Hepatitis C virus treatment response to Direct Acting Antivirals among adolescents with HIV/HCV coinfection: real world data from Ukraine

Short title: DAA use in adolescents with HIV/HCV in Ukraine

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Conflict of interests
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Author contributions

Conceptualization – CT, FM, RM; Formal Analysis – FM; Funding Acquisition – CT, RM; Participating investigators (cared for study patients): AV; Supervision – CT, HB, IJC; Writing – Original Draft Preparation – FM; Writing – Review & Editing – FM, RM, AV, CT, HB, IJC.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics and patient consent statement

The study protocol was conducted in accordance with the Good Clinical Practice guidelines and approved by the Shupky National Medical Academy of Postgraduate Education, Kiev, Ukraine and the UCL Research Ethics Committee (1956/002). Participants or their legal guardians provided written informed consent/assent.

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Abstract

Direct-acting antivirals (DAAs) have been approved for treating chronic hepatitis C virus (HCV) in children and adolescents. Although DAAs have been used in real- world settings for the treatment of HCV mono-infected adolescents, few reports of real-world use of DAAs in children and adolescents who are coinfected with human immunodeficiency virus (HIV) are available. We evaluated the real-world safety and effectiveness of DAAs in HIV/HCV coinfected adolescents from the Ukraine Paediatric HIV Cohort Study including all those for whom treatment outcomes were available by April 2021. Overall, six co-infected adolescents had received DAA treatment; four with sofosbuvir/ledipasvir (SOF/LDV), one with SOF/LDV+ribavirin and one with SOF/daclatasvir. No patient discontinued treatment due to adverse events and no serious adverse events were reported. All six patients achieved sustained virologic response by 12 weeks after the end of therapy. DAA treatment was well tolerated and effective in adolescents with HIV/HCV co-infection in a real-world setting.

Introduction

An estimated 3.26 million children and adolescents worldwide have chronic hepatitis C virus (HCV) infection (1). From 2018, international guidelines have recommended use of Direct Acting Antiviral (DAA) regimens for adolescents ≥12 years with chronic HCV, irrespective of disease stage (2). In the pre-DAA era, populations coinfected with HCV and human immunodeficiency virus (HIV) were considered one of the most difficult-to-treat, as HCV treatment success rates in real-world settings were low at around 30% in adults and 50% in children and young people(3,4).

Although there is substantial real-world evidence on DAA use in adults co-infected with HIV/HCV with high cure rates, DAAs have not yet been widely used in co-infected children and adolescents (5). Adults and children with HIV/HCV coinfection have more progressive liver disease than their mono-HCV infected counterparts, and lower success with pegylated-interferon/ribavirin treatment, and are considered a priority group for DAA treatment (1,4,6,7). Data on real-world use of DAAs in adolescents is largely limited to Egypt and Western European settings and has been focused on HCV mono-infected adolescents (8,9). Here, we describe safety and effectiveness of DAA based regimens in adolescents co-infected with HIV/HCV enrolled in the Ukraine Paediatric HIV Cohort Study.

Methods

The Ukraine HIV Paediatric Cohort Study, established in 2011, is an ongoing, multicenter, observational cohort study involving eight participating centers, mostly regional HIV/AIDS centers.

Children and adolescents between birth and <18 years old, with confirmed HIV infection (regardless of mode of acquisition) being cared for at participating centers were eligible for enrolment with consent by parents/guardians and/or assent by the child/adolescent and

prospectively followed-up. Standardized data collection forms were used to collect pseudonymized data on routine clinical care using Research Electronic Data Capture (REDCap) (10). In addition to socio-demographics and HIV-specific data collected at enrolment and during follow-up (including clinical, virological, and immunological status and antiretroviral treatment), HCV-related data including laboratory results, clinical status, and treatment data (history, duration, treatment response, adverse events) were collected for HIV/HCV co-infected participants. Adverse events were documented in routine care with no study-specific data capture.

Data were retrospectively extracted on all co-infected participants who had completed a DAA-based treatment and for whom treatment outcomes were available by April 2021.

Analysis and definitions

Descriptive and summary statistics were used to analyze population characteristics and sustained virologic response (SVR) rates, defined as absence of quantifiable HCV RNA in serum at 12 weeks after the end of therapy (EOT). Effectiveness was assessed as the percentage of patients who achieved SVR12. Alanine aminotransferase (ALT) levels >40U/L were considered elevated.

The study protocol was approved by the Shupky National Medical Academy of Postgraduate Education, Kiev, Ukraine and the UCL Research Ethics Committee (1956/002).

Results

Six HIV/HCV co-infected adolescents were identified as ever having received DAA treatment, four were treated with sofosbuvir/ledipasvir (SOF/LDV) (400/90mg), one with sofosbuvir/daclatasvir (SOF/DAC) (400/60mg) and one with SOF/LDV plus ribavirin (675mg). Patient characteristics are described in Table 1. Age at DAA start ranged from 12 to 17 years. These patients were treated between December 2017 and January 2021.

All patients were HCV treatment naïve prior to treatment with DAAs and were receiving antiretroviral therapy (ART) - five were on emtricitabine/tenofovir disoproxil (TDF) plus efavirenz and one on TDF/lamivudine plus dolutegravir. All had undetectable plasma HIV viral load (<20 copies/mL) before initiating HCV treatment and continued the same ART regimens throughout HCV treatment. Three patients were reported as having a history of tuberculosis (TB)- one of extra-pulmonary TB and two of pulmonary TB. Two patients had received 6-month isoniazid preventive therapy for TB, 3 and 6 years prior to initiating treatment with SOF/LDV.

All six adolescents were treated with DAAs for 12 weeks and all achieved SVR12. Data were available from liver ultrasound for four patients prior to starting SOF/LDV: all showed changes in liver parenchyma and increased liver echogenicity. Five patients had elevated ALT prior to treatment start, at a mean of 80U/L (median 74U/L). A decline in ALT was observed in all patients, with a mean of 23U/L (median 21U/L) within 3-30 weeks after end of treatment. No adverse events, treatment discontinuations or dose adjustments for DAA were documented.

Discussion

Although DAAs have been approved for treatment of adolescents since 2017, DAA use for treatment of HIV/HCV co-infected children and adolescents in real-world settings has only been reported for two adolescents from Poland (11). In this study we report outcomes of six adolescents living with HIV and chronic HCV in the Ukraine Paediatric HIV Cohort Study who have received DAAs to date. Similar to the results from Poland (11), our analysis showed that DAA-based treatment was well tolerated and all patients achieved SVR12 within routine clinical practice.

Liver disease represents a major cause of morbidity and mortality among persons living with HIV. WHO estimates that 2.3 million of the 37 million people living with HIV globally are co-infected with HCV (12). Although HCV co-infection among children living with HIV is less prevalent than that among adults (3) previous studies indicate accelerated liver fibrosis progression and worse treatment outcomes with interferon in children and young people with HIV/HCV co-infection compared to those with HCV monoinfection (3,4). The results of this study, albeit based on a small sample, add to the currently minimal evidence base of treatment outcomes in adolescents with HIV/HCV coinfection in routine care settings. The favorable treatment outcomes observed underscore the importance of early treatment to prevent liver disease progression and onward transmission to others.

Despite the importance of early treatment in the co-infected population, the lack of DAA safety, efficacy and pharmacokinetic data among children and adolescents has precluded treatment in this priority group (3,7). In a study from Spain, 27 vertically HIV/HCV coinfected individuals were treated with DAAs in early adulthood (median age at treatment 23 years), all achieved SVR12 with no serious adverse events reported (7). The study also reported that due to “lack of scientific experience” of using DAAs in paediatric patients, 22 of the 49 HIV/HCV vertically-coinfected individuals in care were not treated (7). It is important to note that one-third of these young adults had developed advanced liver fibrosis (F3-F4 on the Metavir scale) by time of DAA initiation, further emphasizing the importance of early treatment in the coinfected paediatric population.

The off-label use of DAAs in our Ukrainian cohort should be interpreted in the context of treatment guidelines. The European Medicines Agency approved SOF/LDV for the treatment of HCV in adolescents in June 2017 and the first patient in this cohort received SOF/LDV

soon after, in December 2017. At this time, the European Association for the Study of Liver (EASL) 2016 guidelines did not recommend treating adolescents with DAAs (13). It was not until 2018 when EASL guidelines recommended 12-week SOF/LDV for HCV-monoinfected adolescents (genotype 1) and in 2020 recommended that adolescents with HCV monoinfection or HCV/HIV co-infection be treated with pangenotypic regimens (SOF/Velpatasvir (VEL), SOF/VEL/Voxilaprevir, Glecaprevir/Pibrentasvir and Grazoprevir/Elbasvir) (2,14). However, these HCV drugs (as well as SOF/DAC) are contraindicated with efavirenz-containing ART regimens because of an expected reduction in plasma exposure of DAAs. As SOF/LDV is genotype-specific it is no longer recommended by EASL, however, SOF/LDV remains one of the few HCV treatment options for individuals on efavirenz-containing ART regimens as no drug-drug interactions are expected between these drugs (15). For coinfected patients receiving a lamivudine/tenofovir disoproxil/dolutegravir ART regimen, SOF/DAC can be administered as there are no drug-drug interactions expected (15).

All patients in the current study had vertically acquired HCV, were DAA treatment-naïve, and had elevated ALT levels. The safety profile of DAAs was favorable with no discontinuation, dose adjustments or serious AEs documented. Levels of ALT that were elevated at baseline had normalized after end of treatment in all patients. In this small sub-cohort, DAA treatment was effective and well tolerated. Children and adolescents with HIV/HCV co-infection are a priority group for DAA treatment and should be included in HCV microelimination approaches.

To the best of our knowledge, this is the first report of SOF/DAC use for the treatment of HIV/HCV co-infected adolescents, an important sub-population who have unmet need for

HCV treatment (4,7). Although this is the largest report to date of DAA use in the co-infected adolescents, our study is limited by its small sample size. Data from larger paediatric cohorts are needed. Further limitations are the lack of data on laboratory markers such as platelet count and AST, which were not captured here, precluding generation of non-invasive biomarkers of liver disease assessment such as aspartate aminotransferase to platelet ratio index (APRI) and Fibrosis-4 (FIB-4). We were therefore unable to assess liver fibrosis as no liver biopsies or transient elastography results were available.

Conclusion

This real-world data from Ukraine shows that DAAs were effective and well tolerated in this small sub-cohort of treated HIV/HCV co-infected adolescents. Alternative pangenotypic DAA regimens are now available and recommended for treating HIV/HCV co-infected patients. However, SOF/LDV remains an important treatment option for co-infected patients on efavirenz based ART regimens. This study highlights the need to urgently scale-up treatment of HIV/HCV co-infected adolescents to cure them of one of their chronic infections.

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Table

Table 1 Patient characteristics

Patient	Sex	Age at HIV diagnosis (years)	ART regimen at DAA start	Age at HCV diagnosis (years)	HCV genotype	Age at HCV treatment start (years)	DAA regimen	Pre-DAA treatment		Post-DAA treatment		SVR12
								ALT (U/L)	HCV RNA copies/ml	ALT (U/L)	HCV RNA copies/ml	
1	Male	11	FTC/TDF/EFV	13	1b	17	SOF/LDV	73	20,300,000	28	UD	Yes
2	Male	2	FTC/TDF/EFV	2	1b	14	SOF/LDV	123	183,466	18	UD	Yes
3	Male	1	FTC/TDF/EFV	2	1b	16	SOF/LDV	74	14,620	33	UD	Yes
4	Female	1	FTC/TDF/EFV	9	1b	13	SOF/LDV	58	245,000	15	UD	Yes
5	Male	6	3TC/TDF/DTG	5	3a	12	SOF/DAC	124	6,100,000	24	UD	Yes
6	Female	1	FTC/TDF/EFV	1	1b	15	SOF/LDV+riba	27	3400000	17	UD	Yes

EFV: efavirenz; DTG: dolutegravir; FTC: emtricitabine; TDF: tenofovir disoproxil; 3TC: lamivudine; UD: undetectable