Epidemiology of HCV and HIV in Patients with Coagulation Disorders

Yaakov Maor, M.D.
Department of Gastroenterology and Hepatology
Kaplan Medical Center
HCV and HIV Infection in Hemophilia

• Since the ‘70 hemophilia patients were treated with concentrated coagulation factors – Derived from >20,000 donors

• During the ‘80 most hemophiliacs acquired HCV and many contracted HIV as well

• Many HIV/HCV patients succumbed to AIDS
HCV and HIV Infection in Hemophilia

• Since 1987 all coagulation factor concentrates are undergoing virucidal process

• HAART regimens introduced in the ’90 revolutionized the prognosis of HIV infection

• HCV infection has assumed much greater importance among HIV co-infected

• Patients are HCV infected for over 20 years
Incidence of HCV Among Hemophilia A Patients in the US*

HIV Infection in Hemophilia Patients

Cumulative infections by year

Cumulative deaths by year

Individuals infected by year

Deaths due to AIDS by year
Characteristics of HIV/HCV Co-Infected Hemophilic Patients

- A higher rate of progression to cirrhosis
- Accelerated progression to liver failure
- 21-fold more likely to develop hepatic decompensation after a median of 15 years
- Sevenfold increased liver-related death
- Hepatocellular carcinoma appears to develop after a shorter duration of infection
The Israeli National Hemophilia Center
INHC

- Hemophilia patients in Israel were treated at one center from the beginning of the ‘70
- The INHC was officially founded in 1987
The Israeli National Hemophilia Center - INHC

• Multidisciplinary management of patients with bleeding disorders under one roof including:
  ▪ Hematology - Coagulation experts
  ▪ Nurses
  ▪ Orthopedic surgeons
  ▪ Physical therapists
  ▪ Social worker
  ▪ Psychologist
  ▪ HIV and Hepatology experts

  Specialized in coagulation disorders
HCV and HIV/HCV at the INHC

• Since 2000 regular hepatology consultation was established

• All patients with hemophilia and other coagulation disorders were screened for HCV and HIV – Targeting mainly those born <1986

• Patients were evaluated for the characteristics of their viral infection and severity of liver disease
HCV and HIV/HCV at the INHC

- Patients were consulted, and closely followed throughout their anti-HCV treatment

- Treatment was coordinated with both: **Hemophilia Nurse** and **HIV specialist**
Immunization

• International guidelines recommend universal HAV and HBV immunization for patients with inherited coagulation disorders

• Both HCV infected and non-infected hemophilia patients were screened for HAV and HBV and immunized

• An annual follow-up of antibodies is conducted
HCV and HIV at the Israeli National Hemophilia Center - INHC

Up-date of Maor Y et al. Haemophilia 2006
HCV Infection in Hemophilia Patients Born Before 1986

Total No. = 248

HCV Ab-Pos. No. = 195 (79%)

With Virology Data No. = 180 (73%)

HCV Mono-Infected No. = 127 (70%)

HIV/HCV Co-Infect. No. = 28* (16%)

HCV RNA-Negative No. = 25 (14%)

*3 patients were HCV RNA-negative
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>HCV (No.=127)</th>
<th>HCV/HIV (No.=28)</th>
<th>RNA-Neg (No.=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>36 ± 14</td>
<td>37 ± 10</td>
<td>35 ± 15</td>
</tr>
<tr>
<td></td>
<td>(16 – 71)</td>
<td>(26 – 64)</td>
<td>(16 – 58)</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>6 (5)</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Israeli (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jews</td>
<td>53 (45)</td>
<td>20 (83)</td>
<td>9 (39)</td>
</tr>
<tr>
<td>Arabs</td>
<td>12 (10)</td>
<td>3 (13)</td>
<td>3 (13)</td>
</tr>
<tr>
<td><strong>Immigrants (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former USSR</td>
<td>39 (33)</td>
<td><strong>0</strong></td>
<td>10 (44)</td>
</tr>
<tr>
<td>Arab Countr.</td>
<td>9 (7)</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.001 for HIV/HCV vs. HCV and vs. RNA-Neg.*
## Coagulation Disorder

<table>
<thead>
<tr>
<th></th>
<th>HCV (No.=127)</th>
<th>HCV/HIV (No.=28)</th>
<th>RNA-Neg (No.=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemophilia (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemophilia A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>93 (74)</td>
<td><strong>25 (93)</strong>*</td>
<td>16 (64)</td>
</tr>
<tr>
<td>Mild/Moderate</td>
<td>11/1 (9/0.8)</td>
<td>0/2 (0/7)</td>
<td>5/1 (20/4)</td>
</tr>
<tr>
<td><strong>Hemophilia B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>5 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/Moderate</td>
<td>1/2 (0.8/2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vWD</td>
<td>6 (5)</td>
<td></td>
<td>1 (4)</td>
</tr>
<tr>
<td>Glanzmann</td>
<td>3 (2)</td>
<td></td>
<td>1 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (3)</td>
<td></td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

*p=0.01 for HIV/HCV vs. RNA-Neg.; p=0.03 for HIV/HCV vs. HCV
# Coagulation and Blood Products

<table>
<thead>
<tr>
<th>Coagulation Factors (%)</th>
<th>HCV (No.=127)</th>
<th>HCV/HIV (No.=28)</th>
<th>RNA-Neg (No.=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1987</td>
<td>51 (48)</td>
<td><strong>23 (96)</strong>*</td>
<td>6 (35)</td>
</tr>
<tr>
<td>&gt; 1987</td>
<td>55 (52)</td>
<td>1 (4)</td>
<td>11 (65)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency (%)</th>
<th>HCV (No.=127)</th>
<th>HCV/HIV (No.=28)</th>
<th>RNA-Neg (No.=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt;1 mo.)</td>
<td>63 (58)</td>
<td>13 (54)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Medium (&lt;1 mo.)</td>
<td>14 (13)</td>
<td>5 (21)</td>
<td></td>
</tr>
<tr>
<td>Low (&lt;3 mo.)</td>
<td>31 (29)</td>
<td>6 (25)</td>
<td>8 (50)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Trans. (%)</th>
<th>HCV (No.=127)</th>
<th>HCV/HIV (No.=28)</th>
<th>RNA-Neg (No.=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>73 (70)</td>
<td>12 (52)</td>
<td>13 (72)</td>
</tr>
</tbody>
</table>

*p<0.001 for HIV/HCV vs. HCV and vs. RNA-Neg.
### Additional Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors (%)</th>
<th>HCV (No.=127)</th>
<th>HCV/HIV (No.=28)</th>
<th>RNA-Neg (No.=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tattoo</td>
<td>1 (1)</td>
<td>2 (8)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>15 (14)</td>
<td>4 (17)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Tattoo+Alcohol</td>
<td>2 (2)</td>
<td></td>
<td>1 (5)</td>
</tr>
<tr>
<td>IVDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HBV Serology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HBSAg-Pos. DNA-Neg.-1</td>
<td></td>
<td>HBSAg-Pos. DNA-Neg.-1</td>
</tr>
<tr>
<td></td>
<td>HBcAb-1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Distribution of HCV Genotypes

HIV/HCV

- Genotype 1: 59%
- Genotype 1A: 21%
- Genotype 1B: 17%
- Genotype 2: 8%
- Genotype 3: 29%
- Genotype 4: 21%

p = 0.012

HCV

- Genotype 1: 82%
- Genotype 1A: 21%
- Genotype 1B: 48%
- Genotype 2: 3
- Genotype 3: 16%
- Genotype 4: 6%
- Genotype 6: 2%

p = 0.003
## HCV - Viral Load

<table>
<thead>
<tr>
<th>Viral Load</th>
<th>HCV (No.=122)</th>
<th>HIV/HCV (No.=24)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 800,000 IU/mL (%)</td>
<td>66 (54)</td>
<td>10 (42)</td>
</tr>
<tr>
<td>≥ 800,000 IU/mL (%)</td>
<td>56 (46)</td>
<td>14 (58)</td>
</tr>
</tbody>
</table>

*Not including 3 patients with persistent HCV RNA-negative
### Characteristics of HIV Patients (No.=28)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT Treatment (%)</td>
<td>27</td>
</tr>
<tr>
<td><strong>CD$_4^+$ (Cells/mm$^3$)</strong></td>
<td>$382 \pm 207$ (139 – 1,117)</td>
</tr>
<tr>
<td>Viral Load</td>
<td></td>
</tr>
<tr>
<td>&lt;LDL (%)</td>
<td>16 (62)</td>
</tr>
<tr>
<td>Detectable HIV RNA (%)</td>
<td>10 (38)</td>
</tr>
<tr>
<td>Median (Range) (Copies/mL)</td>
<td>2,350 (95 – 920,000)</td>
</tr>
</tbody>
</table>
Evaluation of Fibrosis in HCV and HIV/HCV Infected Hemophilia Patients
Non-Invasive Methods
Liver Biopsy in Hemophilia Patients

• Can safely be performed with no reported major complications

• Coagulation factor administration to achieve 100% replacement is costly

• Is met with reluctance from patients and care providers alike

Therefore – Hemophilia patients are the most appropriate target for implementation of non-invasive methods
FibroTest

↑
Bilirubin
$\alpha_2$ Macroglobulin
GGT

↓
Haptoglobin
Apolipoprotein A1

Score: 0.42
(F1-F2)
Fibrosis Stage by FibroTest

HIV/HCV
- F0/F1: 48%
- F3/F4: 52%

HCV
- F0/F1: 67%
- F3/F4: 33%

$p = 0.05$
FibroScan

• Echo-wave velocity measurement provides a measure of liver stiffness (kilopascals-kPa)

• Liver stiffness correlates with stage of fibrosis
FibroTest vs. FibroScan in HCV and HIV/HCV Infected Hemophilia Patients

Concordance: 62% 69% 85%
Kappa Score: 0.24 0.32 0.44
Treatment of HCV and HIV/HCV Hemophilia Patients

- 62 hemophilia patients were treated: HCV - 51; HIV/HCV - 11
- 58 patients received Peg-IFN + ribavirin
- 4 patients received standard interferon + ribavirin
- Duration of treatment:
  - Genotype 1: - 12 months
  - Genotypes 2/3:
    - HCV - 6 months
    - HIV/HCV - 12 months
Virological Response –
HCV Mono-Infection (No.= 51)

- SVR: 41 (Genotype 1), 33 (All)
- Relapse: 35 (Genotype 1), 40 (All)
- Null Response: 14 (Genotype 1), 12 (All)
- Partial Response: 10 (Genotype 1), 14 (All)
Virological Response –
HIV/HCV Co-Infection (No. = 11)

• Sustained Viral Response - 3 (27%)

• Relapse - 1

• Non-Response
  ▪ Null Response - 2
  ▪ Partial Response - 2
  ▪ Suppression treatment with cont.
    Standard Daily IFN + Ribavirin - 1
Adverse Effects - Anemia

• Significant anemia (Hb <10 mg/dL) occurred in:
  ▪ HCV mono-infection   - 12 (24%)
  ▪ HIV/HCV co-infection - 2 (18%)

• Patients did not report:
  ▪ Increase in bleeding episodes
  ▪ More frequent use of coagulation factors
Treatment Discontinuation

• HCV mono-infection - 10 (20%)

• HIV/HCV co-infection - 2 (18%)

• Major reasons for treatment D/C:
  ▪ Anemia (Including aplastic anemia)
  ▪ Rash
  ▪ Sepsis
  ▪ Depression
  ▪ Hepatic encephalopathy
IL28B Haplotypes and HCV

- Single-nucleotide polymorphism (SNP) in the region of the IL28B gene is:
  - A key predictor of viral response to treatment
  - Important for spontaneous clearance of HCV
IL28B Haplotypes in HIV/HCV Co-Infected Hemophilia Patients

rs12979860

CC = Favorable haplotype
CC Haplotype of rs12979860 and Virological Response

$p=0.0196$

<table>
<thead>
<tr>
<th></th>
<th>SVR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>63</td>
<td>31</td>
</tr>
<tr>
<td>CT</td>
<td>37</td>
<td>9</td>
</tr>
<tr>
<td>CC</td>
<td>37</td>
<td>59</td>
</tr>
</tbody>
</table>
Natural History of HCV and HIV/HCV Infected Hemophilia Patients

Impact of Anti-HCV Treatment
HCV/HIV vs. HCV; \( p=0.015 \)
HCV/HIV vs. Non-HCV; \( p=0.003 \)
HCV vs. Non-HCV; \( p=0.14 \)
HCV/HIV vs. HCV; $p=0.023$
HCV/HIV vs. Non-HCV; $p=0.003$
HCV vs. Non-HCV; $p=0.55$
## Causes of Death

<table>
<thead>
<tr>
<th>Cause</th>
<th>HCV</th>
<th>HIV/HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-Stage Liver Disease</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Liver Transplantation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Septic Arthritis</td>
<td>2*</td>
<td></td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Suicide</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

*1 with clinical cirrhosis
<table>
<thead>
<tr>
<th>Variables</th>
<th>Survived</th>
<th>Dead</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>189</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.1 ± 13.4</td>
<td>45.5 ± 12.8</td>
<td>0.006</td>
<td>45.5 ± 12.8</td>
<td>0.006</td>
</tr>
<tr>
<td>HCV (%)</td>
<td>76.2</td>
<td>100.0</td>
<td>0.066</td>
<td></td>
<td>0.066</td>
</tr>
<tr>
<td>HIV (%)</td>
<td>12.2</td>
<td>45.5</td>
<td>5.120</td>
<td>1.674 - 15.651</td>
<td>0.002</td>
</tr>
<tr>
<td>Severe Hemophilia (%)</td>
<td>75.1</td>
<td>100.0</td>
<td>0.59</td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>Clinical Cirrhosis (%)</td>
<td>2.1</td>
<td>45.5</td>
<td>17.685</td>
<td>6.633 - 47.150</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>High Viral Load* (%)</td>
<td>53.3</td>
<td>50.0</td>
<td>0.859</td>
<td>0.260 - 2.840</td>
<td>0.803</td>
</tr>
<tr>
<td>F3-F4 (by FT**) (%)</td>
<td>35.4</td>
<td>75.0</td>
<td>5.957</td>
<td>0.575 - 49.892</td>
<td>0.097</td>
</tr>
<tr>
<td>Treated (%)</td>
<td>41.0</td>
<td>27.3</td>
<td>0.563</td>
<td>0.155 - 2.038</td>
<td>0.371</td>
</tr>
<tr>
<td>SVR (%)</td>
<td>40.7</td>
<td>33.3</td>
<td>0.740</td>
<td>0.071 - 7.730</td>
<td>0.8</td>
</tr>
<tr>
<td>Genotype 1 (%)</td>
<td>81.3</td>
<td>50.0</td>
<td>0.263</td>
<td>0.081 - 0.851</td>
<td>0.019</td>
</tr>
</tbody>
</table>

*≥800,000 IU/mL; FT-FibroTest
HCV and HIV/HCV in Hemophilia - Summary

• The majority of hemophilia patients born <1986 are infected with HCV

• ~15% are HIV/HCV co-infected
• All hemophilia patients with HIV were exposed to HCV
  ▪ Suggesting that hemophilia patients contracted HCV first

• The majority HIV/HCV co-infected have severe hemophilia and received coagulation factors before 1987
HCV and HIV/HCV in Hemophilia - Summary

• Non-invasive monitoring of liver disease is feasible and a desirable method to prioritize treatment and assess disease progression

• The success rate anti-HCV treatment was inferior compared with other reports

• The prognosis of HIV/HCV co-infected is worse than of HCV mono-infected hemophilia patients
  - Mainly due to liver related mortality
• **Israeli National Hemophilia Center - INHC**
  - Dalia Bashari – Head Nurse
  - Jonathan Schapiro – HIV Specialist
  - Uri Martinowitz – Head of INHC
  For their devoted care of hemophiliacs!

• **Special Thanks**
  - Philippe Halfon – Laboratoire Alphabio France
  For making everything possible!