APSAD Conference 2015 Workshop 11 Nov 2015, Perth

Curing Hepatitis C

Changing Paradigm Of Care And How Drug Health Can Play A Role

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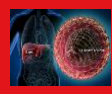

Supporting the HIV, Viral Hepatitis and Sexual Health Workforce

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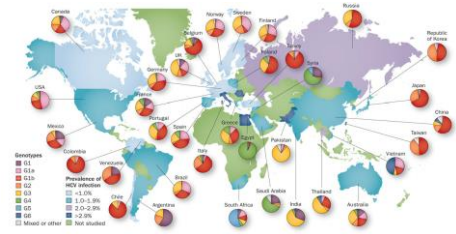
HCV is a global problem

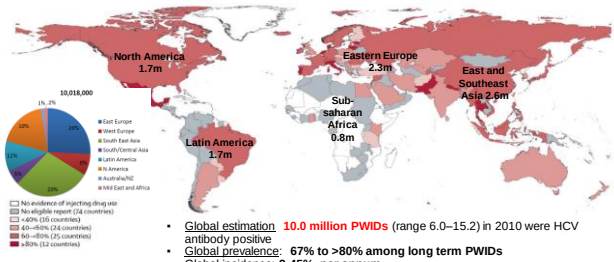
Global prevalence of 2-3%:

- **>185 million** people worldwide have been infected with HCV
- **130–170 million** are chronically infected
- **350,000 deaths** occur each year as a result of HCV-related cirrhosis and liver cancer



Hajarizadeh, B. et al. (2013) Nat. Rev. Gastroenterol. Hepatol. 10, 553-562.

HCV is a major public health problem among PWID



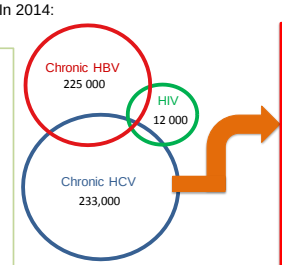
- Global estimation **10.0 million PWIDs** (range 6.0–15.2) in 2010 were HCV antibody positive
- Global prevalence: **67% to >80% among long term PWIDs**
- Global incidence: **2-45% per annum**

Nelson PK, et al. Lancet 2011:378;571-83; Hagan H et al, Am J Epidemiol 2008; 168:1099-109

Estimates of Prevalence of BBV in Australia

In 2014:

Prevalence of HCV is 75–80% among the 47,000 people on OST (50% chronic HCV prevalence), giving an estimate of 24,000 in the OST setting with chronic HCV at any one time, of whom around 12,000 would be active PWID



Day and Haber, 2009

2014 HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report

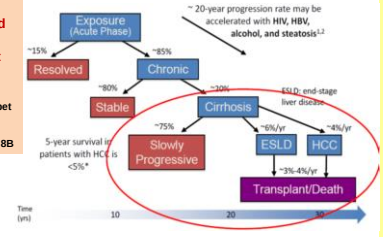
At risk groups

- People who inject drugs account for the majority of new HCV infections
- New at-risk groups
  - Rising rates (22.3%) of HCV infection among young people who inject drugs
    - Over 5 million young people used pharmaceutical opioids non-medically in the past year
  - Iatrogenic transmission (healthcare exposure)
  - Sexual transmission of HCV amongst HIV-infected and HIV-uninfected men who have sex with men (MSM)
- HCV incidence is highest among new injectors:
  - 32% HCV@ 1 year post IDU onset in developed countries
  - 59% HCV @ 1 year post IDU in developing/transitional countries

Altarum Institute. 2013; Martin, T.C., et al., 2013; MMWR 2012

Natural history of HCV infection

Factors associated with viral clearance:
Female
Young age
Race
Immunocompetence
Jaundice
Genetics: IL28B



Determinants of liver disease progression

Prior evidence
Alcohol intake
Age at infection (after 40 y)
Co-infection (HIV or HBV)
Male gender
Stage of fibrosis
Persistently elevated ALT

New evidence
Obesity/hepatic steatosis
Smoking
Cannabis

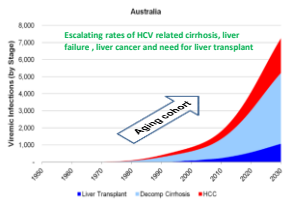
No/limited evidence
HCV genotype: 1b, 3a
HCV viral load

NIH Consens Statement. June 10-12, 2002;19(3):1-46. *NIH Consens Statement*.March 24-26, 1997;15(3):1-41.1. Di Bisceglie AM. *Hepatology*. 2000;31(4):1014-1018. 2. Bialek SR, Terrault NA. *Clin Liver Dis*. 2006;10(4):697-715.

Clinical burden of HCV in Australia

HCV antibody positive HCV RNA positive (viraemia)	310 000 233,274	
Total Infected	**2013**	**%**
F0	84,505	36.2
F1	70,145	30.1
F2	32,754	14.0
F3	**29,698**	**12.7**
Cirrhosis (compensated)	**13,836**	**5.9**
Liver failure	**1,746**	**0.74**
HCC	**589**	**0.25**
Total Infected	**233,274**	**100**

In Australia HCV is currently a major cause of
- Chronic liver disease
- Hepatocellular carcinoma (HCC)
- Liver transplant

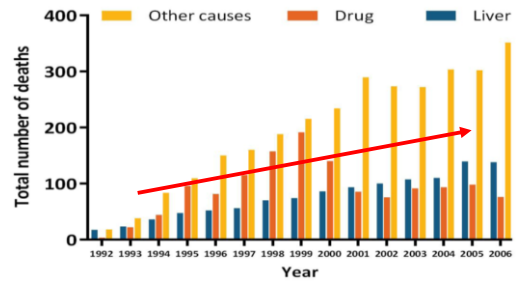


- **In 2013 of the 233 000 with chronic hepatitis C, 1/3 have moderate to severe liver disease**
- **530 died of HCV liver disease related deaths in 2013**

1. The Kirby Institute. Annual Surveillance Report 2013. 2. Ravazi H et al. J Viral Hep. 2014; 21 (Suppl 1): 34-59. 3 Sievert W et al. J Gastroenterol Hepatol 2014; 29 (Suppl 1): 1-9

What is killing people with HCV infection?

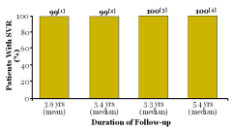
Ageing "cohorts" with increasing liver mortality



Deans G et al, CMAJ Open. 2103 ; Kieland et al, J Hepat 2012 ; Grebely J et al, Seminars in Liver Disease 2011

HCV infection is a curable disease

- **What does cure mean?**
  - **Sustained Viral Response (SVR)**
  - Undetectable HCV RNA 24 (or 12) weeks after completion of antiviral therapy for chronic HCV infection
  - Durable



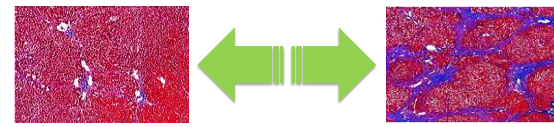
Improvements in non cirrhotic patients
- ↓Progression to cirrhosis
- ↓Incidence of extra-hepatic manifestations (NHL, diabetes)
- ↑Neuro-congnitive functions & HR QOL
- ↑Overall survival

Improvements in cirrhotic patients
- ↓Clinical decompensation and variceal bleeding
- ↓HCC incidence
- Cirrhosis regression
- ↑Liver related survival

Improvements in decompensated patients
- ↓Need for LT
- ↓HCV Recurrence post-LT

Aghemo A et al, J Hepatol 2012;57:1326-35; Ghany MG, et al. Hepatology. 2009;49(4):1335-1374; Hill A et al, AASLD 2014

Cirrhosis regression can occur with SVR



Interferon based therapy
- Meta Analysis (6 studies): 443 patients with cirrhosis
- Of the 137 SVR patients, 73 (53%) showed regression of cirrhosis on biopsy

Interferon free therapy
- 380 patients with cirrhosis treated with 3D+ribavirin
- 48 weeks post treatment, 40% improvement in fibrotest scores in SVR

Akhtar, E et al Liver Int 2015

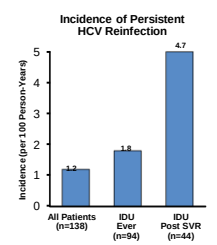
What is the reinfection rate for PWID and active drug users?

- Given the lack of protective immunity, on-going risk behaviours can lead to HCV reinfection after successful treatment
- Incidence of reinfection following IFN based treatment in a meta-analysis of 5 studies among people who inject drugs (PWID)[1]
  - **2.4/100 PY** among patients with a **history of injecting drug use** (IDU)
  - **6.4/100 PY** among patients with **on-going IDU after treatment**
  - In comparison, primary HCV incidence is 6–27 per100 PY[2]
- Risk of reinfection **5-years after SVR** was **8%** a in meta-analysis of 16 studies among PWID or prisoners[3]

1.AspinallE.J. et al. ClinInfect Dis 2013; 2. Grebely J et al. Lancet Infect Dise 2012;12:408-14; 3. Hill A.M. et al. AASLD 2014

Implications of post SVR reinfection

- Cohort of PWID from Norway, Sweden, Denmark (North-C trial, n=428)
  - Abstinent ≥6 months before HCV treatment
  - Genotype 2/3: SVR24 76%
- **12 cases of HCV recurrence** after SVR among the Norwegians (n=138, follow-up >7 years)
  - **All had relapsed to IDU** (n=44)
  - None among the 94 who remained non-IDU
- At the *individual level*, reinfection might compromise long-term benefits of treatment for patients with on-going risk behaviours
- At the *population level*, treating patients at high risk of reinfection may have great prevention potential as these patients are being "kept out of the pool" for a period and prevented from transmitting the virus
- **Harm reduction intervention and education**
  - **Essential for patients at highest risk of reinfection**



PWID: people who inject drugs.

Midgard H S, et al. EASL 2015. Abstract O061; Midgard H et al, INHSU 2015

HCV reinfection in phase 3 studies of Sofosbuvir-containing regimens

- 99.6% concordance of SVR12 (n=3004) and SVR24 (n=2992) in sofosbuvir clinical studies
- 12 patients did not achieve SVR24
- Of the 12 discordant cases, most were due to HCV reinfection
  - Late relapse (n=5): minimal genetic drift between baseline and posttreatment week 24 samples
  - Reinfection (n=7)

Svarovskaia E, et al. *J Hepatol.* 2015;62(suppl 2):S222-S223. Abstract O063.

GUIDELINES

- PWID are a priority population for Hepatitis C treatment
- Same treatment benefits as for other groups
- Potential prevention benefits of treatment

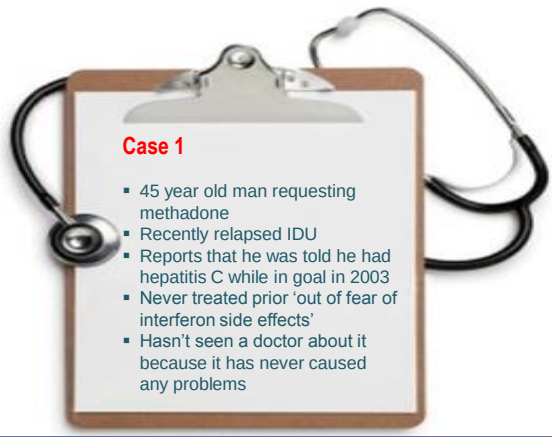
INHSU INTERNATIONAL NETWORK ON HEPATITIS IN SUBSTANCE USERS

International Journal of Drug Policy

Review

Recommendations for the management of hepatitis C virus infection among people who inject drugs

Jason Grebely[a,*], Geert Robaeys[b,c,d], Philip Bruggmann[e], Alessio Aghemo[f], Markus Backmund[g,h], Julie Bruneau[i], Jude Byrne[j], Olav Dalgard[k], Jordan J. Feld[l], Margaret Hellard[m,n], Matthew Hickman[o], Achim Kautz[p], Alain Litwin[q], Andrew R. Lloyd[r], Stefan Mauss[s], Maria Prins[t,u], Tracy Swan[v], Martin Schaefer[w,x], Lynn E. Taylor[y], Gregory J. Dore[a] on behalf of the International Network for Hepatitis in Substance Users

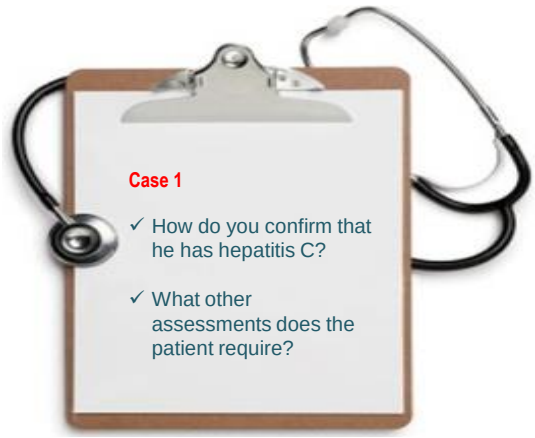


Case 1

- 45 year old man requesting methadone
- Recently relapsed IDU
- Reports that he was told he had hepatitis C while in goal in 2003
- Never treated prior 'out of fear of interferon side effects'
- Hasn't seen a doctor about it because it has never caused any problems

Case 1

- PMH:
  - Hypertension: Perindopril (Coversyl)
  - Dyslipidaemia: Rosuvastatin (Crestor)
- Drinks 30-40g beers daily
- No FHx: liver disease or malignancy; mother DM, father IHD



Case 1

- ✓ How do you confirm that he has hepatitis C?
- ✓ What other assessments does the patient require?

Who should be screened for HCV ?

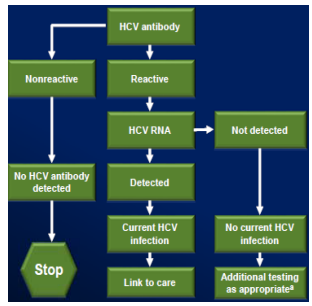
HCV Testing Recommendations

1. Birth cohort testing	
Recommended at least once for persons born between 1945 and 1965	
2. Risk factor screening and testing	
One-time testing should be performed for all persons with behaviors, exposures, or medical conditions associated with an increased risk of HCV infection	
Risk behaviors	Injection drug use, current or ever; intranasal illicit drug use
Risk exposures	Long-term hemodialysis; getting a tattoo in an unregulated setting; healthcare workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood; children born to HCV-infected women; certain prior transfusion or organ transplant recipients
Other medical conditions	HIV infection; unexplained liver disease and chronic hepatitis, including elevated ALT levels

AASLD/IDSA/IAS-USA. http://www.hepatitisc.uw.edu/level3.php?level3=58.

Identifying HCV infection

- Positive **HCV antibody test** indicates 1 of the following:
  - Current HCV infection
  - Past HCV infection that has resolved
  - False-positive result
- **HCV RNA testing** required to confirm current HCV infection
  - Qualitative PCR tests (pos/neg)..... **IS HCV PRESENT?**
  - Quantitative PCR tests (viral load).....**HOW MUCH HCV IS PRESENT?**
- **HCV genotype**



AASLD/IDSA/IAS-USA. http://www.hepatitisc.uw.edu/level3.php?level3=58.

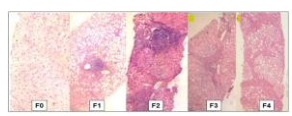
After diagnosing HCV infection you need to:

- Determine the impact of HCV infection on the liver
  - Likelihood of advanced liver disease / cirrhosis
- Define other factors that may influence the disease progression and/or the response to treatment
  - Eg, alcohol use, metabolic risk factors
- Exclude other causes of chronic hepatitis
- Provide the patient and doctor with adequate information to make decisions on treatment

Assessment of fibrosis is critical

Cirrhosis or no cirrhosis, that is the question

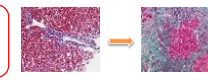
- **Determines degree of liver damage**
- **Determines need for treatment**
- **Determines management**
  - Timing of initiation of treatment
  - Choice of treatment regimen
  - Decision to use ribavirin
  - Duration of treatment
- **Determine post treatment follow up**
  - If cirrhosis: HCC screening, variceal surveillance

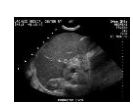


- *All patients should have fibrosis assessment at diagnosis*
- If cirrhosis is clinically obvious → no need for liver biopsy

Staging hepatic fibrosis

Rule out clinical evidence of cirrhosis:
- Exam: jaundice, ascites, varices, encephalopathy
- Labs: platelet count <100, 000 , high INR, low albumin, high bilirubin





Imaging: US, CT, MRI
Insensitive for advanced fibrosis / early cirrhosis

Liver biopsy
Percutaneous
Transjugular
Laparoscopic

(Serum) Biomarkers
Proprietary
Common tests
Markers of hepatic function or matrix production or degradation

Transient elastography
Fibroscan

Fontaine H et al. Gastro Clin Biol 2007;31:504-9

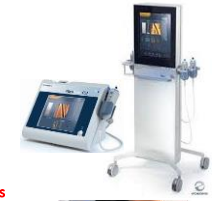
Liver tests are not reliable

- Most have abnormal ALT or AST
  - Normal ALT: women: <19 U/L, men: <30 U/L
  - ALT may fluctuate over time
  - Affected by other factors: eg, alcohol use, obesity, etc

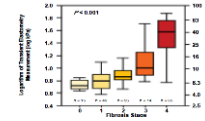
- ALT does not offer reliable information regarding prognosis or degree of fibrosis
  - Up to 40% have normal ALT
    - 5-30% of patients with normal ALT will have advanced fibrosis
    - 1.3% will have cirrhosis

Prati D et al, Ann Intern Med 2002;137:1-10; Ghany MG et al Hepatol 2009;49(4):1335-74; Synder N et al, J Clin Gastroenterol 2006;40(6):535-42; Chou R & Wasson N, Ann Intern Med 2013;158(11):807-20

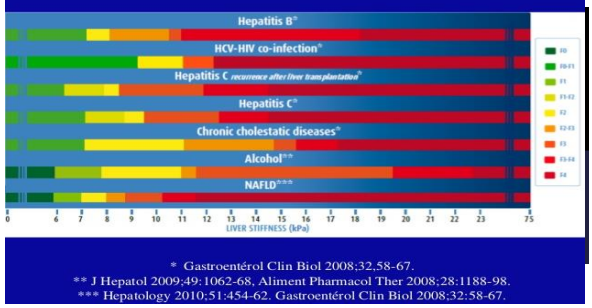
Fibroscan



- Methodology
  - Ultrasonic transducer sends a vibration wave into the liver
  - Elastic shear wave propagates through the liver
  - Velocity of wave correlates with tissue stiffness
  - The stiffer the liver is, the greater the degree of fibrosis
- Does not give the reason for the fibrosis nor provide information on other liver pathology apart from steatosis
- Accurate for identification of **normal liver and cirrhosis**
  - Poor discriminatory ability in the intermediate strata of fibrosis (F1-3)
- Reduced the need for liver biopsy
  - Patient friendly: non invasive, simple, quick



Correlation between LSM & fibrosis stage



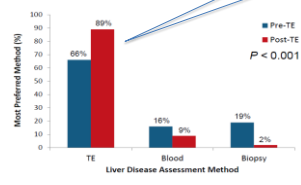
* Gastroentérol Clin Biol 2008;32,58-67.
** J Hepatol 2009;49:1062-68, Aliment Pharmacol Ther 2008;28:1188-98.
*** Hepatology 2010;51:454-62. Gastroentérol Clin Biol 2008;32:58-67.

The LiveRLife Study: Fibroscan is a tool to increase screening and access to therapy

Participants (n=253)

Recruitment from:
- Kirketon Road Centre
- Sydney Medically Supervised Injecting Centre
- Newcastle Pharmacotherapy Service (OST)
- Coffs Harbour Drug and Alcohol Services (OST)

Fibroscan is the preferred method to assess disease staging



Marshall AD, et al. International Journal of Drug Policy 2015;26:984-991

Case 1

Examination
BP 136/78, BMI 27
No signs of chronic liver disease

Laboratory results
FBC: Hb 154, WCC 6.2, PLT 236
LFT: Bilirubin 14, Albumin 40, ALT 56, AST 68, GGT 88, ALP 102
EUC: creatinine 87, eGFR >90
AFP: 4
Normal lipid studies

Case 1

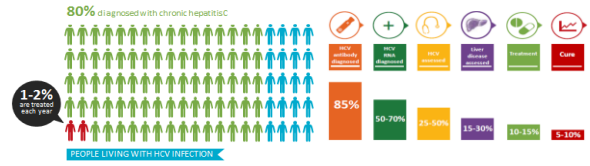
Liver screen: immunity to HAV, HBV; no HIV, no haemochromatosis, autoimmune liver disease, or impaired glucose tolerance

Fibroscan: 6.8 kPa

Case 1

- ✓ The challenge is now to link him into care
- ✓ Overcome his fear about treatment
- ✓ Current treatment vs future treatment – timeline

Low treatment uptake in Australia



Tx rate: 1-2% pa

1847 treated in 2005
3397 treated in 2009
2360 treated in 2012
2808 treated in 2013

Without significant improvement in treatment rates Australia faces escalating rates of liver disease from HCV, including a **230% increase in liver-related deaths; 245% increase in liver cancer; and a 180% increase in liver cirrhosis by 2030**

1. Grebely J & Dore GJ. Antiviral Research 2014; 104:62-72. 2.Ravazi H et al. J Viral Hep. 2014; 21 (Suppl 1): 34-59

Barriers to HCV treatment for PWID

- Individual: concerns about treatment side-effects, efficacy & duration; stigma/confidentiality; venous access; limited knowledge; mistrust
- Clinical: concerns about co-morbidities, adherence, substance use, re-infection & side effect management
- Social/structural: homelessness, poverty, geographical isolation, stigma, criminalisation, marginalisation, OST access, limited social supports, caring demands, health care systems

- Changing HCV tx landscape: new drugs will ameliorate some barriers but bring new challenges (eg, cost)

Adeyemi 2004, Bova 2010, Bruggman 2012, 2004, Cooper 2010, Evon 2010, Fleming 2003, Grebley 2009, 2013, Groom 2008, Hall 2004, Hallinan 2007, Jowett 2001, McLaren 2008, McNally 2006, Mehta 2008, Morrill 2005, Nunes 2006, Restrepo 2005, Rocco 2004, Stoove 2005, Treloar 2010, Volk 2010, Wagner 20009, Zickmund 2007

Case 1

He wants to be treated now.

- ✓ What are his treatment options?

Current standard of care in Australia 2015

Genotype 1
PegIFN + Ribavirin + Simeprevir for 24-48 weeks

Note: Telaprevir/Boceprevir is no longer recommended

Genotype 2,3
PegIFN + Ribavirin, for 24 weeks (48 weeks if F3/4 unless RVR)

Genotype 4,5,6
PegIFN + Ribavirin, for 48 weeks

Current PBS subsidised treatment

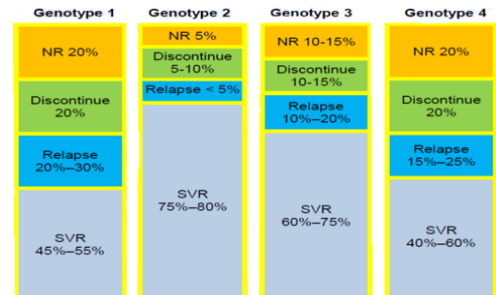
Ribavirin		Weight based 800 – 1400mg BD
Pegylated interferon α 2a	Pegasys	180 mcg weekly SCI
Pegylated interferon α 2b	Pegatron	Weight based 1.5 µg/kg/wk SCI
Simeprevir	Olysio	150 mg daily

PBS requirements* for HCV treatment eligibility
- HCV RNA positive
- No major contraindications
- Not pregnant/breastfeeding
- Using 2 forms of contraception
- Treated in association with liver clinic

* Do not need liver biopsy or raised ALT or significant fibrosis

Treatment costs in Australia:
- Free if have a Medicare card
- Dispensing co-payment is payable to hospital pharmacy.
- Current payment is $7-40 per month (depend on private or public patient and Healthcare Card or Senior's Card)

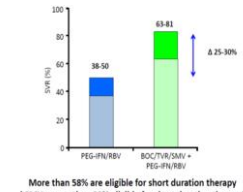
Efficacy of Peginterferon + Ribavirin



1. Manns M, et al. *Lancet*. 2001;358:958-965. 2. Fried M, et al. *N Engl J Med*. 2002;347:975-982. 3. Kamal SM, et al. *Hepatol*. 2007; 46:1732-1740. 4. Khuroo MS, et al. *Aliment Pharmacol Ther*. 2004;20:931-938. 5. Conjeevaram H, et al. *Gastroenterol*. 2006;131:470-477.

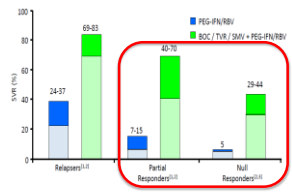
HCV GT 1: SVR rates with first gen protease inhibitors (BOC / TVR / SMV)

Treatment naïve patients



More than 58% are eligible for short duration therapy
(SMV - more than 80% eligible for short duration therapy)

Treatment experienced patients

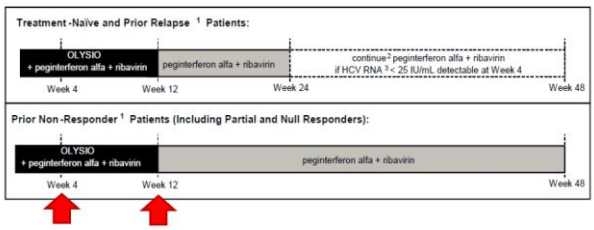


Case 1

Hepatitis C, genotype 1b
Treatment naïve
Non cirrhotic

- ✓ What regimen? Duration?
- ✓ What result can he expect?
- ✓ What side effects may he develop?

Figure 1: Duration of Treatment with OLYSIO, Peginterferon Alfa and Ribavirin

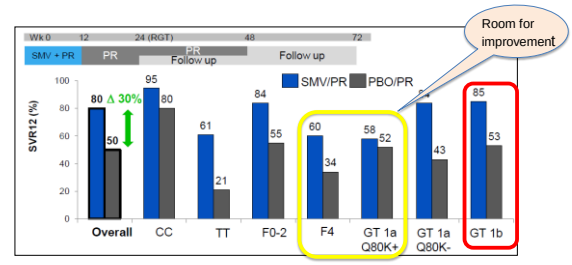


HCV RNA	Action
Treatment Week 4: ≥ 25 IU/mL	Discontinue OLYSIO, peginterferon alfa and ribavirin
Treatment Week 12: detectable[1]	Discontinue peginterferon alfa and ribavirin (treatment with OLYSIO is complete at Week 12)

[1] Re-evaluation of HCV RNA is recommended in case of detectable HCV RNA after previous undetectable HCV RNA to confirm HCV RNA levels prior to discontinuing HCV treatment.

SVR12 rates for SMV in treatment naïve GT 1

Pooled data from QUEST 1 and 2



- Pooled data, 785 patients, 521 received SMV (TMC435)
- 44% female, median age 47, 30% CC, 48% GT 1a, Q80K 17% overall, 10% F4, 15% F3
- Discontinuations 3% SMV, 2% PBO
- 459/521 (88%) met RGT criteria, 405/459 (88%) achieved SVR12

Jacobson IM, et al. Lancet. 2014;384:403-13;
Manns M, et al. Lancet. 2014;384:414-26.

Side effects of current treatment

Peg-IFN	Ribavirin	Simeprevir
Flu-like	Anaemia	Rash, pruritis
Mood disturbance	Rash	Photosensitivity
Cytopaenias	Cough	Nausea
Thinning hair	Dyspnoea	Myalgia
Weight loss	Dysguesia	Reversible hyperbilirubinaemia
Insomnia	Gout	
Depression /psychosis	Teratogenicity	
Thyroid dysfunction		
Exacerbation of psoriasis, epilepsy		

Case 1

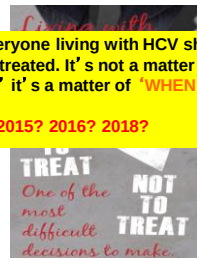
- ✓ If treatment is deferred, the next challenge is to keep him engaged in care
- ✓ Does he understand what informed deferral means?
- ✓ Are there any risks?

Decision-making: treat now or wait?

Liver disease

Everyone living with HCV should be treated. It's not a matter of 'IF' it's a matter of 'WHEN'

… 2015? 2016? 2018?



Public health

Personal issues

Reasons to treat now!

- Easier to treat milder disease
- Avoid progression of disease
  - Determining disease progression is not an exact science
  - Reduce risk of developing HCC
  - If we wait until advanced fibrosis, need to do lifelong screening for HCC even if cured (expense, logistics, patient anxiety)
- Uncertainty about timelines for approval and reimbursement of next generation agents
- Access to clinical trials, compassionate access or early access programme
- Public health issue – treatment as prevention
- If patient has no contraindications and is motivated, treat him!

HEPATOLOGY

EDITORIALS

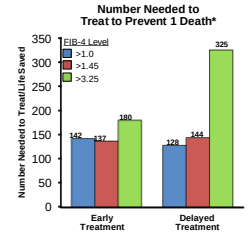
Aronson A, Jensen D, Hepatology 2012;56:1591

Informed Deferral: A Moral Requirement for Entry Into the Hepatitis C Virus Treatment Warehouse

- **Warehousing** – deferral of therapy based on provider recommendation
  - Common while awaiting the approval of protease inhibitors
  - Now re-occurring during the wait for interferon-free regimens
- Treatment deferral should be viewed as an active, not passive treatment decision
- Uncertainties for discussion with patient:
  - Limitations in staging and predicting progression, waiting time for desired therapies, development of other co-morbidities, risk of transmission and future insurance coverage

Can HCV treatment be safely delayed?

- VA Clinical Case Registry (n=187,860; 1999-2010) in USA
- HCV prevalence: 5.4%
- **SVR significantly reduced the risk of future liver death by 45%**
- **Delaying treatment decreased the chance of achieving SVR because of more advanced liver fibrosis**

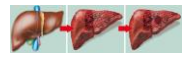


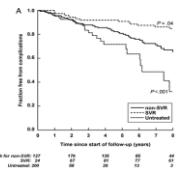
*Before/after 3 FIB-4 levels.

McCoombs JS, et al EASL 2015. Abstract O003.

Risk of HCC remains after SVR in HCV patients with advanced hepatic fibrosis

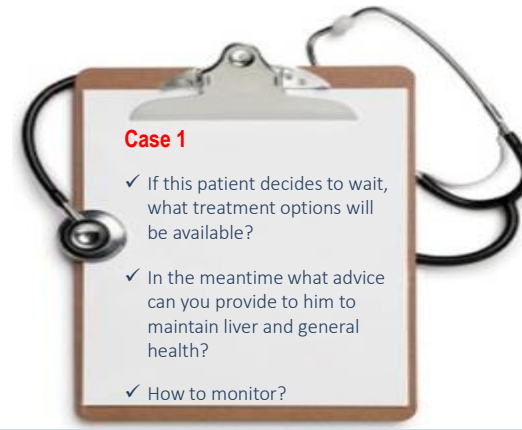
- Prospective evaluation of risk of HCC, liver decompensation, and death in 351 patients with HCV-related cirrhosis (110 with SVR, 93 with no SVR, 48 untreated)[1]
- **SVR reduced incidence of HCC, liver decompensation, and death**
  - **6 patients with SVR developed HCC at 0.04, 0.64, 2.4, 7.4, 7.4, and 7.6 years**
- Meta-analysis (n=1000)
  - Patients with HCV-induced cirrhosis who achieve SVR remain at risk for HCC
  - 51 events of HCC developed over 5.1 years of follow-up
  - Risk increased with age, severity of liver disease, and presence of diabetes mellitus





Continued HCC surveillance is necessary for patients with cirrhosis who achieve an SVR

1. Aleman S et al. Clin Infect Dis 2013;57:230-36; van der Meer AJ, et al. *Hepatology*. 2013;58(suppl 1):280A. Abstract 143.



Case 1

- ✓ If this patient decides to wait, what treatment options will be available?
- ✓ In the meantime what advice can you provide to him to maintain liver and general health?
- ✓ How to monitor?

Current HCV management strategies

- Liver disease staging for all people with chronic HCV, particularly those >40 years
- F0-3 defer therapy to await IFN-free therapy
- F4 recommend IFN-based therapy or IFN-free access
- Post-treatment repeat liver disease staging for those with F3-4

Much can be done to improve liver disease in HCV patients before antiviral treatment

Patient Counselling

- Preventing HCV transmission
- HCV antibodies are not protective
- Avoid alcohol
- Avoid illicit drugs including cannabis, tobacco
- Avoid new medicines, including over the counter and herbal agents, without first checking with their doctor
- Maintain a healthy diet, exercise and lose weight if necessary
- Sources of support (e.g., social, emotional, financial)

LOVE YOUR LIVER

Clinical Management

- HAV and HBV vaccinations
- Management of comorbidities (depression, diabetes, obesity, and hypertension)
- Medication assessment (for any products that may harm the liver)
- If patient has advanced fibrosis or cirrhosis, HCC and variceal surveillance
- Bone disease screening, surveillance, and management

Alcohol use in HCV patients

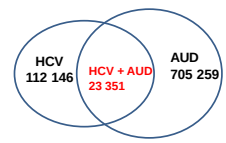
- Most research has been done in patients with ongoing chronic HCV infection
  - Alcohol speeds up progression of HCV
  - Abstinence is recommended

- No clear evidence in patients after cure
  - Advanced fibrosis / cirrhosis: abstinence is recommended
  - Early fibrosis: mild (social) alcohol use is acceptable

Ghany MC et al, Hepatology. 2009 Apr;49(4):1335-74.

Confounding role of severe comorbidities and alcohol use disorders on prognosis in chronic HCV

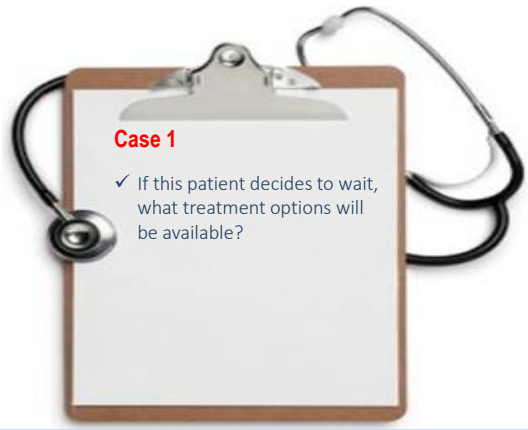
- French National Hospital Discharge Database included data on all public and private acute and post acute care
- **28,953,755 adults** who had at least one hospital stay from 2008 to 2012
- Of these hospitalized patients, 0.02% had liver transplantation, 0.27% were treated for primary liver cancer, and 1.7% treated for end-stage liver disease. And 1,506,453 people (5.2%) died in the hospital



Patient Characteristic	Liver-Related Event, %	In-Hospital Death, %
Alcohol use disorder	46.3	33.7
No alcohol problem, major comorbidity	39.9	57.5
No alcohol problem, no comorbidity	13.8	8.8

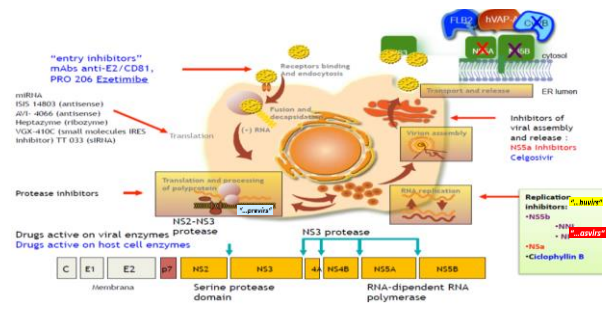
Schwarzinger M et al. EASL 2015. Abstract G16

Alcohol withdrawal or abstinence was associated with a significantly reduced rate of liver complications or mortality by ~30%



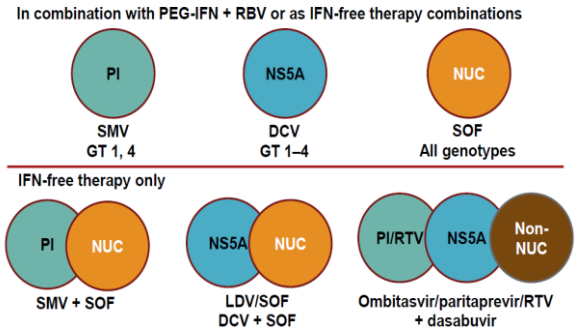
HCV targets for therapy

Directly acting antiviral agents (DAAs)



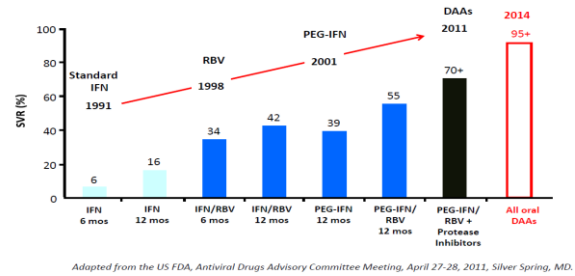
Lindenbach BD & Rice CM. *Nature* 2005;436:933-938

DAAs available for chronic HCV



Hepatitis C therapy is a "very rapidly moving field"

Rapid Evolution of HCV Treatment



Adapted from the US FDA, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.

Snapshot of IFN-free regimens in non cirrhotic patients

Study	Regimen (12 weeks)	HCV genotype	Treatment experience	SVR12, %
OPTIMIST-1[1]	SMV + SOF	1a and 1b	Naïve and experienced	97
ION-2[2]	SOF/LDV	1a and 1b	Experienced	95
ION-3[3]	SOF/LDV	1a and 1b	Naïve	95
PEARL-III[4]	OBV/r/PRV + DSV	1b	Naïve	99
PEARL-IV[4]	OBV/r/PRV + DSV + RBV	1a	Naïve	97
PEARL-II[5]	OBV/r/PRV + DSV	1b	Experienced	100
SAPPHIRE-II[6]	OBV/r/PRV + DSV + RBV	1a	Experienced	96
FISSION[7]	SOF + RBV (12w)	2	Naïve and experienced	97
VALENCE[8]	SOF + RBV (24w)	3	Naïve	84

1. Kwo P, et al. EASL 2015. Poster LP14 2. Afdhal N, et al. NEJM 2014;370:1483–93 3. Kowdley K, et al. NEJM 2014;370:1879–88 4. Ferenci P, et al. NEJM 2014;370:1983–92 5. Andreone P, et al. Gastroenterology 2014;147:359–65 6. Zeuzem S, et al. NEJM 2015;370;1604–14. 7. Lawitz E, et al. *N Engl J Med* 2013;368:1878-87. 8. Jacobson IM, et al. *N Engl J Med* 2013;368:1867-77

DAAs are well tolerated

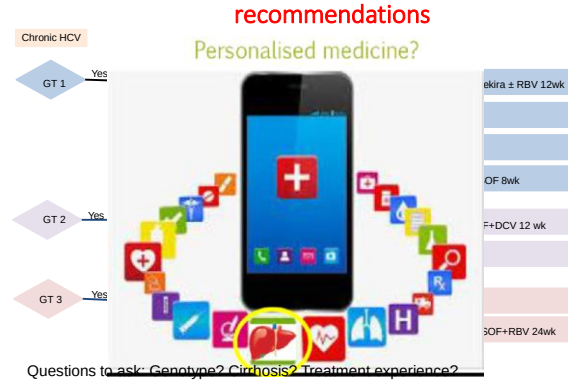
Common Adverse Events	
SOF	Fatigue
LDV/SOF	Fatigue, headache
SMV	Pruritus, nausea, myalgia, dyspnea, photosensitivity, rash
PTV/OMB/DSB	Fatigue, nausea, pruritus, skin reactions, insomnia, asthenia, ALT elevations, bilirubin elevations, anemia
Serious Adverse Events	
SOF	None
LDV/SOF	None
SMV	Photosensitivity, rash, jaundice (cirrhosis)
PTV/OMB/DSB	None

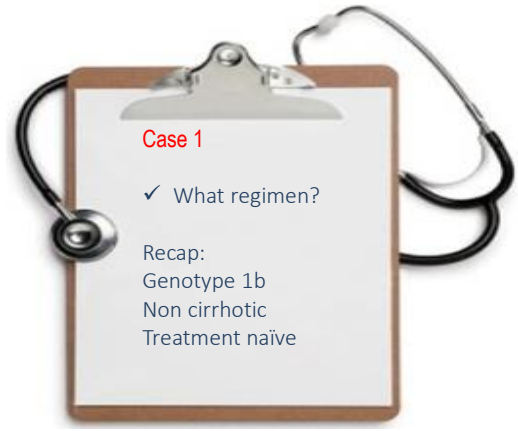
PBAC recommendations

Drug	
Sofosbuvir + Ribavirin	GT 2 TN and TE
Sofosbuvir/Ledipasvir	GT1 TN and TE
Sofosbuvir + Daclatasvir	GT1 TN and TE GT 3 TN and TE
Sofosbuvir + PEG-IFN + Ribavirin	GT1 TN and TE GT 3 TN and TE
Paritaprevir/r + Ombitasvir+ Dasabavir +/- Ribavirin	GT1 TN and TE

- No liver disease stage restrictions
- Potential for General Scheduling (S85) prescribing (GP prescribing and community pharmacy dispensing)
  - Restrictions? Creditalling?
- Ongoing price negotiations
- Federal Cabinet approval required
  - Cost of treating ~ 62,000 patients with these DAAs over the next 5 years would cost over $3 billion
- Probable PBS listing Feb 2016

Potential IFN free regimens based on PBAC recommendations



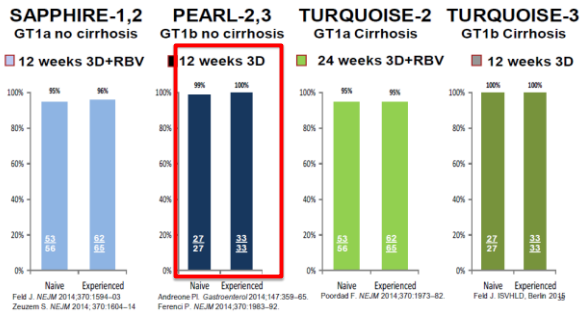


AbbVie-3D regimen in HCV GT 1:

Viekira: Paritaprevir/Ritonavir/Ombitasvir+Dasabuvir ± RBV

- **Paritaprevir**
  - NS3/4A protease inhibitor
  - Boosted with **Ritonivir** (r)
  - Once daily 150mg
- **Ombitasvir**
  - NS5A inhibitor
  - Once daily, 25mg, co-formulated with Paritaprevir/r
- **Dasabuvir**
  - NS5B inhibitor
  - Twice daily 250mg
- **Ribavirin if Genotype 1 or 1a**
  - 1000mg daily if <75kg, 1200mg daily if >75 kg

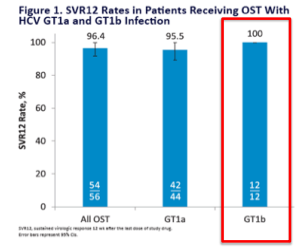
Efficacy of Viekira in HCV GT-1



Similar SVR rates for those on opioid substitution therapy

- Phase II, multicenter, open-label, single-arm study in treatment-naïve or peginterferon/ribavirin treatment-experienced HCV genotype 1-infected patients on **methadone or buprenorphine ± naloxone**
- Ombitasvir/ritonavir/paritaprevir + dasabuvir ± ribavirin

Common adverse events	
Nausea	19 (50.0)
Fatigue	18 (47.4)
Headache	12 (31.6)
Insomnia	7 (18.4)
Rash	6 (15.8)
Anxiety	5 (13.2)
Arthralgia	5 (13.2)
Anemia	4 (10.5)
Irritability	4 (10.5)
Vomiting	4 (10.5)



Lalezari J et al J Hepatol 2015;63:364-69

Gilead's Harvoni in HCV GT 1: Ledipasvir/Sofosbuvir

- **Ledipasvir** (NS5A inhibitor)
  - Picomolar potency against HCV GT 1a and 1b[1]
  - Once-daily, oral, 90 mg

LDV NS5A inhibitor

- **Sofosbuvir** (NS5B polymerase inhibitor)
  - Potent pan-genotypic antiviral activity
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet

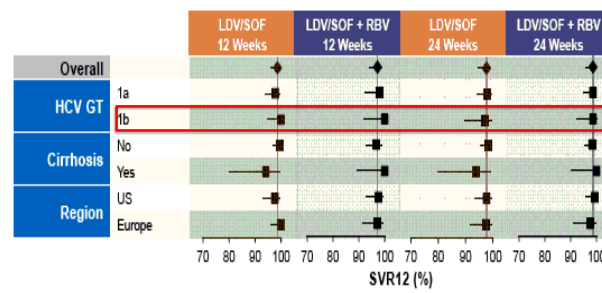
SOF nucleotide polymerase inhibitor

- **Ledipasvir/Sofosbuvir FDC**
  - Once-daily, oral fixed-dose (90/400 mg) combination tablet

LDV NS5A inhibitor + SOF nucleotide polymerase inhibitor

1. Lawitz E, et al. EASL 2011, poster 1219

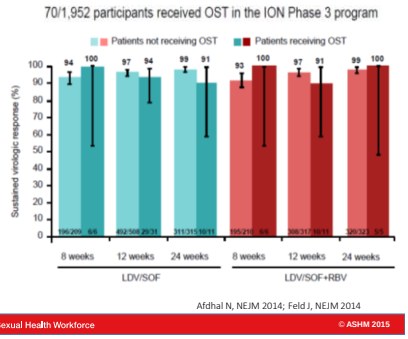
Efficacy of LDV/SOF (Harvoni) ± RBV in HCV GT 1



Afdhal N, et al. N Engl J Med. 2014;370:1889-98.

Ledipasvir/sofosbuvir is efficacious and well-tolerated among people receiving OST

- No significant differences were identified between OST and non-OST participants:
  - Overall SVR12 (94% vs. 97%, p=0.29)
  - Adherence to LDV/SOF alone≥80% (94% vs. 96%, p=0.33)
  - Proportion with AEs (89% vs. 80%, p=0.07)
- No cases of HCV reinfection were observed up to SVR24



Afdhal N, NEJM 2014; Feld J, NEJM 2014

Case 1

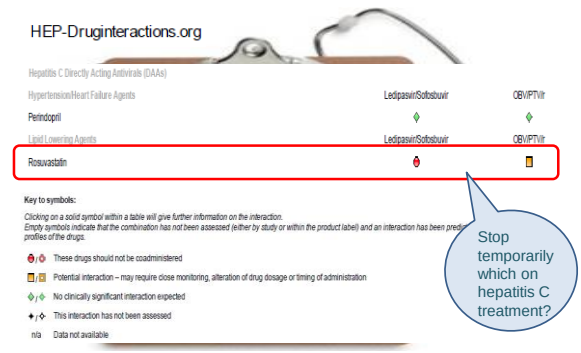
He is on Methadone, Perindopril and Rosuvastatin

- ✓ Check for drug interactions
- ✓ Monitor adherence

Web resources for drug interactions

- Not specific to ARV
  - University of Liverpool
    - www.hep-druginteractions.org
  - Toronto General Hospital
    - http://www.hcvdruginfo.ca/
  - University of Buffalo ACTG Pharmacology Support Laboratory
    - http://tdm.pharm.buffalo.edu/home/di_search/
- Specific to ARV
  - DHHS Guidelines Drug Interaction Tables
    - www.aidsinfo.nih.gov

For this case 1:



No interactions with Methadone

Case 1

He has is treated with Viekira through EAP

- ✓ What on treatment monitoring is required?
- ✓ How important is adherence?

On treatment monitoring

- Side effects
- Compliance

- Week 4
  - Laboratory:
    - Hyperbilirubinaemia, transaminitis
    - Anaemia if on Ribavirin
    - HCV PCR
  - Compliance

Impact of IDU on adherence

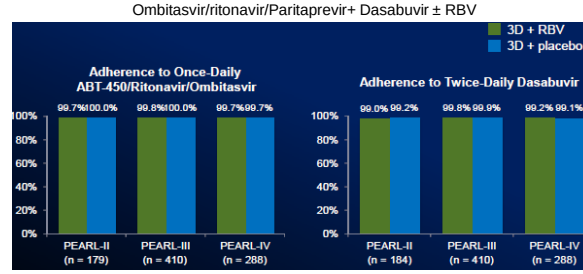
- History of IDU recent drug use at treatment initiation have limited impact on adherence or treatment completion
  - Some studies have found lower treatment completion in those with a history of IDU or recent drug use
- Occasional drug use during treatment does not seem to impact adherence or treatment completion
  - Lower adherence has been observed in persons with frequent drug use (daily/every other day) during treatment
- Factors associated with adherence/treatment completion include lower education and unstable housing

1) Grebely J, J Hepatology 2011. 2) Marcellin P, Liver Int 2011. 3) Lo Re V, Clin Infect Dis 2009. 4) Manolakopoulos Liver Int 2010. 5) Wilkinson M, Aliment Pharmacol Ther 2009. 5) Sola R, AIDS Res Hum Retroviruses 2006. 6) Sylvestre DL, Eur J Gastroenterol Hepatol 2007. 7) Hellard M, Clin Infect Dis 2009. 8) Robaeys G, Eur J Gastroenterol Hepatol 2006. 9) Papadopoulos V, Arq Gastroenterol 2010.10) Jafferbhoy H, J Viral Hepat 2012. 11) Cournot M, Gastroenterol Clin Biol 2004.

Adherence to Viekira

- 3 phase 3 studies of Viekira and RBV in patients with HCV genotype 1
  - Mean adherence >98.5% for all patients

Ombitasvir/ritonavir/Paritaprevir+ Dasabuvir ± RBV



Bernstein DE, et al. AASLD 2014 Abstract 1953

Adherence with DAA regimens NIAID Synergy Trial

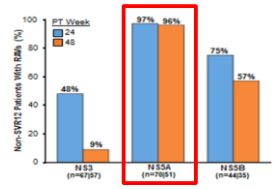
- Phase II trial: 60 treatment naïve, genotype 1 – 3 arms
  - Sofosbuvir + Ledipasvir (FDC) 12 weeks 1 pill QD (n=20)
  - FDC + GS9451 6 weeks 2 pills QD (n=20)
  - FDC + GS9669 6 weeks 3 pills QD (n=20)

- Adherence declines with increasing pill burden
- Adherence declines during 12-week treatment
- Common reasons for non-adherence were feeling that drugs were working (39%), forgetting (35%) and absence from home (32%)

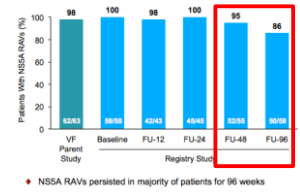
Petersen et al. CROI 2014, #667

What about resistance?.... Resistance persists especially for NS5A

Persistence of Resistance associated Variants (RAVs) with Ombitasvir/ Paritaprevir/R + Dasabuvir



Persistence of NS5A RAVs after treatment with Ledipasvir



Adherence is crucial to success of treatment and prevention of resistance and relapse

Krishnan P et al EASL 2015 Abstract 0057

Dvory-Sobol H, et al EASL 2015 Abstract 0059

Case 2

53 yo secretary

- Diagnosed with HCV 2010: brief IVDU in 20s, blood transfusion during 1st pregnancy
- Treated with peg-interferon and ribavirin for 24 weeks but was a null-responder (failed to achieve negative HCV RNA during treatment)
- Clinically well
- Drinks 10-20g wine daily
- No significant clinical findings on examination. BMI 27

Case 2

- HCV genotype: 3a
- HCV RNA 1.23 x 10^7 IU/ml
- LFT: Alb 35, bil 19, AST 106, ALT 125, GGT 75, ALP 125
- FBC: Hb 12.5, WCC 4.5, plts 121
- INR 1.2
- AFP 14
- Fibroscan score: 16.1 kPa

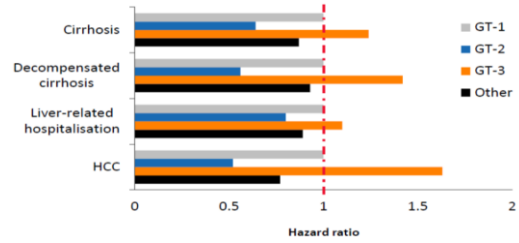
Case 2

This patient has genotype 3a with a fibroscan score 16.1 kPa.

✓ Before treating her what other management issues do you need to consider in patient with cirrhosis?

HCV GT-3 patients are at a higher risk for late-stage liver disease events and death

VA observational study – cohort of 28 769 patients from 1999-2014



McCombs J et al, JAMA Intern Med 2014;174:2014-12

Managing of cirrhosis

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Liver transplant

Screen for varices (EGD):
- Large varices → beta-block/EVL
- Small varices → EGD in 1-2 yrs
- No varices → EGD in 2-3 yrs

Screen for HCC:
- Ultrasound every 6 months

- Stop alcohol
- Vaccinations
- Lifestyle changes

Case 2

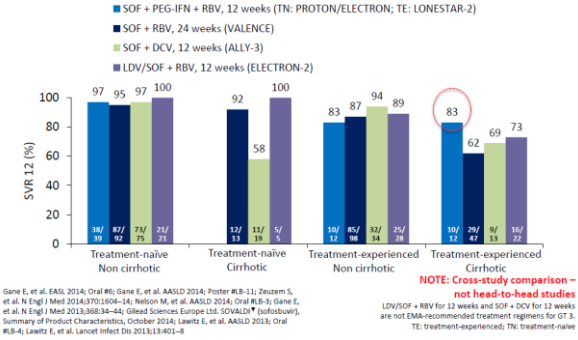
- HCC screening
  - AFP 14
  - Ultrasound: small cirrhotic liver is cirrhotic, splenomegaly (15cm), no ascites. No liver masses
- Gastroscopy: grade 1 varices

Case 2

- Genotype 3a
- Cirrhotic
- Treatment experienced: null responder to PEG/RBV

✓ What are her treatment options?

SVR12 rates in treatment-naïve and -experienced GT 3 patients with SOF-based



Gane E, et al. EASL 2014; Oral #6; Gane E, et al. AASLD 2014; Poster #LB-11; Zeuzem S, et al. N Engl J Med 2014;370:1604–14; Nelson M, et al. AASLD 2014; Oral #LB-3; Gane E, et al. N Engl J Med 2013;368:34–44; Gilead Sciences Europe Ltd. SOVALDI® (sofosbuvir), Summary of Product Characteristics, October 2014; Lawitz E, et al. AASLD 2013; Oral #LB-4; Lawitz E, et al. Lancet Infect Dis 2013;13:401–8

NOTE: Cross-study comparison – not head-to-head studies

LDV/SOF + RBV for 12 weeks and SOF + DCV for 12 weeks are not EMA-recommended treatment regimens for GT 3.
TE: treatment-experienced; TN: treatment-naive

PWIDs did just as well – similar results to SOF registration trials

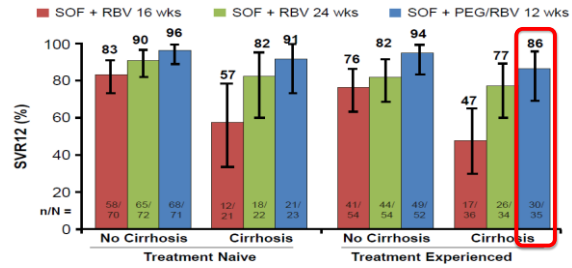
Cohort (n=60) of PWIDs initiating treatment on-site at an opiate agonist treatment program with sofosbuvir-based regimens in New York

Virologic Outcome	N (%)
Overall ETR	58 (95)
Overall SVR12	49 (80)
Genotype 1 (n=21)	18 of 21 (86)
G1 (SOF/RBV/PEG; n=7)	7 of 7 (100)
G1 (SOF/RBV; n=15)	11 of 14 (79)
Genotypes 2 and 3 (n=39)	31 of 39 (79)
G2 (SOF/RBV; n=17)	13 of 17 (76)
G3 (SOF/RBV/PEG; n=1)	1 of 1 (100)
G3 (SOF/RBV; n=21)	17 of 21 (81)
Genotype 4	0 of 1 (0)
G4 (SOF/RBV; n=1)	0 of 1 (0)

- Adherence significantly decreases over 24 week period suggesting shorter courses of treatment (≤ 12 weeks) important in people who inject drugs
- No association between active drug use (either prior or during treatment) and SVR

Litwin AH et al, INHSU 2015

BOSON: SOF based regimens in HCV GT 3

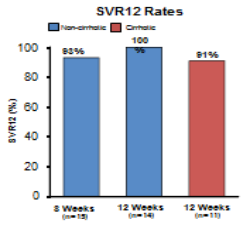


- Clear advantage to Peg/RBV/SOF –especially in cirrhosis
- Only 1 treatment-discontinuation –good safety

Foster GR, et al. *EASL 2015*. Abstract L05.

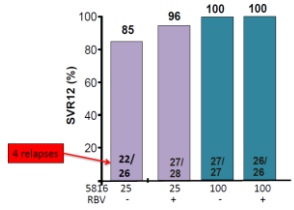
Wait for future combo…

C-SWIFT: Grazoprevir/Elbasvir + Sofosbuvir

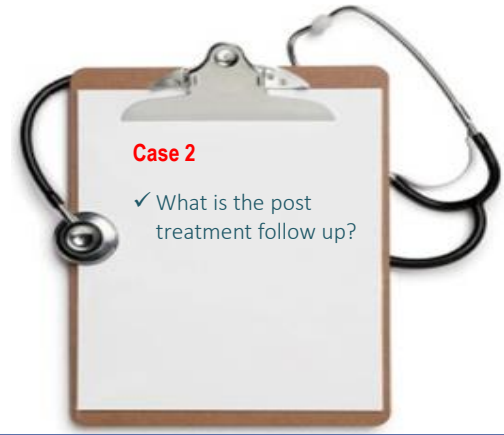


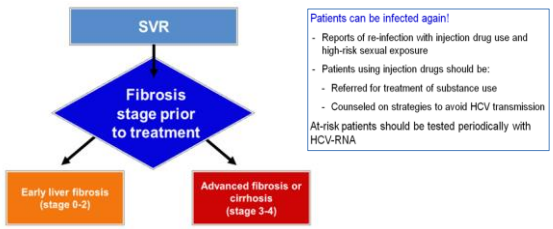
Poordad F, et al. EASL 2015. Abstract O006.

ELECTRON-2: Sofosbuvir + Velpatasvir (GS-5816) ± RBV in non cirrhotic treatment naïve GT3a



Pianko S et al, AASLD 2014; Gane EJ, et al. AASLD 2014. Abstract 79.





Patients can be infected again!

- Reports of re-infection with injection drug use and high-risk sexual exposure
- Patients using injection drugs should be:
  - Referred for treatment of substance use
  - Counseled on strategies to avoid HCV transmission

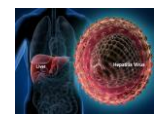
At-risk patients should be tested periodically with HCV-RNA

Monitoring in Patients with Sustained Virological Response (SVR) and Early Liver Fibrosis Stage

- Annual liver tests and complete blood count
  - Repeat HCV-RNA if liver enzymes were normal and become abnormal
  - Does the patient have another liver diagnosis? (e.g. fatty liver, HBV, hemochromatosis)
    - May have persistently abnormal results after HCV cure
    - If so, follow up for progression of liver disease
- Liver cancer surveillance: not indicated
- Variceal surveillance: not indicated

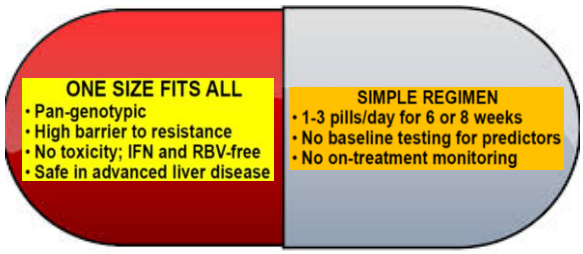
Monitoring in Patients with Sustained Virological Response (SVR) and Advanced Liver Fibrosis

- Routine clinic appointments 1-2 times per year
  - Consider alternating with hepatology follow-up
- History, exam for signs of cirrhosis decompensation
  - Bleeding? Edema? Ascites? Confusion?
- Screening endoscopy (for varices) / HCC screening
- Comprehensive metabolic profile, INR, CBC
  - Repeat HCV RNA if abnormal liver enzymes
  - Calculate MELD score
    - Total bilirubin, creatinine, INR
    - Transplant evaluation if MELD >15

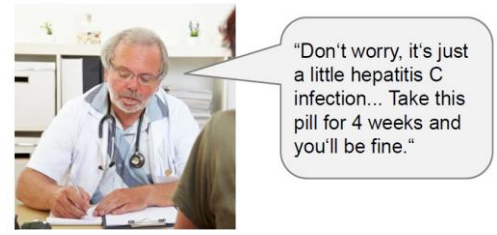


What's in the pipeline for HCV?

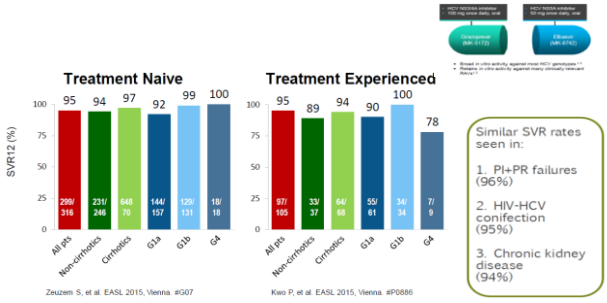
Future hope……



Ideal future scenario:
Hepatitis C just a minor nuisance?



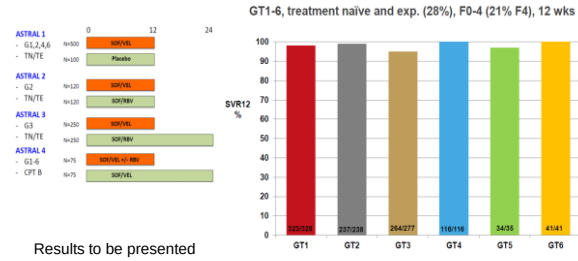
C-EDGE: Grazoprevir/Elbasvir in treatment-naïve, HCV genotypes 1, 4, or 6



Zeuzem S, et al. EASL 2015, Vienna. #G07

Kwo P, et al. EASL 2015, Vienna. #P0886

ASTRAL 1-4: Sofosbuvir/Velpatasvir



Results to be presented at AASLD 2015

Gilead press release, 21 Sep 2015

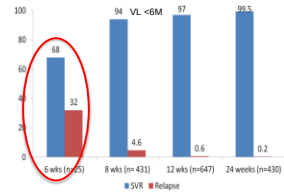
simplify

A phase II, open-label, multi-centre, international trial of sofosbuvir and GS-5816 for people with chronic hepatitis C virus infection and recent injection drug use

- SOF/VEL x 12 weeks
- Recent injection drug use (within 6 months)
- Genotypes 1 to 6
- International, multi-centre study to treat 100 people with goal of 90% SVR12
- Starting to enroll now…

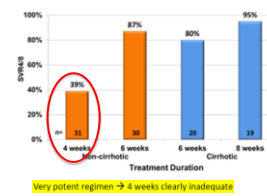
How short can we go?

Sofosbuvir/Ledipasvir in treatment naïve GT1, no cirrhosis (6 and 8 weeks), or ± cirrhosis (12 and 24 weeks)



Gane EJ et al Gastro 2014; Kowdley KV et al NEJM 2014; Adhfal N et al NEJM 2014

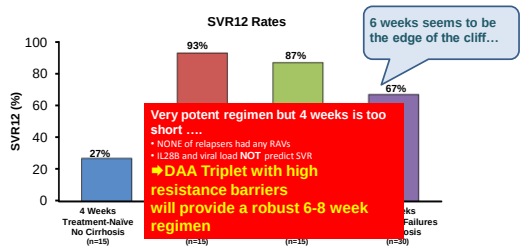
C-SWIFT: Grazoprevir/Elbasvir + Sofosbuvir in treatment naïve GT 1 ± cirrhosis for 4,6,8 weeks



Very potent regimen → 4 weeks clearly inadequate

Lawitz E et al, AASLD 2014 Abstract LB-33

LEPTON: Sofosbuvir (NS5B) /GS-5816 (NS5A) + GS-9857 (NS3) in GT 1 and 3 ± Cirrhosis



Gane E, et al. *J Hepatol.* 2015;62(suppl 2):S264. Abstract LP03; Poordad F, et al EASL 2015.

The HCV Challenge: 'trace and treat'

Find them and get them onto treatment

- For PWIDs or people in OST the finding has already been done
- The patients are accessible in services
- But we must proactively screen them and link them to care

- Successful engagement is heavily influenced by the nature of the provider/clinic
- Clinical teams are very important

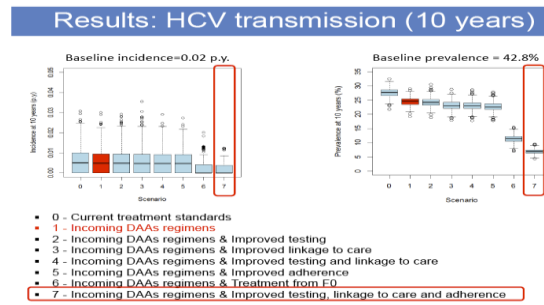
Foster G 2014

Access to treatment must be improved to reduce or eliminate the burden of the

Increasing efficacy without increasing access to therapy means that the new treatments will not have any major impact on the disease burden of HCV

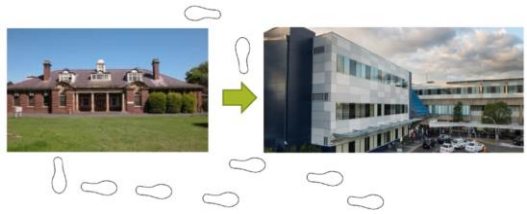
- Targeted programs for those with risk of transmitting:
  - PWID, prisoners, HIV+ MSM, antenatal women
- Expansion of treatment – different models of care: liver clinic, D&A clinics, prisons, primary care
- Support by pharmaceutical industry (Gilead HCV treatment expansion program)
- Partnerships & public health advocacy
- Improvement in implementation of primary prevention strategies – NSP, OST

Impact of new DAA-containing regimens on HCV transmission among IDUs



Cousien A et al EASL 2014

Referral to specialists in hospital-based liver clinics…… it's easy to get lost!



Liver clinics can't treat everyone!

- Lack capacity even if we had access to the drugs
- We need to move out of specialty clinics

- Although DAAs are more potent and better tolerated, regimens still complicated…so we need to simplify

Other players....

Framework for HCV control strategy for PWID

Prevent new infections	Detect and care for existing infections	Reduce chronic infections
HCV prevention activities • Access to syringes & other equipment • OST • Safe injection education • Outreach to those not engaged	**Screening and diagnosis** • Antibody screening • RNA test to confirm infection • Clinical evaluation to determine disease stage • Monitoring disease progression • Reduce alcohol use	**HCV care and treatment** • Treat to cure infection • Support adherence to treatment • Support post-cure to prevent reinfection

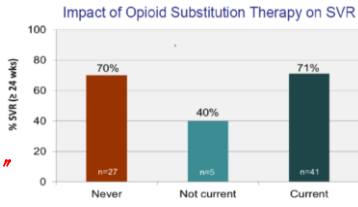
Role for Drug Health

Co-locating these services increases their impact on HCV control

Enhancing Treatment of Hepatitis C in OST Settings(ETHOS) Study

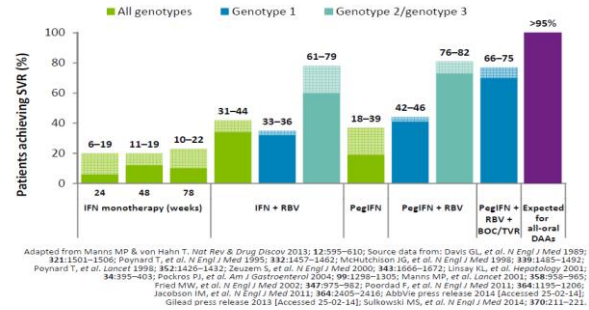
Effectively engaging PWIDs in HCV care through HCV assessment and treatment, via HCV nursing and HCV specialist support in integrated opioid substitution treatment (OST) or community health clinics (CHCs) can increase engagement in HCV care

"One stop shop"



Alavi et al Clin Infect Dis 2013

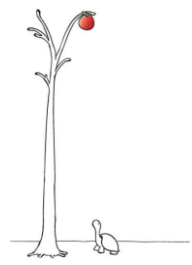
Is eradication the next stage in the evolution of HCV treatment?



Adapted from Manns MP & von Hahn T. *Nat Rev & Drug Discov* 2013; **12**:595–610; Source data from: Davis GL, *et al. N Engl J Med* 1989; **321**:1501–1506; Poynard T, *et al. N Engl J Med* 1995; **332**:1457–1462; McHutchison JG, *et al. N Engl J Med* 1998; **339**:1485–1492; Poynard T, *et al. Lancet* 1998; **352**:1426–1432; Zeuzem S, *et al. N Engl J Med* 2000; **343**:1666–1672; Linsay KL, *et al. Hepatology* 2001; **34**:395–403; Packros PJ, *et al. Am J Gastroenterol* 2004; **99**:1298–1305; Manns MP, *et al. Lancet* 2001; **358**:958–965; Fried MW, *et al. N Engl J Med* 2002; **347**:975–982; Poordad F, *et al. N Engl J Med* 2011; **364**:1195–1206; Jacobson IM, *et al. N Engl J Med* 2011; **364**:2405–2416; AbbVie press release 2014 [Accessed 25-02-14]; Gilead press release 2013 [Accessed 25-02-14]; Sulkowski MS, *et al. N Engl J Med* 2014; **370**:211–221.

Viral Eradication with Interferon Based Regimes was Never Going to Occur... But, DAAs Provide an Opportunity to Eradicate HCV

but....



There are still ***major challenges***

HCV treatment as prevention

The prospect of an all-oral, pan-genotypic, 2- to 3-month treatment courses without major side effects or drug interactions and rates of SVR >90%, offers hope for the elimination / eradication of HCV infection

Reasons to strive for HCV elimination through treatment

- Rising burden of HCV-related liver disease and mortality
- Evidence for extra-hepatic HCV morbidity and mortality
- Entering new era of highly effective DAA-based therapy (SVR 90-95%)
- Modest success in HCV prevention through harm reduction (eg, needle and syringe exchange, opioid substitution therapy)

Strategies towards HCV elimination

- Prevent transmission of incident infection
- Prevent progression to clinical disease
- Broad expansion of HCV treatment access
- Targeted programs for those with risk of transmitting:
  - PWID, prisoners, HIV+ MSM, antenatal women
- Develop simplified regimens for use in other models of care
- Partnerships & public health advocacy
- Drug price reform

PWID network structure plays a role in HCV transmission

- HCV elimination as a public health problem is possible but we need to treat people who drive transmission as well as those with chronic infection
- The network may impact on the effectiveness of treatment strategies
- With the advent of new DAAs there is an opportunity to exploit PWID networks to target HCV treatment
- The "bring a friend strategy" had a greater impact on HCV prevalence than treating PWID "randomly"
- May improve cost effectiveness of treating PWID

Hellard M et al, INHSU 2015

Take home message

- Hepatitis C can be cured especially with the new DAAs
- Routinely screen high-risk adults
- Link these patient into care
- Patient counselling appropriate lifestyle modifications is also critical to chronic HCV care as it is also a liver disease not just an infection
- Follow patients with HCV who achieve SVR in an effort to avert risk of reinfection

ashm Supporting the HIV, Viral Hepatitis and Sexual Health Workforce
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Thank you

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