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MAJOR ARTICLE

Antiretroviral Use in the CEASE Cohort Study and Implications for Direct-Acting Antiviral Therapy in Human Immunodeficiency Virus/Hepatitis C Virus Coinfection

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Background. Interferon-free direct-acting antiviral (DAA) regimens for hepatitis C virus (HCV) provide a major advance in clinical management, including in human immunodeficiency virus (HIV)/HCV coinfection. Drug-drug interactions (DDIs) with combination antiretroviral therapy (cART) require consideration. This study aimed to characterize the cART regimens in HIV/HCV-coinfected individuals and assess the clinical significance of DDIs with DAAs in a real-world cohort.

Methods. This analysis included participants enrolled in CEASE-D, a prospective cohort of HIV/HCV-coinfected individuals in Sydney, Australia, between July 2014 and December 2015. A simulation of potential DDIs between participants' cART and interferon-free DAA regimens was performed using www.hep-druginteractions.org and relevant prescribing information.

Results. In individuals on cART with HCV genotype (GT) 1 and 4 (n = 128), category 3 DDIs (contraindicated or not recommended) were noted in 0% with sofosbuvir/ledipasvir, 0% with sofosbuvir plus daclatasvir, 17% with sofosbuvir/velpatasvir, 36% with ombitasvir/paritaprevir/ritonavir ± dasabuvir, 51% with grazoprevir/elbasvir, and 51% with sofosbuvir plus simeprevir; current cART regimens were suitable for coadministration in 100%, 100%, 73%, 64%, 49%, and 49%, respectively. In individuals with HCV GT 2 or 3 (n = 53), category 3 DDIs were evident in 0% with sofosbuvir plus daclatasvir, 0% with sofosbuvir and ribavirin, and 13% with sofosbuvir/velpatasvir; current cART regimens were suitable in 100%, 100%, and 81%, respectively.

Conclusions. Potential DDIs are expected and will impact on DAA prescribing in HIV/HCV coinfection. Sofosbuvir in combination with an NS5A inhibitor or ribavirin appeared to be the most suitable regimens in this cohort. Evaluation of potential DDIs is required to prevent adverse events or treatment failure.

Keywords. antiretroviral therapy; direct-acting antiviral therapy; drug-drug interactions; hepatitis C; HIV.

The global burden of disease attributed to human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection is substantial, with anti-HCV antibody prevalence estimated at 1.6%–2.8% [1] and HIV antibody prevalence estimated at 0.8% [2]. Based on global HIV and HCV prevalence and estimates of the overlap in these epidemics, 2–5 million people are estimated to be coinfected with HIV and HCV [3, 4]. The natural history of HIV and HCV are significantly impacted by the coexistence of the other virus, with accelerated liver disease progression and increases in all-cause, acquired immune deficiency syndrome-related and liver-related morbidity, hospitalization, and mortality, even in those people receiving combination antiretroviral therapy (cART) [5–7]. Although the number of deaths related to HIV is falling [2], the number of deaths attributed to HCV-related liver disease is rising [8].

Interferon (IFN)-based HCV therapy has had limited success in HIV-positive populations, with concerns regarding efficacy and tolerability. Although a sustained virological response (SVR) reduces both liver- and nonliver-related complications and mortality, therapy with pegylated-IFN and ribavirin resulted in SVR in less than 30% of HIV-positive individuals with HCV genotype (GT) 1 [9, 10]. With the addition of telaprevir or boceprevir, efficacy improved, but additional adverse events and drug-drug interactions (DDIs) further complicated therapy [11, 12].

The availability of IFN-free, direct-acting antiviral (DAA) regimens for HCV offers considerable promise in the management of HIV/HCV coinfection [13–17], with high efficacy, improved tolerability, shorter treatment duration, and lower pill burden [18]. However, in the context of concomitant cART,

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DDIs require consideration. To date, all approved DAAs demonstrate interactions with CYP450 enzymes or transporters, including P-glycoprotein and breast cancer resistance protein, with potential implications for DDIs (summarized in Supplementary Table 1). Safety data on potentially significant antiretroviral and DAA DDIs in HIV/HCV-coinfected individuals are limited to the drug combinations permitted in phase II and III trials, with most trials having strict antiretroviral eligibility criteria (summarized in Supplementary Table 2). Data are emerging on the real-world relevance of DDIs in HCV-infected populations using IFN-free DAA therapy [19–22].

The aim of this analysis was to assess the clinical significance of DDIs between participants' currently prescribed cART and IFN-free DAA regimens in a real-world HIV/HCV-coinfected cohort.

METHODS

Study Design and Participants

The Control and Elimination within Australia of Hepatitis C From People Living With HIV (CEASE) project is a prospective 5-year plan of enhanced HCV monitoring, primary care-based workforce development, rapid scale-up of HCV treatment, and public health policy action in HIV-positive individuals within Australia. Data used in this analysis were collated from the first component of this project, "CEASE-D: Surveillance of HCV", an ongoing prospective cohort study.

Enrollment in CEASE-D commenced in July 2014 at 5 sites in Sydney, New South Wales (tertiary hospital, n = 1; primary care practice, n = 4). The study population for this analysis included all individuals enrolled until December 2015 (n = 257). Human immunodeficiency virus-positive participants were eligible for enrollment if they were 18 years of age or older and anti-HCV antibody positive. All participants were asked whether they would consider HCV therapy, both IFN-containing and IFN-free. Participants with detectable HCV ribonucleic acid (RNA) were considered for suitability of IFN-free DAA therapy. Further assessment of DDIs between cART and DAAs was based upon those with documented HCV GT and cART regimen (Figure 1).

Assessment of Liver Disease

Initial laboratory assessments were conducted in concert with the participants' standard-of-care with the presence of HCV RNA assessed using the COBAS TaqMan HCV RNA assay, version 2.0 (lower limit of quantitation, 25 IU/mL; lower limit of detection, 15 IU/mL; Roche Diagnostics, Branchburg, NJ).

Fibrosis stage was graded by METAVIR classification, based on liver biopsy or transient elastography within 6 months of enrollment. For transient elastography, the following cutoff values were used: F0/F1, <7.1 kPa; F1/F2, ≥7.1 kPa; F2, ≥8.7 kPa; F3, ≥9.5 kPa; F3/F4, ≥12.5 kPa; and F4, ≥14.5 kPa [23, 24].

Assessment and Classification of Potential Drug-Drug Interactions

The following approved and US Food and Drug Administration (FDA)-filed IFN-free DAA regimens were assessed: sofosbuvir/ledipasvir [25]; ombitasvir/paritaprevir/ritonavir and dasabuvir (PrOD) (with and without ribavirin) [26]; ombitasvir/paritaprevir/ritonavir (PrO) (with ribavirin) [26]; grazoprevir/elbasvir [27]; sofosbuvir plus simeprevir [28]; sofosbuvir [29] plus daclatasvir [30]; sofosbuvir plus ribavirin; and sofosbuvir/velpatasvir [31–33]. Potential DDIs between the listed DAAs and documented antiretroviral drugs received by each individual were simulated according to the most recent literature, available prescribing information (as of April 2016), and the University of Liverpool DDI tool (www.hep-druginteractions.org). For each HCV GT, DAA regimens chosen for analysis were based upon the 2015 EASL Clinical Practice Guidelines [34] and

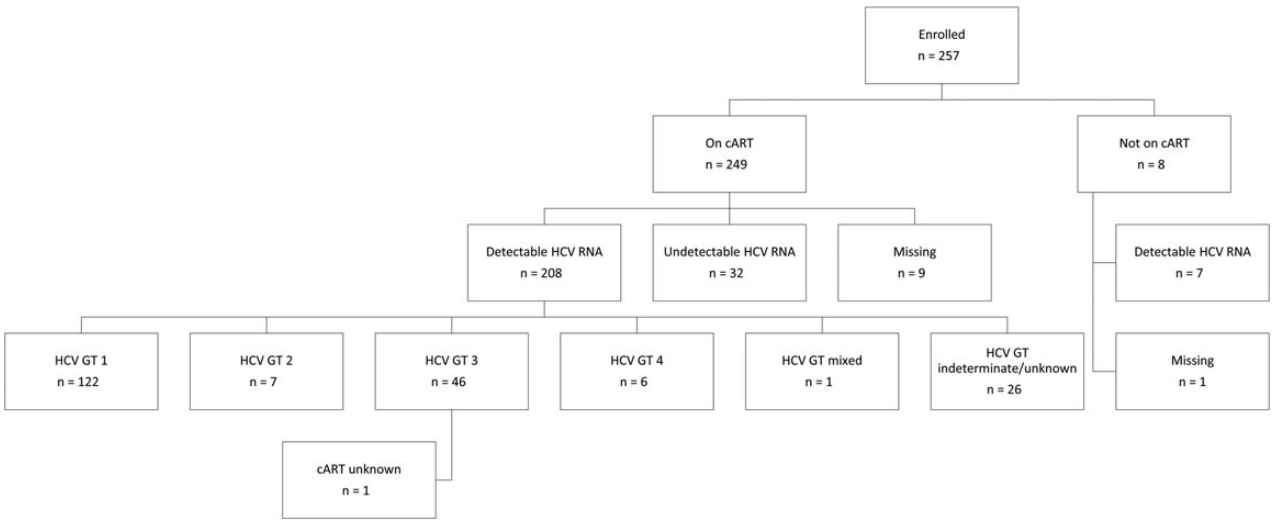

Figure 1. Participant disposition. Abbreviations: cART, combination antiretroviral therapy; GT, genotype; HCV, hepatitis C virus; RNA, ribonucleic acid.

available prescribing information. Because no participants in this cohort would have had additional significant DDIs related to ribavirin, DAA regimens with and without ribavirin were analyzed together (in the case of PrOD ± ribavirin for HCV GT 1a and 1b and PrO + ribavirin for GT4). The relationship and potential interaction between the DAA regimen and specific antiretroviral agents was designated as follows: category 1, no clinically significant DDI; category 2, potentially significant DDI—requiring additional monitoring for toxicity, adjustment of dose, or timing of administration; category 3, coadministration not recommended or contraindicated; or category 4, no data available. Category 2 included dose adjustment of daclatasvir and ritonavir-boosted HIV protease inhibitors. If a participant took more than 1 drug with different risks for a DDI, the highest category was chosen to determine the risk for that participant with a respective treatment regimen. Category 1 and 2 DDIs were considered suitable for coadministration of the DAA and cART regimen.

Primary Study Endpoint

The primary study endpoint was the proportion of HIV/HCV-coinfected individuals receiving suitable cART for coadministration with the above-listed, approved IFN-free DAA regimens.

Ethics and Study Oversight

All study participants provided written informed consent before study procedures. The study protocol was approved by St Vincent's Hospital, Sydney Human Research Ethics Committee (primary study committee), as well as by the institutional review board or independent ethics committee at each participating site and was conducted according to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines and local regulatory requirements. The study was registered with ClinicalTrials.gov (NCT02102451).

Statistical Analysis

Categorical parameters were summarized as number and proportion. Continuous variables were summarized by either mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. The number and proportion of individuals with DDIs category 1–4 was summarized by HCV GT for each DAA regimen. Analysis was performed using STATA (version 14.0; StataCorp, College Station, TX).

RESULTS

Participant Enrollment Characteristics

Between July 2014 and December 2015, 257 individuals positive for HIV and anti-HCV antibody were enrolled in CEASE-D (Figure 1). Demographic and enrollment characteristics are presented in Table 1. The participants were predominantly white (85%) males (95%; mean age 47 years, SD = 9) with well controlled HIV-infection (median CD4 count, 587×10^6/L; IQR, 430–800; HIV viral load below the limit of detection, 72%). Hepatitis C virus RNA was detected in 84% (n = 215). In those with detectable HCV RNA, the predominant HCV GTs were 1 (58%; 1a, n = 99; 1b, n = 12; no subtype, n = 14) and 3 (23%). The major modes of HCV acquisition were injecting drug use (52%) and sexual exposure in men who have sex with men (29%). Significant fibrosis or cirrhosis (METAVIR F3 or F4) was evident in 19%. Of those individuals who had had transient elastography within the 6 months before enrollment, median liver stiffness measurement was 6.2 kPa (IQR = 4.9, 8.8 kPa; range = 3.0, 65.2 kPa). Thirty-two percent (n = 82) had previously received treatment for HCV.

Current Combination Antiretroviral Therapy

Ninety-seven percent of participants were receiving cART (n = 249), consisting of combinations of 17 individual antiretroviral agents. For 1 participant, the current cART regimen was unknown. As expected, participants were receiving a median of 3 antiretrovirals (range, 2–6), with 24% receiving 4 (n = 59) and 5% receiving ≥5 (n = 12) antiretrovirals. Thirteen percent (n = 32) were receiving antiretrovirals from 3 or more classes. Most individuals were receiving a nucleoside reverse-transcriptase inhibitor/nucleotide reverse-transcriptase inhibitor (NRTI/NtRTI) backbone with an integrase inhibitor (II) (37%), nonnucleoside reverse transcriptase inhibitor (NNRTI) (27%), or protease inhibitor (PI) (19%) (Supplementary Table 3). The 3 most common cART regimens were tenofovir disoproxil (TDF) + emtricitabine - + efavirenz (12%, n = 31), abacavir + lamivudine + dolutegravir (11%, n = 27), and TDF + emtricitabine + rilpivirine (10%, n = 26). For the cART regimens specific to those with detectable HCV RNA being considered for DAA therapy, see Figure 2 and Supplementary Table 3.

Drug-Drug Interactions Between Direct-Acting Antivirals and Combination Antiretroviral Therapy

Prescribed antiretroviral agents in those with detectable HCV RNA and their potential for DDIs with IFN-free DAAs in this cohort are displayed in Figure 2 and Table 2. The risk of a clinically significant DDI with currently prescribed cART varied markedly between DAA regimens.

In participants on cART with HCV GT 1 and 4 and detectable HCV RNA (n = 128) (Supplementary Figure 1), category 1 (no clinically significant interaction) DDIs were expected in 29% with sofosbuvir/ledipasvir, 59% with sofosbuvir plus daclatasvir, 73% with sofosbuvir/velpatasvir, 36% with PrO ± D (±ribavirin), 49% with grazoprevir/elbasvir, and 49% with sofosbuvir plus simeprevir. Category 2 DDIs were expected in 71% with sofosbuvir/ledipasvir, 41% with sofosbuvir plus daclatasvir, and 28% with PrO ± D (±ribavirin). No category 2 DDIs were expected with sofosbuvir/velpatasvir, grazoprevir/elbasvir, and sofosbuvir plus simeprevir. Specifically, category 1 and 2 DDIs were expected in 35% and 30%, respectively, with PrOD in HCV GT 1 and in 50% and 0%, respectively, with PrO in HCV GT 4. In the case of sofosbuvir plus daclatasvir, all category 2 DDIs involved DAA dose adjustment; an increase in

Table 1. Participant Enrollment Characteristics

Demographic and Clinical Characteristics	Total Study Population (n = 257)	On cART		
		Detectable HCV RNA (n = 208)	Undetectable HCV RNA (n = 32)	Missing HCV RNA (n = 9)
Age (years), n (%)				
<30	8 (3)	6 (3)	0	0
30–39	49 (19)	38 (18)	8 (25)	1 (11)
40–49	98 (38)	82 (39)	12 (38)	2 (22)
50–59	76 (30)	58 (28)	10 (31)	6 (67)
≥60	26 (10)	24 (12)	2 (6)	0
Mean age (SD)	47 (9)	47 (9)	47 (9)	50 (8)
Gender, n (%)				
Male	244 (95)	198 (95)	29 (91)	9 (100)
Female	11 (4)	9 (4)	2 (6)	0
Transgender	2 (1)	1 (1)	1 (3)	0
Ethnicity, n (%)				
White	219 (85)	178 (86)	26 (81)	8 (89)
Asian	19 (7)	15 (7)	2 (6)	1 (11)
Hispanic	5 (2)	4 (2)	1 (3)	0
Indian	2 (1)	1 (1)	1 (3)	0
Aboriginal/Torres Strait Islander	4 (2)	4 (2)	0	0
Other/not specified	8 (3)	6 (3)	2 (6)	0
On cART, n (%)	249 (97)[a]	208 (100)	32 (100)	9 (100)
Median CD4 count, cells $\times 10^6$/L (IQR)	587 (430–800)	596 (436–809)	553 (419–772)	615 (560–836)
HIV viral load below limit of detection, n (%)	184 (72)	149 (72)	28 (88)	5 (56)
HCV RNA detected, n (%)	215 (84)	208 (100)	0	NA
Median $\log_{10}$ HCV RNA (IQR)	6.1 (5.5–6.7)	6.1 (5.4–6.7)	NA	NA
HCV genotype, n (%)[b]				
1	125 (58)	122 (59)	NA	NA
2	7 (3)	7 (3)	NA	NA
3	49 (23)	46 (22)	NA	NA
4	6 (3)	6 (3)	NA	NA
Mixed[c]	1 (1)	1 (1)	NA	NA
Unknown/missing	27 (13)	26 (13)	NA	NA
Mode of HCV acquisition, n (%)				
Injecting drug use	133 (52)	103 (50)	20 (63)	6 (67)
Sexual exposure: MSM	75 (29)	64 (31)	7 (22)	2 (22)
Sexual exposure: heterosexual	9 (4)	8 (4)	1 (3)	0
Tattooing	2 (1)	2 (1)	0	0
Transfusion	3 (1)	1 (1)	0	1 (11)
Other	3 (1)	2 (1)	2 (6)	0
Unknown/missing	32 (12)	28 (13)	2 (6)	0
Prior HCV therapy	82 (32)	58 (28)	19 (59)	5 (56)
Fibrosis stage (METAVIR), n (%)				
≤F2	164 (64)	137 (66)	20 (63)	2 (22)
F3/4	48 (19)	37 (18)	5 (16)	1 (11)
Not available	45 (18)	29 (14)	7 (22)	6 (67)

Abbreviations: cART, combination antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; NA, not applicable; RNA, ribonucleic acid; SD, standard deviation.

[a] cART regimen unknown for 1 individual.

[b] HCV genotype distribution in those with detectable HCV RNA.

[c] Mixed HCV genotype: GT 1a and 3.

daclatasvir dose to 90 mg daily would be required in 23% (n = 30) due to an interaction with a NNRTI (efavirenz, n = 22; etravirine, n = 7; nevirapine, n = 3), and a reduction in daclatasvir dose to 30 mg daily would be required in 16% (n = 21) due to an interaction with a pharmacokinetic booster (atazanavir/ritonavir, n = 12; saquinavir/ritonavir, n = 1; elvitegravir/cobicistat, n = 8). Category 2 DDIs that would require minor antiretroviral adjustment (ritonavir-boosted atazanavir,

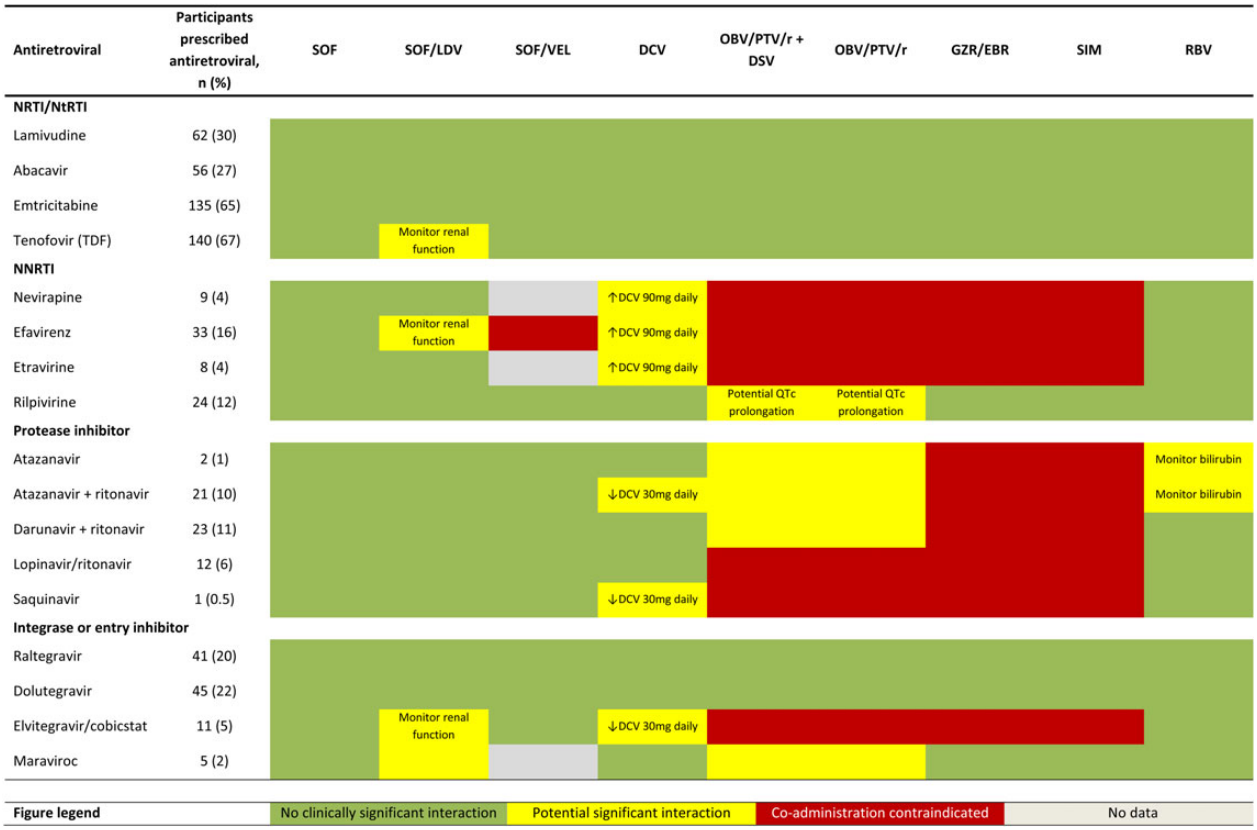

Figure 2. Concomitant use of antiretroviral drugs and approved interferon-free direct-acting antiviral (DAA) regimens in the CEASE-D cohort. Antiretrovirals prescribed for participants with detectable hepatitis C virus (HCV) ribonucleic acid, regardless of HCV genotype. Antiretroviral agents involved in drug-drug interactions (DDIs) and suggested actions per DAA agents regimen. Color code is as follows: green, category 1, no significant DDI; yellow, category 2, potentially significant DDI possible; and red, category 3, coadministration either not recommended or contraindicated. The clinical significance of the drug interaction is based on individual DAA prescribing information and www.hep-druginteractions.org. Abbreviations: DCV, daclatasvir; GZR/EBR, grazoprevir/elbasvir; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI/NtRTI, nucleoside reverse-transcriptase inhibitor/nucleotide reverse-transcriptase inhibitor; PI, protease inhibitor; PrO ± D, ombitasvir/paritaprevir/ritonavir fixed dose combination with or without dasabuvir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SOF/LDV, sofosbuvir/ledipasvir fixed-dose combination; SOF/VEL, sofosbuvir/velpatasvir fixed-dose combination.

n = 11 or darunavir, n = 7) were noted in 14% with PrO ± D. Category 3 DDIs (contraindicated or not recommended for coadministration) were noted in 36% with PrO ± D, 51% with grazoprevir/elbasvir, 51% with sofobuvir plus simeprevir, and 17% with sofobuvir/velpatasvir. No category 3 DDIs were expected with sofosbuvir/ledipasvir and sofosbuvir plus daclatasvir. The antiretroviral drug classes associated with category 3 DDIs were predominantly the NNRTIs and HIV PIs (PrOD, n = 62—NNRTI 77%, PI 29%, II with cobicistat 13%; grazoprevir/elbasvir, n = 65—NNRTI 49%, PI 46%, II with cobicistat 12%; sofosbuvir plus simeprevir, n = 65—NNRTI 49%, PI 46%, II with cobicistat 12%; sofosbuvir/velpatasvir, n = 22—NNRTI 100%). No data are available for the potential DDIs between sofosbuvir/velpatasvir and nevirapine, etravirine, and maraviroc (category 4 DDI, 9%). Given the known interaction with efavirenz, it would be expected that coadministration of sofosbuvir/velpatasvir and nevirapine or etravirine would be contraindicated. The current cART regimens were suitable for coadministration with sofosbuvir/ledipasvir and sofosbuvir plus daclatasvir in 100% and 100%, respectively. However, DDIs impacted on the suitability for coadministration of the current cART regimens and sofosbuvir/velpatasvir (73%), PrO ± D (64%), grazoprevir/elbasvir (49%), and sofosbuvir plus simeprevir (49%).

In participants on cART with HCV GT 2 and 3 and detectable HCV RNA (n = 53; GT 2, n = 7; GT 3 46, including 1 mixed GT 1a/3a infection) (Supplementary Figure 2), category 1 DDIs were expected in 89% with sofosbuvir plus ribavirin, 68% with sofosbuvir plus daclatasvir, and 81% with sofosbuvir/velpatasvir. Category 2 DDIs were expected in 11% with sofosbuvir plus ribavirin, 32% with sofosbuvir plus daclatasvir, and 0 with sofosbuvir/velpatasvir. All category 2 DDIs related to sofosbuvir and daclatasvir involved dose adjustment of daclatasvir (n = 17; elvitegravir/cobicistat, n = 2; efavirenz, n = 7; nevirapine, n = 3; ritonavir-boosted atazanavir, n = 5). No category 3 DDIs were noted with sofosbuvir plus ribavirin and sofosbuvir plus daclatasvir. However, category 3 and 4 DDIs were noted in 13% and 6%, respectively, with sofosbuvir/velpatasvir (with all category 3 DDIs related to efavirenz and all category 4 DDIs

Table 2. Suitability of Current cART Regimen for Coadministration With DAA Regimen by HCV Genotype

DDI Category, n (%)	HCV GT 1 and 4 (n = 128)						HCV GT 2 and 3 (n = 53)[a]			HCV GT Indeterminate/ Unknown (n = 26)	
	SOF/LDV	PrO±DSV±RBV	GZR/EBR	SOF + SIM	SOF + DCV	SOF/VEL	SOF + RBV	SOF + DCV	SOF/VEL	SOF + DCV	SOF/VEL
Category 1: No significant DDI	37 (29)	46 (36)	63 (49)	63 (49)	75 (59)	94 (73)	47 (89)	36 (68)	43 (81)	12 (46)	17 (65)
Category 2: Potentially significant DDI	91 (71)	36 (28)	0	0	53 (41)	0	6 (11)	17 (32)	0	14 (54)	0
Adjust DAA					53 (41)			17 (32)		14 (54)	
Additional monitoring	91 (71)	18 (14)					6 (11)				
Adjust cART dose or timing of administration		18 (14)									
Category 3: Not recommended or contraindicated	0	46 (36)	65 (51)	65 (51)	0	22 (17)			7 (13)		5 (19)
Category 4: No data	0	0	0	0	0	12 (9)[b]			3 (6)[b]		4 (15)[b]
Suitable for coadministration	128 (100)	82 (64)	63 (49)	63 (49)	128 (100)	94 (73)	56 (100)	56 (100)	43 (81)	26 (100)	17 (65)
Antiretroviral class associated with category 3 DDI[c]											
NNRTI		31 (67)	31 (48)	31 (48)		22 (100)			7 (100)		5 (100)
PI		12 (26)	31 (48)	31 (48)							
Integrase inhibitor with cobicistat		8 (17)	8 (12)	8 (12)							

Abbreviations: cART; combination antiretroviral therapy; DAA, direct-acting antiviral agent; DCV, daclatasvir; DDI, drug-drug interaction; DSV, dasabuvir; FDC, fixed-dose combination; GT, genotype; GZR/EBR, grazoprevir/elbasvir; HCV, hepatitis C virus; NRTI/NtRTI, nucleoside reverse-transcriptase inhibitor/nucleotide reverse-transcriptase inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; PrO ± D ± RBV, ombitasvir/paritaprevir/ritonavir fixed-dose combination with or without dasabuvir (without ribavirin in genotype 1b); SOF, sofosbuvir; SOF+DCV, sofosbuvir/daclatasvir; SOF/LDV, sofosbuvir/ledipasvir fixed-dose combination; SOF+RBV, sofosbuvir/ribavirin; SOF/VEL, sofosbuvir/velpatasvir fixed-dose combination.

[a] Includes 1 participant with mixed infection (GT 1a/3a).

[b] No data available for coadministration of maraviroc, nevirapine, or etravirine with SOF/VEL; given the interaction with efavirenz, category 3 DDI expected with nevirapine and etravirine.

[c] Individuals may be prescribed more than 1 antiretroviral class resulting in a category 3 DDI (not recommended or contraindicated).

related to nevirapine). Current cART regimens were suitable for coadministration with sofosbuvir plus ribavirin and sofosbuvir plus daclatasvir in 100%, with no antiretroviral alterations required. With sofosbuvir/velpatasvir, current cART regimens were suitable for coadministration in 81%.

In participants on cART with HCV GT indeterminate or unknown (n = 26), 2 pan-genotypic regimens were assessed. Category 1 DDIs were expected in 46% with sofosbuvir plus daclatasvir and 65% with sofosbuvir/velpatasvir. Category 2 DDIs were expected in 54% with sofosbuvir plus daclatasvir and 0 with sofosbuvir/velpatasvir. No category 3 DDIs were noted with sofosbuvir plus daclatasvir. Category 3 and 4 DDIs were noted in 19% and 15%, respectively, with sofosbuvir/velpatasvir (with all category 3 DDIs related to efavirenz and all category 4 DDIs related to nevirapine or etravirine). Current cART regimens were suitable for coadministration with sofosbuvir plus daclatasvir in 100% and sofosbuvir/velpatasvir in 65%.

CONCLUSIONS

The availability of highly effective, well tolerated, IFN-free DAA regimens for HCV should diminish barriers to therapy in HIV/HCV coinfection. However, treatment of HIV/HCV-coinfected individuals will require an awareness of the potential DDIs between specific DAAs and HIV antiretroviral agents by both prescribers and clinical pharmacists to prevent morbidity and ensure treatment efficacy. In this real-world cohort of HIV/HCV-coinfected individuals, there was significant potential for DDIs between currently prescribed cART and approved or FDA-filed IFN-free DAA regimens. Most participants were receiving cART regimens that were suitable for coadministration with sofosbuvir and a first-generation NS5A inhibitor. However, based on current prescribing information, the DAA regimens including HCV NS3/4a PIs were not appropriate for coadministration in more than half of study participants. In addition, HIV/HCV-coinfected individuals need to have achieved HIV RNA suppression before initiation of PrO ± D, because the low-dose ritonavir required to boost paritaprevir may select for HIV PI resistance; 28% of the CEASE-D cohort did not demonstrate HIV RNA suppression.

Representative of the broader HIV/HCV-infected population in many countries, most individuals in this cohort had HCV GT 1 infection, which has significant implications for choice of DAA regimen. Only 16% (n = 20) of those with HCV GT 1 or 4 were receiving cART, which demonstrated no clinically significant DDIs with all of the assessed IFN-free DAA regimens; those without any significant DDIs were all prescribed 2 NRTIs (abacavir/lamivudine) and an integrase inhibitor (dolutegravir or raltegravir).

Although antiretroviral switches may be performed to allow coadministration with specific DAAs [21], as we have demonstrated in the CEASE-D cohort, most HIV-positive individuals on cART, even those receiving complex regimens with agents

from 3 or more classes, should be able to receive a suitable IFN-free, HCV DAA regimen (in line with current international guidelines [34, 35]) without altering their current antiretroviral regimen. This is important to note in the context of current limitations or restrictions placed upon DAA access in many countries, largely mediated by payers. The flexibility to individualize therapy and prescribe an appropriate DAA regimen is essential to maximize safety and efficacy. However, if required, changes in the antiretroviral regimen should be undertaken in collaboration with a HIV physician [35]. As international cART guidelines change, regimens favoring integrase inhibitor use are anticipated, which should reduce the proportion with significant DDIs [36].

Drug-drug interaction management presents increasing challenges as the number of drugs prescribed increases per individual; in this cohort, for those on cART, 98% took 3 or more drugs, irrespective of other concomitant medications and before DAA prescription. To date, most HIV/HCV-coinfected individuals have been treated in specialist centers. However, as DAA prescription becomes increasingly commonplace outside of these settings, recognition of relevant DDI with cART remains important for optimal management of coinfected patients.

Primarily, 2 scenarios need to be considered and avoided: (1) an increase in plasma drug levels, potentially leading to adverse events, and (2) a reduction in plasma drug levels, potentially resulting in loss of efficacy. Considering commonly prescribed antiretrovirals within the CEASE-D cohort, particular DDIs and potentially significant clinical events are notable. In line with international guidelines, tenofovir-containing cART regimens were commonly prescribed in this cohort (65%). An increase in tenofovir concentrations when TDF is coadministered with sofosbuvir/ledipasvir and efavirenz, rilpivirine, or a boosted-protease or integrase inhibitor has raised concerns regarding nephrotoxicity [25]. However, data from clinical trials and real-world cohorts provide some reassurance [13, 22, 37]. In the Phase III ION-4 trial, only 1% of participants were noted to have an increase in baseline serum creatinine $\geq$0.4 mg/dL ($\geq$35 μmol/L) while on treatment [13]. In addition, recent FDA approval of tenofovir alafenamide provides a potentially safer alternative for coadministration if concerns regarding renal toxicity persist [31]. Human immunodeficiency virus PIs were prescribed in 29%, with implications for daclatasvir and HCV NS3/4a PIs. Concomitant use of elbasvir/grazoprevir with HIV PIs is contraindicated due to organic anion-transporting polypeptide (OATP) 1B inhibition and resultant marked increase in grazoprevir area under the curve and potential for alanine aminotransferase elevation [27]. A reduction in DAA drug level may impact on SVR and selection of resistance-associated variants [38]. Efavirenz (prescribed in 15%), an inducer of CYP3A, markedly reduces grazoprevir/elbasvir [27], PrO [26], velpatasvir [33], and daclatasvir serum concentrations [30]. As such, efavirenz is contraindicated with grazoprevir/elbasvir, PrO, and sofosbuvir/velpatasvir, and an increase in daclatasvir dose is necessary if coadministered with efavirenz, etravirine, or nevirapine; this latter DDI could impact 25% of the CEASE-D cohort. A reduction in antiretroviral drug level may lead to HIV virological failure. Darunavir serum trough concentrations are reduced by 50% when coadministered with PrO, so caution should be exercised in individuals with a history of HIV PI resistance [39].

The main limitation of this study is that cohort enrollment is currently restricted to 5 treatment centers in Sydney, Australia, which may limit generalizability. However, given that antiretroviral use in CEASE-D is similar to that in the overall Australian HIV Observational Database, our results are likely to be applicable to the broader HIV/HCV population in Australia and representative of coinfected populations in many high-income settings. Given the extensive use of TDF + emtricitabine + efavirenz in HIV-positive populations in low- and middle-income countries, the choice of DAA regimen in those with HIV/HCV coinfection will be impacted by potential DDIs. Sofosbuvir plus daclatasvir would be suitable in this setting given its pan-genotypic activity and the ability to dose adjust daclatasvir. Other limitations are the lack of data to determine what proportion of individuals could safely switch antiretrovirals for the duration of their HCV treatment and the inability to assess other comorbidities and competing polypharmacy in this cohort.

Although offering greater efficacy, tolerability, and simplicity than IFN-containing regimens, DDIs will impact on DAA prescribing in HIV/HCV coinfection. The combinations of sofosbuvir plus an NS5A inhibitor and sofosbuvir plus ribavirin appear to be suitable for coadministration with commonly used antiretroviral agents, making these DAA regimens appealing for use in HIV/HCV coinfection. However, the use of an HCV NS3/4a PI-containing DAA regimen poses more challenges. The involvement of clinical pharmacists in assessing DDI risk before commencing DAA therapy may be warranted. Evaluation of potential DDIs is required to prevent adverse events or treatment failure.

Supplementary Data

Supplementary material is available online at *Open Forum Infectious Diseases* online (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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