Pre-conference Nurses’ Course

Dr Emma Thomson
University of Glasgow Centre for Virus Research, UK
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<table>
<thead>
<tr>
<th>COMPETING INTEREST OF FINANCIAL VALUE &gt; £1,000:</th>
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<tbody>
<tr>
<td>Speaker Name</td>
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<tr>
<td>Emma Thomson</td>
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<td>Date</td>
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The arguments for treating promptly vs waiting for eligibility for DAAs

Dr Emma Thomson
EHHC 2015
A tale of two cities...

London

Glasgow
Treat promptly or wait for DAAs

Early

• Treat early and avoid disease
• If HIV co-infected outcome is worse
• Resistance – RAVs have more impact in late infection
• Reduce secondary cases
• Cost – IFN is cheaper
• Treat early – loss to follow-up

Delayed

• Not everyone progresses to severe disease - cost
• IFN is toxic so wait for DAAs
• Address behaviours first – may need to treat multiple times for reinfection
• Delay – spontaneous clearance may occur (early infection)
HCV is not a benign disease: Natural history of infection

- **HCV Infection**
  - Acute Hepatitis, 70-80% Asymptomatic
  - Clearance of HCV, RNA 15-40%
  - Chronic Hepatitis, 60-85%
  - Cirrhosis, ~20%

- **Progression**
  - 6 Months
  - 10-30 Years

- **Extra-hepatic Manifestations**
  - CNS
  - Joints
  - Skin
  - Kidneys
  - Immune system

- **Transplantation**
  - End-Stage Liver Disease
  - Hepatocellular Carcinoma

- **Progression to cirrhosis accelerated in HIV coinfection**
Early treatment is more effective and less toxic than late treatment.

<table>
<thead>
<tr>
<th>Patients with mild-moderate fibrosis</th>
</tr>
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<tbody>
<tr>
<td>SVR rates &gt;90%</td>
</tr>
<tr>
<td>RAVs have very little impact</td>
</tr>
<tr>
<td>Shorter duration (8 weeks in eligible patients)</td>
</tr>
<tr>
<td>No need for RBV</td>
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<table>
<thead>
<tr>
<th>Patients with cirrhosis</th>
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<tbody>
<tr>
<td>SVR rates lower, especially in genotype 3</td>
</tr>
<tr>
<td>Impact of RAVs higher</td>
</tr>
<tr>
<td>Longer duration (12-24 weeks)</td>
</tr>
<tr>
<td>RBV may be used to maximise likelihood of SVR</td>
</tr>
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</table>
Early Access Programme – treatment in cirrhosis results in lower SVR rates

<table>
<thead>
<tr>
<th></th>
<th>Sof/DCV +/- Ribavirin</th>
<th>Sof/LDV +/- Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>gt1</strong></td>
<td>91%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>gt3</strong></td>
<td>82%</td>
<td>64%</td>
</tr>
</tbody>
</table>

% SVR

- DCV: 43, 104
- LDV: 174, 61
Impact of RAVs is worse in patients with cirrhosis
OPTIMIST: Baseline NS3 Q80K mutation lowers SVR rates in cirrhotic patients treated with SIM/SOF

If we treat early, ribavirin can be avoided

<table>
<thead>
<tr>
<th>SVR12, %</th>
<th>Total (N = 513)</th>
<th>Treatment Naive (n = 161)</th>
<th>Treatment Experienced (n = 352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>96</td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>12 wks ± RBV</td>
<td>95</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>24 wks ± RBV</td>
<td>98</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>Without RBV</td>
<td>95</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>With RBV</td>
<td>97</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>12 wks without RBV</td>
<td>92</td>
<td>96</td>
<td>90</td>
</tr>
<tr>
<td>12 wks with RBV</td>
<td>96</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>24 wks without RBV</td>
<td>98</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>24 wks with RBV</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Treat early and stop transmission
Treatment prevents onward transmission
Treating a small number of patients reduces prevalence
What about treating very early infection?
Acute HCV UK
T cell-mediated immunity to HCV

Acute HCV UK cohort

Wellcome Trust £1M
200/500 patients
2000 samples
PBMCs and plasma

Whole genome sequencing

Functional T cell assays
Acute HCV in HIV-positive men: an emerging epidemic

Increased numbers of acute hepatitis C infections in HIV-positive homosexual men; is sexual transmission feeding the increase?
R Brown, D Ash, Y Gillmore, M Atkins, S Mandall, B Gazzard, M Nelson
9 Stephens Centre, Chelsea and Westminster Hospital, 365 Fulham Road, London, SW10 9NH, UK

Treatment of acute hepatitis C infection in HIV-infected patients: a retrospective analysis of eleven cases
Virohep Medical Ltd, London, UK

Sexual transmission of hepatitis C in homosexual men
Ray T A, den Hollander JG, Beld MG, van der Ende ME, van der Meir J

A cluster of acute hepatitis C virus infection among men who have sex with men - results from contact tracing and public health implications
Hannelore M. Götz, Gerard van Doornum, Hubert G.M. Nieters, Jan G. den Hollander, H. Bong Blau, and Onno de Zwart

Liver Fibrosis during an Outbreak of Acute Hepatitis C Virus Infection in HIV-Infected Men: A Prospective Cohort Study
David S. Farnet, Alphonse J. Wind, Danyelle C. Castrov, Andrea A. O’Phlover, Douglas J. Siemicki, Michael F. Melmon, Susan B. Zhang, M. Susan Lowery, and Andrea D. Bursac

AIDS and Hepatitis C Infection in HIV-Infected Patients: An Early Stage Study
D. Gazzard, M. F. Melmon, D. A. O’Phlover, D. L. Holm, and M. D. Zemans
9 Stephens Centre

Acute hepatitis C in HIV-infected men who have sex
France January 2006 AIDS

Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy
Joanne Serpa, Marie-Laure Chazot, Dominique Ratine, Caroline Dupont, Anik Valet-Pichard, Hélène Fontaine, Jean-Paul Vial, Christophe Pernet, Elisabeth Rosier, Christine Rou並不, Lawrence Weiss, and Stanislas Pél
Ecole de Medicine France, France

Recruitment and follow-up of injecting drug users in the setting of early hepatitis C treatment: Insights from the ATACHC study
Oanh K. Nguyen, Gregory J. Dus, John M. Kaldor, Margaret E. Hellard, on behalf of the ATACHC Protocol Steering Committee

USA January 2006 JAIDS
Clinical Presentation and Course of Acute Hepatitis C Infection in HIV-Infected Patients
USA September 2008 JID

France July 2004 HIV Medicine

A cluster of hepatitis C virus infection among men who have sex with men - results from contact tracing and public health implications
Hannelore M. Götz, Gerard van Doornum, Hubert G.M. Nieters, Jan G. den Hollander, H. Bong Blau, and Onno de Zwart

Netherlands June 2005 AIDS

Netherlands January 2004 Ned Tijdschr Geneskd

Acute HCV in HIV-positive men: an emerging epidemic

UK August 2004 STI

France July 2004 JViralHep

Netherlands January 2004 JViralHep

Netherlands June 2005 JViralHep

Australia January October 2007 Int J Drug Policy

Germany March 2005 JViralHep
Emergence of genotype 4d in HIV infected MSM
Acquisition of acute HCV is often associated with high risk behaviours.

<table>
<thead>
<tr>
<th>Sexual practice</th>
<th>Controls (%)</th>
<th>Cases (%)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active oral sex (no ejaculation)</td>
<td>112 (94.1)</td>
<td>57 (96.6)</td>
<td>0.73</td>
</tr>
<tr>
<td>Active oral sex (ejaculation)</td>
<td>56 (47.1)</td>
<td>37 (62.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Active oral sex with condoms (safe)</td>
<td>12 (10.1)</td>
<td>5 (8.5)</td>
<td>0.94</td>
</tr>
<tr>
<td>Passive oral sex (no ejaculation)</td>
<td>109 (91.6)</td>
<td>52 (89.7)</td>
<td>0.89</td>
</tr>
<tr>
<td>Passive oral sex (ejaculation)</td>
<td>42 (35.3)</td>
<td>30 (50.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Passive oral sex with condoms (safe)</td>
<td>11 (9.2)</td>
<td>2 (3.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Receptive UAI (no ejaculation)</td>
<td>60 (50.4)</td>
<td>53 (89.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Receptive UAI (ejaculation)</td>
<td>42 (35.3)</td>
<td>46 (78.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Receptive AI with condoms (safe)</td>
<td>83 (69.8)</td>
<td>44 (74.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>Insertive UAI (no ejaculation)</td>
<td>57 (47.9)</td>
<td>49 (83.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Insertive UAI (ejaculation)</td>
<td>39 (32.8)</td>
<td>34 (57.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Insertive AI with condoms (safe)</td>
<td>82 (68.9)</td>
<td>40 (69.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Passive rimming</td>
<td>92 (77.3)</td>
<td>58 (98.3)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Active rimming</td>
<td>92 (77.3)</td>
<td>54 (91.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Insertive fingering</td>
<td>31 (26.3)</td>
<td>44 (74.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Receptive fingering</td>
<td>15 (12.6)</td>
<td>34 (57.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Use of sex toys</td>
<td>51 (42.9)</td>
<td>46 (78.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lifetime sexually transmitted infection (%)</td>
<td>78 (67.8)</td>
<td>51 (92)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**Group sex participation (group of >2 individuals):**

<table>
<thead>
<tr>
<th>Group sex practices</th>
<th>Controls (%)</th>
<th>Cases (%)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptive UAI</td>
<td>26 (41.3)</td>
<td>49 (94.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Insertive UAI</td>
<td>30 (47.6)</td>
<td>44 (84.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Receptive fingering</td>
<td>9 (14.3)</td>
<td>29 (55.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Insertive fingering</td>
<td>10 (15.9)</td>
<td>35 (67.3)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Group sex by number of sex practices:**

<table>
<thead>
<tr>
<th>0–1</th>
<th>2</th>
<th>3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>94 (78.3)</td>
<td>11 (18.6)</td>
<td></td>
</tr>
<tr>
<td>14 (11.7)</td>
<td>15 (25.4)</td>
<td></td>
</tr>
<tr>
<td>12 (10.0)</td>
<td>33 (55.9)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*The proportions who have ever had each type of sex were compared using chi-squared tests (or Fisher’s exact test if appropriate). Anal intercourse (AI), unprotected anal intercourse (UAI).
Treatment failure – reinfection or recrudescence? Should we stop and reduce reinfection risk before treatment?
Relapse is not associated with reinfection but is associated with varying dominance of pre-existing strains – we are over-estimating reinfection risk

Abdelrahman et al, Hepatology 2015
So should we treat early – in acute rather than chronic infection and can we reduce the duration of therapy?

<table>
<thead>
<tr>
<th>Study</th>
<th>DAA</th>
<th>Genotype</th>
<th>HIV</th>
<th>Duration</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch Acute HCV in HIV Study – DAHHS 57</td>
<td>BOC/IFN/RBV</td>
<td>1</td>
<td>Positive</td>
<td>12 weeks</td>
<td>86% RVR 100% No RVR 50%</td>
</tr>
<tr>
<td>Open label (Fierer et al) 36</td>
<td>TEL/IFN/RBV</td>
<td>1</td>
<td>Positive</td>
<td>12 weeks (RVR)</td>
<td>89%</td>
</tr>
<tr>
<td>SWIFT-C</td>
<td>SOF/RBV</td>
<td>Any</td>
<td>Positive</td>
<td>12</td>
<td>59%</td>
</tr>
<tr>
<td>DARE C II 16</td>
<td>SOF/RBV</td>
<td>Any</td>
<td>Mixed</td>
<td>6</td>
<td>SVR4 – 27%</td>
</tr>
<tr>
<td>SLAM C 29</td>
<td>SOF/LED 14 or SOF/SIM 15</td>
<td></td>
<td></td>
<td>4 weeks (SOF/LED) 8 weeks (SOF/SIM)</td>
<td>93% (BOTH ARMS)</td>
</tr>
</tbody>
</table>
Waiting for 3-6 months allows time for spontaneous clearance to occur

- New positive HCV PCR n=200 (112 FU complete)
  - Chronic infection n=95 (85%)
  - Spontaneous clearance n=17 (15%)
  - Late relapse/reinfection n=1
  - Lost to follow-up
    - Moved abroad n=4
    - Moved within UK n=3
  - Not treated n=26
    - Declined n=15
    - Co-morbidity n=11†
  - Treated
    - 1 year pegylated IFNα and ribavirin +/- PI n=62

- SVR n=50 (81%)
- Reinfection or late relapse n=4 (8%)
- Treatment failure (null response/relapse) n=12 (19%)
- Spontaneous clearance after relapse n=2 (17%)

† Co-morbidities resulting in decision to delay or withhold treatment
  - Severe depression n=5
  - Metastatic melanoma n=1
  - Castlemans syndrome n=1
  - Pulmonary Kaposi’s sarcoma n=1
  - Squamous cell cancer lung n=1
  - Epilepsy n=1
  - Pulmonary tuberculosis n=1

Thomson E et al, Gut 2011
DAA treatment availability

London 2003-2015

Glasgow - HCV treatment regimens 2001-2015
DAA treatment is highly effective in HIV-co-infected patients

The Glasgow Co-infected Cohort (GCC)

Pre 2012

IFN/RBV
BOC/IFN/RBV
SIM/IFN/RBV
SOF/IFN/RBV
TEL/IFN/RBV
GRAZ/ELB
LED/SOF++-RBV
OMB/PAR/DAS
SIM/SOF
SOF/DAC++-RBV

2012-14

IFN/RBV
BOC/IFN/RBV
SIM/IFN/RBV
SOF/IFN/RBV
TEL/IFN/RBV
GRAZ/ELB
LED/SOF++-RBV
OMB/PAR/DAS
SIM/SOF
SOF/DAC++-RBV

2014-15

IFN/RBV
BOC/IFN/RBV
SIM/IFN/RBV
SOF/IFN/RBV
SOF/DAC++-RBV

Pre-6/11/13
SVR 74% (n=38)

Last prescription of IFN/RBV – 6/11/13

Post-6/11/13
SVR 100% (n=49)
Disparity in market prices for HCV DAAs

Andrieux-Meyer et al The Lancet Global Health 2015
Hepatitis C drug maker puts profit ahead of patients
US Senate report

*BMJ* 2015;351:h6573

- Harvoni costs $1000 a pill or $84 000 (£56 000; €79 000)
- Senator Ron Wyden

“Over the eight months Gilead spent determining the price of Sovaldi, the company repeatedly made clear its primary focus was outmaneuvering potential competitors to ensure its drugs had the greatest share of the market, for the highest price, for the longest period of time.”

“Gilead pursued a calculated scheme for pricing and marketing its hepatitis C drug based on one primary goal, maximizing revenue, regardless of the human consequences”

- Gilead

“We stand behind the pricing of our therapies because of the benefit they bring to patients and the significant value they represent to payers, providers, and our entire healthcare system by reducing the long-term costs associated with managing chronic HCV. Enabling patient access to Sovaldi and Harvoni is a top priority for Gilead.”

- Gilead Company documents – Kevin Young

“Let’s not fold to advocacy pressure in 2014 ... Let’s hold our position whatever competitors do or whatever the headlines.”
Conclusions

• We should not have to wait for DAA availability and we should treat now

• Exceptions
  • Previous treatment failure with multiple RAVs
  • Acute HCV

• We need lower drug costs to make this happen – accessibility to treatment is vital