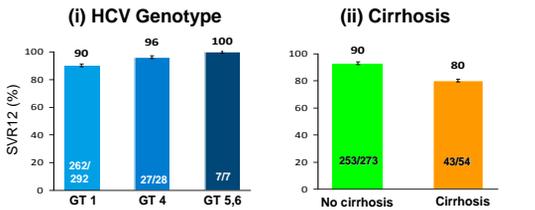
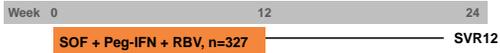
**SOF/RBV in HIV/HCV co-infection  
PHOTON-1: Safety**

- SOF/RBV well tolerated, with a low rate of treatment discontinuations due to adverse events
- Side-effect profile that of ribavirin
- No Resistance to SOF in Relapsers
- 2 HCV breakthrough; non-adherence to SOF
- 2 HIV breakthrough; non-adherence to ART

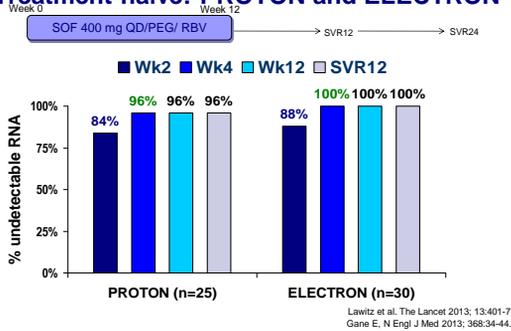
Sulkowski M, et al; AASLD 2013 Abstract 212  
Naggi S, et al. CROI 2014 Abstract 26

**SOF + PEG/RBV  
in HCV GT 1-6**

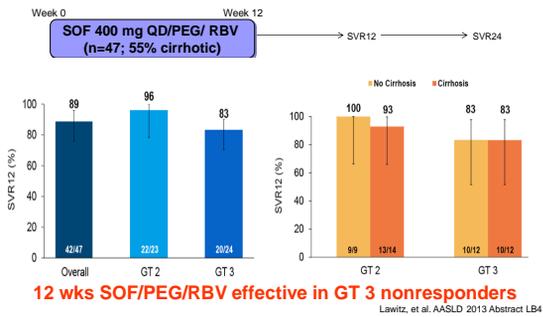
**Add Peg-IFN to SOF/RBV in GT 1-6  
The NEUTRINO Study**



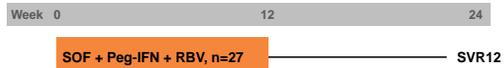
### Add Peg-IFN to SOF/RBV in GT-2/3 Treatment-naïve: PROTON and ELECTRON



### Add Peg-IFN to SOF/RBV to GT-2/3 Nonresponders: LONESTAR Study



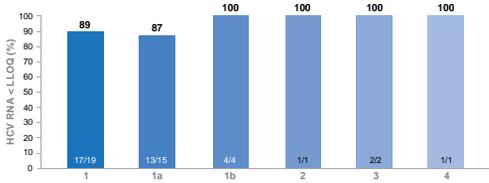
### Add Peg-IFN to SOF/RBV in HCV/HIV GT 1-6 Phase 2 Study Design



- **Open label**
  - SOF 400 mg QD + Peg-IFN-alfa-2a 180 µg/week + RBV 1000–1200 mg/day for 12 weeks (no RGT)
- **Treatment-naïve, genotype 1-4**
- **CD4 >200**
- **Allowed ART: Emtricitabine/tenofovir plus**
  - Efavirenz
  - Atazanavir/ritonavir
  - Raltegravir
  - Darunavir/ritonavir
  - Rilpivirine

Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster 714.36

## SOF+PEG/RBV in HCV/HIV coinfection GT 1-6 Phase 2 Efficacy

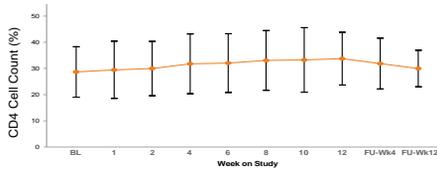


- ◆ Consistent efficacy across all HCV genotypes
- ◆ Similar to results in HCV mono-infection

Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster 714.37

## SOF+PEG/RBV in HCV/HIV coinfection GT 1-6 Phase 2 Safety

- Well tolerated with no SAEs
- 2 discontinuations (anaemia)
- No HIV virologic rebound
- No changes to ARV regimens throughout study
- No significant change in the CD4 cell count %



BL, baseline; FU, follow-up

Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster 714.38

## 2014 AASLD / IDSA Recommendations for DAA therapy for HIV/HCV Genotypes 2-6

### Genotype 2

- IFN naïve: SOF/RBV for 12 weeks
- IFN non-responder: SOF/PEG/RBV for 12 weeks

### Genotype 3

- IFN naïve: SOF/RBV for 24 weeks
- IFN non-responder: SOF/PEG/RBV for 12 weeks

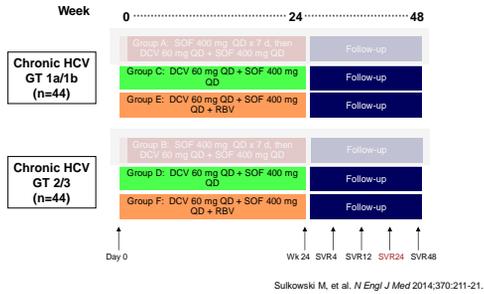
### Genotype 4,5,6

- ALL: SOF/PEG/RBV for 12 weeks

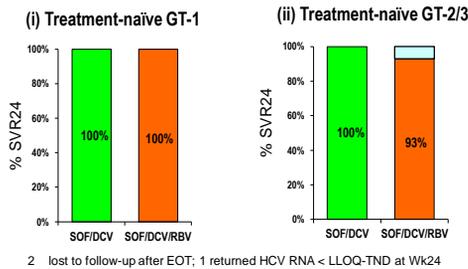


<http://www.hcvguidelines.org/>

## Add a second pan-genotypic DAA to SOF: An NS5A inhibitor (Daclatasvir)



## Sofosbuvir plus Daclatasvir in HCV GT1/2/3 Phase 2 Programme



Sulkowski M, et al. *N Engl J Med* 2014;370:211-21.

## LDV/SOF in HIV/HCV co-infection NIAID study

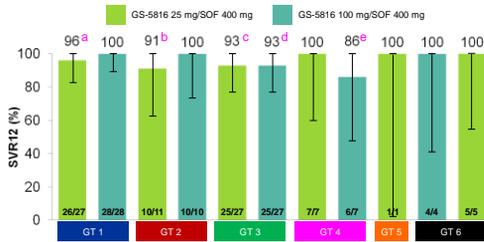


- Phase II open-label study (N = 50)
  - HCV treatment-naïve or -experienced HIV+ patients
  - 74% on ART various standard regimens
- Safety profile excellent
  - No toxicity, no SAEs no discontinuation
  - (No ribavirin!)

Osinusi A, et al. *EASL* 2014, London, O14



### GS-5816/SOF in HCV GT 1-6



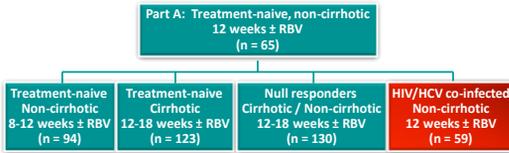
- Overall, 97% achieved SVR12
- Only 4 virologic failures, only 1 on 100mg GS-5816

Everson G, et al. EASL 2014

### Merck Multi-genotypic DAA combination

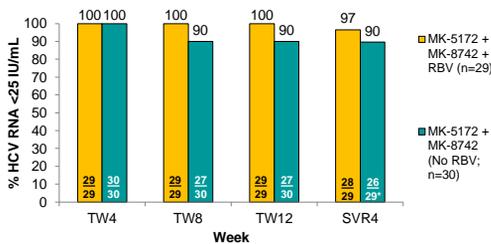
- MK-5172 is a 2<sup>nd</sup> Gen Macrocytic Protease inhibitor**
  - Pangenotypic at 400mg doses but ALT elevations
  - Reduced antiviral effect in GT-3 at 100mg dose
- MK-8742 is a 2<sup>nd</sup> Gen NS5A inhibitor**
  - pangenotypic

#### C-WORTHy: MK-5172/MK-8742 ± RBV in 471 HCV GT-1



Sulkowski M, et al. EASL 2014

### Merck Multi-genotypic DAA combination



- Only 3 virologic failures, all subtype 1a
- Phase III C-Edge CO-INFXN study in progress
  - 12 weeks MK-5172/MK-8742 FDC without RBV
  - HCV GTs 1, 4, 5, 6

Sulkowski M, et al. EASL 2014



