HIV/Hepatitis co-infection

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Aims

• Context

• Guidelines- “highlights”
  – BHIVA Hepatitis Guidelines 2013 (updated 2014)
  – BHIVA Guidelines on vaccination 2015
  – EACS guidelines Oct 2019 (+ EASL)
HIV/hepatitis co-infection
What is hepatitis?

• ‘hepat’ = liver
• ‘itis’ = inflammation
• Viral hepatitis....

  – A  [VACCINE PREVENTABLE]
  – B
  – C  Blood, sexually transmitted, often chronic
  – D  Only with B, usually chronic
  – E  Faeco-oral, rarely chronic
      (vaccine not available in UK further trials currently underway in USA)
Hepatitis A - outbreak update

- 74% MSM, 63% in London
- Early cases acquired abroad
- Transmission later mainly in UK
- 3 G1a strains - UK/Europe to Feb 18:
  - Spanish strain: 56/666
  - Europride strain: 168/379
  - Berlin strain: 39/103
- Vaccination recommended to at risk MSM
Hepatitis A

- Faecal-oral transmission
- Incubation period 15-45 days (average 28 days)
- Infectious 2 weeks pre jaundice and one week after jaundice
  Viraemia may continue for up to 90 days in PLWHIV
- Up to half of adults asymptomatic – with little or no jaundice
- More common in: travel, MSM, PWID
- Can cause fulminant hepatitis – rare <1 % but mortality 45%

- 2016 England and Wales n=444
- 2017 England and Wales n=942
**Europe figures to Feb 18**

Event 1 – Cluster VRD_521_2016 (n=666) ‘Spanish strain’
UK reports in MSM (n=56), links with travel to Spain, later Portugal and Italy. Phylogenetic links with Central/South America

Event 2 – Cluster RIVM-HAV16-090 (n=379) ‘Europride strain’
Reports from Netherlands, including high-risk MSM EUROPRIDE attendees (Amsterdam July/Aug 2016), most later cases UK (n=168), France, Italy. Phylogenetic links with Asia

Event 3 – Cluster V16-25801 (n=103) ‘Berlin strain’
Germany, UK (n=39). Phylogenetic links with South America
# British HIV Association guidelines on the use of vaccines in HIV-positive adults: summary of recommendations

## Infection/disease

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Replicating</th>
<th>Primary course</th>
<th>Indication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccines with broad indications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Inactivated</td>
<td>No</td>
<td>2 or 3 doses</td>
<td>Non-immune, at risk; 3 doses if CD4 count &lt;350 cells/μL</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Subunit</td>
<td>No</td>
<td>4 doses</td>
<td>All non-immune; Dose: Engerix B 2x20μg; HBsVAXPRO 40μg; Fendrix 20μg</td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>VLP</td>
<td>No</td>
<td>3 doses</td>
<td>Age and gender related; 4vHPV or 5vHPV preferred; see BHIVA guidance</td>
</tr>
<tr>
<td>Influenza</td>
<td>Inactivated</td>
<td>No</td>
<td>1 dose</td>
<td>All, yearly; Quadrivalent vaccine preferred</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>Conjugated</td>
<td>No</td>
<td>2 doses</td>
<td>Age related, at risk; MenACWY; combined as Hib/MenC; follow national guidance</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>Recombinant protein + OMV</td>
<td>No</td>
<td>2 doses</td>
<td>Age related, at risk; MenB; follow national guidance</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>Conjugated</td>
<td>No</td>
<td>1 dose</td>
<td>All, once; PCV-13</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Polysaccharide</td>
<td>No</td>
<td>1 dose</td>
<td>At risk, once; PPV-23; follow national guidance</td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>Live attenuated</td>
<td>Yes</td>
<td>2 doses</td>
<td>All non-immune; Combined as MMR; CD4 count &gt;200 cells/μL</td>
</tr>
<tr>
<td>Varicella (chickenpox)</td>
<td>Live attenuated</td>
<td>Yes</td>
<td>2 doses</td>
<td>All non-immune; CD4 count &gt;200 cells/μL</td>
</tr>
<tr>
<td>Herpes zoster (shingles)</td>
<td>Live attenuated</td>
<td>Yes</td>
<td>1 dose</td>
<td>All non-immune; CD4 count &gt;200 cells/μL; VZV IgG +; follow national guidance</td>
</tr>
<tr>
<td><strong>Vaccines with predominantly travel-related indications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholera</td>
<td>Inactivated + subunit</td>
<td>No</td>
<td>2 doses</td>
<td>Selective use; WC/rbs; oral administration</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Vero cell-derived inactivated</td>
<td>No</td>
<td>2 doses</td>
<td>Combined as Td/IPV vaccine</td>
</tr>
<tr>
<td>Tick-borne encephalitis</td>
<td>Inactivated</td>
<td>No</td>
<td>3–4 doses</td>
<td>Combined as Td/IPV vaccine</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Toxoid</td>
<td>No</td>
<td>1 dose</td>
<td>Combined as Td/IPV vaccine</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Toxoid</td>
<td>No</td>
<td>1 dose</td>
<td>Combined as Td/IPV vaccine</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>Inactivated</td>
<td>No</td>
<td>1 dose</td>
<td>Combined as Td/IPV vaccine</td>
</tr>
<tr>
<td>Rabies</td>
<td>Cell-culture derived</td>
<td>No</td>
<td>3 doses</td>
<td>5 doses for post-exposure prophylaxis</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Polysaccharide</td>
<td>No</td>
<td>1 dose</td>
<td>VICPS; parenteral</td>
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<tr>
<td>Yellow Fever</td>
<td>Live attenuated</td>
<td>Yes</td>
<td>1 dose</td>
<td>&lt;60 years only; CD4 count &gt;200 cells/μL</td>
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<tr>
<td><strong>Vaccines with selected indications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthrax</td>
<td>Filtrate of bacterial proteins</td>
<td>No</td>
<td>4 doses</td>
<td>Occupational</td>
</tr>
<tr>
<td>Haemophilus influenzae B</td>
<td>Conjugated</td>
<td>No</td>
<td>1 dose</td>
<td>At risk; Combined as Hib/MenC</td>
</tr>
<tr>
<td><strong>Not preferred and contraindicated vaccines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A/B combined</td>
<td>No</td>
<td>Not preferred</td>
<td>Reduced immunogenicity</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A/typhoid combined</td>
<td>No</td>
<td>Not preferred</td>
<td>Reduced HAV immunogenicity</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>Live attenuated</td>
<td>Yes</td>
<td>Non preferred</td>
<td>Oral administration</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>BCG</td>
<td>Yes</td>
<td>Contraindicated</td>
<td></td>
</tr>
<tr>
<td>Typhoid</td>
<td>Live attenuated</td>
<td>Yes</td>
<td>Contraindicated</td>
<td>Oral administration</td>
</tr>
</tbody>
</table>

VLP: virus-like particle; OVM: outer membrane vesicles; Hib: Haemophilus Influenzae B; Td/IPV: tetanus/diphtheria/inactivated poliovirus; dTaP/IPV: diphtheria/tetanus/acellular pertussis/inactivated poliovirus; VZV: varicella zoster virus; AVP: anthrax vaccine precipitated; VICPS: Vi capsular polysaccharide vaccine

Hep A vaccine – 2- 3 doses ( 3 if CD4 count < 350 cells/ul)

2 doses HAV vaccine in non- HIV population give 25 years protection? Lifelong?
Distribution of hepatitis A cases by gender and male-to-female ratio, January 2012 to March 2018, as of 19 March 2018, EU/EEA
HIV and Hepatitis B/C co-infection

Rank in terms of global prevalence – 2017 figures

1. HBV = 257 million – 1% HIV co-infected
2. HCV = 71 million
3. HIV = 37 million – HBV prevalence 7.4%

• Prevalence of detectable sAg in HIV in UK = 6.9%
  – More common in Black/Other ethnicity, PWID, MSM

WHO figures 2017 [www.who.int](http://www.who.int) accessed Jan 2020
WHO Global Hepatitis Report 2017

• **Viral Hepatitis** caused 1.34 million deaths in 2015
  – comparable to TB, higher than HIV
• **Mortality** from TB, HIV and malaria falling whilst
  – from hepatitis it’s increasing
• **Eliminate** viral hepatitis as a public health threat by 2030
  – reducing new infections by 90% and mortality by 65%

**Mechanisms:**
– HBV vaccination
– Access to DAA treatment for HCV
– Improved safety in healthcare settings

WHO Global Hepatitis report 2017
Prevalence of Chronic Hep B in adults

**Globally**
- 257 million (3.5% population) chronic HBV
- 2.7 million HIV/HBV
- Global prevalence of HBV in HIV patients 7.4%
- > Half of all liver cancers associated with HBV
- 650,000 deaths per year

**UK**
- 180,000 cases

World Health Organization

HBV genotypes (currently 10)

Findings inconsistent across geographical areas - more work needed
- B associated with less active disease, slower progression, and lower incidence of HCC than C
- A and B respond better to IFN than C and D
- Genotype does not predict on-treatment response to oral agents: NOT routinely performed

Geographic Distribution of HBV genotypes
- A = Northern Europe, North America, Southern Africa
- B & C = Asia
- D = Southern Europe, the Middle East & India
- E = West Africa
- F = Central & South America
- G = France, Germany & USA
- H = Central America
- I = Vietnam and Laos
- J = Ryuku Island in Japan

Genotype D most common in UK (31%)
HBV England- acute cases HBV 2016

Diagnosis:
• HBs Ag positive
• anti Hep B core IgM positive and consistent LFTS

Routes of transmission for acute cases
• ~ 50% heterosexual sex
• ~ 20% MSM sex
• Of remaining 30%
  – ~ 50% PWID, ~ 6% healthcare, ~ 2% piercing/ tattoo/ acupuncture

30% of all new cases reported a relevant travel history

Acute HBV mono-infection

• More than 95% of adults with acute HBV do not require specific treatment as they will fully recover spontaneously

• Only patients with severe acute HBV should be treated with NRTI and considered for liver transplantation
  – Coagulopathy (INR >1,5)
  – Or protracted course jaundice > 4 weeks
  – or acute liver failure

EASL Guidelines 2017
Developing Chronic Hep B

- Depends on age acquired:
  - 90% infected perinatally
  - 20-50% children 1-5 years
  - 5% of previously healthy adults (higher if immunocompromised)
Complications of HBV

• 20-30% develop progressive liver disease

• Progression risk:
  – relates to level of viral replication in the liver
  – Accelerated if other hepatic comorbidity eg alcohol, steatosis etc

• Individuals with active inflammation where there is rapid cell turnover and/or cirrhosis are at increased risk of developing HCC

• Risk of onward transmission to partners/ MTC
5%-10% of chronic HBV-infected individuals

30% of chronic HBV-infected individuals

23% of patients decompensate within 5 years of developing cirrhosis

Natural history with HIV/HBV co-infection

- Lower rates of clearance of Hep B e Ag
- Increased serum HBV DNA viral load\(^1\)
- More rapid onset of fibrosis, cirrhosis and HCC
- Several HBV drugs also have HIV activity
  - High risk of HIV resistance if not given as combination treatment

PLWHIV - mortality

Chronic viral hepatitis 447 (11%)
### Blood markers, nomenclature

- **HBsAg**: Surface antigen
  - HBV protein antigen shell found on surface of HBV. Indicates HBV infection.
- **HBeAg**: e antigen
  - Antigen found between nucleocapsid layer and lipid envelope. Indicates active infection.
- **HBcAg**: Core
  - Inner protein antigen layer - not present in blood therefore not tested for.
- **HBV DNA**: Virus DNA
  - Presence indicates active infection.
- **Anti-HBc IgM**: IgM antibodies to HBcAg
  - Indicates acute HBV infection.
- **Anti-HBC**: Total antibodies to HBcAg
  - Indicates HBV infection at some time.
- **Anti-HBe**: Antibody to HBeAg
  - Indicates clearance of eAntigen.
- **Anti HBs**: Surface Antibody
  - Marker of past infection or vaccination.
HIV/HBV co-infection Vaccination

Male MSM

- HIV+, treatment naive
- Results- Negative: Hep B sAg, Hep B cAb, Hep B sAb
- CD4 540

1. 20ug X 3
2. 40ug X 3
3. 40ug X 4
4. Hold off until CD4 count improved
5. Other
**Hep B vaccine**: 4 doses recommended for all non-immune

Dose – vaccine brand dependent:

- **Engerix B**: 2 x 20 µg
- **HBvaxPro**: 40 µg
- **Fendrix**: 20 µg

**BHIVA**: Schedule 0, 1, 2 and 6 months (1B)
Diagnosing and assessing HBV infection

• Virology tests
  – HBsAg, HBeAg (HBsAg can be quantified if required)
  – HBV DNA quantify
  – Genotype/ resistance testing not routinely recommended
  – Check Hep Delta Antibody – if positive check Hep Delta viral load
  – Check HAV status and vaccinate if non-immune

• Tests of liver inflammation and liver function
  – Transaminases (ALT, AST) <20 women; <35 men:
    (can have fibrosis with normal ALT),
  – bilirubin, albumin, platelets, clotting

• Assess liver fibrosis at baseline
  – Non-invasive test eg transient elastography (Fibroscan)
  – Serum fibrosis markers eg AST/platelet ratio (APRI)
  – Consider biopsy if clinical uncertainty

• Assess comorbidities: alcohol, smoking, steatosis, metabolic, HIV
Fibroscan®
Assessment of liver

USS elastography
• Measures velocity of 50MHz shear wave passing through live and converted to a stiffness score (kPA)

Median of 10 readings:
>60% success rate
IQR:median < 30%

HBV: < 6KPa = <F2 & >12KPa = F4
HIV/HBV: < 6KPa = <F2 & >11KPa = F4

Fibroscan scoring card converts stiffness score to METAVIR fibrosis stage F0 (no fibrosis) to F4 (cirrhosis or advanced fibrosis)

- BHIVA guidelines use >11 kPA HBV
- and >14.5 kPA HCV to strongly predict cirrhosis
- Score thresholds in HIV co-infection not well established
Natural history and assessment of patients with chronic HBV infection

**HBV Markers**
- HBsAg
- HBeAg/ anti Hbe
- HBV DNA

**Liver disease**
- Biochemical parameters ALT
- Fibrosis markers: non-invasive markers of fibrosis (elastography or biomarkers) or liver biopsy in selected cases

**HBeAg positive**

<table>
<thead>
<tr>
<th>Chronic Infection</th>
<th>Chronic hepatitis</th>
<th>Chronic infection</th>
<th>Chronic hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>High</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>HBeAG</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>&gt;10^7 IU/ml</td>
<td>10^4 -10^7 IU/ml</td>
<td>&lt;2,000 IU/ml**</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>None/minimal</td>
<td>Moderate/Severe</td>
<td>None</td>
</tr>
<tr>
<td>Old Terminology</td>
<td>Immune tolerant</td>
<td>Immune reactive</td>
<td>Inactive carrier</td>
</tr>
</tbody>
</table>

**HBeAg negative**

<table>
<thead>
<tr>
<th>Chronic Infection</th>
<th>Chronic hepatitis</th>
<th>Chronic infection</th>
<th>Chronic hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>High/Intermediate</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>HBeAG</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>10^4 -10^7 IU/ml</td>
<td>&gt;2,000 IU/ml</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>Elevated*</td>
<td>Normal</td>
<td>Elevated*</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>Moderate/Severe</td>
<td>None</td>
<td>Moderate/Severe</td>
</tr>
<tr>
<td>Old Terminology</td>
<td>Immune reactive</td>
<td>Inactive carrier</td>
<td>HBeAg negative chronic hepatitis</td>
</tr>
</tbody>
</table>

**EASL Hepatitis B Guidelines 2017**

**http://www.easl.eu/medias/cpg/management of hepatitis B virus infection/English report.pdf**

**HBV DNA levels can be between 2,000 and 20,000 in some patients without signs of chronic hepatitis, * Persistently or intermittently,**
Natural history – Acute course

Symptoms

- HBeAg
- anti-HBe
- Total anti-HBc
- HBsAg
- IgM anti-HBc
- anti-HBs

Weeks after Exposure

Titre

0 4 8 12 16 20 24 28 32 36 // 52 // 100
Natural history – chronic course

<table>
<thead>
<tr>
<th>Acute (6 months)</th>
<th>Chronic (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg</td>
<td>anti-HBe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Total anti-HBc</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>IgM anti-HBc</th>
</tr>
</thead>
</table>

Weeks after Exposure

Years

Titre

0 4 8 12 16 20 24 28 32 36 52
# Examples of HBV results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Negative</td>
</tr>
<tr>
<td>HBeAg</td>
<td>-</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Not detected</td>
</tr>
<tr>
<td>Anti HBC</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti HBC IgM</td>
<td>-</td>
</tr>
<tr>
<td>Anti Hbe</td>
<td>-</td>
</tr>
<tr>
<td>Anti HBs</td>
<td>132 IU/ml</td>
</tr>
</tbody>
</table>
### Examples of HBV results - 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HBeAg</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Not detected</td>
<td></td>
</tr>
<tr>
<td>Anti HBC</td>
<td>Negative</td>
<td>No prior HBV infection</td>
</tr>
<tr>
<td>Anti HBC IgM</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Anti Hbe</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Anti HBs</td>
<td>132 IU/ml</td>
<td>Successful vaccination titre</td>
</tr>
</tbody>
</table>

BHIVA:
If non-responder to vaccination ie Anti HBs < 10 iu/ml:
- 3 further doses at monthly intervals
- retest for Anti HBs 4-8 weeks after last dose

Or Depending on level of risk:
- defer repeat vaccination until CD4 >350
- Consider inclusion of TDF in ART if not immune
Examples of HBV results-2

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti HBC</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti HBs</td>
<td>&lt;10 IU/ml</td>
</tr>
</tbody>
</table>
## Examples of HBV results-2

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Current infection – needs further assessment</td>
</tr>
<tr>
<td>Anti HBC</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti HBs</td>
<td>&lt;10 IU/ml</td>
<td></td>
</tr>
</tbody>
</table>
Examples of HBV results - 3

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti HBC</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti HBs</td>
<td>&lt;10 IU/ml</td>
</tr>
</tbody>
</table>

**Isolated Anti HBC - Possibilities include:**
- “Naturally immune” ie past infection with waning sAB titre
- False positive core Ab
- Chronic carrier with low levels of Hep B sAg

**Action required:**
- Check HBV DNA
- Repeat serology test
- Give booster/ vaccinate if DNA negative
## Examples of HBV results - 4

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Positive</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Positive</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>125,280 IU/ml ($10^5$)</td>
</tr>
<tr>
<td>Anti HBC</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti HBC IgM</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti Hbe</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti HBs</td>
<td>&lt;10 IU/ml</td>
</tr>
<tr>
<td>ALT</td>
<td>350</td>
</tr>
</tbody>
</table>
### Examples of HBV results - 4

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Current HBV infection</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Positive</td>
<td>High infectivity</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>125,280 IU/ml ($10^5$)</td>
<td>High infectivity</td>
</tr>
<tr>
<td>Anti HBC</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti HBC IgM</td>
<td>Positive</td>
<td>ACUTE infection</td>
</tr>
<tr>
<td>Anti Hbe</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti HBs</td>
<td>&lt;10 IU/ml</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>350</td>
<td></td>
</tr>
</tbody>
</table>
### Examples of HBV results- 5

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Positive</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Positive</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>520,130 IU/ml (10^5)</td>
</tr>
<tr>
<td>Anti HBC</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti HBC IgM</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti HBs</td>
<td>&lt;10 IU/ml</td>
</tr>
<tr>
<td>ALT</td>
<td>25</td>
</tr>
</tbody>
</table>
Natural history and assessment of patients with chronic HBV infection

**HBV Markers**
- HBsAg
- HBeAg/ anti Hbe
- HBV DNA

**Liver disease**
- Biochemical parameters ALT
- Fibrosis markers: non-invasive markers of fibrosis (elastography or biomarkers) or liver biopsy in selected cases

**HBeAg positive**

<table>
<thead>
<tr>
<th>Chronic Infection</th>
<th>Chronic hepatitis</th>
<th>Chronic infection</th>
<th>Chronic hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>High</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>HBeAG</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>&gt;10⁷ IU/ml</td>
<td>10⁴ -10⁷ IU/ml</td>
<td>&lt;2,000 IU/ml**</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>Elevated*</td>
<td>Normal</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>None/minimal</td>
<td>Moderate/Severe</td>
<td>None</td>
</tr>
<tr>
<td>Old Terminology</td>
<td>Immune tolerant</td>
<td>Immune reactive</td>
<td>Inactive carrier</td>
</tr>
</tbody>
</table>

**HBeAg negative**

*Persistently or intermittently,

**HBV DNA levels can be between 2,000 and 20,000 in some patients without signs of chronic hepatitis,**

### Examples of HBV results- 5

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Current HBV infection</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Positive</td>
<td>High infectivity</td>
</tr>
<tr>
<td><strong>HBV DNA</strong></td>
<td>520,130 IU/ml (10⁵)</td>
<td>High infectivity</td>
</tr>
<tr>
<td>Anti HBC</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti HBC IgM</td>
<td>Negative</td>
<td>Not acute</td>
</tr>
<tr>
<td>Anti HBs</td>
<td>&lt;10 IU/ml</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>25</td>
<td>Tolerating viraemia</td>
</tr>
</tbody>
</table>

**??**
- New nomenclature: “chronic infection”
- Previously “immune tolerant”
- BUT Viraemia a little low for EASL definition >10⁷ IU/ml

**Action:**
- Repeat monitoring bloods and fibroscan 2-4 months
- Review pattern of previous results +/- discuss at MDT
- Consider liver biopsy/ treat

NB normal ALT: females 19-25 IU/ml, males 40 IU/ml
### Examples of HBV results - 6

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>HBeAg</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>HBV DNA</td>
<td>30,130 IU/ml ($10^4$)</td>
<td></td>
</tr>
<tr>
<td>Anti HBC</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti Hbe</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti HBs</td>
<td>&lt;10 IU/ml</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>
Examples of HBV results - 6

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Positive</td>
<td>Current HBV infection</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Positive</td>
<td>High infectivity</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>30,130 IU/ml (10^4)</td>
<td>Lower levels</td>
</tr>
<tr>
<td>Anti HBC</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti Hbe</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti HBs</td>
<td>&lt;10 IU/ml</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>96</td>
<td>Elevated &gt;2 x ULN</td>
</tr>
</tbody>
</table>

Chronic hepatitis
“immune reactive”
HBV/HIV treatment

When?
• All patients with HIV (HBV active HIV therapy)

What?
• Nucleoside/nucleotide analogues (years- indefinite)
• Tenofovir disoproxil/ Tenofovir alafenamide
• If intolerant – entecavir HBV resistance low risk)
  – fully active ART
• Lamivudine/ adefovir/ telbivudine not recommended
  – high risk of resistance

End of treatment goals:
1. Ideal: sustained HBsAg loss +/- anti-HBs
2. HBeAg +ve: durable seroconversion to anti-HBe
3. Otherwise: HBV DNA < 10-15 IU/ml
**HBV / HIV**

- Avoid discontinuation of NRTI – risk of liver flare
- Hep B Viral response slower to decline,
  - may take >48 weeks but continue therapy if ongoing decline
- May achieve eAb seroconversion,
  - loss of sAg rare in HIV
- If Anti HBC consider NRTI if undergoing immunosuppression/ chemo (NICE)

**Aims of treatment/ endpoints**
- Minimise liver damage, prevent progressive liver disease and HCC
- Normalisation of ALT
- Suppression of HBV DNA
- HBeAg +ve: durable seroconversion to anti-HBe
- Loss of HBsAg loss and development of anti-HBs
- ? Change to level of HBsAg titre...?

https://www.nice.org.uk/guidance/CG165/chapter/1Recommendations#antiviral-treatment
HIV/HBV co-infection
HBsAg loss in HBeAg positive patients

Not head-to-head trials; different patient populations and trial designs

Extended Treatment With Nucleos(t)ide Analogue*s
vs 1 Yr Peginterferon Treatment

*With sustained undetectable HBV DNA.

HIV/HBV co-infection
HBsAg loss in HBeAg negative, HB eAB positive patients

*Not head-to-head trials; different patient populations and trial designs*

Extended Treatment With Nucleos(t)ide Analogues*
Vs 1 Yr Peginterferon Treatment

*With sustained undetectable HBV DNA.

HIV/HBV co-infection
HBeAg seroconversion rates

*With sustained undetectable HBV DNA.

Hepatitis B – resistance

Resistance rates among nucleos(t)ide-naïve patients

LAM= Lamivudine
ADV=Adefovir
LdT= Telbivudine
ETV=Entecavir
TDF=Tenofovir

*Collation of currently available data – not from head-to-head studies
HIV/HBV co-infection

Suppressed HBV DNA at 1 year

*By PCR-based assay (LLD ~ 50 IU/mL) except for some LAM studies.

HIV/HBV co-infection
Potency vs genetic barrier to resistance

- TDF
- ETV
- LdT
- LAM
- ADV

Nucleoside analogue
Nucleotide analogue

Likelihood of resistance development
Potency of HBV DNA suppression
## HIV/HBV co-infection
### Resistance pathways

<table>
<thead>
<tr>
<th>HBV Resistance mutations</th>
<th>LAM</th>
<th>ETV</th>
<th>TBV</th>
<th>ADV</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>M204V/I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L180M + M204V</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A181T/V</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N236T</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A181T/V + N236T</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L180M + M204V/I + I169T + V173L + M250V</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L180M + M204V/I + T184G + S202I/G</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HIV/HBV co-infection
renal impairment

Male MSM, on Atripla 7 months
• HIV+: CD4 600, VL not detected
• HBsAg positive: HBV DNA not detected
• Now:
  – Cr increase, proteinuria, glycosuria, low phosphate

➢ What do you do?
Primary endpoint (non inferiority margin of 10%):  
- HBV DNA <29 IU/mL at Week 48

Key secondary endpoints
- HBV DNA <29 IU/mL at Week 96
- ALT normalization (central lab and AASLD criteria)
- Serology (HBsAg loss/seroconversion)
  - 90% retention rate through Week 96

Inclusion criteria:
- HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males), >38 U/L (females), eGFR_{CG} >50 mL/min
### Serologic Response At Week 96

<table>
<thead>
<tr>
<th></th>
<th>Study 108 (HBeAg-) (N=425)</th>
<th>Study 110 (HBeAg+) (N=873)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAF n=285</td>
<td>TDF n=140</td>
</tr>
<tr>
<td><strong>HBeAg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>HBsAg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss</td>
<td>1/281 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>1/281 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Improved serologic responses with higher rates of HBeAg seroconversion with TAF vs TDF
- Significantly higher ALT normalization rate with TAF vs TDF
Antiviral Efficacy of TAF and TDF at Week 96

Rates of Viral Suppression (ITT)
HBV DNA <29 IU/mL

- No resistance was detected through 96 weeks
- No significant difference between TAF and TDF
- 90% retention rate through Week 96
- Similar rates of mean HBV DNA decline (log10 change) at all time points across both studies

HBV DNA suppression was comparable between TAF and TDF treatment up to Week 96
HIV/HBV co-infection renal impairment

Male MSM, on Atripla 7 months

- HIV+: CD4 600, VL not detected
- HBsAg positive: HBV DNA not detected
- Now:
  - Cr increase, proteinuria, glycosuria, low phosphate

What do you do?

- Switch TDF to TAF
- BUT If EGFR continues to fall calculate creatinine clearance and reduce dose/ frequency accordingly

Limits of renal function for TDF/TAF/ entecavir as per SPCs

- TAF CrCl < 15 mL/min only use if on HD- once a week dose post HD
- TDF CrCl < 10 mL/min only use if on HD, - once a week dose post HD
- entecavir CrCL< 10ml +/- HD dose reduce
Study 1249: HIV/HBV Co-infected Adults on E/C/F/TAF

Study Design

**Phase 3, 48-week, multicentred, single-arm, open-label study**

**HIV suppressed* & HBV-infected** adults
CrCl ≥50 mL/min

N=72

E/C/F/TAF OD

Key inclusion criteria
* HIV-1 RNA <50 copies/mL for ≥6 months
** HBV DNA ≤9 log_{10} (+HBsAg for ≥6 months)

Week 24
Primary endpoint

Week 48
Secondary endpoint

**Efficacy endpoint**
Proportion with HIV RNA <50 copies/mL (Snapshot) and HBV DNA <29 IU/mL (missing=failure) at Weeks 24 and 48

**Safety endpoints**
Safety and tolerability through Weeks 24 and 48, ALT normalisation, HBsAg to sAb and HBeAg to eAb seroconversion, and changes in liver fibrosis stage

^ Two subjects were ineligible for enrollment because they did not meet the definition of chronic HBV infection (discovered after study enrollment). Therefore, the full safety analysis set included all 74 subjects, but the final efficacy analysis set excluded these two subjects, leading to a final efficacy analysis set of 72 subjects.

^^ By FibroTest

Gallant, J et al, 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 19–22 July 2015 Vancouver, British Columbia, Canada, Presentation #WELBPE13
Antiviral Efficacy at Weeks 24 (Primary Endpoint) and 48

E/C/F/TAF achieved high rates of HIV and HBV suppression at Week 48

*Note: 86% of patients had baseline HBV DNA <29 IU/mL
Monitoring HBV treatment

6 monthly follow-up
- Serology 6-12 monthly
- Hep B DNA 6 monthly

Assess need for HCC surveillance EACS (2018):
- All cirrhotic HBV and HCV coinfected patients
  - even if HCV cured or HBV DNA suppressed
- Stage F3 considered by individual risk
- HBV non-cirrhotics according to EASL guidelines
  - age, HDV status, Asian/African, FH of HCC

- Cirrhosis surveillance
  - 6 monthly Liver USS + AFP
  - Child Pugh score (Bil, PT, Alb, ascites, encephalopathy): decompensated = B7
  - Vitamin D
  - If platelets <150 Endoscopy
  - DEXA
HIV/HCV co-infection

35-40 million

HIV

2.5 million

HCV

71 million

- Prevalence of HCV in HIV in UK = 8.9%
  - More common in PWID & MSM
HIV/HCV co-infection
Genotype distribution
UK CHIC HIV/HCV prevalence

Prevalence: 10.4% (95% CI 10.1%-10.8%)

DAA therapies
HIV/HCV co-infection

Acute HCV

Canada²³: ~30 cases
Prevalence of chronic HCV/HIV²⁴
19%: 11.200

USA¹,²: 55 cases
Prevalence chronic HCV/HIV¹²-⁴
15 – 30%: 180.000 – 360.000

Lebanon²²: 1 case
Prevalence of chronic HCV/HIV²⁵
49%: 1.500

Europe: 1068 cases
Prevalence chronic HCV/HIV¹⁴,¹⁵
25%: 185.500
-UK³,⁴ 552
-Germany⁵,¹⁸,²⁷ 157
-France⁶,⁷ 126
-Netherlands⁸,¹⁷ 97
-Belgium²⁰ 69
-Swiss⁹ 23
-Italy¹⁰ 21
-Denmark²¹ 13
-Spain²⁶ ~8

Taiwan²⁸: 28 cases
Prevalence of chronic HCV/HIV²⁹
55%: 8.800

Australia¹¹: 47 cases
Prevalence chronic HCV/HIV¹⁶,¹⁹
< 1%: 1.000

Acute hepatitis C
-evolution in substance use

IDU or ‘slamming’ has become more common place

Social site and apps have made finding Chem-Sex easy and anonymous
### The Future of acute hepatitis C evolution in substance use

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal Meth</td>
<td>0%</td>
<td>40%</td>
<td>51%</td>
</tr>
<tr>
<td>GHB / GBL</td>
<td>3.2%</td>
<td>27%</td>
<td>46%</td>
</tr>
<tr>
<td>Mephedrone</td>
<td>0%</td>
<td>18%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Of the Sex-Drug users presenting to antidote

- 95% are using to facilitate sex
- 49% injecting crystal and mephedrone (a decade ago – 0%)
- Average number sexual partners per “episode” is 5
- 75% are HIV positive
  - 60% report being non-compliant with ARV’s while “high”
Diagnosing Acute HCV in HIV?

- HCV RNA 7-21 days
- ALT 2-8 weeks usually
- HCV Ag approx. 35 days
  - NB false negative especially at low RNA)
- HCV Ab 51 days to > 1 year
  - usually remains positive following treatment or spontaneous cure
  - not useful for re-infection
  - not protective against re-infection
We may be missing some diagnoses using just serology in co-infection....

- after a first positive HCV-RNA
  - 37% anti-HCV positive 3 months later
  - 86% anti-HCV positive 6 months later
  - 5% without seroconversion after 1 year

Thomson et al. AIDS 2009;23:89–93
Acute HCV - When to initiate Treatment

Diagnosis of acute HCV (HCV RNA – positive)

- Week 4: Decay HCV RNA
  - >2 log reduction
  - ≤2 log reduction → Treat

- Week 8: HCV RNA
  - rebound → Treat

- Week 12: HCV RNA
  - further decay
  - positive → Treat
  - negative → repeat HCV RNA according to local protocol
HIV/HCV co-infection
Elimination by 2025

NHS England sets out plans to be first in the world to eliminate Hepatitis C
29 January 2018

England could be the first country in the world to eliminate Hepatitis C, under ambitious plans announced by the NHS today.
NHS leaders today called on the pharmaceutical industry to work with them to provide best value for money for treatments so that in its 70th year, the NHS can commit to eliminating Hepatitis C in England at least five years earlier than the World Health Organisation goal of 2030.
Impact of therapy on mortality

Deaths from HCV or HCC in patients with HCV (PHE report on HCV 2016)
Hepatitis C Operational Delivery Networks

- NHSE aim to maximise appropriate uptake and completion of HCV treatment and achieve cure
- Ensure equitable access to treatments across the country
- All patients who need DAAs must be discussed and treatment decided on at regional ODN
- ODN base treatment decisions on – NHSE, NICE
- Improve QOL, to prevent premature death and reduce the risk of onward transmission
- 22 ODNs- designed on estimated HCV prevalence
Current Antiviral Targets

- **NS3/4 Protease Inhibitors**
  - Role in HCV life cycle not well defined

- **NS5B polymerase Inhibitors**
  - Nucleoside/nucleotide
  - Nonnucleoside

- **NS5A Inhibitors**
<table>
<thead>
<tr>
<th>NS3/4a protease inhibitors **-EVIR</th>
<th>NS5a inhibitors **-ASVIR</th>
<th>NS3b polymerase inhibitors **-UVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grazoprevir</td>
<td>Daclatasvir</td>
<td>Sofosbuvir (NRTI)</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>Elbasavir</td>
<td>Dasabuvir (NNRTI)</td>
</tr>
<tr>
<td>Glecaprevir</td>
<td>Ledipasvir</td>
<td></td>
</tr>
<tr>
<td>Voxilaprevir</td>
<td>Ombitasvir</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Velpatasvir</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pibrentasvir</td>
<td></td>
</tr>
</tbody>
</table>

**HCV fixed dose Combinations**

<table>
<thead>
<tr>
<th>HCV fixed dose Combinations</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvoni</td>
<td>Ledipasvir/Sofosbuvir</td>
</tr>
<tr>
<td>Zepatier</td>
<td>Elbasvir/Grazoprevir</td>
</tr>
<tr>
<td>Abbvie (3D/4D)</td>
<td>Ombitasvir/Paritaprevir/Ritonavir +/- Dasabuvir</td>
</tr>
<tr>
<td>Epclusa</td>
<td>Sofosbuvir/Velpatasvir</td>
</tr>
<tr>
<td>Maviret</td>
<td>Glecaprevir/Pivrentasvir</td>
</tr>
<tr>
<td>Vosevi</td>
<td>Sofosbuvir/Velpatasvir/Voxilaprevir</td>
</tr>
</tbody>
</table>
Managing HIV/HCV co-infection
2018 DAA

Non-pangenotypic
- elbasvir & grazoprevir
  - G1a/1b/4
  - 12 to 16 weeks 1 tablet od
  - +/- RBV (G1a or 4)
  - CI in decompensation
  - Can use in severe renal impairment
  - SVR > 90-95%
- ledipasvir & sofosbuvir
  - G1/4/5/6
  - 8-12 weeks 1 tablet od
  - +/- RBV (cirrhosis)
  - Can be used in decompensation
  - CI in severe renal impairment
  - SVR > 90-95%
- ombitasvir, paritaprevir, ritonavir, dasabuvir
  - G1
  - 12 to 24 weeks 2 daily with food
  - +/- RBV (cirrhosis) wt based bd
  - CI in decompensation
  - Can use in severe renal impairment
  - SVR > 90-95%

Pangenotypic
- glecaprevir & pibrentasvir
  - 8 to 16 weeks 3 tablets od with food
  - CI in decompensation
  - Can use in severe renal impairment
  - SVR > 90-95%
- sofosbuvir & velpatasvir
  - 12 weeks 1 tablet od
  - +/- RBV (decompensated cirrhosis)
  - Can use in decompensation
  - CI in severe renal impairment
  - SVR > 90-95%
- Sofosbuvir, velpatasvir, voxilaprevir
  - 8-12 weeks 1 tablet od with food
  - CI in decompensation
  - CI in severe renal impairment
  - SVR > 90-95%
HIV/HCV co-infection
Elimination by 2025

Sofosbuvir for treating chronic hepatitis C
Issued: February 2015
NICE technology appraisal guidance 330
guidance.nice.org.uk/ta330

Ledipasvir–sofosbuvir for treating chronic hepatitis C
Technology appraisal guidance
Published: 25 November 2015
nice.org.uk/guidance/ta363

Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C
Technology appraisal guidance
Published: 25 November 2015
nice.org.uk/guidance/ta365

Daclatasvir for treating chronic hepatitis C
Technology appraisal guidance
Published: 25 November 2015
nice.org.uk/guidance/ta364

Elbasvir–grazoprevir for treating chronic hepatitis C
Technology appraisal guidance
Published: 26 October 2016
nice.org.uk/guidance/ta413

Sofosbuvir–velpatasvir for treating chronic hepatitis C
Technology appraisal guidance
Published: 25 January 2017
nice.org.uk/guidance/ta430

Glecaprevir with pibrentasvir for treating chronic hepatitis C
[ID1085]
In development [GID-TA10169] | Expected publication date: 24 January 2018

Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C
Technology appraisal guidance
Published: 21 February 2018
nice.org.uk/guidance/ta507
Buyers Clubs Worldwide

- 1150 HCV-patients
- SOF, DCV, LDV via Buyers Clubs in Australia, China, Russia, South-East-Asia

Baseline Fibrosis

- F0: 16%
- F1: 19%
- F2: 29%
- F3: 10%
- F4 (cirrhosis): 26%

SVR12 rates

- % HCV RNA < 30 IU/mL
- GT1: 97% (108/111)
- GT2: 100% (9/9)
- GT3: 96% (53/55)
- GT4: 100% (2/2)
- GT5 & GT6: 100% (2/2)

- Overall SVR12 currently 90% (454/503)

Hill A et al CROI 2017 #569
HCV UK numbers treated

• 2015-2018:
  – Approx 25,000 HCV + treated within the NHSE programme
  – No significant waiting lists remain
  – Now 2nd line treatment available (Sof/Vel/Vox) for small number who aren’t cured first time.

• But…
  – Retreatment now possible
  – Wait 6 months before treating in acute infection ... at the moment
HIV/HCV co-infection
Assessment of liver

- AND abdominal USS
- AND liver screen

Median of 10 readings:
>60% success rate
IQR: median < 30%

<table>
<thead>
<tr>
<th>HCV:</th>
<th>&lt; 7KPa = &lt;F2 &amp; &gt;12KPa = F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/HCV:</td>
<td>&lt; 7KPa = &lt;F2 &amp; &gt;14KPa = F4</td>
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</tbody>
</table>

Stratification of patients for treatment with HCV DAAs

- Genotype
  - special groups eligible for pangenotypic – varies with ODN
- If cirrhotic: compensated or decompensated
- Baseline HCV RNA levels- less relevant now
- Treatment naïve or experienced

- NS5A RAS Resistance testing only for certain circumstances / genotypes
  - GT1a prior to Elbasvir/Grazoprevir (no longer done routinely by most ODNs)
  - GT3a with compensated cirrhosis prior to Sofosbuvir/Velpatasvir.
  - all patients with decompensated cirrhosis prior to DAA therapy.
  - subtypes not commonly found in high income countries, genotypes 4, 5 and 6.
  - all patients with previous exposure to NS3 and/or NS5A inhibitors, prior to re-treatment.
  - Subtypes Genotype 1, e, g, h, Genotype 4 c, e,f, k, r
Classification of cirrhosis

• Decompensated patients are defined as those with any ONE of the following:
  – Childs-Pugh B or C cirrhosis
  – Patient’s with an on-going or previous recovered episode of decompensation – ascites and or variceal haemorrhage and or encephalopathy
  – Patients with a platelet count of <50,000 at the time of treatment initiation
<table>
<thead>
<tr>
<th></th>
<th>NAÏVE</th>
<th>Rx EXPERIENCED</th>
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HIV/HCV co-infection
Assessment of treatment success

The new SVR 12

HCV RNA not detected 12 **weeks** after treatment

HIV and Hepatitis C - which ART?

- Depends on drug – drug interactions
>90% SVR12 across treatment-naïve
GT 1, 2, 3, 4, 5, 6

<table>
<thead>
<tr>
<th>GT 1</th>
<th>GT 2</th>
<th>GT 3</th>
<th>GT 4</th>
<th>GT 5/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEUTRINO(^1)</td>
<td>FISSION &amp; VALENCE(^{1,2})</td>
<td>VALENCE(^2)</td>
<td>NEUTRINO(^1)</td>
<td>NEUTRINO(^1)</td>
</tr>
<tr>
<td>262/292</td>
<td>68/70</td>
<td>98/105</td>
<td>27/28</td>
<td>7/7</td>
</tr>
</tbody>
</table>

Lawitz E et al NEJM 2013:368 1878-87
Zeuzen AASLD 2013 Poster #1085
HIV+ respond similarly to HCV mono-infected patients in clinical trials

<table>
<thead>
<tr>
<th>Treatment regimen, patient characteristics, studies [Refs]</th>
<th>Co-infection</th>
<th>Mono-infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOC + PegIFN + RBV, GT1 TN, P05411[^1][^10] SPRINT-2[^93]</td>
<td>66% (42/64)</td>
<td>66% (242/366)</td>
</tr>
<tr>
<td>TVR + PegIFN + RBV, GT1 TN, VX08-950-110[^101] ADVANCE[^94]</td>
<td>74% (28/38)</td>
<td>75% (271/363)</td>
</tr>
<tr>
<td>SOF + PegIFN + RBV, GT1 TN, P7977-1910[^102] NEUTRINO[^113]</td>
<td>89% (17/19)</td>
<td>89% (261/292)</td>
</tr>
<tr>
<td>FDV + PegIFN + RBV, GT1 TN (or TR), STARTVerso4[^103] STARTVerso1 and 2[^114]</td>
<td>72% (221/308)</td>
<td>73% (760/1045)</td>
</tr>
<tr>
<td>SMV + PegIFN + RBV, GT1 TN, C21[^105] QUEST-1 and -2[^115,116]</td>
<td>79% (42/53)</td>
<td>80% (419/521)</td>
</tr>
<tr>
<td>SMV + PegIFN + RBV, GT1 TE, C21[^105] ASPIRE[^117]</td>
<td>68% (36/53)</td>
<td>67% (44/66)</td>
</tr>
<tr>
<td>SOF + RBV, GT1 TN, PHOTON-1 and -2[^106,107] NIH SPARE[^118]</td>
<td>81% (182/226)</td>
<td>74% (26/35)</td>
</tr>
<tr>
<td>SOF + RBV, GT2 TN, PHOTON-1 and -2[^106,107] VALENCE[^119], FISSION[^113]</td>
<td>89% (40/45)</td>
<td>97% (99/102)</td>
</tr>
<tr>
<td>SOF + RBV, GT3 TN, PHOTON-2[^107] VALENCE[^119]</td>
<td>91% (52/57)</td>
<td>94% (99/105)</td>
</tr>
<tr>
<td>SOF + RBV, GT3 TE, PHOTON-1 and -2[^106,107] VALENCE[^119]</td>
<td>86% (57/66)</td>
<td>79% (114/145)</td>
</tr>
<tr>
<td>SOF + RBV, GT4 TN, PHOTON-2[^107] Ruane et al[^120]</td>
<td>84% (26/31)</td>
<td>100% (14/14)</td>
</tr>
<tr>
<td>3D + RBV, GT1 TN or TE, TURQUOISE-I[^108] SAPPHIRE-I and -II[^122,123], TURQUOISE-II[^123]</td>
<td>94% (29/31)</td>
<td>95% (932/978)</td>
</tr>
<tr>
<td>SOF/LDV, GT1 TN, ERADICATE[^109] ION-1[^114]</td>
<td>100% (10/10)</td>
<td>100% (211/214)</td>
</tr>
<tr>
<td>Grazoprevir + Elbasvir +/- RBV, GT1 TN, C-WORTHY[^110] C-WORTHY[^125,126]</td>
<td>93% (54/58)</td>
<td>95% (123/129)</td>
</tr>
</tbody>
</table>
Are SVR rates similar in all HIV/HCV coinfected pts?

- GECCO Cohort (9 German centres)
- n=1505
- 1156 mono-, 349 coinfected
- Liver cirrhosis 29% (31% vs. 22%)
- Overall-SVR 95%, 95% monoinfected, 94% coinfected

SVR12 According to CD4 and Cirrhosis Status

<table>
<thead>
<tr>
<th>CD4 Status</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥350</td>
<td>97.2</td>
</tr>
<tr>
<td>&lt;350</td>
<td>90.9</td>
</tr>
<tr>
<td>≥350</td>
<td>88.4</td>
</tr>
<tr>
<td>&lt;350</td>
<td>82.8</td>
</tr>
</tbody>
</table>

SVR lower in pts. with CD4 <350/μl and liver cirrhosis
HIV/HEV co-infection

RNA virus

Transmission
• G1&G2 developing world, faecal-oral spread
• G3&G4 developed world, zoonotic (pigs) – secondary transmission rare

Test for HEV if:
• Abnormal liver function or cirrhosis and other common causes excluded

How:
• Serology if CD4>200 (& ?PCR)
• PCR if CD4<200 on both blood and stool samples

Treatment:
• If acute HEV – no treatment
• If chronic HEV (RNA positive > 6 months)...
• Optimize ART, consider oral ribavirin for 3 months, consider Interferon
Thank you – questions?