16th Annual Conference of the
National HIV Nurses Association (NHIVNA)

National HIV Nurses Association

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North Manchester General Hospital

26-27 June 2014- City Hall, Cardiff

2nd Generation Treatment for Hepatitis C and HIV Coinfection

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Lead Nurse Hepatitis
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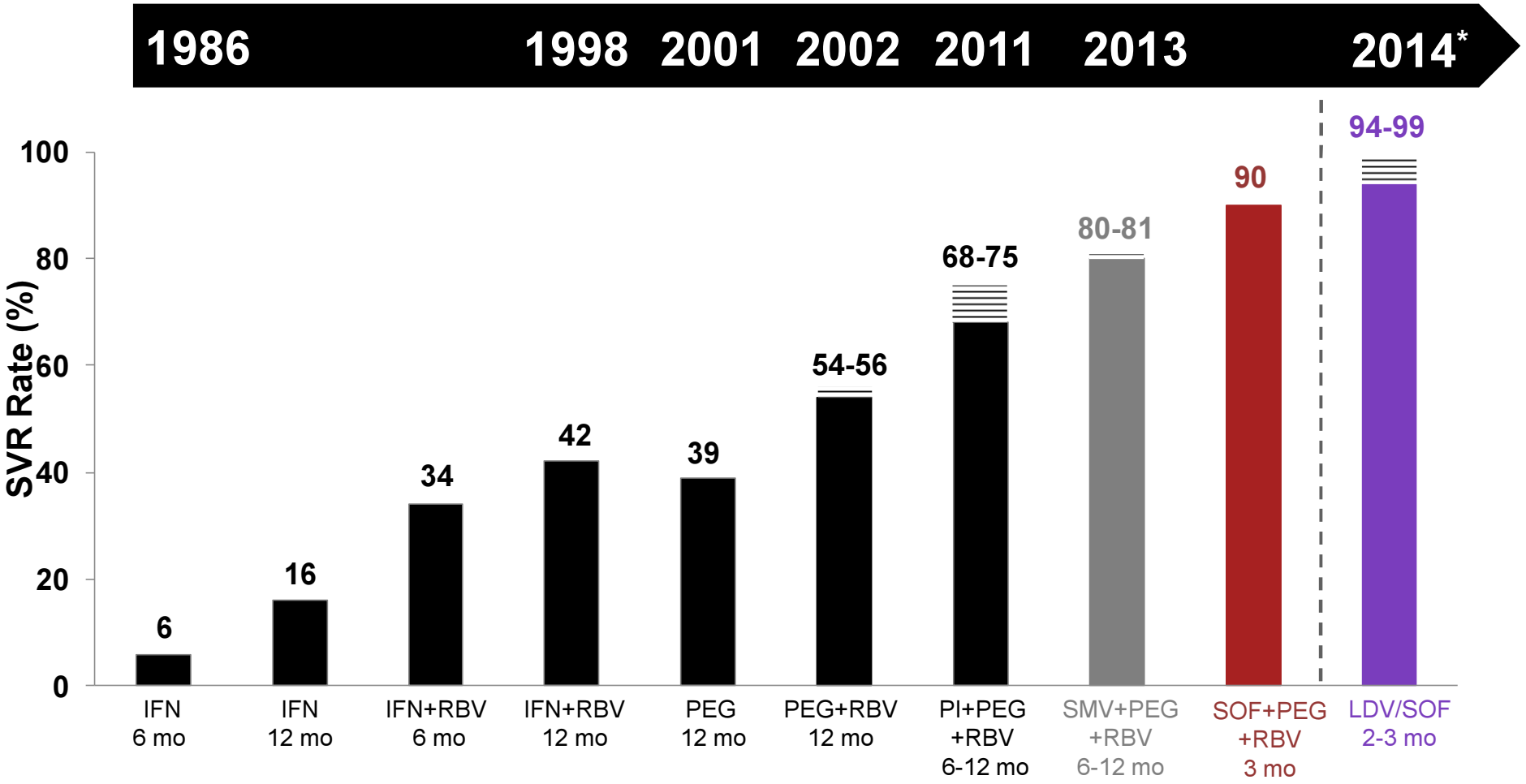
What's New ?

- Sofosbuvir
- Simeprevir

- Daclatasvir
- Ledipasvir

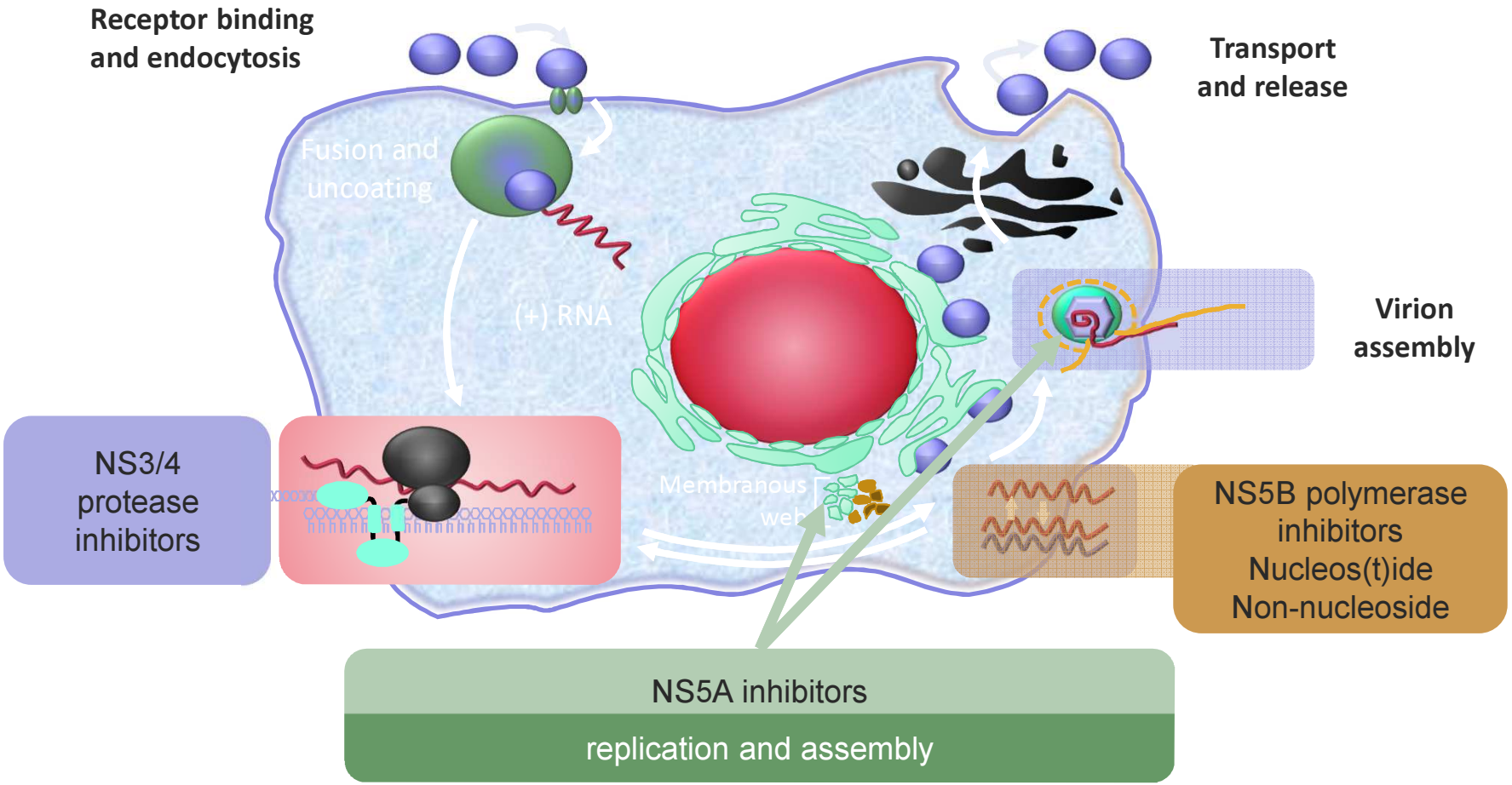
High SVR Rates with LDV/SOF in HCV Genotype 1 Treatment-Naïve Patients



Year of data presentation at EASL 2014 and publication in *NEJM

Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2013. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2014. Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster #1425. Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413. Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02; Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12 [Epub ahead of print]; Kowdley K, et al. *N Engl J Med* 2014; 2014 Apr 11 [Epub ahead of print]

HCV Life Cycle and Targets for Direct-Acting Antivirals (DAAs)

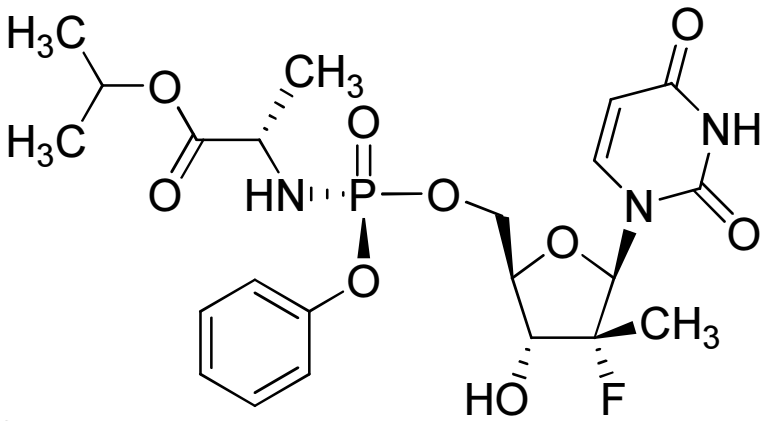


Adapted from Manns MP, et al. *Nat Rev Drug Discov*. 2007;6:991-1000.

Sofosbuvir

Sofosbuvir (SOF, GS-7977)

- HCV-specific uridine nucleotide NS5B polymerase inhibitor (chain terminator)
- Potent antiviral activity against HCV genotypes 1–6
- High barrier to resistance
- Once daily, oral, 400mg tablet
- Favorable clinical pharmacology profile



  - No food effect
  - Renally cleared - limited potential for drug interactions
  - No CYP3A/4 metabolism
    - limited potential for drug interactions
- Well-tolerated with an excellent safety profile in clinical studies to date (>3000 patients)

SOF Drug Interaction Data

- **No clinically significant DDIs observed between SOF and the following ARVs[2]**
  - **NRTIs:** TDF/FTC
  - **NNRTIs:** EFV and RPV
  - **PIs:** DRV+RTV
  - **INI:** RAL
- **Methadone: no clinically relevant DDI observed with SOF[3]**
- **No clinically significant interaction was observed with co-administration of SOF and Cyclosporine A (CsA) or Tacrolimus (TAC)[1]**
  - High dose CsA increased systemic SOF exposure (AUC) ~10%
  - Increase in total drug-related material with no increase in nucleotide metabolite
  - Not considered clinically significant
  - Based on these results, CsA or TAC can be co-administered with SOF
- **Coadministration of inducers of the intestinal drug transporter P-gp is not recommended [4]**
  - Anticonvulsants, antimycobacterials

1. Mathias A, et al. AASLD 2012; Boston. #1869; 2. Kirby B, et al. AASLD 2012; Boston. #1877; 3. Lawitz E, et al. EASL 2012, #1130; 4. Sovaldi SmPC.

Recommended treatment duration for sofosbuvir combination therapy

‡

Patient population *	Treatment	Duration
Patients with GT 1, 4, 5 or 6 CHC	**SOVALDI + RBV + PEG-IFN**	**12 weeks[a,b]**
	SOVALDI + RBV *Only for use in patients ineligible or intolerant to PEG-IFN*	**24 weeks**
Patients with GT 2 CHC	**SOVALDI + RBV**	**12 weeks[b]**
Patients with GT 3 CHC	**SOVALDI + RBV + PEG-IFN**	**12 weeks[b]**
	SOVALDI + RBV	**24 weeks**
Patients with CHC awaiting liver transplantation	**SOVALDI + RBV**	**Until liver transplantation[c]**

* Includes patients co-infected with human immunodeficiency virus (HIV)

† The dose of RBV when used in combination with SOVALDI is weight-based (<75 kg = 1000 mg and ≥75 kg = 1200 mg), administered orally in 2 divided doses with food

a. For previously treated patients with HCV GT 1 infection, no data exists with the combination of SOVALDI, RBV and PEG-IFN

b. Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, Black race, IL28B non-CC genotype, prior null response to PEG-IFN and RBV therapy)

c. See Special patient populations – Patients awaiting liver transplantation

All-Oral Therapy of SOF + RBV in HIV/HCV Coinfection

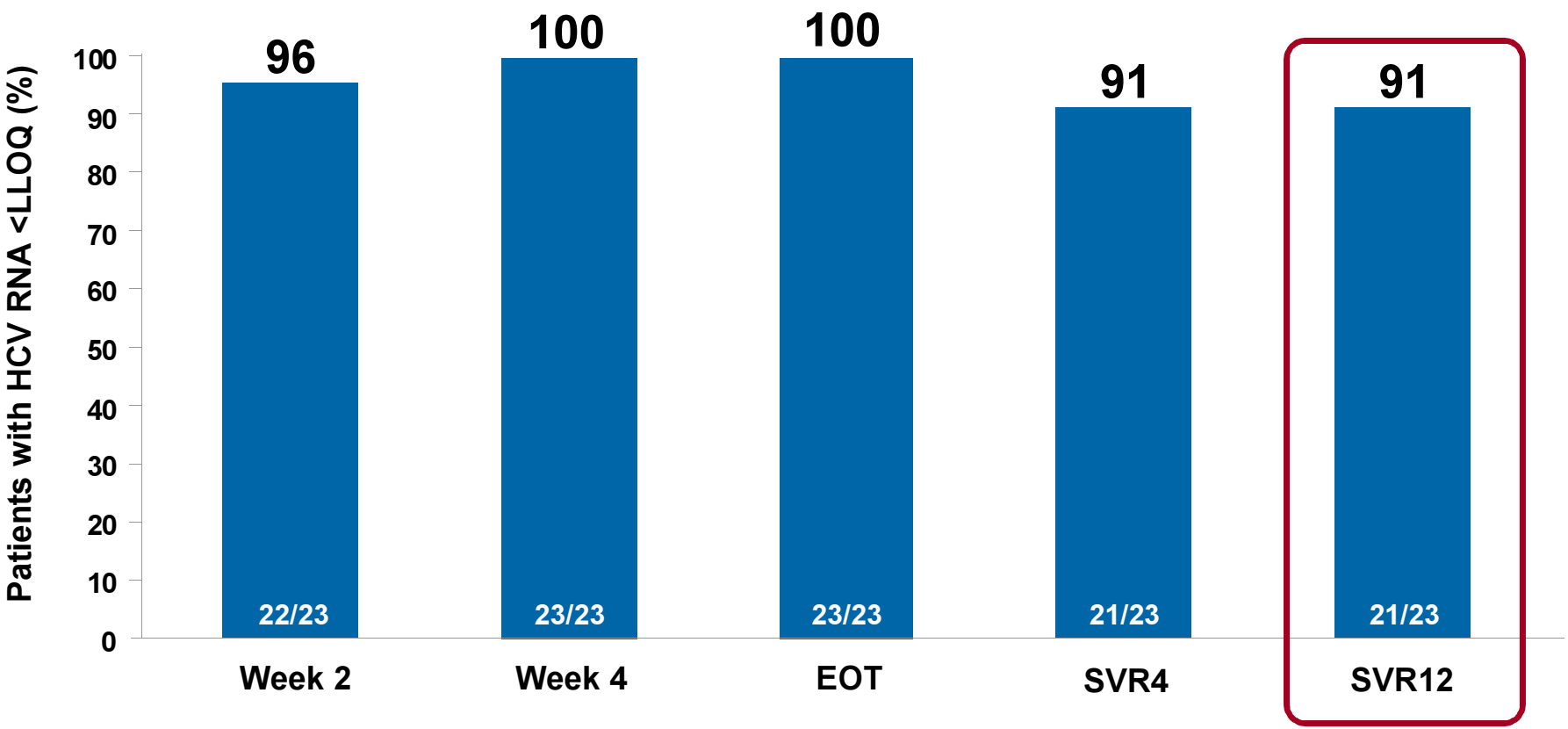
PHOTON-1 Conclusions

- The IFN-free regimen of SOF + RBV resulted in high SVR12 rates in HCV treatment-naïve, HIV-infected patients with GT 1, 76% GT2,88% and G3 67%
  coinfection
  - SVR12 rates were similar to those observed in patients with HCV monoinfection
- SOF + RBV was effectively co-administered with multiple antiretroviral regimens including inhibitors of HIV-1 protease, reverse transcriptase (non-nucleoside/nucleoside) and integrase
  - Viral breakthrough seen exclusively in the setting of poor adherence
  - No effect on CD4 T-cell percent
- No resistance (deep sequencing) was observed in virologic failures
- SOF was well-tolerated, with a low rate of treatment discontinuations due to adverse events

Sulkowski MS, et al. AASLD 2013. Washington, DC. Oral #212

SOF + PegIFN + RBV in HIV/HCV Coinfection

Virologic Response and SVR12

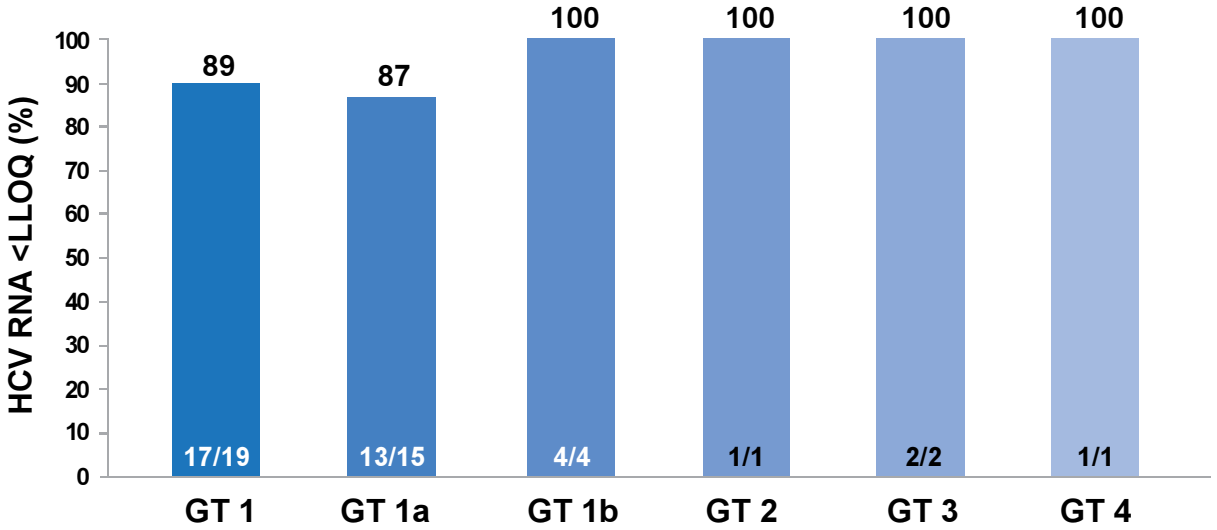


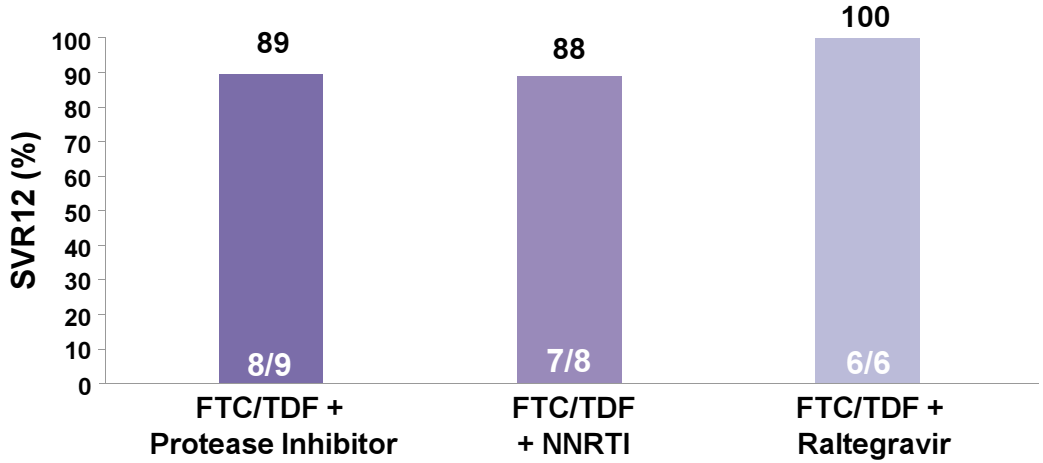
- There was no on-treatment HCV or HIV virologic breakthrough
- Relapse occurred in 1 patient and accounted for all virologic failures
- Two patients discontinued treatment early due to adverse events, one of whom achieved SVR12 after receiving 8 weeks of SOF + PegIFN + RBV

Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster #714

SOF + PegIFN + RBV in HIV/HCV Coinfection

SVR12 According to HCV Genotype and HIV ARV Regimen





NNRTI, non-nucleoside reverse transcriptase inhibitor

Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster #714

Short Duration of SOF + PegIFN + RBV x 12 Weeks

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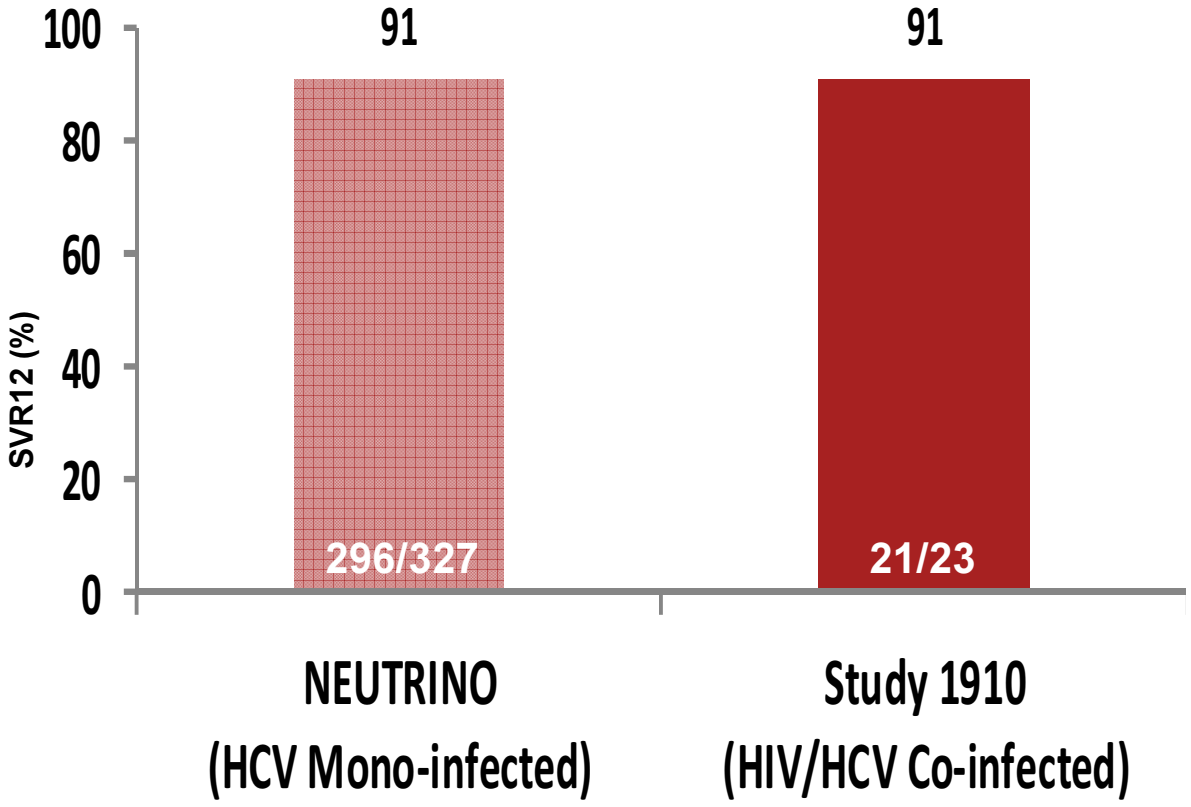
Comparison of HCV Mono-infected to HIV/HCV Co-infected



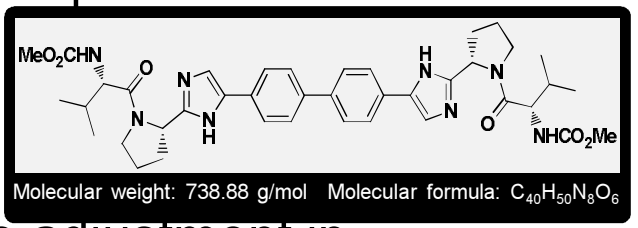
Similar response rates in HIV/HCV co-infected patients compared with HCV mono-infected patients

Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02
Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster #714

Daclatasvir

Daclatasvir (DCV): Key properties

- **Highly selective** HCV NS5A replication complex inhibitor[1,2]
- High **potency** (picomolar EC_{50}) in vitro[1,2]
- **Pangenotypic** coverage in vitro[3]
- **Once-daily dosing**[2] without need for dose adjustment in hepatically impaired patients[4]
- Lack of significant **drug interactions**[5-9]
- Clinical efficacy has been shown in **difficult- to-treat patient populations** in combination with a variety of agents targeting different HCV components[10-15]
- Generally **well tolerated**[1,2,10-15]



Molecular weight: 738.88 g/mol Molecular formula: $C_{40}H_{50}N_8O_6$

1. Gao et al. Nature. 2010;465:96.; 2. Nettles et al. Hepatology. 2011;54:1956; 3. Gao et al. Curr Opin Virol. 2013;3:514; 4. Bifano et al. AASLD 2011, Poster 1362; 5. Bifano et al. AASLD 2010. Abstract 827; 6. Eley et al. 8th Intl Workshop on Clinical Pharmacology of Hepatitis Therapy. 2013. Oral presentation 014 PK; 7. Bifano et al. Antivir Ther. 2013;18:931.; 8. Bifano et al. AASLD 2013. Poster 1081; 9 Bifano et al. EASL 2013. Abstract 794; 10. Everson et al. AASLD 2012. Oral presentation LB-3.; 11. Sulkowski et al. AASLD 2012. Oral presentation LB-2.; 12. Lok et al. N Engl J Med. 2012;366:216.; 13. Chayama et al. Hepatology. 2012;55:742.; 14. Hezode et al. Hepatology. 2012;56(suppl):553A; 15. Sulkowski et al. N Engl J Med 2014;370:211–21

Drug–drug interactions with DCV

Concomitant drug	Effect of DCV on PK of other drug	Effect on DCV PK	Clinical comment
HAART[1] **TDF**	None	None	• No clinically meaningful interaction • Reduced to 30 mg QD with ATV/r (300/100 mg QD) • Increased to 90 mg QD with EFV (600 mg QD)
ATV/r	None	↑	
EFV	None	↓	
Omeprazole[2]	None	None	None
Oral contraceptives[3]	None	None	None
Immuno-suppressives[4]	None	None	None
Other DAAs[5] **ASV**	None	None	None
SOF	None	None	

1. Bifano et al. Antivir Ther 2013;18(7):931-40; 2. Bifano et al. EASL 2013, abstract 794. 3. Bifano et al. AASLD 2011, poster 1362.
4. Bifano M, et al. AASLD 2013, poster 1081. 5.

Daclatasvir Main Points

- Inhibits the multiple functions of NS5A preventing HCV replication.
- Lack of any significant drug to drug interactions
- No dose adjustment in severe renal or hepatic impairment
- Daclatasvir and Sofosbuvir in combination with Ribavirin show SVR rates in G1 up to 95 -100%. G2 and G3 89 to 90%
- Cirrhotic patients up to 91%
- Well tolerated once daily dosing.

Simeprevir

Simepravir NS3/4A protease inhibitor

- For use in combination with peginterferon alfa and ribavirin in patients with HCV genotype 1 and 4 infection with compensated liver disease (including cirrhosis)
- Orally 150mg once daily with food
- For treatment-naïve, HIV positive, prior relapser and those who have cirrhosis. Simepravir should be initiated in combination with peginterferon alfa and ribavirin for 12 weeks followed by 12 weeks peginterferon alpha and Ribavirin totalling 24 weeks.
- All prior non and partial responders, plus HIV positive patients with cirrhosis, should receive an additional 36 weeks of peginterferon alfa and ribavirin after completing 12 weeks of Simepravir, peginterferon alfa and ribavirin (total treatment duration of 48 weeks)

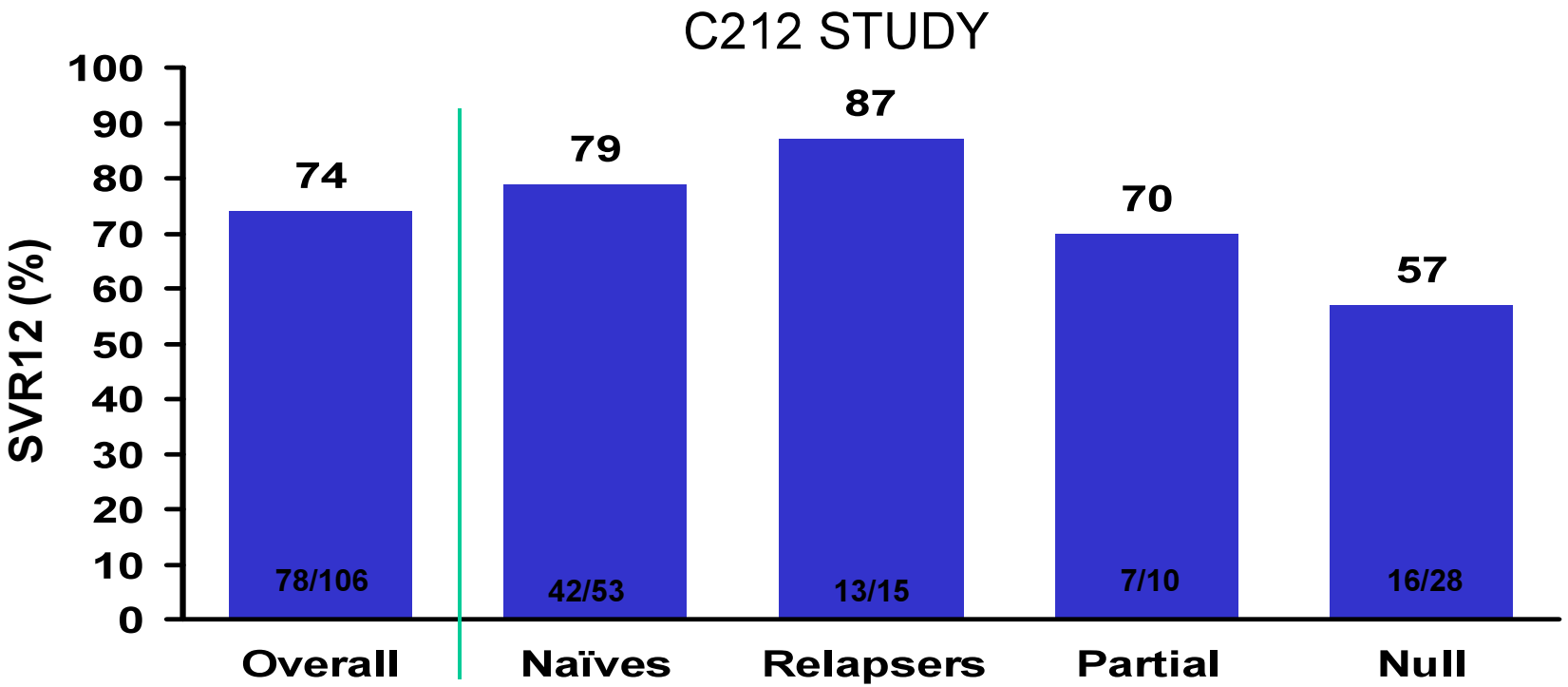
Stopping Rules

- -HCV-RNA levels at week 4 ≥ 25 IU/mL: Discontinue simeprevir, peginterferon alfa and ribavirin
- -HCV-RNA levels at week 12 ≥ 25 IU/mL: Discontinue peginterferon alfa and ribavirin (treatment with Simeprevir completed at week 12)
- -HCV-RNA levels at week 24 ≥ 25 IU/mL: Discontinue peginterferon alfa and ribavirin

Dosing considerations

- Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended (will be paid for by the company)
- Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism
- Must be taken with food as a whole tablet

Effect of simeprevir on genotype 1 HCV/HIV co-infected patients



- SVR12 rates were high irrespective of baseline Metavir fibrosis score.
- Simeprevir was generally well tolerated with safety similar to studies in patients without HIV and high SVR12 rates in HCV treatment-naïve patients, prior null-responders, -partial responders and -relapsers co-infected with HIV-1.

Dieterich D et al. 14th EACS 2013 LBPS9/5

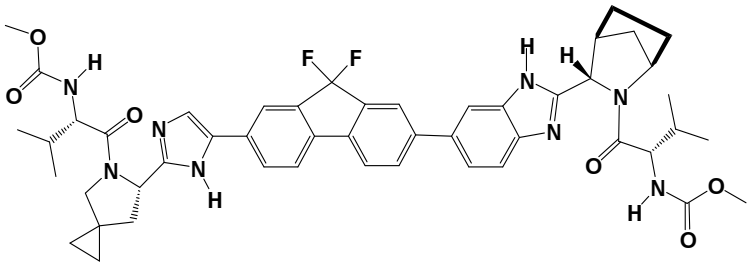
Drug interactions – ARVs & Simeprevir

HIV drug	Can be used?
Efavirenz	
Etravirine	
Rilpivirine	
Nevirapine	
Darunavir/r	
Lopinavir/r	
Raltegravir	
Tenofovir	
Cobicistat	

Ledipasvir

Ledipasvir (LDV, GS-5885): NS5A Inhibitor

- NS5A is essential for RNA replication and post-replication assembly and secretion
- LDV has picomolar potency against genotype 1a and 1b HCV



- Effective against signature NS5B-resistant mutant S282T
- Once daily oral dosing
- Dosed in >3000 patients
- No clinically significant drug-drug interactions with sofosbuvir

Lawitz EJ et al, *J Hepatol* 2012; 57: 24–31; Gane EJ, et al. CROI 2013; Atlanta, GA. Oral #41LB

Ledipasvir / Sofosbuvir Combination

- For use in Genotypes 1a 1b 4a 5a and 6a
- Ledipasvir (formerly GS-5885) is a potent inhibitor of HCV NS5A
- Sofosbuvir is a nucleotide analog inhibitor of hepatitis C virus NS5B polymerase—the key enzyme mediating HCV RNA replication.
- Ledipasvir/sofosbuvir (90/400 mg) fixed dose combination PO once daily, with or without food
- The proposed clinical use for ledipasvir-sofosbuvir would be in treatment-naive and treatment-experienced patients with genotype 1 chronic HCV infection
- An 8-week course of ledipasvir-sofosbuvir will be used for treatment naive patients
- A 12-week course will be indicated for treatment experienced (partial and null responders) and patients with cirrhosis.

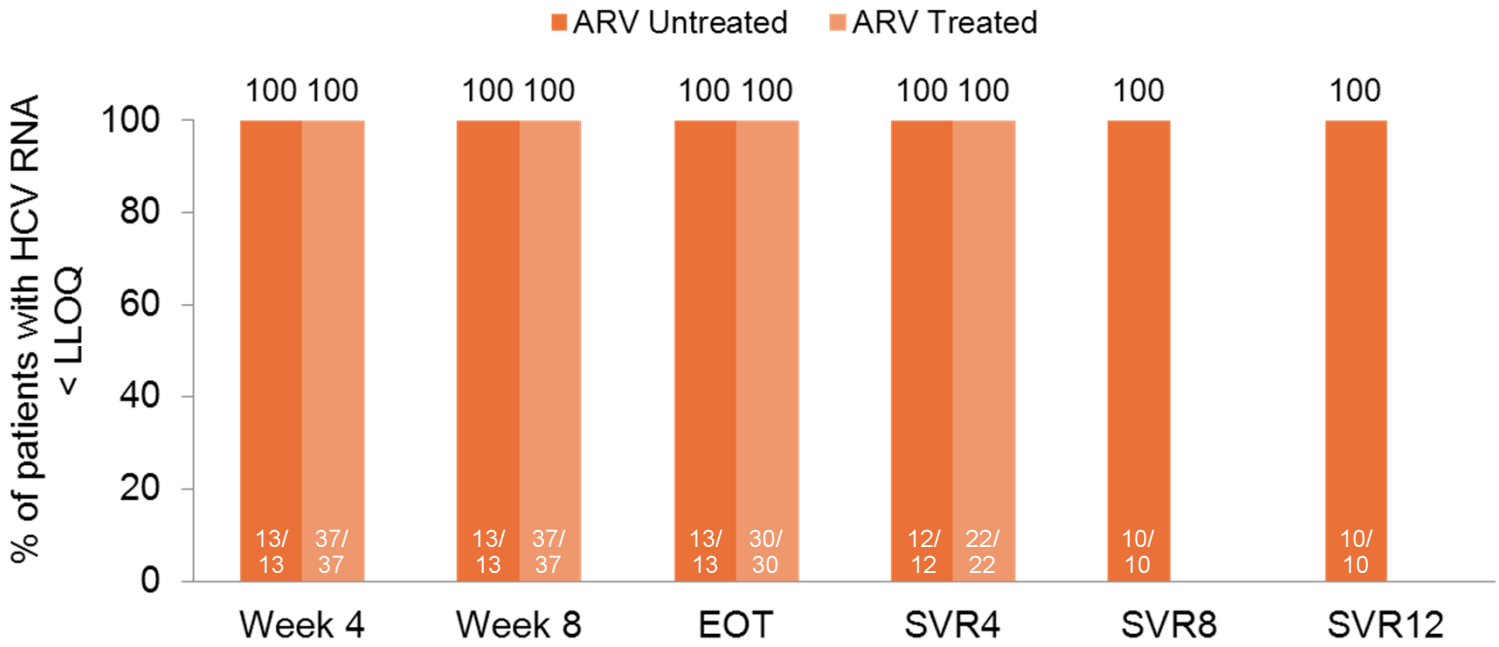
Major Drug Interactions:

- Ledipasvir undergoes minimal metabolism and expectations are that this medication will have few clinically significant drug-drug interactions

- In general, Sofosbuvir is considered to have relatively few clinically significant drug-drug interactions, but co administration of Sofosbuvir with the following medications is not recommended because these medications may significantly lower Sofosbuvir levels:

- Anticonvulsants: carbamazepine, oxycarbazepine, phenobarbital, and phenytoin
- Antimycobacterials: rifabutin, rifampin, rifapentine
- Herbal Supplements: St.John's wort
- HIV Protease Inhibitors: tipranavir

Treatment Response



- The IFN and RBV free regimen of LDV/SOF in HCV/HIV co-infected patients resulted in SVR12 of 100% in ARV untreated patients and SVR4 of 100% in ARV treated patients
- LDV/SOF STR was generally well tolerated with no discontinuations
- Actively enrolling ION-4 (target of 300 GT 1 and GT 4 HCV/HIV patients). NCT 02073656.

Osinusi A, EASL, 2014, O14

What to choose?

- Sofosbuvir with Ribavarin on its own or with Interferon
- Sofosbuvir with Daclatasvir/Ledipasvir no Ribavirin or interferon
- Simepravir with interferon and Ribavirin or Simepravir with Sofosbuvir. Must be Q80K negative.
- It will depend on NICE guidance and COST!!!!!!

Sofosbuvir 35k	Gilead
Daclatasvir 35k	BMS
Simepravir 23k	Janssen
Ledipasvir ????	Gilead

Avaliability

- Sofosbuvir and or Daclatasvir/ Ledipasvir available on compassionate grounds currently
- Sofosbuvir and Simepravir are licenced but awaiting NICE approval hopefully September to November.
- Daclatasvir going to NICE around October.
- Ledipasvir to NICE early next year.
- Many trials on going - LONE STAR – Texas is looking at oral/oral therapies for G1 8 weeks only !!!

Thank you

- All the contributors to this presentation

- Kevin Whitley Medical Liaison Gilead
- Joyeta Das Medical Liason BMS
- Charlotte Butterfield Janssen

- Dr Alison Uriel and Dr Andy Ustianowski for support.

- NHIVNA for this opportunity to speak

- Gilead for my train fare from Manchester.