AIDS

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Title: Co-infection with HIV and HCV in 229 children and young adults living in Europe

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Abstract

Objective: To characterise children, adolescents and young adults infected with HIV/HCV vertically or before age 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 >18 months and <25 years, with HIV/HCV acquired vertically or in childhood, were included. Anonymised 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 (CDC stage 1) and 131 of 179 on antiretroviral therapy (ART) 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 ALT >40 IU/L at their last test. Of 97 patients with transient elastography, 12 had results >9 kPa; this was associated with duration of HCV infection (p=0.033), but not with CD4 count, ART use or gender in univariable analysis. Of 17 subjects with liver biopsies, 6 had bridging fibrosis and one cirrhosis. Twenty-five (11%) had been treated successfully for HCV.

Conclusions

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

Key words: human immunodeficiency virus, hepatitis C, coinfection, paediatric, vertical infection

Introduction

Worldwide around 20-30% of the 34 million HIV-infected individuals are estimated to have chronic HCV infection, although rates of HIV/HCV co-infection 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 extra-hepatic morbidity and mortality, through immune activation and chronic inflammation [1, 5].

Although HCV co-infection 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 co-infection in childhood and adolescence. The few studies on HIV/HCV co-infected 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 co-infection. For example, little is understood about the sub-group of children who progress to serious liver disease during childhood, or the impact of HCV-related inflammation on extra-hepatic manifestations.

Most children with HIV/HCV co-infection acquire this vertically from their mothers [9, 10] or through nosocomial transmission in health-care settings, although the latter route is now limited to specific lower- and middle-income settings where blood and medical injecting safety remains inadequate [11]. Adolescents may also acquire HIV/HCV co-infection 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 co-infection in children, adolescents and young adults infected with HIV/HCV vertically or before age 18 within our European paediatric HIV cohort collaboration, in order to characterise 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 (EPPICC), which conducts epidemiological research on HIV-infected pregnant women and children [14] and was part of the EuroCoord network (www.eurocoord.net).

Children aged >18 months, adolescents and young adults aged <25 years, with HIV and chronic HCV coinfection acquired vertically or in childhood (i.e. up to age 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 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 ≥2 consecutive serum samples taken 6 months apart) were excluded. Age > 18 months was chosen as inclusion criteria to rule out misdiagnoses due the presence of passively transferred maternal antibodies [16].

Eleven cohorts from 10 countries provided anonymised 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 (TE)).

Definitions

Patients were considered chronically infected if HCV RNA was detected in ≥2 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 based on detection of HIV-1 antibody and/or positive HIV RNA or DNA PCR in ≥2 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 UK) and Southern Europe (Italy and Spain).

HIV-associated immunodeficiency was defined as (i) none or mild, (ii) moderate and (iii) severe, based on CDC 1994 classification [17]. The limit of detection of HIV RNA assays ranged from <20 to <150 copies/ml. The upper limit of normal (ULN) cut-off for AST and ALT was defined as 40 IU/L. Division of AIDS (DAIDS) 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 re-assigned 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 co-infected adults[20, 21], but not children. APRI was calculated using the formula APRI=(AST/upper limit of normal) / platelets [10^9/L] X 100 [22]. An APRI score of >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] X AST [U/L]) / (platelets [10^9/L] X (ALT [U/L])1/2)[20]. A FIB-4 score of >3.25 was taken as 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 X^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, NC, USA).

Results

A total of 229 HCV/HIV co-infected children and young people were included of whom 98 were male and 130 female (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). There were 34 patients who were diagnosed with HCV at ≥18 years (median, age 21) 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 extra-pulmonary). 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 (GT) was known for 184 (80%) subjects, with GT1 and GT3 predominating and comprising overall 44% and 25% respectively (Table 1). Fifty-eight percent (65/113) of subjects living in Central and Eastern Europe and 55% (34/62) in Southern Europe had GT1 infection, compared with 22% (2/9) in Northern Europe, where the largest proportion of subjects had GT4 (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 subjects with data on presence of hepatomegaly and/or splenomegaly during the previous 12 months of follow-up, 86 (42%) had isolated hepatomegaly, 39 (19%) 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 non-vertically 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 TE results available (Table 2), with median age at investigation of 17.6 years (IQR, 13.0, 21.6 years). Of the 12 patients with TE results >9.5 kPa, eight had GT1 (67%) and two each had GT3 and GT4. Duration of HCV infection among those with TE results of <9.5 kPa was significantly lower (10.7 years, IQR 3.7, 18.0) compared with subjects with greater liver stiffness (18 years, IQR 13.9, 19.2) (p=0.033). There was no association between TE results and CD4 count categories, ART use or gender in univariable analysis.

Seventeen (8%) subjects 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 TE results and having a biopsy (p=0.22) or with having an elevated ALT or AST (p=0.6). 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, had improvement of both fibrosis and inflammation by one score with no HCV treatment given. The second young person (vertically-infected, GT3a), aged 14 and 19.5 at first and second biopsies, 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 plus ribavirin (pegIFN/RBV), five (2.2%) had completed pegIFN/RBV treatment but were awaiting 24 weeks post-treatment SVR (SVR24) result and 25 (10.9%) had been treated successfully. Median age at initiation of pegIFN/RBV treatment was 17.2 years (IQR, 3.5, 24.0). HCV genotype distribution was 28 (51%) GT1, one GT2, 21 (38%) GT3 and three (5%) GT4 (two missing). Forty-seven (85%) of the patients on pegIFN/RBV were receiving concurrent ART. The SVR24 rates were 32% (8/25) for GT1 and 79% (15/19) for GT3; the one treated patient with GT2 achieved an SVR24, but none of the three treated patients with GT4 did so.

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

Discussion

In this study we have characterized the population of children and young people living with vertically or childhood-acquired HIV/HCV co-infection 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 co-infection, 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 aging 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 co-infected 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], GT1 was the most common followed by GT3, although GT4 was the most common genotype in Northern Europe. Our small numbers preclude firm conclusions on genotype distribution [28]. Among HCV mono-infected children in the Italian Observatory Study, GT1 and GT2 were prevalent among adolescents, but infections with GT3 and GT4 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 co-infected children suggests they may be less likely to spontaneously clear HCV than adults or than mono-infected children [7]. Among children with chronic HCV mono-infection, 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 found that 30% of HCV mono-infected children had more severe fibrosis in a repeat biopsy conducted on average 6 years after their first [33], 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 co-infected adults also remain [36, 37]. In one study among nearly 300 HIV/HCV co-infected adults with repeat liver biopsies, 34% had progression of ≥1 METAVIR stage over a median 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 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 TE results were available for 42% of our study population but the value of these scores and of TE 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 mono-infection in the European Paediatric Hepatitis C Network (EPHN) [30]. A Spanish study also reported higher ALT levels in HIV-co-infected versus mono-infected 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 non-vertically acquired infection in our study, who were more likely to have hepatomegaly than vertically-infected children and young people.

Historical cohorts of HCV mono-infected 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 co-infected children and young people than in those with HCV mono-infection [29, 32], consistent with adult studies [1, 5, 36]. Chronic HCV infection in the context of HIV co-infection 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 non-vertically 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 non-liver related morbidity and mortality in HCV co-infected 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 co-infected individuals do as well, or even better in achieving SVR after DAA treatment than HCV-mono-infected 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 co-infection versus HCV mono-infection, particularly for GT1 and GT4 [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%), whilst no children in some countries had been treated. Patients were significantly more likely to be treated if they had advanced fibrosis as defined by TE (e.g. five-fold increased odds of treatment for patients with ≥9.6 *vs* ≤7.2 kPa) and if they were aged more than 18 years [43].

This 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 TE 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 non-vertical mode of transmission as diagnosis date was taken as a proxy. Interpretation of the APRI, FIB-4 and TE results should allow for the absence of large paediatric HCV studies validating these markers.

This is the first study describing a large population of HIV/HCV co-infected children and young people across Europe. As clinical management of co-infected children has previously relied on extrapolation from adult studies, our findings will contribute to better understanding of this co-infection in childhood. We describe a substantial proportion of HIV/HCV co-infected 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 co-infected children for HCV treatment.

References

1. Soriano V, Barreiro P, Sherman KE. The changing epidemiology of liver disease in HIV patients. *AIDS reviews* 2013,**15**:25-31.
2. Danta M, Semmo N, Fabris P, Brown D, Pybus OG, Sabin CA, *et al.* Impact of HIV on host-virus interactions during early hepatitis C virus infection. *The Journal of infectious diseases* 2008,**197**:1558-1566.
3. Soto B, Sanchez-Quijano A, Rodrigo L, del Olmo JA, Garcia-Bengoechea M, Hernandez-Quero J, *et al.* Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *Journal of hepatology* 1997,**26**:1-5.
4. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, *et al.* Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet* 2000,**356**:1800-1805.
5. Lee MH, Yang HI, Lu SN, Jen CL, You SL, Wang LY, *et al.* Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *The Journal of infectious diseases* 2012,**206**:469-477.
6. Chung RT, Baumert TF. Curing chronic hepatitis C--the arc of a medical triumph. *The New England journal of medicine* 2014,**370**:1576-1578.
7. Claret-Teruel G, Noguera-Julian A, Esteva C, Munoz-Almagro C, Sanchez E, Jimenez R, *et al.* Impact of human immunodeficiency virus coinfection on the progression of mother-to-child transmitted hepatitis C virus infection. *Pediatr Infect Dis J* 2011,**30**:801-804.

8. Rosso R, Di Biagio A, Mikulska M, Nicco E, Bernardini C, Viscoli C. Safety and efficacy of pegylated interferon and ribavirin in adolescents with human immunodeficiency virus and hepatitis C virus acquired perinatally. *Journal of medical virology* 2010,**82**:1110-1114.

9. Polis CB, Shah SN, Johnson KE, Gupta A. Impact of maternal HIV coinfection on the vertical transmission of hepatitis C virus: a meta-analysis. *Clinical Infectious Diseases* 2007,**44**:1123-1131.

10. England K, Thorne C, Newell ML. Vertically acquired paediatric coinfection with HIV and hepatitis C virus. *The Lancet. Infectious diseases* 2006,**6**:83-90.

11. England K, Thorne C, Castelli-Gattinara G, Vigano A, El Mehabresh MI, Newell ML. HIV and HCV progression in parenterally coinfected children. *Current HIV research* 2009,**7**:346-353.

12. Busza J, Douthwaite M, Bani R, Scutelniciuc O, Preda M, Simic D. Injecting behaviour and service use among young injectors in Albania, Moldova, Romania and Serbia. *Int J Drug Policy* 2013,**24**:423-431.

13. Chatterjee S, Tempalski B, Pouget ER, Cooper HL, Cleland CM, Friedman SR. Changes in the prevalence of injection drug use among adolescents and young adults in large U.S. metropolitan areas. *AIDS Behav* 2011,**15**:1570-1578.

14. Judd A. Early antiretroviral therapy in HIV-1-infected infants, 1996-2008: treatment response and duration of first-line regimens. *AIDS* 2011,**25**:2279-2287.

15. Kissin DM, Zapata L, Yorick R, Vinogradova EN, Volkova GV, Cherkassova E, *et al.* HIV seroprevalence in street youth, St. Petersburg, Russia. *AIDS* 2007,**21**:2333-2340.

16. Indolfi G, Azzari C, Resti M. Perinatal transmission of hepatitis C virus. *J Pediatr* 2013,**163**:1549-1552 e1541.

17. Caldwell MB, Oxtoby MJ, Simonds RJ, Lindegren ML, Rogers MF. 1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less Than 13 Years of Age. *Morbidity and Mortality Weekly Report: Recommendations and Reports* 1994,**43**:iii-10.

18. Division of AIDS National Institute of AIDS and Infectious Disease. National Institutes of Health, Department of Health and Human Services, US Division of AIDS (DAIDS) table for grading the severity of adult and paediatric adverse events. Version 2.0, November 2014. In. Bethesda, US; 2014.

19. Shiha GZ, K. Ishak versus METAVIR: Terminology, Convertibility and Correlation with Laboratory Changes in Chronic Hepatitis C. In: *Liver biopsy*. Edited by Takahash H: InTech; 2011.

20. 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**:1317-1325.

21. Al-Mohri H, Murphy T, Lu Y, Lalonde RG, Klein MB. Evaluating liver fibrosis progression and the impact of antiretroviral therapy in HIV and hepatitis C coinfection using a noninvasive marker. *Journal of acquired immune deficiency syndromes* 2007,**44**:463-469.

22. Wai CT, Greenson 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**:518-526.

23. McGoogan KE, Smith PB, Choi SS, Berman W, Jhaveri R. Performance of the AST-to-platelet ratio index as a noninvasive marker of fibrosis in pediatric patients with chronic viral hepatitis. *Journal of pediatric gastroenterology and nutrition* 2010,**50**:344-346.

24. Floridia M, Tamburrini E, Anzidei G, Tibaldi C, Muggiasca ML, Guaraldi G, *et al.* Declining HCV seroprevalence in pregnant women with HIV. *Epidemiology and infection* 2010,**138**:1317-1321.

25. Foster C, Judd A, Tookey P, Tudor-Williams G, Dunn D, Shingadia D, *et al.* Young people in the United Kingdom and Ireland with perinatally acquired HIV: the pediatric legacy for adult services. *AIDS patient care and STDs* 2009,**23**:159-166.

26. Kissin DM, Mandel MG, Akatova N, Belyakov NA, Rakhmanova AG, Voronin EE, *et al.* Five-year trends in epidemiology and prevention of mother-to-child HIV transmission, St. Petersburg, Russia: results from perinatal HIV surveillance. *BMC infectious diseases* 2011,**11**:292.

27. Bailey H, Townsend CL, Semenenko I, Malyuta R, Cortina-Borja M, Thorne C. Impact of expanded access to combination antiretroviral therapy in pregnancy: results from a cohort study in Ukraine. *Bulletin of the World Health Organization* 2013,**91**:491-500.

28. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, *et al.* Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* 2015,**61**:77-87.

29. Bortolotti F, Verucchi G, Camma C, Cabibbo G, Zancan L, Indolfi G, *et al.* Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterology* 2008,**134**:1900-1907.

30. European Paediatric Hepatitis C Virus Network. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. *Clin Infect Dis* 2005,**41**:45-51.

31. Guido M, Bortolotti F, Leandro G, Jara P, Hierro L, Larrauri J, *et al.* Fibrosis in chronic hepatitis C acquired in infancy: is it only a matter of time? *Am J Gastroenterol* 2003,**98**:660-663.

32. Goodman ZD, Makhlouf HR, Liu L, Balistreri W, Gonzalez-Peralta RP, Haber B, *et al.* Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial. *Hepatology* 2008,**47**:836-843.

33. Mohan P, Barton BA, Narkewicz MR, Molleston JP, Gonzalez-Peralta RP, Rosenthal P, *et al.* Evaluating progression of liver disease from repeat liver biopsies in children with chronic hepatitis C: a retrospective study. *Hepatology* 2013,**58**:1580-1586.

34. Mack CL, Gonzalez-Peralta RP, Gupta N, Leung D, Narkewicz MR, Roberts EA, *et al.* NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. *J Pediatr Gastroenterol Nutr* 2012,**54**:838-855.

35. Badizadegan K, Jonas MM, Ott MJ, Nelson SP, Perez-Atayde AR. Histopathology of the liver in children with chronic hepatitis C viral infection. *Hepatology* 1998,**28**:1416-1423.

36. Konerman MA, Mehta SH, Sutcliffe CG, Vu T, Higgins Y, Torbenson MS, *et al.* Fibrosis progression in human immunodeficiency virus/hepatitis C virus coinfected adults: prospective analysis of 435 liver biopsy pairs. *Hepatology* 2014,**59**:767-775.

37. Rollet-Kurhajec KC, Moodie EE, Walmsley S, Cooper C, Pick N, Klein MB. Hepatic Fibrosis Progression in HIV-Hepatitis C Virus Co-Infection - The Effect of Sex on Risk of Significant Fibrosis Measured by Aspartate-to-Platelet Ratio Index. *PloS one* 2015,**10**:e0129868.

38. Kekitiinwa A, Lee KJ, Walker AS, Maganda A, Doerholt K, Kitaka SB, *et al.* Differences in factors associated with initial growth, CD4, and viral load responses to ART in HIV-infected children in Kampala, Uganda, and the United Kingdom/Ireland. *Journal of acquired immune deficiency syndromes* 2008,**49**:384-392.

39. Thorne C, Indolfi G, Turkova A, Giaquinto C, Nastouli E. Treating hepatitis C virus in children: time for a new paradigm. *Journal of Viral Eradication* 2015,**1**:203-205.

40. Macias J, Neukam K, Merchante N, Pineda JA. Latest pharmacotherapy options for treating hepatitis C in HIV-infected patients. *Expert opinion on pharmacotherapy* 2014,**15**:1837-1848.

41. Druyts E, Thorlund K, Wu P, Kanters S, Yaya S, Cooper CL, *et al.* Efficacy and safety of pegylated interferon alfa-2a or alfa-2b plus ribavirin for the treatment of chronic hepatitis C in children and adolescents: a systematic review and meta-analysis. *Clin Infect Dis* 2013,**56**:961-967.

42. Abdel-Hady M, Bansal S, Davison SM, Brown M, Tizzard SA, Mulla S, *et al.* Treatment of chronic viral hepatitis C in children and adolescents: UK experience. *Archives of disease in childhood* 2014,**99**:505-510.

43. Turkova A, Giacomet V, Goetghebuer T, Miloenko M, Nicolini LA, Noguera-Julian A, *et al.* HCV treatment in children and young adults with HIV/HCV co-infection in Europe. *Journal of Viral Eradication* 2015,**1**:179-184.

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	101 (69.7)	44 (52.4)	
(i) none or mild suppression	24 (16.6)	29 (34.5)	
(ii) moderate suppression	6 (4.1)	4 (4.8)	
(iii) severe suppression	14 (9.7)	7 (8.3)	p=0.018
unknown			
Age at last follow-up			
<11 years	60 (41.4)	7 (8.3)	
11-17 years	42 (29.0)	24 (28.6)	
18-24 years	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)	p=0.50
3	40 (27.6)	17 (20.2)	(among
4	17 (11.7)	4 (4.8)	known
unknown	18 (12.4)	27 (32.1)	values)

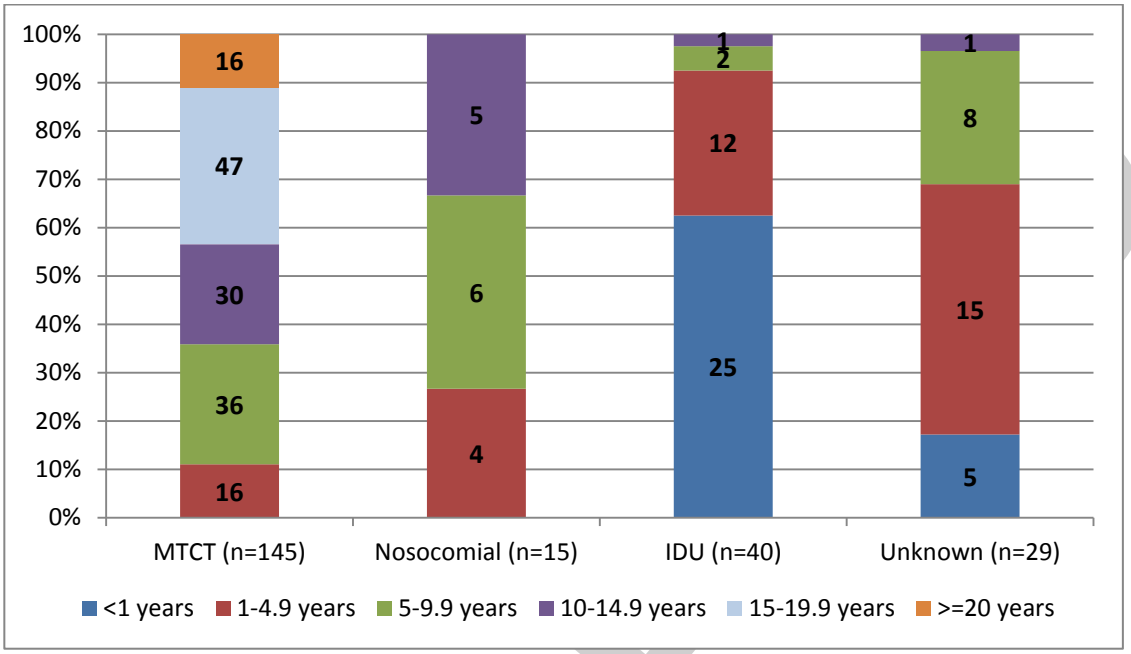
Table 2: Liver enzyme measures, non-invasive markers of fibrosis and transient elastography

	Vertically acquired HCV	HCV acquired by other routes		Total
		N (%)		
ALT				
Number with measurement available*	131	82		213
DAIDS grading				
non-elevated	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#	7 (3.3)
AST				
Number with measurement available*	77	34		111
DAIDS grading				
non-elevated	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#	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^	4 (4.1)

* at last clinic visit; # X^2 test with grades 2 and 3 grouped together; ^ X^2 test with 9.6-12.5 and >12.5 grouped together

Figure 1: Duration of HCV infection, by mode of acquisition



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