Coinfection with HIV and hepatitis C virus in 229 children and young adults living in Europe

The European Paediatric HIV/HCV Co-infection Study Group in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) in EuroCoord*

Objective: To characterize children, adolescents and young adults infected with HIV/hepatitis C virus (HCV) vertically or before age of 18 years and living in Europe regarding mode of acquisition, HCV genotype, clinical status and treatment.

Design: Retrospective, cross-sectional study using pooled data from 11 European paediatric HIV cohorts.

Methods: Patients aged more than 18 months and less than 25 years, with HIV/HCV acquired vertically or in childhood, were included. Anonymized individual patient data were collected using a standard protocol and modified HIV Cohorts Data Exchange Protocol.

Results: Of 229 patients included, 142 (62%) had vertically acquired infection. Median age at last follow-up was 16.2 years. Most children had HCV genotype 1 (101/184, 55%) or 3 (57/184, 31%). One-fifth (46/214) had a previous AIDS diagnosis (data missing on prior AIDS diagnoses for 15). At their last clinic visit, 70% (145/208) had no/mild immunosuppression (Centers for Disease Control and Prevention stage 1), and 131 of 179 on antiretroviral therapy had undetectable HIV RNA (assay thresholds varied from <20 to <150 copies/ml). Overall, 42% (86/204) had hepatomegaly in the previous year, and 55% (116/213) had alanine aminotransferase more than 40 IU/l at their last test. Of 97 patients with transient elastography, 12 had results more than 9 kPa; this was associated with duration of HCV infection ($P = 0.033$), but not with CD4$^+$ cell count, antiretroviral therapy use or sex in univariable analysis. Of 17 patients with liver biopsies, six had bridging fibrosis and one had cirrhosis. Twenty-five (11%) had been treated successfully for HCV.

Conclusion: The high proportion of patients with progressive liver disease underscores the need for close monitoring and earlier and more effective HCV treatment.

Introduction

Worldwide, around 20–30% of the 34 million HIV-infected individuals are estimated to have chronic HCV infection, although rates of HIV/HCV coinfection vary between and within populations [1]. Adult studies have demonstrated that HIV modifies the natural history of HCV infection, with increased probability of chronicity after infection, higher HCV viral load and accelerated liver disease progression amongst those chronically infected [2–4]. Chronic HCV infection is the main cause of liver disease and mortality in HIV-infected adults and also contributes to extrahepatic morbidity and mortality through immune activation and chronic inflammation [1,5].

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Although HCV coinfection in HIV-infected adults has been much studied from epidemiological and clinical perspectives, with a current focus on HCV treatment with direct acting antivirals (DAAs) [6], much less is known about HIV/HCV coinfection in childhood and adolescence. The few studies on HIV/HCV coinfected children and adolescents to date have been small and limited to single hospitals or countries, and thus important questions remain with respect to HCV genotype distribution, disease progression and availability and response to HCV treatment [7,8]. Such changes are compounded by striking gaps in our understanding of the natural history of HCV infection in children without coinfection. For example, little is understood about the subgroup of children who progress to serious liver disease during childhood or the impact of HCV-related inflammation on extrahepatic manifestations.

Most children with HIV/HCV coinfection acquire this vertically from their mothers [9,10] or through noso-comial transmission in healthcare settings, although the latter route is now limited to specific lower-income and middle-income settings in which blood and medical injecting safety remains inadequate [11]. Adolescents may also acquire HIV/HCV coinfection horizontally. Young people who inject drugs may be particularly vulnerable to acquisition of blood-borne viruses, reflecting poor access to harm-reduction services and risky injecting practices; increases in injecting drug use among adolescents and young people, with accompanying outbreaks of HIV and/or HCV, have been reported in Europe [12], as well as in the United States [13].

We conducted a descriptive epidemiological study of HIV/HCV coinfection in children, adolescents and young adults infected with HIV/HCV vertically or before age 18 years within our European paediatric HIV cohort collaboration to characterize this subpopulation with respect to mode of acquisition, HCV genotype, clinical status and treatment.

Methods

We conducted a retrospective, cross-sectional observational study, using pooled data from paediatric HIV cohorts in the European Pregnancy and Paediatric HIV Cohort Collaboration that conducts epidemiological research on HIV-infected pregnant women and children [14] and was part of the EuroCoord network (www.eurocoord.net).

Children aged more than 18 months, adolescents and young adults aged less than 25 years, with HIV and chronic HCV coinfection acquired vertically or in childhood (i.e. up to age of 18 years), irrespective of acquisition route, were eligible for inclusion. It is difficult to establish age at acquisition of infection in patients

infected through injecting drug use. We included in our study population 34 young people (all living in eastern Europe) who were reported as having acquired HCV via injecting drug use, but were not diagnosed until aged 18–24 years, including three patients whose HIV infection was nosocomially acquired in childhood. The rationale for including this group of 34 young people was that the majority likely acquired HCV infection before age of 18 years, given that initiation of injecting drug use usually starts in mid-adolescence in this setting [15]. Patients with positive anti-HCV antibodies who spontaneously cleared HCV (i.e. disappearance of HCV RNA in at least 2 consecutive serum samples taken 6 months apart) were excluded. Age more than 18 months was chosen as inclusion criteria to rule out misdiagnoses due to the presence of passively transferred maternal antibodies [16].

Eleven cohorts from 10 countries provided anonymized individual patient data, collected according to a standard protocol, with data specification based on the HIV Cohorts Data Exchange Protocol (www.hicdep.org). Variables included socio-demographics, data on HCV and HIV acquisition, disease and treatment, laboratory tests and liver investigations (e.g. biopsy, transient elastography).

Definitions

Patients were considered chronically infected if HCV RNA was detected in at least two blood samples at least 6 months apart; we included chronically infected patients who subsequently achieved sustained virologic response (SVR) following treatment. HIV-1 infection was defined on the basis of detection of HIV-1 antibody and/or positive HIV RNA or DNA PCR in at least two blood samples.

For patients with vertically acquired HCV, birthdate was used as presumed date of HCV infection. For the remainder, HCV diagnosis date was used as proxy date of infection, with calculated duration of HCV infection therefore a minimum estimate. Geographic region of residence was defined as central and eastern Europe (Poland, Romania, Russia and Ukraine), northern Europe (Belgium, Germany, Switzerland and United Kingdom) and southern Europe (Italy and Spain).

HIV-associated immunodeficiency was defined as none or mild, moderate and severe based on Centers for Disease Control and Prevention 1994 classification [17]. The limit of detection of HIV RNA assays ranged from less than 20 to less than 150 copies/ml. The upper limit of normal (ULN) cut-off for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) was defined as 40 IU/l. Division of AIDS classification for grading the severity of adverse events was used to classify ALT and AST elevations [18].

Liver fibrosis stages evaluated by liver biopsy scoring systems other than METAVIR were reassigned

Table 1. Socio-demographic and clinical characteristics, by mode of HCV acquisition.

	Vertical acquisition	Other acquisition	
	N (%)		
N	145	84	
Country of residence			
Belgium	2 (1.4)	1 (1.2)	
Germany	1 (0.7)	0	
Italy	19 (13.1)	1 (1.2)	
Poland	3 (2.1)	1 (1.2)	
Romania	0	33 (39.3)	
Russia	18 (12.4)	31 (36.9)	
Spain	44 (30.3)	2 (2.4)	
Switzerland	3 (2.1)	0	
UK	2 (1.4)	1 (1.12)	
Ukraine	53 (36.6)	14 (16.7)	
Region of origin			
CE Europe	74 (51.0)	79 (94.0)	
N Europe	3 (2.1)	0	
S Europe	52 (35.9)	3 (3.6)	
Africa	2 (1.4)	2 (2.4)	
Missing/unknown	14 (9.7)	0	$P < 0.001$
Current HIV clinical stage			
Not symptomatic	5 (3.4)	0	
CDC A/WHO 1 or 2	47 (32.4)	29 (34.5)	
CDC B/WHO 3	52 (35.9)	27 (32.1)	
CDC C/WHO 4	24 (16.6)	17 (20.2)	
Unknown	17 (11.7)	11 (13.1)	$P = 0.45$
Current CDC immune stage			
None or mild suppression	101 (69.7)	44 (52.4)	
Moderate suppression	24 (16.6)	29 (34.5)	
Severe suppression	6 (4.1)	4 (4.8)	
Unknown	14 (9.7)	7 (8.3)	$P = 0.018$
Age at last follow-up (years)			
<11	60 (41.4)	7 (8.3)	
11–17	42 (29.0)	24 (28.6)	
18–24	43 (29.7)	53 (63.1)	$P < 0.001$
Age at HCV diagnosis			
Median (IQR) (years)	2.3 (1.5, 6.0)	17.3 (10.0, 21.5)	$P < 0.001$
HCV genotype			
1	66 (45.5)	35 (41.7)	
2	4 (2.8)	1 (1.2)	
3	40 (27.6)	17 (20.2)	
4	17 (11.7)	4 (4.8)	
Unknown	18 (12.4)	27 (32.1)	$P = 0.50$ (among known values)

IQR, interquartile range.

METAVIR fibrosis stage [19]. Two surrogate biomarkers for liver fibrosis were used: AST-to-platelet ratio index (APRI) and the FIB-4 score, which have been validated in HIV/HCV coinfected adults [20,21], but not children. APRI was calculated using the formula $APRI = (AST/ULN)/platelets (10^9/l) \times 100$ [22]. An APRI score more than 1.5 was taken as a predictor of significant fibrosis [21−23]. The FIB-4 score was calculated using the formula $FIB-4 = [age\ (years) \times AST\ (U/l)]/[platelets (10^9/l) \times ALT\ (U/l)^{1/2}]$ [20]. A FIB-4 score more than 3.25 was taken as an indicator of advanced fibrosis [20].

Medians are presented with interquartile range (IQR) and were compared using the Wilcoxon−Mann−Whitney test. Univariable comparisons were assessed using the χ^2 test for trend. Comparisons of clinical status and laboratory markers were conducted using data from the most recent visit date or the last available measurement, with the exception of those patients who achieved a SVR following HCV treatment, for whom the last measure prior to treatment was used. Statistics were conducted using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

Results

A total of 229 HCV/HIV coinfected children and young people were included, of whom 98 were men and 130 women (one missing sex). Median age at last clinical follow-up was 16.2 years (IQR 10.0, 20.2); this was higher in northern and southern Europe than in central and eastern Europe (18.1 versus 13.8 years, $P < 0.001$). Overall, 206 participants were white, four were

black-African, two were Asian and the rest (17, 7%) had missing ethnicity. Socio-demographic and key clinical characteristics are presented in Table 1, stratified by mode of acquisition. A total of 145 (63%) had acquired HCV vertically, 15 (7%) nosocomially, 40 (17%) through injecting drug use and 29 (13%) had unknown mode of acquisition. Mode of HIV acquisition was usually consistent with that for HCV infection, although three Romanian patients nosocomially infected with HIV in childhood acquired HCV through injecting drug use (HCV diagnosed at ages 17, 19 and 23 years). There were 34 patients who were diagnosed with HCV at at least 18 years (median age 21 years) overall.

One-fifth (46/214, 21%) of patients had a history of AIDS (15 missing data), with median age at AIDS diagnosis of 5.1 years (IQR 1.5, 10.1); HIV encephalopathy was the most common AIDS-defining condition ($n = 11$), followed by *Pneumocystis jirovecii* pneumonia ($n = 8$) and *Mycobacterium tuberculosis* ($n = 7$ pulmonary, $n = 3$ extrapulmonary). Overall, 5% (10/213) had severe immunosuppression at their most recent clinical visit (Table 1), with 70% (145/213) having no or mild immunosuppression. Most (179/218) patients were on antiretroviral therapy (ART). Among 179 on ART, 131 (73%) had undetectable HIV RNA at their most recent visit.

Overall, HCV genotype was known for 184 (80%) patients, with genotype 1 and genotype 3 predominating and comprising overall 44 and 25%, respectively (Table 1). Fifty-eight percent (65/113) of patients living in central and eastern Europe and 55% (34/62) in southern Europe had genotype 1 infection, compared with 22% (2/9) in northern Europe, where the largest proportion of patients had genotype 4 (4/9). Figure 1 presents duration of HCV infection by mode of acquisition; median duration was 13.3 years (IQR 8.6, 18.1) among those vertically infected, although regional differences were apparent, with a median duration of 9.3 years (IQR 5.7, 10.8) in central and eastern Europe, 18.0 years (IQR 17.9, 18.1) in northern Europe and 18.2 years (IQR 16.1, 20.1) in southern Europe ($P < 0.001$).
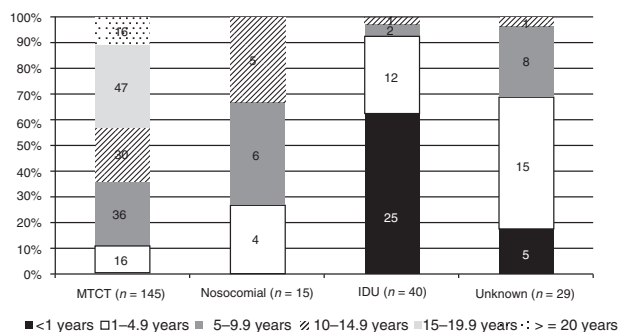
Among 204 patients with data on presence of hepatomegaly and/or splenomegaly during the previous 12 months of follow-up, 86 (42%) had isolated hepatomegaly, 39 (19%) had isolated splenomegaly and 35 (17%) had hepatosplenomegaly. A smaller proportion of vertically infected patients had hepatomegaly compared with those with other acquisition modes [36.7% (51/139) versus 56.4% (35/62), $P < 0.01$], but the proportion with splenomegaly did not vary between these groups [18.8% (26/138) versus 20.6% (13/63), $P = 0.77$].

ALT measurements were available for 213 patients and AST for 111 patients, of whom 116 (55%) and 68 (61%), respectively, had levels above the ULN at their most recent test. A significantly greater proportion of patients with nonvertically acquired HCV had elevated liver enzymes compared with vertically infected individuals (Table 2). APRI and FIB-4 scores are summarized in Table 2. A total of 97 children and young people had transient elastography results available (Table 2), with median age at investigation of 17.6 years (IQR 13.0, 21.6). Of the 12 patients with transient elastography results more than 9.5 kPa, eight had genotype 1 (67%) and two each had genotype 3 and genotype 4. Duration of HCV infection among those with transient elastography results of less than 9.5 kPa was significantly lower (10.7 years, IQR 3.7, 18.0) compared with patients with greater liver stiffness (18 years, IQR 13.9, 19.2) ($P = 0.033$). There was no association between transient elastography results and CD4$^+$ cell count categories, ART use or sex in univariable analysis.

Seventeen (8%) patients from eight cohorts had results from at least one liver biopsy reported. Twelve (71%) of these patients had acquired HCV vertically, one via IDU and three nosocomially (one unknown). Median age at first biopsy was 13 years (range, 3–22). There was no association between transient elastography results and having a biopsy ($P = 0.22$) or with having an elevated ALT or AST ($P = 0.60$). Seven patients had a fibrosis score of F3 and one of F2, with the remainder having no fibrosis or portal fibrosis without septa; moderate inflammation was present in 13 biopsies and mild inflammation in three. Two patients had repeat liver biopsies: one child, aged 9 and 11.5 years at first and second biopsies, respectively, had improvement of both fibrosis and inflammation by one score with no HCV treatment given. The second young person (vertically infected, genotype 3a), aged 14 and 19.5 years at first and second biopsies, respectively, progressed from periportal and portal fibrosis to cirrhosis and died of decompensated cirrhosis aged 21 years.

Overall, 174 (76.0%) of the 229 patients were HCV treatment-naïve, 25 (10.9%) had been unsuccessfully treated with pegylated interferon and ribavirin (pegIFN/RBV), five (2.2%) had completed pegIFN/RBV treatment but were awaiting 24-week posttreatment SVR (SVR24) result and 25 (10.9%) had been treated

Fig. 1. Duration of HCV infection, by mode of acquisition.

Table 2. Liver enzyme measures, noninvasive markers of fibrosis and transient elastography.

	Vertically acquired HCV	HCV acquired by other routes		Total
		N (%)		
ALT				
Number with measurement available[a]	131	82		213
DAIDS grading				
Nonelevated	83 (63.4)	33 (40.2)		116 (54.5)
Mild elevation (grade 1)	37 (28.2)	29 (35.4)		66 (31.0)
Moderate elevation (grade 2)	11 (8.4)	13 (15.9)		24 (11.3)
Severe elevation (grade 3)	0	7 (8.5)	$P = 0.0007^{b}$	7 (3.3)
AST				
Number with measurement available[a]	77	34		111
DAIDS grading				
Nonelevated	47 (61.0)	15 (44.1)		62 (55.9)
Mild elevation (grade 1)	27 (35.1)	8 (23.5)		35 (31.5)
Moderate elevation (grade 2)	2 (2.6)	7 (20.6)		9 (8.1)
Severe elevation (grade 3)	1 (1.3)	4 (11.8)	$P = 0.0002^{b}$	5 (4.5)
APRI				
Number with biomarker available	79	48		127
APRI score				
<0.5 (no significant fibrosis)	45 (57.0)	12 (25.0)		57 (44.9)
0.5–1.5	29 (36.7)	23 (47.9)		52 (40.9)
>1.5 (significant fibrosis)	5 (6.3)	13 (27.1)	$P = 0.0002$	18 (14.2)
FIB-4				
Number with biomarker available	79	48		127
FIB-4 groups				
≤1.45 (no advanced fibrosis)	73 (92.4)	41 (85.4)		114 (89.8)
1.46–3.25	5 (6.3)	6 (12.5)		11 (8.7)
>3.25 (advanced fibrosis/cirrhosis)	1 (1.3)	1 (2.1)		2 (1.6)
Transient elastography				
Number with measurement available	62	35		97
Liver stiffness (kPa)				
<5.8	30 (48.4)	11 (31.4)		41 (42.3)
5.9–9.5	23 (37.1)	21 (60.0)		44 (45.4)
9.6–12.5	6 (9.7)	2 (5.7)		8 (8.2)
>12.5	3 (4.8)	1 (2.9)	$P = 0.09^{c}$	4 (4.1)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, AST-to-platelet ratio index; DAIDS, Division of AIDS.
[a]At last clinic visit.
[b]χ^2 test with grades 2 and 3 grouped together.
[c]χ^2 test with 9.6–12.5 and more than 12.5 grouped together.

successfully. Median age at initiation of pegIFN/RBV treatment was 17.2 years (IQR 3.5, 24.0). HCV genotype distribution was 28 (51%) genotype 1, one genotype 2, 21 (38%) genotype 3 and three (5%) genotype 4 (two missing). Forty-seven (85%) of the patients on pegIFN/RBV were receiving concurrent ART. The SVR24 rates were 32% (8/25) for genotype 1 and 79% (15/19) for genotype 3; the one treated patient with genotype 2 achieved an SVR24, but none of the three treated patients with genotype 4 did so.

In addition to the death above, one other vertically infected patient died following *Pneumocystis jirovecii* pneumonia at age 20 years.

Discussion

In this study, we have characterized the population of children and young people living with vertically or childhood–acquired HIV/HCV coinfection and followed in European paediatric HIV cohorts. No previous description of the HIV/HCV epidemic in children and adolescents across the European region exists. We demonstrate some important regional differences, show that chronic HCV infection in the presence of HIV coinfection is associated with progressive liver disease in a substantial proportion of these children and young people and highlight the low HCV treatment rates.

The cohort of vertically infected patients living in northern and southern Europe were older than those living elsewhere. This reflects the general ageing of paediatric HIV cohorts, declining HIV mother-to-child transmission (MTCT) and the decreasing HCV prevalence in HIV-positive women in these regions [24,25]. In contrast, central and eastern Europe has a younger HIV epidemic, higher HIV MTCT rates (particularly among women who inject drugs, reflecting poorer access to optimum interventions) and a greater proportion of HIV/HCV coinfected pregnant women [26,27]. In our study, similar to the adult genotype distribution in Global

Burden of Disease European regions reported in a recent meta-analysis [26], genotype 1 was the most common followed by genotype 3, although genotype 4 was the most common genotype in northern Europe. Our small numbers preclude firm conclusions on genotype distribution [28]. Among HCV monoinfected children in the Italian Observatory Study, genotype 1 and genotype 2 were prevalent among adolescents, but infections with genotype 3 and genotype 4 were increasing [29].

It is expected that most children becoming HCV-infected in Europe will develop chronic infection, with around 7–20% experiencing spontaneous viral clearance [29,30]. The limited literature available on HIV/HCV coinfected children suggests that they may be less likely to spontaneously clear HCV than adults or than monoinfected children [7]. Among children with chronic HCV monoinfection, 2–3% are expected to progress to cirrhosis in childhood [29]. As probability of liver fibrosis generally increases with age and duration of infection, young adults with HCV acquired vertically or in early childhood may be at risk of end-stage liver disease in early adulthood [31,32]. However, understanding of liver fibrosis progression in childhood and beyond in individuals with vertically or childhood-acquired HCV is incomplete. Mohan et al. [33] found that 30% of HCV monoinfected children had more severe fibrosis in a repeat biopsy conducted on average 6 years after their first, demonstrating that liver fibrosis does progress in childhood; other studies show that some children can progress rapidly, developing severe fibrosis after relatively short durations of HCV infection [34,35].

Questions regarding rates of and risk factors for hepatic fibrosis progression in HIV/HCV coinfected adults also remain [36,37]. In one study, among nearly 300 HIV/HCV coinfected adults with repeat liver biopsies, 34% had progression of at least one METAVIR stage over a median of 2.5 years despite 86% having no or minimal fibrosis at their first biopsy; risk factors for progression included elevated liver enzymes, obesity and hepatic steatosis, but not ART, CD4$^+$ cell count or HIV RNA levels [36]. In the present study, of the 17 patients with liver biopsies, 40% had bridging fibrosis and one went on to develop cirrhosis. However, these biopsy results should be interpreted cautiously due to small numbers and potential bias. We were able to calculate APRI and FIB-4 scores for around half of our study population, and transient elastography results were available for 42% of our study population but the value of these scores and of transient elastography has not yet been established in children.

More than half of our participants had raised ALT/AST at their most recent visit, higher than the 30% reported for HCV monoinfection in the European Paediatric Hepatitis C Network (EPHN) [30]. A Spanish study also reported higher ALT levels in HIV-coinfected versus monoinfected children [7]. Around 40% of our study population had hepatomegaly and/or splenomegaly during the previous year, compared with 10% reported in the EPHN [30]; this may be partly explained by the larger numbers of participants with nonvertically acquired infection in our study, who were more likely to have hepatomegaly than vertically infected children and young people.

Historical cohorts of HCV monoinfected children present a clinical picture of a generally mild disease in terms of symptoms, laboratory and histopathology findings [29,30]. Our findings suggest worse liver disease in HIV/HCV coinfected children and young people than in those with HCV monoinfection [29,32], consistent with adult studies [1,5,36]. Chronic HCV infection in the context of HIV coinfection may thus be considered as a potentially aggressive infection associated with severe and rapidly progressing liver damage. We found that liver enzyme elevations at the most recent clinic visit were significantly more common among nonvertically infected patients. This group also had greater probability of significant fibrosis according to APRI score, despite shorter duration of HCV infection. Future research using longitudinal data, accounting for other factors associated with development of liver fibrosis, is required.

Regarding HIV disease, most patients had previously experienced moderate or severe clinical symptoms, but most had no or mild immunosuppression at their most recent visit. The finding that three-quarters of those treated had undetectable HIV RNA load is similar to other paediatric HIV cohorts [14,38]. It is debatable whether HCV progression is modified where HIV infection is well controlled; adult studies have shown increased risk of nonliver-related morbidity and mortality in HCV coinfected individuals due to persistent inflammation and immune activation [1,5], providing the rationale to treat HCV in this population as early as possible.

Current standard of care for paediatric HCV treatment remains pegIFN/RBV as DAAs have not yet been licensed for paediatric use [39]. Current guidelines recommend that treatment with pegIFN/RBV is considered for children with persistently elevated liver enzymes and/or liver fibrosis [34]. Adult trials show that HIV/HCV coinfected individuals do as well, or even better in achieving SVR after DAA treatment than HCV-monoinfected persons [6,40]. Our findings, together with a previous small case series [8], demonstrate worse outcomes with pegIFN/RBV in children and young people with HIV/HCV coinfection versus HCV monoinfection, particularly for genotype 1 and genotype 4 [41,42]. In a separate analysis, we showed that HCV treatment coverage in this population varied substantially by country, with the highest treatment rates in Russia (61%), whereas no children in some countries had been

treated. Patients were significantly more likely to be treated if they had advanced fibrosis as defined by transient elastography (e.g. five-fold increased odds of treatment for patients with ≥9.6 versus ≤7.2 kPa) and if they were aged more than 18 years [43].

The current study was limited by its cross-sectional, retrospective design and the observational data, which resulted in missing data for some variables and limited details regarding transient elastography and liver biopsy methodology, which were carried out and interpreted as per routine practice at the participating cohorts' sites. Interpretation of the liver biopsy results must take into account the fact that the 17 patients with biopsies were from eight cohorts and biopsies were assessed by different pathologists using different grading and staging systems. Duration of HCV infection will have been underestimated in patients with nonvertical mode of transmission as diagnosis date was taken as a proxy. Interpretation of the APRI, FIB-4 and transient elastography results should allow for the absence of large paediatric HCV studies validating these markers.

The current study is the first one describing a large population of HIV/HCV coinfected children and young people across Europe. As clinical management of coinfected children has previously relied on extrapolation from adult studies, our findings will contribute to better understanding of this coinfection in childhood. We describe a substantial proportion of HIV/HCV coinfected children and young people with progressive liver disease, with low response to standard treatment with pegIFN/RBV among the minority treated to date. Considering this, the improved life expectancy in HIV-infected children and the excellent outcomes in adults with HIV/HCV infection treated with DAAs, these observations support the need of HIV/HCV coinfected children for HCV treatment.

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