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# Human immunodeficiency and hepatitis virus infections and their associated conditions and treatments among people with haemophilia

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**Summary.** Treatment with contaminated plasma products before 1990 resulted in extraordinary prevalence rates of human immunodeficiency virus (HIV) and hepatitis B and C viruses (HBV, HCV). In the Second Multicentre Haemophilia Cohort Study (MHCS-II) during 2001–03, 30% of HCV-seropositive survivors had HIV and 4.6% were HBV carriers. Highly active antiretroviral therapy (HAART) radically altered the consequences of HIV/HCV coinfection. Whereas opportunistic infections predominated previously, current major complications are liver failure and bleeding (exacerbated by decreased clotting factor synthesis, hypersplenic thrombocytopenia, and oesophageal varices). Most HIV-positives in MHCS-II were HIV RNA-negative and had > 200 $CD4^+$ cells $\mu L^{-1}$, but only 59% were on HAART. With HIV, especially after 41 years of age, liver disease was apparent (jaundice in 5%, ascites 7%, hepatomegaly 9%, splenomegaly 19%). HAART increases survival but may contribute to various comorbidities. Without HIV, sustained HCV clearance is obtained in > 50% with combined pegylated interferons plus ribavirin, but data in haemophilic populations, especially with HIV, are limited. In MHCS-II, HCV RNA negativity was 41% following standard interferon plus ribavirin; among interferon-naïve participants (implying spontaneous HCV clearance), HCV RNA negativity was 12% with and 25% without HIV. Without HIV, spontaneous HCV clearance was much more likely with early age at infection and particularly with recent birth (late 1970s or early 1980s) but not with bleeding propensity or its treatment. Most (72%) participants had received no anti-HCV therapy. Hepatic and haematological conditions are likely to increase during the coming years unless most adult haemophiliacs are successfully treated for HIV, HCV or both.

**Keywords:** haemophilia, HCV, HIV, virus treatment

## Introduction

Human immunodeficiency virus type 1 (HIV-1) is a new human pathogen. It entered the human population recently, approximately in the mid-20th century, probably through hunting and slaughtering of infected primates in central Africa [1]. By the late 1970s, the virus had spread, primarily through sexual contact, first to urban Africa and subsequently to developed countries. The first cases of opportunistic infection and malignancy, now known as acquired immunodeficiency syndrome (AIDS), were reported from New York and California in 1981 [2]. A year later, the first cases in people with haemophilia were reported from Colorado and Ohio [3].

In contrast to HIV-1, the origin of hepatitis C virus (HCV) is unknown, but it has been present in the human population for millennia. Thus, HCV almost certainly was always a contaminant of blood and plasma donated for transfusion, as the prevalence in USA population was 1.8% [4]. Use of clotting-factor concentrates had been associated with abnormalities in liver function tests during the 1970s and with low CD4+ lymphocyte count following the initial reports of AIDS. However, these associations were weak, as most individuals have few symptoms of primary infection with HIV-1 or HCV. That changed with the discovery and development of sensitive and specific diagnostic tests for HIV-1 in 1984 and HCV in 1989 [5–7].

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The majority of HCV infections result in both chronic viraemia, often at high levels, and chronic hepatitis [4,8,9]. In contrast, patients who spontaneously clear HCV show normal hepatic function and liver histopathology years after primary infection [10,11]. Spontaneous clearance of HCV occurs in 10–45% of non-haemophilic patients [8,9,11–13], almost always within a year of primary infection [14]. The determinants of spontaneous clearance remain poorly defined. Broad, vigorous, innate and perhaps cell-mediated adaptive immune responses appear to be required for clearance of HCV [15], but HCV re-infection can occur in patients who have previously cleared virus [16,17]. The likelihood of clearance is reduced with repeated exposures and especially with HIV coinfection [17,18]. Conversely, it is more likely with a single exposure, such as with contaminated anti-D immunoglobulin [12]. Mother-to-infant transmission of HCV is associated with a 75% clearance rate within the first 2 years of life [19]. In contrast, among HIV-negative haemophilia patients in the Haemophilia Growth and Development study, clearance rate was 14.3%, down to only 2.5% among HIV-positive haemophilia patients [20]. Similarly, clearance rate was 13.7% in an HCV-exposed cohort of HIV-negative patients with haemophilia in Italy and 9% in a mixed group of HIV-positive and negative patients in the UK [10,21].

Fifteen years after the discovery of HCV and more than 20 years after most HIV-1 infections began in people with haemophilia, there continues to be uncertainty about the natural history of HCV infection and of the effects and later manifestations of HIV-1 coinfection. To better identify, quantify and develop markers for end-stage liver disease (ESLD) and other complications of HCV, as well as later complications of HIV-1 and its treatment, we initiated the Second Multicentre Haemophilia Cohort Study (MHCS-II). At 52 collaborating haemophilia centres in North and South America and Europe, MHCS-II enrolled all patients who had a congenital coagulation disorder [haemophilia A or B (congenital factor VIII or IX deficiency), vonWillebrand's disease, or other, hereafter referred to as haemophilia], who had reached 13 years of age, and who had serological or molecular evidence of HCV or HIV-1 infection.

## Discussion

Because HIV-1 had not previously been in the pool of donated blood, the epidemic transmission of this virus through contaminated clotting-factor concentrates was limited to the period between 1978 and 1987 [22]. Perhaps because of differences in procedures for factor (F) VIII (from plasma cryoprecipitate) and FIX (from plasma cryosupernate), the HIV-1 epidemic was slightly less severe and started slightly later in FIX than FVIII recipients (Fig. 1) [22]. The incidence of HIV-1 (risk per unit of time) among users of FVIII concentrate peaked in 1982, contemporaneous with the first cases of AIDS in people with haemophilia (Fig. 2). The incidence fell rapidly for four reasons. Firstly, nearly all of the regular users were already infected by the end of 1982. Secondly, when haemophilia and transfusion-associated AIDS was recognized, people estimated to be at increased risk were excluded from the donor pool. Thirdly, use of heat-treated concentrates (and subsequently additional virus-inactivation procedures) became standard clinical practice. Finally, screening of donated blood and plasma was implemented in the USA in March 1985. HIV-1 infections continued to appear among FIX recipients into 1987, probably because of the later licensure of heat-treated FIX products.

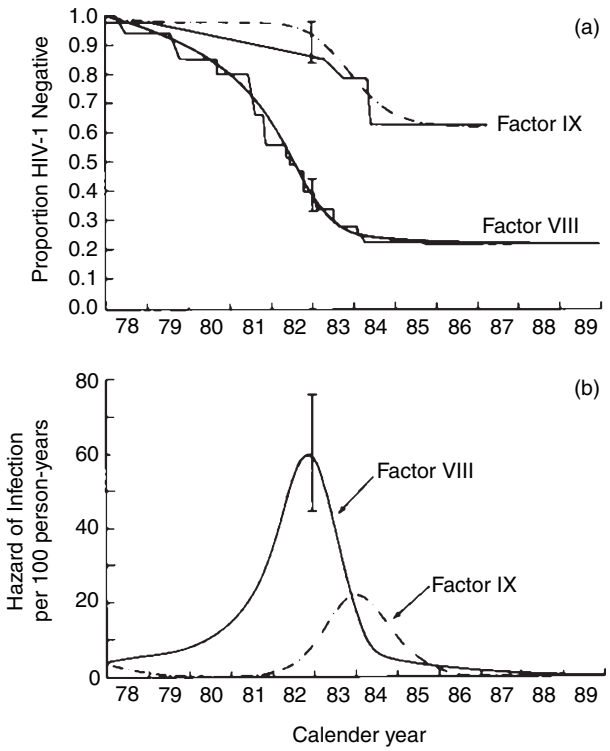


**Fig. 1.** Reconstruction of the HIV-1 epidemic among persons with haemophilia in the USA from Kroner *et al.* [22], separately for those with FVIII and FIX deficiency. (a) Survival without HIV-1 antibody seroconversion by Kaplan–Meier and spline smoothing methods; (b) hazard of HIV-1 antibody seroconversion corresponding to the data in (a).

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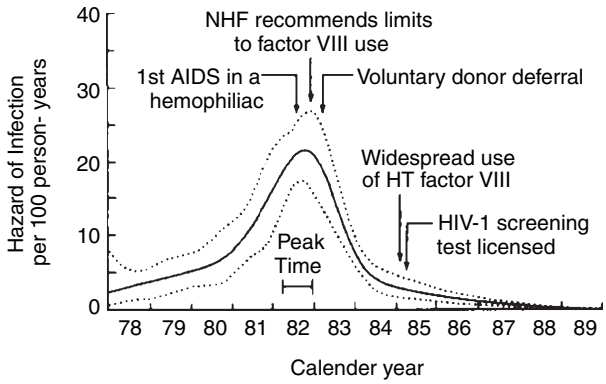


**Fig. 2.** Reconstruction of the HIV-1 epidemic among persons with haemophilia in the USA from Kroner *et al.* [22]. The hazard of HIV-1 antibody seroconversion (with 95% confidence envelope) is presented, annotated with milestones.

By the end of 1987, 78% of the FVIII recipients and 37% of the FIX recipients had been infected.

Thanks to steps to control HIV-1, few new HCV infections were occurring among people with haemophilia by the time that HCV was discovered (in 1989) and that screening donated blood for HCV antibodies was implemented (in 1990). Nonetheless, because HCV levels are higher in plasma and because the virus had been in the pool longer than HIV-1, by 1990 the seroprevalence of HCV was nearly 100% among patients who had received frequent infusions of plasma-derived FVIII or FIX concentrates [23]. Overall, approximately two-thirds of the HCV-infected haemophilia patients in the USA and many other countries were coinfected with HIV-1 [23–25]. Many haemophilic patients died of AIDS between 1985 and 1996, before highly active antiretroviral therapy (HAART) became available [26,27].

In the initial analysis of data from the MHCS-II cohort of HCV-seropositive people with haemophilia and related coagulation disorders, we found a generally low prevalence of clinical manifestations of decompensated ESLD between April 2001 to January 2004 (median June 2002). This is not surprising given the lethality of decompensated ESLD. Even so, there were signs of impending problems for this cohort, as ascites was reported in 33 (5%) of those aged over 41 years, including 11 (7%) who had HIV-1 coinfection. Likewise, hepatomegaly was noted in 8% and splenomegaly in 11% among these older participants. Adjusted for age, the prevalence rates of ascites, hepatomegaly, splenomegaly and persistent jaundice were 2- to 3-fold higher with HIV-1. Also of concern was a high prevalence of subclinical conditions that are likely to indicate active HCV infection or possibly cirrhosis. Whether these subclinical conditions are harbingers of serious disease is unknown and will be examined during the ensuing years.

Co-infection with hepatitis B virus (HBV) may further increase the risk of chronic liver disease. In the MHCS-II, 74% of the HIV-1-positive and 51% of the HIV-1-negative participants had evidence of current or previous HBV infection. In an earlier prospective cohort study, the risk of decompensated ESLD was increased 8.1-fold for carriers of hepatitis B surface antigen (HBsAg) and 3.4-fold for the much larger group of haemophiliacs who had cleared HBsAg [28]. The risk of ESLD for this latter group could be due to hepatic injury prior to resolution of HBV infection or to 'occult' HBV replication occurring at a level detectable only with PCR [29]. In the initial analysis of MHCS-II data, except for a marginally significant increased prevalence of ascites with chronic carriage of HBsAg, HBV status did not confound the strong associations of hepatic conditions with HIV-1 positivity and older age. Because of the mutual interference of both hepatitis viruses, ultrasensitive PCR methods will be needed to better understand the role of HBV among patients who also have HCV infection [30].

Alcohol consumption poses an additional risk for those with HCV infection. As changes in health or medication use may have prompted MHCS-II participants to change their drinking habits, we analysed historical use of alcohol (drinking during the year before knowledge of the participant's HCV positivity) rather than recent alcohol use. Self-reported use of alcohol is fraught with uncertainty. Nonetheless, our participants' self-reported drinking patterns were highly consistent over time, and the few participants who reported signs or symptoms of alcoholism also reported generally high alcohol consumption. We were relieved to find that alcohol consumption in the MHCS-II was low overall. Half of the cohort reported no alcohol consumption; 22% reported consumption of more than 24 g (2 drinks) per week; and 2.6% reported more than 240 g (20 drinks) per week. Further research, including prospective follow-up and histopathological analysis, will be needed to clarify whether the risk of HCV-related liver disease is increased with low-level use of alcohol [31,32].

Nearly one-third of the MHCS-II participants were infected with HIV-1, many of whom were infected in childhood and all of whom have survived with HIV-1 for more than 15 years [22,33]. As survivors, it is not surprising that relatively few of them have had an AIDS-defining opportunistic infection or malignancy (17%) or laboratory-defined AIDS [e.g. $CD4^+$ count below 200 cells $\mu L^{-1}$ (24%)]. Although only 59% of

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the HIV-1-positive participants were currently receiving a recommended HAART regimen, 80% currently had a CD4+ count of 200 cells $\mu L^{-1}$ or higher. HIV-1 RNA could not be detected in plasma in 23% of those currently on no anti-HIV-1 medications, compared to 2.4% of representative haemophilic plasma samples that were frozen early in the epidemic [34]. As expected, HIV-1 RNA could not be detected in 63% of MHCS-II participants receiving HAART. The 18% who were receiving antiretroviral regimens that are not currently recommended is consistent with the proportion of patients for whom current HAART combinations are ineffective or intolerable [35].

In contrast to use of HAART, only a minority of MHCS-II participants had been treated for their HCV infection. Although our data reveal the scale of hepatic disease that is likely to manifest in the haemophilic population during the coming years, there is no means by which to target individuals for treatment with current therapies. HCV genotyping is helpful, as interferon plus ribavirin is more effective against HCV genotype 2 or 3 than against genotype 1 [36]. Liver biopsy also is helpful to identify pathology unrelated to HCV as well as the extent of HCV-related fibrosis and necroinflammatory activity. Accumulating evidence suggests that liver biopsy, particularly by the transjugular route, can be performed safely in haemophiliacs, provided that there is close coordination between the haematologist and the interventional radiologist or hepatologist, as well as the achievement of adequate haemostasis prior to the procedure [37]. However, because one cannot accurately predict the likelihood of success with current anti-HCV therapy, research on the use of non-invasive predictors of cirrhosis and ESLD are a priority for future investigation within the context of our study [38].

This initial analysis has several limitations, the most important of which is its cross-sectional design. Many of the associations that we found have face validity, as not only the temporal sequence but, at least for some conditions, the pathophysiological effects of ageing and HIV-1 infection have been documented. From the current work, however, causality cannot be ascribed merely from the association of two prevalent conditions. Longitudinal analysis of data and specimens that are currently being collected should provide clarity. A second limitation is that our data on use of alcohol were self-reported, allowing not only for inaccuracy in these exposure measures but also the possibility for bias. Thirdly, the haemophilic population differs from others, particularly with respect to young age at infection, multiple and possibly simultaneous infections, and currently only survivors among those who were infected. Finally, although we have the largest cohort of persons with haemophilia yet assembled, many of the conditions were noted in only a few per cent of the participants. Such infrequency, especially in subgroup analyses, increases the possibility that some of the observed associations occurred merely by chance.

In summary, early in the 21st century, persons with haemophilia in developed nations have a high prevalence of infections with plasma-borne viruses that they acquired and have survived with for more than a decade. HCV is a major concern, as three-quarters of the population is chronically infected, interferon-based treatment is infrequently prescribed and often unsuccessful, and non-invasive ways to identify patients most likely to develop serious hepatic disease are undefined. This is a population of HIV-1/AIDS survivors, three-fifths of whom are on HAART, half of whom do not have detectable HIV-1 in their plasma, and one-fifth of whom currently have laboratory-defined AIDS. Nonetheless, we observed that coinfection with HIV-1 and HCV was associated with signs of ESLD and with subclinical abnormalities, most of which could not be simply ascribed to HAART or other anti-HIV-1 regimens. HCV-associated hepatocellular carcinoma had occurred or was found at enrolment in four participants in our cohort. Prospective follow-up will be needed to see whether the abnormalities that we observed are harbingers of a major epidemic of liver disease and whether non-hepatic manifestations of HCV and late complications of HIV-1/AIDS will emerge as well.

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