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SPECIAL CONFERENCE

Co-organised with

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

NEW PERSPECTIVES IN HEPATITIS C VIRUS INFECTION – THE ROADMAP FOR CURE

23-24 SEPTEMBER 2016
PARIS, FRANCE

Scientific Organising Committee
Thomas Berg, *Germany*
Raymond Chung, *United States*
Xavier Forns, *Spain*
Norah Terrault, *United States*

12 CME Credits

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WELCOME MESSAGE

Dear Colleagues,

Welcome to our special conference 'NEW PERSPECTIVES IN HEPATITIS C VIRUS INFECTION – THE ROADMAP FOR CURE' hosted by the European Association for the Study of the Liver (EASL) and co-organised with the American Association for the Study of Liver Diseases (AASLD) in Paris, France from 23-24 September 2016.

The recent and rapid advances in the treatment of hepatitis C have completely changed the scenario of this disease in the past months. It is not always easy to be updated in the field, due to the huge amount of data coming from a large number of published studies. Antiviral drugs that are still not approved in some countries are already classified as "old" and current treatment regimens may be replaced by new ones by the time the meeting takes place. The aim of this conference is to summarize the information available, as well as to provide a critical review and analysis of the best available data (some unpublished data will be relevant). With this goal in mind, this meeting will give hepatologists, as well as other specialists interested in hepatitis C, the opportunity to catch up with the new advances in the field and be able to apply them in clinical practice. To reach this aim, an international panel of key experts and participants will actively interact to resolve pending issues and to highlight areas needing further analysis and investigation.

EPIDEMIOLOGY OF HCV IN DIFFERENT AREAS OF THE WORLD

- Virology and pathogenesis
- Natural history of the disease and impact of the new treatments on the long-term consequences of chronic HCV infection
- Assessment of the disease
- Therapy, with special emphasis on difficult-to-treat populations or unsolved issues
- HCV eradication strategies

We look forward to welcoming you to Paris for this exciting scientific event.

Sincerely,

The Scientific Committee

SCIENTIFIC ORGANISING COMMITTEE

Thomas Berg
Germany

Raymond Chung
United States

Xavier Forns
Spain

Norah Terrault
United States

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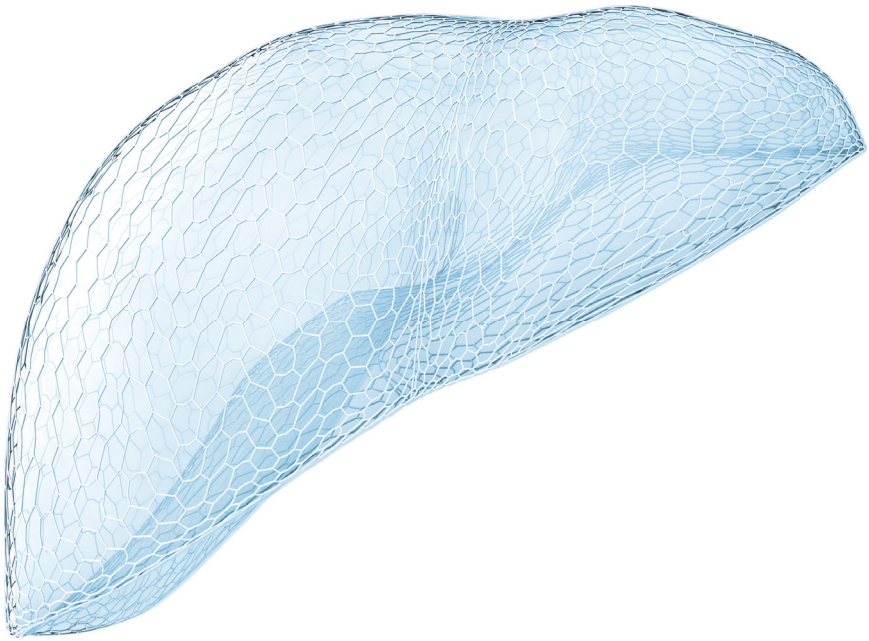

Registration & Abstract submission opening : **30 September 2016**
Abstract submission: **22 November 2016**
End of early fee registration: **31 December 2016**

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GENERAL **INFORMATION**

GENERAL INFORMATION

CONFERENCE VENUE

Marriott Rive Gauche,
17 boulevard Saint Jacques
Paris, France

LANGUAGE

The official language of the conference is English.

CLIMATE

Paris has a humid continental climate with warm summers and no dry season. In September, the weather begins to cool down, when the autumn season is just around the corner. The average temperature for this month starts off at 17.5°C and drops to 14.5°C by the end of September. Daily highs decrease from 22°C to 19°C across the month, almost never exceeding 27°C or falling below 14°C.

NAME BADGES

All participants are kindly requested to wear their name badges throughout the EASL Special Conference in order to be admitted to the lecture halls and other scheduled activities.

REGISTRATION AND ACCOMMODATION

All participants are invited to register online in order to save time upon their arrival at the conference.

Hotel accommodation for the EASL Special Conference will be offered to participants during the online registration process. Detailed information, as well as access to the online registration is available on the EASL website www.easl.eu. Registered participants are entitled to reduced rates at the conference hotel.

REGISTRATION DESK

The onsite registration desk will be open at the conference venue at the following times:

Thursday	
22 September 2016	16:00 – 19:30
Friday	
23 September 2016	07:00 – 20:00
Saturday	
24 September 2016	06:30 – 16:30

CME ACCREDITATION

The 'EASL – AASLD SPECIAL CONFERENCE NEW PERSPECTIVES IN HEPATITIS C VIRUS INFECTION – THE ROADMAP FOR CURE' is accredited by the European Accreditation Council for Continuing Medical Education (EACCME) to provide the following CME activity for medical specialists. The EACCME is an institution of the European Union of Medical Specialists (UEMS), www.uems.net

The 'EASL – AASLD SPECIAL CONFERENCE NEW PERSPECTIVES IN HEPATITIS C VIRUS INFECTION – THE ROADMAP FOR CURE' is designated for a maximum of (or 'for up to') 12 hours of European external CME credits. Each medical specialist should claim only those hours of

credit that he/she actually spent in the educational activity.

Through an agreement between the European Union of Medical Specialists and the American Medical Association, physicians may convert EACCME credits to an equivalent number of AMA PRA Category 1 Credits™. Information on the process to convert EACCME credit to AMA credit can be found at www.ama-assn.org/go/internationalcme

Live educational activities, occurring outside of Canada, recognized by the UEMS-EACCME for ECMEC credits are deemed to be Accredited Group Learning Activities (Section 1) as defined by the Maintenance of Certification Program of The Royal College of Physicians and Surgeons of Canada.

All attendees will receive an email with a link to a questionnaire at the end of the conference. Upon completion of the questionnaire, attendees will receive their certificates of attendance.

No certificate of attendance will be printed onsite.

Certificates of attendance will only be sent to delegates who attended the conference.

ACCESS PARIS

Paris is a destination with very good transport links (airlines and high-speed train). The city has two international airports, Paris Roissy-Charles de Gaulles and Paris Orly.

For information regarding air travel visit: www.aeroportsdeparis.fr/

For details regarding trains, visit the official national railway website: www.sncf.com

TRANSPORT TO THE VENUE

The conference venue, Marriott Rive Gauche hotel, is located in the 14th district near Gare Montparnasse.

From Roissy-Charles de Gaulle Airport

Bus service, fee:
EUR 17.50 (one way)
Subway service, fee:
EUR 10.00 (one way)
Estimated taxi fare:
EUR 65.00 (one way)

From Paris/Orly Airport

Bus service, fee:
EUR 7.50 (one way)
Subway service, fee:
EUR 11.30 (one way)
Estimated taxi fare:
EUR 35.00 (one way)

Bus Station

Glacière Auguste Blanqui 0.1 miles NE (200 meters)

Subway Station

Denfert Rochereau 0.3 miles W (500 meters)
Glaciere 0.1 miles E (200 meters)

GENERAL INFORMATION

Train Station

Gare Montparnasse 1.2 miles NW (2 km)
Gare du Nord (Eurostar Connection) 4 miles N (6 km)

For more details on public transportation options please visit:
Air france buses:
www.lescarsairfrance.com
RATP (Paris public transportation):
www.ratp.fr

PARTICIPANTS' LIST

The participants' list will be displayed and located at the EASL booth.

DRESS CODE AND SMOKING POLICY

Dress code is informal for all occasions. This will be a non-smoking event.

BANKING, SAFETY AND SECURITY

The currency used in France is the EURO. Foreign currency can be exchanged at banks, bureau de change and automatic currency exchange machines.

Please do not leave bags or suitcases unattended at any time, whether inside or outside the session halls. Hotels strongly recommend that you use their safety deposit boxes for your valuables.

LIABILITY AND INSURANCE

The EASL Office cannot accept liability for personal accidents or loss of or damage to private property of participants. Participants are advised to take out their own personal travel and health insurance for their trip.

SCIENTIFIC **PROGRAMME**

SCIENTIFIC **PROGRAMME**

DAY I – FRIDAY 23 SEPTEMBER 2016

08:00 – 08:10	**Welcome and Introduction** Thomas Berg, *Germany* Raymond Chung, *United States* Xavier Forns, *Spain* Norah Terrault, *United States*

SESSION I: EPIDEMIOLOGY OF HCV: TODAY AND TOMORROW (PAST – PRESENT – FUTURE)

Chairs: Massimo Colombo, *Italy*
John Ward, *United States*

08:10 – 08:30	**PHYLOGENY AND MOLECULAR EVOLUTION OF HCV – HISTORY OF THE HCV EPIDEMICS** Peter Simmonds, *United Kingdom*
08:30 – 08:50	**THE GLOBAL HCV EPIDEMIOLOGY** John Ward, *United States*
08:50 – 09:10	**CURRENT EPIDEMIOLOGY IN HIGH RISK POPULATIONS AND THE RISK OF REINFECTION** Gregory Dore, *Australia*
09:10 – 09:30	**PREDICTING THE FUTURE HCV EPIDEMIOLOGY** Maud Lemoine, *United Kingdom*
09:30 – 09:50	Q & A
09:50 – 10:30	***ePoster Session 1 and coffee break***

SESSION 2: VIROLOGY AND PATHOGENESIS

Chairs: Thomas Baumert, *France*
Raymond Chung, *United States*

10:30 – 11:00	**STATE OF THE ART: FROM HCV DISCOVERY TOWARDS VACCINE STRATEGIES** Jens Bukh, *Denmark*

11:00 – 11:20	**HOST – VIRAL INTERACTIONS AND THE ROLE OF GENETICS** Raymond Chung, *United States*
11:20 – 11:40	**IMMUNE PATHOGENESIS OF ACUTE AND CHRONIC HCV INFECTION** Robert Thimme, *Germany*
11:40 – 12:00	**HCV AND METABOLISM** Francesco Negro, *Switzerland*
12:00 – 12:20	**PATHOGENESIS OF HCV-INDUCED HCC** Yujin Hoshida, *United States*
12:20 – 12:40	Q & A
12:40 – 13:00	***ePoster Session 2***
13:00 – 14:00	***Industry symposium and Lunch***

SESSION 3: LONG-TERM CONSEQUENCES

Chairs: Geoffrey M. Dusheiko, *United Kingdom*
Zobair Younossi, *United States*

14:00 – 14:20	**NATURAL HISTORY OF HCV INFECTION – PREDICTING DISEASE PROGRESSION** Andrew Muir, *United States*
14:20 – 14:40	**HOW SUSTAINED VIROLOGIC RESPONSE IMPACTS HEPATIC AND EXTRAHEPATIC OUTCOMES OF HEPATITIS C INFECTION?** Zobair Younossi, *United States*
14:40 – 15:10	**THE POINT OF NO RETURN: LONG-TERM RISKS DESPITE HCV ERADICATION** – The clinician perspective: Antonio Craxi, *Italy* – The pathologist perspective: Pierre Bedossa, *France*
15:10 – 15:40	Q & A
15:40 – 16:10	***ePoster Session 3 and coffee break***

SESSION 4: ASSESSMENT OF HCV DISEASE

Chairs: Thomas Berg, *Germany*
Guadalupe Garcia Tsao, *United States*

16:10 – 16:30	**STAGING OF FIBROSIS IN 2016 – ARE NON-INVASIVE TESTS ENOUGH?** Laurent Castera, *France*
16:30 – 16:50	**THE ROLE OF LIVER BIOPSY AND HVPG MEASUREMENT IN THE DAA ERA** Guadalupe Garcia Tsao, *United States*
16:50 – 17:10	**IMPORTANCE OF BASELINE RESISTANCE TESTING** Christoph Sarrazin, *Germany*
17:10 – 17:30	**NEXT GENERATION DIAGNOSTIC TOOLS – READY TO USE?** Jean-Michel Pawlotsky, *France*
17:30 – 17:50	Q & A

17:50 – 18:50	***ePoster Session Best poster (4) and 5***

DAY 2 – SATURDAY 24 SEPTEMBER 2016

07:00 – 08:00	***Industry symposium***

SESSION 5: TREATMENT OF HCV

Chairs: Xavier Forns, *Spain*
Nezam Afdhal, *United States*

08:00 – 08:30	**STATE OF THE ART: FROM THE REPLICON SYSTEM TO THE DEVELOPMENT OF DAAS** Raffaele De Francesco, *Italy*
08:30 – 08:50	**MANAGEMENT OF ACUTE HEPATITIS C** Heiner Wedemeyer, *Germany*

THE TREATMENT APPROACH ACCORDING TO HCV GENOTYPE

08:50 – 09:10	**THE TREATMENT APPROACH FOR A PATIENT WITH HCV TYPE 1** Nezam Afdhal, *United States*
09:10 – 09:30	**THE TREATMENT APPROACH FOR A PATIENT WITH HCV TYPE 2** Alessandra Mangia, *Italy*
09:30 – 09:50	**THE TREATMENT APPROACH FOR A PATIENT WITH HCV TYPE 3** Maria Buti, *Spain*
09:50 – 10:10	**THE TREATMENT APPROACH FOR A PATIENT WITH HCV TYPES 4-6** Imam Waked, *Egypt*
10:10 – 10:30	Q & A

10:30 – 11:00 ***ePoster Session 6 and coffee break***

SESSION 6: REMAINING CHALLENGES IN THE TREATMENT OF HCV

Chairs: François Durand, *France*
Norah Terrault, *United States*

HCV TREATMENT IN THE LIVER TRANSPLANT SETTING

11:00 – 11:20	**TREATING THE PATIENT WITH DECOMPENSATED DISEASE OR IS ON THE WAIT LIST FOR LIVER TRANSPLANTATION** Greg Everson, *United States*
11:20 – 11:40	**TREATING THE POST-TRANSPLANT PATIENT** Xavier Forns, *Spain*

HOW TO MANAGE YOUR PATIENT WITH...

11:40 – 12:00	**KIDNEY FAILURE** Stanislas Pol, *France*
12:00 – 12:20	**HCV-HIV CO-INFECTION: FEW CHALLENGES REMAIN** Susanna Naggie, *United States*

12:20 – 12:40	**DAA FAILURE** Stefan Zeuzem, *Germany*
12:40 – 13:00	Q & A
13:00 – 14:00	***Industry symposium and lunch***

SESSION 7: ROADMAP TO CURE

Chairs: Alessio Aghemo, *Italy*
Greg Dore, *Australia*

14:00 – 14:20	**INCREASING TREATMENT RATE: STRATEGIES FOR A COUNTRY AND RISK-ADAPTED SCREENING APPROACH** Jordan Feld, *Canada*
14:20 – 14:40	**ROADMAP TO CURE – THE PATIENTS' VIEW** Livia Alimena, *Belgium*
14:40 – 15:00	**THE ROADMAP TO CURE IS A GLOBE: THE POPULATION PERSPECTIVE** David Thomas, *United States*
15:00 – 15:20	**ROADBLOCK TO CURE** Philippa Easterbrook, *Switzerland*
15:20 – 16:00	**ROUND TABLE DISCUSSION: ACCESS TO TREATMENT IN 2016** Panelists: Marc Bourlière, *France*, Graham Foster, *United Kingdom*, Andrew Muir, *United States* & David Nelson, *United States*
16:00 – 16:30	***ePoster Session 7 and coffee break***

SESSION 8: HCV TREATMENTS PERSPECTIVES

Chairs: Patrick Marcellin, *France*
David Nelson, *United States*

16:30 – 16:50	**NEXT GENERATION DAAS – HOW SHORT CAN WE GO?** David Nelson, *United States*
16:50 – 17:10	**ENTRY INHIBITORS FOR PREVENTION AND CURE OF HCV INFECTION** Thomas Baumert, *France*
17:10 – 17:30	**FUTURE PERSPECTIVES AND UNRESOLVED ISSUES** Michael Manns, *Germany*
17:30 – 17:50	Q & A
17:50 – 18:00	**Concluding remarks** Thomas Berg, *Germany* Raymond Chung, *United States* Xavier Forns, *Spain* Norah Terrault, *United States*

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GENEVA, SWITZERLAND

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Basic Programme: HCC and the hallmarks of cancer
Tom Luedde, *Germany*
Helen Reeves, *United Kingdom*

Clinical Programme: Liver cancer management
Alejandro Forner, *Spain*
Franco Trevisani, *Italy*

Join EASL in Geneva

Abstract submission deadline: **28 November 2016**

Early registration ends: **18 December 2016**

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ePoster
PRESENTATIONS

FRIDAY 23 SEPTEMBER 2016

ePoster presentations I: 10:00 – 10:30

Screen	Title	Abstract	Presenter
1	ELEVATED SERUM DIPEPTIDYL PEPTIDASE 4 (DPPIV) AND INTERFERON GAMMA INDUCIBLE PROTEIN-10 (IP-10) LEVELS DEMONSTRATED IN OBESE PATIENTS WITH CHRONIC HEPATITIS (CHC) POTENTIALLY LINK OBESITY TO UNFAVORABLE TREATMENT RESPONSE OUTCOME	107	*Kriangsak Charoensuk*
2	HCV HEV CO-INFECTION: A POSSIBLE AGGRAVATING FACTOR AFFECTING THE PROGNOSIS OF EGYPTIAN CHRONIC HEPATIC PATIENTS	116	*Mohammed Elhendawy*
3	CHARACTERIZATION OF HEMOSTATIC PROFILE CHANGES DURING IFN-FREE ANTIVIRAL THERAPY IN HCV-RELATED CIRRHOSIS: THE ROLE OF THROMBINE GENERATION TEST AND PROTHROMBOTIC MICROPARTICLES	121	*Alberto Zanetto*
4	CONCOMITANT USE OF ANTIVIRALS AND CHEMOTHERAPY IN HEPATITIS C VIRUS-INFECTED PATIENTS WITH CANCER	126	*Minas Platon Economides*
5	ELIMINATING HEPATITIS C IN SPAIN: BRIDGING FROM THE NATIONAL HEALTH PLAN	130	*María Buti*
6	PERCEPTIONS OF HCV TREATMENT AND CORRELATES TO WILLINGNESS TO INITIATE TREATMENT IN HCV+ METHADONE CLIENTS	134	*Sarah Bass*

Screen	Title	Abstract	Presenter
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8	METHADONE TREATMENT AND DOSES IN PATIENTS WITH HCV INFECTION AND HCV/HIV COINFECTION: A REANALYSE OF PROTEUS STUDY	141	*Carlos Roncero*
9	CLINICAL CHARACTERIZATION AND ECONOMIC IMPACT EVALUATION OF ANTI-HCV DAA TREATMENT FAILURE: REAL LIFE DATA FROM THE ITALIAN PLATFORM FOR THE STUDY OF VIRAL HEPATITIS THERAPIES (PITER)	144	*Loreta Kondili*
10	EARLY ALLOGRAFT DYSFUNCTION IN HEPATITIS C RECIPIENTS IS REDUCED BY PRE OR PERI LIVER TRANSPLANT VIRAL ERADICATION	146	*Silvia Martini*

ePoster presentations 2: 12:40 – 13:00

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2	COMPREHENSIVE COMMUNITY-BASED HCV SCREENING OF HIV/HCV CO-INFECTED AND HCV MONO-INFECTED PATIENTS IN NEPAL: A MODEL FOR RESOURCE-LIMITED SETTINGS	215	*Holly Murphy*
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4	THE ASSOCIATION OF POLYMORPHISMS IN MDA5 AND IFNL4 GENES WITH SPONTANEOUS AND TREATMENT-INDUCED HCV CLEARANCE IN THAI POPULATIONS	227	*Pisit Tangkijvanich*
5	DEVELOPMENT OF AN IN-HOUSE MULTIPLEX RT-PCR METHOD FOR THE HEPATITIS C VIRUS GENOTYPE 1B ASSOCIATED WITH REDUCED RESPONSE TO COMBINATION TREATMENT REGIMENS CONTAINING SIMEPREVIR, DACLATASVIR OR ASUNAPREVIR	240	*Hyewon Park*

Screen	Title	Abstract	Presenter
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4	ESTIMATING THE PREVALENCE OF HEPATITIS C IN PEOPLE WHO INJECT DRUGS USING RESPONDENT DRIVEN SAMPLING – A SYSTEMATIC REVIEW	149	*Ryan Buchanan*
5	ANTI-HCV E1E2 ANTIBODIES CAN PREDICT RELAPSE TO DIRECT-ACTING ANTIVIRALS (DAA)	150	*Marie-Anne Petit*
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Screen	Title	Abstract	Presenter
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BEST ePOSTER PRESENTATIONS

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2	NATURAL NS3, NS5A AND NS5B HCV RESISTANCE IS COMMON ACROSS HCV-GENOTYPES 1 TO 4, AND SPECIFIC SUBSTITUTIONS CAN AFFECT NS5A INHIBITORS EFFICACY IN REAL-WORLD CLINICAL PRACTICE	113	*Valeria Cento*
3	EXPOSURE-RESPONSE ANALYSES TO DEMONSTRATE SIMILAR EFFICACY AND BETTER TOLERABILITY FOR LOW DOSE RIBAVIRIN COMPARED TO WEIGHT BASED RIBAVIRIN WITH THE 3D REGIMEN (OMBITASVIR/PARITAPREVIR/RITONAVIR AND DASABUVIR) IN HCV GT1 INFECTION	115	*Akshanth Polepally*
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5	E2 GLYCOPROTEIN EPITOPE MAPPING IN ANTIBODY ASSOCIATED HEPATITIS C VIRUS	155	*Amruta Naik*

Screen	Title	Abstract	Presenter
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INVITED SPEAKERS' **ABSTRACTS**

Phylogeny and molecular evolution of HCV – history of the HCV epidemics

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HCV chronically infects 170 million people worldwide, 3% of the world's population and creates a huge disease burden from chronic progressive liver disease. As its spread is primarily through parenteral routes, HCV has historically targeted recipients of blood transfusion and medical treatment and vaccination with unsterilised needles. However, HCV has extensively spread more recently through needle-sharing drug abuse, and this now represents the primary route of ongoing transmission of infection in Western countries following the introduction of effective blood donor screening and blood product inactivation steps in the 1990s.

Reconstructions of the epidemic history of HCV are largely based on modelling evolutionary histories of currently circulating variants and by identifying historical factors that would facilitate the spread of a primarily blood borne virus. Both consistently indicate relatively recent dates for its worldwide spread from the 1930s-1940s onwards although this precedes the emergence of the AIDS epidemic from Africa by some decades. Indeed, the restriction of HCV transmission to primarily parenteral routes implicates medical treatment with unsterilised needles (including large scale vaccination programmes), blood transfusion and more recently injecting drug use as routes as the principal means of HCV spread. None of these routes were common before the second World War and supports the current model for the spread of genotypes 1b and type 2 subtypes from the 1940s/1950s, overlaid by more recent transmission among IDUs from the 1960s onwards.

This scenario is strongly supported by genetic analysis of HCV genotypes and subtypes most frequently detected among IDUs and those infected previously through medical treatment. 1a and 1b subtypes have shown relatively small and constant population sizes from the early 20th century followed by an exponential period of population growth between the 1940s and 1980s in the USA. The slowing of population growth thereafter is additionally consistent with reductions in blood transfusion risk through HIV-1 followed by HCV screening and the expansion of needle exchange programs that have led to significant falls in HCV incidence among IDUs. Emphasizing the global nature of the recent spread of HCV, parallel phylogeographic analyses have revealed similar demographic histories of these subtypes in Brazil, Indonesia and Japan. A detailed analysis of reconstructed population sizes of HCV and the emergence of parenteral routes of exposure in Japan Egypt and the USA further strengthens these conclusions, including the close links between HCV emergence and parenteral antischistosomal therapy. In

Egypt, the extremely high population prevalence of HCV is dominated by genotype 4a, whose spread can be reconstructed to have occurred between the 1930s-1950s, a period that coincides with targeted extensive antischistosomal injection campaigns using largely unsterilised injection equipment.
Collectively, these and several further combined phylogenetic and epidemiological reconstructions provide a convincing narrative for the spread of HCV worldwide. Although earlier by some decades, its spread is paralleled by the explosive worldwide spread of HIV-1 from Africa from the 1980s onwards leading to the current AIDS pandemic.

Disclosure of Interest: None Declared

Global HCV epidemiology

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Hepatitis C virus (HCV) is a blood-borne pathogen classified into seven genotypes which vary in frequency geographically. Genotype 1 and 3 account for 46% and 30% of infections globally. Risks for HCV transmission includes occurs following receipt of unscreened blood and blood products, other health care exposures and exposures to unsafe injections particularly for persons who inject drugs (PWID). Perinatal and sexual exposures can also result in HCV infection. Of persons exposed to HCV, 50-80% will develop chronic HCV. Over decades of infection, HCV infected persons are at increased risk for liver cirrhosis and liver cancer; alcohol use and HIV infection accelerate disease progression. HCV infection is also a risk for extra-hepatic manifestations. In the absence of curative therapy, 19%-40% of HCV infected persons are at risk for HCV related death. Worldwide approximately 70 – 130 million persons have chronic HCV. Certain countries in Asia, northern Africa and Eastern Europe have high HCV prevalence including Egypt, Mongolia, Pakistan, Taiwan and Georgia; Vietnam has high rates of HBV and HCV infection. Within countries, certain populations have high HCV prevalence particularly PWID, incarcerated populations, and persons with frequent health care exposures. HCV prevalence tends to highest in older aged cohorts reflecting rates of HCV transmission in the past. Models suggest HCV prevalence is declining in most countries. However HCV-related disease and mortality are increasing. In 2013, 705,000 deaths were attributed to HCV an 84% increase in deaths since 1990. Improvements in infection control in health care settings, harm reduction among PWID and theoretically, curative HCV therapy can reduce transmission. Testing, linked to care and HCV treatment substantially reduces f all-cause mortality, and hepatocellular carcinoma. However, most HCV infected persons remain undiagnosed and not receiving HCV care or treatment. Additional epidemiologic data, public health planning, and capacity building are needed to implement HCV, testing, care, treatment and other interventions necessary to eliminate HCV transmission and disease as public health threats.

Disclosure of Interest: None Declared

Current epidemiology in high risk populations and the risk of reinfection

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Highly effective, well tolerated interferon-free direct-acting antivirals (DAA) have revolutionised hepatitis C virus (HCV) treatment, with all-oral combination DAA regimens providing cure in greater than 95% of individuals with chronic infection. The availability of DAA therapy has led to significant therapeutic optimism with the possibility of broad treatment uptake and subsequent HCV elimination. DAA treatment scale-up in marginalised populations previously deemed unsuitable for interferon-based therapy is now a possibility. Modelling suggests significant benefit in treating those at high risk of ongoing transmission, with both individual and population level benefits. However, concerns regarding HCV reinfection persist.

High risk behaviour, including unsafe injecting among people who inject drugs (PWID) and unsafe sex among HIV-infected men who have sex with me (MSM), has the potential to produce high rates of both initial HCV infection and HCV reinfection following successful HCV treatment. A recent meta-analysis demonstrated post-SVR re-infection rates of 0.2% per annum for those without reported risk behaviour, 2.2% per annum among high-risk PWID and prisoner populations, and 3.2% per annum among those with HIV co-infection. DAA therapeutic optimism has the potential to increase risk behaviour. Modelling studies show that even with stable rates of ongoing HCV risk behaviour, increasing numbers of HCV reinfections will be seen with higher treatment levels, particularly in the initial years of DAA therapy scale-up. Sustained HCV treatment scale-up, including access to retreatment for reinfection, will however reduce the HCV viraemic pool among high risk populations leading to eventual reduction in re-infections.

Key elements of enhancing the potential of DAA therapy among high risk populations include: 1) access to harm-reduction strategies for PWID, including needle and syringe programs and opioid substitution therapy; 2) enhanced HCV testing and linkage to care; 3) removal of DAA restrictions based on ongoing drug use; 4) DAA drug price reform and removal of restrictions based on liver disease stage; 5) post-treatment monitoring for HCV reinfection and access to DAA therapy for retreatment. Ongoing monitoring of DAA treatment outcomes, including reinfection, and HCV risk behaviour will be crucial to evaluate the impact of DAA therapy, and determine the population-level potential for HCV treatment as prevention strategies.

Disclosure of Interest: G. Dore: Grant/Research Support: Conflict with: Gilead, Abbvie, BMS, Merck, Consultant / Advisor: Conflict with: Gilead, Abbvie, BMS, Merck, Sponsored Lectures; National or International: Conflict with: Gilead, Abbvie, BMS, Merck, Other: Conflict with: Gilead, Abbvie, BMS, Merck.

Predicting the future HCV epidemiology

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"Prediction is very difficult, especially if it's about the future." .... Albert Einstein.

Growing awareness, increased rates of diagnosis, increased rates of treatment and increased treatment success are going to impact the incidence, prevalence, morbidity and mortality of HCV in the next few years. However, there are likely to be enormous differences in the rates of change between countries and between global regions.

Treatment rates and cure rates for HCV are rapidly increasing in virtually all high income countries. It is reasonable to assume that the majority of patients already under care in hospitals in western countries will be treated and cured within the next 5 years. This is already beginning to impact on referrals for liver transplantation and admissions for decompensated cirrhosis. As treatment of cirrhotic patients reduces the incidence of hepatocellular carcinoma there should be a substantial reduction in tumour incidence within 2 years.

The proportion of patients with undiagnosed infection remains high even in high income countries with notable exceptions such as France. Progress towards the elimination goals set out in the World Health Assembly resolution in 2016 will depend on the investment in case finding. Those countries which commit to diagnosing patients in drug treatment units, prisons and immigrant communities will see rapid changes in the incidence and prevalence of HCV. However, there will remain a significant prevalence amongst hard to access populations such as the PWIDs who have not yet engaged with drug treatment units.

The outlook for low and middle income countries (LMIC) is not so optimistic for a number of reasons. Firstly, with the exception of Egypt, there are very few HCV diagnosis and treatment programmes and the rates of diagnosis are vanishingly small. Secondly, as the transmission of HCV is frequently iatrogenic there are no easily identifiable populations on which to focus public health efforts. Thirdly there is a rapid increase in injection drug use in LMIC which is associated with high rates of HCV transmission. On the positive side generic drugs are already available in many LMIC and prices are beginning to fall. Nevertheless the prospects in many LMIC are for increasing prevalence, morbidity and mortality for the foreseeable future.

Disclosure of Interest: None Declared

Host – viral interactions and the role of genetics

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Clearance of hepatitis C is dependent on an orchestrated response by the innate and adaptive immune responses. HCV has evolved remarkable strategies to assure its chronicity including subversion of these immune responses. HCV has also usurped a broad array of host cellular functions for its own lifecycle, including functions related to biosynthesis and metabolism of cholesterol. Host genetic polymorphisms also contribute to the immune control of HCV, including those found in the type III interferon, IFN-L3 and IFN-L4. Other IFN-related genes also play a contributory role to viral clearance. Polymorphisms in other loci, including PNPLA3 and EGF, can also contribute to the natural history of chronic HCV-related liver disease and HCC risk.

Disclosure of Interest: None Declared

Immune pathogenesis of acute and chronic HCV infection

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Only a minority of patients can clear hepatitis C virus (HCV) spontaneously during acute infection and this correlates with a rapid induction of innate, especially interferon (IFN) induced genes, and a delayed induction of adaptive immune responses. However, the majority of patients is unable to clear the virus and develops viral persistence in face of an on-going innate and adaptive immune response that significantly contributes to immune pathogenesis. In recent years, we have learned a great deal about the strategies the virus uses to escape these immune responses. For example, to escape innate immunity, the HCV NS3/4A protease can efficiently cleave and inactivate two important signalling molecules in the sensory pathways that react to HCV pathogen-associated molecular patterns to induce IFNs, i.e., the mitochondrial anti-viral signalling protein (MAVS) and the Toll-IL-1 receptor-domain-containing adaptor-inducing IFN-β (TRIF). Despite these escape mechanisms, IFN-stimulated genes (ISGs) are induced in a large proportion of patients with chronic infection. The mechanisms that protect HCV from IFN-mediated innate immune reactions are not entirely understood, but might involve blockade of ISG protein translation at the ribosome, localization of viral replication to cell compartments that are not accessible to anti-viral IFN-stimulated effector systems, or direct antagonism of effector systems by viral proteins. Escape from adaptive immune responses can be achieved by emergence of viral escape mutations that avoid recognition by antibodies and T cells. In addition, chronic infection is characterized by the presence of functionally and phenotypically altered NK and T cell responses that are unable to clear the virus but most likely contribute to the on-going liver disease. The recent development of direct-acting antiviral (DAA) therapy, which is associated with sustained virological response rates of more than 90%, for the treatment of chronic HCV infection allows, for the first time, evaluation of the impact of chronic infection and its treatment-induced clearance on different immune cells in the absence of IFN therapy and its known inhibitory and activating functions. First studies in DAA-treated HCV patients have shown that on-treatment viral clearance is accompanied by a rapid downregulation of ISGs in liver and blood, a normalization of NK-cell phenotype and function and a restoration of HCV-specific $CD8^+$T-cell proliferation. These results clearly indicate the strong impact of chronic antigen stimulation on immunopathogenesis and even more importantly, the ability to restore at least some of these altered immune functions simply by antigen removal. The biological and possible clinical relevance of these novel findings will be discussed.

Disclosure of Interest: None Declared

HCV and metabolism

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Hepatitis C virus (HCV) is a major cause of chronic liver disease worldwide, infecting an estimated 3% of the global population. Morbidity and mortality associated with HCV are not only due to the end-stage sequelae of chronic hepatitis, including decompensated cirrhosis and hepatocellular carcinoma, but also to a vast range of extrahepatic disorders, including type 2 diabetes and cardiovascular outcomes. The physiopathology of HCV infection is characterized by several interactions with the host lipid and glucose metabolism, leading, respectively, to steatosis and insulin resistance (IR), two pathologic features shared by the metabolic syndrome. Both steatosis and IR induced by HCV may play a role in clinical outcomes associated with hepatitis C. Steatosis has been largely associated with HCV genotype 3 infection, where the severity of fat accumulation correlates with the viral load. Moreover, successful antiviral terapy results into the disappearance of fat from hepatocytes. Although it is unclear whether viral steatosis affects liver fibrosis progression rate or response to antivirals, molecular pathways leading to fatty liver in genotype 3 infection seem to be implicated also in liver carcinogenesis. Thus, it has been suggested that this may explain, at least in part, the higher risk of development of hepatocellular carcinoma in patients with this viral genotype. On the other hand, although IR and diabetes may characterize several chronic liver disorders, a large amount of epidemiological and experimental data show that HCV directly alters glucose metabolism, leading to IR. This, in turns, in susceptible patients (e.g. older or obese), may proceed to overt type 2 diabetes. Mechanisms of HCV-associated IR involve both direct interference with the hepatocyte insulin signaling pathway, and indirect mechanism via the hepatocyte production of solutes capable of impair glucose uptake in metabolically sensitive organs (striated muscle, adipose tissue). The clinical consequences of HCV-induced IR and diabetes are significant, encompassing a reduced virological response to interferon-alpha, an accelerated fibrosis progression rate and an increased risk of developing hepatocellular carcinoma. Thus, therapy-induced viral clearance reduces the risk of developing diabetes or other glucose metabolism disturbances during follow-up, as well as the risk of cardiovascular complications of diabetes, such as ischemic stroke and nephropathy. Thus, treatment of HCV eradication seems justified also in patients without advanced liver disease but at risk of metabolic and cardiovascular complications.

Disclosure of Interest: None Declared

Pathogenesis of HCV-induced HCC

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HCV is still one of the major HCC etiologies globally, by generating chronic organ inflammation that leads to progressive fibrogenesis and carcinogenesis in the liver. Despite the successful development of highly effective and less toxic direct-acting antivirals (DAA), HCV eradication at population level will take time, and HCV-induced HCC is estimated to increase in the next decades. Of note, epidemiological studies have indicated that HCC risk persists over a decade even after sustained virologic response (SVR) by interferon-based regimens. HCC risk after DAA-based SVR is still controversial. In addition, recent studies have suggested that certain HCV strains are associated with substantially higher HCC risk after SVR. These findings clearly indicate that it is still highly relevant to elucidate mechanisms of HCV-induced liver carcinogenesis, which could contribute to identification of rational HCC chemoprevention targets and therapies. This lecture will overview direct and indirect carcinogenic effects of HCV reported in literature, and discuss potential strategies to utilize the molecular information in the context of HCV-induced HCC prevention in the era of DAA.

Disclosure of Interest: None Declared

Natural history of HCV infection – predicting disease progression

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Hepatitis C virus (HCV) infection has a complex disease course that results from an interplay of the virus and the infected patient. The long time course over decades and the subtle nature of most cases of acute infection have limited the ability to design and implement prospective studies to well characterize the natural history. Previous cross-sectional and retrospective studies have reported varying rates of fibrosis and cirrhosis, and most of the morbidity and risk of mortality with HCV infection occurs among patients who develop cirrhosis. The preponderance of evidence has supported that approximately 20 to 30% of patients will develop cirrhosis, but there is also a group of patients who are unlikely to develop cirrhosis even after decades of infection. For patients who present at earlier stages of disease, clinicians would like to predict those patients at greatest risk for the development of cirrhosis. Although direct acting antiviral agents can eradicate HCV and alter the course of the infection and avoid these life-threatening complications of portal hypertension and hepatocellular carcinoma, many patients do still not have access to these medications at this time. For those countries and groups with limited access to antiviral medications, understanding of those patients at greatest risk for the development of cirrhosis can guide allocation of resources. The wide risk of the development of cirrhosis has led to consideration of contributions of genetic factors. Although the IL28B polymorphism is associated with clearance of acute HCV infection, this has not been associated with the development of fibrosis or cirrhosis. A number of studies have suggested racial variation and specifically that that black patients have lower rates of fibrosis with HCV. Early natural history studies demonstrated that progression to cirrhosis was associated with older age at infection, alcohol use and male sex. In particular, studies of cohorts of young women with exposure to HCV infection have shown low rates of fibrosis. Studies have not generally found that viral factors including level of viremia and genotype predict fibrosis progression, although genotype 3 has been associated with fibrosis through the development of steatosis. Co-infection with HBV or HIV infection has also been associated with a more aggressive natural history. Although HIV studies have not been entirely consistent, factors generally associated with fibrosis development include lower CD4 count and lack of treatment with HIV antiviral agents. Patients also can perhaps impact risk of HCV fibrosis through behaviors and self-management. Diabetes mellitus and obesity have been associated with steatosis and the development of fibrosis. Alcohol use and marijuana are also associated with increased fibrosis in patients with

HCV, and coffee intake has been consistently associated with less fibrosis. In addition to antiviral therapy, strategies for liver wellness should therefore be discussed with patients. Once patients develop compensated cirrhosis, clinicians monitor these patients closely for progression with clinical events of portal hypertension and hepatocellular carcinoma. Despite this late stage of the disease course, many patients will remain in this compensated cirrhosis state for a number of years. There is still an opportunity to treat HCV and alter the long term outcome at this point. Understanding of the natural history can be especially important to guide patients about their individual prognosis as they present and consider antiviral treatment and other management strategies.

Disclosure of Interest: A. Muir: Grant/Research Support: Conflict with: Abbvie, BMS, Gilead, Merck.

How sustained virologic response impacts hepatic and extrahepatic outcomes of hepatitis C infection?

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Clinical and Epidemiologic Burden of HCV infection:

1) Epidemiologic Burden of HCV: Hepatitis C virus (HCV) infection is responsible for significant global clinical and economic burden. The clinical burden of HCV is related to its prevalence and clinical consequences. The global prevalence of HCV suggests that 170-200 million individuals have evidence for HCV infection. This prevalence rate is highest in Egypt and North Africa and lowest among the blood donors from Northern European countries. A second aspect of the epidemiology of HCV infection relates to its potential for chronicity and its natural history. In this context, acute HCV infection is self-limiting in 15-25% of patients while 75%-85% of the infected patients develop chronicity. In turn, chronic HCV infection can lead to both liver disease and some extrahepatic consequences.

2) Hepatic and Extrahepatic Consequences of HCV Infection: The most important hepatic manifestation of HCV is chronic hepatitis which can lead to cirrhosis and hepatocellular carcinoma (HCC). The rate of progression to cirrhosis in the United States and Europe is approximately 15% (range 8%–24%), while in Japan, this progression rate ranges between 30% to 46%. Furthermore, in the Western countries, 0.7%–1.3% of HCV develop HCC, while in the Far East and Japan this rate is higher ranging from 10% to 19%. A number of factors can accelerate the rate of progression of HCV-related liver disease including excessive alcohol consumption, age, coinfection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) and comorbid conditions such as immunosuppression, insulin resistance, superimposed non-alcoholic steatohepatitis (NASH) or hemochromatosis. In the context of the clinical progression, HCV-related cirrhosis and HCC significantly contribute to increased mortality. For patients with compensated cirrhosis, 3, 5, and 10-years survival rates are 96%, 91%, and 79%, respectively. Once decompensated cirrhosis occurs, the 5-year survival of HCV patients can be as low as 50%.

Other important clinical consequences of HCV infection are extrahepatic manifestations (EHMs). In a recent meta-analysis, the prevalence of 12 different EHMs of HCV ranged from 0.21% for ESRD to 24.5% for depression with the odds of developing these EHMs ranging from 1.58 (1.30-1.86) for DM to 8.53 (4.15-17.52) for PCT. Furthermore, the risk for development of cardiovascular disease (CVD) in HCV+ was 1.20 (95% CI: 1.03–1.40), while the OR for stroke was 1.35 (95% CI:1.00–1.82). In addition to these EHMs, other less established EHMs of HCV include neurological diseases such as Parkinson's

disease and other solid tumors. Although less well documented, it is plausible that these EHMs of HCV may also negatively affect patients' survival.

The Clinical Benefits of SVR:

The recent direct acting anti-viral regimens for HCV are associated with 98% sustained virologic response (SVR) with excellent tolerability profile and relatively simple administration schedules. In fact, these high SVR rates are not only seen in clinical trials but also in the real world clinical practices. Although SVR is the preferred outcome, it is only important because it can be considered a surrogate for patients' survival. In fact, long term data of patients with SVR suggest improvements in liver-related mortality, mortality from the extrahepatic manifestations and lower rates of HCC. Although the long term data regarding the association of SVR with improved clinical outcomes of the newer anti-viral regimens have not been published, it is highly plausible that similar long term clinical benefits can be expected. In contrast, there are some suggestions that interferon regimens may improve survival not only by eradicating HCV, but also as a result of their anti-neoplastic properties. Nevertheless, the low efficacy and high side effect profile of interferon regimens can outweigh any theoretical anti-cancer benefit it may provide.

Patient Reported Burden of HCV Infection:

In a similar fashion that SVR is considered to be the surrogate markers of patients' survival, patient-reported outcomes (PROs) are important surrogate markers of patient experience. In this context, HCV infection has been shown to have a negative impact on patient experience. PROs are defined as measurements of a patient's state of health as perceived by the patient and are reported directly from the patient without any modification. PRO data has provided evidence that patients with HCV infection experience tremendous impairment in in their health related quality of life (HRQOL), especially in the domains of physical functioning, mental health, and work productivity as a result of the virus itself. In this context, WP can estimate both absenteeism (being absent from work) and presenteeism (impairment due to decreased productivity while working). In recent studies using multivariate analyses, severity of liver disease (presence of advanced liver disease), and psychiatric co-morbidities, especially depression, are important drivers of PRO and WP impairment.

The PRO Benefits of SVR:

In a recent systematic review, it was clearly documented that treatment with interferon causes severe HRQL impairment which persisted up to 12 weeks post treatment, regardless of the patients' SVR status. In contrast, the use of the new interferon- and ribavirin-free all oral regimens for HCV treatment have resulted in significant improvement in patients' HRQL scores as early as 2 weeks into the treatment, especially in those domains most affected by the hepatitis C virus [physical functioning, work productivity (presenteeism), social functioning, activity]. In fact, by the end of treatment with the DAA's many of the significantly improved scores closely approximated or surpassed the HRQL scores of the general population without HCV. These PRO gains have also been observed in patients with both early and advanced fibrosis. In fact, the PRO score changes between patients with both early and advanced fibrosis were not only similar during treatment

but also after achieving SVR. Furthermore, these PRO gains hold true even in the co-infected populations (HCV-HIV) and the hard to treat patients (treatment failures and retreatment). It is important to note that PRO gains seem to become more prominent with longer follow up. Although still unproven, these PRO improvements may allow HCV infected patients who achieve SVR to enjoy similar HRQL scores to those who are not infected.

The Economic Burden of HCV:

In addition to the clinical burden and PRO burden, HCV infection places a significant economic burden to the society. The economic issues of HCV can be divided into four categories:

1) The Economic burden of HCV-related liver disease: In 2011, the total economic burden of HCV-related liver disease in the United States was estimated to be 6.1 billion dollars annually. Similar studies from Italy, Europe, and Asia have shown the tremendous economic burden of HCV in other parts of the world. Additionally, most of these studies have provided convincing evidence that the cost of treating HCV substantially increases with the progression of liver disease adding to the economic burden of HCV.

2) The Economic burden of HCV-related extrahepatic manifestations: In a recent study, the cost of the EHM of HCV in the United States was estimated to be around $1.5 billion per year. Although the initial studies used data from the United States, it is important to collect and report similar data from the rest of the world.

3) The Economic burden of work productivity loss due to HCV infection: HCV infection is associated with reduced work productivity (WP). HCV appears to affect absenteeism from work leading to substantial economic burden to employers. HCV infection is also associated with increased rates of presenteeism. The indirect economic burden of work productivity loss in the U.S. has been estimated to be approximately $7.1 billion per year, while the work productivity loss from 5 major European countries (France, Germany, Spain, Italy, and United Kingdom) has been estimated to be 2.6 billion Euros per year.

4) The Economic benefits of SVR: There are several different ways to evaluate HCV treatment. The first is the partial economic analysis, more commonly known as a budgetary cost analysis, where the cost of treatment is examined without considering treatment outcomes (SVR, treatment side effects, clinical and economic consequences). Results from this type of analyses may lead to the false perception that cheaper drugs are more cost-effective. A second type of analysis is a full economic analysis which considers drug costs, treatment monitoring costs, and clinical outcomes. This type of analysis provides the true net benefit or loss of the treatment program. The cost-benefit analysis will require both costs and outcomes to be assessed in monetary terms. In reality, the outcomes of HCV treatment cannot easily be reflected in a monetary value. Therefore, a more realistic analysis for HCV is a cost-effectiveness where the outcome provided is a relevant clinical outcome such as HCV cure or SVR (cost per SVR). This approach is practical and allows different treatments of the same disease to be compared according to a standard outcome. A third type of economic analysis assesses the cost of treatment per years of life gained.

This is the most robust type of analysis which considers cost, years of life gained, and quality of life associated with these years of life. This type of economic analysis, which is called a cost-utility analysis, is considered the gold standard. These types of analyses assess the cost of treatment per quality adjusted years of life gained ($/QALY). In this type of analysis, the quality adjustment of outcome is determined through societal estimation for willingness to pay threshold, (WTP) which indicates what the society is willing to pay for an additional quality-adjusted year of life achieved by the treatment. Historically, in the United States and most European countries, a WTP threshold of $50,000 per QALY has been used. In this respect, the World Health Organization (WHO) considers the WTP threshold to be less than 3-5 times the gross domestic product of a country.

Although the budgetary partial economic analyses have shown the cost of the new regimens to be high, the cost-effectiveness and cost utility analyses have documented the advantages of the new regimens over the old interferon-based regimens. Focusing on the cost per SVR or cost per HCV cure of the new regimens, costs for treatment has been shown to be significantly lower for the newer regimens as compared to the older regimens. Additionally, using the cost-utility method of analysis shows that these new regimens are highly cost effective from the societal perspective, with incremental cost-effectiveness ratios (ICER) below WTP thresholds in most of the Western countries.

Conclusions:

It is clear that HCV infection leads to a number of important clinical, PRO, and economic consequences. Considering this comprehensive and multi-faceted burden of HCV, it is critical that the entire spectrum of HCV is assessed to fully comprehend its impact on the patient and the society. Similarly, the benefit of treatment and achieving SVR must be assessed in this comprehensive manner. This approach will help patients, healthcare providers and policymakers reach better informed decisions about this important disease, and its treatment to better benefit the patient and the society as a whole.

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Disclosure of Interest: None Declared

The point of no return: long term risks despite HCV eradication – The clinician's view

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The recent advances achieved in the treatment of HCV by the development of new direct-acting antiviral agents (DAAs) allow to treat, with a very high likelihood to obtain a sustained virological response, a broad spectrum of patients, including those with advanced liver disease. Although all patients with HCV infection will benefit from the availability of oral DAA combination therapies, patients with compensated and decompensated cirrhosis, previously unreachable with IFN-conating regimens, exhibit very high (87%–98%) SVR rates with oral DAA combination therapy. These patients, who have a greater risk of progression of liver disease, hepatocellular carcinoma, and death, previously had low response rates or even absolute contraindications to treatments with interferon.

Data from large trials comparing pre- and post-treatment liver biopsies demonstrate improvements in inflammation as well as fibrosis after SVR. However, albeit the histological semiquantitative and quantitative evaluation of liver fibrosis remain the most reliable parameters to assess short-term benefit of viral clearance, several methodologies have been proposed for the noninvasive monitoring of liver fibrosis in chronic HCV hepatitis. Indeed, with the introduction of IFN-free regimens for HCV, monitoring of fibrosis regression following SVR will be largely performed with transient elastography (TE) even if we still not have reliable data on the performance of this technique in assessing the true reduction of liver fibrosis since its result may be influenced by many factors like the reduction of necroinflammation, changes.

In many cohorts of patients with established HCV cirrhosis, the achievement of SVR was related with a significant lower risk to develop progression of portal hypertension, liver decompensation, hepatocellular carcinoma and liver related death.

Also the last Baveno Consensus changed the recommendation for surveillance of esophageal varices according to the clearance of the aetiological factor, suggesting to repeat surveillance endoscopy at longer intervals in patients with SVR.

Nevertheless, in all studies analyzing the long term benefit of SVR in patients with cirrhosis, a small subset of patients experienced a progress to cirrhosis despite SVR, developing EV progression and or LD and HCC. The potential mechanisms involved in those cases of disease progression despite SVR are not still explained and therefore the outcome of single patient is not clearly predictable. For this reason clinical and ultrasound surveillance should be performed also in patients with HCV clearance.

We should also take into account that by the use of DAAs we are "curing" the HCV infection in a considerable number of patients with clinical significant portal hypertension and/or with previous or concomitant signs of liver decompensation. Only preliminary data suggest that in a part of those patients, SVR may be able to reduce MELD score or HVPG but further studies are necessary to better focus this issue and assess if exist "a point of no return" for cirrhosis regression.

The potential impact of HCV eradication for these highest-risk populations could be enormous, including decreases in hepatocellular carcinoma and liver transplantation, as well as prolonged survival. However, not all may benefiti from eradication. While the liver has the ability to repair injured tissue and there is evidence to suggest that fibrosis induced by chronic HCV infection is reversible, a point of no return most probably exhists. Up to now, patients with decompensated HCV cirrhosis had only the chance of OLT to survive. Whether viral eradication will translate to improved clinical outcomes over time remains to be seen.

Disclosure of Interest: A. Craxi: Grant/Research Support: Conflict with: BMS, Gilead, Roche, Janssen, MSD, Abbvie, Consultant / Advisor: Conflict with: BMS, Gilead, Roche, Janssen, MSD, Abbvie, Sponsored Lectures; National or International: Conflict with: BMS, Gilead, Roche, Janssen, MSD, Abbvie, V. Calvaruso: None Declared

Staging of fibrosis in 2016 – are non-invasive tests enough?

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Non-invasive tests have emerged over the past decade challenging liver biopsy for staging liver fibrosis. They rely on two different but complementary approaches: a "biological" approach based on the dosage of serum markers; a "physical" approach based on the measurement of liver stiffness using ultrasound-based elastography techniques. The practical advantages of serum biomarkers include their high applicability (>95%) and their potential widespread availability (non-patented). However, none are liver specific. Advantages of transient elastography include a short procedure time (<5 minutes), short learning curve, immediate results, and the ability to perform the test at the bedside or in an outpatient clinic. Although transient elastography analysis has excellent inter- and intra-observer agreement, its applicability (80%) is not as good as that of serum biomarkers, particularly in case of obesity or limited operator experience. Overestimation of liver stiffness values has been reported with several confounding factors including transaminases flares, extrahepatic cholestasis, congestive heart failure and food intake.

To date the most extensively studied and validated non-invasive tests in patients with chronic hepatitis C include transient elastography, FibroTest® (a patented serum biomarker) and APRI (a non-patented serum biomarker). Transient elastography has high diagnostic accuracy (AUROC>0.90) for cirrhosis (better at ruling in than ruling out) whereas its combination with serum biomarkers improves the diagnostic utility for significant fibrosis. Among novel ultrasound-based elastography techniques, Acoustic Radiation Force Impulse imaging (ARFI) and Supersonic shear wave elastography have accuracy similar to that of transient elastography but better applicability.

Non-invasive tests are increasingly included in national and international guidelines, as first line tools for prioritising patients with hepatitis C for novel antiviral treatment, leaving liver biopsy reserved for patients with unexplained discordance or suspected additional aetiologies of liver disease. In addition to staging of liver fibrosis, data on the prognostic value of these methods have increased in the past few years and are of great importance for patient care.

Disclosure of Interest: L. Castera: Sponsored Lectures; National or International: Conflict with: Echosens, Biopredictive.

The role of liver biopsy and HVPG measurement in the DAA era

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Monitoring disease progression, mainly progression to cirrhosis, has been essential in chronic hepatitis C given important management and prognostic implications. However, in the era of DAAs when the majority of patients achieve sustained virological response (SVR), monitoring disease regression is also essential as this will have not only important clinical implications regarding screening (or not) for complications of cirrhosis but also important pathophysiological implications regarding mechanisms of liver repair and regeneration and their relationship to clinical outcomes.

Two main invasive methods have been used to monitor disease progression in hepatitis C: liver biopsy and measurements of portal pressure by the hepatic venous pressure gradient (HVPG), an indirect measure of portal pressure.

Several studies have correlated stage of liver fibrosis with the degree of portal hypertension (PH) in patients with chronic hepatitis C (1, 2). Patients with advanced liver fibrosis/cirrhosis (METAVIR 3-4 or Ishak 5-6) almost uniformly have an HVPG of at least 6 mmHg (with a normal value of 3-5 mmHg indicating absence of PH) (1, 2). In patients with post-transplant recurrent hepatitis C a significant proportion of patients without a histological diagnosis of cirrhosis had an HVPG ≥6 mmHg (i.e. they had PH) and most of them developed decompensated cirrhosis (ascites, encephalopathy) in a median follow-up of 28 months (1), demonstrating that HVPG is more accurate than biopsy in diagnosing compensated cirrhosis.

In cirrhosis, portal pressure increases initially as a consequence of an increased resistance to flow due to architectural distortion mostly secondary to fibrosis and regenerative nodules. Additionally, active intrahepatic vasoconstriction and an increase in portal venous inflow that results from splanchnic arteriolar vasodilatation and a hyperdynamic circulatory state are important contributors to the portal hypertensive state. Therefore, static evaluation of architectural abnormalities will not reflect complex hemodynamic changes that occur in the intrahepatic and extrahepatic circulation and that contribute to the development of decompensation.

In patients with compensated cirrhosis and no varices, an HVPG ≥10 mmHg predicts the development of varices (3), decompensation (4)and hepatocellular carcinoma (5). In fact, a new prognostic staging system divides patients with compensated cirrhosis into those with mild PH (HVPG ≥6 but 15% are likely to have CSPH (8-10) while patients with thin septa are unlikely to have CSPH. Biologically, thick (older) fibrous septa are

more resistant to degradation because collagen cross-linking is increased (11). Therefore, it could be proposed that regression of HCV cirrhosis with etiological agents (e.g. DAAs) is more likely to occur in patients with mild PH.

It is uncertain whether a reduction in HVPG to levels below 6 mmHg after therapy indicate cirrhosis regression. This will require prospective studies evaluating HVPG, structural abnormalities on liver biopsy, as well as markers of liver synthetic function and their relationship to the development (or not) of CSPH/clinical outcomes at several time points after viral elimination.

In patients with CSPH, who are more likely to have thick septa, cirrhosis regression would be less likely but this also requires prospective evaluation. Evidence in the literature suggests that the presence of CSPH prior to antiviral treatment is the main factor that predicts the development of decompensating events despite SVR in patients with compensated HCV cirrhosis (12). In fact, we recently reported a case of a patient with compensated cirrhosis and varices (i.e. with CSPH) who, 4 years after SVR and having normalized liver synthetic function, developed massive variceal hemorrhage (13). Further studies correlating changes in HVPG, liver synthetic function and clinical outcomes at several time points after SVR will be necessary.

In patients with decompensated cirrhosis, in whom regression of cirrhosis is improbable and in whom clinical complications (progression or regression) can be more easily monitored, the role of liver biopsy and HVPG would be limited to research.

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Disclosure of Interest: None Declared

Importance of baseline resistance testing

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Antiviral combination regimens of direct acting antivirals (DAAs) are the new standard treatment for hepatitis C virus (HCV) infection.

DAAs select for viral variants who confer a certain level of resistance and these variants are generated during viral replication by chance. As the replicational turnover of HCV is high and the fidelety is low more or less all single and double possible variants are generated during viral replication.

Therefore, monotherapies with single DAA typically are insufficient to achieve a sustained virologic response (SVR) with viral eradication.

For all combination regimens of several DAAs pre-existant viral variants who confer resistance to the used drugs are typically associated with reduced SVR rates. However, if the barrier to resistance of the combination regimen is high enough no or only a minor effect of resistance associated variants (RAVs) is visible. Moreover, single amino acid substitions within the HCV target genes of DAAs called resistance associated substitutions (RAS) typically only in combination with other negative predictors lead to a significant decline of SVR rates.

These additional negative predictors for currently used DAA regimens are HCV subtype 1a, HCV genotype 3, presence of cirrhosis and failure to interferon alfa-based pre-treatment.

Based on the data of approval studies currently only for single DAA regimens baseline resistance testing is required.

For the combination treatment with grazoprevir and elbasvir for 12 weeks in all HCV genotype 1a infected patients baseline resistance testing is of importance as SVR rates are significantly reduced from >95% to approx. 50% in patients with baseline NS5A RAS. Alternatively, all HCV genotype 1a infected patients can be offered a treatment of grazoprevir plus elbasvir in addition with ribavirin for 16 weeks as this was shown to overcome baseline resistance issues.

For ledipasvir plus sofosbuvir for 12 weeks in genotype 1 infected patients a decline of SVR rates of >10% was shown in patients with HCV genotype 1a infection, cirrhosis and also in patients with failure to pre-treatment with interferon alfa-based regimens. With the addition of ribavirin and treatment extension to 24 weeks this can be mostly overcome.

For the daclatasvir plus sofosbuvir in HCV genotype 1 to 6 infected patients insufficient data are available to understand the importance of baseline resistance.

For the pangenotypic regimen of velpatasvir and sofosbuvir for 12 weeks no effect of baseline RAS has been observed in HCV genotype 1, 2, 4, 5 and 6 infected patients.
For HCV genotype 3 infected patients generally baseline RAS have the highest impact on SVR as no regimen currently is available with a sufficiently high barrier to resistance. Mainly the presence of the major RAS Y93H is associated with significantly reduced SVR rates in patients who recieved daclatasvir and sofosbuvir (SVR approx. 60%) as well as those who were treated with velpatasvir and sofosbuvir (SVR approx. 80%). As NS5A RAS are observed in approx. 10% of HCV genotype 3 infected patients baseline resistance testing is recommended. Although it is curruntly not clear from prospective controlled trials that extension of treatment duration and / or the addition of ribavirin can overcome NS5A RAS in HCV genotype 3 infected patients this is recommended to improve SVR rates.
The 3D regimen of paritaprevir/r, ombitasvir and dasabuvir with (HCV genotype 1a) and without (HCV genotype 1b) ribavirin was recently shown not to be significantly affected by baseline RAS within NS3, NS5A and NS5B genes when used for HCV genotype 1 infected patients. For HCV genotype 4 insufficient data are available.
In the future more regimens with second generation DAAs which have significant antiviral activity also on RAVs as well as combination regimens targeting NS3, NS5A and NS5B genes are expected which most likely will overcome issues with baseline resistance in DAA-naive patients.
For patients with failure to DAA-based interferon-free regimens the presence of RAVs is very likely (>80%) and re-treatment with the same regimen is no associated with high SVR rates. As no standard regimens are established for rescue treatment of DAA-failures resistance testing may be used to select suitable DAA regimens for salvage therapies.

Disclosure of Interest: C. Sarrazin: Grant/Research Support: Conflict with: Abbott, Gilead, Janssen, Qiagen, Roche, Siemens, Consultant / Advisor: Conflict with: Abbott, Abbvie, BMS, Gilead, Janssen, Merck/MSD, Roche, Sponsored Lectures; National or International: Conflict with: Abbott, Abbvie, BMS, Gilead, Janssen, Merck/MSD, Qiagen, Roche, Siemens.

Next-generation diagnostic tools: ready to use?

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The development of new HCV therapies yielding rates of HCV infection cure above 95% in most groups of patients makes it necessary that new virological tools be available to increase diagnosis and access to care and simplify therapy. Large-scale screening must be implemented within the framework of national plans. Rapid diagnostic tests detecting anti-HCV antibodies from various matrices, including fingerstick capillary and saliva, have been shown to be sensitive and specific. Dried blood spots may help sample blood in places where no virology laboratories are available and transport them to central facilities for anti-HCV antibody and HCV RNA testing. New HCV RNA detection and quantification assays based on real-time PCR or real-time transcription-mediated amplification have been developed and can accurately quantify replication at baseline, on treatment and after its withdrawal to assess the sustained virological response. HCV core antigen quantification is a surrogate marker of HCV replication and can be used as an alternative to HCV RNA detection and quantification to diagnose HCV infection and to monitor therapy. HCV resistance testing is not recommended prior to initial therapy but, if available, it could help guide certain treatment decisions. Unfortunately, HCV resistance assays are not standardized and amplification may be challenging for some genotypes and some genomic regions, making them unavailable to many treating physicians. Optimal therapy can be administered without this information.

Disclosure of Interest: None Declared

From the replicon system to the development of DAAs

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Chronic infection with the hepatitis C virus (HCV) still represents one of the major global public health problems, as it is responsible for more than 350,000 deaths worldwide on a yearly basis. No vaccine to prevent new HCV infections exists. Successful eradication of the virus following antiviral therapy, however, has been associated with improved clinical outcome and reduced mortality rates. Thus, the achievable goal of the treatment for chronic hepatitis C is a sustained virological cure.

After the discovery of the virus at the end of the 80s, HCV antiviral research struggled for a long time because of the inability to achieve viral replication in cell culture. The development of the HCV replicon cell culture system some 10 years later, conversely, catalyzed a dramatic acceleration in the growth in basic knowledge and substantially improved our ability to identify, characterize and optimize candidate antiviral agents. Owing also to the discovery of the replicon first, and the complete cell culture infection systems later, the treatment of HCV infection has evolved at an extremely rapid pace over the past several years. In particular, the development of direct-acting antivirals (DAA), which potently inhibit different stages in the viral life cycle, has led to the rapid replacement of long and poorly tolerated α-interferon-based therapies with shorter, well-tolerated, all-oral therapies that can achieve cure rates of >90% in most patient populations. Historically, the first HCV DAA to gain approval to market were targeting the NS3/4A protease. Later, two additional viral proteins, the RNA-dependent RNA polymerase (residing in NS5B) and the NS5A protein have emerged as promising drug targets and a number of antivirals targeting these proteins have either reached the market or are in late clinical development. Understanding the mechanisms of action of the various agents, including the molecular basis for resistance, will help guide clinical use of anti-HCV DAAs. In this presentation, I will provide a mechanistic description of NS3/4A protease inhibitors, nucleotide and non-nucleotide inhibitors of the NS5B viral polymerase, and inhibitors of the NS5A protein. I will explain the critical role that the HCV cell culture systems had in facilitating DAA discovery and development as well as in the study antiviral drug susceptibility and resistance. I will also provide a summary of the most important important clinical results and discuss the remaining challenges in the anti-HCV drug development efforts.

Disclosure of Interest: None Declared

Management of acute hepatitis C

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Historically, acute hepatitis C has been treated with IFNa-based therapies. Treatment of acute hepatitis C did not require the addition of ribavirin and 12-24 weeks of pegylated interferon alfa cured between 85%>100% of patients. With the introduction of direct acting antivirals against HCV for the treatment of chronic hepatitis C, IFNa is no longer recommended in patients with acute hepatitis C. Only preliminary data are available yet exploring the safety and efficacy of IFN-free regimens in acute or early hepatitis C. Potential benefits of early treatment of acute hepatitis C could be that shorter therapies might be sufficient which would reduce the overall costs of antiviral drugs. Moreover, early treatment might prevent spread of HCV in high risk populations.

The combination of ledipasvir and sofosbuvir for 6 weeks has been explored in both HCV monoinfected patients as well as in HIV-positive individuals with acute hepatitis C. In the HepNet Acute HCV-IV study all 20 patients with acute hepatitis C genotype 1 monoinfection cured HCV with this regimen (Deterding et al., EASL-ILC 2016). In a parallel trial performed in HIV-coinfected individuals, few relapses were observed which all occurred in patients with very high baseline viral load (>9 Million IU/ml) (Rockstroh et al., CROI 2016). Very importantly, early treatment of symptomatic acute hepatitis C was safe and led to a repid improvement of liver enzymes and also hepatitis-associated symptoms.

Future trials will need to investigate if even shorter therapies might be sufficient in some patients with acute hepatitis C. Moreover, other DAA regimens need to be investigated in acute hepatitis C. In addition, future trials should also include HCV genotypes 2 and 3.

Disclosure of Interest: H. Wedemeyer: Grant/Research Support: Conflict with: Abbvie, Gilead, Roche, BMS, Consultant / Advisor: Conflict with: Abbvie, Abbott, BMS, Gilead, Janssen, Roche, Merck, Sponsored Lectures; National or International: Conflict with: Abbvie, Gilead, BMS, Merck/MSD.

The treatment approach for a patient with HCV type 2

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European guidelines released in 2014 stated that for treatment of patients with GT2 three different options were available, one yet based on interferon in combination with sofosbuvir and ribavirin (RBV), the second on sofosbuvir and RBV only and the third on sofosbuvir and daclatasvir. These treatment options were recommended without differences in patients with or without cirrhosis.
In phase III studies, sofosbuvir and RBV resulted associated with 90% rates of SVR12. Criticisms were raised on the basis of limited number of patients with cirrhosis enrolled into the registration studies. Did real life data confirm SVR results of registration studies? It seems that, when used for the proper duration, the combination's results, attained in registration studies, with sofosbuvir and RBV compared very well with real life results and appeared associated with acceptable safety profile.
Recent studies from Europe suggested that geographical factors had an impact on possible lower rates of response at the time of genotype specific treatment. The most important for GT2 was the presence of a recombinant HCV genotype 2k/1b strain not recognized by the commonly used genotyping dot blot assay Innolipa, unable to amplify both the 5'and 3' regions of the HCV genome. By Innolipa assays, genotyping of the chimera virus results in an incorrect genotype 2 call. The presence of the chimera virus was investigated by direct sequencing in patients from Germany, Israel and Italy and it was detected in 17% and 25% of patients from Germany and Israel; by contrast it was not found in any of the serum sample of patients with GT2 infection collected in Italy. Therefore, the role of a potential incorrect recognition, by the commonly used inverse dot blot genotyping method, of a chimera 2k/1b virus as a reason for relapse to sofosbuvir and ribavirin combination in genotype 2 infected patients from Italy, was ruled out.
Are there other factors predictive of virological relapse for GT2? What to do in case of relapse after the past sofosbuvir based treatments? These some questions this presentation will focus on.
The final part of the presentation will be dedicated to the discussion of the role of RBV.
Are RBV free regimens available for patients with GT2? The pangenotypic combination of velpatasvir (100 mg/daily) and sofosbuvir (400 mg/daily) for 12 weeks as single tablet once a daily regimen will immediately offer an efficient, RBV free and short alternative to patients with GT2 with or without cirrhosis and regardless past treatment failure. Indeed, SVR rates of 100% were practically reported in phase III studies used to attain EMA approval last July 1st, following that of FDA on June 28th.

The second combination is under evaluation in phase III studies and is based on the pangenotypic NS3 inhibitor glecaprevir combined with the pangenotypic NS5 inhibitor pibrentasvir to be also used as single pill, once a daily.
For the future, triple regimens containing pangenotypic NS5A velpatasvir, pangenotypic voxilaprevir, former GS-9857, and sofosbuvir, currently under investigation in phase III studies, will allow for every HCV genotype including GT2 100% SVR rates after only 8 weeks of treatment, regardless of severity of liver disease and previous treatment experience, increasing the number of treated patients and hopefully reducing the treatment costs.

Disclosure of Interest: A. Mangia: Grant/Research Support: Conflict with: Janssen, MSD, Consultant / Advisor: Conflict with: Gilead Sciences, Sponsored Lectures; National or International: Conflict with: BMS, Gilead Sciences, Janssen.

The treatment approach for a patient with HCV type 3

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Several drugs are available for the treatment of chronic HCV genotype 3 (G3) infection: pegylated interferon alfa, ribavirin (RBV), and direct-acting antiviral (DAA) agents, sofosbuvir (SOF), daclatasvir (DCV), and two fixed-dose combinations of ledipasvir and sofosbuvir (LDV/SOF) or SOF and velpatasvir (VEL). Two therapeutic strategies have been developed: 1) interferon-based regimens (PegIFN plus RBV or PegIFN plus SOF and RBV), 2) interferon-free regimens, consisting on SOF plus RBV, SOF plus DCV, LDV/SOF and SOF/VEL These last are the most used due to their high efficacy and favorable safety profile.

Therapy of patients without liver cirrhosis.

All-oral combinations are associated with excellent sustained virological response (SVR) rates in treatment-naïve G3 patients without liver cirrhosis. SOF+RBV for 24 weeks provides an SVR of 95%. SOF and DCV for 12 weeks or SOF/VEL for 12 weeks yield a rate higher of 95%. SOF and DCV and SOF/VEL have a few advantages: they are ribavirin-free options with a better safety profile, and the duration of therapy is shorter.

Therapy for patients with compensated cirrhosis

In HCV G3 patients with cirrhosis, the regimen providing the highest SVR is SOF/VEL for 12 weeks, with SVR rates of 85% in treatment-experienced patients and 91% in naive patients. When this regimen was compared with SOF and RBV for 24 weeks SVR was lower, at only 80%. In the real world setting (TARGET Study), patients with cirrhosis received SOF/RBV for 24 weeks. SVR12 was 58% in treatment-naive patients and only 42% in patients who had failed previous therapy, indicating that this regimen is suboptimal for patients with cirrhosis. the TARGET trial included 197 patients with G3 infection.

In the ALLY-3 Study, SOF and DCV for 12 weeks provided an SVR of 58% in patients with cirrhosis. Later studies that added RBV to SOF and DCV in a 12-week regimen showed SVR rates of 88% treatment-naïve and 86% in treatment-experienced patients with cirrhosis. Extending therapy duration with these 3 drugs to 16 weeks did not seem to increase SVR rates. In the real-world setting, several studies have evaluated SOF/DCV and SOF LDV with or without RBV in patients with compensated and decompensated cirrhosis. In the French study, including nearly 80 G3-infected patients, SOF/DCV with or without RBV for 12 or 24 weeks gave SVR rates between 82% and 100%, with a poorer safety profile in the RBV-containing arms. In the UK study, including 172 decompensated G3 patients, 105 received SOF/DCV for 12 weeks, with an SVR12 of 71.4%, and 57 SOF/

LDV and RBV for 12 weeks, with an SVR12 of 65%. One limitation of real- world studies is that SVR response is not reported in a uniform manner (eg, per patients treated, per patients who completed follow-up, or by modify intention to treat, etc…), which makes comparison of the results between studies difficult.

New Drugs for G3 Patients

Sofosbuvir/velpatasvir and GS-9857

In a phase-2 trial, 41 treatment-naïve or previously-treated patients infected with HCV G3 with or without cirrhosis received SOF/VEL plus GS-9857 (a protease inhibitor) once daily for 6 or 8 weeks. Six weeks of this combination led to an SVR12 in 15/18 (83%) treatment-naïve patients with cirrhosis, and 8 weeks produced an SVR12 in 19/19 (100%) patients with cirrhosis who had failed PegIFN-RBV and 4/4 (100%) patients who had failed an all-oral regimen of 2 or more DAAs. The most common reported adverse events were headache, nausea, and fatigue.

ABT-493 and ABT-530

In the phase-2 SURVEYOR-II study, ABT-493 + ABT-530 mg for 12 weeks achieved an SVR in 96% (26/27) of treatment-naïve, non-cirrhotic G3-infected patients. A 8 weeks of this combination was given in 29 naïve patients without cirrhosis. SVR4 was achieved in 97% of patients. In another study, 48 G3-infected patients with cirrhosis received ABT-493 + ABT-530 with or without RBV. SVR12 was achieved in 24/24 (100%) and 24/24 (100%) of patients, irrespectively of RBV.

In summary, therapy for patients infected by HCV genotype 3 is moving forward. In treatment-naïve patients with or without cirrhosis, the combination of SOF and either DCV or VEL achieves high SVR rates. However, in treatment-experienced patients with cirrhosis, SVR rates remain below 90%. For these patients, new drugs are now under investigation, with promising perspectives

Disclosure of Interest: M. Buti: Grant/Research Support: Conflict with: Gilead, Consultant / Advisor: Conflict with: Gilead, Janseen, MSD, Merck, BMS.

The treatment approach for a patient with HCV types 4-6

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Globally, genotype 4 (G4) accounts for around 13% of all anti-HCV infections, ranking after G1 (46%), G3 (26%) and 2 (13%), with the least common genotypes globally being G6 (2%), and G5 (1%). HCV-G4 is mainly prevalent in the Middle East and Sub-Saharan Africa, HCV-G5 is endemic to South Africa, and G6 infection is found primarily in East and Southeast Asia.

The sustained virological response (SVR) rates reported in the real-life Prophesys study with pegylated interferon (PEG) and ribavirin (RBV) therapy for 48 weeks were poor for G4 patients (SVR24 in 41% of 317 patients), while response rates were better for G5 and G6 patients (although with very small sample sizes: SVR24 67% for 15 G5 patients, and 80% for 10 G6 patients).

The introduction of direct acting antivirals for HCV (DAAs) changed the outcome of therapy dramatically for genotypes 4-6 patients. In the NEUTRINO trial with sofosbuvir (SOF) plus PEG-RBV for 12 weeks, all but one of 28 G4 patient (96.5%) and all patients with G5 (n=1) and G6 (n=6) achieved SVR12.

With interferon-free therapy, SOF-RBV therapy for 24 weeks for G4 was effective in 87% of patients treated in clinical trials[7]. Using the same regimen in real-life setting in 5,667 patients with advanced fibrosis/cirrhosis in Egypt resulted in a 79% SVR12 rate.

Combination DAAs for G4 also showed high SVR12 rates: SOF-simeprevir (SIM) therapy without RBV for 12 weeks in the OSIRIS trial showed 100% response rate in patients with and without cirrhosis, and SOF-SIM therapy in real-life setting resulted in a 96.5% SVR12 rate in 2,643 patients. Using paritaprevir/ritonavir/ombitasvir fixed dose combination with RBV for 160 G4 patients in the AGATE-II study resulted in an SVR12 rate of 94% in patients without cirrhosis and 95% in patients with cirrhosis, and in 97.5% SVR12 in the AGAE-I study that included 120 patients with cirrhosis.

With SOF/ledipasvir (LED) in 21 G4 patients, one patients stopped treatment after one dose, and all other patients (95%) achieved SVR12, and a study that included 41 G5 patients showed an SVR12 rate of 95% (39/41). Similarly a study of SOF-LED therapy in 25 G6 patients with seven different G6 subtypes resulted in SVR12 rate of 96%, and the 1 patient who failed therapy had discontinued therapy at week 8 because of drug use.

The phase III program of SOF-velpatasvir included 116 G4, 35 G5 and 41 G6 patient with and without cirrhosis. All G4 and G6 patients (100%), and all but one G5 patients (97%) achieved SVR 12, including all treatment experienced patients.

Grazoprevir – elbasvir combination was more effective in G4 than in G5-6 in the C-SCAPE

study: SVR12 for 20 G4 patients was 100% in patients who received RBV, and 90% in patients treated without RBV, for 8 G5 patients: 75% with RBV and 25% without RBV, and for 8 G6: 75% with or without RBV. The same treatment was also more effective in G4 in the C-EDGE trial: SVR12 100% for 18 G4 patients and 80% for 10 G6 patients. These results and the availability of different effective DAA combinations has changed the outcome of therapy for HCV-G4-6 patients.

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Disclosure of Interest: None Declared

Treating the patient who has decompensated liver disease or is on the wait list for liver transplantation

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In the midst of waiting for a "Liver" – something changed, dramatically!

Direct-acting antiviral drugs (DAAs) for the treatment of the hepatitis C virus have arrived and now promise to potentially changed the paradigm of "Waiting for The Liver". These highly effective and well tolerated drugs have revolutionized therapy for patients infected with advanced HCV. Rates of sustained virologic response (SVR) are 95% or higher in patients with compensated cirrhosis and 80 to 90% in patients with decompensated cirrhosis. Encouraged by the tolerability of DAAs and the high rates of SVR in these cirrhotic populations, many hepatologists and transplant physicians have begun to treat many of the patients with decompensated liver disease or patients on waiting lists for liver transplantation.

There are two expected benefits of achieving SVR in decompensated patients or in patients on the waiting list for liver transplantation: stabilization or improvement of liver disease, and, prevention of post-transplant recurrence of HCV infection. Improvement in liver function and the hepatic and portal circulations could reduce risk for liver-related complications, decrease waitlist mortality, and potentially eliminate the need for liver transplantation. Recent studies have proven that treating HCV patients with DAAs prior to liver transplantation can reduce post-transplant recurrence. But the goal of reversal of liver disease to the point of reducing waitlist mortality and eliminating the need for liver transplantation remains elusive. A recent report by Belli and colleagues demonstrates that patients on liver transplant waiting lists who achieve SVR with DAAs may experience hepatic improvement and be inactivated or delisted for transplantation. These findings seem to imply that mortality and rates of liver transplantation will decrease in the HCV patients achieving SVR, but this remains to be proven.

There is a backlog of HCV cases on the liver transplant waiting list. In the US, over half of HCV patients are listed at MELD <20 and about one-third of all waiting list deaths occur in this low-MELD group. Even though curing HCV in low-MELD patients might not alter liver transplant rates, it certainly could reduce waitlist mortality. If the patient is cured and survives longer, will that translate into sustained survival benefit, reduction in liver decompensation, reduction in risk of HCC, and improved liver function and physiology. Or, will the positive effect of reduction in immediate mortality rates only be a transient short-term effect? In long-term follow-up will the inactivated and delisted patients still die

of liver decompensation or HCC or get re-listed for transplantation? In the latter case, one could argue that inactivation and delisting might actually be harmful.
In conclusion, the new DAAs have arrived and have begun to change the landscape of treatment and management of the HCV patient with advanced disease. The overall success of treating patients with decompensated liver disease or patients on the waiting list will depend on the results of long-term studies of clinical outcomes.

Disclosure of Interest: None Declared

Treatment of post-transplant patient

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Treatment of post-transplant hepatitis C has changed dramatically over the last 2 years. First, due to the fact that in most transplant programs patients with HCV-related liver disease awaiting a liver transplantation undergo antiviral therapy. Most of them achieve a virological response that is maintained after transplantation and thus, the incidence of hepatitis C post-transplant has decreased significantly. Second, the safety and efficacy of current antiviral regimens is excellent. Indeed, among patients with mild fibrosis or compensated cirrhosis sofosbuvir plus ledipasvir (G1 and G4) or sofosbuvir plus daclatasvir (G1-4) therapy achieve SVR rates close to 100%. The only limitations are: 1- all clinical trials and most real-life data use ribavirin, which is not optimal in patients who often have an altered GFR and anemia; 2- drug-drug interaction are more frequent and should be carefully evaluated in this population; 3- SVR rates are slightly lower in G3 patients and in those with decompensated cirrhosis.

Despite there is still room for improvement, most patients with hepatitis C recurrence can be safely treated with antiviral drugs that offer an excellent cure rates. For this reasons all transplant patients with hepatitis C recurrence are candidates and should undergo antiviral treatment. Preliminary data strongly suggest that HCV eradication is associated with histological and clinical improvement, but more data are necessary on this particular topic.

Disclosure of Interest: None Declared

Kidney failure

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Chronic hepatitis C (CHC) is significantly associated with a risk of renal deterioration over time. Renal impairment, especially stage 4-5 chronic kidney disease, increases the risk of: 1) the prevalence and incidence (in dialysis/transplantation) of HCV infection, 2) liver deterioration during kidney transplantation, and 3) allograft failure and patient mortality. HCV-infected dialysis patients have a higher mortality than non-infected dialysis patients and than HCV-infected kidney recipients. The harmful impact of HCV emphasizes the need for oral antiviral therapies in patients with chronic kidney disease. Symptomatic cryoglobulinemic vasculitis and extensive liver fibrosis are already approved indications for early access to oral antiviral treatment. Patients with stage 4-5 chronic kidney disease should also be given priority: dialysis patients (whatever the stage of fibrosis and whether or not they are candidates for kidney transplantation) as well as all kidney recipients. The results of treatment of HCV with direct acting anti-viral (DAAs) drugs in patients with late chronic kidney disease are excellent, similar to those in the general population, even though additional clinical trials are definitely needed, particularly to optimize adjustment of treatment to kidney function and determine the risk of drug-drug interactions.

Disclosure of Interest: S. Pol: Grant/Research Support: Conflict with: Roche, Janssen, Gilead, Bristol Myers Squibb, Other: Conflict with: Presonal fees: Roche, Janssen, Gilead, Bristol Myers Squibb, Boehringer Ingelheim, Merck, Novartis, and Abbvie.

HIV-HCV co-infection: Few challenges remain

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The availability of direct acting antivirals for treatment of HCV has provided some of the greatest benefit to historically difficult to treat patient populations, including those with HIV/HCV co-infection. With similar efficacy now reported across multiple DAA regimens, HIV-infection is no longer viewed as a special population with an unmet medical need. Yet HIV/HCV co-infected patients do still pose particular challenges to HCV treatment and management due to complex liver pathogenesis, higher risk of acute HCV infection and re-infection, and potential for drug interactions with antiretrovirals that are frequently not addressed in registration trials. This discussion will focus on unique challenges within the HIV-infected patient population as it relates to liver disease progression after SVR and frequency of drug interactions with antiretrovirals and DAA. Common drug interactions, including but not limited to antiretrovirals, will be discussed and management options when interactions are encountered will be reviewed. Potential for pharmacogenomics to play a role in this particular population will also be discussed.

Disclosure of Interest: S. Naggie: Grant/Research Support: Conflict with: BMS, AbbVie, Gilead, Janssen, Tacere, Merck, Vertex, Consultant / Advisor: Conflict with: Merck.

Increasing treatment rate: strategies for a country and risk-adapted screening approach

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With the development of highly effective, very well tolerated direct-acting antivirals (DAAs), it is now possible to cure the vast majority of treated individuals. These rapid advances and high cure rates have led to discussion of the prospect of national elimination and even global eradication of HCV. However, although treatment is extremely effective for those that receive it, the vast majority of individuals worldwide living with HCV infection remain undiagnosed. For elimination and certainly for eradication to be a realistic possibility, massive efforts to screen and identify those infected must first take place. Diagnosis rates vary widely in different countries but remain below 50% in many high-income countries and are likely below 5% in many developing countries, including those with a very high prevalence of disease. In most countries, screening to date has largely relied on primary care providers screening patients who they deem to be at increased risk of HCV infection. However, this type of simple risk-based screening, while important, has been relatively ineffective in most regions. This has led some countries to implement population-based screening approaches to increase screening uptake, while others have tried to better identify high-risk groups. Population-based screening approaches to date include birth-cohort screening in the US, age-based screening in France and hospital and/or emergency-room based programs in various regions, while other countries such as Australia have ensured very broad coverage of screening among those at high risk of infection such as people who inject drugs. The optimal screening strategy for a given location depends most importantly on the epidemiology of infection but also on resources available for screening, access to appropriate screening tests, access to care and treatment for those identified and of course financial resources to support all of these efforts. The benefits of risk-adapted versus population-based screening will be discussed using specific examples to illustrate successes and failures in this critically important aspect of HCV public health strategy.

Disclosure of Interest: None Declared

The roadmap to cure is a globe: the population perspective

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Introduction: Worldwide, an estimated 135 million persons have chronic HCV infection. HCV is found nearly everywhere, but some countries have far more than others. The highest national prevalence has been reported in Egypt, where infection was spread inadvertently by an effort to eradicate schistosomiasis by injections. Infection is also unevenly distributed in most places among persons born before 1965, also probably representing widespread transmission from unsafe medical injections in that age cohort. Within populations, infection is highest in persons who inject drugs. Thus, the road to cure has to pass through every region of the world and reach extremely diverse, often marginalized, and often asymptomatic people groups.

Unfortunately, most of those with HCV infection live in uncharted territory; that is to say, they are not aware of their infection. Precise figures are not available, but even in some resource rich regions of the world, awareness of infection is estimated at 50%. Awareness of infection has to be much lower in other places such as India, some parts of China, South East Asia, sub-Saharan Africa, Russia and some Eastern European countries.

The cost of treatment makes HCV cure often 'the road less traveled'. Even steeply discounted pricing can be difficult to afford for some, and lack of public health infrastructure and the marginalization of many infected people are serious global obstacles.

While challenges remain, there is strong potential to end the epidemic. Inexpensive, accurate point of care testing exists. Cure is readily achievable as pan-genotypic treatments are already available. As importantly, there is also global precedent of delivering relatively expensive treatment to unreached peoples with HIV infection, a much more difficult challenge given the lifelong need for medications. There are also encouraging examples of HCV care delivery to people who inject drugs and even national, test-and-treat campaigns that get us started on the roadmap to cure.

Disclosure of Interest: None Declared

Next generation DAAs- how short can we go?

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With the development of multiple, potent direct antiviral agents (DAAs) for hepatitis C, combination drug therapies have allowed shortened treatment duration. In the last five years we have already seen the standard duration of therapy decrease from 48 weeks to 24 weeks and now 12 weeks for most patients. Current clinical trial data has shown that select populations can be cured in as short as 3-4 weeks of combination therapy with three DAAs. If treatment costs remain high, this approach could save resources and is very appealing. However, these regimens have thus far demonstrated acceptable SVR only in highly selected populations (patients with low fibrosis scores, low viral load, absence of resistance associated substitutions, favorable IL28B genotype, and/or HCV genotype 1b) or have used response guided therapy to select those that are "ultra-rapid responders". To date, no regimen has allowed shortening of therapy below 8-12 weeks in a broad population that includes advanced fibrosis and treatment experienced populations. As next generation DAAs continue to maximize potency and raise the barrier to resistance, the opportunities to pursue individualized and more universal, shorter duration may become a reality. This presentation will include a review of current and future options to shorten therapy and identify predictors of treatment response to short duration therapies and optimal combination of DAAs.

Disclosure of Interest: D. R. Nelson: Grant/Research Support: Conflict with: Abbvie, BMS, Gilead, Janssen, Merck.

Entry inhibitors for prevention and cure of HCV infection

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While direct-acting antivirals (DAAs) can cure the large majority of patients, patients with defined genotypes, advanced liver disease or prior nonresponders to pegylated interferon-based regimens may need alternative or complementary therapies. Moreover, despite viral cure, patients with advanced fibrosis remain at significant risk for the development of hepatocellular carcinoma. Furthermore, new evidence suggests that the occurrence of liver cancer appears not to be reduced in DAA-treated cirrhotic patients. By blocking viral cell entry into hepatocytes, HCV entry inhibitors target the very first step of viral infection and provide a complementary of action for viral erradication. Over the past two decades, advances in HCV model systems have enabled a detailed understanding of HCV cell entry and its clinical impact. Many of the virus-host interactions in HCV entry have now been identified and explored as antiviral targets. Furthermore, viral entry is recognized as an important factor for graft reinfection and establishment of persistent infection. HCV entry inhibitors, therefore, offer promising opportunities to address the limitations of DAAs. Here, we summarize recent advances in the mechanism of HCV entry, review compounds in preclinical and clinical development and discuss perspectives of entry inhibitors for antiviral therapy and prevention of liver disease and cancer.

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Disclosure of Interest: None Declared

Hepatitis C therapy: future perspectives and unresolved issues

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With the latest all-oral interferon- and ribavirin-free regimens based on direct actingantivirals (DAA) against the hepatitis C virus (HCV) sustained virological response rates (SVR) of > 90% are achieved which is equivalent to cure. Since a prophylactic HCV vaccine is not available yet global control of HCV infection will have to rely on the use of effective and safe antiviral therapies. Different approaches may apply to different parts of the world. However, remaining challenges have to be addressed for the long-term goal of worldwide HCVeradication. Effective HCV screening programs need to be installed and "treatment as prevention" has to be put in practice. In particular high risk groups for de novo or reinfection and thus further spread of the virus need to be addressed. The role of resistance associated variants (or substitutions) and of chimeric viruses such as the recently described St. Petersburg variant and their management remain a challenge for individual patients. Further challenges remain patients with renal insufficiency and here in particular those with decompensated end stage liver disease. Only sofosbuvir based regimen are approved for patient population with decompensated liver disease but contraindicated in end stage renal disease.

In the era of DAA therapies genotype 3 patients have been the most difficult to treat HCV genotype. However, sofosbuvir plus daclatasvir (SOF/DCV) and recently SOF/velpatasvir (SOF/VEL) have improved therapeutic possibilities. Still treatment experienced genotype 3 patients with decompensated liver disease remain a challenge. In patients with decompensated liver disease, Child B & C cirrhosis, the point-of-no-return until which HCV elimination is still beneficial to the patient still has to be defined. The role of HCV therapy in the management of patients with hepatocellular carcinoma (HCC) also still has to be defined. A recent very interesting topic is what impact HCV elimination might have on HCC development in cirrhotic patients following DAA therapies. This may be influenced by HCV's impact on the innate immune system. Exploring the shortest possible HCV therapy is another challenge as is the identification and optimum treatment for acute hepatitis C. Without effective screening programs and access to and affordability of HCV drugs a treat as prevention strategy will not succeed. Treat as prevention also means eliminating HCV from special populations like persons who inject drugs (PWID) or organ transplant populations; liver and non-liver transplants as well as bone marrow and stem cell transplantation. Once HCV therapies are not only effective and safe but also accessible and affordable HCV therapies will be given to all HCV carriers irrespective of

grade or stage of liver disease including those with extrahepatic manifestations like fatigue and lymphoproliferative disorders.
We already know from the era of interferon based therapies that HCV elimination not only improves liver related but also overall mortality. Access to therapy remains the major challenge to combat successfully the global health burden caused by hepatitis C. Individual countries already started successful eradication programs. Generic drugs of high quality are available in some parts of the world. Whether hepatitis C becomes the first chronic viral infection to be eradicated without a prophylactic vaccine remains to be shown. However a prophylactic HCV vaccine is still desirable and an unmet need.

Disclosure of Interest: None Declared

ePOSTER
ABSTRACTS

Friday 23 September 2016
ePoster Session I: 10:00 – 10:30

Screen I: ABSTRACT-107

Elevated serum dipeptidyl peptidase 4 (DPPIV) and interferon gamma inducible protein-10 (IP-10) levels demonstrated in obese patients with chronic hepatitis (CHC) potentially link obesity to unfavorable treatment response outcome

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Introduction: Obesity is a negative predictor of successful treatment outcome in CHC patients. DPP4 (CD26) and IP- 10 are proved to predicted unfavorable treatment response in chronic hepatitis C. Previous study, DPP4 is a novel adipokine and potentially link to obesity, insulin resistance and metabolic syndrome. Furthermore, mature human adipocytes in vitro express and secrete the chemokine IP- 10. We hypothesized that obesity, which shown to be a negative treatment outcome in CHC, might relate to immune dysregulation in these patients through a pathway linked to IP-10 or CD26.

Aims: The purpose of this study was to investigate the association between T-helper1/2 cytokines, IP-10 and DPP4 levels in these obese CHC patients.

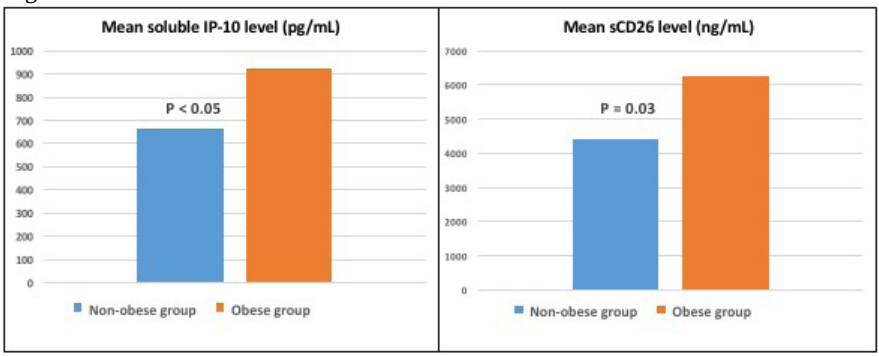
Material and Methods: The CHC patients were included to participate in this study: non-obese (BMI < 25 kg/m2) and obese (BMI ≥ 30 kg/m2) groups. Baseline characteristics including gender, age, liver function tests, HCV genotype and viral load were assessed. Basal blood samples were collected to determine Th-1/2 related cytokines, plasma DPP4 and IP-10 levels.

Results: A total of 86 CHC patients were included to participate in this study: 54 non-obese (BMI < 25 kg/m2) and 32 obese (BMI ≥ 30 kg/m2). While there were no significant

differences in the baseline characteristics between two groups, the significantly higher rate of dia- betes and metabolic syndrome in obese group was observed. There was no significant changes of the Th-1/ 2 cytokines in both groups. The mean IP-10 and DPP4 in obese group were 924.9 pg/mL and 6.265.3 ng/mL respectively, and in non-obese group were 622.1 pg/mL and 4394.1 ng/mL respectively. The higher IP-10 and DPP4 levels in CHC patients with obesity were demonstrated, compared with non-obese group ($p < 0.05$), (Fig. 1).

Conclusions: This study demonstrated evidence of the significant elevation of serum IP-10 and DPP4 levels in obese CHC patients. These results connect the link and give one explanation of why obesity is an unfavorable predic- tive factor and could have effects on treatment response in patients with chronic hepatitis.

Figure:



Disclosure of Interest: None Declared

Screen 2: YI-ABSTRACT-II6

HCV HEV co-infection: a possible aggravating factor affecting the prognosis of Egyptian chronic hepatic patients

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Introduction: HCV is a worldwide health problem with the highest prevalence in Egypt. HCV is the leading cause of hepatocellular carcinoma and chronic liver disease Egypt. A high prevalence of antibodies to hepatitis E virus has been reported in developing countries. Some studies have reported a high prevalence of HEV antibodies in patients with chronic liver disease and others have suggested that superinfection in chronic liver disease may lead to increased morbidity and mortality

Aims: To study the prevalence of HCV infection and its sequelae among inhabitants of an Egyptian village in the Nile delta region and to evaluate the association between anti-HEV infection and chronic liver disease.

Material and Methods: This cross sectional study included 2085 inhabitants of Nagreej village, Basyoun, Gharbia Governorate; a small Egyptian village in the Nile delta region. Mass HCV screening was performed for the residents with random sampling for HEV detection

Results: In the present study, the overall HCV prevalence was 25.9%. Prevalence rates increased with age and the male gender. The risk factors of acquiring viral infection, reported in the patients' past history revealed parenteral therapy for Schistosomiasis by tarter emetic injection to be at the top of the list; followed by blood transfusion. Other recorded risk factors were dental procedures; history of previous surgical operation, hospital admission, use of contaminated needles, tattooing & drug abuse.

Random sampling for HEV IgM and IgG prevalence in healthy controls and chronic liver disease patients was performed. The age and sex of the studied groups were matched. HEV was positive in 30/60 with chronic HCV (50%), 72/75 cirrhotics (96%), 72/75 having HCC (96%), and in 33/60 control subjects (55%). The percentage was significantly higher among cirrhotics and those with HCC than in chronic HCV and healthy controls. HEV IgM was –ve in all studied populations

Conclusions: Egypt still has a high prevalence of HCV infection mainly in the older populations. Egyptian patients with cirrhosis and HCC have a significantly higher seroprevalence of anti-HEV compared to healthy individuals from the same geographical area. HCV-HEV coinfection may worsen the prognosis of Egyptian chronic hepatic patients. The role and association of anti-HEV with advanced stages of chronic liver disease, remain to be determined

Disclosure of Interest: None Declared

Characterization of hemostatic profile changes during IFN-free antiviral therapy in HCV-related cirrhosis: the role of thrombine generation test and prothrombotic microparticles

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Introduction: Advanced liver disease is characterized by hemostatic alterations that can lead to both bleeding and thrombotic complications. Since standard coagulation tests failed to detect the degree of this disequilibrium, whole blood tests have been proposed. Both the thrombin generation test (TG) and the characterization of pro-thrombotic microparticles (MP) have been studied in cirrhosis and alterations toward hypercoagulability have been correlated with increased risk of portal vein thrombosis (PVT). However, studies that analyze those findings in patients with HCV cirrhosis treated with IFN-free antiviral therapy (DAA) are lacking

Aims: To evaluate the impact of HCV eradication in coagulation profile of patients with HCV related cirrhosis by TG and MP profile as well as to correlate the hemostatic profile with risk of PVT.

Material and Methods: patients with HCV cirrhosis treated with DAA were prospectively enrolled. TG test [with and without trombomodulin (TM)] and dosage of plasma level of endothelial (E)-MP, platelet (P)-MP and tissue factor (TF) bearing MP (measured by cytoflowrimetry) were performed at baseline (B), at the end of therapy (EOT) and 12 weeks (12W) after EOT. During follow-up, PVT onset was recorded.

Results: 64 patients were enrolled (Child A/B/C 54/8/2). All patients achieved sustained virological response 12W after EOT. Both EOT and 12W after EOT endogenous thrombin potential (with TM) and lag time (with TM) were lower and longer in comparison with

baseline values, respectively (p<0.01). B-levels of E- [1351 (1162–2213) MP/μL], P- [1034 (339–2167) MP/μL] and TF-MP [122 (51–165) MP/μL] were significantly higher than EOT-levels [580 (367–794) MP/μL, p<0.001; 437 (208–835) MP/μL, p<0.005; 44 (26– 76) MP/μL, p<0.01] and 12W after EOT-levels [156 (103–258) MP/μL p<0.01, 375 (198–444) MP/μL p<0.02, 38 (31–72) MP/μL p<0.01], respectively. Plasma levels of 12W after EOT-MP were similar to those of healthy controls (p=0.2). Median follow up was 7 months (1-12). We did not observe any PVT during follow-up.

Conclusions: Eradication of HCV is associated with significant changes in hemostatic profile, possibly related to both reduction of inflammatory systemic condition and to improvement of liver function. This amelioration may partially correct the disequilibrium of the hemostatic imbalance leading to a reduction in the risk of PVT. Further studies are needed to confirm these results.

Disclosure of Interest: None Declared

Screen 4: ABSTRACT-I26

Concomitant use of antivirals and chemotherapy in hepatitis C virus-infected patients with cancer

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Introduction: Antiviral therapy (AVT) improves outcomes in hepatitis C virus (HCV)-infected cancer patients. These patients are frequently excluded from clinical trials on AVT or chemotherapy as the side effects associated with previous standard of care with pegylated interferon (IFN) and ribavirin can exacerbate underlying hematological abnormalities of cancer patients. Newer direct-acting antiviral regimens have few side effects in general population.

Aims: We aimed to examine the safety and clinically significant drug-drug interactions (DDIs) observed in patients who received simultaneous AVT and chemotherapy.

Material and Methods: Medical records of patients seen in MD Anderson were reviewed. Patients seen from 1/2008-10/2012 were reviewed retrospectively, whereas those seen from 11/2012-6/2016 were studied prospectively. Patients received concomitant chemotherapy and AVT, if based on metabolism and clearance, a DDI was unlikely. Adverse events (AEs) were graded according to the division of AIDS Table (version 2.0). AEs were monitored throughout AVT and up to 3 months after its completion. Sustained virological response (SVR) was defined as absence of serum HCV RNA 24 weeks after end of treatment. Cirrhosis was diagnosed via biopsy or with the use of, imaging and noninvasive fibrosis markers.

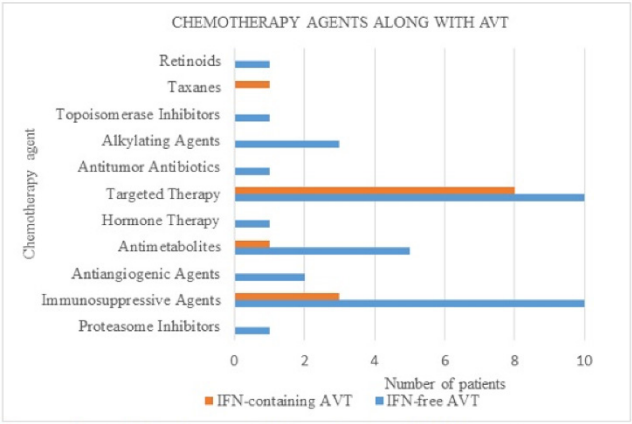
Results: Thirty patients received concomitant AVT and chemotherapy between 1/2008 and 6/2016. Concomitant treatment was started either for virologic (20; 67%) or oncologic (10; 33%) reasons. Virologic reasons included achievement of SVR to reduce liver disease progression in patients already receiving chemotherapy. Oncologic reasons

consisted of patients who at the time of AVT, developed cancer progression and the need of chemotherapy was raised. The chemotherapy agents used along with AVT are depicted in figure 1. AVT consisted of IFN-based (10; 33%) and IFN-free (20; 67%) regimens. When compared with IFN-free AVT, chemotherapy given with IFN-based AVT was more frequently associated with any type of AEs and especially with hematological (100% vs 35%, p<0.01) and psychiatric (70% vs 20%, p=0.01) AEs. Physicians changed the AVT regimens in two patients (7%) in anticipation of DDIs between daclatasvir and tacrolimus. The overall SVR rate was 87% (26/30).

Conclusions: HCV-targeted AVT can be used concomitantly with selected antineoplastic agents under close monitoring for DDIs. This therapeutic intervention may prevent delays in the administration of chemotherapy in HCV-infected cancer patients.

Figure:

Figure 1. Different chemotherapeutic regimens used concomitantly with AVT



Taxanes: docetaxel; Topoisomerase inhibitors: irinotecan; Alkylating agents: cyclophosphamide, oxaliplatin; Antitumor antibiotics: doxorubicin; Targeted therapy: trastuzumab, pertuzumab, rituximab, bevacizumab, tamoxifen, sorafenib; Hormone therapy: anastrazole; Antimetabolites: 5-flurouracil, gemcitabine, hydroxyurea; Antiangiogenic agents: lenalidomide; Immunosuppressive agents: corticorsteroids, tacrolimus; Proteasome inhibitors: bortezomib.

Disclosure of Interest: M. P. Economides: None Declared, P. Mahale: None Declared, A. Kyvernitakis: None Declared, F. Turturro: None Declared, H. Kantarjian: None Declared, A. Naing: None Declared, J. Hosry: None Declared, T. Shigle: None Declared, A. Kaseb: None Declared, H. Torres: Grant: Conflict with: Gilead Sciences,Merck & Co., Inc.,

and Vertex Pharmaceuticals, with all funds paid to MD Anderson, Consultant: Conflict with: Gilead Sciences, Merck & Co., Janssen Pharmaceuticals, Vertex Pharmaceuticals, Genetech, Novartis, Astellas Pharma, Pfizer Inc., and Theravance Biopharma, Inc.

Eliminating hepatitis C in Spain: bridging from the National Health plan

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Introduction: Chronic hepatitis C (CHC) is responsible for a large burden of disease and high use of resources. In 2015, 426,998 prevalent cases of CHC in Spain were estimated, of which 131,528 were diagnosed. Combining the availability of new direct antiviral agents (DAA) and public health policies, the Spanish Ministry of Health implemented a National Strategic Plan for CHC (SPCHC) treating 38,067 patients in 2015 with different degrees of moderate-advanced fibrosis (≥F2).

Aims: To compare the impact of the SPCHC on CHC prevalence, decompensated cirrhosis, mortality, hepatocellular carcinoma (HCC) and liver transplants avoided in ten years with two alternative strategies: 1) ***Incremental strategy*** increasing the number of newly diagnosed and treated patients; and 2) ***Disease elimination strategy*** for obtaining the elimination of the CHC (less than 20,000 prevalent cases) in ten years.

Material and Methods: A disease progression model including demographic, epidemiological, CHC progression and DAA efficacy data was used. Data were obtained from the best scientific evidence and validated by Spanish experts. Three scenarios were constructed: 1) reproduces the SPCHC strategy (5,500 newly diagnosed patients per year, capacity to treat 38,000 patients per year in 2015 and 2016, and 20,000 patients per year after 2017, and treating ≥F2); 2) incremental strategy (adding to the SPCHC an increase to 15,000 new cases diagnosed annually, and the capacity to treat 38,000 patients per

year); and 3) elimination strategy (screening efforts need to increase to diagnose 40,000 new cases annually starting in 2016 with treatment expanded to 50,000 ≥F0 patients annually by 2017).

Results: Under the SPCHC, fewer than 20,000 patients a year can be treated because there are not enough eligible patients to treat and the treatment is restricted to those ≥F2. Compared to SPCHC, in 10 years: 1) the incremental strategy will decrease prevalence by 53,534 cases, deaths by 1,421, decompensated cirrhosis by 1,622, HCC cases by 1,314, and liver transplant avoided by 0; 2) the elimination strategy will decrease prevalence by 276,443 cases, deaths by 3,393, decompensated cirrhosis by 3,857, HCC cases by 3,166, and liver transplant by 722.

Conclusions: The SPCHC has been successful in providing the capability to treat 9% of the estimated prevalent CHC population in one year. It's a sound starting point to leverage moving to a 2.0 SPCHC and an elimination strategy. Expanding screening and access to treatment policies are the key elements to be addressed.

Disclosure of Interest: M. Buti: Grant: Conflict with: Gilead., Consultant: Conflict with: Gilead; MSD; AbbVie; Janssen., Sponsored lectures (National or International): Conflict with: Gilead; MSD; AbbVie; Janssen., J. L. Calleja: Consultant: Conflict with: Abbvie, Gilead, BMS, MSD, Sponsored lectures (National or International): Conflict with: Abbvie, Gilead, BMS, MSD, J. Garcia-Samaniego: Consultant: Conflict with: Gilead, Abbvie, Janssen, BMS, Sponsored lectures (National or International): Conflict with: Gilead, Abbvie, Janssen, BMS, M. A. Serra: Consultant: Conflict with: Abbvie, MSD, Gilead, BMS, Janssen., Sponsored lectures (National or International): Conflict with: Abbvie, MSD, Gilead, BMS, Janssen., J. Crespo: Grant: Conflict with: MSD, Gilead, Consultant: Conflict with: MSD, Gilead, Abbvie, BMS, Sponsored lectures (National or International): Conflict with: MSD, Gilead, Abbvie, BMS, M. Romero: None Declared, M. A. Simon: None Declared, A. J. Blasco: None Declared, P. Lazaro: None Declared, S. Robbins: Employee: Conflict with: CDA, Other: Conflict with: CDA has received research grants from Gilead and AbbVie, H. Razavi: Employee: Conflict with: CDA., Other: Conflict with: CDA has received research grants from Gilead and AbbVie. Dr. Razavi is the founder and owner of CDA.

Perceptions of HCV treatment and correlates to willingness to initiate treatment in HCV+ methadone clients

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Introduction: WHO and CDC goals to eliminate hepatitis C (HCV) will be reached only if we achieve sizable increases in treatment initiation among underserved groups. Methadone (MMT) clients in the U.S. demonstrate 67-96% HCV seropositivity, but low treatment rates (<11%). To facilitate treatment of this group we must better understand their perceptions of medical care and HCV treatment.

Aims:

1) To determine and HCV care perceptions among HCV+ methadone clients.

2) To measure association between perceptions and interest in HCV treatment initiation.

Material and Methods: We administered surveys to 100 HCV+ MMT clients from four Philadelphia MMT programs collecting socio-demographic and HCV factors and scaled attitude scores about experiences with the healthcare system, knowledge about HCV and its treatment, psychosocial barriers to initiating treatment, other factors which impact care decisions, and level of interest in initiating HCV care if it were offered. We used bivariate methods (χ^2, r and ANOVA) and then ordinal regression analysis to examine factors and perceptions associated with interest in treatment initiation.

Results: On bivariate analysis, education level and discussion about HCV treatment with care providers were significantly associated ($p<0.05$) with interest in treatment initiation, but age, race, gender, insurance type, difficulty paying for healthcare, and time since screening were not. Perceptions significantly associated ($p<0.05$) with interest in treatment initiation included treatment barriers and benefits. Perceptions independently associated with increased interest in treatment by ordinal regression include: lower agreement with

statements that there is too much paperwork (OR=.718; 95%CI=.564-.914), another treatment will be available soon (OR=.832, CI .725-.955) don't have a support system (OR=.820; CI= .701-.960), trouble taking medications (OR=.753 CI .603-.940) and being afraid of treatment side effects (OR=.865; CI=.751-.995) and higher agreement with statements about trouble making medical appointments (OR=1.48; CI 1.14-1.92), had positive interactions with healthcare providers (OR=1.30; CI=1.03- 1.57), feel they have had enough HCV education (OR=1.30, CI 1.08-1.57) and believe HCV treatment is easy and cures quickly (OR=1.54, CI:1.21-1.96).

Conclusions: Results indicate that interventions must address positive attitudes about getting treatment and counter negative perceptions based on previous treatment protocols to move HCV+ MMT clients towards initiating care.

Disclosure of Interest: A. Jessop: Grant: Conflict with: Gilead Sciences, S. Bass: Grant: Conflict with: Gilead Sciences, M. Gutierrez: Grant: Conflict with: Gilead Sciences, M. Gashat: Grant: Conflict with: Gilead Sciences.

A program of testing and treat intended to eliminate hepatitis C in a prison: the JAILFREE-C study

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Introduction: National Strategy Plan for tackle Hepatitis C in Spain considers as a priority the infected patients in prisons. Accordingly we planned a project in a Northern region of Spain (Cantabria) with 600k inhabitants and focused to the regional long-stay prison of El Dueso

Aims: 1) Perform a systematic screening of infections related to blood-borne viruses 2) Evaluate the efficacy and safety of an IFN-free antiviral regimen, including the impact on the rates of reinfections at short/long term

Material and Methods: The project was planned to start in 1Q 2016 following 3 consecutive phases: 1) viral testing and characterization, 2) treatment of HCV infected inmates, 3) follow-up of patients for 30 months. All new entries in the prison are to be tested immediately and treatment initiated in the first week if HCV-positive. The list of variables to be analyzed include: 1) Demographics, clinical, and virological variables, including NS5a baseline resistance and deep analysis of nucleotide sequence quasispecies complexity of HVR1 region, 2) Endothelial dysfunction and neurocognitive function tests before treatment and 6 months after, 3) Efficacy, safety and QoL throughout the study, and 4) Rates of persistent HCV infection, reinfection and super-infection.

Results: Up to now 436 inmates have been included being full tested for blood-borne viruses. The majority of inmates were male (98%) with a median age of 59 yrs. Seventy patients were anti-HCV positive (16%), of these 52 (74%) were HCV RNA positive. HCV genotypes were GT3 (56%), GT1 (36%), and GT4 (8%). Seven patients were HIV-coinfected (13%), and none HBV-coinfected. Fibrosis distribution was: F0-1 51.9%; F2 11.5%; F3 13.4% and F4 23%. The mean MELD score was 8. All viremic patients have been treated with LDV/SOF+/-RBV 12 wks (49 patients) or 8 wks (3 patients). All patients achieved EOT response. No serious AEs were reported and no patients discontinued due to AEs. Baseline NS5A RAS were found in 19% of the patients and were more frequent in HCV GT3 (36%). Viral diversity of the HVR1 region was high, irrespective of the HCV genotype. In 4Q 2016 SVR12 will be available for all treated inmates, including the remaining variables of this long-term study.

Conclusions: In this Spanish prison the HCV prevalence is x15 times the described in the general population, showing a different profile of HCV genotypes and a high viral diversity in HVR1. An elimination program of this nature is intended as a pilot experience that could be extended to other prisons.

Disclosure of Interest: None Declared

Methadone treatment and doses in patients with HCV infection and HCV/HIV coinfection: a reanalyse of proteus study

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Introduction: Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are prevalent infections in opiate-dependent patients (ODP). Opiate replacement treatment (ORT) with methadone or buprenorphine are the most common treatments in ODP. However, little is known about outcomes in OPD with HCV infection and HCV/HIV coinfection who are in ORT. Also, it is not well established whether methadone doses could be higher in ODP with these infections.

Aims: Reanalyse the database of PROTEUS study, using 2 principal variables: methadone dose and presence of HCV infection or HCV/HIV coinfection.

Material and Methods: The PROTEUS study was a descriptive, observational, cross-sectional study, conducted in 74 treatment centres for ODP in Spain (recruitment period was September 2008 - March 2009); it was approved by The Clinical Research Ethics Committee of Vall d'Hebron Hospital (Barcelona, Spain), in line to the Declaration of Helsinki. Patients were over 18 years old, had a diagnosis of Opiate Dependence (DSM-IV-TR criteria), were included in an ORT and signed a written informed consent. The database was reanalysed, main independent variables were the presence of HCV or HCV/HIV infections. Methadone dose was the main dependent variable, and the doses were stratified. Other variables recorded included were age, gender and psychiatric comorbidities. Differences among groups were analysed.

Results: 621 ODP were recruited (84.1% male, mean age: 38.9years, SD: 7.9), information about HCV status was available in 378 cases and for HVC/HIV coinfection was available in 580 patients. 297 were infected by HCV whilst 109 patients were coinfected.

HIV/HCV-coinfected patients received higher methadone doses with statistical significance when compared with patients without infections. No differences in methadone doses were found in HCV-infected.

Conclusions: Findings suggest that methadone doses is higher in patients with HCV/HIV coinfection compared with patients with no infection, whilst there are no differences in methadone doses in HCV-infected patients in contrast with non-infected patients. Also, HCV infection generates no difference in the permanence in an ORT.

Figure:

Table 1

Methadone treatment characteristics by HCV

Variable		Total	HCV +	HCV -	p
Patients		378 (61.9%)	297	81	
Methadone dose	Total	376	295	81	0.6924
	<40	130 (34.6%)	104 (35.3%)	26 (32.1%)	
	40-80	147 (39.1%)	112 (38.0%)	35 (43.2%)	
	>80	99 (26.3%)	79 (26.8%)	20 (24.7%)	
	N missing	2	2	0	
mg/day	Mean±SD	62.85±53.27	64.24±56.52	57.77±39.13	0.8687
MMP stay	Yes	321 (84.9%)	249 (83.8%)	72 (88.9%)	0.2602

Methadone treatment characteristics by HCV/HIV

Variable		Total	HIV/AIDS+ and HCV+	Other patients	p
Patients		580 (93.4%)	109	471	
Methadone dose	Total	576	109	467	<0.0001*
	<40	220 (38.2%)	24 (22.0%)	196 (42.0%)	
	40-80	232 (40.3%)	42 (38.5%)	190 (40.7%)	
	>80	124 (21.5%)	43 (39.4%)	81 (17.3%)	
	N missing	4	0	4	
mg/day	Mean (SD)	56.78 (47.44)	86.39 (75.80)	49.87 (34.53)	<0.0001*
MMP stay	Yes	480 (82.8%)	98 (89.9%)	382 (81.1%)	0.0283*

(MMP stay: Methadone maintenance programme stay

Disclosure of Interest: C. Roncero: Grant: Conflict with: PROTEUS project was supported by a Reckitt-Benckiser/Indivior grant. Reckitt-Benckiser had no role in the study design, data compilation, analysis or interpretation of the information, writing the manuscript, or the decision to submit the paper for publication., R. Palma-Alvarez: None Declared, D. Fuster: None Declared, A. Esojo: None Declared, M. Perea: None Declared, L. Rodriguez-Cintas: None Declared, N. Martinez-Luna: None Declared, J. Alvarez: None Declared

Clinical characterization and economic impact evaluation of anti- HCV daa treatment failure: real life data from the italian platform for the study of viral hepatitis therapies (PITER)

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Aims: Clinical, virological and therapy data of patients who failed to eradicate HCV infection following an IFN free DAA regimen, from 22 clinical centers that actively take part in the PITER platform, were analyzed.

Results: Of 4029 patients who had undergone a DAA IFN free treatment during 2015/2016 and reached the 12 weeks post treatment evaluation, 130 (3,2%) failed to

achieve a sustained virological response (SVR12): mean age was 57 years (range 34-77 years); 70% were male; 60% were IFN treatment experienced. Of these 130 patients,5 were treated for Mixed Crioglobulinemia Syndrome in F2 fibrosis stage, the remaining were on the cirrhosis stage of liver disease (69%, 27% and 4% Child-Pugh Class A,B and C respectively); 3% had HCV recurrence post liver transplantation(LT). The following DAA regimens were used: Sofosbuvir+Ribavirin in 53%(Genotype (Gt)1: 40%;Gt3: 47%;Gt4: 3%); Sofosbuvir+Simeprevir in 25% /+ Ribavirin in 63%:(Gt1a: 18%; Gt 1b:70%;Gt 3/Gt4/Gt5 in 4% respectively); Sofosbuvir+Ledipasvir in 9% /+Ribavirin in17% (Gt1:92% and Gt4:8%); Ombitasvir/Paritaprevir/r+Dasabuvir (3D) in 8%/+ Ribavirin in 80%(Gt1:80%;Gt2:20%); Sofosbuvir+Daclatasvir in 5%/+ Ribavirin in 50% (Gt3:100%). Of 130 patients, 44(34%) are on a second DAA regimen (+-Ribavirin) based on Sofosbuvir+Daclatasvir in 55%; Sofosbuvir and Ledipasvir in 41% and 3D regimen in 4% of patients. Following the first DAA treatment failure. preliminary results have shown:HCC occurrence in 15 (11.5%) patients (in 67% firstly diagnosed during/post treatment in 33% HCC recurrence); LT in 1 patient; hospitalizations in 17% of patients (1-4 hospitalisations from 1-20 days).The number of outpatients' visits was 740 (1- 23 visits/patient); the number of diagnostic/therapeutic procedures: 320 (1 - 20/ patient). A validated probabilistic economic model that includes all cost's drivers for patients who failed to eradicate HCV infection following a first DDA regimen has been constructed. Further results of short time clinical events following treatment failure, SVR12 rates of the second DAA regimens used (still ongoing) and the overall economic burden of treatment failure will be available in due course.

Conclusions: Real life data, based on the PITER platform, indicate that about 3% of patients failed to achieve HCV viral eradication after first line interferon free DAA regimens, part of them considered as suboptimal to date. Clinical and economic burden of this unfavorable event is significant and need to be better addressed.

Disclosure of Interest: None Declared

Early allograft dysfunction in hepatitis C recipients is reduced by pre or peri liver transplant viral eradication

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Introduction: Early allograft dysfunction (EAD) after liver transplantation (LT) was defined as the presence of at least 1 among: bilirubin ≥10 mg/dL or INR ≥1.6 on day 7 and AST/ALT >2000 IU/L within the first 7 days after LT (Olthoff KM et al. Liver Transpl 2010; 16: 943-949). EAD was associated with graft and patient survival at 6 months, donor age >45 years and MELD being significant EAD risk factors. While donor age is rising to meet the organ shortage, direct-acting antiviral agents (DAAs) are revolutionizing the outcomes of HCV-positive patients.

Aims: In this study we evaluated EAD incidence and risk factors in HCV-positive recipients.

Material and Methods: From November 2002 to April 2016, 592 HCV-positive patients underwent a first LT in our Center with grafts from brain dead HCV-negative donors. Median recipient age was 56 years, males 80.6%, median body mass index 25 kg/m^2, median MELD score at LT 15, 53.0% of the patients were affected by hepatocellular carcinoma; median donor age 63 years. At LT, 523 patients (88.3%) were HCV RNA positive and 69 (11.7%) negative. HCV RNA negativization was achieved and maintained with pre-LT antiviral therapy (53 patients) or pre-LT + preemptive post-LT course (16 patients); 52 patients (75.4%) received DAAs plus ribavirin and 17 (24.6%) peginterferon plus ribavirin.

Results: Overall EAD incidence was 53.2%; 6-month graft and patient survival rates were 86.9% and 91.0%, respectively, in EAD recipients vs. 97.4% and 97.8% in those without EAD ($p<0.001$ for both). Figure 1 shows the differences between EAD and non-EAD patients at univariate analysis. At multivariable logistic regression, graft macrovesicular

steatosis ≥30% (odds ratio, OR 7.60, p=0.013), cold ischemia time ≥8 hours (OR 2.22, p<0.0001), HCV RNA positivity at LT (OR 1.82, p=0.043), MELD score at LT <15 (OR 0.61, p=0.018) were significant predictors of EAD.

Conclusions: In our HCV-positive patients, we found a negative impact of EAD on 6-month graft and patient survival, while pre-LT or peri-LT HCV RNA negativization reduced EAD incidence. Preventing graft HCV infection at reperfusion by HCV therapy and minimizing cold ischemia time could improve LT outcomes, especially in countries mostly relying on elderly donors.

Figure:

	Early allograft dysfunction (n=315)	No Early allograft dysfunction (n=277)	p-value
Recipient features			
Age (years)	55.3 [49.6-61.2]	55.9 [50.9-61.1]	0.2010
Male gender	262 (83.2%)	215 (77.6%)	0.0881
Hepatocellular carcinoma	155 (49.2%)	159 (57.4%)	**0.0462**
MELD at LT	16 [12-21]	14 [10-18]	**<0.0001**
HCV RNA negativity al LT	26 (8.3%)	43 (15.5%)	**0.0060**
Donor features			
Age (years)	62.9 [50.1-71.8]	63.0 [51.9-73.0]	0.5956
Male gender	188 (59.7%)	144 (52.0%)	0.0597
Cause of brain death			
Cerebrovascular	241 (76.5%)	187 (67.5%)	**0.0243**
Trauma	53 (16.8%)	52 (18.8%)	
Anoxia	17 (5.4%)	32 (11.5%)	
Other	4 (1.3%)	6 (2.2%)	
Body Mass Index (Kg/m^2)	25 [23-28]	25 [23-27]	0.0733
Body Mass Index ≥30 Kg/m^2	42 (13.3%)	24 (8.7%)	0.0717
HBcAb positivity	45 (14.3%)	23 (8.3%)	**0.0227**
Macrovesicular steatosis ≥30%	10 (3.2%)	2 (0.7%)	**0.0359**
Transplant procedure			
Cold Ischemia Time (min)	493 [430-562]	439 [365-515]	**<0.0001**
Cold Ischemia Time ≥8 hours	178 (56.5%)	81 (35.4%)	**<0.0001**
Warm ischemia time (min)	23 [20-28]	23 [20-27]	0.7154
Donor-Recipient match			
Donor age x Recipient MELD	960 [664-1340]	823 [555-1094]	**<0.0001**

Numerical variables are expressed as median [Q1-Q3].

Categorical variables are expressed as numbers (prevalence, %).

Disclosure of Interest: S. Martini: Other: Conflict with: Regional Advisory Board Gilead, F. Tandoi: None Declared, B. Lavezzo: None Declared, S. Strona: None Declared, M. Sacco: None Declared, F. Maione: None Declared, D. Arese: None Declared, G. Rizza: None Declared, F. Lupo: None Declared, G. Saracco: Other: Conflict with: Advisory board AbbVie, Gilead, MSD, M. Salizzoni: None Declared, R. Romagnoli: None Declared

Saturday 24 September 2016
ePoster Session 2: 12:40 – 13:00

Screen I: ABSTRACT-202

Patients with HCV GT 1/4 infection and compensated cirrhosis, without baseline NS5A RASs, could be treated with SOF + NS5A inhibitor for 12 weeks without RBV

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Introduction: Current guidelines recommend that the combination of sofosbuvir (SOF) + an NS5A inhibitor should be given for 12 weeks with RBV or extended to 24 weeks without RBV in patients with GT1/4 infection and compensated cirrhosis. However, high SVR rates were reported in these patients when treated for 12 weeks without RBV, suggesting that this regimen is optimal in some patients.

Aims: The objective of the study was to evaluate the effect of the presence of detectable NS5A RAS at baseline on SVR in patients infected with GT1/4 treated with SOF + NS5A inhibitor for 12 weeks without ribavirin.

Material and Methods: A cohort of 181 consecutive patients from a single center infected with GT1 (1a: n=58; 1b: n=77; 1d: n=1) and 4 (n=45) were treated with SOF + DCV (n=140) or SOF + LDV (n=41) for 12 weeks without RBV. Patients had a mean age of 60 years and 57.8% were treatment-experienced. Compensated cirrhosis (defined as FibroScan>12.5 kPa) was present in 49.7% (n=90) of patients. NS5A resistance associated substitutions (RASs) were assessed at baseline and at treatment failure by means of population sequencing. Antiviral efficacy was assessed monthly during treatment and at post-treatment weeks 4 and 12.

Results: At baseline, NS5A RASs were detected in 10.3% of GT1a-, 33.8% of GT1b-, and 20.0% of GT4 patients. No difference was observed between cirrhotics and non-

cirrhotics. The most frequent RASs were M28V/T in GT1a, L28M, R30Q and Y93H in GT1b and L28M/V in GT4. Overall, SVR12 was achieved in 97% (175/181) and was more frequent in non-cirrhotics (100%; 91/91) than in cirrhotics (93.3%; 84/90), p<0.001. The effect of baseline NS5A RASs on SVR according to cirrhosis is shown in the table:

	Presence of NS5A RASs SVR12, N (%)	Absence of NS5A RASs SVR12, N (%)
No cirrhosis	(23/23) 100%	(68/68) 100%
Cirrhosis	(13/19) 68.4%	(73/73) 100%

Gender, age, previous treatment history, baseline HCV-RNA levels, and current treatment regimen did not affect the rates of SVR12.

Conclusions: Patients infected with GT1/4 with compensated cirrhosis and without baseline NS5A RAS can be treated with SOF + an NS5A inhibitor without RBV for 12 weeks, like non-cirrhotics with or without baseline NS5A RASs. By contrast, 12 weeks without RBV is not appropriate in patients with compensated cirrhosis and baseline NS5A RAS, who were shown to benefit from ribavirin add-on. Thus, if available and reliable, baseline resistance testing can be used to inform treatment decisions in patients with compensated cirrhosis receiving SOF + an NS5A inhibitors.

Disclosure of Interest: S. Fourati: Grant: Conflict with: Gilead, Sponsored lectures (National or International): Conflict with: Gilead, Abbvie, F. Roudot-Thoraval: None Declared, S. Chevaliez: None Declared, G. Scoazec: None Declared, A. Soulier: None Declared, A. Varaut: None Declared, M. Francois: None Declared, L. Poiteau: None Declared, A. Mallat: None Declared, J.-M. Pawlotsky: None Declared, C. Hézode: None Declared

Screen 2: ABSTRACT-215

Comprehensive community-based HCV screening of HIV/HCV co-infected and HCV mono-infected patients in Nepal: a model for resource-limited settings

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Introduction: With direct acting antiviral (DAA) therapy for hepatitis C (HCV) treatment optimal screening models are needed. We implemented community-based screening of mono- and HIV co-infected persons in Nepal where >150,000 individuals are living with HCV genotype 3 (GT3: 60%) and GT1: 40% (Kinkel, H). To date, viral assays for HCV diagnosis have been lacking.

Aims: Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH (German Development Cooperation), with the Global Fund, implemented comprehensive HCV screening at 3 opioid substitution treatment (OST) sites in Nepal. We applied findings to design a simple screening model for rapid expansion of DAA therapy.

Material and Methods: We introduced quantitative HCV RNA and genotype (GT) testing (Sacace, Italy) at OST sites with Hepatitis B Virus (HBV), Human Immunodeficiency Virus (HIV) RNA (Sacace), CD4+ T cell count, complete blood cell count, platelets (Plt) and liver transaminases (AST). We calculated AST/Plt Ratio Index (APRI) and tested a subset by fibroscan. We screened for depression (PHQ-9), substance use (ASSIST-WHO), and tuberculosis.

Results: Among 617 active or prior IDUs self-reporting HCV, 593 (96%) were antiHCV Ab+; 81% had detectable HCV RNA (44% GT1a, 56% GT3a). HIV RNA was detectable among 18% of 283 HIV+ patients despite CD4>200 and antiretroviral therapy (ARV)

necessitating ARV modification. Fourteen patients (2.2%) were diagnosed with active HBV including 9 HIV+; 7 cleared HCV. The majority of 25 antiHCV Ab- patients were HIV+ (52%) or HBSAg+ (16%). An APRI cut-off of 2 (compared to fibroscan >9.5) had 51% sensitivity, 95% specificity (89% negative predictive value) for advanced fibrosis.

Conclusions: This first OST-site based HCV screening in Nepal has lessons for expanding access to treatment. Despite self-reported HCV infection, many patients had cleared the virus while HIV suppression was suboptimal demonstrating the need for viral assays. Characterizaion of co-infections and co-morbidities was work intensive but essential for optimal HIV and HBV suppression and substance management prior to therapy. APRI was less reliable for predicting fibrosis among HIV+. Results of this model support a "way forward" with site- and comorbidity-specific APRI cut-offs, qualitative HCV testing and GT-nonspecific DAA regimens. To extend HCV therapy to resource-limited settings our OST-based comprehensive HCV screening model identified "essential" activities for treatment success.

Disclosure of Interest: None Declared

Screen 3: ABSTRACT-224

Effectiveness and Safety of new DAAs for Chronic HCV infection in a real life experience of Italian association of hospital hepatologist (CLEO)

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Introduction: Direct Antiviral Agents (DAAs) for HCV therapy represents a step ahead in the cure of chronic hepatitis C. Despite the reported safety of such drugs in several clinical trials, few data are available on adverse effects in real life settings.

Aims: We aimed to verify effectiveness and safety of new antivirals in persistent HCV infection.

Material and Methods: We evaluated 470 patients with severe chronic HCV hepatitis eligible to treatment according to Italian recommendations. Patients underwent the following regimens: Sofosbuvir + Ribavirin, Sofosbuvir + Simeprevir +/- Ribavirin, Sofosbuvir + Daclatasvir +/- Ribavirin, Ledipasvir+Sofosbuvir +/- Ribavirin and Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir plus ribavirin.

Results: 40% out 470 patients were female (mean age 64) while 60% were male (mean age 66). According with Italian epidemiology, genotype 1 was harboured from 65% of all treated patients, Genotype 2 from 19%, genotype 3 from 7% and Genoype 4 from 4%. About 70% of all treated patients were classified as F4 upon Metavir score while F3 patients where 29%. 17% were on Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir (12 or 24 weeks +/- Ribavirin) 22% were on Sofosbuvir/Ledipasvir schedule (12 or 24 weeks +/- Ribavirin) 19% were on Daclatasvir plus Sofosbuvir, while patients undergoing Simprevir plus Sofosbuvir (+/- Ribavirin) were 23% and Sofosbuvir plus Ribavirin were 19%, respectively.

We found an overall SVR rate of 96%. Non responder patients were 60% on Simeprevir plus Sofosbuvir, 20% on Sofosbuvir plus Ribavirin and 10% on Sofosbuvir plus Daclatasvir. More frequent side effects were asthenia and anemia in about 20% and 10% of the patients, respectively. We believe relevant to report that 3% of treatment discontinuation, in our case series, was due to major, potentially life-threatening, adverse events.

Conclusions: Second wave HCV DAAs fully confirmed the great effectiveness in our real world experience, according to the previously found SVR rates; however their clinical use requires careful management of patients by expert clinicians to avoid unrecognized potentially life-threatening AEs which may affect adherence of patients and effectiveness of therapy in clinical practice.

Disclosure of Interest: None Declared

Screen 4: ABSTRACT-227

The association of polymorphisms in MDA5 and IFNL4 genes with spontaneous and treatment-induced HCV clearance in Thai populations

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Introduction: Recent studies have shown an association of single nucleotide polymorphisms (SNPs) in the melanoma differentiation-associated gene 5 (MDA5) and interferon lambda-4 (IFNL4) genes with spontaneous recovery from hepatitis C virus (HCV) infection. However, the importance of these SNPs in Thai individuals remains to be elucidated.

Aims: The aim of this study was to determine the association of SNPs MDA5 (rs3747517) and IFNL4 (ss469415590) with HCV clearance in Thai populations.

Material and Methods: A total of 201 patients with chronic HCV infection and 107 individuals with HCV spontaneous clearance (with matched age and gender) were enrolled. Additional 103 healthy controls were also recruited. DNA extracted from blood samples was analyzed for SNPs rs3747517 and ss469415590.

Results: Among patients with chronic HCV infection, the distribution of HCV genotype 1, 3 and 6 was 30.3%, 47.8% and 21.9%, respectively. Patients with chronic HCV infection had similar mean age compared to those with HCV clearance (48.9 ± 11.2 vs. 47.4 ± 10.8 years, P=0.236) but were older than healthy controls (46.1 ± 5.3 years, P=0.016). There was no difference between each group with respect to gender distribution. The frequency of CC, CT and TT genotypes of rs3747517 in the HCV group was 9.4%, 44.3% and 46.3%, respectively, which was not significantly different to that of the HCV clearance group (8.4%, 41.1% and 50.5%, respectively) and healthy controls (10.7%, 35.9% and 53.4%, respectively). The distribution of TT/TT, DG/TT, and DG/DG genotypes of ss469415590 in the HCV group was 85.6%, 12.4% and 2.0%, respectively, which was significantly different to that of the HCV clearance group (95.3%, 3.7% and 1.0%,

respectively) and healthy controls (94.2%, 5.8% and 0%, respectively) (P=0.031). Among patients with chronic HCV infection receiving pegylated interferon and ribavirin therapy, those with TT/TT genotype had significantly higher sustained virological response (SVR) rates in comparison to those with non-TT/TT genotype (82.6% vs. 55.2%, P=0.002). However, there was no such association between rs3747517 genotypes and SVR.

Conclusions: These data demonstrated that IFNL4 polymorphism was significantly associated with HCV spontaneous clearance and treatment response in Thai population. In contrast, there was no association of MDA5 polymorphism with spontaneous and treatment-induced HCV clearance.

Disclosure of Interest: None Declared

Screen 5: ABSTRACT-240

Development of an in-house multiplex RT-PCR method for the hepatitis C virus genotype Ib associated with reduced response to combination treatment regimens containing simeprevir, daclatasvir or asunaprevir

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Introduction: Resistance-associated variants (RAV) of hepatitis C virus (HCV) occurs by chance or, more frequently, use of antiviral drugs. Resistance mutation for protease inhibitor (PI) occupies 9-48% of people who carry HCV genotype 1a (GT1a) but only 0.5-4.9% carriers with HCV GT1b.

Aims: We aimed to develop a multiplex PCR assay for HCV GT1b to detect the NS3 Q80K and NS5A L31I or Y93H mutations and other polymorphisms possibly related to drug resistance.

Material and Methods: Sixty cDNA from HCV carriers with already known HCV genotypes. A primer set is designed to select HCV GT1b fist. Then four primer pairs were designed and evaluated for the detection of Q80K at NS3 or L31I/Y93H at NS5A. PCR was performed. The sensitivity, specialty among HCV genotypes were evaluated simultaneously. The presence of mutations or SNP's is confirmed by sanger sequencing methods.

Results: HCV GT1b is discriminate well by first PCR reaction. The multiplex RT-PCR was successfully applied for the detection of Q80K at NS3 or L31I/Y93H at NS5A. The sensitivity was 40 copies/ml and the specificity was 100%.

Conclusions: This multiplex RT-PCR provides a useful tool to screen for the NS3 Q80K, NS5A L31I or Y93H and other HCV protease inhibitor drug resistance mutations.

Disclosure of Interest: None Declared

It is necessary to discontinue the treatment in patients with liver cirrhosis and variceal bleeding during treatment with ombitasvir/paritaprevir/ritonavir, dasabuvir and ribavirin?

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Introduction: Patients with compensated cirrhosis are at high risk of progression to decompensated liver disease. Successful antiviral treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin (3D +/- R) leading to a sustained virological response (SVR) may decrease the progression of fibrosis, improving life expectancy for these patients. There is limited real-world data on the safety profile of 3D +/- R regimens and FDA is warning that treatment can cause hepatic decompensation, hepatic failure, including death.

Aims: to evaluate incidence of variceal bleeding in patients with HCV (chronic hepatitis virus C infection) liver cirrhosis treated with 3D +/- R regimen.

Material and Methods: Data on demographics, clinical features, adverse events, virological response were collected in a prospective study conducted in 7 centers in Romania.

Results: 507 patients with compensated liver cirrhosis (HCV genotype 1b infection) were included. Esophageal varices were documented in 28.5% of patients (27.4% grade I, 49.5% grade II, 23.1% grade III); all patients with risk for variceal bleeding (grade II/III esophageal varices) were treated with beta blockers agents for prevention of variceal hemorrhage. Two cases of variceal bleeding occurred in our patients: both patient were male, 48 years old, with Child A 5 cirrhosis and grade III esophageal varices (treated with propranolol for prevention of variceal hemorrhage), naives to antiviral treatment, and with no history of decompensation.

The standard therapy of esophageal bleeding has controlled the acute bleeding and the prophylaxis of possible complication precipitated by bleeding was made. All the drugs used were checked for medication interactions before administration. The bleeding appeared in six week of antiviral treatment in both cases, and after disscution with patients and reconsent the treatment was not discontinued. During hospitalization and up to end of treatment no change in Child stage was recorded. Sustained viral response was achieved by both patients.

Conclusions: Although 28.5% of patients had esophageal varices, variceal bleeding is a rare adverse event during 3D+R treatment. Considering that the bleeding means decompensation of cirrhosis should we discontinue the treatment? The evolution of our cases suggests that the treatment can be continued in safety and probably, the best attitude is to eradicate the esophageal varices before the initiation of antiviral treatment.

Disclosure of Interest: None Declared

Screen 7: ABSTRACT-246

Metabolic changes in the early post-liver transplant setting: Is there a difference in insulin resistance, adiponectin and leptin levels between cirrhotic patients transplanted for viral hepatitis C compared to other etiologies?

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Introduction: Both liver cirrhosis and chronic hepatitis C virus (HCV) infection are considered to cause metabolic disarrangements resulting in increased insulin resistance, possibly by means of disturbance of adipocytokine levels. Improvements of metabolic status following liver transplantation (LT) have been reported by various authors. However, long-term outcomes of transplanted patients are worsened by the occurrence of metabolic syndrome or its components, leading to an increased cardiovascular morbidity and mortality. It is reasonable to postulate that different metabolic changes occur at different time-points following LT.

Aims: The aim of this study was to evaluate metabolic markers such as insulin resistance (IR), and adipocytokines adiponectin (AND) and leptin (LPN) early post-LT, and to investigate their patterns in HCV+ patients vs. other etiologies.

Material and Methods: Serum samples were obtained from sixty-four patients (43 male) pre- and 3 months post LT. The predominant etiology included alcoholic cirrhosis (61%), followed by HCVG1+ cirrhosis (23.4%). No patients with non-alcoholic steatohepatitis were included. IR was assessed by the Homeostasis Model Assessment 2 (HOMA-2) model and ADN and LPN concentrations were determined by validated enzyme-immunoassay methods. Statistical analysis was conducted by IBM SPSS Statistics 23 software.

Results: A significant decrease of early post-LT IR was noted, with pre-transplant values of 3.83; CI 2.86-4.79, dropping to 1.92; CI 1.51-2.24 following LT (p=0.00). The mean baseline ADN levels (20.53 mg/L; CI 17.94-23.12) and LPN levels (14.25 ug/L; CI

11.05-17.46) decreased significantly following LT (p=0.00; p=0.012) in the whole cohort. Subanalysis of the HCV+ group revealed only a significant ADN level decrease with a preoperative mean of 22,76 mg/L dropping to 14.49 mg/L postoperatively (p=0.003) while IR and LPN levels decreased but without reaching statistical significance. No differences were noted in AND/LPN between HCV+ and HCV- patients both pre- and post-operatively.

Conclusions: Our results show a paradoxical decrease in insulin-sensitising adipocytokines ADN and LPN in the context of IR amelioration. This effect could possibly be explained by external factors such as steroid use in the first weeks following LT. Further on, a less favourable metabolic pattern for HCV+ patients was observed with persisting levels of IR post-LT.

Disclosure of Interest: None Declared

Screen 8: YI-ABSTRACT-248

Update in relationship between CAI9.9 and fibrosis in a cohort of patients with viral hepatitis and without malignancies. CaI9.9 levels reflect the progression of fibrosis and is related with HCV infection

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Introduction: Several previous studies have shown that CA19-9 serum level can increase in patients affected by non-malignant diseases. In particular, in patients with idiopathic interstitial pneumonia, idiopathic pulmonary fibrosis and collagen-associated diseases, but also in liver diseases as for example fibrosis and cirrhosis.

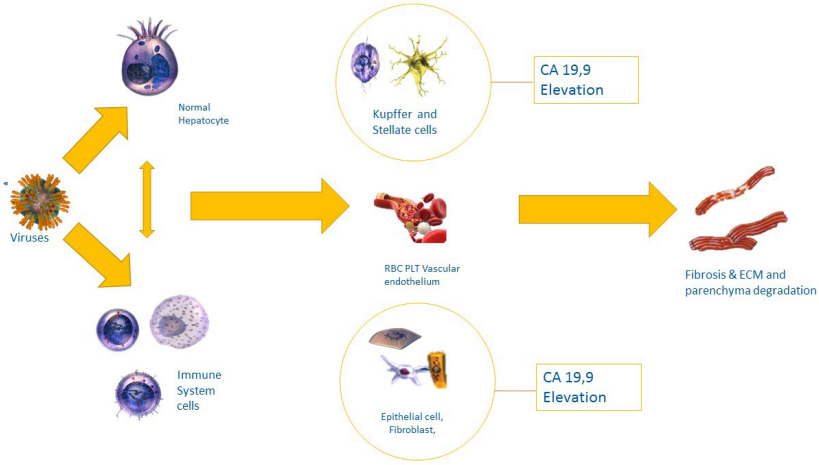
Aims: We want report our experience in patients with chronic viral hepatitis but without malignant disease, cholestasis or other chronic diseases that may explain the increase in CA19-9 serum. This could be a good chance to measure fibrosis in addiction other methods and moreover to highlight new pathways involved in fibrogenesis and is involved to role of HCV.

Material and Methods: 215 Caucasian patients with viral hepatitis were enrolled (118 males, 97 females) excluding patients with cancer, severe jaundice, chronic airways and kidney diseases, prostatic diseases, autoimmune diseases, and diabetes mellitus. None of the patients consumed alcohol or were taking hepatotoxic drugs. Clinical, hematochemical, virological, diagnostic imaging and histological analysis were performed. Selected patients were randomized into two groups based upon viral etiology. Further CA19-9 valuations were performed each 6 months for three consecutive years, repeating diagnostic for malignancies.

Results: The increase of CA19.9 serum levels is frequent in chronic viral hepatitis. In our population CA19.9 correlates significantly (∘∘ < 0.05) with the grade of liver fibrosis. Our data show a correlation between elevation of CA19.9 serum levels and viral etiology, showing a high statistical significance when HCV-infected are compared to the HBV-infected patients(∘∘ < 0.001).

Conclusions: Augmented CA19-9 serum blood levels are frequent in chronic viral hepatitis. This does not necessarily indicate concurrent cancer, but seems to correlate with the grade of liver fibrosis. In our data CA19-9 is higher in HCV-infected patients (Group 1) compared with HBV (Group2). This could be related to fibrogenic HCV properties (i.e. NSPs). Further investigations could clarify the role of CA19-9 as an indirect marker of fibrosis. We propose that CA19-9 may be used in combination with the other markers already in use, in order to increase our diagnostic accuracy and therapeutic possibilities.

Figure:



Disclosure of Interest: None Declared

Real life experience with DAAs in resource limited settings

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Introduction: In era of direct-acting antiviral (DAA) for chronic hepatitis C, the Romanian National Health System is struggling to combine a safe, but cost-effective regimen to obtain sustained virologic response (SVR) for patients with compensated advanced liver disease (cALD). Currently, the only DAA regimen available in our country is Viekiera-pak for 12 or 24 weeks.

Aims: In the light of the new Viekiera-pak's "black box" warning for acute on chronic hepatic failure (ACLF) is essential to identify patients with high risk of ACLF.

Material and Methods: We analyzed all patients with cALD approved for treatment in our center, with a focus on causes of decompensation or treatment interruption due to adverse eve.

Results: One hundred and eighty four patients were included [59(38-84) years, 49.5% males] since December 2015. At baseline, all patients were compensated ChildA cALD patients, with no previous decompensation. By June 2016, 98 (53%) already finished therapy, and 12 of 12 (100 %) achieving SVR12. 7 patients (3.8%) interrupted therapy, 5 (2.7%) with decompensation. The causes for treatment withdraw were: ACLF (3 patients, 1.6%), variceal bleeding (2 patients), stroke (1 patient) and severe rash (1 patient). Two patients (1.08%) died, one with ACLF and the other with variceal bleeding.

Decompensated patients had at baseline significantly lower platelets count (p=0.006) and Albumin (p=0.024), higher ALT(p=0.022), GGT(p=0.016), INR(p=0.007) and liver stiffness (p=0.05). Also, all patients with decompensation had PLT<150.000 (p=0.027),

LS>20kPa (p=0.018). Combination of low PLT and increased LS had the strongest association with decompensation (p=0.004). However, in multivariate analysis none of the above variables was independently associated with decompensation.

Conclusions: The real life experience in a tertiary Romanian center with ritonavir/paritaprevir/ombitasvir and dasabuvir regimen with RBV shows excellent virologic response, but also significant (3.8%) adverse events and not negligible (1%) mortality. Although none of variables was independently predicted decompensation, low platelets and increased liver stiffness seem to be indicators of bad outcome.

Disclosure of Interest: None Declared

The safety, tolerability and efficacy of paritaprevir/ritonavir/ombitasvir and dasabuvir with ribavirin in a large real life multi-center cohort of genotype Ib HCV infected patients with liver cirrhosis at the edge of decompensation

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Introduction: The paritaprevir/ritonavir/ombitasvir and dasabuvir + ribavirin (3D + R) regimen is the only antiviral treatment approved for reimbursement in Romania for patients with HCV genotype 1b compensated cirrhosis. The registration studies enrolled a limited number of patients with advanced liver disease and a postmarketing warning signal appeared on the risk of decompensation during treatment.

Aims: The aim of this study was to evaluate the safety, tolerability and efficacy of 3D+R in patients with Child score A6 and/or Baveno 2, considered at the edge of decompensation.

Material and Methods: Data on demographics, clinical features, safety and virological response were collected in a prospective study conducted in 7 academic centers from Romania. All patients fulfilled the mandatory conditions imposed by National Insurance Company: compensated cirrhotics with or without previous decompensation, with no evidence of hepatocellular carcinoma, with no age limit. We analyzed patients with Child score A6 and/or Baveno 2. The patients were monitored at 2,4,8 and 12 weeks of treatment and as needed by symptoms, signs of decompensation, liver function tests, hemogram.

Results: Out of 319 genotype 1b HCV liver cirrhosis patients who completed the therapy so far, 93 (29.1%), mean age 59.2 (range 48-74) yrs, 56% women were at the edge of decompensation, defined as Child-Pugh class A score 6 and/or Baveno stage 2. Adverse events (AEs) were frequent (the most common: anemia-43%, pruritus-27%, insomnia-25%), none leading to treatment discontinuation. Severe AEs occurred in 3 patients (3.22%): two cases of variceal bleeding, they both continued treatment after re-signing a new informed consent, and one case of severe depression leading to treatment discontinuation. Both patients with bleeding were known with grade III oesophageal varices and were under beta-blockers primary prophylaxis. No deaths occurred. Per-protocol analysis at EOT showed 100% efficacy, while intention to treat efficacy at EOT was 99%. At date, SVR12 was evaluated in 11 patients and was 100%; the final results will be presented at the meeting.

Conclusions: Treatment with 3D+R in patients at the edge of decompensation is highly effective, safe and well tolerated.

Disclosure of Interest: None Declared

Screen I: YI-ABSTRACT-117

Scleroligation is a safe and effective new technique for eradication of gastroesophageal varices

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Introduction: Gastric varices occur in 5–33% of patients with portal hypertension. Concomitant gastro esophageal varices are the most common type. Both endoscopic sclerotherapy and band ligation are very effective in controlling acute esophageal varices bleeding and preventing rebleeding. Scleroligation has been found to be effective too, but as yet has not been evaluated in gastro esophageal varices.

Aims: Evaluation of a new scleroligation technique for management of bleeding gastro-esophageal varices regarding efficacy, complications, variceal recurrence, and survival.
Material and Methods: This study was conducted on 120 cirrhotic patients with bleeding gastro-esophageal varices, randomly divided into two groups:
Group I: 60 patients treated by endoscopic band ligation.
Group II: 60 patients treated by combined sclerotherapy and band ligation (scleroligation).
Results: The number of sessions was lower in the scleroligation group than in the band ligation group (p = 0.001). Cost and survival were comparable in the two groups.
The scleroligation group had less complications, recurrence rates were 20% in comparison to 26.7% in the band ligation group. Recurrence was significantly higher in patients with larger varices, ulceration, higher grades of PHG, GAVE, anemia, a higher portal vein diameter and more advanced liver disease.

Conclusions: Scleroligation appears to be faster, safer and more effective in eradication of gastroesophageal varices than band ligation alone. Studies on larger numbers of patients are needed to confirm these results.

Disclosure of Interest: None Declared

Use of perceptual mapping to understand barriers and facilitators to HCV treatment initiation in methadone users

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Introduction: MMT clients have a 67-96% HCV seropositivity rate and without treatment may develop liver cirrhosis or hepatocellular carcinoma. However, only about 11% initiate treatment. Despite increased access to new treatments, limited research has focused on the unique perceptions of treatment initiation in MMT clients.

Aims: Aims of this research include: 1. Understand how MMT clients perceive HCV treatment and perceived barriers to initiating treatment; 2. Describe the differences between perceptions of HCV+ and HCV- MMT clients using 3-dimensional models and vector modeling; 3. Develop strategies based on results for "best practice" to engage HCV+ MMT clients into treatment.

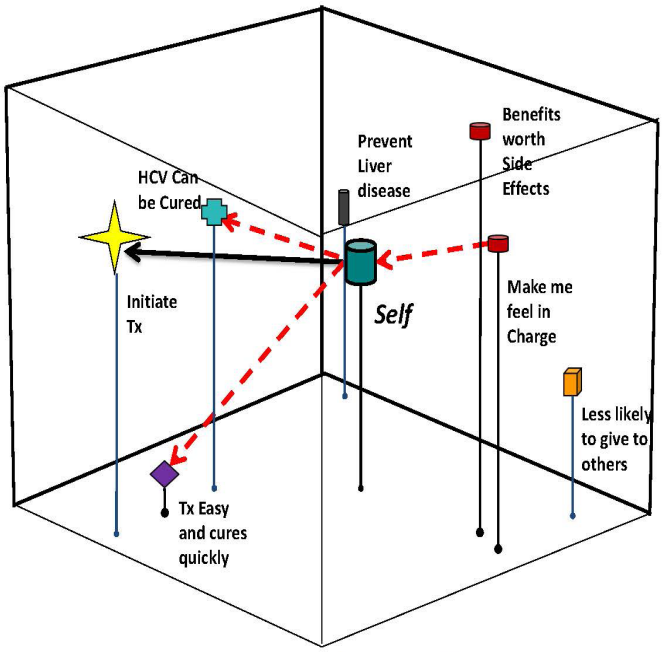
Material and Methods: 150 MMT clients who were both HCV+ and HCV- at four Philadelphia methadone centers were surveyed in person. Perceptual mapping (multidimensional scaling) and vector modeling methods were used to create 3-dimensional maps to show how barriers and facilitators to HCV treatment decision making are related, and how message/intervention strategies can be tailored for a specific audience. These commercial marketing techniques, used to influence consumers toward product purchasing, can be used to understand the unique perceptions of a decision to enhance informed medical decision making.

Results: Perceptual maps show clear conceptual differences about barriers and benefits, beliefs about healthcare, and overall knowledge of HCV. Those who were HCV+ believed that treatment was "worth it", but also were concerned about others believing they might have HIV and that not having symptoms was a reason for not being treated. Neither group saw significant benefits to treatments, although the concepts of being "cured" and

"being in charge" were closest to the group, indicating a significant message strategy for an intervention. No issues of trust in healthcare providers were observed.

Conclusions: These methods are useful in helping understand MMT clients' unique perceptions regarding HCV treatment. To increase informed decision making, interventions must include messages that address negative perceptions of treatment and promote their benefits, rather than focusing on mistrust of medical providers.

Figure:



Perceptual Map: Benefits
HCV Treatment Initiation, HCV+ MMT Clients – Question Block 1

Disclosure of Interest: S. Bass: None Declared, A. Jessop: Grant: Conflict with: Gilead Sciences, M. Gashat: Grant: Conflict with: Gilead Sciences, M. Gutierrez: Grant: Conflict with: Gilead Sciences, L. Maurer: Grant: Conflict with: Gilead Sciences.

High efficacy of interferon-free treatments in real-world patients with chronic hepatitis C. A Spanish multicenter study: final data

Huascar Ramos[1], Pedro Linares[2], Isabel Martín [3], Ester Badia[4], Carolina Almohalla[5], Francisco Jorquera[* 6], Judith Gómez [4], Diana Joao [2], Sara Calvo[7], Isidro García [8], Pilar Conde[9], Begoña Álvarez [2], Guillermo Karpman [10], Sara Lorenzo [11], Visitación Gozalo [4], Marina de Benito[12], Mónica Vásquez[13], Lourdes Ruiz [11], Felipe Jiménez [3], Federico Sáez-Royuela[4, 4] and Asociación Castellano y Leonesa de Hepatología (ACyLHE)

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Introduction: The development of new direct-acting antivirals (DAA) for the treatment of chronic hepatitis C virus (HCV) infection has led to rates of sustained virological response (SVR) >90%, according to registry studies.

Aims: Few studies have assessed the efficacy of these treatments in clinical practice. Final data is presented.

Material and Methods: A multicentric, descriptive, observational, and prospective study was conducted to analyse the data of 463 HCV patients who received interferon (IFN)-free treatments (December 1, 2014 to August 31, 2015). The SVR was evaluated 12 weeks after completing treatment (SVR12).

Results: Baseline characteristics: 67% males, mean age 56 ± 11 years, BMI 26 ± 4.4, hemoglobin 14.8 ± 1.8 mg/dL, platelets 158,472 ± 71,964/mm^3, alanine transaminase (ALT) 81 ± 61 UI/mL, and HCV RNA 2,943,512± 5,140,186 UI/mL. The IL28B polymorphisms were: CT (63%), CC (22%), and TT (15%).

Seventy-eight percent of the patients had genotype (G)1 (67% subtype 1b, 31% 1a, and 2% unknown), 10% had G3, 10% G4, and 2% G2. The mean fibrosis level determined by transient elastography (TE) was 18 ± 13 kPa; 56% presented F4 cirrhosis (>12.5 kPa). A total of 60% had received previous treatment; IFN and ribavirin (RBV) (67%) or triple therapy with PI.

The combinations of DAA most often used included sofosbuvir (SOF) + simeprevir (SMV) (36%); SOF + ledipasvir (25%); ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) + dasabuvir (20%); and SOF + daclatasvir (DCV) (12%). RBV was administered to 43% of the patients.

The most frecuent treatment combination for G1 and G4 patients was SOF + SMV (41% and 42%, respectively), for G3 and G2 patients, SOF + DCV (80% and 46%, respectively). The majority of the G1, G3, and G4 patients (92%, 69%, and 87%, respectively) were treated for 12 weeks, and 55% of the G2 patients were treated for 24 weeks. RBV was administered to 37%, 64%, 71%, and 60% of the G1, G2, G3, and G4 patients, respectively.

The SVR12 rate was 94.6%. The rates of SVR12 for G1, G2, G3, and G4 patients are 95%, 100%, 93%, and 96%, respectively.

Conclusions: In our clinical practice, patients with HCV who received IFN-free treatments presented high rates of SVR12 (94.6%), which is similar to the results of other registry studies.

Disclosure of Interest: H. Ramos: None Declared, P. Linares: None Declared, I. Martín: None Declared, E. Badia: None Declared, C. Almohalla: None Declared, F. Jorquera: None Declared, J. Gómez: None Declared, D. Joao: None Declared, S. Calvo: None Declared, I. García: None Declared, P. Conde: None Declared, B. Álvarez: None Declared, G. Karpman: None Declared, S. Lorenzo: None Declared, V. Gozalo: None Declared, M. de Benito: None Declared, M. Vásquez: None Declared, L. Ruiz: None Declared, F. Jiménez: None Declared, F. Sáez-Royuela: Sponsored lectures (National or International): Conflict with: Janssen Cilag, Gilead Sciences S.L., AbbVie Spain S.L.

Estimating the prevalence of hepatitis C in people who inject drugs using respondent driven sampling – a systematic review

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Introduction: New, more effective and better-tolerated therapies have increased the accessibility to Hepatitis C (HCV) treatment for people who inject drugs (PWID). To plan for the future financial costs of treatment it is essential to accurately estimate HCV prevalence within this population.
Respondent-driven sampling (RDS) is a novel survey technique, which can provide prevalence estimates in hidden populations such as PWID.

Aims: The aim of this systematic review is to identify published articles reporting the use of RDS in PWID to test and document HCV prevalence and describe the operational conduct of each survey.

Material and Methods: Searches were undertaken in accordance with PRISMA systematic review guidelines. Included studies were English language publications in peer-reviewed journals, which reported the use of RDS to recruit PWID for HCV testing and prevalence estimation.
This systematic review was registered with Prospero (registration number CRD 42015019245).

Results: Twenty-four articles met the inclusion criteria (Figure 1). The majority reported a survey in an urban population (n=22; 92%) although they varied in scale (range 1-15 survey sites).

All surveys sites distributed two or three recruitment coupons and the majority of surveys (14; 82%) were completed in less than 12 months. A target sample size was reported in 10

articles of which four (40%) recorded the use of a design effect in making the calculation. The average final sample size was 500 (81-1000), which was achieved through two to 82 *seeds* (mean 8.1).
Where reported all survey sites reached equilibrium, passed through between five and 50 *waves* of recruitment (mean 17.2) and 96% (53 out of 55) achieved >90% of the target sample size. Sixteen (67%) articles went on to calculate and publish a population sero-prevalence for HCV (mean HCV sero-prevalence, 44%, range 4.1-97%).

Conclusions: RDS is an effective survey method for recruiting PWID from urban communities and can be used to estimate an HCV population prevalence. In the future the operational conduct of each survey should be clearly recorded to convey survey validity and caution needs to be applied to survey design, including the use of an adequate design effect, to ensure an adequate sample size is recruited.

Figure:

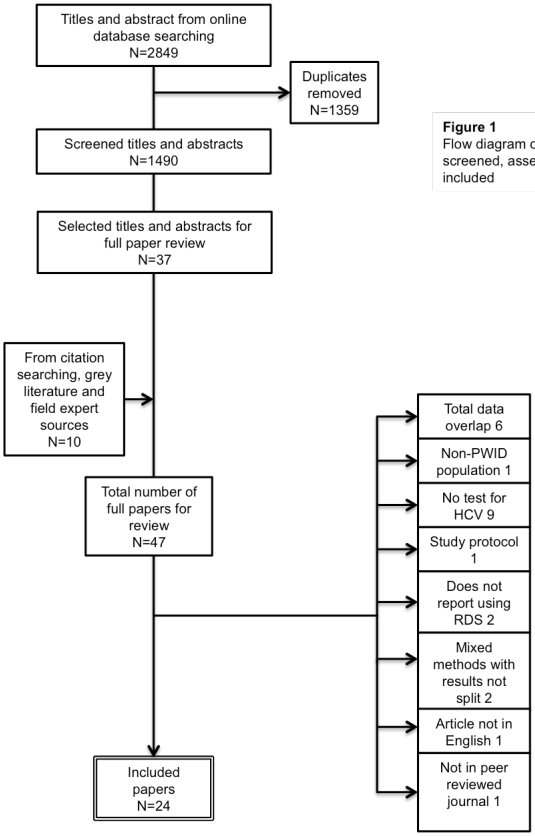

Figure 1
Flow diagram of studies screened, assessed and included

Disclosure of Interest: R. Buchanan: Grant: Conflict with: Gilead Fellowship grant 2014, J. Coad: None Declared, L. Grellier: None Declared, S. Khakoo: None Declared, J. Parkes: None Declared

Anti-HCV EIE2 antibodies can predict relapse to direct-acting antivirals (DAA)

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Introduction: We showed previously that anti-E1E2 directed against a single epitope expressed on the surface of circulating HCV particles were associated with spontaneous clearance/cure of patients and predictive before treatment of a sustained viral response (SVR) to bi- or tri -therapy (PEG-IFN/RBV ± protease inhibitors: BOC or TVR) in naïve or experienced patients who failed prior treatments, whatever the viral genotype (GT).

Aims: This work aims to: (1) investigate the prevalence of anti-E1E2 before, during and after treatment, (2) correlate anti-E1E2 kinetics and viral elimination: rapid (<8wks) or slow (>12wks), and (3) compare anti-E1E2 response in SVR patients and relapsers to determine the anti-E1E2 predictive value in the DAA era.

Material and Methods: This study was carried out on 2 patients groups: **(A)** a first SVR series of 27 patients: 18 GT1, 7 GT4 and 2 GT3, most of them failed prior bi- and/or tri-therapy (78 %), were at F3/F4 stage (55%), and received treatment with SOF/DCV+RBV (R) in 52% or SOF/SIM in 22% of cases without pegylated IFN (P). **(B)** The second series included 16 relapsers (8 GT1, 4 GT3a, 3 GT4, 1 GT2). Three received PR+SOF, and 13 IFN free treatment with DAA (2 SOF, 4 SOF/DCV, 2 SOF/SIM, 3 SOF/LDV, 2 PTV/r+OBV±DSB) + R in 54% of cases. All patients were treated for 12 or 24 wks.

Results: (A) In the first SVR series 21 out of 27 patients (75%) reacted for anti-E1E2 before starting treatment and most of them were associated with low baseline viremia <6 log, early elimination of virus (<8wks) and high baseline anti-E1E2 titer ≥ 1/1000. **(B)** In the relapse series, only 2 out of 16 (12.5%) were positive for anti-E1E2 before treatment. ROC curve analysis of the anti-E1E2 response, in SVR compared to relapsers, shows an

area under the curve (AUC) = 0.8423 (p <0.001) with 88% positive and 70% negative predictive values, respectively.

Conclusions: These results do confirm the link between anti-E1E2 and HCV clearance under DAAs, alike with spontaneous cure and SVR after bi- or tri-therapy. They demonstrate a correlation between the presence of anti-E1E2 prior treatment and early HCV RNA elimination kinetics. More interestingly, the absence of anti-E1E2 response prior treatment looks like a promising predictive biomarker of relapse. Whether and how anti-E1E2 monitoring could help to optimize DAAs'duration deserves further study.

Disclosure of Interest: M.-A. Petit: None Declared, V. Victor: None Declared, B. Pascale: None Declared, P. Pierre: None Declared, B. Isabelle: None Declared, Z. Fabien: Consultant: Conflict with: Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp and Dohme, Roche, L. Vincent: None Declared, M. Patrice: None Declared, C. Isabelle: None Declared, L. Sylvie: None Declared, T. Christian: Grant: Conflict with: MSD, Roche, Janssen, Flamel Technologies, Consultant: Conflict with: Janssen, MSD, Flamel Technologies.

Screen 6: ABSTRACT-151

Chronic infection with hepatitis C virus: a large number of patients is lost to follow-up

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Introduction: Highly effective antiviral treatment is now available for chronic infection with hepatitis C virus (HCV). However, many patients diagnosed with HCV in the past have been lost to follow-up in hospital care and potentially miss out on treatment.

Aims: To retrieve patients lost to follow-up and bring them back into care.

Material and Methods: We explored data files of the local microbiological laboratory to identify all registered cases of chronic HCV in our region for the past 15 years. Identified cases were compared with patients currently known in our hospital or cured. Patients were considered lost to follow up if no follow-up appointment with any hepatitis specialist was scheduled. After patients lost to follow-up have been identified, they will be approached via their primary health care physician and invited for evaluation at our hospital.

Results: 499 cases of chronic HCV were identified. 39 (7.6%) patients were deceased, 12/39 (31%) had a liver-related death, 14/39 (36%) non-liver related death and in 13/39 (33%) the cause of death was unknown. 170 (38%) patients were considered lost to follow-up. Among them, only 107 (63%) patients were eligible for retrieval. Of the remaining 63 patients, 12/63 (19%) had an unclear legal status, 17/63 (27%) were imprisoned, 15/63 (24%) resided in another region and in 19/63 (30%) patients the primary care physician was not known. All patients eligible for retrieval are currently approached via their primary care physician and invited for evaluation at our hospital.

Conclusions: A considerable part of patients with chronic HCV infection is lost to follow-up. Structural retrieval of these patients will lead to the identification of patients with an indication for treatment.

Disclosure of Interest: N. Beekmans: Grant: Conflict with: Gilead ISR IN-NL-174-2008, M. Klemt-Kropp: Consultant: Conflict with: AbbVie Care Multidisciplinary Advisory Board, Sponsored lectures (National or International): Conflict with: Roche, Janssen, AbbVie.

GEODE-II: efficacy and safety of ombitasvir/paritaprevir/ritonavir and dasabuvir with low-dose ribavirin QD in patients with genotype Ia chronic hepatitis C virus infection without cirrhosis

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Introduction: Ribavirin (RBV), a component of guidelines-recommended treatment regimens for certain patient populations with hepatitis C virus (HCV) infection is known to cause decreases in haemoglobin and/or elevations of indirect bilirubin. RBV is typically administered at a weight-based daily dosage of 1000–1200 mg.

Aims: This study investigated the safety and efficacy of the direct-acting antiviral agents (DAAs) ombitasvir/paritaprevir (identified by AbbVie and Enanta)/ritonavir (OBV/PTV/r)+dasabuvir (DSV) with a fixed low dose of RBV in patients with genotype 1a (GT1a) chronic HCV infection without cirrhosis.

Material and Methods: GEODE-II is a Phase 3, open-label, multi-center study designed to evaluate the safety and efficacy of OBV/PTV/r+DSV co-administered with low-dose RBV (600 mg QD) for 12 weeks in GT1a HCV-infected patients without cirrhosis,

who are either HCV treatment-naïve (TN) or treatment-experienced (TE) to previous interferon (IFN) or pegylated IFN ± RBV therapy. Efficacy is assessed by sustained virologic response at post-treatment week 12 (SVR12) compared with historic SVR12 rates for the same regimen coadministered with weight based RBV. Safety is assessed in all patients receiving at least 1 dose of study drugs.

Results: A total of 105 patients (52% female, 86% white) were enrolled in this study, of whom 89% were TN. As of the data cut-off date (May 11, 2016) 79 patients reached the end of treatment. The SVR4 rate was 94% for 71 intent-to-treat (ITT) patients who reached post-treatment week 4. AEs were mostly mild or moderate in severity, with fatigue (25%), headache (13%) and insomnia (11%) the most frequently reported. One patient had a breakthrough, 1 relapsed, 3 discontinued study drug for non-viral failures and 1 patient was discontinued due to a drug related AE. No subjects required RBV dose reduction as per protocol. Grade 1 haemoglobin-level abnormalities were reported in 15/104 patients (14%), while both grade 1 (n=9, 9%) and grade 2 (n=5, 5%) elevated total bilirubin levels were reported. Full safety data and SVR12 rates will be available at the meeting.

Conclusions: Preliminary data from this ongoing study demonstrate an SVR4 rate of 94% in the ITT population. The regimen was well tolerated and haemoglobin and bilirubin abnormalities were observed infrequently. These preliminary results suggest that the use of low-dose RBV with the 3-DAA regimen may be sufficient for most patients to achieve SVR while reducing RBV-related AEs.

Disclosure of Interest: F. Poordad: Grant: Conflict with: AbbVie, Achillion Pharmaceuticals, Anadys Pharmaceuticals, Biolex Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, Gilead Sciences, GlaxoSmithKline, GlobeImmune, Idenix Pharmaceuticals, Idera Pharmaceuticals, Intercept Pharmaceuticals, Janssen, Medarex, Medtronic, Merck, Novartis, Santaris Pharmaceuticals, Scynexis Pharmaceuticals, Vertex Pharmaceuticals, ZymoGenetics., Consultant: Conflict with: AbbVie, Achillion Pharmaceuticals, Anadys Pharmaceuticals, Biolex Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, GlobeImmune, Idenix, Merck, Novartis, Tibotec/Janssen, Theravance, Vertex, Other: Conflict with: Gilead, Kadmon, Merck, Onyx/Bayer, Genentech, GlaxoSmithKline, Salix, Vertex., S. Sedghi: None Declared, P. Pockros: Grant: Conflict with: Gilead, AbbVie, Janssen, Bristol-Myers Squibb, Merck, Conatus, Roche Molecular, Consultant: Conflict with: Gilead, AbbVie, Janssen, Bristol-Myers Squibb, N. Ravendhran: Grant: Conflict with: BMS, GILEAD, MERCK, SALIX, Other: Conflict with: AbbVie, Gilead, Merck, Salix, BMS, R. Reindollar: Grant: Conflict with: AbbVie, BMS, Cepheid, Gilead, Intercept, Janssen, Consultant: Conflict with: AbbVie, BMS, Gilead, Janssen, M. Lucey: Grant: Conflict with: AbbVie, Gilead, Salix, M. Epstein: Consultant: Conflict with: Eli Lilly, IMHS, ASPIRE BARIATRIC, L. Bank: Grant: Conflict with: Gilead, Abbvie, BMS

and Merck, Other: Conflict with: Gilead, BMS and Abbvie Immunology, D. Bernstein: Grant: Conflict with: GIlead, Pharmasset, Vertex, BMS, Consultant: Conflict with: Merck, Other: Conflict with: Gilead, R. Trinh: Employee: Conflict with: AbbVie Inc., P. Krishnan: Consultant: Conflict with:, Stockholder: Conflict with:, Employee: Conflict with: AbbVie Inc., T. Pilot-Matias: Employee: Conflict with: AbbVie Inc., A. Polepally: Employee: Conflict with: AbbVie Inc., R. Pothacamury: Employee: Conflict with: AbbVie Inc., K. Unnebrink: Employee: Conflict with: AbbVie Deutschland GmbH&Co KG, M. Martinez: Employee: Conflict with: AbbVie Inc., D. Nelson: Grant: Conflict with: Abbot, BMS, Beohringer Ingelheim, Gilead, Genentech, Merck, Bayer, Idenix, Vertex, Jansen, Other: Conflict with: Merck.

Screen 8: ABSTRACT-160

Truncated 16 weeks dual sofosbuvir/ribavirin therapy not inferior to the recommended 24 weeks course in the subset analysis of chronic HCV genotype 4 patients who had very rapid virologic response

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Introduction: The governmental mass treatment campaign for Egyptian patients with chronic hepatitis C virus infection, with the new directly acting antiviral drugs, carried-out in the Egyptian national liver centers has prioritized the advanced difficult to treat cases with F3 and F4 liver cirrhosis. This has impacted the overall cure rate (sustained virologic response at 12 weeks after completion of treatment (SVR12)). There are no enough data about the efficacy of treatment in the easy to treat naive non advanced cases. It is not even known whether response-guided, shorter courses of treatment than the generally recommended could be justifiable in the subset of patients who shows very rapid virologic response to therapy (undetectable serum HCV RNA level at week 2).

Aims: We aimed to compare the sustained virologic response rates after a truncated 16 weeks course of dual Sofosbuvir/ribavirin therapy versus the recommended 24 weeks in the subset of non-cirrhotic chronic HCV genotype 4 patients who had shown a very rapid virologic response at week 2.

Material and Methods: Among our included, non-cirrhotic, chronic HCV genotype 4 patients who were already on treatment with a dual therapy in the form of Sofosbuvir one tablet 400 mg daily, plus weight based ribavirin, we randomized 38 consecutive patients, who had shown vRVR into either 16 or 24 weeks course duration in a 1:1.5 block randomization technique. The final sustained virologic response at week 12 post-treatment (SVR12) were compared between the 2 groups.

Results: No significant difference in SVR12 rates were found in patients who had been randomized to either 16 or 24 weeks duration after having a vRVR. Both groups had 100% (95% CI, (78.2-100% & 85.2-100%) SVR12 rates respectively. There was a significant

association between the vRVR and the SVR12, with 100% (38/38) of those who had vRVR in our included patients achieved a final SVR12 (High Positive Predictive Value (PPV).

Conclusions: We can conclude from our study that the vRVR and the early response kinetics might be used as a basis for a personalized course of treatment. This could shorten unnecessary long treatment courses in rapid responders and might help to avoid relapses in slow responders.

Disclosure of Interest: M. Yakoot: None Declared, A. Abdo: None Declared, S. Helmy: Employee: Conflict with: Working at Pharco Corporate.

Screen 9: ABSTRACT-162

Ribavirin management in HCV genotype 4 patients receiving ombitasvir/paritaprevir/ritonavir with ribavirin in AGATE-I

Christophe Hézode[*1], Tarek Hassanein[2], Yves Horsmans[3], Hermann Laferl[4], José L. Calleja[5], Antonio Olveira[6], Christophe Moreno[7], George Papatheodoridis[8], Magdy Elkhashab[9], Marisol Martinez[10], Yao Yu[10], Rebecca Redman[10], Roula Qaqish [10], Niloufar Mobashery[10], Tarik Asselah[11]

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Aims: We describe the management of ribavirin (RBV) dosing due to anaemia-related adverse events (AEs) in the ongoing phase 3 multinational AGATE-I study of the 2 direct-acting regimen of ombitasvir and paritaprevir (identified by AbbVie and Enanta) co-dosed with ritonavir (OBV/PTV/r) in hepatitis C virus genotype 4-infected treatment-naive or interferon (IFN)/RBV- or pegylated IFN/RBV-experienced patients with compensated cirrhosis.

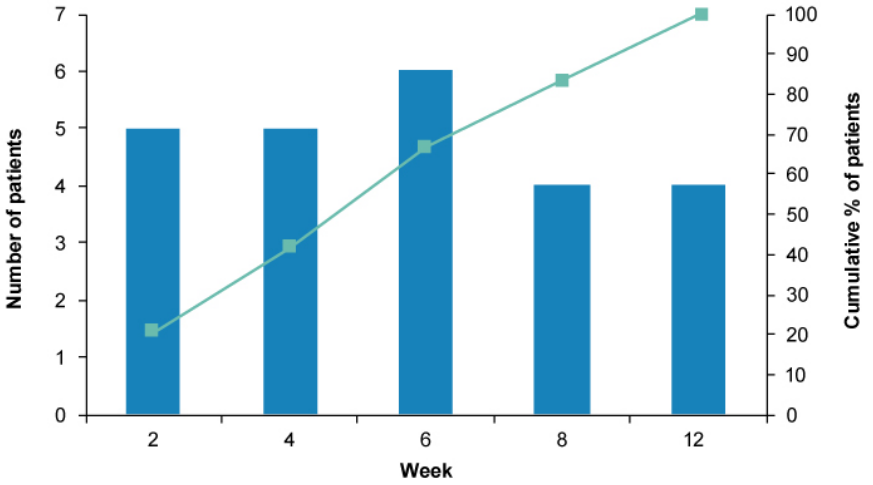
Material and Methods: All patients in Part I of AGATE-I who received OBV/PTV/r (25/150/100 mg) once daily plus RBV for 12 weeks or 16 weeks were included in the analysis. RBV was dosed according to body weight with a total daily dose of 1,000 mg if <75 kg or 1,200 mg if ≥75 kg. Stepwise logistic regression models assessed predictors associated with RBV dose reductions due to decrease in haemoglobin.

Results: 20% of patients (24/120) who received at least 1 dose of OBV/PTV/r + RBV had an RBV dose reduction due to decrease in haemoglobin; all achieved SVR12. No patient prematurely discontinued treatment due to RBV toxicity. Three patients received a blood transfusion and 1 patient received erythropoietin due to anaemia-related AEs. Mean baseline haemoglobin levels were 14.0 and 14.9 g/dl in patients requiring RBV dose reduction and those who did not, respectively. In patients who required RBV dose reduction, most received 1,000 (38%) or 800 (33%) mg after first RBV dose reduction; at end of treatment, most were receiving 1,000 (25%), 800 (29%) or 600 (17%) mg. The median time to first RBV dose reduction was 43 days (range 15–88); 67% of RBV dose reductions due to decrease in haemoglobin occurred within the first 6 weeks of treatment. In patients with RBV dose reduction and those without, mean haemoglobin levels declined within 4 weeks of treatment, plateaued from week 4 (10.7 g/dl and 13.0 g/dl, respectively) until end of treatment, and returned to near baseline levels by post-treatment week 8 (13.3 g/dl and 14.8 g/dl, respectively). Stepwise logistic regression identified lower baseline haemoglobin and lower baseline creatinine clearance as significant risk factors ($p<.05$) for RBV dose reduction.

Conclusions: Most patients who received OBV/PTV/r + RBV did not require an RBV dose reduction. Reducing RBV dose stabilised haemoglobin levels and did not negatively impact SVR12 rates. In patients with an RBV dose reduction, most were receiving 600–1,000 mg RBV at end of treatment.

Figure:

Figure: Summary of first RBV dose reduction due to decrease in haemoglobin by study visit week (N=24)



Solid bars represent numbers of patients at each study visit having their first RBV dose modification; line represents cumulative proportion of patients at each study visit with an RBV dose modification.

Disclosure of Interest: C. Hézode: Other: Conflict with: participation in AbbVie-sponsored clinical studies., T. Hassanein: Other: Conflict with: participation in AbbVie-sponsored clinical studies,Y. Horsmans: Consultant: Conflict with: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, H. Laferl: Grant: Conflict with: Travel Grants: AbbVie, Gilead Sciences, Roche, J. Calleja: Other: Conflict with: Advisor/Lecturer: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, Janssen, A. Olveira: Other: Conflict with: participation in AbbVie-sponsored clinical studies, C. Moreno: Grant: Conflict with: Research Grants: AbbVie, Gilead Sciences, Janssen, Consultant: Conflict with: Consultant: AbbVie, Gilead Sciences, Janssen, Merck Sharp & Dohme, Bristol-Myers Squibb, G. Papatheodoridis: Grant: Conflict with: Advisor/Lecturer/Research Grants: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, Roche, Other: Conflict with: Clinical Trials: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis, Regulus Therapeutics, Roche; Data Safety Management Board: Gilead, M. Elkhashab: Grant: Conflict with: Advisor/Research Grants: AbbVie, Merck Sharp & Dohme, Eisai, Gilead Sciences, Bristol-Myers Squibb, M. Martinez: Employee: Conflict with: employee of AbbVie and may hold stock or options, Y. Yu: Employee: Conflict with: employee of AbbVie and may hold stock or options, R. Redman: Employee: Conflict with: employee of AbbVie and may hold stock or options, R. Qaqish: Other: Conflict with: participation in AbbVie-sponsored clinical studies, N. Mobashery: Employee: Conflict with: employee of AbbVie and may hold stock or options, T. Asselah: Other: Conflict with: participation in AbbVie-sponsored clinical studies.

Reduced rates of recurrent viremia in HCV-treated people who inject drugs (PWID) using all oral-therapy administered within a multidisciplinary model of care

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Introduction: Understanding and mitigating the risk of recurrent viremia (RV) following successful Hepatitis C virus (HCV) therapy is essential to the design of treatment programs for HCV-infected PWID. In this population, a recent meta-analysis estimates this risk at up to 32/1000 person-years of follow-up (PYFU). Strategies to reduce this rate must be considered.

Aims: Delivery of better tolerated and more effective all-oral therapies within a multidisciplinary model of care may address issues of high rates of recurrent viremia in a productive way.

Material and Methods: An observational, retrospective study was conducted among HCV-infected patients seen at the Vancouver Infectious Diseases Centre (VIDC). We included all active PWID having received HCV therapy and having achieved a sustained virologic response (SVR). All individuals had access to multidisciplinary care to address medical, psychiatric, addiction-related, and social needs prior to, during and after HCV therapy. After achievement of SVR, HCV is repeated every 6 months, more frequently if acute hepatitis is suspected. The primary endpoint was the detection of recurrent viremia following SVR.

Results: Seventy active PWID who achieved SVR were included in this analysis, with a mean age of 53 years, 85% male, 60% genotype 1, 57% HIV co-infected, 22% cirrhotic, 83% treatment-naïve, 63%/70% using heroin/stimulants, 58% on opiate substitution therapy. Forty-four achieved SVR while on all-oral HCV therapy (72% of these on 8-12 week courses of therapy), 42% received ribavirin and 20% of patients were cirrhotic (Fibroscan >12.5 kPa). With a mean of 5.5 PYFU, the rate of RV was 12.9/1000 PYFU (95% CI, 3.1-15.7), a rate 60% lower than recently reported in the recent meta-analysis.

Characteristics of the five cases of RV include: mean age 52 years, all male, 80% GT 1, 100% HIV co-infection, 100% amphetamine use, 80% heroin use, and 60% cirrhotic.

Conclusions: The treatment of HCV-infected PWID with currently available all-oral regimens is both safe and highly effective, replicating the efficacy reported in clinical trials in a population that was not systematically included in these trials. The rates of RV in HCV-infected active PWID achieving SVR may be lowered from that reported in the current medical literature by providing therapy within a multidisciplinary model of care with long-term engagement. Our data support expansion of HCV treatment programs among active PWID and suggest a way this could be done while mitigating the risk of recurrent viremia.

Disclosure of Interest: None Declared

Friday 23 September 2016
ePoster Session 4: 17:50 – 18:20

Screen I: YI-ABSTRACT-110

Understanding factors associated with hepatitis C spontaneous viral clearance: a meta-analysis

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Introduction: New advances in the treatment of hepatitis C provide high levels of sustained viral response but their expense limits availability in publicly funded health systems. Understanding which patients are likely to clear virus spontaneously without treatment and the timing of this is important for informing how treatment should be most effectively targeted.

Aims: This review aims to ascertain more precise estimates of viral clearance rates, and better define the factors that predict clearance.

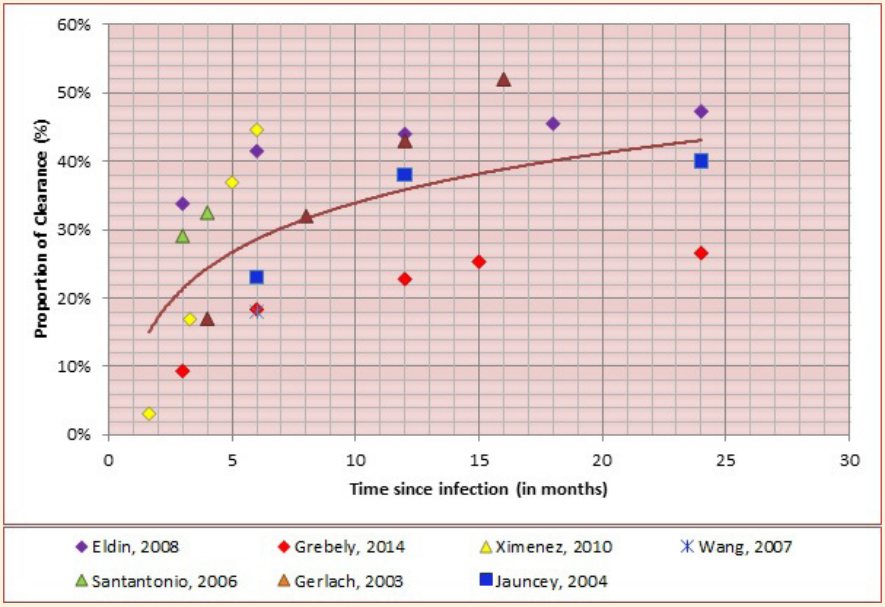
Material and Methods: We did a systematic review and searched in Ovid Embase, Ovid Medline and Pubmed from 1st January 1994 to 30th June 2015 for studies reported spontaneous viral clearance (SVC) and/or factors associated with clearance. The initial screening and full text review was done by two independent reviewers. To identify publication bias, heterogeneity was investigated using I^2. To investigate the relationship between time since infection and SVC we plotted rates of viral clearance against follow-up time.

Results: Seventy four studies were included in analysis, comprising 52 studies where the proportion achieving HCV (Hepatitis C Virus) clearance could be estimated and 44 studies which assessed factors associated with SVC, representing a total of 25,238 individuals. To ensure precise estimates of clearance, we restricted our analysis to 7 studies which provide information of clearance in different time points after the initial infection, representing a total of 1,195 individuals. Based on meta-analysis output, the rates of

spontaneous clearance were 21.8% (95% CI: 9-44.1%), 27.9% (95% CI: 17.2-41.8%), 36.1% (95% CI: 23.5-50.9%), and 37.1% (95% CI: 23.7-52.8%) within 3, 6, 12, and 24 months after infection respectively. We found that those who had not spontaneously cleared by 12 months were unlikely to do so. Meta-analysis of clinical, demographic, and behavioural factors associated with clearance found that female sex, hepatitis B co-infection, symptomatic infection, non-black or non-indigenous race, infection with genotype-1, younger age, an absence of alcohol or drug problems and HIV negative patients were predictors of spontaneous clearance.

Conclusions: This study suggests that patients continue to spontaneously clear HCV up to at least 12 months following initial infection. Given the high costs of treatment, it may be important to give sufficient time for patients to spontaneously clear infection before initiating treatment.

Figure:



Disclosure of Interest: None Declared

Screen 2: YI- ABSTRACT-II3

Natural NS3, NS5A and NS5B HCV resistance is common across HCV-genotypes I to 4, and specific substitutions can affect NS5A inhibitors efficacy in real-world clinical practice

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Introduction: Natural resistance-associated substitutions (RASs) have highly variable prevalence in different HCV genotypes (GTs).

Aims: We investigate the frequency of natural RASs, and the role of NS5A-RASs on treatment efficacy, in a large real-life database including the 4 main HCV-GTs.

Material and Methods: RASs in NS3 (N=1032), NS5A (N=833) and NS5B (N=496) were analysed in 1193 HCV-infected DAA-naïve patients (pts). Sanger-sequencing was performed on 714 GT1a, 989 GT1b, 135 GT2c, 333 GT3a, 24 GT4a and 166 GT4d samples. RASs with fold-change ≥100 were defined as major.

Results: Overall, 415/1193 (35%) pts showed natural RASs, independently by cirrhosis, but with important differences for GT/subtypes. GT1a, GT1b and GT4a frequently showed NS3 RASs (52-20-36%, respectively), with high prevalence of 80K in GT1a (17%). The 80K was never found in GT4. Major RASs D168A/E/T/V had 3% prevalence in GT2c and 4% in GT4d. Also in NS5A, GT1a, GT1b and GT4a showed the highest prevalence of RASs (10-31-38%, respectively). Major NS5A RASs were detected in 10% GT1a (28V, 30H/R, 31M, 93C/H), 9% GT1b (30R, 93H), 5% GT2c (31M, 93H), 4% GT3a (93H) and 2% GT4d (30S). The most common major NS5A RAS was 93H. In NS5B, the major sofosbuvir 282T RAS was never found, while the putative RASs 159F and 316N were exclusively detected in GT1b (13% and 19%) often in association (phy=0.67, $p<0.001$ by covariation analysis). Among 372 pts with resistance test in all 3 genes, 10% showed multiple RASs. The most prevalent association was NS3+NS5A RASs (3%, mainly GT1 and 4). Only 2 GT1b pts showed RASs on 3 drug-targets.
Lastly, 138 pts treated with a NS5A-inhibitor were studied to evaluate the potential role of natural NS5A-RASs. Among 26 non-cirrhotic pts, none had major RASs, and all 4 with baseline minor NS5A RASs (GT1b: 30Q, 31M, 58S, 92T) reached a sustained viral response (SVR12). Among 112 cirrhotic pts, 4 showed major NS5A RASs (fold-change >1000). Two of them, (GT1b:93H; GT4d:30S) were treated with not-recommended regimens, without ribavirin, and experienced virological failure. On the contrary, the other 2 (GT1b:93H; GT1a:30R) received a recommended-regimen with ribavirin and reached SVR.

Conclusions: Natural RASs are common across all HCV-GTs, and up to 10% of pts show multiple-class resistance, though only the so-called major mutations seem to have a clinical relevance. Thus, qualitative identification of only major natural RASs (rather than all) is required to properly guide DAA-based therapy.

Disclosure of Interest: None Declared

Screen 3: ABSTRACT-II5

Exposure-response analyses to demonstrate similar efficacy and better tolerability for low dose ribavirin compared to weight based ribavirin with the 3D regimen (ombitasvir/paritaprevir/ritonavir and dasabuvir) in HCV GTI infection

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Introduction: The 3D regimen (ombitasvir/paritaprevir/ritonavir and dasabuvir) ± weight based ribavirin (RBV) is approved for the treatment of hepatitis C virus (HCV) genotype 1 (GT1) infection. With the potent 3D regimen, RBV dose reduction is expected to improve tolerability with minimal impact on efficacy.

Aims: The objectives of the analyses were to predict the efficacy (percent 12-week sustained virologic response [%SVR_{12}]) and the safety event incidence rates (total bilirubin [TBIL] elevation and hemoglobin [Hgb] reduction) for the 3D regimen + low dose (600 mg) RBV (3D + LDR) compared to the 3D regimen + weight based (1000 or 1200 mg daily) RBV (3D + WBR).

Material and Methods: Efficacy and safety data were available from six phase 3 and two phase 2 studies (3D ± WBR). Multiple linear logistic regression (MLR) model was developed (SAS 9.2) to establish the relationship between SVR_{12} and trough concentrations (C_{trough}) of DAAs and RBV for the GT1a infected subjects only (N = 1253). GT1b subjects were not included as they achieved >99% SVR_{12}. Separate MLR models for the relationship between safety incidence rates (by severity) and area under the concentration-time curve (AUC) values were developed (R 3.0.1) using the data of GT1 infected subjects from six phase 3 studies and one phase 2 study (N = 2346). Relevant covariates were included in the models based on statistical and clinical significance. The final models were used to predict the %SVR_{12}, grade 3 TBIL elevation and grade 2 Hgb reduction for 3D + LDR compared to 3D + WBR.

Results: C_{trough} values of DAAs, RBV along with age, sex, cirrhosis (presence *vs* absence), baseline viral load, and interleukin-28B (IL28B) genotype (non-CC *vs* CC) were associated with SVR_{12}. The expected change in SVR_{12} for 3D + LDR compared to 3D + WBR was < 1% across easy-to-treat (non-cirrhotic, female, IL28B CC) to hard-to-treat (cirrhotic, male, IL28B non-CC) GT1a subpopulations. In safety analyses, paritaprevir and RBV AUC values and baseline TBIL were associated with TBIL elevation; RBV AUC, baseline Hgb, sex, and cirrhosis were associated with Hgb reduction. The predicted probability of grade 3 TBIL elevation and grade 2 Hgb reduction with 3D + LDR were 2.3% and 0.7% which were significantly lower than observed 5.1% and 6.9% with 3D + WBR, respectively.

Conclusions: Exposure-response analyses demonstrated that lowering the RBV dose (to 600 mg) from weight based dosing with 3D regimen would improve tolerability with minimal or no effect on SVR_{12} (<1% change) in HCV GT1 infection.

Disclosure of Interest: A. Polepally: Stockholder: Conflict with: AbbVie Inc.,, Employee: Conflict with: AbbVie Inc.,, Other: Conflict with: AbbVie contributed to the study design, research, and interpretation of data, writing, reviewing, and approving the publication. All authors are AbbVie employees and may hold AbbVie stocks or options., B. Hosmane: Consultant: Conflict with: AbbVie Inc.,, Stockholder: Conflict with: AbbVie Inc.,, C.-W. Lin: Stockholder: Conflict with: AbbVie Inc.,, Employee: Conflict with: AbbVie Inc.,, M. Minocha: Stockholder: Conflict with: AbbVie Inc.,, Employee: Conflict with: AbbVie Inc.,, H. Wang: Stockholder: Conflict with: AbbVie Inc.,, Employee: Conflict with: AbbVie Inc.,, A. Khatri: Stockholder: Conflict with: AbbVie Inc.,, Employee: Conflict with: AbbVie Inc.,, R. Menon: Stockholder: Conflict with: AbbVie Inc.,, Employee: Conflict with: AbbVie Inc.,

Screen 4: YI-ABSTRACT-120

Sofosbuvir and ribavirin combination safety and efficacy for treating HCV GT 3 infection in patients with severe renal impairment or end stage renal disease

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Introduction: Limited data is available on the safety and efficacy of DAA'S for treating HCV infection in patients with severe renal impairment or end stage renal disease. Although RBV free regimens are increasingly becoming available, but backbone medicine sofosbuvir is in all these regimens.

Aims: To evaluate efficacy & safety of Sofosbuvir + Ribavirin in patients with stage 4 or 5 chronic kidney disease and HCV GT 3 infection in real life setup.

Material and Methods: A prospective study was conducted on patients with HCV Genotype 3 and CKD stage 4 (eGFR 15-30 ml/min/1.73m^2) or stage 5 (eGFR <185ml/min/1.73m^2 or requiring dialysis) who were started on sofosbuvir + RBV or Sofosbuvir alone between Apr 2015 to Apr 2016. Clinical and lab data, degree of fibrosis, SVR 4 and SVR12, SVR24 and on therapy adverse effects were noted.

Results: Forty patients were included; baseline features are shown in Table. All patients completed treatment. Sofosbuvir was given in full dose 400mg/day while fourteen patients received RBV 200mg /day; five patients received 200mg /48h. RBV was stopped in two patients, because of adverse effects: hemo globin decline <8 g/dl and gastrointestinal intolerance. Erythropoietin was given in six patients, due to anemia and CKD. 36/40 patients achieved SVR 24.

Conclusions: Efficacy of SOF + RIBA combination with stage 4 or 5 CKD and HCV Geno 3 infections is almost similar to that observed in these with normal renal function. RIBA use was however associated with severe adverse effects and it should be monitored, on case to case basis.

Figure:

VARIABLES	N = 40
Age (years) mean + SD	53 (43 -63)
Male ; Female ration	1:1
Degree of Fibrosis F0 – F1 F2 F3 F4	 10 8 12 10
CKD stage n (%). 4 (eGFR 15- 30 ml/min/ 1.73m^2) 5 (eGFR <15ml/min/1.73m^2 or dialysis)	 22 18
HCV Viral load mean all having Genotype 3.	5.79x10^6 IU /ml
Previous Treatment. Naïve Previous treatment	 25 15
Liver Stiffness Kpa	23.6 (0.8)

Disclosure of Interest: None Declared

Screen 5: YI-ABSTRACT-I55

E2 glycoprotein epitope mapping in antibody associated hepatitis C virus

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Introduction: Humoral immune system responds to the chronic hepatitis C virus (HCV) infection by producing neutralizing antibodies (nAb). In this study we identified E1E2 glycoprotein sequence which was targeted by host humoral immune system.

Aims: Uniquely our study focused on characterizing epitopes targeted by patient derived virus free Fab (VF-Fab) using chemically linked peptides on scaffolds (CLIPS) technology.

Material and Methods: HCV infectious sera from genotype 1b was segregated into antibody (Ab) free and antibody associated virus (AAV) population. Based on the available anti-HCV monoclonal nAb mapping information we selected amino acid region from 385-620 for conformational epitope mapping. A library of peptides (Linear peptides, loop mimics and helical structure) was synthesized using CLIPS technology (Pepscan Presto; Lelystad). VF-Fab fragments were obtained from HCV genotype 1a (n=1), genotype 1b(n=2) and genotype 3a(n=1) by treating the source sera with proteinase K. The binding of each of the VF-Fab to the synthesized peptides was tested in a PEPSCAN-based ELISA.

Results: Five binding motifs were identified by four VF-Fab in the AAV sequence upon peptide mapping. We identified five different binding motifs. Two ($AN2_{434-446}$, $AN3_{429-448}$) out of five motifs share amino acid resides with HuMAb AR3C and CBH-2 and lie on the neutralization face of the E2. Epitope $AN5_{606-615}$ is a part of epitope targeted by mAb 2C21. Epitopes $AN1_{394-406}$ which lies in the HVR1 and $AN4_{540-515}$ have not been reported previously.

Conclusions: In summary, we identified epitopes in the AAV sequence which was targeted naturally by host immune system and was recognised by VF-Fabs derived from HCV infected patients.

Disclosure of Interest: None Declared

Screen 6: ABSTRACT-I63

GARNET: High SVR rates following eight-week treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir for patients with HCV genotype Ib infection

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Introduction: Ombitasvir, paritaprevir (identified by AbbVie and Enanta) co-administered with ritonavir, and dasabuvir comprise the 3 direct-acting antiviral (DAA; 3D) regimen OBV/PTV/r + DSV approved for hepatitis C virus (HCV) genotype (GT) 1 infection. Previous data reported high rates of sustained virologic response (HCV RNA <LLOQ; SVR) at post-treatment week 12 (PTW12; SVR12) following 8 and 12 weeks of 3D treatment with and without ribavirin (RBV), respectively.

Aims: This is the first study evaluating an 8-week treatment duration of 3D without RBV in HCV GT1b-infected patients without cirrhosis.

Material and Methods: GARNET is a multicentre, open-label, single-arm study investigating the safety and efficacy of an 8-week treatment duration of once-daily OBV/PTV/r (25/150/100 mg) + twice-daily DSV (250 mg) in treatment-naïve patients with chronic HCV GT1b infection without cirrhosis. Safety and available rates of HCV RNA <LLOQ at end of treatment (EOT) and at PTW4 (SVR4) are reported.

Results: The study enrolled 166 patients across 20 sites. Select baseline demographics, safety, and laboratory abnormalities are presented in Table 1. To date, 164/166 (99%) patients with available data had HCV RNA <LLOQ at EOT or a subsequent visit. Of the 70 patients that have reached PTW4, 100% achieved SVR4. Two patients did not achieve HCV RNA <LLOQ at EOT: one failed to suppress HCV RNA and was later

identified as having HCV GT6 infection, and one discontinued treatment on day 32 due to non-compliance. One patient discontinued treatment on day 45 due to Grade 3 hyperbilirubinemia which was considered possibly related to study drug and is resolving following discontinuation. This patient was asymptomatic and achieved SVR4. The majority of AEs were mild in severity, and the most common AEs were headache (14%) and fatigue (11%). Grade 3 lab abnormalities were rare.

Conclusions: High SVR4 rates were demonstrated in patients with HCV GT1b infection without cirrhosis following 8-week, RBV-free treatment with the 3D regimen. Treatment was well-tolerated, with most AEs being mild in severity. Full SVR12 data will be presented at the meeting.

Figure:

Table 1. Safety & Baseline Demographics

Event, n (%)	3D for 8 Weeks N=165
Female	93 (56)
Fibrosis Stage: F0-F1/F2/F3, n	141/9/15
Baseline viral load ≥6 million	12 (7)
Any AE	67 (41)
Serious AEs	1 (1)*
Laboratory abnormalities	
ALT Grade ≥3 (>5 x ULN)[a]	0†
Total bilirubin Grade 3 (>3 x ULN)[b]	1 (1)†
Haemoglobin, Grade ≥2 (<10 g/dL)[b]	0†

ALT, alanine aminotransferase; ULN, upper limit of normal
[a]Post-nadir; [b]Post-baseline
*Syncope, assessed as not related to study drug
†N=164

Disclosure of Interest: T. Welzel: Consultant: Conflict with: AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, Janssen, Novartis., S. Zeuzem: Consultant: Conflict with: Abbvie, BMS, Gilead, Janssen, Merck/MSD, E. Dumas: Employee: Conflict with: AbbVie Inc., T. Asselah: Consultant: Conflict with: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche, Other: Conflict with: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb,

Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche., D. Shaw: None Declared, R. Hazzan: None Declared, X. Forns: Grant: Conflict with: Jansen, AbbVie, Other: Conflict with: Janssen, Gilead, AbbVie, T. Pilot Matias: Employee: Conflict with: AbbVie Inc., W. Lu: Employee: Conflict with: AbbVie Inc., D. Cohen: Employee: Conflict with: AbbVie Inc., J. Feld: Grant: Conflict with: AbbVie, Boehringer Ingelheim, Gilead Sciences, Janssen, Merck, and Regulus, Consultant: Conflict with: AbbVie, Achillion, BI, BMS, Gilead, Janssen, and Merck.

Screen 7: ABSTRACT-I78

Short duration treatment with AL-335 and odalasvir (ODV), with or without simeprevir (SMV), in treatment naïve patients with hepatitis C virus (HCV) genotype (GT) I infection

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Introduction: AL-335, ODV, and SMV are potent inhibitors of HCV nonstructural proteins 5B, 5A, and 3/4, respectively.

Aims: Determine the pharmacokinetics (PK), efficacy, and safety of AL-335+ODV±SMV in HCV-infected subjects.

Material and Methods: This is an ongoing open-label study evaluating various dosing regimens of AL-335+ODV±SMV for 6-8 weeks in treatment-naïve, HCV GT 1 or 3 infected patients with or without compensated cirrhosis. Efficacy, PK and safety data from completed cohorts are discussed. Emerging results from these and additional completed cohorts will be presented at the conference.

Results: Preliminary efficacy for 80 treatment naïve, GT 1 infected subjects without cirrhosis who have completed dosing are shown in the Table.

Cohort #	Dose			Dosing Duration (weeks)	Number (%) with undetectable* HCV RNA (EOT or SVR)
	AL-335 (mg QD)	ODV (mg)	SMV (mg QD)		
1	400	50 QD	100	8	20/20 (100%), SVR24
2	800	50 QOD	--	8	18/20 (90%), SVR12
3	800	50 QOD	75	8	20/20 (100%), SVR4
4	800	50 QOD	75	6	20/20 (100%), EOT

*Or below the limit of quantitation (N=2; Cohort 4 only)
EOT: end of treatment; QD: every day; QOD: every other day; RNA: ribonucleic acid;
SVR: sustained virologic response

AL-335+ODV±SMV was generally safe and well tolerated. The majority of adverse events (AEs) were mild, most commonly headache, fatigue, and upper respiratory tract infection. There was a single serious AE (Mobitz Type 1 2nd degree atrioventricular block in Cohort 1), which was attributed to treatment. This ECG abnormality was not associated with clinical or echocardiological abnormalities and resolved following treatment discontinuation. No clinically significant laboratory abnormalities were observed.
Consistent with prior studies, increasing AL-335 dose from 400 to 800 mg increased ALS-022227 (parent nucleoside of AL-335) exposure less than proportionally. Observed ODV and SMV exposures in Cohort 1 were higher than anticipated. Reducing ODV dosing from QD to QOD decreased ODV exposure proportionally. Reducing SMV dosing from 100mg to 75mg QD decreased SMV exposure less than proportionally.

Conclusions: AL-335+ODV±SMV for 6 or 8 weeks was well tolerated and highly effective in noncirrhotic patients with HCV GT 1 infection. Ongoing cohorts are evaluating this regimen in patients with HCV GT 3 infection and also GT 1 or 3 infected subjects with cirrhosis.

Disclosure of Interest: E. Gane: Consultant: Conflict with: Gilead, AbbVie, Merck, Janssen, Roche, Achillion, Novira, Alnylam, Sponsored lectures (National or International): Conflict with: Gilead, AbbVie, Merck, Alnylam, M. McClure: Employee: Conflict with: Alios BioPharma, D. Apelian: Employee: Conflict with: Achillion, C. Westland: Employee: Conflict with: Alios BioPharma, T. Kakuda: Employee: Conflict with: Alios BioPharma, S. Chanda: Employee: Conflict with: Alios BioPharma, L. Blatt: Employee: Conflict with: Alios BioPharma, L. Beigelman: Employee: Conflict with: Alios BioPharma, D. Smith: Employee: Conflict with: Alios, J. Fry: Employee: Conflict with: Alios BioPharma.

Screen 8: ABSTRACT-180

The risk of cardiovascular outcomes in HCV mono-infection, HCV-HIV co-infection and the impact of HCV-antiviral therapy: A Systematic Review

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Introduction: It is estimated that approximately 185 million people worldwide are infected with the hepatitis C virus (HCV) and that over 350 000 people die yearly from this viral infection. Recent studies have suggested that HCV may lead to an increased risk of cardiovascular outcomes. There is conflicting evidence to support this and it is unclear whether HCV-antiviral therapy impacts cardiovascular outcomes.

Aims: The objective of this study was to summarize the association between HCV-infection and cardiovascular outcomes and differentiate this risk based on HCV mono-infection and HCV- HIV co-infection. This study further evaluated the effects that HCV antiviral therapy, viral load and viral clearance have on modifying this association.

Material and Methods: A comprehensive systematic search of the literature was conducted using Medline and EMBASE publications between 1989 and October 2015 to identify all relevant studies. A qualitative analysis was performed to synthesize results.

Results: A review of the literature yielded 28 studies that met inclusion criteria. A subgroup analysis of only cohort studies favoured a positive association between HCV and the risk of a cerebrovascular outcome with most studies estimating at least a 20% increased risk of an event. A similar association was demonstrated with cardiovascular mortality. HCV treatment was associated with a 38-62% reduction in the risk of stroke and 23% reduction in the risk of acute coronary syndrome. Sustained virological response was associated with a 30% reduction in the risk of any cardiovascular outcome.

Conclusions: This study suggests that HCV increases the risk of cerebrovascular outcomes and cardiovascular mortality in HCV-infected participants. The literature in HCV-HIV infected is limited and less consistent. This study provides some evidence to

suggest that HCV-treatment may lead to improved cardiovascular outcomes. Additional well-designed prospective studies are needed to explore the association between HCV and cardiovascular outcomes based on viral load, genotype and co-infection. Further studies are needed to determine if the treatment benefits demonstrated with interferon-based regimens persist with the use of Direct Acting Antiviral therapies.

Disclosure of Interest: None Declared

Screen 9: YI-ABSTRACT-213

Virological failures to direct acting antivirals (DAAs) interferon-free regimens in real life show frequent resistance associated variants and may require re-treatment with unconventional strategies

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Aims: Aim of this study was to characterize, in a real life setting, the pattern of resistance-associated-substitutions (RASs) in failures to direct acting antivirals (DAAs).

Material and Methods: Among 340 patients (pts), 138 failed a DAA+IFN regimen, while 202 failed DAA-only therapies. Of the latter, 182 (GT1a-1b-2c-3a-4a/d/n/r=39-60-9-41-33; 65% treatment-experienced, 9 with NS3-inhibitors; 81% cirrhotic) with available resistance test at failure in NS3/NS5A/NS5B (by Sanger sequencing) were analyzed.

Results: The majority of pts experienced a virological relapse (81%), 12% had a breakthrough and 7% were non-responder; 89/182 (49%) failed a suboptimal/not-recommended regimen according to current guidelines, mainly: sofosbuvir (SOF)±ribavirin (RBV) (N=71), simeprevir (SMV) or asunaprevir (ASU)+daclatasvir (DCV)±RBV (N=12), paritaprevir/r+ombitasvir+dasabuvir (3D)+RBV (N=6: 5/1=GT3/2). Among 51% (93/182) failing a recommended regimen, the most common were: SMV+SOF±RBV (N=52), DCV/Ledipasvir(LDV)+SOF±RBV (N=21), 3D/2D±RBV (N=12).
8/182 (4.4%) failing pts had a misclassified genotype: in particular, of 7 previously classified as GT1, 5 were GT3a and 1 GT2c failing 3D±RBV, while another was GT4d failing ASU+DCV+RBV. Overall, 53% of pts showed at least one RAS related to the DAA-failure; RASs prevalence was significantly higher in breakthrough/non responders than in relapsers (94% *vs* 43%, p<0.001).
RASs related to the DAA-class at failure varied in prevalence according to the inhibitors used: 92% NS5A-RASs in NS5A-failing pts (N=51), 77% NS3-RASs in NS3-failures (N=82), 20% NS5B-RASs in SOF-failures (N=152) and 23% NS5B-RASs in dasabuvir-failures (N=17). Notably, 46% of pts treated with ≥2 DAA classes showed RASs on ≥2 DAA-targets, including 13/13 NS3-NS5A-failures, and 10/17 (59%) in 3D-failures. Overall, 13% of pts showed also resistance in a target out of DAAs used, probably due to natural resistance.

5/10 SOF breakthrough/non-responder pts showed the S282T RAS (3 GT4; 1 GT1b 1 GT3). Interestingly, the potentially SOF RAS L159F was found in 20/142 SOF-relapsers (35% GT1b, 9% GT3).

Conclusions: Due to natural RASs, HCV resistance test at failure should be recommended for all 3 genes (NS3/NS5A/NS5B). In a real life setting, RASs prevalence at failure was remarkably high and frequently in ≥2 DAAs-targets. This advocates for appropriate retreatments, sometimes based upon unconventional, more aggressive/prolonged, resistance-based regimens.

Disclosure of Interest: None Declared

Friday 23 September 2016
ePoster Session 5: 18:20 – 18:50

Screen I: YI-ABSTRACT-167

Enhancing detection and treatment of chronic Hepatitis C virus in vulnerable (homeless) adults through dedicated community liver clinics: preliminary results of VALID (Vulnerable Adults LIver Disease) study

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Introduction: Homeless adults, a vulnerable disenfranchised & stigmatised cohort, are particularly at risk of Hepatitis C virus (HCV) & chronic liver disease (CLD) due to high prevalence of alcohol & substance misuse. This vulnerable group don't engage with hospital services. Hence community strategies are needed to improve the detection of HCV related CLD in this special population.

Aims: We designed a community liver service in Southeast England, with an aim of detecting, staging & treating HCV related CLD in homeless adults aged ≥ 50 years.

Material and Methods: In October 2015, as part of a 2-yr cohort study, we set up a new service at a major homeless hostel & a primary care practice that caters to the homeless. We enrolled consecutive aged ≥50 yrs. Individuals were offered blood borne virus (BBV) tests, alcohol & substance misuse assessment and mobile Transient Elastography (TE). Clinically significant hepatic fibrosis (CSHF) was defined as liver stiffness measurement (LSM) ≥8 kPa.

Results: In the 7 months period 41 individuals were enrolled. Mean age of participants was 54.2 yrs + 3.7 & 83% were males. Twenty one (51%) were homeless or living in hostels at the time of recruitment. Positive HCV antibody was detected in 11 participants (27%),

while HIV & hepatitis B core antibody were found in one (2.4%) and four participants (9.7%) respectively. Ten out of 11 (91%) individuals with positive HCV antibody consented to further testing, eight (80%) having a positive HCV PCR. The prevailing genotype was 1a (75%). The majority (80.5%) were drinking alcohol excessively, the AUDIT questionnaire revealing that 24 individuals (59%) had alcohol dependence (score > 20/40). Thirty (73%) had history of substance misuse with 24 (58%) individuals having mental illnesses. Of the 41 participants, 12 (29%) had CSHF (LSM ≥8 kPa). The main aetiological factors for CLD in these 12 individuals were alcohol (6), HCV (2) or both (4). Of the 8 individuals with positive HCV RNA, one has commenced community based HCV treatment with direct acting antivirals with two more currently being worked up for therapy.

Conclusions: Preliminary results of VALID study show that about 30% of homeless adults have CSHF with chronic HCV infection being the aetiology for CLD in 50%. Till date there has been an excellent uptake of community based liver service by this cohort. Mobile TE was perceived as a powerful tool to facilitate engagement. Our initial results endorse the need for this easy to replicate model of liver care for vulnerable homeless elderly.

Disclosure of Interest: A. Hashim: None Declared, T. Worthley: None Declared, L. Macken: None Declared, G. P. Aithal: None Declared, S. Verma: Grant: Conflict with: Research Grants from Gilead, National Institute of Health Research (NIHR) and the Dunhill Medical Trust. Travel grants from Gilead, Janssen, BMS and Abbvie.

Cascade of care of HCV-infected patients identified through community pop-up clinics

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Introduction: Of the 18,000 residents living in Vancouver's Downtown East Side (DTES), over 70% are infected with HCV. Despite the availability of curative HCV therapy, only a minority of these individuals are receiving healthcare, much less treated for their HCV infection. We developed a model of community-based clinical interventions, offering point-of-care testing for HCV along with incentives to help increase engagement and retention in care.

Aims: Through this model, we sought to define the cascade of care for HCV infection. In particular, we wanted to determine what factors lead to long-term engagement in care and the potential feasibility of applying our model to other communities with an equally high prevalence of HCV infection.

Material and Methods: We developed a model known as "Community Pop-Up Clinics," or CPCs, held at various DTES sites once a week. They are led by a physician, a nurse, and four support personnel. Individuals wishing to receive HCV point-of-care testing are registered and provided with information about the OraQuick® HCV Rapid antibody test. As an incentive for their participation, a $10 gift card is provided. Individuals found to carry HCV antibodies are offered immediate on-site medical consultation and a follow-up appointment to address their medical, psychological, social, and addiction-related needs. CPC participants also complete a questionnaire to collect demographic, clinical, and knowledge-based information.

Results: To date, 2257 individuals have been evaluated at a CPC (>1/8 of the DTES population). Of these, 710 (31.5%) screened positive for HCV antibodies, including 53 (2.4%) co-infected with HIV. In total, 168 (23.7%) HCV-infected subjects have been engaged in care, most (80%) attending VIDC regularly. Of those engaged, the mean age

was 51.2 years, 138 (82.1%) were male, 16 (9.5%) First Nations, 33 (19.6%) homeless, and 120 (36.3%) were people who actively inject drugs on a daily basis. Of those receiving all-oral HCV treatment, SVR has been achieved in 93.8% cases, with only 2 treatment failures (one early discontinuation and one virologic relapse).

Conclusions: The CPC model applied to Vancouver's Downtown East Side has successfully identified over 700 HCV-infected individuals and engaged a significant percentage of them in care. Through the CPC pathway, many individuals who were not previously linked to care have progressed to HCV treatment and have been able to achieve SVR. This model has the potential to address the HCV pandemic in Vancouver's inner city and beyond.

Disclosure of Interest: None Declared

Screen 3: ABSTRACT-I70

Renal function evolution in patients infected with HCV and basal estimated glomerular filtration rate (GFRE) between 30–60 ml/min/1,73 m^2 treated with ombitasvir/paritaprevir/ritonavir and dasabuvir (3D) vs regimens based on sofosbuvir (SOF)

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Introduction: Guidelines and recommendations of the IFN-free regimens based on DAAs to treat chronic Hepatitis C (HCV), according to the renal function of the patient, only takes into consideration the contraindication of the Sofosbuvir use on patients with glomerular filtration rate (GFR) under 30 ml/min, due to its nephrotoxic effect and to the increase in the concentration of metabolites that increases side effects. However, there are not evidences with patients treated with SOF with a GFR between 30 – 60 ml/min, since this patient profile has not been studied in clinical development studies. On the other side, it has been studied with 3D but with limited evidence.

Aims: Determine the GFRe evolution on week 12 post-treatment vs. basal on patients with basal GFR between 30 – 60 ml/min treated with 3D with or without RBV or Sofosbuvir-based regimens with or without RBV.

Material and Methods: 43 HCV patients were studied with a basal GFRe between 30 – 60 ml/min measured by the MDRD4 formula. 8 patients were treated with 3D (5 of them with RBV), 35 with SOF (31 with Harvoni, 1 with RBV and 3 with Simeprevir). The GFRe was analyzed at week 12 post-treatment, so was the SVR.

Results: The change in GFR with the 3D regimen (basal vs 12w) was 56.6 ± 12.6 vs 51.7 ± 13.1 ml/min (ns), and with SOF 57.8± 14.7 vs 48.6 ± 11.1 ml/min (p=0.004). Patients

with a decrease over a 20% in GFRe vs basal, none of those were treated with 3D and 12 (34.3%) were treated with SOF. The proteinuria was measured on 14 patients, 1 on 3D and 13 on SOF. The proteinuria decreased more than 20% in the patient treated with 3D and 8 of 13 (61.5%) treated with SOF. Out of the total 26 patients, 10 patients showed a positive proteinuria and was not modified with the treatment, out of those only 3 had a proteinuria higher than 1 gr/mg. Only three patients showed hematuria.

Conclusions: 1.- Impaired renal function has been observed on those patients with a basal GFRe between 30-60 ml/min and treated with Sofosbuvir-based therapies (p=0.004) and not on those treated with 3D (ns). 2.- 34% of the patients treated with Sofosbuvir had over a 20% decrease in the GFRe vs basal. 3,. Neither the proteinuria nor the hematuria were corrected post treatment.

Disclosure of Interest: None Declared

Molecular recognition studies of dasabuvir, tegobuvir, and setrobuvir against natural hepatitis C Virus NS5B polymerase variants

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Introduction: Management of Hepatitis C virus (HCV) infection changed after development of direct-acting antiviral (DAAs), including NS5B polymerase inhibitors. However, several amino acid (AA) changes give rise to resistance-associated substitutions (RASs), which could lead to therapy failure.

Aims: We aimed at predicting the binding affinity of non-nucleoside inhibitors (NNI) such as dasabuvir (DSV), tegobuvir (TGV), and setrobuvir (STV) by molecular docking against NS5B polymerase, carrying 316N RAS (conferring resistance to DSV), in HCV1b isolates from a patients' cohort.

Material and Methods: Serum samples from 19 DAA-naïve patients infected by HCV were collected. NS5B region was sequenced by Sanger method, then genotype/subtype by subtyping tools, and phylogenetic analysis was determined. AA substitutions in NS5B sequences by Geno2pheno were investigated. *In silico* study started from the X-Ray models of NS5B deposited in Protein Data Bank. For each isolate, the mutants were generated by single-residue replacement and submitted to molecular dynamics simulations (MDs) using Desmond package. Molecular recognition studies were performed by means of Glide docking program and ΔEmodel variation (kcal/mol) was calculated between wild-type (WT) and mutated complexes.

Results: All patients were infected by HCV1b, median age was 61 years (range 46-71) and 13/19 were males. Surgery was the most frequent risk factor reported and treatment included NS3/4A and NS5A inhibitors. At the end of therapy, 14 patients had undetectable viremia, while 5 had a virological breakthrough. The 316N RAS was found

in 6/19 isolates and, among them, 2 were from patients with therapy failure. Concerning *in silico* study, DSV recognition ($\Delta Emodel_{Mutants}$= -0,23 kcal/mol) in 254K, 300T, 316N and 338A mutated complexes showed a thermodynamic profile similar to that of WT. Therefore these natural substitutions, outside NS5B polymerase active site, in presence of 316N RAS, did not affect binding affinity of DSV towards the mutated enzyme. Moreover, an opposite impact on TGV ($\Delta Emodel_{Mutants}$= -3,49 kcal/mol) and STV ($\Delta Emodel_{Mutants}$= +6,08 kcal/mol) molecular recognition against the enzyme were observed.

Conclusions: The 316N RAS and associated natural substitutions in HCV polymerase should be evaluated in patients who had virological breakthrough to previous treatment. The structural insights of these mechanisms may be useful to guide therapeutic approach with NS5B NNIs.

Disclosure of Interest: None Declared

Screen 5: ABSTRACT-I86

Using telemedicine to monitor patients on treatment of HCV infection in prison

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Introduction: Distance is a critical factor regarding the health services provided thorough Telemedicine. This factor must be understood not only as a geographical issue, but also responds to economic, social or security reasons, as occurs in prisons.

Aims: To perform a teleconsultation program (TCP) between the prison "El Dueso" and the HUMV hospital (Spain), devoted to monitor the anti-HCV therapy in the infected inmate population.

Material and Methods: In 1Q 2016 the TCP was established by the video collaboration tool "Reúnete-Red SARA", available to all public administrations in Spain. Patients answered an anonymous five-level Likert-type satisfaction questionnaire (1: strongly disagree, 2: disagree, 3: neither agree nor disagree, 4: agree, 5: strongly agree) composed of 11 questions: Question 1 (Q1), I was able to see the doctor through the screen; Q2, I was able to hear the doctor well through the speakers; Q3, The doctor could hear me without trouble; Q4, I felt comfortable talking to the doctor through the screen; Q5, When I started the consultation I was not more nervous than usual; Q6, During the consultation I was relaxed; Q7, I could explain what I wanted to the doctor; Q8, I understood the instructions the doctor gave me; Q9, I am in accordance with the timeliness of consultation; Q10, My privacy and confidentiality was respected; Q11, Overall, I am satisfied with the service received. Questions that scored > 4 points indicate high level of satisfaction.

Results: So far 85 teleconsultations have been performed (100% of treated patients). All patients answered the satisfaction questionnaire. The mode score was 5 (range: 1-5) with a mean score of 4.5 points (DE = 0.21). Audio channels and video teleconsultation

questions yielded satisfactory mean scores [Q1, 4.52 (DE = 0.60); Q3, 4.45 (0.84); Q9, 4.19 (1.32)]. Patients claimed to have been able to explain themselves clearly [Q7, 4.51 (1.17)] and they did understand the indications received by the doctors [Q8, 4.67 (0.46)]. Some patients were more nervous than usual at the beginning of teleconsultation [Q5, 4.04 (1.37)], although this did not prevent the successful development of the session and throughout the consultation they remained relaxed [Q6, 4.49 (1.22)]. Finally, patients thought teleconsultations respected the principles of confidentiality and privacy [Q10, 4.61 (1.35)].

Conclusions: Teleconsultation is a form of telemedicine well accepted by inmate patients. Their use for clinical monitoring of HCV treatments can be extended to other prisons.

Disclosure of Interest: None Declared

Screen 6: ABSTRACT-I88

Treatment of chronic hepatitis C treatment in real life: the new direct-acting antivirals

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Introduction: The new generation Direct-Acting Antivirals (DAA) revolutionized the Hepatitis C virus (HCV) treatment. Since 2015, DAA became available in Portugal due to a universal access policy.

Aims: Our aim is to assess the efficacy of DAA in clinical practice.

Material and Methods: We performed a retrospective study of chronic HCV patients treated with DAA between 01/2015 and 05/2016. The patients were identified in the Infectious Diseases and Gastroenterology databases. The primary outcome was "sustained virologic response" (SVR) and the secondary outcome was the adverse effects. We used the most appropriate measures of central tendency and of distribution according to the variable's distribution.

Results: From 1026 patients with chronic HCV, 756 started the DAA treatment, 611 ended the treatment and 519 completed 12 weeks after treatment evaluation.

From these 519 patients, 72.6% were men and 28.9% had co-infection with Human Immunodeficiency Virus (HIV). The median age was 52. Two-hundred and sixty-three (50.7%) patients were treatment naïve; the most frequent previous treatment was Pegylated interferon-ribavirin (242, 94.2%). Cirrhosis was prevalent in our population: 38.8%. The most frequent genotype was genotype 1 (71.6%) followed by genotype 3 (17.5%), 4 (10.4%) and 2 (0.4%). The majority of our patients received sofosbuvir-ledipasvir (73.4%); the other given treatments were: sofosbuvir-ledipasvir-ribavirin (15.8%), sofosbuvir-ribavirin (9.8%) and sofosbuvir-daclatasvir (1.0%). The duration of treatment was 12 weeks in 35.3% and 24 weeks in 64.7%. Not considering the HIV treatment

modifications, 10.9% needed to stop or change chronic medication due to interactions with the DAAs. The adverse effects with DAA were reported in 28.5%: the most frequent were headache, asthenia and nausea. Five-hundred and four patients (97.3%) had SVR at week 12 after treatment. From the 14 patients that did not cure the HCV infection, 4 had to stop the medication due to adverse events (2 severe anaemia, 1 alveolar haemorrhage, 1 acute renal failure), 4 did not have treatment compliance and in 6 the HCV infection relapsed after treatment. These patients with relapse did not have HIV co-infection, 3 had cirrhosis and were genotypes 1 (1 patient), 3 (4 patients) and 4 (1 patients).

Conclusions: Our results confirm in real life the efficacy and tolerability of these DAA treatments. Neither cirrhosis nor HIV co-infection seems to impact their high efficacy.

Disclosure of Interest: None Declared

Screen 7: ABSTRACT-I89

Interferon-free anti-HCV regimens in CKD patients: a single centre experience

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Introduction: HCV eradication before kidney transplantation prevents HCV reactivation under immunosuppression and improves long-term survival of kidney transplant recipients. Therefore, antiviral treatment should be considered in all kidney transplant candidates. However, optimal treatment strategies for chronic kidney disease patients (CKD) stage 4 and 5 with HCV infection are still being evaluated.

Aims: The aim of our study was to retrospectively assess safety and efficacy of interferon-free regimens in patients with CKD stage 4 and 5, enlisted for kidney transplantation.

Material and Methods: We evaluated 19 CKD (2 and 17 CKD stage 4 and 5, respectively) patients treated for chronic HCV infection, 12 males and 7 females, of average age of 52 years. 15 patients had HCV genotype (GT) 1 (13 GT 1b, 2 GT 1a), 4 patients were infected with GT 3a. The mean initial viremia was 2.14x106 IU/ml (range 3.11x104 –1.11x107 IU/ml). Eleven patients were treatment-naive, 8 treatment-experienced. The stage of liver fibrosis was assessed by shear-wave elastography in 18 patients, 7 of whom had fibrosis stage F1, 2 stage 2, 1 stage F3 and 8 patients had cirrhosis (F4). The regimen choice depended on actual local availability of the antivirals. 11 patients were treated with sofosbuvir (SOF, daily dose 200 mg) in combination with simeprevir (SIM, 150 mg/day, 4 patients with GT 1b) or daclatasvir (DCV, 60 mg/day, 7 patients: 2 with GT 1a, 1 GT 1b and 4 GT 3a). Anitiviral combination ombitasvir/paritaprevir/dasabuvir (3D) was administered to 8 patients including 2 patients with CKD4. We did not use ribavirin (RBV) in any antiviral regimen in order to increase treatment tolerability. Sustained virological response (SVR) was assessed 12 weeks after the end of therapy.

Results: The 12-week treatment period was completed in all 19 patients. All patients

achieved HCV RNA negativity on treatment (15 at treatment week 4, 4 at week 8) and all patients achieved SVR12 (100%) irrespectively of GT, fibrosis stage and the treatment used. The only two reported serious adverse events were not related to anti-HCV medication (1 infectious endocarditis, 1 arteriovenous phistula occlusion). 4 patients reported nausea, 1 presented with diarrhoea possibly related to administered medications. No significant progression of anaemia was observed.

Conclusions: In conclusion, our data suggest that the reduced dose of SOF in combination with DCV or SIM as well as 3D antiviral regimen are highly effective and may be safely used in CKD patients even without RBV.

Disclosure of Interest: S. Fraňková: Consultant: Conflict with: Gilead, Abbvie, MSD, BMS, Janssen, Sponsored lectures (National or International): Conflict with: Gilead, Abbvie, MSD, BMS, Janssen, R. Šenkeříková: None Declared, O. Viklický: None Declared, J. Špičák: None Declared, D. Merta: None Declared, J. Šperl: Grant: Conflict with: Gilead, Consultant: Conflict with: Gilead, Abbvie, MSD, BMS, Janssen, Sponsored lectures (National or International): Conflict with: Gilead, Abbvie, MSD, BMS, Janssen.

Screen 8: ABSTRACT-I90

Treatment of chronic hepatitis C in human immunodeficiency virus infected patients with new generation direct-acting antivirals – real-life data from a Portuguese centre

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Introduction: The Direct-Acting Antivirals (DAA) revolutionized the Hepatitis C virus (HCV) infection treatment. Since 2015, DAA became available in Portugal due to a universal access policy. Its use in Human Immunodeficiency Virus (HIV) infected patients has some peculiarities, specially due to drug interactions.

Aims: Our aim is to assess the DAA efficacy in real life, to address the interactions between the HCV-HIV treatments and to monitor fibrosis, transaminases and alpha-fetoprotein (AFP) changes with treatment.

Material and Methods: We performed a retrospective study of HCV-HIV patients treated with DAA between 02/2015 and 05/2016. The primary outcome was "sustained virologic response" (SVR) at week 12 after treatment and the secondary outcomes were changes in fibrosis, transaminases and AFP. We used the most appropriate measures of central tendency/distribution and statistical test.

Results: We included 211 patients that completed 12 weeks after treatment evaluation (from 402 patients with chronic HCV-HIV, 275 started the DAA treatment). Eighty-nine percent (188) were men and the mean age was 45.8 (SD 6.4). The majority acquired the infection through drug abuse (91.5%) and 64% were HCV treatment naïve. The most frequent HCV genotype was 1 (78.7%), followed by 3 (10.9%). The cirrhotic rate was 29.9%.
Concerning the HIV treatment, 208 (98.6%) patients were on treatment. In 68 patients (32.7%) the HIV treatment had to be changed due to drug interactions: efavirenz (36.8%), boosted atazanavir (27.9%), boosted lopinavir (23.5%), nevirapine (8.8%) and boosted elvitegravir (1.5%). The patients changed the HIV treatment to raltegravir, rilpivirine, boosted darunavir or dolutegravir.

Regarding HCV treatment, the majority did sofosbuvir/ledipasvir (86.3%), followed by sofosbuvir/ribavirin (8.1%) and sofosbuvir/ledipasvir/ribavirin (5.7%). The duration of treatment was 12 weeks in 51.2% and 24 weeks in 48.8%.
Our SVR rate was 97.6% (206 patients cured the infection): 4 patients did not cured the infection owing to lack of adherence and in one patient the treatment was stopped (acute renal failure).
There were no statistically significant differences in the HIV viral load or CD4 count during the treatment (Friedman test).
The elastography stiffness, AFP and transaminases decreased in a statistically significant manner comparing before and after treatment (Wilcoxon test).

Conclusions: Our results confirm in real life the efficacy of these DAA with improvement of fibrosis, hepatic cytolysis and AFP.

Disclosure of Interest: None Declared

Screen 9: ABSTRACT-I92

Circulating microRNAs as noninvasive biomarkers for the detection of different stages of liver fibrosis in Egyptian HCV patients

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Introduction: In liver fibrosis, miRNAs play an essential role in activating HSCs proliferation, differentiation and migration. To study regulation of genes at the miRNA level is a huge advantage as gene expression, is regulated at an epigenetic level before even proteins get formed.

Aims: The aim of the study is to develop a non-invasive diagnostic tool based on measuring the serum levels of different miRNAs in order to detect HCV-induced liver fibrosis at the early stages of the disease.

Material and Methods: Subjects of the current study included 36 cases of chronic hepatitis C (CHC) with early stage of fibrosis, 35 cases of CHC with stage 4 of fibrosis admitted to department of hepato-gastroenterology, TBRI. Fifteen subjects were included as normal controls. Five main miRNAs (miR-214, miR-221/222, miR-9, miR-125b, miR-128) were measured using real-time reverse transcription-polymerase chain reaction.

Results: Circulating levels of miR-214, miR-221/222, miR-9, miR-125b, miR-128 were significantly increased ($P < 0.01$) incases of both CHC with early stage of fibrosis and CHC with stage 4 compared to control group. Also, there was a significant increase ($p < 0.01$) in CHC with stage 4 of fibrosis group versus CHC with early fibrosis group.

Conclusions: Our data suggest that circulating miRNAs could serve as novel biomarkers for the detection and assessment of liver fibrosis.

Disclosure of Interest: None Declared

Impact of HCV1a migration patterns on the public health policy regarding genotyping of the Q80K resistance-associated variant in Italy

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Introduction: Viral factors can impair the efficacy of direct-acting antiviral (DAA) based therapies for the hepatitis C virus (HCV). An important example is the naturally occurring and highly prevalent Q80K variant in the NS3 gene, which can interfere with the action of simeprevir.

Aims: Italy has a comparatively high HCV prevalence among Western European countries, such that the public health impact of the Q80K variant may be more pronounced. This motivated us to initiate a study relating the Italian HCV1a epidemic with that in other countries, with the emphasis on the migration patterns of the Q80K variant.

Material and Methods: Newly generated NS3 sequence data from 183 HCV1a Italian patients were complemented with publicly available time and geo-referenced virus genetic data from around the world. An integrated Bayesian inference approach was used to

elucidate the population level transmission patterns through time and space using a model that allows for different migration rates depending on the direction of movement.

Results: The NS3 polymorphism Q80K revealed to be highly abundant in one of the two clades in which HCV1a segregates, but is rarely observed in the other clade. The high Q80K prevalence in this clade can be traced to a single origin in the United States. From there it spread globally, including to several European countries. This variant was introduced in Italy around 1960. Phylogeographic reconstructions also show that seeding into Italy was initially dominated by the US, but its relative importance declined in favour of introductions with a European continental origin. Italy also acted as a hub for the onward HCV1a dissemination within Europe, which can involve Q80K strains. An exploration of the within-country migration patterns revealed mixing of strains between North, Central and South Italy, which suggests that the Italian epidemic is quite uniform and does not evolve in local subepidemics.

Conclusions: We find indications that immigration and national circulation, both in complex patterns, fuel the Italian HCV1a epidemic. This precludes a clear differentiation between HCV1a patients at risk to acquire the NS3 variant Q80K. In turn, this implies that genotyping should not target specific groups, but that it may be cost-effective to test all HCV1a patients eligible for therapy with simeprevir for the absence of the Q80K polymorphism.

Disclosure of Interest: None Declared

Screen I: ABSTRACT-251

Low rate of drug-drug interaction management during interferon-free simeprevir therapy - An integrated analysis of interventional and observational clinical studies

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Introduction: The widespread use of direct acting antivirals (DAA) for chronic hepatitis C has raised the question of the clinical relevance of drug-drug interactions (DDI) with frequently prescribed medications.

Aims: To investigate the impact of known or potential pharmacokinetic (PK) interactions between the hepatitis C virus (HCV) protease inhibitor simeprevir (SMV) and concomitant medications on DDI management and safety profile.

Material and Methods: We pooled data across 9 prospective clinical studies of SMV in interferon-free combinations in HCV patients treated for ≥12 weeks (n=876). Subjects who started antihypertensive (AHD), anxiolytic (AXD), or lipid-lowering drugs (LLD) prior to SMV therapy were grouped based on known DDI profiles of the concomitant drug relative to SMV (Liverpool DDI database, SMV Summary of Product Characteristics): "green" (no interaction) or "amber" (known/potential interaction). Safety was investigated

during SMV treatment (12 weeks). Outcomes of co-administration were assessed during screening and SMV treatment (12 weeks) using a composite endpoint of discontinuation, interruption, or dose modification of the concomitant medication.

Results: 409 (47%), 153 (17%), and 96 (11%) subjects were on any AHD, AXD, or LLD, respectively. Subjects represented a diverse population (female 34%-41%; black/African American 14%-27%; cirrhosis 37%-49%) with high numbers of concomitant medications (10+: 22%-46%). The rate of meeting the composite endpoint was generally low. Subjects on green and amber AHDs had similar outcomes. Numerical differences were seen between green and amber AXD and LLD (Table 1). Discontinuations of amber drugs often occurred prior to or on day 1 of SMV therapy (7/14 amber AHD; 6/15 amber AXD; 3/7 amber LLD). Most amber AHD dose modifications were single changes (6/10) with subsequent discontinuation in 1 patient. Dose changes of amber LLDs were single dose reductions of statins which mostly (5/7) occurred prior to or on day 1 of SMV therapy with 1 subsequent discontinuation. SMV treatment was generally well tolerated with very low rates of discontinuations. No relevant differences in the frequency of AEs and SAEs at least possibly related to SMV were observed.

Conclusions: In this population with a high prevalence of advanced liver disease and polypharmacy, co-administration of AHD, AXD, and LLD with known/potential PK DDIs with SMV did not result in relevant DDI management needs or an increased risk of SMV-associated AEs.

Figure:

Table 1 Outcomes

	Antihypertensives		Anxiolytics		Lipid-lowering	
DDI population (subjects with both green AND amber drugs were counted in both groups)	**N=409**		**N=153**		**N=96**	
	Green AHD n=357 (87%)	**Amber AHD n=157 (38%)**	**Green AXD n=32 (21%)**	**Amber AXD n=127 (83%)**	**Green LLD n=42 (44%)**	**Amber LLD n=67 (70%)**
Composite Endpoint	38 (10.6%)	22 (14.0%)	1 (3.1%)	17 (13.4%)	3 (7.1%)	13 (19.4%)
Permanent stop	26 (7.3%)	14 (8.9%)	1 (3.1%)	15 (11.8%)	3 (7.1%)	7 (10.4%)
Dose change	20 (5.6%)	10 (6.4%)	0	3 (2.4%)	0	7 (10.4%)
Dose interruption	2 (0.6%)	0	0	0	0	0
Safety population (subjects with both green AND amber drugs were counted only in the amber group)	**N=403**		**N=149**		**N=91**	
	Green AHD n=251 (62%)	**Amber AHD n=152 (38%)**	**Green AXD n=26 (17%)**	**Amber AXD n=123 (83%)**	**Green LLD n=27 (30%)**	**Amber LLD n=64 (70%)**
Subjects with at least one adverse event at least possibly related to SMV (AE)	93 (37.1%)	67 (44.1%)	9 (34.6%)	49 (39.8%)	11 (40.7%)	21 (32.8%)
Subjects with Grade 3/4 AEs at least possibly related to SMV	4 (1.6%)	2 (1.3%)	0	1 (0.8%)	0	0
Subjects with a serious AE at least possibly related to SMV	1 (0.4%)	0	0	0	0	1 (1.6%)
Discontinuation of SMV due to AEs	3 (1.2%)	1 (0.7%)	0	0	1 (3.7%)	0

Disclosure of Interest: F. Marra: Consultant: Conflict with: abbvie, gilead, bms, merck, Sponsored lectures (National or International): Conflict with: abbvie, gilead, bms, merck, janssen, C. Höner zu Siederdissen: Grant: Conflict with: Gilead (travel grant), Sponsored lectures (National or International): Conflict with: Gilead, Roche, MSD, S. Khoo: Grant: Conflict with: ViiV, Merck, Janssen, Sponsored lectures (National or International): Conflict with: Gilead, Merck, Viiv, M. Cornberg: Grant: Conflict with: Roche, Consultant: Conflict with: Abbvie, Bristol-Myers Squibb, Gilead, MSD Sharp & Dohme, Janssen-Cilag, Roche, Sponsored lectures (National or International): Conflict with: Abbvie, Bristol-Myers Squibb, Gilead, MSD Sharp & Dohme, Janssen-Cilag, Roche, Falk, M. Schlag: Employee: Conflict with: Janssen, S. Ouwerkerk-Mahadevan: Employee: Conflict with: Janssen, C. Bicer: Employee: Conflict with: Janssen, I. Lonjon-Domanec: Employee: Conflict with: Janssen, W. Jessner: Employee: Conflict with: Janssen, M. Beumont-Mauviel: Employee: Conflict with: Janssen, R. Kalmeijer: Employee: Conflict with: Janssen, D. Back: Grant: Conflict with: Abbvie, BMS, Gilead, Janssen, Merck, Viiv, Consultant: Conflict with: Merck, Janssen, Viiv, Sponsored lectures (National or International): Conflict with: Abbvie, BMS, Gilead, Janssen, Merck, Viiv, F. Glaue: None Declared

Screen 2: ABSTRACT-I95

Sofosbuvir plus ribavirin for treatment of cirrhotic HCV patients genotype-4

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Introduction: Egypt has the highest hepatitis C virus prevalence in the world. Sofosbuvir is a new highly effective drug for treatment of hepatitis C virus (HCV) infection. Compared to previous treatments, sofosbuvir-based regimens provide a higher cure rate, fewer side effects, and a two- to four-fold reduced duration of therapy.

Aims: to evaluate the antiviral efficacy, safety, and tolerability of sofosbuvir (SOF) plus ribavirin (RBV) in Egyptian patients with liver cirrhosis due to chronic hepatitis C virus (HCV) infection.

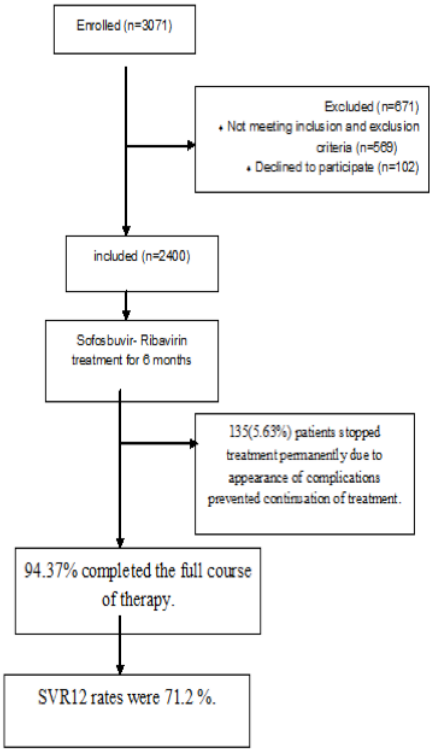
Material and Methods: We studied 2400 cirrhotic Egyptian patients with chronic HCV infection treated with dual therapy with Sofosbuvir and ribavirin for 24 weeks. Efficacy was determined by assessment of serum HCV RNA. Any adverse events during treatment were recorded.

Results: 2400 cirrhotic egyptian patients with chronic HCV infection treated with sofosbuvir and ribavirin for 24 weeks were enrolled in the study, their mean age (SD) was 53.9±6.5 years, 64.54 % were males, they were all cirrhotics, 3.41% were treatment-experienced; baseline mean HCV RNA was 4.33 x 10^6 IU/ml. Overall, 94.37% completed the full course of therapy. Overall, SVR12 rates were 71.2 %. The most common adverse events were fatigue, myalgia, headache, insomnia, and anemia. 135 patients stopped treatment permanently due to appearance of complications prevented continuation of treatment (44 cases with hepatic encephalopathy with sever elevated bilirubin and 91 cases with ascites).

Conclusions: Sofosbuvir and ribavirin is safe and effective treatment for HCV genotype-4 patients with liver cirrhosis. However, further studies are needed to establish treatment regimen for this population with a higher SVR rates.

Figure:

Figure 1 Flow diagram of Sofosbuvir-ribavirin therapy in HCV - genotype 4 cirrhotic patients:



n, number of patients.

Disclosure of Interest: None Declared

Screen 3: ABSTRACT-I96

Testing for blood borne viruses in the emergency department of a large London hospital

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Introduction: Novel therapies against hepatitis C virus (HCV) have recently been licensed but access to treatment may be limited due to a high proportion of undiagnosed infection. UK national HCV and hepatitis B virus (HBV) seroprevalence is estimated at 0.4% and 0.3% respectively but this conceals hotspots of high seroprevalence and local data are lacking.

Aims: The aim was to identify local HCV and HBV seroprevalence.

Material and Methods: This was an opt-out blood borne virus (BBV) testing program in the emergency department (ED) of a large London hospital. Individuals of age 16-65 years accepted either routine BBV testing (HCV, HBV, HIV) or a standalone HIV test. Assays were performed for anti-HCV IgG, HBV surface antigen (HBsAg) costing £3.50 and £3.60 and respectively, and HIV-1/-2 antibody/antigen.

Results: Of 13248 ED attendees over 29 weeks, 2865 (21.6%) accepted BBV screening; 1073 (8.1%) accepted a standalone HIV test; 3938 (29.7%) therefore tested for HIV. Numbers positive for anti-HCV, HBsAg and HIV are shown in the Table. The positive test cost for anti-HCV and HBsAg was £193 and £938, respectively.

Table. Seroprevalence of anti-HCV, HBsAg and HIV for 2865 ED attendees

	Anti-HCV	HBsAg	HIV
Total no. of positive tests	**52 (1.8)**	**11 (0.4)**	**20 (0.5)***
Previously known diagnosis (at other centres)	29	4	11
Confirmed new diagnosis	4	3	7
Other – including patients not yet contacted	18	4	2
Negative on repeat testing	1	0	0

Brackets denote %. * for 3938 (2865+1073) attendees.

Conclusions: Low numbers were tested for BBV, although we could not determine if this was due to low uptake or offer of testing. Local seroprevalence of HCV infection was 4.5 times the national average, but comparable for HBV and HIV. Results were limited by the difficulty in contacting many of those diagnosed with a BBV positive test to confirm previous testing. Further work is required on the cost effectiveness of universal screening for HCV in ED and other non-traditional settings.

Disclosure of Interest: None Declared

Screen 4: ABSTRACT-I99

Clinical and immunological effect of direct acting antivirals in patients with hepatitis C virus-associated cryoglobulinemic vasculitis

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Introduction: Direct-acting antivirals (DAAs) have dramatically changed HCV therapy. However, experience in patients with HCV-cryoglobulinemic vasculitis (CV) is limited.

Aims: To evaluate clinical and immunological outcomes in subjects with circulating cryoglobulins (CC) undergoing interferon-free regimens.

Material and Methods: Prospective and single center study in HCV patients with CC treated with DAAs. Patients were grouped into asymptomatic with cryoglobulins (ACC) and patients with CV. Complete immunological response (CIR) was defined by complement normalization and cryoglobulins negativization 12 weeks after the end of therapy. Among those with CV, clinical remission was considered complete if BVAS (vasculitis disease activity score) was 0 or all affected organs improved, and partial if BVAS was <50% from baseline.

Results: 65 patients were included, 36 CV and 29 ACC. The groups did not differ in age (median 61 years), genotype (83% G1b), non-response to previous therapy (50%) or antiviral regimen [3D (33%) and LDV/SOF (29%)]. Female gender was more common in CV group (72% vs 48%) and cirrhosis in ACC group (69% vs 47%). CV patients showed significantly elevated rheumatoid factor (RF) (80 vs 20 IU/mL, p=0.01) and lower C4 complement (0.02 vs 0.06 g/L, p=0.01). No significant differences between the 2 groups were observed in cryoglobulin levels (3 vs 2.3 %, p=0.1). Among CV, most common manifestations were asthenia (70%), purpura (66%), polyneuropathy (50%), arthralgia (31%) and renal involvement (22%). SVR rate was 92% (CV: 92% and ACC: 93%).

Cryoglobulins and C4 improved equally in both groups, but RF fall was greater in CV (-25 vs 0 IU, p=0.03). CIR was similarly achieved in both groups (36% vs 48%, p=0.3). Cryoglobulins >2.7% at baseline was associated to non CIR (OR=6.7, IC95 2.2-20.1, p=0.01). All but 7 patients achieved clinical remission (complete: 69%, partial: 11%) with median BVAS score falling from 8 (4-12) to 3 (0-3) (p<0.01). Purpura and arthralgia disappeared in 90% (32/35) of patients and renal and neurological symptoms improved in 75% (6/8) and 77% (14/18) of subjects, respectively. Corticosteroids could be reduced in 75% (9/12) of subjects.

Conclusions: Despite a short follow-up, 42% of patients with HCV and CC achieved a CIR after SVR. Higher baseline cryoglobulin level (>2.7%) was the only independent factor related to nonresponse. SVR was associated with clinical improvement in a great proportion of CV patients (80%).

Disclosure of Interest: M. Bonacci: None Declared, J. Hernandez Rodriguez: None Declared, M. Londoño: Consultant: Conflict with: Gilead, Jansen, BMS, Z. Mariño: None Declared, P. Gonzalez: None Declared, J. Sachez Tapias: None Declared, M. Ramos Casals: None Declared, X. Forns: Consultant: Conflict with: Gilead, Jansen, Abbvie, S. Lens: Consultant: Conflict with: Gilead, Jansen, Abbvie.

Screen 5: ABSTRACT-200

Inpatients with chronic HCV infection, antiviral treatment with DAAs can be managed by specialized nurses. Results of a large real-life cohort

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Introduction: The availability of effective DAAs for the treatment of chronic HCV infection has resulted in a major increase of the number of patients susceptible to benefit from these new therapeutic approaches. Many of these patients have advanced liver disease and require rapid access to antiviral treatment. Therefore, innovative strategies are needed to optimize patient management, cope with large cohorts of patients and accelerate treatment initiation.

Aims: The objective of this study was to compare the management of selected HCV patients treated with DAAs between hepatologist physicians and specialized nurses in a tertiary care center.

Material and Methods: 548 patients, candidates for all-oral DAA regimens, were prospectively allocated to treatment supervised either by a hepatologist physician (n=261, group P) or a specialized nurse (n=287, group N). Key exclusion criteria were Child C cirrhosis, hepatocellular carcinoma, or severe comorbidities. Cirrhosis was defined by FibroScan score>12.5 kPa, or FibroTest score>0.75. Patients received all-oral regimens according to international guidelines, including mainly SOF+DCV±RBV (56.6%), SOF+LDV±RBV (25%) or SOF+SIM±RBV (11.9%).

Results: 60.6% of patients were male and median age at DAA treatment initiation was 59.4. Cirrhosis was present in 47.1%; 30 patients were Child B; median MELD score was 6. 10.8% of patients were organ-transplanted. 13.9% had renal failure, 17.9% diabetes and 37.8% hypertension; 1.1% had HCV-HIV co-infection. HCV genotype 1 was predominant (61.2%), followed by genotypes 4 (17.7%), 3 (13.3%), 2 (5.9%), 5 (1.1%) and 6 (0.7%). 46.4% of patients were naive of treatment. 86.1% were treated for 12w and 13.9% for 24w. There were no significant differences in baseline characteristics

and treatment duration between groups P and N. Overall, SVR12 rate was 92.7% (91.2%, group P vs 94.1%, group N). Premature treatment discontinuations occurred in 1.8% (1.9 %, group P vs 1.7%, group N). Severe adverse events were observed in 3.5% (4.3%, group P vs 2.8%, group N). Death during treatment period was reported in 0.9% (1.5%, group P vs 0.3%, group N). Loss to follow up (1.8% in the overall population) was significantly more frequent in group P (3.4%) than in group N (0.3%) (p=0.008).

Conclusions: This study in a large real-life cohort shows that all-oral DAA regimens can be safely and successfully managed by specialized nurses. This strategy may accelerate DAA treatment access for all HCV patients.

Disclosure of Interest: None Declared

Screen6: YI-ABSTRACT-204

High SVR4 in the treatment of chronic HCV genotype 4 patients with sofosbuvir and daclatasvir (both generic)

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Introduction: Hepatitis C virus (HCV) is a major medical problem in Egypt, with genotype 4 the prevalent genotype. The introduction of the new oral directly acting antiviral drugs in the national treatment program in Egypt since late 2014 was a great achievement.
According to EASL guidelines 2015, patients with genotype 4 maybe treated with daily combination of Sofosbuvir/Daclatasvir with or without ribavirin for 12 or 24 weeks in treatment naïve and treatment experienced patients.

Aims: We evaluated the safety and efficacy of Sofosbuvir with Daclatasvir with or without ribavirin in Egyptian chronic HCV patients.

Material and Methods: This multicentre study included 102 patients with evidence of chronic HCV infection for more than 6 months. All patients received Sofosbuvir (Sofolanork, Mash premiere) 400 mg plus Daclatasvir (Daklanork, Mash premiere) 60 mg with or withour Ribavirin for 12 or 24 weeks according to EASL guidelines. The end point was a sustained virological response at 4 (SVR4) and 12 (SVR12) weeks post treatment.

Results:

	Number and percentage
Mean Age	50.45
Male/Female	66/36
Prior treatment experience	13 (12.7 %)
Cirrhotics	34 (33.33 %)
Sof/Dacla 12 weeks	61 (59.8 %)
Sof/Dacla/Riba 12 weeks	31 (30.4 %)
Sof/Dacla 24 weeks	2 (1.96 %)
Sof/Dacla/Riba 24 weeks	8 (7.84 %)
SVR 4	102 (100 %)
SVR 12	24/24

In our 102 patients, 13 (12.7%) were treatment experienced, 66 (64.7%) were males and 34 (33.3%) were cirrhotics. Most of our patients (61 patients [59.8 %]) received Sofosbuvir and Daclatasvir for 12 weeks while in 31 cirrhotic patients (30.4 %) Ribavirin was added. 2 (1.96 %) Cirrhotic patients were treated with Sofosbuvir and Daclatasvir for 24 weeks as they were intolerable to ribavirin while 8 (7.84 %) relapser patients on previous Sofosbuvir containing regimen were treated with Sofosbuvir, Daclatasvir and Ribavirin for 24 weeks.
All patients were followed up where all of them attended their week 4 post treatment visit with a negative HCV RNA achieving SVR4 while only 24 of them reached the date of their week 12 post treatment visit also with negative HCV RNA achieving SVR12
Sofosbuvir and Daclatasvir were well tolerated; most adverse events were mild in severity and included fatigue and headache while Ribavirin side effects included mainly anaemia and this was managed efficiently with dose reduction.

Conclusions: The use of generic products of Sofosbuvir and Daclatasvir with or without ribavirin is an extremely effective and well tolerable treatment for Egyptian chronic HCV patients.

Disclosure of Interest: None Declared

Screen 7: YI-ABSTRACT-209

HCV eradication is not associated with drop-out due to HCC progression in patients awaiting liver transplantation: a monocentric experience

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Introduction: Recently it has been open a debate on the hypotesis that the loss of intrahepatic immune surveillance, due to viral eradication with Direct Antiviral Agents (DAAs), may be associated with increased recurrence of HCC in HCV patients who previuously achieved complete response. However, data on the impact that this may have in terms of drop-out in HCV patients with HCC awaiting for liver transplantation (LT), are lacking.

Material and Methods: All HCV patients with HCC listed for LT between 01/2015 and 05/2016, and successfully treated with DAAs achieving sustained virological response, were retrospectively evaluated (cases). For each patient severity of liver disease and HCC characteristics were taken into account. A group of naive patients listed for HCV-related cirrhosis and HCC, with similar liver disease stage and HCC characteristics were also enrolled (controls).

Results: Fourty-one patients were enrolled (23cases/18controls); HCC characteristics at time of listing for LT were comparable between the 2 groups: median number of HCC nodules was 2.26 (range 1-6) in cases group vs 2.0 (range 1-5) in controls group (p=0.3); median nodule's diameter was 25mm (range 8mm-52mm) in cases group vs 24mm (10mm-53mm) in controls group (p=0.2). Median follow-up was 200 days (range 30-527), during which 2/23 (8.7%) and 2/18 (11%) drop-out events due to HCC progression between cases and controls were respectively registered (p=0.2).

Conclusions: Viral eradication doesn't seem to be associated with increased risk of drop-out due to neoplastic disease progression in HCV patients awaiting LT.

Disclosure of Interest: None Declared

HCV direct–acting drugs in real life: results of a French single-center cohort

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Aims: To report the efficacy and safety of oral combinations of direct antiviral agents (DAA) given for chronic hepatitis C in our tertiary reference center.

Material and Methods: Data from patients receiving DAA in our center were collected retrospectively and prospectively from January 2015 – date of establishment of multidisciplinary consultation meetings. Sustained virological response (SVR) was defined as an undetectable HCV viral load 3 months after end-of-treatment.

Results: Between November 2013 and May 2016, 996 DAA-based treatment lines were initiated: 40% (n = 399) of the DAA combination contained sofosbuvir + ledipasvir, 29% (n = 293) sofosbuvir + daclatasvir, 11% (n = 109) sofosbuvir + simeprevir, 6% (n = 59) ombitasvir + ritonavir + paritaprevir +/- dasabuvir (2D +/- 3D), 5% (n = 48) sofosbuvir + ribavirin and 0.7% (n = 7) grazoprevir + elbasvir. Cirrhosis was present in 40% (n=400) of patients and 58% (n=578) were treatment-naive. Ribavirin was included in 38% (n=376) of DAA combinations. The proportion of patients with cirrhosis decreased over time: 69% in 2014, 29% in 2015 and 17% in 2016. 24 (2.4%) patients were lost of follow-up. The overall SVR rate was 91.6% and increased over time with the evolution of combinations and the reduction of patient's severity. 12 (1.2%) patients died under treatment or within 3 months after end-of-treatment: 4 patients died from a liver-related complication (hepatocellular carcinoma, end-stage liver disease, acute liver failure), 3 patients from sepsis, 2 patients from hemorrhagic stroke and 3 patients with risk factors of cardiovascular disease from unexplained sudden deaths. 35 patients who failed a first DAA-based regimen were retreated empirically according to EASL recommendations. Among the 24 patients who reached 3 months after end-of-treatment, all (100%) achieved SVR.

Conclusions: In a single tertiary centre, SVR rate of DAA was 90%. The empirical retreatment of patients after a first DAA regimen failure is promising since no failure after second line have been yet observed. Prevalence of cirrhosis decreased over time. Risk of severe side effects must not be neglected with 1.2% of deaths, among them a third were related to unexplained sudden deaths.

Disclosure of Interest: L. Anne: None Declared, L. Kramer: Consultant: Conflict with: Gilead, Other: Conflict with: Abbvie, Gilead, P. Sultanik: None Declared, P. Tremeaux: None Declared, J.-F. Meritet: None Declared, A. Vallet-Pichard: Other: Conflict with: Gilead bms MSD abbvie roche janssen, H. Fontaine: None Declared, V. Mallet: None Declared, P. Sogni: None Declared, A. Rosenberg: None Declared, S. Pol: Grant: Conflict with: BMS, Gilead, Roche, MSD, Consultant: Conflict with: GSK, BMS, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Sanofi, Novartis, Vertex, Abbvie, Sponsored lectures (National or International): Conflict with: GSK, BMS, Boehringer Ingelheim, Janssen Gilead, Roche, MSD, Sanofi, Novartis, Vertex, Abbvie.

Screen 9: ABSTRACT-221

Safety and effectiveness of 12 and 24-week regimens of ledipasvir/sofosbuvir (LDV/SOF) in treatment experienced genotype 1 cirrhosis: interim analysis HCV-target, a prospective, observational study

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Introduction: Several all-oral regimens are available for the treatment of patients with chronic HCV.

Aims: The aim of this study is to evaluate the safety and effectiveness of LDV/SOF +/- RBV for 12 or 24 weeks in treatment experienced, Genotype 1 patients with cirrhosis treated as part of routine clinical practice and followed in HCV-TARGET (HCVT), a multicentre, prospective, observational cohort study.

Material and Methods: Patients who initiated HCV treatment were enrolled and treated according to the regional standards of care at academic (n=38) and community medical centres (n=13) in North America (n=47) and Europe (n=4). Information was collected from the medical records and abstracted into a unique centralized data core. Independent data monitors review data entries for completeness and accuracy. Demographic, clinical, adverse events (AEs) and virological data were collected throughout treatment and post-treatment follow-up.

Results: The data are current through June 14, 2016; 631 experienced, GT1 patients with cirrhosis started treatment with LDV/SOF+/-RBV (15 remain on treatment). 22 (3.5%) discontinued treatment early; 9 due to AE (1%), and 2 due to virological failure (<1%). Of the 594 who completed treatment to date, 27 remain in post treatment follow up and 14 were lost to follow up. 536 patients completed either 12 or 24 weeks of LDV/SOF +/- RBV and have virological outcomes and make up the efficacy reporting population. **Efficacy:** SVR12 for the 12 and 24 week groups combined was 94% (390/412); 12-wks 98% (44/45) and for 24-wks 94% (346/367). Among patients treated with the addition of RBV, SVR12 for the 12 and 24 week groups combined was 96% (119/124); 12-wks 97% (64/66) and for 24-wks 95% (55/58). Patients with a history of decompensation were more likely to receive 24 weeks, have RBV added, and overall had a SVR of 92% (195/212). **Safety:** Adverse events were reported in 78% of pts with fatigue, headache, nausea and diarrhea being the most frequently reported AE's. Anemia, insomnia and pruritus were the most frequently reported AEs in patients treated with Ribavirin. 63 patients experienced SAEs (46 in LDV/SOF (11%) and 17 (14%) in LDV/SOF+RBV treated patients). 7 patient deaths were reported.

Conclusions: Preliminary safety and efficacy data from HCV-TARGET suggests that LDV/SOF +/- RBV is generally safe, well tolerated, and highly effective across a broad spectrum of patients with advanced liver disease and prior treatment failure, including those with a prior history of decompensation.

Figure:

	LDV/SOF		LDV/SOF + RBV	
	12 wk N=45	24 wk N=367	12 wk N=66	24 wk N=58
Male	32 (71.1%)	232 (63.2%)	46 (69.7%)	39 (67.2%)
Age (median)	63.0	61.0	60.0	61.0
Race White	32 (71.1%)	284 (77.4%)	58 (87.9%)	40 (69.0%)
Black or African American	7 (15.6%)	57 (15.5%)	6 (9.1%)	5 (8.6%)
Genotype/subtype 1a	33 (73.3%)	247 (67.3%)	39 (59.1%)	36 (62.1%)
1b	7 (15.6%)	81 (22.1%)	23 (34.8%)	15 (25.9%)
1Nos	5 (11.1%)	39 (10.6%)	4 (6.1%)	7 (12.1%)
History of prior decompensation	7 (15.6%)	151 (41.1%)	17 (25.8%)	37 (63.8%)
SAEs (nPt with SAEs)	3	43	9	8
SVR12 (n/n,%)	44/45 (98%)	346/367 (94%)	64/66 (97%)	55/58 (95%)
95% CIs	88-100	91-96	89-100	86-99

Disclosure of Interest: M. Shiffman: None Declared, J. Lim: Grant: Conflict with: BMS, Gilead, Janssen, Hologic, Merck (All to Institution, Consultant: Conflict with: BMS Gilead, Janssen, Merck, A. Lok: Grant: Conflict with: AbbVie, Idenix, BMS, Gilead, Merck, Consultant: Conflict with: Gilead and Merck, S. Zeuzem: Consultant: Conflict with: Abbvie, BMS, Gilead, Janssen, Merck, Sponsored lectures (National or International): Conflict with: Abbvie, BMS, Gilead, Janssen, Merck, N. Terrault: Grant: Conflict with: Gilead, AbbVie, Merck, Eisai, Biotest, Consultant: Conflict with: Merck, Achillion, BMS, Janssen, Other: Conflict with: Research grants from NIH, J. Park: None Declared, C. Landis: None Declared, M. Hassan: None Declared, J. Gallant: None Declared, A. Kuo: Grant: Conflict with: Gilead, P. Pockros: Grant: Conflict with: Gilead, BMS, AbbVie, Merck, Janssen, Consultant: Conflict with: Gilead, BMS, AbbVie, Merck, Janssen, Sponsored lectures (National or International): Conflict with: Gilead, BMS, AbbVie, Janssen, M. Vainorius: None Declared, L. Akushevich: None Declared, M. Fried: Grant: Conflict with: Genentech/Roche, Merck, Vertex, Janssen, Gilead,Bristol Myers Squibb, AbbVie, Glaxo, Consultant: Conflict with: Genentech/Roche, Tibotec/Janssen, Vertex, Merck, Glaxo, Novartis, AbbVie, Gilead, Bristol Myers Squibb, Other: Conflict with: NIH grants, D. Nelson: Grant: Conflict with: AbbVie, Gilead, BMS, Janssen, Merck, GSK, Z. Ben-Ari: None Declared

The influence of clinical significant portal hypertension on safety, tolerability and efficacy of paritaprevir, ritonavir, ombitasvir, dasabuvir and ribavirin (PrOD+R) in a real-world large cohort of genotype Ib HCV liver cirrhosis patients

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Introduction: There are limited data about the safety and efficacy of PrOD+R in patients with liver cirrhosis with clinical significant portal hypertension. The registration studies included a small number of patients with cirrhosis and the severity of cirrhosis was not stratified according with Baveno stages.

Aims: To evaluate the safety and efficacy of PrOD+R in patients with clinical significant portal hypertension (Baveno 2).

Material and Methods: All patients with HCV genotype 1b compensated cirrhosis Child Pugh A5, A6 treated with PrOD+R for 12 weeks from December 1st, 2015 to March 31, 2016 across 10 academic centers in Romania were prospectively included in a common registry. The patients were divided in two groups by absence/presence of esophageal varices, being classified accordingly as stage Baveno 1 or 2. Efficacy and safety of therapy were comparatively analyzed.

Results: There were 527 patients, 232 male (44.1%), mean age 58.9 years (range 34-82), all cirrhotics (F4 by Fibromax), all Caucasians, and all with HCV genotype 1b infection. Out of 527 patients, 360 (68.3%) were Baveno 1 and 167 (31.7%) were stage Baveno 2. The age, distribution on gender, comorbidities were similar between the two stages of cirrhosis. Discontinuation rate was 1.66% in Baveno 1 (6 patients:1 intestinal obstruction, 2 severe depression, 2 cardiac failure, 1 malignant arrhythmia) and 1.19% (2 patients: 1-hepatic encephalopathy, 1 sepsis with multi-organ failure) in Baveno 2. One patient died in each group due to arrhythmia in Baveno 1 and sepsis in Baveno 2. Liver decompensation events were reported in one patient (0.27%) in Baveno 1 group (ascites remitted under treatment) and did not lead to treatment discontinuation, and in 6 patients (3.59%) (2 ascites, 2 encephalopathy, 2 variceal bleeding) in Baveno 2 group, one episode of encephalopathy leading to treatment discontinuation. The treatment was not interrupted at patients' request and after signing a supplementary informed consent. Per-protocol analysis all patients from both stage groups at EOT achieved negative HCV RNA level. Intent-to-treat EOT was 98.8% in Baveno 1 group and 98.3% in Baveno 2. At date, SVR 12 was evaluated in 68 patients and was 100%; the final results will be presented at the meeting.

Conclusions: Treatment with PrOD+R in patients with Baveno 2 stage genotype 1b compensated HCV cirrhosis is highly effective and safe, similar to that in Baveno 1 stage. However, the liver decompensation events are more frequent and a note of caution need to be taken.

Disclosure of Interest: None Declared

Screen I: ABSTRACT-212

Insulin resistance does not impair response of chronic HCV to direct acting antivirals, and improves with sustained viral response

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Introduction: Insulin resistance (IR) is a common complication in patients with chronic HCV. The impact of IR on the outcome of therapy with direct antivirals has not been studied.

Aims: To assess the impact of DAA therapy on IR status in patients with chronic HCV.

Material and Methods: Five hundred and eleven patients with chronic HCV infection (mean age 50.7±10.4 years, 76.1% males, 359 (70.3%) treatment naïve and 152 (29.7%) pegylated interferon (PEG) and ribavirin (RBV) experienced) were enrolled. Patients with uncontrolled diabetes or other comorbidities, decompensated liver disease, or prior non-response to DAAs were excluded. The Homeostatic Model Assessment (HOMA) was calculated before and 12 weeks after treatment and IR was defined as HOMA>1.9. Patients were treated according the treating physician's choice, and received 12 weeks of either: ombitasvir/ritonavir/paritaprevir/RBV (n=28); sofosbuvir (SOF)/simeprevir (n=36); SOF/ravidasvir (n=101); SOF/PEG/RBV (n=192); or 24 weeks of SOF/RBV (n=154).

Results: Most patients had IR pretreatment (n=412, 80.6%), 262 (51.3%) had fibrosis stage F4, 65 (12.7%) had hypertension, and 126 (24.7%) had diabetes. Sustained virological response at 12 weeks post-treatment (SVR12) was achieved in 465 patients (91%). SVR12 was achieved in 373 of 412 patients with IR (90.5%) and in 92 of 99 patients without IR (92.9%) (p=0.560), and pre-treatment HOMA was not different in

responders and non-responders (median (IQR); 3.21 (2.36) vs. 3.66 (2.88), p=0.098). The number of patients with IR decreased significantly in patients who achieved SVR (table) much more than in non-responders (p<0.0001) and HOMA improved significantly more in patients with SVR than in non-responders (median decrease (IQR) = -1.09 (1.8) vs. -0.07 (2.57), p=0.001).). All treatment protocols were associated with comparable HOMA improvement (p=0.101). Significant predictors of SVR12 included age (p=0.017; OR: 0.96, 95% CI: 0.929 - 0.993), serum albumin (p=0.029, OR: 1.99, 95% CI: 1.074 - 3.675), platelets (p=0.001, OR: 1.01, 95% CI: 1.004-1.015) and liver stiffness (p=0.021, OR:0.98, 95%CI: 0.959-0.997), but not pre-treatment IR (p=0.06; 95% CI: 0.832-1.002).

		Responders	Non-responders	p
Pre-treatment IR, n (%)	Yes	373 (80.2)	39 (84.8)	0.560
	No	92 (19.8)	7 (15.2)	
Post-treatment IR, n (%)	Yes	205 (44.1)	37 (80.4)	0.0001
	No	260 (55.9)	9 (19.6)	

Conclusions: IR does not impair response of patients with HCV treated with DAAs, and improves significantly in patients who achieve an SVR.

Disclosure of Interest: M. Elhelbawy: None Declared, W. Abdelrazek: None Declared, A. Alsebaey: None Declared, M. S. Hashem: None Declared, H. Elshinnawy: None Declared, I. Waked: Grant: Conflict with: Gilead, Consultant: Conflict with: Janssen, Sponsored lectures (National or International): Conflict with: Abbvie, Stockholder: Conflict with: Pharco.

Meta-analysis of the real-world effectiveness of ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in patients with HCV genotype I or 4 infection

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Introduction: The direct-acting antiviral regimen of ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r) ± dasabuvir (DSV) ± ribavirin (RBV) demonstrated high rates of sustained viral response at post-treatment week 12 (SVR12) in clinical trials for treatment of hepatitis C virus (HCV) genotypes (GT) 1 and 4. In the present study, we conducted meta-analyses of published literature to confirm the real-world effectiveness of this regimen in patients with HCV GT1 or 4 infections.

Material and Methods: Searches of published literature (including major conferences) were conducted using hepatitis C virus, its synonyms, and the regimen of interest. Discovered real-world datasets underwent Freeman-Tukey transformation to determine the SVR rate and 95% confidence interval (CI) for each dataset reporting relevant values.

Results: In total, 19 unique patient cohorts across 12 countries were identified, totaling 5,088 patients. The overall SVR12 rate for GT1 was 96.8%; for patients with GT4 it was 98.9%. Individual rates and confidence intervals for each genotype and subgroup, cirrhotic and noncirrhotic, are shown in Table 1. The virologic relapse rate of GT1 patients was 1.0% (95% CI 0.5 – 1.8%), across 3524 patients in 9 studies. The rate of hepatic decompensation in GT1 patients was 1.0% across 5 studies, including 3440 patients, 70% of which had cirrhosis.

Conclusions: Real World SVR12 rates for OBV/PTV/r ± DSV ± RBV were consistently high across HCV GT1 and 4 irrespective of cirrhosis status, confirming effectiveness within a diverse patient population across multiple cohorts and countries. The real world virologic relapse rate was low (1%). Safety meta-analyses, including drug discontinuation rates, will be available upon presentation.

Figure:

Table 1. Freeman-Tukey Real-World SVR12 Rates by Subgroup*

HCV Genotype	SVR12 (%)	95% CI	Total N (# cohorts)
GT1 Overall	96.8	95.8 - 97.7	5046 (18)
No Cirrhosis	98.0	96.6 - 99.1	681 (6)
Cirrhosis	97.0	94.7 - 98.8	2070 (8)
1a	93.8	87.8 - 98.0	535 (5)
No Cirrhosis	96.5	91.8 - 99.5	125 (2)
Cirrhosis	93.9	89.6 - 97.3	193 (3)
1b	97.9	97.0 - 98.9	1750 (7)
No Cirrhosis	98.9	96.9 - 100	337 (3)
Cirrhosis	98.0	96.4 - 99.1	715 (4)
GT4 Overall	98.9	94.2 - 100	112 (3)
No Cirrhosis	100	96.7 - 100	51 (1)
Cirrhosis	99.0	82.3 - 100	19 (2)

*Subgroup data were calculated for each study only where data breakdowns were originally available

Disclosure of Interest: H. Wedemeyer: Grant: Conflict with: Abbott, Bristol-Meyers Squibb, MSD, Novartis, Roche, Consultant: Conflict with: Abbott, AbbVie, Achillion, Bristol-Meyers Squibb, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, ITS, Janssen, Merck, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, A. Craxí: None Declared, E. Zuckerman: Consultant: Conflict with: AbbVie, Merck, Gilead, Bristol-Meyers Squibb, Roche, Neopharm, D. Dieterich: Consultant: Conflict with: Gilead, Bristol-Meyers Squibb, AbbVie, Janssen, Merck, R. Flisiak: Consultant: Conflict with: AbbVie, Alfa Wasserman, Bristol-Meyers Squibb, Gilead Sciences, Janssen, Merck, Roche, S. Roberts: Consultant: Conflict with: AbbVie, Gilead, MSD, Janssen, Bristol-Meyers Squibb, Roche, A. Pangerl: Employee: Conflict with: AbbVie, Z. Zhang: Employee: Conflict with: AbbVie, M. Martinez: Employee: Conflict with: AbbVie, Y. Bao: Employee: Conflict with: AbbVie, J.-L. Calleja: Consultant: Conflict with: AbbVie, Bristol-Meyers Squibb, Gilead Sciences, MSD.

Effect of interferon free antiviral treatment on lipid metabolism, lipid oxidation and insulin-resistance in chronic hepatitis C patients with advanced liver disease

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Introduction: Chronic HCV infection may affect host lipid metabolism and induce hypocholesterolemia, insulin resistance (IR),diabetes, atherosclerosis and steatosis. Low density cholesterol (LDL-C) is an atherogenic lipoprotein and its oxidated form (oxLDL) is involved in the formation of atherosclerotic plaques.

Aims: We investigated the changes of serum lipids and IR during and after DAA treatment of HCV.

Material and Methods: We enrolled 77 HCV pts (57.1% males, age 58.7±11.2 yrs, BMI 24.7±3.9, 74% HCV Genotype 1) with advanced fibrosis or cirrhosis (liver stiffness 19.1±9.9 KPa) treated with DAA (70% with ribavirin). HOMA-score, total, low and high density cholesterol (TC, LDL-C, HDL-C), Tryglicerides (TG) and oxLDL levels have been evaluated at baseline (T0), end-of-treatment (EOT) and after 12-weeks of follow-up (FU).

Results: TC and LDL-C levels significantly increased during antiviral therapy and FU. Notably also oxLDL levels increased during the study period, while HDLC did not change and TG levels declined only during treatment (Table). A significant decrease of HOMA-IR occurred during therapy and remained stable during FU (Table). The baseline proportion of patients with HOMA-IR≥2.5 and HOMA-IR≥4 were 72.7% and 45.5%, respectively, and the proportion of HOMA-IR≥4 significaantly decreased after treatment to 32.5% (p=0.03). (Table). The decline of HOMA-IR during antiviral treatment was gender-related, since men experienced a marked reduction of IR both during treatment

and FU while women had no changes.

Conclusions: A significant increase in total, LDL and oxLDL cholesterol levels was observed in pts with advanced liver disease treated with DAA. The rapid change of lipid metabolic profile that is observed in such pts may increase the cardiovascular risk and suggest the potential benefit of statin co-administration during or immediately after DAA therapy. The improvement of insulin resistance underlines the strong relationship between HCV and diabetes. Finally, the modulation of the metabolic changes observed during treatment according to gender is an interesting aspect of the interplay between virus and host and an area of future research.

Figure:

Table: Changes of serum lipids and insulin resistance during and after DAA treatment of HCV

Parameters (mean ± ds)	T0 (N°=77)	EOT (N°=77)	p	FU3 (N°=58)	p
Total cholesterol (TC), mg/dL	155.56 ± 34.48	170.29 ± 33.09	<0.001	181.6 ± 40.71	0.002
LDL cholesterol (LDLC), mg/dL	82.36 ± 31.99	94.97 ± 25.02	<0.001	109.28 ± 31.4	<0.001
Tryglicerides (TG), mg/dL	119.26 ± 64.08	100.24 ± 61.56	0.001	117.83 ± 133.87	0.129
HOMA-IR	4.46 ± 3.08	3.5 ± 2.07	0.01	3.62 ± 1.95	0.259
Oxidized LDL cholesterol (oxLDL), U/L	57.66 ± 17.71	-	-	79.66 ± 15.41	<0.001

Disclosure of Interest: None Declared

Efficacy and safety of paritaprevir/ritonavir, ombitasvir and dasabuvir + ribavirin for treatment of HCV genotype Ib compensated cirrhosis in patients aged 65 years or older

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Introduction: Historically, advanced age (>65years) has been a major limitation of interferon based therapy because of its poor response and tolerability. The interferon-free antiviral regimens are effective and safe, allowing treatment for older patients with no age limit.

Aims: The aim of this study is to analyze efficacy and safety of paritaprevir/ritonavir, ombitasvir and dasabuvir and ribavirin (3D+R) for 12 weeks treatment of hepatitis C virus (HCV) genotype 1b- compensated cirrhosis in patients aged 65 years or older.

Material and Methods: 527 naïve and experienced patients with HCV genotype 1b compensated cirrhosis treated with 3D+ R were prospectively included and treated with 3D+ R for 12 weeks across 10 academic centers in Romania from December 1st, 2015 to March 31. The patients were divided in two groups by age: > 65 yrs and <65yrs. Efficacy and safety of 3D+R therapy were analyzed and compared between two groups.

Results: There were 527 patients, 232 male (44%), mean age 59 yrs (range 34-82), all cirrhotics (F4 by Fibromax), all Caucasians, and all with HCV genotype 1b infection. Out of 527 patients, 145 (27.5 %) were 65 yrs or older, mean age 69.3 yrs (range 65-82 yrs), most female (62%), and 52% treatment experienced, while 382 were <65yrs, mean 54 yrs (range 34-64), most female (54%) and 65.7% treatment experienced. Adverse events (AEs) were frequent but manageable (none leading to discontinuation), the most common being in both age groups mild anemia, asthenia, insomnia. Severe AEs leading to treatment discontinuation were reported in 3 patients (2.06%) in older group (1-hepatic encephalopaty, 2-cardiac failure) compared to 5 patients (1.3%) in younger group (1-intestinal occlusion, 1-cardiac arythmia, 1-sepsis with multi-organ failure, 2-severe depression). Two patients died in younger group (1-cardiac arythmia and 1 sepsis with multiorgan failure) and none in ≥65yrs. Severe adverse events, other than liver decompensation, not leading to discontinuation were reported in 7 patients (4.82%) in ≥65yrs and in 10 patients (2.61%) in the younger group. Per-protocol analysis all patients from both age groups at EOT achieved negative HCV RNA level. Intent-to-treat EOT was 97.93% in ≥65yrs and 98.69% in <65yrs. At date, SVR 12 was evaluated in 68 patients and was 100%; the final results will be presented at the meeting.

Conclusions: Treatment with 3D+R regimens in patients aged 65yrs or older with HCV genoptype 1b compensated cirrhosis is highly effective and safe, similar to that in younger patients.

Disclosure of Interest: None Declared

The association of genetic variations in PNPLA3 and DHCR7 genes with severity of liver fibrosis in Thai patients with chronic hepatitis C

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Introduction: Hepatitis C virus (HCV) is a common cause of liver fibrosis and cirrhosis. There is increasing evidence that host genetic variations may influence the natural history of chronic HCV infection.

Aims: The aim of this study was to determine the correlation between single nucleotide polymorphisms (SNPs) of PNPLA3 (rs738409) and DHCR7 (rs12785878) and severity of liver fibrosis in Thai populations.

Material and Methods: A total of 250 patients with HCV mono-infection, 200 patients with HCV/HIV co-infection, 74 patients with HCV spontaneous clearance and 200 healthy controls were enrolled. The SNPs were detected by allelic discrimination using real-time PCR with TaqMan probes. Liver fibrosis was assessed by transient elastography.

Results: The frequency of CC, CG and GG genotypes of rs738409 in the HCV group was 53.2%, 39.2% and 6.5%, respectively. In the HCV clearance group, the corresponding genotypes were 36.1%, 45.8% and 18.1%. The frequency of GG was significantly higher in the HCV clearance than the HCV group (odds ratio (OR)=2.62, 95% confidence interval (CI)=1.27-5.4, P=0.0094). In addition, the frequency of TT, TG and GG genotypes of rs12785878 in the HCV group were 5.6%, 38.5% and 55.9%, respectively. The corresponding genotypes in the HCV/HIV group were 3.5%, 39.2% and 57.3%, respectively. In the control group, the corresponding genotypes were 12.1%, 41.9% and 46.0%, respectively. The frequency of GG genotype was significantly higher in the HCV and HCV/HIV groups than the control group (in HCV; OR=2.62, 95% (CI=1.27-5.4, P=0.0094, in HCV/HIV; OR=4.29, 95% CI=1.77-10.42 P=0.0013). Moreover, the data showed that the genotype frequency of rs12785878 was correlated with advanced fibrosis in patients with HCV (P=0.016).

Conclusions: DHCR7 rs12785878 polymorphism was significantly associated with the severity of liver fibrosis in HCV and might be used as a biomarker for predicting liver fibrosis in Thai population.

Disclosure of Interest: None Declared

Analysis of baseline variants in GT1a-infected patients treated with 3D with and without RBV, and cirrhotic GT1a patients treated with 3D plus RBV for 12 or 24 weeks

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Introduction: The 3D regimen [ombitasvir (OBV)/paritaprevir (PTV; identified by AbbVie and Enanta)/ritonavir (r) and dasabuvir (DSV)] ± ribavirin (RBV), is highly effective and is approved in the US and EU for treatment of HCV GT1 infection. We found no impact of baseline resistance-associated variants (RAVs) on SVR in patients treated with 3D + RBV (GT1a) or without RBV (GT1b) according to label recommendations.

Aims: Here we assessed impact of RAVs on SVR, including non-recommended regimens, in Phase 3 studies PEARL-IV (GT1a treatment-naïve non-cirrhotic patients treated with 3D ± RBV) and TURQUOISE-II (GT1a cirrhotic patients treated with 3D + RBV for 12 or 24 weeks).

Material and Methods: Deep sequencing was conducted using Illumina. Early discontinuations for non-virologic reasons were excluded. Prevalence and impact of baseline RAVs on SVR were determined using a 15% variant detection threshold. Impact of baseline RAVs conferring ≥5-fold resistance to components of 3D on SVR12 was determined by comparing SVR rates in patients with or without RAVs.

Results: SVR12 rates (mITT) in PEARL-IV were 98% and 92% in GT1a patients treated for 12 weeks with or without RBV, and 97% and 91% in GT1a cirrhotic patients in TURQUOISE-II treated for 24 or 12 weeks, respectively. OBV-specific NS5A RAVs were present in 8 - 13% of patients across groups. NS3 and NS5B RAVs were rare (<3%). In the RBV-free arm of PEARL-IV, SVR rates were 72% (13/18) and 93% (143/154) in patients with or without baseline OBV RAVs, respectively. The majority of patients (10/16) with virologic failure (VF) did not have baseline RAVs, indicating that RAVs alone do not

explain VF in this arm. In TURQUOISE-II, there was no significant impact of baseline OBV RAVs on SVR for GT1a cirrhotic patients treated for 12 weeks (94% vs. 91% with or without RAVs) or 24 weeks (92% vs. 97% with or without RAVs).

Conclusions: In TURQUOISE-II baseline OBV-specific NS5A RAVs did not impact treatment outcome in GT1a cirrhotic patients treated with 3D + RBV for either 12 or 24 weeks. In PEARL-IV, baseline OBV RAVs were associated with lower SVR in GT1a patients treated without RBV, but the SVR rate in patients without baseline RAVs was still lower than for the recommended regimen that includes RBV. These data support the recommendation that patients with GT1a infection should be treated with the RBV-containing regimen as indicated in the product label; results from baseline resistance testing would not impact this recommendation.

Disclosure of Interest: C. Sarrazin: Grant: Conflict with: Abbott, Gilead, Janssen, Qiagen, Roche, Siemens, Consultant: Conflict with: Abbott, AbbVie, BMS, Gilead, Janssen, Merck/MSD, Roche, Sponsored lectures (National or International): Conflict with: Abbott, AbbVie, Achillion, BMS, Gilead, Janssen, Merck/MSD, Qiagen, Roche, Siemens, M. Sulkowski: Grant: Conflict with: AbbVie, BMS, Gilead, Merck, Janssen, Consultant: Conflict with: AbbVie, Achillion, Cocrystal, BMS, Gilead, Janssen, P. Krishnan: Stockholder: Conflict with: AbbVie, Employee: Conflict with: AbbVie, R. Tripathi: Stockholder: Conflict with: AbbVie, Employee: Conflict with: AbbVie, G. Schnell: Stockholder: Conflict with: AbbVie, Employee: Conflict with: AbbVie, D. Cohen: Stockholder: Conflict with: AbbVie, Employee: Conflict with: AbbVie, R. Trinh: Stockholder: Conflict with: AbbVie, Employee: Conflict with: AbbVie, L. Rodrigues-Jr.: Stockholder: Conflict with: AbbVie, Employee: Conflict with: AbbVie,Y. Luo: Stockholder: Conflict with: AbbVie, Employee: Conflict with: AbbVie, N. Shulman: Stockholder: Conflict with: AbbVie, Employee: Conflict with: AbbVie, T. Pilot-Matias: Stockholder: Conflict with: AbbVie, Employee: Conflict with: AbbVie, C. Collins: Stockholder: Conflict with: AbbVie, Employee: Conflict with: AbbVie.

Different prevalence of HCV resistance, genetic distance and HCV quantification within blood and liver tissues (tumoral and non tumoral tissues) in HCC/cirrhotic transplanted patients

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Introduction: HCV reinfection is a constant event in liver transplant, suggesting existence of viral compartmentalization and/or HCV reservoirs affecting chances of cure.

Aims: We investigated HCV-RNA variability and prevalence of resistance associated variants (RAVs), in plasma (PL), hepatic tumoral (TT), and not tumoral (NT) tissue samples in patients (pts) undergoing liver transplant (LT) or hepatic resection (HR), mainly due to hepatocarcinoma (HCC) and/or cirrhosis.

Material and Methods: 18 HCV infected pts (5 GT1a, 8 GT1b, 4 GT3a, 1 GT4d) undergoing LT or HR (N=15/ 3) due to HCC with/without cirrhosis (N=9/ 5), only cirrhosis (N=3), or without HCC/cirrhosis (N=1) were analysed. HCV-RNA was quantified by Abbott M2000 RealTime in all compartments. NS3/NS5A/NS5B in PL and/or NT/TT were analysed in all pts by Sanger-sequencing and in 4 pts by Ultra-deep pyrosequencing (UDPS, cutoff >1%). RAVs prevalence was evaluated.

Results: At the time of LT/HR, PL HCV-RNA was quantifiable in 17/18 pts (range: 2.6-6.3 LogIU/ml). Interestingly, pt.27 arrived at LT after 6 weeks of sofosbuvir+ribavirin with undetectable PL HCV-RNA, but still quantifiable liver HCV-RNA, higher in TT than in NT (51 vs 7 IU/µgRNA). Untreated HCC pts, differently, showed lower HCV-RNA in TT compared to NT (median [IQR]=4.0[1.2-4.3] vs. 4.3[3.1-4.9] LogIU/µgRNA, respectively; Mann-Whitney p=0.19). Moreover, a significant HCV-RNA correlation

between PL and NT was observed (Pearson: rho=0.60, p=0.02) mainly in cirrhotic pts (rho=0.70, p=0.03). RAVs compartmentalization was found by Sanger and UDPS in 4/18 GT1b pts, 2 cirrhotic and 2 not, and in 1 GT1a cirrhotic pt only by UDPS (see table). UDPS showed significant genetic-distances (≥0.02) at NS3/NS5A/NS5B levels among liver and plasma, higher in non-cirrhotic pts, suggesting a potential compartmentalization of viral variants. Phylogenetic trees in non-cirrhotic pts showed well define clusters among/within compartments, with PL/NT-sequences often closely located. Differently, in cirrhotic pts, mixed clusters of NT/TT/PL-sequences were observed, indicating lower compartmentalization.

Conclusions: NT and TT compartments showed different HCV-RNA amount, RAVs and genetic variability. In general, PL and NT showed more similar profiles if compared to TT. This scenario was less marked in cirrhotic pts, probably due to the tissue damage. These results, although preliminary, support the hypothesis of possible HCV strain diversifications in the liver, explaining cases of failure also in the era of new direct antivirals.

Figure:

							NS3-Protease			NS5A			NS5B-Polymerase		
							RAVs			RAVs			RAVs		
Patient	Genotype	HCC	Cirrhosis	LT	Compartment	HCV-RNA	Bulk	UDPS (%)	G.D.	Bulk	UDPS (%)	G.D.	Bulk	UDPS (%)	G.D.
PT.2	1b	YES	NO	NO	TT	12185 IU/µg RNA	none	none	TT_NT:0.028	none	none	TT_NT:0.029	L159F, C316N	L159F (100), C316N (100)	TT_NT:0.016
					NT	85709 IU/µg RNA	none	**S122G** (6.9)	NT_PL:0.016	**Y93H/Y/S**	**Y93H** (32.3), **Y93S** (22.8)	NT_PL:0.024	L159F, C316N	L159F (100), C316N (100)	NT_PL:0.034
					PL	410 IU/ml	none	**S122G** (17.0)	PL_TT:0.025	none	**Y93H** (37.7)	PL_TT:0.027	L159F, C316N	L159F (100), C316N (100)	PL_TT:0.031
PT.22	1b	YES	NO	NO	TT	80523 IU/µg RNA	none	S122N (6.6)	TT_NT:0.048	Y93H/Y	Y93H (53.6)	TT_NT:0.042	none	**S556G (22.7)**	TT_NT:0.04
					NT	145889 IU/µg RNA	**S122N/T/S**	S122N (4.6), **S122T** (6.7)	NT_PL:0.041	Y93H/Y	Y93H (90.24), **R30Q** (2)	NT_PL:0.037	none	none	NT_PL:0.032
					PL	54503 IU/ml	**S122N/T/S**	S122N (12.6), **S122T** (8.9)	PL_TT:0.047	none	Y93H (52.12), **R30Q** (2.8)	PL_TT:0.045	none	none	PL_TT:0.039
					PL 28 w post-LT	3433 IU/ml*	none	-		none	-		n.a.	-	
PT.57	1b	YES	YES	YES	TT	-	-	T54S (100), V55I (100), S122N (37.6), **S122T** (37.2)	TT_NT:0.031	-	R30L (57.8), Y93H (79.5)	TT_NT:0.013	L159F, C316N	L159F (100), C316N (100)	TT_NT:0.023
					NT	-	-	T54S (100), V55I (98.4), S122N (60.8)	NT_PL:0.029	none	R30L (55.8), Y93H (79.2)	NT_PL:0.021	L159F, C316N	L159F (100), C316N (100), **M414T** (2.0)	NT_PL:0.017
					PL	-	T54S, V55I, S122N/5	T54S (100), V55I (97), **Q80L** (1.8), S122N (59.2)	PL_TT:0.033	**R30R/L Y93H/Y**	R30L (41.6), Y93H (58.6)	PL_TT:0.016	L159F, C316N	L159F (100), C316N (100)	PL_TT:0.025
					PL 16 w pre-LT	800000 IU/ml	T54S, V55I, S122N/5	-		none	-		-	-	
PT.27*	1b	YES	YES	YES	NT	7IU/µg	-	-		-			-		
					TT	51IU/µg	none	-		none	-		none	-	
					PL 4 w pre-LT	212875 IU/ml	n.a.	-		none	-		**S556G**	-	
PT.15	1a	YES	YES	YES	TT	13151 IU/µg RNA	none	**V36M** (17.7), **S122N** (3.2)	TT_NT:0.025	none	none	TT_NT:0.033	none	none	TT_NT:0.019
					NT	22127 IU/µg RNA	none	**T54A** (3.6), **S122G** (1.5)	NT_PL:0.024	none	none	NT_PL:0.020	none	none	NT_PL:0.019
					PL	119144 IU/ml	none	**V36M** (28.4), **S122G** (1.6)	PL_TT:0.028	none	-	PL_TT:0.027	none	none	PL_TT:0.016

Table. Prevalence of NS3, NS5A and NS5B resistance associated variants (RAVs) found in different compartments of HCC/transplanted patients by both population-sequencing and UDPS. In bold are indicated UDPS and Sanger RAVs compartmentalization. For UDPS sequences are indicated genetic distance (G.D.) among compartments. *PT.27 had undetectable HCV-RNA at the time of liver transplant (LT). "-" indicates data not available. Tumoral tissue (TT); non-tumoral tissue (NT); plasma (PL).

Disclosure of Interest: None Declared

Efficacy and safety of the combination of sofosbuvir and simeprevir with/without ribavirin in a large cohort of cirrhotic patients in Spain

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Introduction: The combination of Sofosbuvir (SOF) plus Simeprevir (SMV) with or without ribavirin (RBV), has been shown to be effective and safe when used in compensated cirrhotic patients infected with the hepatitis C virus (HCV) genotypes (GT) 1 or 4. This combination was the first all-oral available antiviral therapy in Spain. However, no data has been published to date regarding its efficacy and safety in real-life cirrhotic patients in Spain.

Aims: The aim of this multicentric study was to assess the Spanish clinical experience of the use of SOF/SMV (±RBV) in a large cohort of real-life compensated cirrhotic patients.

Material and Methods: Retrospective analysis of data from HCV GT1 and 4 infected cirrhotic patients treated with this oral combination in Spain.

Results: Nine-hundred and 67 cirrhotic patients were included. The majority of patients were male (60.1%) and were 60(19-94) years old. Patients were infected with GT1a(19.6%), 1b(69.2%) or 4(8.7%). The median transient elastographic measurement was 22KPa (IQR: 16.8-33.3). MELD score was 8(IQR 7-10); the majority of patients (76.2%) were Child-Pugh A score at baseline. One third of the cohort had a history of previous decompensation (45.5% ascites). Up to 63% of had previously failed to antiviral therapies, among which 115(19.7%) patients had received a previous protease inhibitor. Baseline median ALT was 71(5-513) and viral load (HCV-RNA) was 6.08$\log_{10}$ (1.28-7.73). The majority of patients (91.7%) were treated for 12 weeks; 61% received RBV.

Fifty-six patients are still on follow-up; overall, 841/911 patients were cured (92.3% sustained virological response rate, SVR). There were no differences between genotypes or previous treatment history. However, the use of RBV, a less advanced liver disease (MELD, Child-Pugh Score), or the absence of portal hypertension (evaluated as a platelet count $\geq 90 \times 10^9$/mL) were significantly related with better SVR rates ($p<0.05$). In the multivariate analysis, treatment with RBV and a lower MELD score remained significantly related with SVR. Almost half of the cohort (48%) had adverse events (AE) (asthenia, rash or hyperbilirubinemia), significantly more frequent in those receiving RBV. However, serious AE, early discontinuations and decompensation during therapy were low (5.5%, 2.4% and 6.2% respectively).

Conclusions: The combination of SOF/SMV with or without RBV has been shown to be effective and safe when used in compensated GT1 and 4 HCV cirrhotic patients.

Disclosure of Interest: None Declared

Efficacy and effectiveness of DAA containing regimens in patients with genotype 3 HCV infection: a systematic literature review

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Introduction: Genotype 3 (GT3) is the second most common genotype of hepatitis C virus and, compared with others genotypes, GT3 patients have relatively faster rates of fibrosis progression, higher prevalence of severe (Grade 3) steatosis, and a higher incidence of hepatocellular carcinoma. With fewer therapeutic options, GT3 patients with advanced fibrosis, especially those with cirrhosis, are a challenging population to treat.

Aims: To provide a comprehensive evaluation of the recent clinical trials (CT) and real world (RW) efficacy data of DAA containing regimens in cirrhotic patients with genotype 3 infection.

Material and Methods: A systematic search of literature indexed in MEDLINE and EMBASE within the last 5 years (i.e., from Feb. 2011 to May 2016) was conducted using specified keywords to identify all interventional or observational studies published in English providing data on the efficacy or effectiveness of DAA containing regimens as measured by SVR12 in cirrhotic patients with a chronic hepatitis C infection with GT3 virus. The search of indexed literature was supplemented with a search of 5 non-indexed literature sources in the past year: AASLD, EASL, APASL, CROI, WHO. To be included in this report, the publications needed to display SVR rates in GT3 cirrhotic population by each HCV regimen separately. CT in HCV-HIV co-infected patients were not included.

Results: 22 CT and 10 observational studies were identified. Results on the efficacy and effectiveness of DAA containing regimens in cirrhotic patients are summarised in table 1. The heterogeneity of range of SVR rates with the different treatment regimens and duration is high. NS5A inhibitor containing regimens showed a better efficacy than NS5B inhibitors alone. In patients treated with 12 weeks regimens, ribavirin seems to be always beneficial for increasing SVR rate, especially in experienced patients. The SVR observed

in the RW studies (including the EAP programs data) confirmed the results of the pivotal CT.

Conclusions: Oral antiviral HCV treatments have improved the outlook for GT3 patients. However, relapse rates in treatment experienced GT3 cirrhotic patients remain greater than 5-10%, with newest NS5A inhibitors; although the data are incomplete, ribavirin may be required for 12 week treatment courses for this group.

Figure:

Table 1: Efficacy and effectiveness of DAA containing regimens in GT3 cirrhotic patients (SVR12)

Treatment regimen	Treatment history	CLINICAL TRIAL			REAL WORD DATA		
		Study	N°	SVR12 % [IC95%]	Study	N°	SVR12 % [IC95%]
DCV+SOF (12 wks)	Naïve	ALLY-3	19	58 [34-80]			
	Experienced	ALLY-3	13	69 [39-91]			
	Naïve or experienced				French EAP (ATU)	33	70 [51-84]
					UK EAP (decomp)	5	60 [15-95]
DCV+SOF (24 wks)	Naïve or experienced				French EAP (ATU)	135	86 [80-92]
					EU EAP**(all)	42	88 [74-96]
					EU EAP**(decomp)	24	79 [58-93]
					German registry*	NR	93 [NR]
	Experienced				German registry*	NR	100 [NR]
DCV+SOF+RBV (12 wks)	Experienced	Ally-3+	16	88 [62-98]			
	Naïve or experienced	Ally-3+	18	83 [59-96]	UK EAP (decomp)	105	71 [84-79]
		Ally-1	6	83 [36-100]	French EAP (ATU)	4	100 [40-100]
					German registry*	NR	89 [NR]
					Scottish registry	27	81 [62-94]
DCV+SOF+RBV (16 wks)	Experienced	Ally-3+	14	86 [57-98]			
	Naïve or experienced	Ally-3+	18	89 [65-99]			
DCV+SOF+RBV (24 wks)	Naïve or experienced				French EAP (ATU)	48	81 [67-91]
					EU EAP**(all)	29	86 [68-96]
					EU EAP**(decomp)	17	88 [64-99]
					German registry*	NR	94 [NR]
	Experienced				German registry*	NR	91 [NR]
LDV+SOF (12 wks)	Naïve or experienced				UK EAP (decomp)	5	40 [15-72]
	Naïve	ELECTRON-2	6	100 [54-100]			
		Canadian CT	39	79 [64-91]			
LDV+SOF+RBV (12 wks)	Experienced	ELECTRON-2	22	73 [50-89]			
	Naïve or experienced				UK EAP(decomp)	57	65 [51-72]
					German registry*	NR	70 [NR]
LDV+SOF+RBV (24 wks)	Naïve or experienced				German registry*	NR	77 [NR]
	Experienced				German registry*	NR	64 [NR]
SOF+PegIFN+RBV (12 wks)	Naïve	BOSON	23	91 [72-99]			
	Experienced	BOSON	35	86 [70-95]	German registry	NR	79 [NR]
		LONESTAR-2	12	83 [52-98]			
	DAA relapsers	NR (Esteban 2014)	8	88 [47-100]			
	Naïve or experienced				German registry	44	85 [70-93]
SOF+RBV (12 wks)	Experienced	FUSION	26	19 [7-39]			
	Naïve or experienced	POSITRON	14	21 [5-51]			
SOF+RBV (16 wks)	Naïve	BOSON	21	57 [34-78]			
		NR (Shah 2016)	7	100 [59-100]			
		Russian trial	6	83 [36-100]			
	Experienced	BOSON	36	47 [30-65]			
		FUSION	23	61 [38-80]			
SOF+RBV (24 wks)	Naïve	ASTRAL-3	45	73 [58-85]	HCV-TARGET	26	62 [41-80]
		BOSON	22	82 [60-95]			
		VALENCE	13	92 [64-100]			
		NR (Shah 2016)	7	86 [42-100]			
		Russian trial	5	80 [15-95]			
	Experienced	VALENCE	47	62 [46-75]	HCV-TARGET	45	44 [30-60]
		ASTRAL-3	38	58 [41-74]	German registry	NR	67 [NR]
		BOSON	34	77 [59-89]			
	DAA relapsers	NR (Esteban 2014)	15	47 [21-73]			
	Naïve or experienced				NR (Naffisi 2015)	20	33 [13-59]
					German registry	69	65 [53-76]
					NR (Maasoumy 2015)	19	53 [28-76]
					NR (Deterding 2015)	22	50 [28-72]
					NR (Wu 2015)	NR	88 [NR]
VEL100+SOF (12wks)	Naïve	ASTRAL-3	43	93 [81-99]			
	Experienced	ASTRAL-3	37	89 [75-97]			
		GS-US-342-0109	26	88 [70-96]			
	Naïve or experienced	ASTRAL4 (decomp)	14	50 [23-77]			
VEL100+SOF (24wks)	Naïve or experienced	ASTRAL4 (decomp)	12	50 [21-79]			
VEL100+SOF+RBV (12wks)	Experienced	GS-US-342-0109	26	96 [80-100]			
	Naïve or experienced	ASTRAL4 (decomp)	13	85 [55-98]			
VEL25+SOF (12wks)	Experienced	GS-US-342-0109	26	58 [37-77]			
VEL25+SOF+RBV (12wks)	Experienced	GS-US-342-0109	25	84 [64-96]			
VEL100+SOF+GS-9857 (6 wks)	Naïve	LEPTON	18	83 [59-96]			
VEL100+SOF+GS-9857 (8 wks)	Naïve	GS-US-367-1168/9	18	94 [73-100]			
	Experienced	LEPTON	19	100 [82-100]			
GZR/EBR+SOF (12 wks)	Naïve	C-SWIFT	11	90 [55-100]			
ABT-493+ABT-530 (24 wks)	Naïve	SURVEYOR-2	24	100 [86-100]			
ABT-493+ABT-530+RBV (24 wks)	Naïve	SURVEYOR-2	24	100 [86-100]			

*Sample size; ** excluding UK; †DCV-based regimen: 201 patients, LDV-based regimen: 115 patients.

Disclosure of Interest: L. Lacoin: Employee: Conflict with: Bristol-Myers Squibb, H. Fathi: Employee: Conflict with: Bristol-Myers Squibb, B. Jones: Consultant: Conflict with: HEOR Limited was paid by BMS to do this research, J. Gordon: Consultant: Conflict with: HEOR Limited is paid by BMS to do this research, A. Clark: Employee: Conflict with: Bristol-Myers Squibb, G. Dusheiko: Consultant: Conflict with: for Bristol-Myers Squibb in this project.

Screen I0: ABSTRACT-242

Safety and effectiveness of I2 and 24-week regimens of paritaprevir/r, ombitasvir, dasabuvir (PrOD) for the treatment of hepatitis C genotype Ia infection: interim analysis HCV-target, a prospective, observational study

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Introduction: Clinicians may utilize different durations of therapy for the treatment of patients with chronic HCV.

Aims: The aim of this study is to evaluate the safety and effectiveness of 12 and 24 weeks of PrOD+RBV for HCV Genotype 1a infection as part of routine clinical practice as reported to HCV-TARGET (HCVT), a multicentre, prospective, observational cohort study.

Material and Methods: Patients who initiated HCV treatment were enrolled and treated according to the regional standards of care at academic (n=38) and community medical centres (n=13) in North America (n=47) and Europe (n=4). Information was collected from the medical records and abstracted into a unique centralized data core. Independent data monitors systematically reviewed data entries for completeness and accuracy. Demographic, clinical, adverse events (AEs) and virological data were collected throughout treatment and post-treatment follow-up.

Results: The data are current through June 14, 2016; 329 GT1a patients started treatment with PrOD +RBV; 76 patients are still on treatment. Less than 5% (n=20) discontinued treatment early; 12 discontinued due to AE (4%), and 1 discontinued treatment due to virological failure (<1%). Of 233 patients on PrOD +RBV who have completed treatment to date, 53 patients are in post treatment follow up (53 and 27) and 6 were lost to post treatment follow up. 173 patients who completed 12 or 24 week with PrOD +RBV have virological outcomes available and make up the reporting population. HCV G1a pts who received 24 weeks of therapy were more likely to be treatment experienced (76%) and have cirrhosis (71%). Of note, a 17% of cirrhotic patients were treated for only 12 weeks. Efficacy: SVR12 for the 12 and 24 week regimens combined was 94% (163/173); 12-wk regimen 94% (127/135) and for 24-wk regimen 95% (36/38). Safety: Headache, nausea and diarrhea where the most frequently reported AEs with anemia, insomnia and pruritus most frequently reported in patients on regimens which included Ribavirin. A total of 6 patients experienced SAEs. Complete safety and efficacy data for the cohort will be presented.

Conclusions: Preliminary safety and efficacy data from HCV-TARGET suggests that the PrOD regimen is generally safe, well tolerated, and highly effective across a broad spectrum of patients with genotype 1a.

Figure:

	PrOD + RBV	
	12 wk N=135	24 wk N=38
Male	90 (66.7%)	26 (68.4%)
Age (median)	57.0	59.0
Race White	102 (75.6%)	25 (65.8%)
Black or African American	27 (20.0%)	10 (26.3%)
Other or Pending	6 (4.4%)	3 (7.9%)
Treatment experienced	48 (35.6%)	29 (76.3%)
Treatment naive	87 (64.4%)	9 (23.7%)
Cirrhosis	23 (17.0%)	27 (71.1%)
History of prior decompensation	9 (39.1%)	10 (37.0%)
SAEs (nPt with SAEs)	3	3
SVR12 (n/n,%)	127/135 (94%)	36/38 (95%)
95% CIs	89-97	82-99

Disclosure of Interest: M. Shiffman: None Declared, J. Lim: Grant: Conflict with: BMS, Gilead, Janssen, Hologic, Merck (All to Institution), Consultant: Conflict with: BMS Gilead, Janssen, Merck, A. Lok: Grant: Conflict with: AbbVie, Idenix, BMS, Gilead, Merck, Consultant: Conflict with: Gilead and Merck, S. Zeuzem: Consultant: Conflict with: Abbvie, BMS, Gilead, Janssen, Merck, Sponsored lectures (National or International): Conflict with: Abbvie, BMS, Gilead, Janssen, Merck, N. Terrault: Grant: Conflict with: Gilead, AbbVie, Merck, Eisai, Biotest, Consultant: Conflict with: Merck, Achillion, BMS, Janssen, Other: Conflict with: NIH research grants, J. Park: None Declared, C. Landis: None Declared, M. Hassan: None Declared, J. Gallant: None Declared, A. Kuo: Grant: Conflict with: Gilead, P. Pockros: Grant: Conflict with: Gilead, BMS, AbbVie, Merck, Janssen, Consultant: Conflict with: Gilead, BMS, AbbVie, Merck, Janssen, Sponsored lectures (National or International): Conflict with: Gilead, BMS, AbbVie, Janssen, M. Vainorius: None Declared, L. Akushevich: None Declared, M. Fried: Grant: Conflict with: Genentech/Roche, Merck, Vertex, Janssen, Gilead,Bristol Myers Squibb, AbbVie, Glaxo, Consultant: Conflict with: Genentech/Roche, Tibotec/Janssen, Vertex, Merck, Glaxo, Novartis, AbbVie, Gilead, Bristol Myers Squibb, Other: Conflict with: NIH research grants, D. Nelson: Grant: Conflict with: AbbVie, Gilead, BMS, Janssen, Merck, GSK, Z. Ben-Ari: None Declared

INDUSTRY

SYMPOSIA PROGRAMMES

Gilead Sciences Europe Ltd

FRIDAY 23 SEPTEMBER 2016 – FORUM LEVEL -1
13:00 – 14:00

INDUSTRY

BREAKING DOWN BARRIERS TO HCV ELIMINATION

Chairs: Nezam Afdhal, *USA*
Jean-Michel Pawlotsky, *France*

13:00 – 13:03	**Welcome and introduction** Jean-Michel Pawlotsky, *France*
13:03 – 13:18	**Making HCV elimination a reality** Jean-Michel Pawlotsky, *France*
13:18 – 13:33	**Linking more patients to care** Greg Dore, *Australia*
13:33 – 13:48	**Maximising the value of cure** Homie Razavi, *USA*
13:48- 13:58	**Achieving test–treat–cure for all patients** Panel discussion, facilitated by Nezam Afdhal, *USA*
13:58 -14:00	**Summary and close** Nezam Afdhal, *USA*

AbbVie, Inc

SATURDAY 24 SEPTEMBER 2016 - FORUM LEVEL -1
07:00 – 08:00

DRIVING CHANGE IN HCV TREATMENTS: THE ROAD TO CURE

Chair: Heiner Wedemeyer, *Germany*

07:00 – 07:05	**Welcome** Heiner Wedemeyer, *Germany*
07:05 – 07:15	**GT1: How are current treatments evolving?** Tarik Asselah, *France*
07:15 – 07:25	**CKD: Still difficult to cure?** Stanislas Pol, *France*
07:25 – 07:35	**RWE: How are the real-world data stacking up?** Ashley Brown, *United Kingdom*
07:35 – 07:45	**A glimpse into the future: Pan-genotypic regimens** Heiner Wedemeyer, *Germany*
07:45 – 08:00	**Q&A and close** Heiner Wedemeyer, *Germany*

MSD

SATURDAY 24 SEPTEMBER 2016 – FORUM LEVEL -1
13:00 – 14:00

NEW PERSPECTIVES FOR PATIENTS: BROADENING THE SCOPE OF TREATMENT

Chair: Jean-Michel Pawlotsky, *France*

13:00 – 13:05	**Welcome and introduction** Jean-Michel Pawlotsky, *France*
13:05 – 13:30	**Less severe fibrosis doesn't always mean less complex** Lawrence Serfaty, *France*
13:30 – 13:50	**Broadening the scope to new patient populations** Steven Flamm, *USA*
13:50 – 14:00	**Q&A and closing remarks** Jean-Michel Pawlotsky, *France*

INDUSTRY

COMPANY PROFILES

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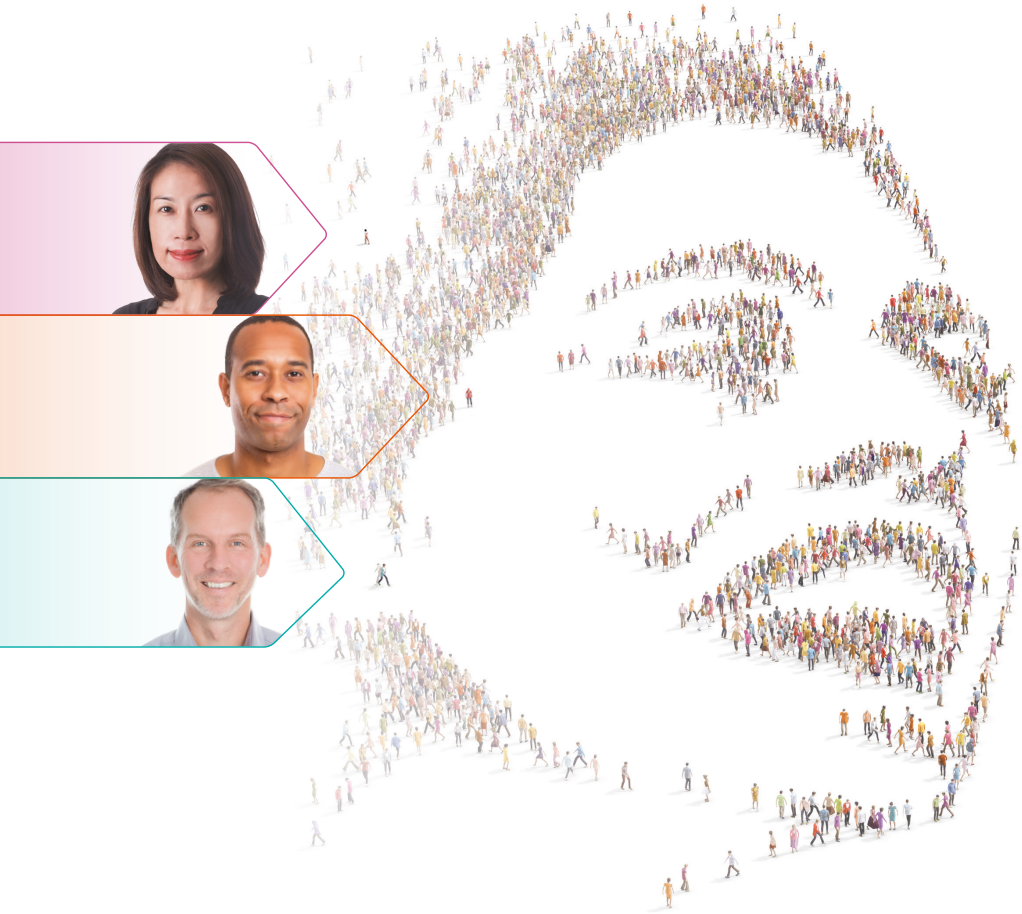

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GILEAD

Date of preparation: August 2016 HCV/IHQ/16-05//1707j

Where a 25-year legacy of innovation in chronic **HEPATITIS C** treatment[1–3] meets

AN UNWAVERING COMMITMENT TO THE TASK AT HAND

HEPATITIS C IS A SERIOUS BURDEN THAT CAN HAVE DIRE CONSEQUENCES[4]

According to the World Health Organization, the human cost of hepatitis C–related liver diseases is staggering: It claims the lives of approximately 500,000 people per year.[5] However, recent advances in care have led many to believe that elimination of hepatitis C is possible. MSD remains committed more than ever to providing innovative solutions for advancement of chronic hepatitis C treatment and to working towards the ultimate goal of hepatitis C elimination.

Learn more about how MSD is addressing the task at hand by visiting ***www.merckconnect.com***

References: 1. PEG-intron and ribavirin combination product approval letter. FDA: August 7, 2001. **2.** Victrelis® (boceprevir), first-in-class oral hepatitis C virus protease inhibitor, approved in the European Union for treatment of chronic hepatitis C [news release EU version]. Whitehouse Station, NJ: MSD; July 18, 2011. **3.** Intron A Registration Life Cycle Status as of January 21, 2011 [FDA]. **4.** World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. April 2014. http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/. Accessed August 4, 2015. **5.** World Health Organization. WHO Key Facts. Hepatitis C. http://www.who.int/mediacentre/factsheets/fs164/en/. Accessed August 11, 2015.

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