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SHORT COMMUNICATION

Use of contraindicated antiretroviral drugs in people with HIV/HCV coinfections receiving HCV treatment with direct-acting antivirals—Results from the EuroSIDA study

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Abstract

Objectives: Our objective was to determine whether antiretroviral drugs (ARVs) were used according to the European AIDS Clinical Society (EACS) guidelines for people with HIV/hepatitis C virus (HCV) coinfection treated with direct-acting antivirals (DAAs) between 30 November 2014 and 31 December 2019 in the pan-European EuroSIDA study.

Methods: At each publication date of the EACS guidelines, plus 3 and 6 months, we calculated the number of people receiving DAAs with potential and actual ARV contraindications ('red shading' in the EACS guidelines). We used logistic regression to investigate factors associated with using contraindicated ARVs.

Results: Among 1406 people starting DAAs, the median age was 51 years, 75% were male, 57% reported injected drug use as an HIV risk, and 76% were from western Europe. Of 1624 treatment episodes, 609 (37.5%) occurred while the patient was receiving ARVs with potential contraindications; among them, 38 (6.2%; 95% confidence interval [CI] 4.3–8.2) involved a contraindicated ARV (18 non-nucleoside reverse transcriptase inhibitors), 16 involved protease inhibitors, and four involved integrase strand transfer inhibitors. The adjusted odds of receiving a contraindicated ARV were higher (3.25; 95% CI 1.40–7.57) among participants from east/central east Europe (vs. south) and lower (0.22; 95% CI 0.08–0.65) for 2015–2018 guidelines (vs. 2014). In total, 29 of the 32 (90.6%) patients receiving a contraindicated ARV and 441 of the 461 (95.7%) with potential ARV contraindications experienced a sustained virological response ≥12 weeks after stopping treatment (SVR12; $p = 0.55$).

Conclusion: In this large heterogenous European cohort, more than one-third of people with HIV/HCV coinfection received DAAs with potential ARV contraindications, but few received a contraindicated ARV. Use of contraindicated ARVs declined over time, corresponding to the increased availability of ARV therapy regimens without interactions with DAA across Europe. Participants who received a contraindicated DAA and ARV combination still had a high rate of SVR12.

KEYWORDS
contraindications, DAA, HCV, HIV, co-infection

INTRODUCTION

Modern direct-acting antiviral (DAA) therapy is associated with high rates of cure among people with hepatitis C virus (HCV) infection, including those co-infected with HIV. Patients with HIV/HCV co-infection can be treated with the same DAA regimens as those with HCV mono-infection [1].

However, potential drug–drug interactions between HCV and HIV medications, as well as with other commonly prescribed medications, including statins and proton pump inhibitors, requires consideration prior to initiation of DAA therapy to prevent adverse effects and treatment failure [2, 3]. In most cases, drug interactions can be managed and are not a barrier for achieving HCV cure (www.hep-druginteractions.org). A study from the Dutch ATHENA cohort in 2017 showed that, among 49 individuals receiving a contraindicated antiretroviral (ARV) regimen prior to initiation of DAA therapy, only two (4%) continued these contraindicated regimens

during DAA therapy [4]. So far, no data have been published from more heterogenous populations, including Eastern Europe, where both HIV and DAA treatment options are more limited [5, 6].

The aims of this study were to determine whether ARVs were used according to the European AIDS Clinical Society (EACS) guidelines for DAA therapy of HIV/HCV coinfection in the pan-European EuroSIDA study, and to compare the rate of sustained virological response (SVR) between those who received a contraindicated DAA/ARV combination and those receiving drugs that were not contraindicated.

METHODS

Study design and participants

Participants were from the EuroSIDA study, a prospective observational cohort of more than 23 000 participants with HIV-1 followed in around 100 hospitals in 35 European countries and Israel and Argentina. Individuals were enrolled into 11 cohorts from 1994 onwards. At recruitment, we obtained the following: demographic and clinical data, complete ARV therapy (ART) history, most recent CD4 cell counts and HIV-RNA measurements, HCV antibody results, HCV-RNA, and HCV genotype. Data were collected prospectively at clinical sites and sent to the coordinating centre at yearly intervals. At each follow-up visit, all CD4 cell counts, HIV-RNA, HCV antibodies, HCV-RNA, HCV genotype, and liver fibrosis results measured since last follow-up were collected, together with start and stop dates for ARVs and HCV drugs. Detailed information about data collected in EuroSIDA has been published elsewhere [7].

Inclusion criteria

We included all people with HIV/HCV co-infection aged ≥18 years on ART who were treated with interferon-free DAA after 30 November 2014, when interferon-free DAA treatment became much more widely used across Europe [8]. The analysis includes data to the end of 2019.

Statistical methods

At 0, 3, and 6 months following each EACS guidelines publication date, we calculated the number of people receiving DAAs where the DAA should not be coadministered with specific ARVs corresponding to the 'red shading' in EACS guidelines. In this group with potential ARV contraindications, we calculated the number who actually received a contraindicated ARV [9–13]. All contraindicated DAA/ARV combinations administered were manually verified in the database.

We evaluated the baseline characteristics of those who received DAA with potential ARV contraindications compared with the characteristics of those who received a contraindicated DAA/ARV combination using chi-squared tests for categorical variables and Kruskal–Wallis tests for continuous variables.

We used logistic regression with robust standard errors to investigate factors associated with using contraindicated ARVs among those with potential contraindications. Models were adjusted for sex, region of Europe (definitions described in Table 1), end-stage liver disease, HCV genotype, age, guideline date, and time elapsed from publication of the guidelines (0, 3, or 6 months).

Baseline is the first date the person is on a DAA at a guideline check date (last date of calendar month of guideline publication date, plus 3 months, plus 6 months).

SVR was defined as a negative HCV-RNA result ≥12 weeks after stopping treatment (SVR12).

Statistical analyses were performed using Statistical Analysis Software, version 9.4.

RESULTS

A total of 1691 patients received DAA therapy after 30 November 2014, of whom 1406 (83%) received ART concomitantly and were included in this study. Table 1 describes their baseline characteristics. The baseline median age was 51 years (interquartile range [IQR] 44–55), and most were white (89%), male (75%), and had injecting drug use as an HIV risk (57%). The majority had genotype 1 (52%); 20% had cirrhosis. Participants were enrolled from the south (31.8%), central west (27.8%), north (16.2%), central east (12.2%), and east (12.0%) of Europe. Among the 1406 participants, 560 (39.8%) had a potential ARV contraindication and 35 (6.3%) received a contraindicated ARV. Characteristics of the 35 individuals treated with contraindicated ARVs were similar to the 525 with a potential contraindication (but where the contraindicated ARV was not used), except that a higher proportion of those with a contraindication were from central east Europe ($p = 0.02$) and had an earlier baseline date ($p = 0.04$) than those with a potential contraindication.

Of 1624 HCV treatment episodes, 609 (37.5%) occurred while the person was receiving ARV with potential contraindications, but only 38 (6.2%; 95% CI 4.3–8.2) occurred with a contraindicated ARV. Although the

TABLE 1 Baseline characteristics

	On DAA at guideline check dates		On DAA with potential ARV contraindications		Participants on a contraindicated DAA/ARV combination	
	n	%	*n*	%	*n*	%
All	1406	100	560	39.8	35	6.3
Sex						
Male	1051	74.8	420	75.0	30	85.7
Female	355	25.2	140	25.0	5	14.3
HIV risk						
MSM	305	21.7	148	26.4	10	28.6
IDU	802	57.0	312	55.7	20	57.1
Hetero	204	14.5	71	12.7	5	14.3
Other	95	6.8	29	5.2	0	0.0
Ethnicity						
White	1246	88.6	494	88.2	34	97.1
Region						
South	447	31.8	179	32.0	12	34.3
Central west	391	27.8	129	23.0	3	8.6
North	228	16.2	98	17.5	3	8.6
Central east	171	12.2	101	18.0	12	34.3
East	169	12.0	53	9.5	5	14.3
HIV VL						
<500 cp/ml	1371	97.5	547	97.7	35	100
Prior						
PriorAIDS	375	26.7	123	22.0	6	17.1
Fibrosis						
F0/1	728	51.8	319	57.0	17	48.6
F2	219	15.6	98	17.5	7	20.0
F3	170	12.1	67	12.0	3	8.6
F4	284	20.2	74	13.2	8	22.9
Unknown	5	0.4	2	0.4	0	0.0
HCV GT						
1	730	51.9	260	4.,4	17	48.6
2	38	2.7	16	2.9	0	0.0
3	255	18.1	86	15.4	0	0.0
4	248	17.6	146	26.1	13	37.1
Unknown	135	9.6	52	9.3	5	14.3

Notes: Definitions of regions of Europe: south: Greece, Israel, Italy, Portugal, Spain, and Argentina; central-west: Austria, Belgium, France, Germany, Luxembourg, and Switzerland; north: Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden, and the UK; central-east: Bosnia-Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia, and Slovenia; east: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, and Ukraine. Liver fibrosis stage was defined according to the METAVIR classification.

Abbreviations: ARV, antiretroviral drug; DAA, direct-acting antiviral; GT, genotype; VL, viral load; IDU, injection drug use; MSM, men who have sex with men.

proportion receiving DAAs with potential ARV contraindications increased over time, only 3/146 (2.1%) treatment episodes with DAAs with potential contraindications administered after the publication of the 2018 guidelines included a contraindicated ARV/DAA combination (Figure 1).

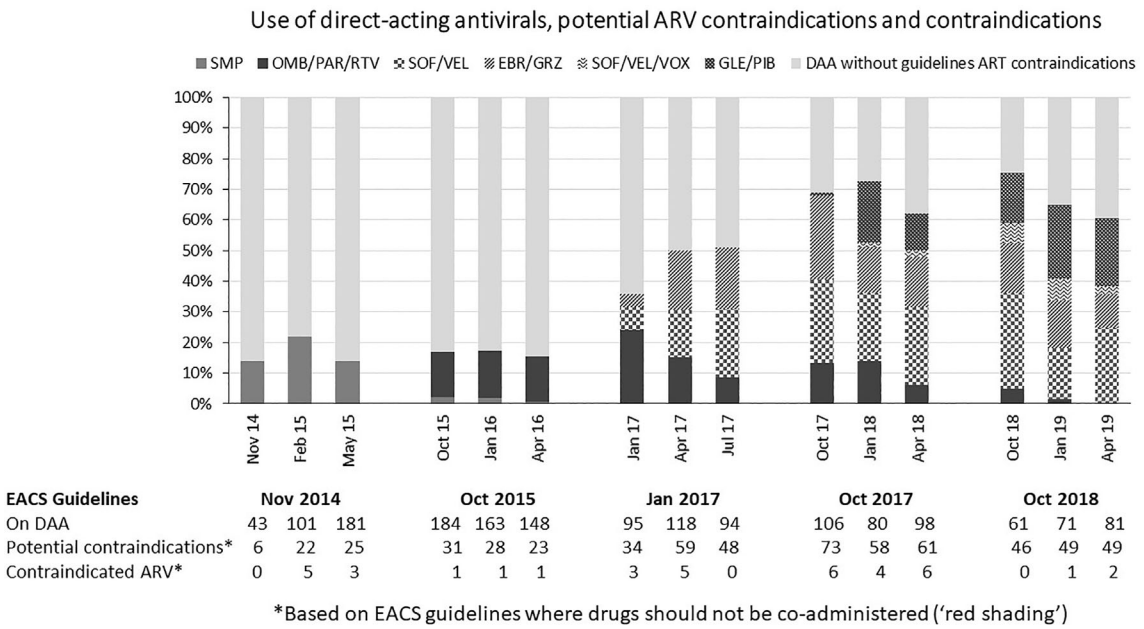

FIGURE 1 Number of DAA treatment episodes and their temporal relation to different versions of the guidelines from the European AIDS Clinical Society (EACS). 'Potential contraindications' are defined as treatment episodes with DAAs where one or more antiretroviral drugs should not be coadministered with the DAA ('red shading' in the EACS guidelines). 'Contraindicated ARV' refers to treatment episodes where a contraindicated DAA/ARV combination was given. A total of 560 participants received DAAs with potential contraindications, and 35 of these patients received a contraindicated DAA/ARV combination. EBR, elbasvir; GLE, glecaprevir; GRZ, grazoprevir; OMB, ombitasvir; PAR, paritaprevir; PIB, pibrentasvir; RTV, ritonavir; SMV, simeprevir; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir

Among the 38 treatment episodes with a contraindicated DAA/ARV combination, 18 contained a non-nucleoside reverse transcriptase inhibitor (NNRTI), 16 contained a protease inhibitor (PI), and four contained elvitegravir/cobicistat. The most common contraindicated ARV/DAA combinations were simeprevir + ritonavir-boosted darunavir, elbasvir/grazoprevir + darunavir and cobicistat, and ombitasvir/paritaprevir/ritonavir + nevirapine (four treatment episodes each). A total of 17 (44.7%) included a combination of drugs that decreases the DAA plasma concentration, 20 (52.7%) included a combination that increases the DAA concentration, and one (2.6%) was a combination with severe tolerability issues (ombitasvir/paritaprevir/ritonavir + efavirenz). The combination of ombitasvir/paritaprevir/ritonavir + nevirapine also increases the exposure to nevirapine. In 37 of the 38 treatment episodes with a contraindicated DAA/ARV combination, there were no premature discontinuations of DAA therapy, and this information was missing for one treatment episode.

The adjusted odds of receiving a contraindicated ARV/DAA combination was higher (3.25; 95% confidence interval [CI] 1.40–7.57) among participants from east/central east (vs. south) Europe and lower (0.22; 95% CI 0.08–0.65) for 2015–2018 guidelines than for the 2014 version. The odds of being on contraindicated ART did not differ significantly according to age and HCV genotype or the time since guidelines were published (0, 3, 6 months).

Data to determine SVR12 were available for 1343/1624 (82.7%) treatment episodes, with no significant differences in availability of data between the three groups ($p = 0.47$). SVR12 was 806/850 (94.8%) among those without ARV interactions, 441/461 (95.7%) in those with potential ARV contraindications, and 29/32 (90.6%) among those receiving a contraindicated ARV ($p = 0.55$). Among the 18 individuals who received a contraindicated DAA/ARV combination that lowers the DAA concentration, 15 had available SVR data; among them, 14/15 (93.3%) achieved SVR12.

DISCUSSION

Real-life data on whether DAAs and ARVs are used according to guidelines in HIV/HCV coinfection and the potential impact of these treatment selections on HCV treatment outcomes are limited. In this analysis, which includes data on 1406 people with HIV/HCV coinfection undergoing DAA therapy between 2014 and 2019 in the large heterogeneous European HIV cohort study EuroSIDA, more than one-third of all patients received DAAs with potential ARV contraindications; however, only

6.2% of them received a contraindicated DAA/ARV combination. In adjusted analyses, participants from east/central east Europe (vs. south) had higher odds of receiving a contraindicated ARV, whereas those treated at the time of the 2015–2018 EACS guidelines had lower odds of receiving a contraindicated ARV than those treated during the time of the 2014 guidelines. Our study did not collect information on the reason a contraindicated drug combination was given, but the observed decline in the use of contraindicated DAA/ARV combinations corresponds to an increased availability of ART regimens without interactions with DAAs across Europe [14].

DAAs and ARVs are commonly metabolized by the same enzymes or transporters. For example, boosted PIs are inhibitors of organic-anion-transporting polypeptide 1B transporter, which is involved in the liver uptake of grazoprevir, daclatasvir, and simeprevir [15, 16]. PIs also inhibit cytochrome P450 (CYP)-3A4, which plays a major role in the metabolism of simeprevir, glecaprevir, elbasvir/grazoprevir, and velpatasvir, [17] and NNRTIs have inducing effects on CYP3A4 [17]. Coadministration can therefore result in either suboptimal plasma concentration of the drugs and risk of treatment failure or increased plasma concentration with increased risk of treatment-limiting toxicity. However, among participants in our study who received a contraindicated DAA/ARV combination, the SVR12 rate was 90.6% and was not statistically significantly lower than in participants who did not receive contraindicated drugs, although this comparison was based on relatively few individuals.

Our study has some limitations. No data on non-ART co-medications with interactions with DAA were available. We also did not have sufficient power to compare across specific DAAs. SVR12 data were not available for all participants. Data on adverse effects of DAA therapy were only collected when DAA therapy was discontinued prematurely. The main strength of our study was the inclusion of a large heterogenous population from European countries where both HIV and HCV treatment options are more limited [8, 14].

To conclude, in this large heterogenous European cohort, more than one-third received DAAs with potential ARV contraindications, but a low proportion received a contraindicated ARV. Use of contraindicated DAA/ARVs declined over time, which corresponds to the increased availability of ART regimens without interactions with DAAs across Europe. Participants who received a contraindicated DAA/ARV combination still had a high rate of SVR12.

AUTHOR CONTRIBUTION

LP, AM, and MN conceptualized and designed the project. AM performed the statistical analyses. MN and LP wrote the first draft of the manuscript. All authors collected and provided data for the study, reviewed and commented on the first draft, and approved the final version of the manuscript.

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CONFLICT OF INTEREST

AM has received travel support, honoraria, and/or consultancy fees from ViiV, Gilead, and Eiland & Bonnin outside the submitted work. GW has received research grants from Gilead Sciences and Roche Diagnostics and honoraria from Gilead, MSD, and ViiV outside the submitted work and all paid to his institution. TB has received grants from Novo Nordisk Foundation, Simonsen Foundation, Lundbeck Foundation, Kai Hansen Foundation, and Erik and Susanna Olesen's Charitable Fund; grants and personal fees from GSK, Pfizer, and Gilead; and personal fees from Boehringer Ingelheim, MSD, and Pentabase ApS, outside the submitted work. All other co-authors reported no conflicts of interest.

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