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 DAs 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 NSSA 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,
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 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...
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 DAAAs 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
Dacalatasvir 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 dacalatasvir 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,

Table 1. Participant Enrollment Characteristics

| Demographic and Clinical Characteristics | Total Study Population (n = 257) | 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                                   | 96 (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)*                       | 208 (100)                    | 32 (100)                    | 9 (100)                |
| Median CD4 count, cells ×10^9/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 (%)*                    |                                 |                              |                             |                        |
| 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†                                  | 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.

* cART regimen unknown for 1 individual.

† HCV genotype distribution in those with detectable HCV RNA.

‡ Mixed HCV genotype: GT 1a and 3.
n = 11 or darunavir, n = 7) were noted in 14% with PrO ± D. Category 3 DDIs (contraindicated or not recommended for co-administration) were noted in 36% with PrO ± D, 51% with grazoprevir/elbasvir, 51% with sofosbuvir plus simeprevir, and 17% with sofosbuvir/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 (Pr0D, n = 6 — 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 maraviro (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%), Pr0 ± 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. No category 2 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 (Pr0D, 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 maraviro (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 contraindi- cated. 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%), Pr0 ± 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)* | 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 (88) | 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 |
| Additional monitoring | 91 (71) | 18 (14) | 6 (11) | 0 | 12 (9) | 0 | 6 (11) | 17 (32) | 0 | 14 (54) | 0 |
| Adjust cART dose or timing of administration | 18 (14) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Category 3: Not recommended or contraindicated | 0 | 46 (36) | 65 (51) | 65 (51) | 0 | 22 (17) | 7 (13) | 56 (100) | 56 (100) | 43 (81) | 26 (100) | 17 (65) |
| Category 4: No data | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 12 (9) | 3 (6) | 4 (15) |
| 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 DDIs

- NNRTI: 31 (67) 31 (48) 31 (48) 22 (100) 7 (100) 5 (100)
- PI: 12 (26) 31 (48) 31 (48) 22 (100) 7 (100) 5 (100)
- 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, nucleoside reverse-transcriptase inhibitor; NtRTI, nucleotide 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.

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

** 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.

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

CONCLUSIONS

The availability of highly effective, well tolerated IFN-free DAA regimens for HCV should diminish barriers to therapy in HIV/HCV-coinfected individuals. Key factors in the clinical decision to coadminister DAA and cART regimens include the choice of the HCV DAA regimen, the potential DDIs between DAAs and HIV antiretroviral agents, and the impact of antiretroviral switch strategies on the efficacy and safety of cART. In this real-world cohort of HIV/HCV-infected individuals, most individuals had achieved HIV RNA suppression before initiation of DAA therapy; therefore, antiretroviral switches were uncommon. The majority of cART regimens were suitable for coadministration with sofosbuvir/velpatasvir (65%) and sofosbuvir/daclatasvir (100%). Category 1 DDIs were noted in 19% and 15%, respectively, with sofosbuvir/velpatasvir. Category 2 DDIs were noted with sofosbuvir/daclatasvir. Category 3 DDIs were noted with sofosbuvir/daclatasvir (with all category 3 DDIs related to efavirenz) or sofosbuvir/velpatasvir. No category 3 DDIs were noted with sofosbuvir/daclatasvir and sofosbuvir/velpatasvir. Category 4 DDIs were noted with sofosbuvir/daclatasvir (with all category 3 DDIs related to efavirenz) or sofosbuvir/velpatasvir. Current cART regimens were suitable for coadministration in more than half of study participants. In addition, most participants were receiving cART regimens that were suitable for 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 related to nevirapine, fosamprenavir, or raltegravir. (abacavir/lamivudine) and an integrase inhibitor (dolutegravir) or 3TC/FTC/emtricitabine and an integrase inhibitor (dolutegravir). 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 related to nevirapine, fosamprenavir, or raltegravir. Current cART regimens were suitable for coadministration in more than half of study participants. In addition, most participants were receiving cART regimens that were suitable for 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 related to nevirapine, fosamprenavir, or raltegravir. (abacavir/lamivudine) and an integrase inhibitor (dolutegravir) or 3TC/FTC/emtricitabine and an integrase inhibitor (dolutegravir). 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 related to nevirapine, fosamprenavir, or raltegravir.
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 lim-
itations or restrictions placed upon DAA access in many coun-
tries, 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 collabora-
tion 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 chal-
enges as the number of drugs prescribed increases per individ-
ual; 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 individ-
uals 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 re-
sulting 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 regi-
mens were commonly prescribed in this cohort (65%). An in-
crease in tenofovir concentrations when TDF is coadministered
with sofosbuvir/ledipasvir and efavirenz, rilpivirine, or a boost-
ed-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 ≥0.4 mg/dL
(≥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/grazoprev
with HIV PIs is contraindicated due to organic anion-trans-
porting polypeptide (OATP) 1B inhibition and resultant
marked increase in grazoprevir area under the curve and poten-
tial 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 in-
ducer of CYP3A, markedly reduces grazoprevir/elbasvir [27],
PrO [26], velpatasvir [33], and daclatasvir serum concentra-
tions [30]. As such, efavirenz is contraindicated with grazoprevir/el-
basvir, 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 antiretro-
viral use in CEASE-D is similar to that in the overall Australian
HIV Observational Database, our results are likely to be appli-
cable to the broader HIV/HCV population in Australia and rep-
resentative of coinfected populations in many high-income
settings. Given the extensive use of TDF + emtricitabine -
+ efavirenz in HIV-positive populations in low- and middle-in-
come countries, the choice of DAA regimen in those with HIV/
HCV coinfection will be impacted by potential DDIs. Sofosbu-
vir 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 propor-
tion of individuals could safely switch antiretrovirals for the du-
eration 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 pre-
scribing in HIV/HCV coinfection. The combinations of sofos-
buvir plus an NS5A inhibitor and sofosbuvir plus ribavirin
appear to be suitable for coadministration with commonly
used antiretroviral agents, making these DAA regimens appeal-
ing for use in HIV/HCV coinfection. However, the use of an
HCV NS3/4a PI-containing DAA regimen poses more chal-
enges. 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/).

Acknowledgments
Disclaimer. The views expressed in this publication do not necessarily
represent the position of the Australian Government.
Financial support. This work was supported by Gilead Sciences, Inc.
and Merck Sharpe & Dohme as an investigator-initiated study. The Kirby
Institute is funded by the Australian Government Department of Health
and Ageing.
Potential conflicts of interest. M. M. has received speaker payments
from Abbvie. G. J. D. is an advisory board member and has received hon-
oraria from Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, and Abb-
Vie; he has received research grant funding from Roche, Merck, Janssen,
Gilead, Bristol-Myers Squibb, Vertex, Boeringher Ingelheim, and AbbVie;
and he has received travel sponsorship from Roche, Merck, Janssen, Gilead,
and Bristol-Myers Squibb. G. V. M. has received research funding, advisory
board payments, and speaker payments from Gilead and research funding.
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