

HCV treatment in children and young adults with HIV/HCV co-infection in Europe

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Abstract

Objectives: To describe use of treatment for chronic hepatitis C virus (HCV) infection in HIV/HCV co-infected children and young people living in Europe and to evaluate treatment outcomes.

Methods: HCV treatment data on children and young people aged <25 years with HIV/HCV co-infection were collected in a cohort collaboration of 11 European paediatric HIV cohorts. Factors associated with receipt of HCV treatment and with sustained virological response 24 weeks after treatment completion (SVR24) were explored.

Results: Of 229 HIV/HCV co-infected patients, 22% had a history of AIDS and of 55 who were treated for HCV, 47 (85%) were receiving combined antiretroviral therapy. The overall HCV treatment rate was 24% ($n=55$) but it varied substantially between countries, with the highest rate being in Russia at 61% (30/49). Other factors associated with treatment receipt were older age [adjusted odds ratio (AOR) 5.24, 95% confidence interval (CI) 1.9–14.4, for 18–24-year-olds vs 11–17-year-olds, $P=0.001$] and advanced fibrosis (AOR 5.5, 95% CI 1.3–23.7; for ≥ 9.6 vs ≤ 7.2 kPa, $P=0.02$). Of 50 patients with known treatment outcomes, 50% attained SVR24. Of these, 16 (80%) had genotype (GT) 2,3 and 8 (29%) had GT 1,4 ($P<0.001$). After adjusting for genotype (GT 1,4 vs GT 2,3), females ($P=0.003$), patients with non-vertical HCV acquisition ($P=0.002$) and those with shorter duration of HCV ($P=0.009$) were more likely to have successful treatment outcomes.

Conclusion: Only half of the HIV/HCV co-infected youth achieved an HCV cure. HCV treatment success appears to be lower in the context of HIV co-infection than in HCV mono-infection, underscoring the urgent need to speed up approvals of new direct-acting antiviral combinations in children.

Keywords: HCV/HIV co-infection, pegylated interferon, ribavirin, children, young people

Introduction

Rates of HIV/HCV co-infection vary between countries, but globally 20–30% of the 34 million HIV-infected people are estimated to have chronic HCV infection, reflecting shared transmission routes in both infections [1,2]. HIV/HCV co-infection increases the risk and progression of liver disease [3,4], and even in the era of highly active antiretroviral therapy (ART), HIV infection remains an independent risk factor for advanced liver disease in co-infected patients [5,6]. Adult studies have shown that chronic HCV co-infection, via immune activation and chronic inflammation, contributes to excessive rates of extrahepatic illnesses, including cardiovascular disease, cancers, renal and bone disorders, and to higher overall and liver-related mortality in HIV-infected individuals [7–11].

HCV co-infection among children living with HIV is less prevalent than among adults. Most children with HIV/HCV co-infection in Europe acquired this vertically from co-infected mothers, with estimated mother-to-child transmission (MTCT) rates of both viruses of 4–10% [12]; however, there are groups of children and

adolescents who acquired HIV/HCV co-infection nosocomially or behaviourally [13–15]. There are limited data on HCV disease progression in HIV/HCV co-infected children [16,17]. Recent results from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) showed that half of children and adolescents had raised liver function test results at their most recent visit, 12% had advanced fibrosis as measured by liver biopsy or transient elastography (TE) [17], suggesting that a substantial proportion of HIV/HCV co-infected youth warrant treatment for HCV disease.

Despite the very rapid development of new direct-acting antiviral (DAA) agents against HCV, which has revolutionised HCV treatment in adults [18], there has been significant delay in their evaluation in the paediatric population, and no DAAs to date have been approved for use in children. Thus, in HCV-infected children combination treatment with pegylated interferon alpha 2a or 2b and ribavirin (peg-IFN/RBV) remains the standard of care.

In HCV mono-infected children, sustained virological response (SVR) rates at 24 weeks after treatment completion (SVR24) with peg-IFN/RBV are reported to be consistently higher compared to adults [19]. Studies of HIV/HCV co-infected adults have reported lower rates of successful treatment outcomes with peg-IFN/RBV than seen in mono-infected adults [20,21]. The data in co-infected children are confined to small case

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series [16,22,23], and thus important questions remain with respect to coverage and response to what is currently considered a standard treatment for HCV in this population.

In this study we describe treatment uptake in HIV/HCV co-infected children and young people in a European cohort collaboration and evaluate treatment outcomes and factors associated with successful outcomes.

Methods

In 2012–2013 we conducted a retrospective cross-sectional cohort study within 11 European paediatric HIV cohorts from 10 countries participating in EPPICC (see acknowledgements). EPPICC performs epidemiological research on the prognosis and outcome of HIV-infected pregnant women, HIV-infected children and children exposed to HIV in utero using data captured from cohorts through routine data collection, and is part of the EuroCoord network (www.eurocoord.net).

Participants

All children and young people with chronic HCV co-infection acquired vertically or in childhood aged >18 months and <25 years at last follow-up were eligible for inclusion.

The data were collected according to the standard HIV Cohorts Data Exchange Protocol (www.hicdep.org) and additional case-note review for HCV-specific variables, with a modified HICDEP table for these variables. Variables included socio-demographics, use of antiretroviral drugs, HIV clinical status, HIV RNA levels, CD4 cell counts and percentages, HCV genotype (GT), HCV disease status, anti-HCV treatment and liver investigations (ALT, AST, liver biopsy, TE).

Definitions

HIV disease was categorised using CDC 1994 [24] or WHO 2007 [25] classifications, depending on which classifications were routinely used in the participating cohorts; for the analysis, CDC A and WHO 1,2; CDC B and WHO 3; and CDC C and WHO 4 were grouped together. HIV immunological stage was categorised using CDC 2014 classification [26].

No or mild fibrosis was defined as METAVIR score F0–F1, moderate fibrosis as METAVIR score F2, and advanced fibrosis as METAVIR score F3–F4, evaluated by liver biopsy [27,28]. In children who had TE only (and no biopsy), advanced fibrosis was defined as liver stiffness of ≥ 9.6 kPa [29].

Duration of HCV infection was calculated as the time between the presumed date of infection and date of last study visit. For patients with reported vertically acquired HCV, birth date was used as the date of HCV infection; for participants with other modes of acquisition, the date of HCV diagnosis was used as a proxy for date of infection.

Successful outcome was defined as sustained virological response 24 weeks after the end of treatment (SVR24). In treatment outcome analysis HCV GT 1 and GT 4 were grouped together as 'hard to treat' with peg-IFN/RBV, and GT 2 and GT 3 defined as 'easier to treat' [19].

Adverse events were rated using the Division of AIDS (DAIDS) classification for grading the severity of adverse events [30]. The upper limit of normal (ULN) cut-off for AST and ALT was defined as 40 IU/L.

Statistical analysis

Univariable comparisons were assessed with the chi-squared test for categorical variables. Logistic regression modelling was used

to identify factors associated with receipt of HCV treatment. Controlling for GT groups ('hard to treat' and 'easier to treat'), the relationship between SVR24 and other explanatory variables, including age, sex, CD4 cell count, HIV viral load, mode of HCV acquisition, duration of HCV infection and liver fibrosis evaluated by TE were examined using a Cochran–Mantel–Haenszel analysis. Statistics were conducted using SAS version 9.3 (SAS Institute Inc, Cary, NC, USA).

Ethical approval

Individual cohorts followed their local ethics approval procedures for this secondary analysis of retrospective data.

Results

There were 229 children and young people with HIV/HCV co-infection included in the study, with a median age at last follow-up of 16.2 years [interquartile range (IQR) 10.0–20.2]. There were three participants from Belgium, one from Germany, 20 from Italy, four from Poland, 33 from Romania, 49 from Russia, three from Switzerland, 46 from Spain, three from the UK and 67 from Ukraine. The GT distribution was GT 1: 101 (44%); GT 2: 5 (2%); GT 3: 57 (25%); GT 4: 21 (9%); and GT unknown 45 (20%). A total of 55 (24%) children and young people had received HCV treatment (peg-IFN/RBV).

HCV treatment uptake

Uptake of HCV treatment varied between countries. No treatment was given in Germany, Poland, Romania, Switzerland, the UK or Ireland. Among the countries where patients received peg-IFN/RBV, treatment rates were 61% (30/49) in Russia, 37% (6/16) in Italy, 33% (1/3) in Belgium, 26% (12/46) in Spain and 9% (6/67) in Ukraine. There was a significant association between age group and HCV treatment receipt, with 15% (10/67) of patients aged 10 years or less, 10% (7/67) aged 11–17 years and 40% (38/95) aged 18–24 years having been treated ($P < 0.0001$). Nearly half of the patients with unknown mode of HCV acquisition had received treatment (44%, 14/32), compared with 20% (29/142) in vertically infected and 20% (8/40) in nosocomially infected patients, and 27% (4/15) in patients who injected drugs ($P = 0.03$). A slightly higher proportion of patients with GT 2,3 were treated than those with GT 1,4: 35% (22/62) versus 25% (31/122), respectively ($P = 0.15$). Among the 95 patients with TE results available, 42% (27/64) with liver stiffness ≤ 7.2 kPa were treated, while 47% (9/19) of those with liver stiffness 7.3–9.5 kPa and 67% (8/12) with advanced fibrosis (≥ 9.6 kPa) were treated ($P = 0.29$).

In adjusted logistic regression analysis, including liver fibrosis stage (evaluated by TE), mode of acquisition, GT group and age group ($n = 184$), factors associated with increased probability of HCV treatment were older age [adjusted odds ratio (AOR) 5.24, 95% confidence interval (CI) 1.9–14.4, for young people aged 18–24 years vs children aged 11–17 years, $P = 0.001$] and advanced fibrosis (AOR 5.5, 95% CI 1.3–23.7, for ≥ 9.6 vs ≤ 7.2 kPa, $P = 0.02$); patients with easier-to-treat GT were more likely to be treated than those with GT 1,4 (AOR 2.1, 95% CI 0.97–4.6, $P = 0.06$).

Characteristics of treated children and young people

Socio-demographic and HIV-related characteristics of the 55 treated patients are presented in Table 1. Most were on ART ($n = 47$, 85%) with undetectable HIV RNA viral load ($n = 40$, 73%) and 60% $n = 33$ had a CD4 cell count ≥ 500 cells/mm³ at their most recent visit. HCV-related characteristics, including type of treatment, are presented in Table 2. Over half of those treated

Table 1. Patient demographics and HIV-related characteristics

Characteristic	Overall (n=55)*
	n (%) or median [IQR]
Age at most recent visit (years)	17.2 [9.9–22.2]
Female	38 (69)
White ethnicity	47 (85)
Country of residence	
Russia	30 (55)
Spain	12 (22)
Italy	6 (11)
Ukraine	6 (11)
Belgium	1 (2)
History of AIDS	12 (22)
Median nadir CD4 count (cells/mm ³), n=35	312 [222–406]
CD4 count at the last visit (cells/mm ³), n=40	579 [356–750]
On ART at last visit	47 (85)
Undetectable HIV RNA at last visit, n=54	40 (74)
HIV clinical staging, n=52	
CDC A/WHO 1 or 2	14 (27)
CDC B/WHO 3	28 (54)
CDC C/WHO 4	10 (19)

IQR, interquartile range; ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization
* Unless stated otherwise

had GT 1 and 28% had GT 3 infection. Most patients (n=38, 69%) were aged 18 years or older at the initiation of treatment for HCV.

ALT and/or AST measurements prior to HCV treatment initiation were available for a subset of patients: 74% (20/27) had ALT levels above the ULN and 56% (14/25) had AST levels above ULN (Table 2). Results of TE prior to starting or during treatment were available for 34 of the treated patients, indicating that 15% had advanced fibrosis or cirrhosis (Table 2). Four patients had results of liver biopsy available prior to treatment; of these three had no or mild fibrosis and one advanced fibrosis.

At treatment start, the median duration of HCV infection was 18 years for vertically infected patients (IQR 10–20 years) and 4 years for the non-vertically infected (IQR 1.7–8.9 years). Patients were initiated on treatment with standard doses as per prescribing information for peg-IFN α -2a, peg-IFN α -2b and ribavirin. The median duration of treatment, independently of HCV genotype, was 47 weeks (range 8–82). There were 11 discontinuations of treatment, all in patients with GT 1,4, with median duration at discontinuation of 20 weeks (range 8–37).

HCV treatment outcomes

The virological outcomes at 24 weeks after the end of treatment were available in 50 of 55 patients (91%) at the time of analysis. Of these, 25 (50%) achieved SVR24 (Figure 1). The SVR24 rates were 29% (8/28) for GT 1,4 and 80% (16/20) for GT 2,3 ($P<0.001$). Of the eight patients with advanced liver fibrosis (6 GT 1, 1 GT 3, 1 GT 4), only one achieved SVR24. SVR24 was not associated with AIDS history: 36% (4/11) with AIDS vs 54% (21/39) without AIDS ($P=0.15$) or median nadir CD4 cell count ($P=0.27$).

Females, patients with non-vertical HCV acquisition and those with shorter duration of HCV infection were more likely to have successful treatment outcomes after adjusting for GT groups (GT 1,4 vs GT 2,3) (Table 3). There was no association between liver fibrosis stage (measured by TE in most patients and liver

Table 2. HCV-related characteristics and treatment

Characteristic	Overall (n=55)*
	n (%) or median [range]
Mode of HCV acquisition	
MTCT	29 (53)
Nosocomial	4 (7)
IDU	8 (15)
Other/unknown	14 (25)
HCV genotype	
GT 1	28 (51)
GT 2	1 (2)
GT 3	21 (38)
GT 4	3 (5)
Unknown	2 (4)
ALT prior to HCV treatment (IU/L), n=27	
Normal	7 (26)
DAIDS grade 1	12 (44)
DAIDS grade 2	7 (26)
DAIDS grade 3	1 (4)
AST prior to HCV treatment (IU/L), n=25	
Normal	11 (44)
DAIDS grade 1	12 (48)
DAIDS grade 2	2 (8)
TE prior to HCV treatment (kPa), n=34	
≤ 7.2	20 (58)
7.3–9.5	9 (26)
9.6–12.5	4 (12)
≥ 12.6	1 (3)
HCV treatment	
Peg-IFN α 2a/RBV	29 (53)
Peg-IFN α 2b/RBV	22 (40)
Unknown	4 (7)
Median duration of treatment (weeks)	47 [8–82]

GT, genotype; IDU, intravenous drug use; MTCT, mother-to-child transmission; peg-IFN, pegylated interferon; RBV, ribavirin; TE, transient elastography
* Unless stated otherwise

biopsy in one patient) prior to treatment start and probability of achieving an SVR24, although liver fibrosis data were only available for a subset of treated patients (71%, 34/48). After additional adjustment for duration of HCV infection (classified as $<10/\geq 10$ years), the probability of achieving SVR24 remained significantly associated with female gender ($P=0.0097$) and with non-vertical mode of HCV acquisition ($P=0.0009$).

Discussion

Overall, a quarter of children and youth living with HIV and HCV co-infection had received HCV treatment with peg-IFN/RBV, with use of treatment varying widely across European cohorts. In general, cohorts with the largest numbers of HIV/HCV co-infected patients had the highest coverage with HCV treatment. Clinical guidelines recommend treatment to be considered for children with chronic HCV infection where there are persistently elevated liver enzymes and/or evidence of liver fibrosis [31]. We found that children and young people in our study were significantly more likely to be treated if they had evidence of advanced fibrosis. Other factors associated with receipt of peg-IFN/RBV were being older than 18 years and having an 'easier-to-treat' genotype.

These treatment rates need to be interpreted in the context of historically low HCV treatment rates in adults with HIV/HCV

Table 3. Factors associated with treatment outcome by HCV genotype groups

Characteristic	Overall (n=48)				P value
	GT 1,4 (n=28)		GT 2,3 (n=20)		
	SVR24	No SVR24	SVR24	No SVR24	
Age, years	n=28		n=20		
<11	1	4	1	2	0.119
11–17	0	2	3	0	
18–24	7	14	12	2	
Gender					
Male	0	10	2	2	0.003
Female	8	10	14	2	
CD4 count before HCV treatment (cells/mm ³)	n=21		n=17		
200–499	4	4	6	0	0.07
≥500	3	10	8	3	
Mode of HCV acquisition	n=28	n=20			
Vertical	1	13	5	4	0.002
Other	7	7	11	0	
TE prior to HCV treatment (kPa)	n=20		n=14		
≤7.2	5	5	7	2	0.16
7.3–9.5	2	3	2	2	
≥9.6	0	5*	1	0	
Duration of HCV infection (years)	n=28		n=19		
<1	1	1	2	0	0.009
1–4.9	2	3	7	0	
5–9.9	1	2	2	2	
10–14.9	4	6	2	0	
15–19.9	0	4	1	0	
≥20	0	4	1	2	

* One patient without TE prior to starting HCV treatment but with a pre-treatment liver fibrosis METAVIR F3 evaluated by liver biopsy is included in this group

co-infection. The latter reflects a range of factors including contraindications, poor adherence to HIV treatment, cost and patient choice. In the HEPVIH study, a French cohort of HIV/HCV co-infected adults, 40% of those eligible for HCV treatment started therapy during 2005–2011. HCV treatment initiation was associated with good adherence to HIV drugs and

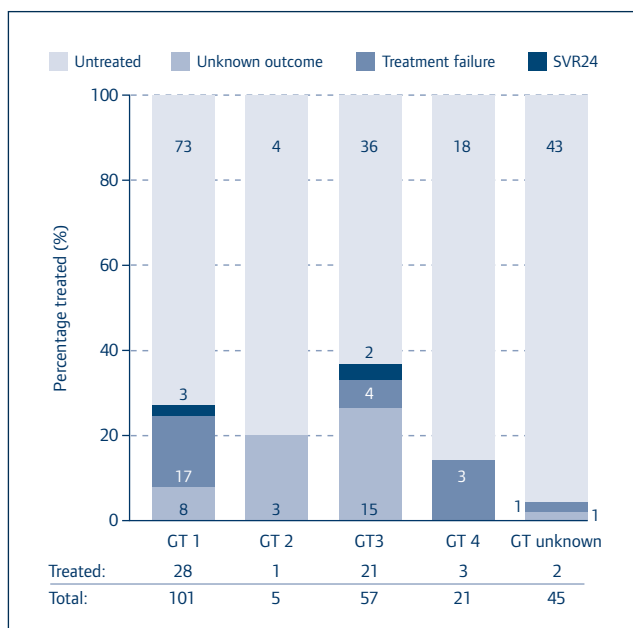


Figure 1. Proportion of subjects treated for HCV and HCV treatment outcomes by HCV genotype (total n=299)

was less frequent in patients with children and in those with cardiovascular disease or respiratory distress [32]. In the EuroSIDA cohort, of nearly 2000 co-infected patients, 25% had received HCV therapy up to 2009, with significant increases in treatment incidence over time, although the researchers identified that around 20% of untreated patients had indications for treatment based on fibrosis stage [33]. With respect to treatment of children living with chronic HCV, data on coverage in Europe are limited. In an Italian multi-centre study of HCV-infected children followed for an average of 11.5 years, a quarter had received treatment [34]; HCV treatment coverage in Italian children with HIV/HCV co-infection here was somewhat higher at 37%. In a national paediatric referral centre in the UK treatment rates were 60% over the period 1990–2008 [35].

Despite that a high proportion of co-infected children and adolescents in EPPICC cohorts had evidence of liver disease, and HCV liver disease progression is recognised to be accelerated in HIV/HCV co-infection, only a quarter of co-infected patients were treated. Although not investigated in this study, the possible reasons for the low treatment uptake were likely to be related to inconvenient administration (e.g. using injectables), long treatment duration, associated toxicities and anticipated poor response.

Only half of the HIV/HCV co-infected youth who received HCV treatment achieved SVR24, with rates of 29% for GT 1,4 and 80% for GT 2,3. A meta-analysis of eight trials of peg-IFN/RBV for treatment of HCV mono-infection reported that overall, 58% of children achieved an SVR24 (52% with GT 1,4 and 89% with GT 2,3) [19]. In a recent retrospective review of children with chronic HCV treated in three UK paediatric liver centres between 2005 and 2010, 76% achieved SVR24 overall: 65% with GT 1 and 89% with GT 2 or GT 3 [36]. Thus, cure rates in our HIV/HCV co-infected population seem particularly low for children with ‘hard-to-treat’ GT 1 and 4. This is consistent with findings for adults with HIV/HCV co-infection, where cure rates for those with GT 1,4 treated with peg-IFN/RBV were 25–40% [37].

We show that unsuccessful treatment outcomes were also more frequently seen in children and young people with vertically acquired HCV and in those with prolonged duration of HCV infection, highlighting the need for early treatment in these groups. Studies in adults demonstrated higher efficacy of IFN-based treatments with shorter duration of HCV infection. In children this association has not been demonstrated, probably due to relatively short duration of the infection and absence/lower prevalence of comorbidities (co-infection, intravenous drug use, alcohol, obesity) compared with adults. With regard to the mode of HCV acquisition, our results agree with the previously published data in HCV-mono-infected children. In the study by Jara *et al.*, treatment was particularly effective in patients with parenterally acquired infection, although statistical significance was not reached, probably due to the small number of enrolled patients [38]. A similar tendency was demonstrated by Wirth *et al.* [39] and by Tajiri *et al.* [40].

Our study showed a higher SVR24 rate among female patients. Gender differences in natural history and treatment response have been reported previously, including higher rates of spontaneous clearance in females [41], higher vertical transmission rates for girls [42] and higher SVR rates with peg-IFN/RBV in females compared to males [43]; the reasons are not well understood but may reflect both biological and behavioural factors (e.g. medication adherence).

With DAAs for paediatric use on the horizon, it is likely that ‘warehousing’ of paediatric patients with HCV (including those with HIV co-infection) may now be occurring. However, for co-infected children with GT 2,3, where high rates of SVR24 can be achieved with peg-IFN/RBV, some clinicians and parents (particularly those who have themselves achieved a cure for GT 2 or 3 disease) may not wish to delay treatment for their children owing to the uncertain timelines for paediatric access to DAAs. This may particularly be the case in light of the known impact of HIV on accelerating HCV disease and the growing evidence to indicate that liver fibrosis progresses during childhood: in a study of 44 children from the PEDS-C trial, with biopsies on average 6 years apart, 30% showed an increase in severity of fibrosis and the proportion of patients with bridging fibrosis/cirrhosis increased from 11% to 20% [44].

The new DAAs provide high cure rates, exceeding 95%, and all studies to date have shown SVR24 rates among HIV/HCV co-infected individuals to be the same or better than those among HCV mono-infected people [45]. There is an urgent need to combine efforts of clinicians, community, pharmaceutical companies and regulatory authorities to speed up approvals of the new DAA combinations in the paediatric population. When the new regimens acquire paediatric approval, HIV/HCV co-infected children should be considered a priority group for the new treatments.

There are some limitations to this study. The study had a cross-sectional design and given the observational nature of the study, there were missing data for some patients. There were 11 treatment discontinuations, but due to the retrospective nature of the study we were not able to find the reasons for discontinuations, and therefore cannot comment on discontinuations secondary to toxicity. Transient elastography data, and therefore most of the data on the stage of liver disease, should be interpreted with caution as the method has not been validated for children with hepatitis C. The duration of HCV infection for patients with non-vertically acquired HCV is likely to be underestimated as it was calculated as the interval between the presumed date of infection and date of last study visit. Therefore the association between HCV treatment outcomes and the duration of HCV infection may be less pronounced than reported. Treatment outcome data were not available for five patients, for whom SVR24 was not yet available at the time of analysis. No data were collected on IL-28 polymorphisms due to rarity of measuring this in our population.

This is the largest study to date describing HCV treatment outcomes with peg-IFN/RBV in HIV/HCV co-infected youth with wide data capture across a number of European countries. In the future, when the new DAAs become available for children, there is potential to cure paediatric HCV in the vast majority of children.

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