National HIV Nurses Association

NHIVNA Pre-conference Study Day

'Current Issues in HIV, Hepatitis and other Blood-borne Viruses'

In collaboration with BASLNF

Royal Armouries International, Leeds

17 June 2015

17th Annual Conference of the
National HIV Nurses Association (NHIVNA)

National HIV Nurses Association

Sue Kidger

North Manchester General Hospital

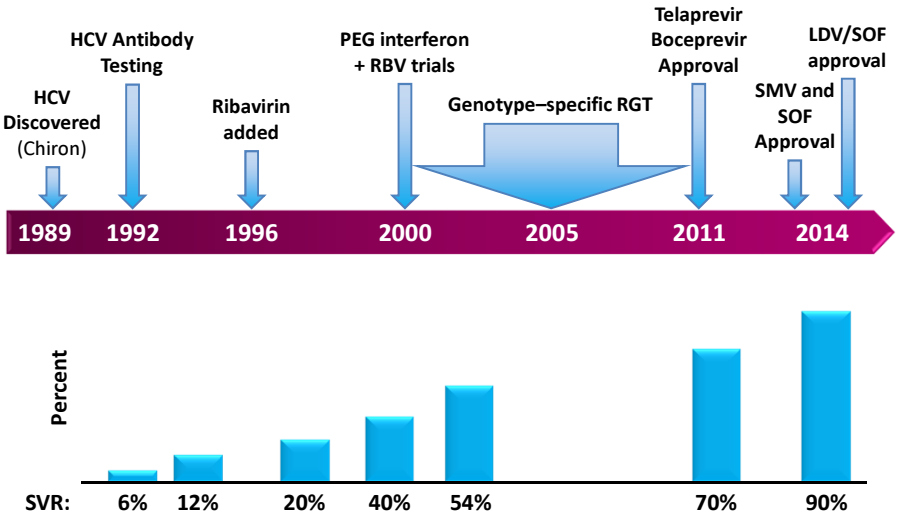
17 - 19 June 2015 - Royal Armouries International, Leeds

The Pennine Acute Hospitals NHS Trust

How the new drugs work in relation to Hepatitis C

Sue Kidger
Lead Hepatitis Specialist Nurse
North West Infectious Diseases (NWID)

A Short History of HCV Therapy



Adapted from Strader DB, et al. *Hepatology* 2004;39:1147–71. Lawitz E, et al. *N Engl J Med*. 2013 Apr 2013

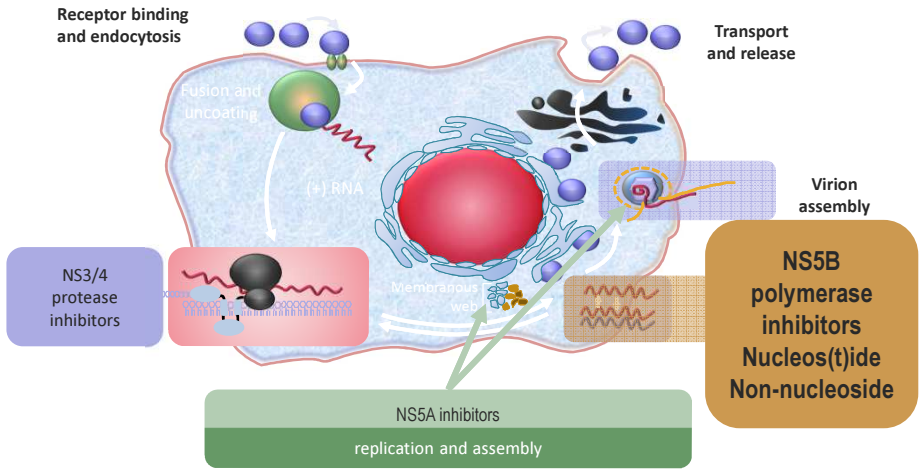
What's New ?

- Sofosbuvir
- Daclatasvir
- Ledipasvir
- Harvoni (Sofosbuvir/Ledipasvir)
- Simeprevir
- Viekirax / Exviera

What is an NS5B

- NS5B is a RNA dependent RNA polymerase
- The HCV virus is made of RNA it needs to make mRNA to direct protein synthesis
- It catalyzes the replication of HCV
- It is the prime target for inhibitors of HCV replication
- Sofosbuvir works as a polymerase inhibitor or chain terminator

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



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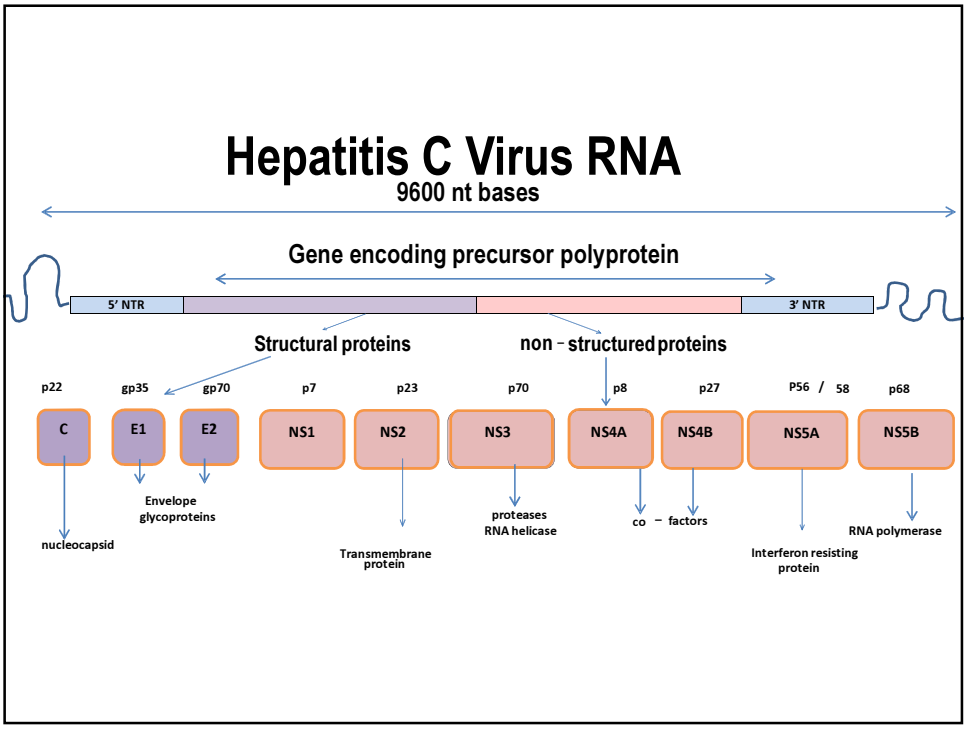
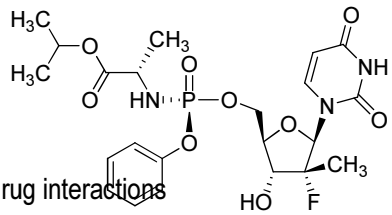
Hepatitis C Virus RNA



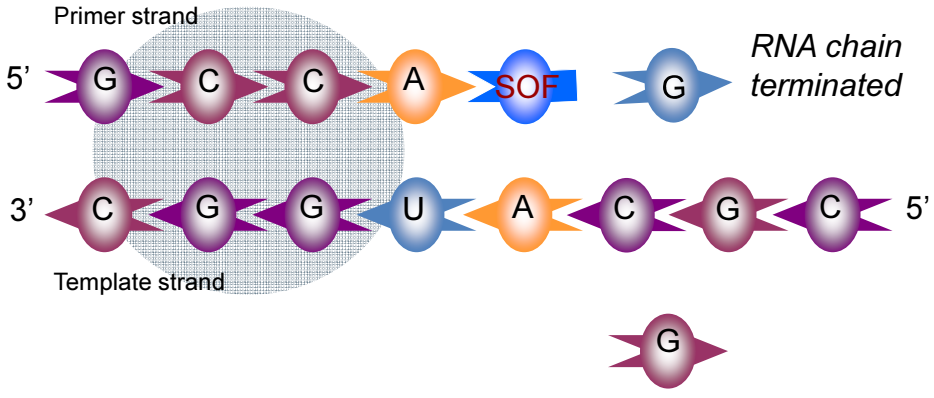
Sofosbuvir (SOF, GS-7977)

- HCV-specific uridine nucleotide NS5B polymerase inhibitor (chain terminator)
- Potent antiviral activity against HCV genotypes 1 – 6
- High barrier to resistance
- Once-daily, oral, 400-mg tablet
- Favourable clinical pharmacology profile
  - No food effect
  - Renally cleared - limited potential for drug interactions
  - No CYP3A/4 metabolism - limited potential for drug interactions



Well-tolerated - excellent safety profile in clinical studies to date (>3000 pts)

HCV RNA Replication: Role of Sofosbuvir

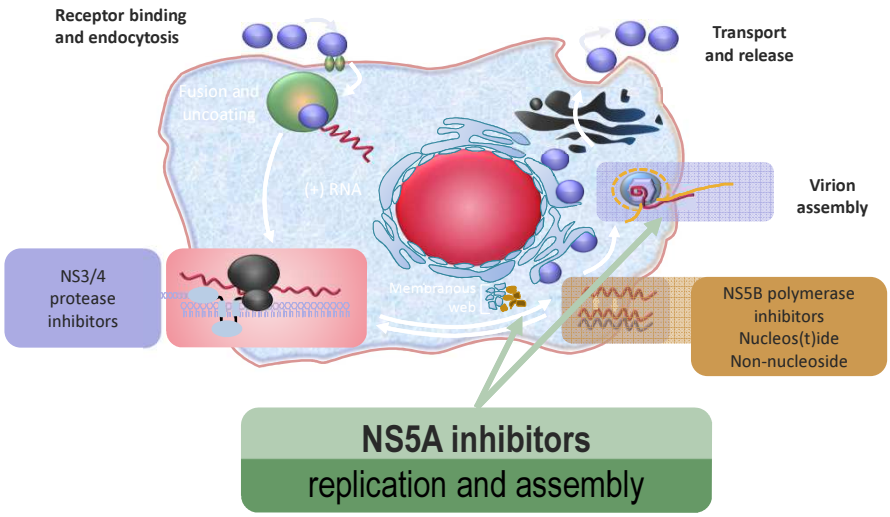


SOF: sofosbuvir

What is a NS5A

- It moderates the host cells interferon response
- Essential component of HCV replication
- Exerts a wide range of effects on cellular pathways and processes
- These processes include inate immunity and host cell growth and proliferation
- Daclatasvir blocks viral replication

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



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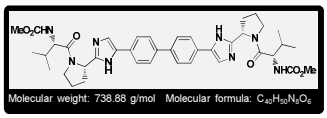
Daclatasvir (DCV): Key properties

- **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]



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

Ombitasvir

- 3 Drug regime Paritaprevir/ ritonavir /dasabuvir
- NS5A

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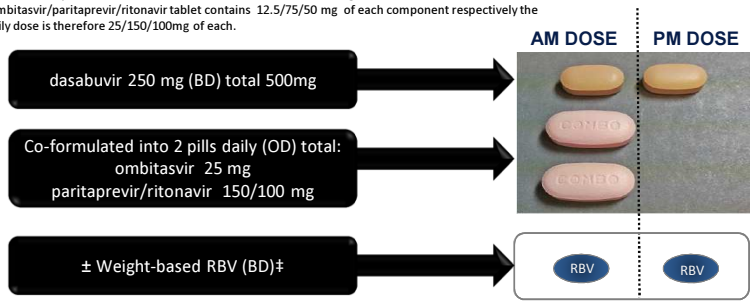
Dosing and administration: Genotype 1

	Ombitasvir (OBV)	Paritaprevir/Ritonavir (PTV/r)	Dasabuvir (DSV)
Delivery*	Oral	Oral	Oral
Dosing†	25 mg OD	150 mg/100 mg OD	250 mg BD
MOA	NS5A inhibitor	NS3/4A protease inhibitor	Non-nucleos(t)ide NS5B-polymerase inhibitor

*To maximise absorption, tablets should be taken with a meal without regard to fat or calorie content;
†Each ombitasvir/paritaprevir/ritonavir tablet contains 12.5/75/50 mg of each component respectively the total daily dose is therefore 25/150/100mg of each.



‡Ribavirin is not required in genotype 1b patients without cirrhosis

[1]Viekirax, Summary of Product Characteristics 2015;
[2]Exviera, Summary of Product Characteristics 2015.

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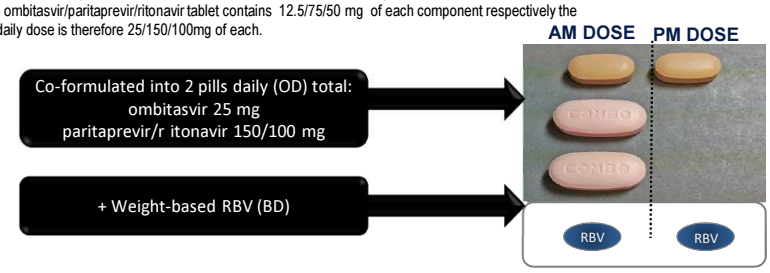
Dosing and administration: Genotype 4

	Ombitasvir (OBV)	Paritaprevir/Ritonavir (PTV/r)
Delivery*	Oral	Oral
Dosing†	25 mg OD	150 mg/100 mg OD
MOA	NS5A inhibitor	NS3/4A protease inhibitor

*To maximise absorption, tablets should be taken with a meal without regard to fat or calorie content;
†Each ombitasvir/paritaprevir/ritonavir tablet contains 12.5/75/50 mg of each component respectively the total daily dose is therefore 25/150/100mg of each.

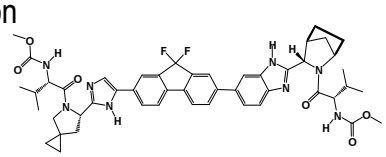


[1]Viekirax, Summary of Product Characteristics 2015.

‡

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



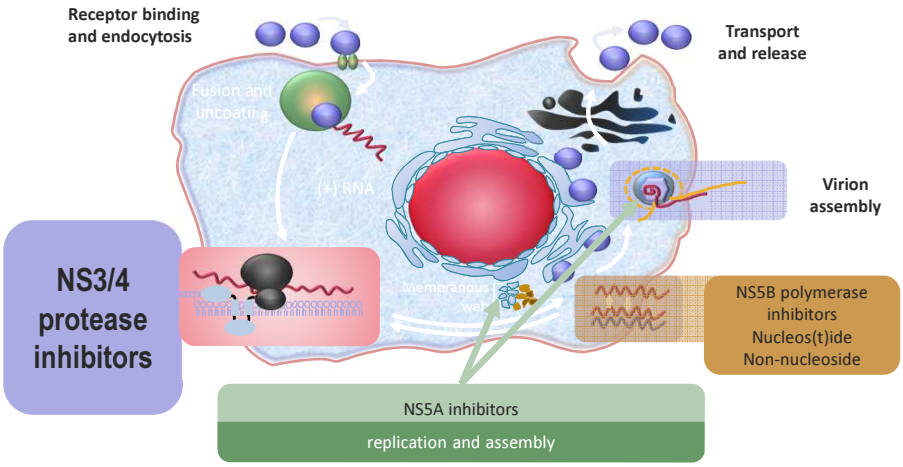
- Effective against signature NS5B-resistant mutant S282T
- Once-daily oral dosing
- Dosed in >3000 patients
- No clinically significant drug-drug interactions with sofosbuvir

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

What is a NS3/4

- HCV encodes a long polyprotein of 3000 amino acids. They have to be chopped up to allow the bits to work
- It is essential for viral replication in cell culture
- The drug targets this process to prevent replication
- Most attractive target to develop new drugs

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



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

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)

Thank you

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BASLNF
British Association for the Study of the Liver Nurse Forum

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