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Antiretroviral Use and Implications for DAA Therapy in HIV/HCV Co-infection

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Introduction

Interferon-free direct-acting antiviral (DAA) regimens for HCV provide a major advance in clinical management, including in HIV/HCV co-infection (1-6).

Safety data on potentially significant antiretroviral and DAA drug-drug interactions (DDIs) in HIV/HCV co-infected individuals are limited to the drug combinations permitted in phase II and III trials, with most having strict antiretroviral eligibility criteria (1-6).

Little data is available on the real-world relevance of DDIs in HIV/HCV co-infected populations using interferon-free therapy.

This study aimed to characterise combination antiretroviral therapy (cART) in HIV/HCV co-infected individuals and assess the clinical significance of DDIs with DAAs in a large real-world cohort.

Methods

Adults (age ≥18 years) with HIV and current or prior HCV co-infection (HCV antibody positive) were eligible for enrolment in the Control and Elimination within Australia of Hepatitis C from people living with HIV (CEASE-D) prospective cohort study. This analysis included all participants enrolled between July 2014 and December 2015 .

Participants with detectable HCV RNA were considered for anti-HCV therapy with assessment of DDIs between an individuals cART and approved interferon-free DAAs by HCV genotype (**Figure 1**). The following DAA regimens were assessed: sofosbuvir/ledipasvir (SOF/LDV); ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) and dasabuvir (DSV); grazoprevir/elbasvir (GZR/EBR); and sofosbuvir (SOF) plus daclatasvir (DCV).

Potential DDIs were simulated according to the most recent literature, available prescribing information (as of December 2015) and the University of Liverpool DDI tool (www.hepdruginteractions.org).

The relationship and potential interaction was designated as follows:

- **Category 1: No clinically significant DDI**
- **Category 2: Potentially significant DDI – requiring dose adjustment, additional monitoring for toxicity or alteration in timing of administration**
- **Category 3: Co-administration not recommended or contra-indicated**
- **Category 4: No data available.**

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 co-administration of the DAA and cART regimen.

Results

257 individuals positive for HIV and anti-HCV antibody were enrolled (**Figure 1** and **Table 1**).

97% (n=249) were receiving cART.

Most individuals were receiving a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI/NtRTI) backbone with an integrase inhibitor (II) (37%), non-nucleoside reverse transcriptase inhibitor (NNRTI) (27%) or protease inhibitor (PI) (19%)

5 most common cART regimens:

- Tenofovir + emtricitabine + efavirenz (12%)
- Abacavir + lamivudine + dolutegravir (11%)
- Tenofovir + emtricitabine + rilpivirine (10%)
- Tenofovir + emtricitabine + raltegravir (8%)
- Tenofovir + emtricitabine + dolutegravir (7%).

Table 1. Participant enrolment characteristics

Demographic and clinical characteristics	N=257
Mean age (SD)	47 (9)
Gender, n (%)	
Male	244 (95)
Female	11 (4)
Transgender	2 (1)
On cART, n (%)	249 (97)
Median CD4 count, cells x10^6/L (IQR)	587 (430-800)
HIV viral load below limit of detection, n (%)	184 (72)
HCV RNA detected, n (%)	215 (84)
Median log$_{10}$ HCV RNA (IQR)	6.1 (5.5-6.7)
Fibrosis stage (METAVIR), n (%)	
≤ F2	164 (64)
F3 or F4	48 (19)
Not available	45 (18)

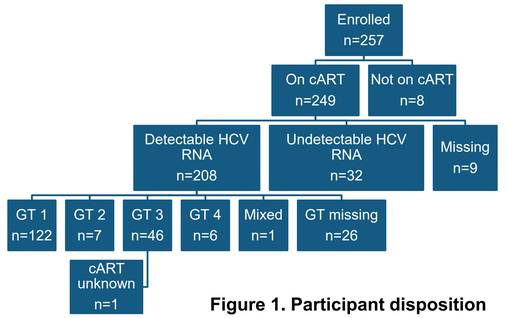

Figure 1. Participant disposition

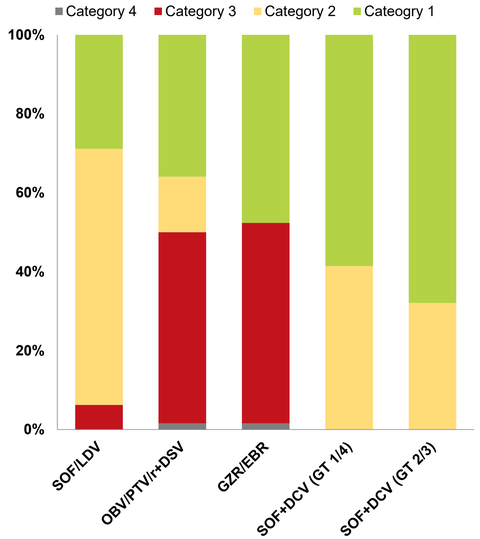

Figure 2. Proportion of participants with significant DDIs between their current cART regimen and approved interferon-free DAA regimens

Drug-drug interactions between DAAs and cART

Prescribed antiretrovirals and their potential for DDIs with approved interferon-free DAAs in this cohort are displayed in **Figure 2** and **Figure 3**.

In participants with HCV GT 1 and 4, current cART regimens were largely suitable for co-administration with SOF/LDV (94%) and SOF + DCV (100%), but not OBV/PTV/r +/- DSV (50%) and GZR/EBR (48%). In participants with HCV GT 2 or 3, current cART regimens were suitable for co-administration with SOF + DCV in 100%.

Antiretroviral	Participants affected n (%)	SOF	SOF/LDV	OBV/PTV/r + DSV	GZR/EBR	DCV
NRTI/NtRTI	239 (96)					
Lamivudine	74 (30)					
Abacavir	68 (27)					
Emtricitabine	157 (63)					
Tenofovir	163 (66)					
NNRTI	91 (36)					
Nevirapine	15 (6)					↑DCV 90mg daily
Efavirenz	37 (15)					↑DCV 90mg daily
Etravirine	11 (4)					↑DCV 90mg daily
Rilpivirine	28 (11)					
Protease inhibitor	73 (29)					
Atazanavir	3 (1)					
Atazanavir/ritonavir	27 (11)					↓DCV 30mg daily
Darunavir/ritonavir	29 (12)					
Lopinavir/ritonaivr	14 (6)					
Saquinavir/ritonavir	1 (0)					↓DCV 30mg daily
Integrase inhibitor	119 (48)					
Raltegravir	49 (20)					
Dolutegravir	54 (22)					
Elvitegravir/cobicstat	16 (6)					↓DCV 30mg daily
Entry inhibitor	7 (3)					
Maraviroc	7 (3)					

Figure legend | No clinical significant DDI | Potential significant DDI | Co-administration not recommended | No data

Figure 3. Concomitant use of selected antiretroviral drugs and IFN-free DAA regimens.

Conclusion

Clinically significant DDIs are expected and will impact on DAA prescribing in HIV/HCV co-infection.

Sofosbuvir/ledipasvir and sofosbuvir plus daclatasvir appeared to be the most suitable combinations in this cohort.

Evaluation of potential DDIs is required to prevent adverse events or treatment failure.

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