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**TECARTUS** ▼ (AUTOLOGOUS ANTI-CD19-TRANSDUCED CD3+ CELLS)

IS INDICATED FOR THE TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA (MCL) AFTER TWO OR MORE LINES OF SYSTEMIC THERAPY INCLUDING A BRUTON'S TYROSINE KINASE (BTK) INHIBITOR<sup>1</sup>

PRESCRIBING INFORMATION

**PATIENTS WITH MCL  
 POST-BTK INHIBITOR  
 FAILURE FACE  
 POOR PROGNOSIS<sup>2-4</sup>**

**REGAIN CONTROL  
 WITH AN ORR OF  
 93% WITH TECARTUS<sup>2</sup>**

(PRIMARY ENDPOINT, IN THE PRIMARY ANALYSIS SET (N=60)<sup>2</sup>)



Kaplan-Meier estimate of the duration of response, as assessed on the basis of review by the independent radiologic review committee, among 56 patients in the primary efficacy analysis who had an objective response. Tick marks indicate censored data.<sup>2</sup> Adapted from Wang M, et al. *N Engl J Med*. 2020.

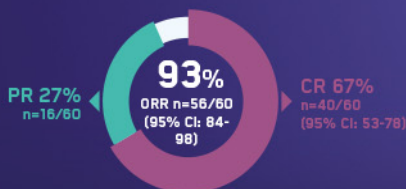
Not an actual patient.

**IN THE PRIMARY ANALYSIS SET  
 (N=60) AT 12.3 MONTHS:<sup>2</sup>**

**EFFECTIVE<sup>2</sup>**

**PRIMARY ENDPOINT:**

PERCENTAGE OF PATIENTS WITH AN OBJECTIVE RESPONSE (CR OR PR)<sup>2</sup>



**DURABLE**

**SECONDARY ENDPOINT: DOR<sup>2</sup>**

The median duration of response was not reached (95% CI: 8.6-NE) at a median follow-up of 12.3 months in the primary efficacy analysis set<sup>2\*</sup>

- In the patients with ≥2 years follow-up, 43% (N=12/28) remained in remission<sup>2</sup>

**RAPID**

Median time to response was 1 month in the primary analysis set<sup>2</sup> (range: 0.8-3.1)<sup>2</sup>

**TOLERABILITY**

Tecartus led to serious and life-threatening toxic events of the type reported with other anti-CD19 CAR T-cell therapies.<sup>2</sup> The most significant and frequently occurring adverse reactions were cytokine release syndrome (91%), infections (56%) and encephalopathy (51%)<sup>1</sup>

Regain control with Tecartus at [www.kitecartforum.co.uk](http://www.kitecartforum.co.uk) (This website contains promotional content)

ZUMA-2 was a phase 2, single-arm, open-label, multicentre trial evaluating the efficacy and safety of a single infusion of Tecartus in adult patients with R/R MCL who had previously received anthracycline or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTKi (ibrutinib or acalabrutinib).<sup>2</sup>

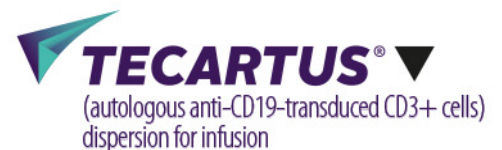
\*Patients are expected to enroll in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Tecartus.<sup>1</sup>

<sup>1</sup>The first 60 patients treated with Tecartus who had at least 7 months follow-up.<sup>2</sup>

BTKi=Bruton's tyrosine kinase inhibitor; CAR=chimeric antigen receptor; CI=confidence interval; CR=complete response; DOR=duration of response; MCL=mantle cell lymphoma; NE=could not be estimated; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; R/R=relapsed/refractory.

REFERENCES: 1. Tecartus. Summary of Product Characteristics. 2. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle cell lymphoma. *N Engl J Med*. 2020;384(14):1331-1342. 3. Smith A, Roman E, Appleton S, et al. Impact of novel therapies for mantle cell lymphoma in the real world setting: a report from the UK's Haematological Malignancy Network (HMNRN). *Br J Haematol*. 2018;181(2):215-228. 4. Smith A, Roman E, Appleton S, et al. Impact of novel therapies for mantle cell lymphoma in the real world setting: a report from the UK's Haematological Malignancy Network (HMNRN) - supplementary appendix. *Br J Haematol*. 2018;181(2):215-228.

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# Viral hepatitis in haemophilia: historical perspective and current management

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## Summary

The introduction of clotting factor concentrates has substantially improved the lives of people with clotting factor deficiencies. Unfortunately, the transmission of blood-borne viral infections through these plasma-derived products led to a huge epidemic of human immunodeficiency virus and viral hepatitis in people with haemophilia (PWH). In a significant proportion of PWH exposed to these viruses, the ensuing decades-long chronic infection resulted in excess morbidity and mortality. Fortunately, developments in the safety of blood products, as well as vaccination and highly effective antiviral treatments have improved the prospects of PWH. The present article reviews the background of the viral hepatitis epidemic in PWH, the natural history of hepatitis B and C infections and their long-term management.

**Keywords:** hepatitis C, HCV, HBV, haemophilia, HIV.

## Treatment of haemophilia

Haemophilia A and B are inherited X-linked bleeding disorders due to deficiency of factor VIII (FVIII) and factor IX (FIX) respectively. The mainstay of their treatment is through infusion of the missing clotting factor. Initial methods of replacement were poor and inefficient, involving transfusion of fresh blood or fresh frozen plasma (FFP), products that contain all the clotting factors in a dilute format. A major advance in FVIII replacement was the discovery that cryoprecipitate contained FVIII in concentrated form and was more efficient (in terms of volume) than FFP in treating people with haemophilia A.<sup>1</sup> However, problems with cryoprecipitate use include the need to be given in hospital, requirement for storage in a freezer, need for thawing

and a high likelihood of allergic reactions. Most of these limitations were overcome by the introduction of plasma-derived lyophilised FVIII and FIX concentrates in the 1970s. This enabled the storage of the products in a domestic refrigerator, allowed full treatment in a small volume and made it possible for patients to treat themselves at home, as well as giving them the freedom to travel. In the 1990s recombinant factor concentrates that did not use human plasma were introduced and are the main form of concentrates in use in Europe and North America today.<sup>2</sup> However, in many parts of the world plasma-derived concentrates still predominate as the main form of treatment for people with haemophilia (PWH).

## Transfusion-transmitted infection

It has been recognised for >80 years that transfusion of blood and blood products could be associated with transfusion-transmitted infection (TTI).<sup>3</sup> This remained a relatively small issue until products from multiple donors were pooled and started to be infused in recipients. In the late 1960s, reports of jaundice started appearing after cryoprecipitate use in PWH. The frequency of post-transfusion hepatitis increased in the 1970s and it was recognised that, whilst many cases were due to hepatitis B, another infective agent termed non-A, non-B hepatitis (NANBH) was involved. In the early 1980s, it became clear that the majority of PWH exposed to pooled plasma-derived concentrates were infected with NANBH, although its significance was uncertain. At around the same time the human immunodeficiency virus (HIV) became recognised as a major cause of TTI. Transfusion-related NANBH was shown in the early 1990s to be almost exclusively due to hepatitis C virus (HCV).<sup>4</sup>

Although HIV and HCV are the most well-known transfusion transmitted viruses, many others have been reported. PWH are susceptible to infection through their plasma-derived FVIII or FIX concentrate treatment only with viruses that can be found in plasma; they are no more susceptible

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than the general population to cell-associated viruses such as the cytomegalovirus, Epstein–Barr virus and several human herpes viruses, which have leucocytes as their mode of transmission.<sup>5</sup>

### Viral hepatitis and HIV in haemophilia

The risk of viral hepatitis and HIV transmission was very small with products produced from single donations such as red cells, platelets, FFP or cryoprecipitate. Notably, treatment of a bleeding episode would often require multiple infusions over several days. Furthermore, a single cryoprecipitate treatment required multiple units of cryoprecipitate. Nonetheless, the total number of required individual donations per bleeding episode was still relatively low for these therapies. The major move to treat PWH with lyophilised pooled plasma concentrates changed all that, as the pools of plasma used for fractionation could contain tens of thousands of individual donations. The level of viraemia in HCV- and HIV-infected individuals is very high and, as no natural immunity existed; most batches of FVIII/FIX were infected with HCV and some with HIV as well. The infectivity of specific batches depended on the plasma source and those relying on volunteer European donors were less infectious (especially for HIV) than batches made by USA manufacturers who collected blood from paid donors using plasma collection facilities sometimes located in prisons or in deprived areas.<sup>6</sup>

The rates of HIV/hepatitis B virus (HBV)/HCV infections in the haemophilic population varied depending on availability and use of cryoprecipitate *versus* lyophilised plasma-derived concentrate and the use of commercial American plasma sourced products *versus* volunteer donor sourced domestic manufacturing.<sup>7,8</sup> In contrast to many countries, only 1% of Finnish PWH (two of 213) tested positive for HIV antibodies between 1985 and 1989.<sup>9</sup> This is likely due to the self-sufficiency for the production of clotting factors of Finland and the low HIV prevalence in the Finnish population at the time. However, even in Finland, 94% of patients with severe haemophilia A, aged >20 years and treated with locally produced lyophilised concentrates from unpaid blood donations were anti-HCV positive in 1999,<sup>10</sup> demonstrating that in contrast to HIV, the pooling of large numbers of plasma donations resulted in high pool infectivity. In the Netherlands, 99% of those treated with non-viral inactivated large pool concentrates were anti-HCV positive, compared to 66% of those treated with cryoprecipitate.<sup>11</sup> A comparison between Scottish PWH who received locally produced factor concentrates and Danish PWH who received both local and American factor concentrates, reported HCV antibody prevalence of 16% and 59% respectively.<sup>12</sup> In Sweden, where both American and Swedish factor concentrates were used, HIV-positive persons with haemophilia A received significantly more American concentrate.<sup>13</sup> Countries with poor access to concentrates have had low levels of viral infections in their PWH.

The pooling of donations was key to the infectivity of concentrates. Whereas pools produced from plasma donations usually included up to 10 000 donors, plasma obtained from whole blood donations could contain plasma from as many as 60 000 donors.<sup>14</sup> The impact of the size of the plasma pool on final infectivity is debated. A modelling study from 1996 showed that the risk of exposure to infectious agents for patients requiring repeated treatments, such as PWH, would only have been minimally affected by large reductions in pool size.<sup>14</sup>

Another issue that reduced the prevalence of infections in persons with mild haemophilia A, was the use of desmopressin that induces the endogenous release of FVIII, which can be sufficient for many treatments.<sup>15</sup>

### The introduction of viral inactivation

The infection of many PWH with HIV led to the introduction of viral inactivation of concentrates in late 1983 and early 1984. The early virally inactivated concentrates were safe in terms of viral transmission when infused into chimpanzees, and although infectivity was reduced especially for HIV, some NANBH infections still occurred in PWH. The later viral inactivation procedures employing higher temperature, wet heat, pressure and chemicals were much more effective in eliminating hepatitis and HIV infectivity from concentrates.<sup>16</sup> Viral transmission was further reduced/eliminated due to the combination of viral inactivation and viral exclusion. Viral exclusion has been achieved through chromatographic and immunoaffinity protein purification techniques applied to high purity concentrates, and dedicated steps such as wet and dry heating, solvent/detergent treatment, and nanofiltration. Finally, procedures such as deferral of donors with risk factors for HIV infection, as well as serological and nucleic acid amplification testing of pooled donations, were introduced to reduce the risk of TTI. Although viral inactivation was highly effective against HIV and HCV, some PWH treated with FVIII in the early 1990s in Europe, the USA and South Africa were infected with hepatitis A virus (HAV), a virus normally transmitted via the faecal–oral route.<sup>17</sup> The reason for this, turned out to be poor efficacy of the viral inactivation processes used at the time against lipid enveloped viruses such as HAV.<sup>17</sup> This resulted in the regulatory authorities recommending that all clotting factor concentrates should undergo two separate viral inactivation steps, a recommendation that is still in use today.<sup>18</sup>

Other concerns related to viral inactivation were the potential adverse effects of the inactivation steps. In particular, this concerned potential immunogenicity of inactivated products, resulting in alloantibodies against administered clotting factors. In Belgium and in the Netherlands, increased incidence of FVIII alloantibodies (inhibitors) was linked to the introduction of new FVIII products virally inactivated through pasteurisation.<sup>19,20</sup> Fortunately, inhibitors

disappeared after switching product. Nonetheless, these occurrences served as a warning for the potential risks of adaptations in production or viral inactivation methods.

### Potential infectivity of current plasma-derived concentrates

Undoubtedly, the current plasma-derived concentrates are the safest they have ever been. The possibility of infection with HIV and HCV is theoretical as the measures instituted by manufacturers will not only prevent infected donors from donating, but the purification process in combination with viral inactivation processes are highly efficient in reducing and inactivating HIV and HCV.<sup>16</sup>

Transmission of other viruses remains possible on rare occasions. Parvovirus B19 causes a childhood illness called fifth disease and has been shown to be still transmissible by concentrates because none of the current viral inactivation steps can destroy it completely.<sup>21</sup> Another group of infective agents that cannot be destroyed by currently used viral inactivation procedures are prions such as classical and variant Creutzfeldt–Jacob Disease (vCJD). Although many PWH have been exposed to plasma products made from donors who went on to develop vCJD, no patient with an inherited bleeding disorder has ever developed symptoms of vCJD. However, one PWH who died from an unrelated cause and received treatment with plasma-derived FVIII and non-leucodepleted red cells was found to have prions in his spleen at autopsy.<sup>22</sup>

### The natural history of HCV infection in haemophilia

Studying the natural course of HCV infection is often limited by unknown dates of infection and inconsistent follow-up. However, for PWH the onset of the infection can be reasonably traced back to the first clotting factor concentrate infusion.<sup>23</sup> Furthermore, in many countries all PWH have been systematically tested for HCV infection, decreasing the risk of selection bias that occurs when patients are tested only once they develop symptoms or signs of chronic hepatitis. Finally, PWH are reviewed regularly at their haemophilia treatment centre, providing reliable follow-up data independent of HCV status. Therefore, PWH are a good population in which to study the natural history of HCV infection.

Acute HCV infection is asymptomatic in most cases and therefore was rarely recognised in PWH during the HCV epidemic. The proportion of HCV-infected PWH in whom the infection did not progress to chronic HCV varies in different reports from 7% to 23%,<sup>24–31</sup> of which most estimates range between 10% and 20%.<sup>24–28,31</sup> These percentages of spontaneous clearance are slightly lower than the average 26% spontaneous clearance rate in other HCV populations.<sup>32</sup> Likely, this is due to the relatively high number of HIV co-infected PWH, which is known to significantly decrease the chance of

spontaneous clearance.<sup>24,33,34</sup> In those in whom the HCV infection progressed to a chronic infection, the most common HCV genotypes were genotype 1 (65–70%), followed by genotype 3 and 2 with 15–20% and 10–15% respectively.<sup>24–27,30,31</sup>

Chronic HCV infection can lead to the development of liver fibrosis and eventually cirrhosis. The ‘gold standard’ for diagnosis of liver fibrosis and cirrhosis is liver biopsy. The main study describing liver biopsy results in PWH is a series of 220 liver biopsies from a cohort of 781 HCV-positive PWH.<sup>35</sup> Advanced fibrosis or cirrhosis (Metavir fibrosis scores of  $\geq$ F3) was seen in 52 (24%), with a slightly higher mean fibrosis score in HIV-infected PWH.<sup>35</sup> It is known that HIV infection accelerates HCV-related liver fibrosis progression.<sup>36</sup> As liver biopsy is an invasive procedure with adherent risk of complications such as bleeding and therefore not routinely performed, potential confounding by indication is important to consider in interpreting these results.

More often than liver biopsy results, non-invasive liver stiffness measurements using transient elastography (TE) are reported as an indicator of liver fibrosis and cirrhosis in PWH (Table 1).<sup>37–42</sup> In these studies, 40–50% of PWH had no or minimal fibrosis (F0–F1) after an infection duration of  $\geq$ 20 years.<sup>37–39</sup> Severe fibrosis or cirrhosis (F3 or F4) was found in 30–35% of PWH.<sup>37–40</sup> These rates of progression to severe fibrosis and cirrhosis are comparable to those found in studies from the general population.<sup>41,42</sup> An important consideration when considering TE results, is that several factors can lead to false-positive elevated values, as explained below. Furthermore, selection bias is likely, as many HIV/HCV co-infected PWH already died because of opportunistic infections by the time TE became available.

Several studies describing the natural history of HCV-infected PWH have focussed on the occurrence of end-stage liver disease (ESLD), which in these studies is usually defined as the occurrence of decompensated cirrhosis, bleeding oesophageal varices, hepatocellular carcinoma (HCC) or liver-related death. In three cohorts with  $\geq$ 30 years of follow-up since HCV infection, the cumulative incidence of ESLD was between 10% and 15%.<sup>24,28,29</sup> The largest of these three cohorts was a multicentre study conducted by our group from the Netherlands and the UK, which included 863 HCV-seropositive patients with a median infection duration of 31 years.<sup>24</sup> Co-infection with HIV was present in 212 (25%) of the patients, whereas co-infection with HBV was uncommon with only 16 hepatitis B surface antigen (HBsAg)-positive patients (2%). Of the 700 HCV-infected patients who developed chronic HCV, ESLD based on the criteria mentioned above occurred in 90 (13%) after a median infection duration of 23 years.<sup>24</sup> This rate was slightly higher in the group of 510 HCV patients without successful antiviral treatment, of whom 88 (17%) developed ESLD. The all-cause mortality at the end of follow-up was 28%, of which 28% was liver-related, being the second cause of death after HIV/acquired immune deficiency syndrome (AIDS) (32%).<sup>24</sup> The largest cohort in which progression of HCV infection to



Table I. Rates of progression of liver fibrosis in HCV-infected PWH as measured with transient elastography.

Reference	Patients, n	Age, years	Infection duration, years	F0-F1, n (%)	F2, n (%)	F3, n (%)	F4, n (%)
Patients with inherited bleeding disorders							
Posthouwer <i>et al.</i> , 2006 <sup>37</sup>	110 HCV mono-infected 11 HIV/HCV co-infected	Median 42 (range 16–86)	Median 34 (range 14–40)	48 (40)	31 (25)	22 (18)	20 (17)
Maor <i>et al.</i> , 2019 <sup>38</sup>	50 HCV-infected, 5 HCV cleared or cured HIV-status not reported	40 ± 14	26 ± 5	25 (45)	12 (22)	10 (18)	8 (15)
Kitson <i>et al.</i> , 2010 <sup>39</sup>	41 HCV mono-infected 18 HCV/HIV co-infected	45 ± 2	16–35, not further specified	28 (48)	12 (20)	7 (12)	12 (20)
Vidovic <i>et al.</i> , 2010 <sup>40</sup>	63 HCV mono-infected 57 HCV/HIV co-infected 40 HCV cleared or cured 14 HIV-infected, HCV cleared or cured	Median 42 (range 22–83)	All > 20, not further specified	<b>F0-F2</b> 123 (71)		<b>F3-F4</b> 51 (29)	
Reference studies from the general population							
Poynard <i>et al.</i> , 2012 <sup>41</sup>	1289 HCV mono-infected	49 (48–50)	Not reported	637 (49)	395 (31)		257 (20)
Shili-Masmoudi <i>et al.</i> , 2019 <sup>42</sup>	1062 HIV/HCV co-infected	Median 46 (IQR 42–49)	Median 21 (IQR 16–25)	831 (78)			231 (22)

HCV, hepatitis C virus; HIV, human immunodeficiency virus; PWH, people with haemophilia.

Data are reported as n (%) or mean ± SD, unless otherwise noted.

ESLD in PWH was evaluated in an American and European collaboration of 16 centres from 2002.<sup>43</sup> In this study, 1818 HCV-seropositive PWH were included with a relatively short median follow-up of 12 years. At the end of follow-up, 137 (8%) participants developed ESLD based on the criteria mentioned above, of which only two cases were HCC.<sup>43</sup>

An important risk factor for both progression of liver fibrosis and occurrence of ESLD in HCV-infected PWH is HIV co-infection. Although in recent years safer and less hepatotoxic antiretroviral therapy has resulted in a more similar progression of liver fibrosis in HIV/HCV co-infected patients,<sup>44</sup> virtually all co-infected PWH have been infected for ≥30 years, before these new treatment modalities became available. As a result, HIV co-infected PWH not only have higher fibrosis scores, but also account for the majority of ESLD cases.<sup>24,26,28,35,37,43</sup> The large haemophilia cohort study from 2002 reported 127 ESLD cases in 1192 HIV-positive PWH compared to only 10 in 624 HIV-negative PWH.<sup>43</sup> Cumulative incidences of ESLD at 16 years of follow-up were 14% and 3% for HIV-positive and -negative HCV-infected PWH respectively. Likewise, in the cohort of 863 HCV-infected PWH with >30 years of follow-up, ESLD rates were 22% and 7% in HIV-positive and -negative HCV-infected individuals respectively.<sup>24</sup> In this cohort, HIV co-infection was the strongest predictor of ESLD occurrence, with a hazard rate of 11.<sup>24</sup>

Besides HIV, several other factors are associated with progression of liver disease and occurrence of ESLD in HCV-positive PWH. The determinant most strongly associated with a decreased risk of developing ESLD is successful HCV antiviral treatment.<sup>24,26–28,30</sup> Nonetheless, despite successful treatment being a strong predictor of decreased ESLD risk, HCC and decompensated cirrhosis still occur after sustained virological response (SVR) or spontaneous clearance. This is infrequent and is predominantly seen in patients with liver cirrhosis before the start of HCV treatment or with other liver-related risk factors such as obesity and alcohol abuse.<sup>24,28</sup> Other factors associated with development of liver cirrhosis or ESLD are age at HCV infection,<sup>24,26,28</sup> age in general<sup>30,31,43</sup> and HBsAg positivity.<sup>26,43</sup>

## The use of antiviral therapy for HCV

The first clinical trial to treat NANBH in haemophilia with interferon (IFN) injections commenced 2 years before the discovery of HCV.<sup>45</sup> In the following decade, the addition of the oral antiviral drug ribavirin and later replacement of standard IFN with PEGylated IFN (PEG-IFN) improved the efficacy of HCV treatment. In 2006, we reviewed the publications on treatment of HCV in haemophilia and included 35 studies with 1151 PWH in the analysis.<sup>46</sup> In treatment-naive HIV-negative PWH, SVR rates were 22% for IFN monotherapy, 43% for IFN with ribavirin and 57% for PEG-IFN with ribavirin. In HIV/HCV co-infected PWH, SVR rates for IFN monotherapy were only 8%, whereas efficacy of IFN with

**Table II.** Overview of studies reporting HCV treatment efficacy in patients with inherited bleeding disorders.

Reference	Study design	Type of antivirals	HCV mono-infected, <i>n</i>	SVR rate, % ( <i>n/N</i> )	HIV/HCV co-infected, <i>n</i>	SVR rate, % ( <i>n/N</i> )
Posthouwer <i>et al.</i> , 2006 <sup>46</sup>	Review	IFN monotherapy	434	22 (95/434)	51	8 (4/51)
		IFN + Rbv	407	41 (165/407)	23	39 (9/23)
		PEG-IFN + Rbv	168	57 (96/168)	0	
Shire <i>et al.</i> , 2006 <sup>47</sup>	Prospective	PEG-IFN + Rbv	11	45 (5/11)	11	27 (3/11)
Posthouwer <i>et al.</i> , 2007 <sup>48</sup>	Retrospective	IFN monotherapy	101	29 (29/101)	35	20 (7/35)
		IFN + Rbv	72	44 (32/72)	2	50 (1/2)
		PEG-IFN + Rbv	62	63 (39/62)	23	48 (11/23)
Maor <i>et al.</i> , 2008 <sup>49</sup>	Retrospective	PEG-IFN + Rbv	37	46 (17/37)	5	20 (1/5)
Katsarou <i>et al.</i> , 2008 <sup>51</sup>	Prospective	PEG-IFN + Rbv	31	58 (18/31)	19	11 (2/19)
Denholm <i>et al.</i> , 2009 <sup>50</sup>	Retrospective	PEG-IFN + Rbv	0		13	8 (1/13)
Alavian <i>et al.</i> , 2010 <sup>53</sup>	Prospective	PEG-IFN + Rbv	367	61 (225/367)	0	
Moghaddam <i>et al.</i> , 2012 <sup>54</sup>	Prospective	PEG-IFN + Rbv	45	96 (43/45)	0	
Honda <i>et al.</i> , 2013 <sup>55</sup>	Retrospective	PEG-IFN + Rbv	23*	65 (15/23)	*	
Lin <i>et al.</i> , 2014 <sup>56</sup>	Prospective	PEG-IFN + Rbv	12	67 (8/12)	0	
Yang <i>et al.</i> , 2015 <sup>52</sup>	Retrospective	PEG-IFN + Rbv	102	86 (88/102)	2	50 (1/2)
Stedman <i>et al.</i> , 2015 <sup>57</sup>	Phase 2 trial	SOF/LDV + Rbv	14	100 (14/14)	0	
Santagostino <i>et al.</i> , 2016 <sup>58</sup>	Phase 3 trial	Lambda-IFN + Rbv + DAC	51	90 (46/51)	0	
Ackens <i>et al.</i> , 2016 <sup>59</sup>	Case report	SOF/DAC	0		2, with ESLD	100 (2/2)
Walsh <i>et al.</i> , 2017 <sup>60</sup>	Phase 2 trial	SOF/LDV, SOF + Rbv	94	98 (92/94)	26	100 (26/26)
Hézode <i>et al.</i> , 2017 <sup>61</sup>	Phase 3 trial	EBR/GZR	101	94 (95/101)	6	83 (5/6)
Lee <i>et al.</i> , 2017 <sup>62</sup>	Prospective	SOF/LDV, SOF + Rbv	30*	93 (28/30)	*	
		or DCV/ASV				
Uemura <i>et al.</i> , 2017 <sup>63</sup>	Prospective	SOF/LDV, SOF + Rbv or SOF/DAC	0		27	100 (27/27)
Wiegand <i>et al.</i> , 2017 <sup>64</sup>	Retrospective	Various DAA regimens	18	94 (17/18)	0	
Mehta <i>et al.</i> , 2017 <sup>65</sup>	Retrospective	SOF/DCV	4	100 (4/4)	0	
Nagao and Hanabusa 2017 <sup>66</sup>	Prospective	SOF/LDV	23	100 (23/23)	20	95 (18/20)
Xiao <i>et al.</i> , 2019 <sup>67</sup>	Retrospective	Various DAA regimens	0		12	100 (12/12)
Mancuso <i>et al.</i> , 2020 <sup>68</sup>	Prospective	Various DAA regimens	160	100 (160/160)	40	95 (38/40)
Guedes <i>et al.</i> , 2020 <sup>69</sup>	Retrospective	Various DAA regimens	16*	100 (16/16)	*	

ASV, asunaprevir; DAA, direct-acting antiviral; DAC, daclatasvir; EBR, elbasvir; ESLD, end-stage liver disease; GZR, grazoprevir; HCV, hepatitis C virus; IFN, interferon; LDV, ledipasvir; PEG-IFN, PEGylated interferon; Rbv, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; VEL, velpatasvir.

\*Human immunodeficiency virus (HIV) status not reported.

ribavirin was comparable to HIV-negative PWH at 39%.<sup>46</sup> Subsequent studies evaluating PEG-IFN efficacy in HIV-positive PWH showed varying results, with the SVR rate ranging from 8% to 50% (Table II).<sup>46–69</sup>

Treatment with PEG-IFN and ribavirin came at the cost of significant side-effects. Moreover, these regimens were less effective in HCV genotype 1 infections,<sup>48</sup> the most common genotype in HCV-infected PWH.<sup>24</sup> The introduction of direct-acting antivirals (DAA) drastically changed the landscape of HCV treatment. At first, so-called ‘triple therapy’ became available, in which the protease inhibitors, telaprevir or boceprevir, were combined with PEG-IFN and ribavirin. These regimens showed high SVR rates of 60–75% in treatment-naïve patients with HCV genotype 1.<sup>70</sup> Apart from several case reports, no haemophilia-specific efficacy studies of these first-generation DAA were published. In 2016, Santagostino *et al.*<sup>58</sup> published a study in which 51 PWH were

treated with a combination of lambda-IFN, ribavirin and the second-generation DAA daclatasvir (DAC), demonstrating 90% efficacy. However, despite its high efficacy this regimen was never widely used, because IFN-free, all-oral DAA regimens were introduced at around the same time. Current DAA can be divided in three classes, all targeting different parts of the viral genome responsible for replication. Besides the NS3-4A serine protease inhibitors (-previr), these are non-structural protein (NS)5A inhibitors (-asvir) and NS5B inhibitors (-buvir). Combinations of these classes of inhibitors result in SVR rates of >95%, in general within 2–3 months of treatment.

Stedman *et al.*<sup>57</sup> were the first to publish IFN-free DAA results specifically for PWH. In their phase II trial published in 2015, all 14 PWH infected with HCV genotype 1 and treated with sofosbuvir (SOF)/ledipasvir (LDV) achieved SVR-12, defined as an undetectable viral load 12 weeks after

cessation of HCV treatment. Subsequently, in 2017, results from four other DAA trials specifically for patients with inherited bleeding disorders were published (Table II).<sup>60–63</sup> In a USA multicentre trial, SOF/LDV was administered to patients with genotype 1 or 4 and SOF plus ribavirin to patients with genotype 2 and 3.<sup>60</sup> The SVR-12 rate in the 120 included patients was 98% (118/120), due to one relapse in a PWH with HCV genotype 3 infection and one being lost to follow-up. In another trial, elbasvir/grazoprevir was given to 47 patients with genotype 1 or 4 and either haemophilia or von Willebrand disease, resulting in an 89% (42/47) SVR-12 rate.<sup>61</sup> In Korea, 30 PWH were treated with different regimens, with a 93% SVR-12 rate due to two failures in genotype 1b patients receiving DAC/asunaprevir.<sup>62</sup> The final DAA trial in PWH was conducted in Japan, where 25 HCV/HIV co-infected PWH also receiving different regimens were all successfully treated.<sup>63</sup>

Besides these trials showing DAA to be highly effective in HCV-infected PWH, they also demonstrated that the drugs were generally well-tolerated and safe. Predominantly mild side-effects were reported in 60–90% of treated patients, being more frequent in those receiving ribavirin.<sup>57,60,61,63</sup> The most frequent side-effects were headache, fatigue and nausea, occurring in 10–30% of patients. Importantly, drug-related haemorrhage was very rare in these four trials, with only one patient having an episode of epistaxis that was considered drug-related.<sup>60</sup> An exception to this low rate of serious adverse events is seen in patients with decompensated Child–Pugh B and C liver cirrhosis. After several reports of liver failure and death following treatment with DAA regimens containing a protease inhibitor (glecaprevir, grazoprevir, voxilaprevir) there was a post-approval United States Food and Drug Administration (FDA) safety warning<sup>71</sup> that these drugs should not be prescribed in patients with current Child–Pugh B and C liver cirrhosis.

DAA efficacy has also been demonstrated in real-world reports of usage including in PWH (Table II). The largest study originates from Italy, in which 200 PWH were treated with different DAA regimens.<sup>68</sup> In this cohort, SVR-12 was achieved in 99% (193/195) of patients, while no DAA-related

serious adverse events were seen. An SVR-12 rate of >94% was also seen in all other published real-world studies (Table I).<sup>59,64–66,68,69,72</sup> This high DAA treatment efficacy corresponds to efficacy rates seen in other HCV patients. Slightly lower SVR rates, although in general still >90%, are seen in patients with genotype 3 infection or cirrhosis, while DAA treatment efficacy does not differ between HCV mono-infected and HIV/HCV co-infected patients.<sup>73</sup> The current state of the art DAA are glecaprevir with pibrentasvir and SOF with velpatasvir, generally prescribed for 8 and 12 weeks respectively. These great advances in HCV treatment have offered the perspective of HCV elimination within the haemophilia population, with Slovenia being the first country to actually report this milestone.<sup>74</sup>

### The natural history of HBV infection in haemophilia

The natural history of HBV is characterised by five different phases (Table III).<sup>75</sup> HBsAg is detectable in the first four phases, which are mainly distinguished by the presence of hepatitis B e antigen (HBeAg) and whether there are increased transaminases as signs of hepatic inflammation.<sup>75,76</sup> Antiviral treatment should in general be considered in patients with prolonged HBeAg-positive or -negative hepatitis [as indicated by prolonged (>3 months) increased transaminases] and in those with signs of advanced fibrosis or cirrhosis. Current suppressive HBV treatment (entecavir, tenofovir disoproxil and tenofovir alafenamide) is very effective and with only limited risk of side-effects. Adequate HBV DNA suppression is eventually achieved by >95% of treated patients, thereby strongly reducing the incidence of cirrhosis, ESLD and HCC.<sup>76</sup> In absence of significant liver fibrosis, HBsAg-positive PWH without current indication for antiviral treatment should be monitored with at least 6 monthly alanine aminotransferase (ALT) measurements, and should be referred for consideration of antiviral treatment if ALT increases above the upper limit of normal.<sup>75</sup>

The fifth phase of HBV infection, most common in PWH, is the phase where serum HBsAg is negative and antibodies

**Table III.** Different phases of hepatitis B virus infection.

	HBeAg positive*		HBeAg negative*		
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis	HBsAg negative
HBsAg	High	High/intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10 <sup>7</sup> iu/ml	10 <sup>4</sup> –10 <sup>7</sup> iu/ml	<2000 iu/ml	>2000 iu/ml	Usually undetectable
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe	None

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Table adapted from the European Association for the Study of the Liver (EASL) HBV guideline.<sup>75</sup>

\*Therapy should particularly be considered in patients with persistent HBeAg-positive or -negative hepatitis and in patients with cirrhosis.

†Can be elevated persistently or intermittently.



to hepatitis B core antigen (anti-HBc) and generally also HBsAg (anti-HBs) are positive.<sup>75,76</sup> Notably, patients who become HBsAg negative do not completely resolve their HBV infection, as they keep integrated covalently closed circular (ccc) HBV DNA in their hepatocytic DNA. Nonetheless, non-cirrhotic patients who achieve HBsAg seroconversion have a minimal risk of developing cirrhosis in the absence of co-factors.<sup>77</sup> However, those who developed cirrhosis remain at significant risk for HCC. An important consideration for PWH ever infected with HBV, is the risk of HBV flare or reactivation during chemotherapy or immunosuppression. In these patients prophylactic antiviral therapy should be considered, depending on HBsAg status and severity of immune suppression.<sup>75,78</sup> During DAA therapy for HCV, HBsAg seroreversion should be monitored, although this occurs infrequently (1.4% of DAA-treated patients).<sup>79</sup>

Literature on the natural history of HBV in PWH is scarce. In recent studies aiming to find risk factors for ESLD, HBV infection was not considered, probably due to its low prevalence.<sup>24,27</sup> In 2002, data from a large combined American and European cohort were published demonstrating a hazard rate for development of ESLD in HIV/HCV co-infected PWH of 8 for those with chronic HBV infection.<sup>43</sup> As discussed by the authors, an important note regarding these numbers is that only 9% of HIV/HCV co-infected PWH in the cohort were HBV unexposed, making the estimate of the impact of HBV infection imprecise. Furthermore, the study was published in a completely different antiviral treatment era. Nonetheless, virtually all PWH infected with these viruses were exposed before 1990, thus this study contains the most representative data on the natural history of HBV infection in PWH.<sup>43</sup>

In order to prevent HBV infection, all children and adults without (previous) HAV or HBV infection and likely to receive plasma-derived concentrates should have been offered HAV and HBV vaccination. In PWH, subcutaneous administration is recommended above intramuscular administration, as it leads to comparable immunogenicity without the risk of intramuscular haematoma.<sup>80,81</sup>

Hepatitis delta virus (HDV) is a defective virus that requires the presence of HBsAg to replicate. Already in 1982, it was reported in Italy that HBsAg-positive PWH were at a high risk of HDV superinfection, with antibodies to the delta virus found in 49% of HBsAg-positive adult PWH and 25% of HBsAg-positive children.<sup>82</sup> Conversely, in Germany anti-HDV was only found in 0.3% of HBsAg-positive blood donors, compared to 50% again in PWH.<sup>83</sup> HDV superinfection severely accelerates the rate of liver fibrosis progression, as already recognised in 1985 when HDV superinfection was found to be significantly more common in HBsAg-positive PWH with fulminant liver disease than without.<sup>84</sup> Due to the low prevalence of HBsAg in PWH today, as well as the risk of liver-related mortality in those infected with HDV long ago, current HDV prevalence in PWH is likely low, although definitive recent data are lacking. Recently a new promising

antiviral agent, bulevirtide, which blocks the entry of HBV and HDV into hepatocytes, was conditionally approved by the European Medicines Agency (EMA).<sup>85</sup>

## Diagnosis, complications and therapeutic considerations in cirrhosis

Although it has been demonstrated that (especially transjugular) liver biopsy can be performed relatively safely in PWH,<sup>86</sup> staging of liver fibrosis is now usually determined with non-invasive methods for which no clotting factor correction is required. The most widely used laboratory-based tests in patients with HCV are the aspartate aminotransferase (AST) to platelet ratio (APRI) and Fibrosis-4 Index for liver fibrosis (FIB-4).<sup>87,88</sup> Both tests require only regularly collected laboratory values and have demonstrated moderate to good accuracy. In a meta-analysis evaluating the accuracy of APRI in patients with HCV, an APRI threshold of 1.0 had a 76% sensitivity, 72% specificity, 55% positive predictive value (PPV) and 69% negative predictive value (NPV) for predicting or excluding cirrhosis.<sup>89</sup> The accuracy of the FIB-4 Index was evaluated in a series of 592 HCV-infected patients, showing a 74% sensitivity, 80% specificity and 95% NPV for excluding severe fibrosis (<F3) at a FIB-4 value <1.45, and a 38% sensitivity, 98% specificity and 82% PPV for predicting severe fibrosis (≥F3) at a FIB-4 value >3.25.<sup>90</sup>

The most frequently used method to assess liver fibrosis at present is TE using FibroScan®. TE is valuable as it is cheap, fast, and non-invasive and has excellent intra- and interobserver variability.<sup>91</sup> TE cut-off values for patients with HCV are ≤7.0 kPa for F0–F1 (no or mild fibrosis); 7.1–9.4 kPa for F2 (moderate fibrosis); 9.5–12.4 kPa for F3 (advanced fibrosis); and ≥12.5 kPa for F4 (cirrhosis).<sup>92</sup> However, TE cannot accurately distinguish F0/1 from F2 or F3 from F4. At a cut-off value of 9.5, TE has 73–86% sensitivity, 85–91% specificity, 71–87% PPV and 81–93% NPV for the presence of advanced fibrosis or cirrhosis (F3/F4).<sup>93,94</sup> Importantly, several patient-related factors can result in false-positive elevated TE values, such as elevated transaminases, extra-hepatic cholestasis, right decompensation from cardiac or pulmonary causes and (more limited) non-fasting conditions.<sup>95</sup> Of particular relevance is that TE is quite unreliable in establishing fibrosis regression in patients with HCV with previous F3/F4 fibrosis who have sustained viral response after successful antiviral therapy. Additional liver biopsy often shows persistent cirrhosis in patients with F0/1 or F2 fibrosis on TE.<sup>96,97</sup> Therefore, patients with radiological evidence of advanced liver disease or F3/F4 fibrosis according to TE before antiviral therapy should in general remain in surveillance for HCC after SVR, even if TE suggests regression of fibrosis after the antiviral therapy.

Radiological imaging is not very sensitive in diagnosis of advanced liver disease. Although ultrasonography, computed tomography and magnetic resonance imaging can detect quite specific indications of advanced cirrhosis such as liver nodularity or portal hypertension, their sensitivities and

NPVs are low. Endoscopic surveillance for oesophageal varices is in general recommended in cirrhotic patients with a TE value  $\geq 25$  kPa and a platelet count  $< 110 \times 10^9$  cells/l.<sup>98</sup> Nevertheless, current insights allow a more restrictive follow-up of surveillance after successful anti-HCV therapy in case of cirrhotic patients without or with small stable varices in absence of previous variceal bleeding or co-factors for progression of fibrosis.<sup>78</sup> Treatment of symptoms of cirrhosis is mainly limited to patients with signs of decompensated cirrhosis, such as hepatic encephalopathy, varices or ascites. Furthermore, as malnutrition and sarcopenia are frequent complications in patients with advanced liver disease, nutrition guidelines recommend dietary counselling, sufficient protein intake, late evening protein intake, and especially in patients with ascites, a maximum daily sodium intake of 80 mmol.<sup>99</sup>

## Hepatocellular carcinoma

Liver cancer, in 90% of cases caused by HCC, is the fifth most prevalent and second most lethal type of cancer globally.<sup>100</sup> Among PWH the impact of HCC is even greater, as it is the most common type of cancer and both HCC incidence and mortality in PWH are greater than in the general population.<sup>101,102</sup> Furthermore, HCC incidence in PWH has been increasing in the recent decades, as was demonstrated by a threefold increase in HCC prevalence between 1998 and 2014 in a large American analysis of hospital discharge data.<sup>101</sup> This increase was more pronounced, albeit not reaching statistical significance, from the 1.7-fold increase in non-haemophilic men during the same period.

An increase in HCC prevalence was also seen in the long-term follow-up study of 700 PWH with chronic HCV.<sup>24</sup> In this study, HCC was diagnosed in 22 (3%) of patients after a median infection duration of 29 years. Notably, nine (41%) of these cases occurred in the last 6 years of the follow-up, which lasted until 2012. HCC prevalence was even higher in similar but smaller cohorts from Ireland, Sweden and Scotland, with respectively 9%, 6% and 5% incidence after 30 years of HCV infection.<sup>25,26,28</sup> Most of these rates are higher than in the general HCV population, where the 30-year HCC risk is estimated to be between 1% and 3%.<sup>103</sup> In contrast to most reports, a large single-centre American study of 222 PWH with chronic HCV, reported only one (0.5%) HCC case, after a median of 28 years of HCV infection.<sup>29</sup> Apart from treating the underlying viral hepatitis and advising to avoid alcohol and being overweight, one could advise reducing coffee consumption considering the negative association of (caffeinated or decaffeinated) coffee (with dose-response relationship up to three cups) and prevalence of cirrhosis or HCC.<sup>104</sup> Furthermore, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (also known as statins) are associated with a lower risk of cirrhosis and HCC in patients with chronic liver disease.<sup>105</sup>

HCC surveillance is indicated for cirrhotic patients with an annual HCC incidence of  $\geq 1.5\%$ .<sup>106</sup> Therefore, all PWH with cirrhosis should be offered HCC surveillance, unless HCC treatment would not be indicated due to severe comorbidity or not possible because of decompensated cirrhosis without the prospect of future liver transplantation, as in decompensated cirrhosis palliative anti-tumour therapy or resection are in general contraindicated. Due to potential understaging with TE, the European Association for the Study of the Liver (EASL) also recommends surveillance in patients with chronic HCV infection and Stage F3 fibrosis.<sup>106</sup> The goal of surveillance is detection of HCC at an early stage, as late-stage HCC has limited treatment options and poor survival. HCC surveillance is usually performed with 6-monthly ultrasonography, with or without the biomarker alpha-fetoprotein (AFP). Importantly, liver inflammation can sometimes cause false-positive elevated AFP levels.<sup>106</sup>

Although successful HCV treatment strongly reduces the risk of HCC development,<sup>107</sup> patients with pre-treatment cirrhosis remain at risk.<sup>108</sup> In a large American non-haemophilic cohort, the annual HCC risks for cirrhotic patients after SVR were 3.7% and 1.2% for patients with pre-SVR FIB-4 scores of  $>$  or  $<$  3.25 respectively.<sup>108</sup> HCC incidence in pre-treatment non-cirrhotic patients was very low in this study. The recently published EASL HCV guideline recommends indefinite HCC surveillance for all successfully treated patients with Metavir F3 or F4 fibrosis scores.<sup>73</sup> As mentioned above, this should also be done when TE would suggest regression of fibrosis post-SVR.

Various treatment options exist for HCC, although curative treatment options are mainly limited to liver transplantation, resection and sometimes radiofrequency ablation (RFA). Survival is most favourable in the selected group of patients who are eligible for liver transplantation. Resection leads to a 5-year survival rate of 60–80%.<sup>106</sup> Unfortunately, recurrence or *de novo* HCC are seen in 70% of patients after resection or RFA.<sup>106,109</sup> In case of advanced local growth or extrahepatic spread, palliative anti-tumour treatment options should be considered (e.g. percutaneous RFA/cryoablation, transarterial chemoembolisation, selective internal radiation therapy and sorafenib).<sup>106,109</sup> There are few data on the impact and prognosis of these treatment strategies for PWH specifically, most of which are summarised in a review by Meijer *et al.*<sup>109</sup>

## Liver transplantation in haemophilia

Orthotopic liver transplantation (OLT) is a definitive treatment option for patients with decompensated cirrhosis or early stage HCC. The first liver transplant in a PWH was reported in 1985.<sup>110</sup> The transplanted liver is able to produce all clotting factors, usually at a sufficient level within 48–72 h post-transplant.<sup>111</sup> As the concentration of produced clotting factors remains stable during long-term follow-up,<sup>111</sup>

an important benefit of OLT in haemophilia is the functional cure of the bleeding disorder.

Several studies have compared OLT outcomes between PWH and non-haemophilic liver transplant recipients, although these are usually small and often lack long-term follow-up data. Despite perioperative clotting factor replacement, PWH undergoing OLT have been reported to have an increased risk of bleeding complications when compared to non-haemophiliacs.<sup>112</sup> However, this does not result in significant difference in in-hospital mortality between these groups.<sup>112</sup> Likewise, the post-transplant survival rates appears similar between PWH and non-haemophiliacs.<sup>113,114</sup> In various studies, the post-transplant survival rate for PWH after 1, 3 and 5 years range between 78% and 90%, 67–80% and 54–67%, respectively.<sup>111,113–115</sup> PWH undergoing OLT now are likely to have an improved survival rate compared to these historical cohorts. The most common cause of death after OLT in these studies was liver failure due to recurrent HCV or HCC,<sup>24,111,113</sup> for which many new treatment options have become available recently. In the general HCV population, this has already resulted in increased post-transplant survival in the DAA era.<sup>116</sup>

### Liver disease in the upcoming era of new haemophilia therapies

Recent developments in haemophilia treatment have included gene therapy where the FVIII and FIX genes are inserted into the liver cells, enabling sustainable production of clotting factors after a single viral vector administration.<sup>117</sup> The most widely used method for gene replacement in rare genetic diseases employs adeno-associated virus (AAV) as the vector. Although AAV has been considered to be a non-integrating vector, it rarely does integrate to a small degree. Importantly, when this low risk of integration is multiplied by the large number of infused AAV vectors and large number of hepatocytes, AAV integration is inevitable and occurs with an estimated frequency of one in 1000–10 000 hepatocytes.<sup>118</sup> In theory, AAV integration next to an oncogene in a fibrotic or cirrhotic liver could lead to HCC development.

Recently, the discussion on whether this is an actual risk of AAV gene therapy has become very relevant after a participant of the UniQure AAV5-FVIII trial developed HCC 1 year after gene replacement therapy.<sup>119</sup> This participant had previously been successfully treated for HCV, had a prior HBV infection and was reported to have evidence of non-alcoholic fatty liver disease. At the time of writing, tumour histology and sequence results are still awaited. Ruling out involvement of AAV integration into the tumour DNA will be crucial for the future of AAV gene therapy.

As a number of other new non-replacement treatments are introduced for the treatment of haemophilia, clinicians should be alert to the facts that the new therapies could cause hepatic dysfunction or that a patient's damaged liver could impact the efficacy and safety of the therapy. We are

not aware of any evidence to suggest that the bispecific antibody, emicizumab, or the anti-tissue factor pathway inhibitor (TFPI) therapies cause or are impacted by hepatic dysfunction. Pasi *et al.*<sup>120</sup> reported that nine of 25 (36%) severe PWH treated with the small interfering RNA (siRNA) molecule Fitusiran developed elevated ALT levels, but these were transient with no chronic sequelae.

### Conclusion

The introduction of viral inactivation of plasma-derived concentrates, as well as the vaccination of patients against HAV and HBV and the increasing use of recombinant products has practically eliminated new hepatitis viral infections in haemophilia. For those already infected the use of DAA has made it possible to clear the HCV from almost all the patients treated. Continued monitoring for HCC is required for individuals who already had cirrhosis at the time of clearance of the HCV.

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Cas J. Isfordink has received research funding from Gilead. Karel J. van Erpecum has participated in Advisory Boards of Gilead, Abbvie, Janssen and MSD and consultancy for Abbvie (no personal benefit, all fees to UMC Utrecht) and participates in the Celine (hepatitis C Elimination In the Netherlands) project (a multicentre initiative to eradicate hepatitis C from the Netherlands: sponsored by Gilead). Marc van der Valk has received consultancy fees through his institution from Abbvie, Janssen, MSD, ViiV, Gilead and unrestricted research support from Abbvie, Janssen, MSD, Gilead. Michael Makris has provided consultancy to Grifols, Sanofi, NovoNordisk and CSL Behring. He is also the project lead for the (European Haemophilia Safety Surveillance (EUHASS) project that receives support from Bayer, BPL, CSL Behring, Kedrion, NovoNordisk, Octapharma, Pfizer, Roche, Sobi and Takeda. Evelien P. Mauser-Bunschoten has no conflict of interests.

### Author contributions

Cas J. Isfordink wrote the first draft of the manuscript. Karel J. van Erpecum, Marc van der Valk, Evelien P. Mauser-Bunschoten and Michael Makris critically reviewed and revised draft manuscripts. All authors have read and approved the final version of the manuscript.

### References

1. Pool JG, Shannon AE. Production of high-potency concentrates of anti-hemophilic globulin in a closed-bag system. *N Engl J Med.* 1965;273:1443–7.
2. Mannucci PM. Back to the future: a recent history of haemophilia treatment. *Haemophilia.* 2008;14:10–8.
3. Beeson P. Jaundice occurring one to four months after transfusion of blood or plasma. *JAMA.* 1943;121:1332–4.
4. Tobler LH, Busch MP. History of posttransfusion hepatitis. *Clin Chem.* 1997;43:1487–93.

5. Preiksaitis JK. The cytomegalovirus-“safe” blood product: is leukoreduction equivalent to antibody screening? *Transfus Med Rev.* 2000;**14**:112–36.
6. James RC, Mustard CA. Geographic location of commercial plasma donation clinics in the United States, 1980–1995. *Am J Public Health.* 2004;**94**:1224–9.
7. Kroner B, Rosenberg P, Aledort L, Alvord G, Goeder J. HIV-1 infection incidence among persons with hemophilia in the United States and western Europe, 1978–1990. Multicenter Hemophilia Cohort Study. *J Acquir Immune Defic Syndr.* 1994;**7**:279–86.
8. Darby SC, Kan SW, Spooner RJ, Giangrande PL, Lee CA, Makris M, et al. The impact of HIV on mortality rates in the complete UK haemophilia population. *AIDS.* 2004;**18**:525–33.
9. Rasi V, Ikkala E, Myllylä G, Nevanlinna HR. Low prevalence of antibodies against human immunodeficiency virus in Finnish haemophiliacs. *Vox Sang.* 1991;**60**:159–61.
10. Ebeling F, Rasi V, Laitinen H, Krusius T. Viral markers and use of factor products among Finnish patients with bleeding disorders. *Haemophilia.* 2008;**7**:42–6.
11. Mauser-Bunschoten EP, Roosendaal G, van den Berg HM, Bresters D, van Drimmelen AA, Cuyper HT, et al. Hepatitis C infection and viremia in Dutch Hemophilia patients. *J Med Virol.* 1995;**45**:241–6.
12. Melbye M, Madhok R, Sarin P, Lowe GO, Goedert J, Froebel K, et al. HTLV-III Seropositivity in European haemophiliacs exposed to factor VIII concentrate imported from the USA. *Lancet.* 1984;**324**:1444–6.
13. Berntorp E, Hansson BG, Böttiger B, Jarevi G, Wedbäck A, Nordenfelt E, et al. HIV seroconversion in Swedish haemophiliacs: relation to type and dosage of factor concentrate. *Eur J Haematol.* 1987;**38**:256–60.
14. Lynch TJ, Weinstein MJ, Tankersley DL, Fratantoni JC, Finlayson JS. Considerations of pool size in the manufacture of plasma derivatives. *Transfusion.* 1996;**36**:770–5.
15. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood.* 1997;**90**:2515–21.
16. Teitel JM. Viral safety of haemophilia treatment products. *Ann Med.* 2000;**32**:485–92.
17. Richardson LC, Evtatt BL. Risk of hepatitis A virus infection in persons with hemophilia receiving plasma-derived products. *Transfus Med Rev.* 2000;**14**:64–73.
18. European Medicines Agency. Guideline on plasma-derived medicinal products [Internet]. [cited 2020 May 20]. Available from: [https://www.ema.europa.eu/en/documents/scientificguideline/guideline-plasma-derived-medicinal-products\\_en.pdf](https://www.ema.europa.eu/en/documents/scientificguideline/guideline-plasma-derived-medicinal-products_en.pdf)
19. Peerlinck K, Arnout J, Gilles JG, Saint-Remy JM, Vermynen J. A higher than expected incidence of factor VIII inhibitors in multitransfused haemophilia A patients treated with an intermediate purity pasteurized factor VIII concentrate. *Thromb Haemost.* 1993;**69**:115–8.
20. Rosendaal FR, Nieuwenhuis HK, Van den Berg HM, Heijboer H, Mauser-Bunschoten EP, Van der Meer J, et al. A sudden increase in factor VIII inhibitor development in multitransfused hemophilia A patients in The Netherlands. *Blood.* 1993;**81**:2180–6.
21. Mauser-Bunschoten EP, Zaaier HL, van Drimmelen AA, de Vries S, Roosendaal G, van den Berg HM, et al. High prevalence of parvovirus B19 IgG antibodies among Dutch hemophilia patients. *Vox Sang.* 1998;**74**:225–7.
22. Peden A, McCardle L, Head MW, Love S, Ward HJ, Cousens SN, et al. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. *Haemophilia.* 2010;**16**:296–304.
23. Makris M, Preston FE, Rosendaal FR, Underwood JCE, Rice KM, Triger DR. The natural history of chronic hepatitis C in haemophiliacs. *Br J Haematol.* 1996;**94**:746–52.
24. Fransen van de Putte DE, Makris M, Fischer K, Yee TT, Kirk L, van Erpecum KJ, et al. Long-term follow-up of hepatitis C infection in a large cohort of patients with inherited bleeding disorders. *J Hepatol.* 2014;**60**:39–45.
25. Khan MM, Tait RC, Kerr R, Ludlam CA, Lowe GDO, Murray W, et al. Hepatitis C infection and outcomes in the Scottish haemophilia population. *Haemophilia.* 2013;**19**:870–5.
26. Murphy N, O'Mahony B, Flanagan P, Noone D, White B, Bergin C, et al. Progression of hepatitis C in the haemophiliac population in Ireland, after 30 years of infection in the pre-DAA treatment era. *Haemophilia.* 2017;**23**:712–20.
27. Qvigstad C, Tait RC, Rauchensteiner S, Berntorp E, de Moerloose P, Schutgens RE, et al. The elevated prevalence of risk factors for chronic liver disease among ageing people with hemophilia and implications for treatment. *Medicine.* 2018;**97**:e12551.
28. Holmström M, Nangarhari A, Öhman J, Duberg AS, Majeed A, Aleman S. Long-term liver-related morbidity and mortality related to chronic hepatitis C virus infection in Swedish patients with inherited bleeding disorders. *Haemophilia.* 2016;**22**:e494–501.
29. Eyster ME, Kong L, Li M, Schreiber IR. Long term survival in persons with hemophilia and chronic hepatitis C: 40 year outcomes of a large single center cohort. *Am J Hematol.* 2016;**91**:E335–40.
30. Giouleme O, Paschos P, Katsoula A, Panteliadou K, Vakalopoulou S, Garipidou V. Hepatitis C infection in a Greek population with inherited bleeding disorders. *Haemophilia.* 2018;**24**:e74–6.
31. Franchini M, Rossetti G, Tagliaferri A, Capra F, de Maria E, Pattacini C, et al. The natural history of chronic hepatitis C in a cohort of HIV-negative Italian patients with hereditary bleeding disorders. *Blood.* 2001;**98**:1836–41.
32. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat.* 2006;**13**:34–41.
33. Zhang M, Rosenberg PS, Brown DL, Preiss L, Konkle BA, Eyster ME, et al. Correlates of spontaneous clearance of hepatitis C virus among people with hemophilia. *Blood.* 2006;**107**:892–7.
34. Konkle BA, Melendez-Morales L, Preiss L, Zhang M, Mathew P, Eyster ME, et al. Correlates of spontaneous clearance of hepatitis C virus among HIV-infected persons with hemophilia. *Blood.* 2006;**108**:1265.
35. Ragni MV, Moore CG, Soadwa K, Nalesnik MA, Zajko AB, Cortese-Hassett A, et al. Impact of HIV on liver fibrosis in men with hepatitis C infection and haemophilia. *Haemophilia.* 2011;**17**:103–11.
36. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The Multivirc Group. *Hepatology.* 1999;**30**:1054–8.
37. Posthouwer D, Mauser-Bunschoten EP, Fischer K, van Erpecum KJ, de Knecht RJ. Significant liver damage in patients with bleeding disorders and chronic hepatitis C: non-invasive assessment of liver fibrosis using transient elastography. *J Thromb Haemost.* 2007;**5**:25–30.
38. Maor Y, Halfon P, Bashari D, Penaranda G, Morali G, Klar R, et al. Fibrotest or Fibroscan for evaluation of liver fibrosis in haemophilia patients infected with hepatitis C. *Haemophilia.* 2010;**16**:148–54.
39. Kitson M, Roberts S, Kemp W, Iser D, Walsh M, McCarthy P, et al. The prevalence of significant liver fibrosis and cirrhosis in haemophilia patients infected with hepatitis C using FibroScan. *Haemophilia.* 2011;**17**:316–7.
40. Vidovic N, Lochowsky RS, Goldmann G, Rockstroh J, Wasmuth JC, Spengler U, et al. Correlation of transient elastography with APRI and FIB-4 in a cohort of patients with congenital bleeding disorders and HCV or HIV/HCV coinfection. *Haemophilia.* 2010;**16**:778–85.
41. Poynard T, de Ledinghen V, Zarski JP, Stanciu C, Munteanu M, Vergniol J, et al. Relative performances of FibroTest, Fibroscan, and biopsy for the assessment of the stage of liver fibrosis in patients with chronic hepatitis C: a step toward the truth in the absence of a gold standard. *J Hepatol.* 2012;**56**:541–8.
42. Shili-Masmoudi S, Sogni P, de Ledinghen V, Esterle L, Valantin MA, Poizat-Martin I, et al. Increased liver stiffness is associated with mortality in HIV/HCV coinfecting subjects: the French nationwide ANRS CO13 HEPAVIH cohort study. *PLoS One.* 2019;**14**:e0211286.

43. Goedert JJ, Eyster ME, Lederman MM, Mandalaki T, De Moerloose P, White GC, et al. End-stage liver disease in persons with hemophilia and transfusion-associated infections. *Blood*. 2002;100:1584–9.
44. Arends JE, Lieveld FI, Boeijen LL, de Kanter CT, van Erpecum KJ, Salmon D, et al. Natural history and treatment of HCV/HIV coinfection: is it time to change paradigms? *J Hepatol*. 2015;63:1254–62.
45. Makris M, Preston F, Triger D, Underwood J, Westlake L, Adelman M. A randomized controlled trial of recombinant interferon-alpha in chronic hepatitis C in hemophiliacs. *Blood*. 1991;78:1672–7.
46. Posthouwer D, Mauser-Bunschoten EP, Fischer K, Makris M. Treatment of chronic hepatitis C in patients with haemophilia: a review of the literature. *Haemophilia*. 2006;12:473–8.
47. Shire NJ, Horn PS, Rouser SD, Stanford S, Eyster ME, Sherman KE, et al. HCV kinetics, quasispecies, and clearance in treated HCV-infected and HCV/HIV-1-coinfected patients with hemophilia. *Hepatology*. 2006;44:1146–57.
48. Posthouwer D, Yee TT, Makris M, Fischer K, Griffioen A, van Veen JJ, et al. Antiviral therapy for chronic hepatitis C in patients with inherited bleeding disorders: an international, multicenter cohort study. *J Thromb Haemost*. 2007;5:1624–9.
49. Maor Y, Schapiro JM, Bashari D, Lurie Y, Safadi R, Segol O, et al. Treatment of hepatitis C in patients with haemophilia – the Israeli National Hemophilia Center experience. *Haemophilia*. 2008;14:336–42.
50. Denholm JT, Wright EJ, Street A, Sasadeusz JJ. HCV treatment with pegylated interferon and ribavirin in patients with haemophilia and HIV/HCV co-infection. *Haemophilia*. 2009;15:538–43.
51. Katsarou O, Theodosiades G, Ioannidou P, Nomikou E, Tseveris B, Kouraba A, et al. Pegylated interferon plus ribavirin combination therapy for chronic hepatitis C in patients with congenital coagulation disorders. *Acta Haematol*. 2008;120:63–9.
52. Yang SY, Lee HW, Lee YJ, Park SJ, Yoo KY, Kim HJ. Highly effective peginterferon  $\alpha$ -2a plus ribavirin combination therapy for chronic hepatitis C in hemophilia in Korea. *Clin Mol Hepatol*. 2015;21:125–30.
53. Alavian S-M, Tabatabaei SV, Keshvari M, Behnavi B, Miri SM, Karimi Elizee P, et al. Peginterferon  $\alpha$ -2a and ribavirin treatment of patients with haemophilia and hepatitis C virus infection: a single-centre study of 367 cases. *Liver Int*. 2010;30:1173–80.
54. Alavi Moghaddam M, Zali MR, Aalaei Andabili SH, Derakhshan F, Miri SM, Alavian SM. High rate of virological response to peginterferon  $\alpha$ -2a-ribavirin among non-cirrhotic Iranian hemophilia patients with chronic hepatitis C. *Iran Red Crescent Med J*. 2012;14:466–9.
55. Honda T, Katano Y, Kuzuya T, Hayashi K, Ishigami M, Itoh A, et al. Comparison of the efficacy of ribavirin plus peginterferon alfa-2b for chronic hepatitis C infection in patients with and without coagulation disorders. *J Med Virol*. 2013;85:228–34.
56. Lin JA, Chen YC, Cheng SN, Chen PJ, Chu HC, Hsieh TY, et al. Peginterferon alfa-2a plus ribavirin for hemophilic patients with chronic hepatitis C virus infection in Taiwan. *J Formos Med Assoc*. 2014;113:727–33.
57. Stedman CA, Hyland RH, Ding X, Pang PS, McHutchison JG, Gane EJ. Once daily ledipasvir/sofosbuvir fixed-dose combination with ribavirin in patients with inherited bleeding disorders and hepatitis C genotype 1 infection. *Haemophilia*. 2016;22:214–7.
58. Santagostino E, Pol S, Oliveira A, Reesink HW, van Erpecum K, Bogomolov P, et al. Daclatasvir/peginterferon lambda-1a/ribavirin in patients with chronic HCV infection and haemophilia who are treatment naïve or prior relapsers to peginterferon alfa-2a/ribavirin. *Haemophilia*. 2016;22:692–9.
59. Ackens R, Posthouwer D. Treatment of chronic hepatitis C with direct acting antiviral agents in patients with haemophilia, end-stage liver disease and coinfecting with HIV. *Haemophilia*. 2016;22:e223–5.
60. Walsh CE, Workowski K, Terrault NA, Sax PE, Cohen A, Bowlus CL, et al. Ledipasvir-sofosbuvir and sofosbuvir plus ribavirin in patients with chronic hepatitis C and bleeding disorders. *Haemophilia*. 2017;23:198–206.
61. Hézode C, Colombo M, Bourlière M, Spengler U, Ben-Ari Z, Strasser SI, et al. Elbasvir/grazoprevir for patients with hepatitis C virus infection and inherited blood disorders: a phase III study. *Hepatology*. 2017;66:736–45.
62. Lee HW, Yoo KY, Won JW, Kim HJ. Direct acting antiviral agents in Korean patients with chronic hepatitis C and hemophilia who are treatment-naïve or treatment-experienced. *Gut Liv*. 2017;11:721–7.
63. Uemura H, Tsukada K, Mizushima D, Aoki T, Watanabe K, Kinai E, et al. Interferon-free therapy with direct acting antivirals for HCV/HIV-1 co-infected Japanese patients with inherited bleeding disorders. *PLoS One*. 2017;12:e0186255.
64. Wiegand J, Schiefke I, Stein K, Berg T, Kullig U, Ende K. Interferon-free treatment of chronic hepatitis C virus infection in patients with inherited bleeding disorders. *Hamostaseologie*. 2017;37:127–30.
65. Mehta R, Kabrawala M, Nandwani S, Desai P, Bhayani V, Patel S, et al. Daclatasvir-Sofosbuvir for treatment of hepatitis C virus in patients with inherited bleeding disorders. *Indian J Gastroenterol*. 2017;36:332–3.
66. Nagao A, Hanabusa H. Brief report: the impact of ledipasvir/sofosbuvir on HIV-positive and HIV-negative Japanese hemophilia patients with 1, 4, and mixed-genotype HCV. *J Acquir Immune Defic Syndr*. 2017;74:418–22.
67. Xiao H, Chen J, Wang J, Li J, Yang F, Lu H. Antiviral therapy for HCV in hemophilia A patients with HIV-1 co-infection. *Medicine*. 2019;98:e16524.
68. Mancuso ME, Linari S, Santagostino E, Bartolozzi D, D'Ambrosio R, Borghi M, et al. High rate of sustained virologic response with direct acting antivirals in hemophiliacs with HCV infection: a multicenter study. *Liver Int*. 2020;40:1062–8.
69. Guedes TP, Garrido M, Morais S, Pedroto I. High rate of SVR with DAA in haemophiliacs with HCV infection: three decades of follow-up of a Portuguese single-centre cohort. *Liver Int*. 2020;40:1783–4.
70. Zoulim F, Bailly F. New approaches to the management of hepatitis C in haemophilia in 2012. *Haemophilia*. 2012;18:28–33.
71. Food and Drug Administration. FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease [Internet]. [cited 2020 Sep 24]. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and>
72. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med*. 2013;368:34–44.
73. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C – final update of the series. *J Hepatol*. 2020;73:1170–218.
74. Maticic M, Lekše A, Kozinc M, Dolničar MB, Andoljšek D, Preložnik Zupan I, et al. Micro-elimination of hepatitis C among patients with congenital bleeding disorders in Slovenia. *J Hepatol*. 2018;68:S193–4.
75. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67:370–98.
76. Seto WK, Lo YR, Pawlotsky JM, Yuen MF. Chronic hepatitis B virus infection. *Lancet*. 2018;392:2313–24.
77. Yuen M, Wong DK, Fung J, Ip P, But D, Hung I, et al. HBsAg seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. *Gastroenterology*. 2008;135:1192–9.
78. Jacobson IM, Lim JK, Fried MW. American Gastroenterological Association Institute Clinical Practice update—expert review: care of patients who have achieved a sustained virologic response after antiviral therapy for chronic hepatitis C infection. *Gastroenterology*. 2017;152:1578–87.
79. Mücke MM, Backus LI, Mücke VT, Coppola N, Preda CM, Yeh ML, et al. Hepatitis B virus reactivation during direct-acting antiviral therapy for hepatitis C: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2018;3:172–80.
80. Carpenter SL, Soucie JM, Presley RJ, Ragni MV, Wicklund BM, Silvey M, et al. Hepatitis B vaccination is effective by subcutaneous route in children with bleeding disorders: a universal data collection database analysis. *Haemophilia*. 2015;21:e39–43.

81. Ragni MV, Lusher JM, Koerper MA, Manco-Johnson M, Krause DS. Safety and immunogenicity of subcutaneous hepatitis A vaccine in children with haemophilia. *Haemophilia*. 2000;**6**:98–103.
82. Rizzetto M, Morello C, Mannucci PM, Gocke DJ, Spero JA, Lewis JH, et al. Delta infection and liver disease in hemophilic carriers of hepatitis B surface antigen. *J Infect Dis*. 1982;**145**:18–22.
83. Roggendorf M, Gmelin K, Zoulek G, Wolf P, Schlipkötter U, Jilg W, et al. Epidemiological studies on the prevalence of hepatitis Delta virus infections in the Federal Republic of Germany. *J Hepatol*. 1986;**2**:230–6.
84. Rosina F, Saracco G, Rizzetto M. Risk of post-transfusion infection with the hepatitis delta virus. A multicenter study. *N Engl J Med*. 1985;**312**:1488–91.
85. Kang C, Syed YY. Bulevirtide: first approval. *Drugs*. 2020;**80**:1601–5.
86. Theodore D, Fried MW, Kleiner DE, Kroner BL, Goedert JJ, Eyster ME, et al. Liver biopsy in patients with inherited disorders of coagulation and chronic hepatitis C. *Haemophilia*. 2004;**10**:413–21.
87. Wai CT, Greenon JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;**38**:518–26.
88. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;**43**:1317–25.
89. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology*. 2011;**53**:726–36.
90. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. *Hepatology*. 2007;**46**:32–6.
91. Fraquelli M, Rigamonti C, Casazza G, Conte D, Donato MF, Ronchi G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. *Gut*. 2007;**56**:968–73.
92. de Lédinghen V, Vergniol J. Transient elastography (FibroScan). *Gastroentérologie Clin Biol*. 2008;**32**:58–67.
93. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology*. 2005;**41**:48–54.
94. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology*. 2005;**128**:343–50.
95. European Association for Study of Liver, Asociacion Latinoamericana para el Estudio del Hígado. EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol*. 2015;**63**:237–64.
96. D'Ambrosio R, Aghemo A, Fraquelli M, Rumi MG, Donato MF, Paradis V, et al. The diagnostic accuracy of Fibroscan® for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. *J Hepatol*. 2013;**59**:251–6.
97. Sultanik P, Kramer L, Soudan D, Bouam S, Meritet J-F, Vallet-Pichard A, et al. The relationship between liver stiffness measurement and outcome in patients with chronic hepatitis C and cirrhosis: a retrospective longitudinal hospital study. *Aliment Pharmacol Ther*. 2016;**44**:505–13.
98. Augustin S, Pons M, Maurice JB, Bureau C, Stefanescu H, Ney M, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. *Hepatology*. 2017;**66**:1980–8.
99. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol*. 2019;**70**:172–93.
100. Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the Global, Regional, and National Level. *JAMA Oncol*. 2017;**3**:1683.
101. Thalappillil A, Ragni MV, Comer DM, Yabes JG. Incidence and risk factors for hepatocellular cancer in individuals with haemophilia: a National Inpatient Sample Study. *Haemophilia*. 2019;**25**:221–8.
102. Hassan S, Monahan R, Mauser-Bunschoten EP, van Vulpen LF, Eikenboom J, Beckers EA, et al. Mortality, life expectancy and causes of death of persons with hemophilia in the Netherlands 2001–2018. *J Thromb Haemost*. 2021;**19**:645–53.
103. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*. 2007;**132**:2557–76.
104. Bravi F, Bosetti C, Tavani A, Gallus S, La Vecchia C. Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. *Clin Gastroenterol Hepatol*. 2013;**11**:1413–21.e1.
105. Facciorusso A, El Aziz MA, Singh S, Pusceddu S, Milione M, Giacomelli L, et al. Statin use decreases the incidence of hepatocellular carcinoma: an updated meta-analysis. *Cancers*. 2020;**12**:874.
106. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;**69**:182–236.
107. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med*. 2013;**158**:329–37.
108. Ioannou GN, Beste LA, Green PK, Singal AG, Tapper EB, Waljee AK, et al. Increased risk for hepatocellular carcinoma persists up to 10 years after HCV eradication in patients with baseline cirrhosis or high FIB-4 scores. *Gastroenterology*. 2019;**157**:1264–78.e4.
109. Meijer K, Haagsma EB. HCV-related liver cancer in people with haemophilia. *Haemophilia*. 2012;**18**:17–24.
110. Lewis JH, Bontempo FA, Spero JA, Ragni MV, Starzl TE. Liver transplantation in a hemophiliac. *N Engl J Med*. 1985;**312**:1189–90.
111. Yokoyama S, Bartlett A, Dar FS, Heneghan M, O'Grady J, Rela M, et al. Outcome of liver transplantation for haemophilia. *HPB (Oxford)*. 2011;**13**:40–5.
112. Mehta KD, Ragni MV. Bleeding and liver transplantation outcomes in haemophilia. *Haemophilia*. 2017;**23**:230–7.
113. Murthy V, Murray D, Hebbali S, Bramhall S, Lester W, Mutimer D, et al. Outcome of liver transplantation in patients with hereditary bleeding disorders: a single centre UK experience. *Haemophilia*. 2016;**22**:e139–44.
114. Ragni MV, Humar A, Stock PG, Blumberg EA, Eghtesad B, Fung JJ, et al. Hemophilia liver transplantation observational study. *Liver Transpl*. 2017;**23**:762–8.
115. Togashi J, Akamatsu N, Tanaka T, Sugawara Y, Tsukada K, Kaneko J, et al. Living donor liver transplantation for hemophilia with special reference to the management of perioperative clotting factor replacement. *Liver Transplant*. 2016;**22**:366–70.
116. Belli LS, Perricone G, Adam R, Cortesi PA, Strazzabosco M, Facchetti R, et al. Impact of DAAs on liver transplantation: major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. *J Hepatol*. 2018;**69**:810–7.
117. Perrin GQ, Herzog RW, Markusic DM. Update on clinical gene therapy for hemophilia. *Blood*. 2019;**407**–14.
118. Batty P, Lillcrap D. Hemophilia gene therapy: approaching the first licensed product. *HemaSphere*. 2021;**5**:e540.
119. uniQure. uniQure Announces Clinical Update on Hemophilia B Gene Therapy Program [Internet]. 2020 [cited 2021 Feb 3]. Available from: [http://uniqure.com/PR\\_Clinical\\_Update\\_FDA\\_Dec2020\\_FINAL\\_12\\_21\\_20.pdf](http://uniqure.com/PR_Clinical_Update_FDA_Dec2020_FINAL_12_21_20.pdf)
120. Pasi KJ, Rangarajan S, Georgiev P, Mant T, Creagh MD, Lissitchkov T, et al. Targeting of antithrombin in hemophilia A or B with RNAi therapy. *N Engl J Med*. 2017;**377**:819–28.