THE ERA OF DAAS: ASSESSING THE PATIENTS' CHARACTERISTICS, CLINICAL IMPACT, AND EMERGENCE OF COMORBIDITIES IN HIV/HCV-COINFECTED VERSUS HIV-INFECTED INDIVIDUALS

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B. Álvarez-Álvarez[1] , L. Prieto-Pérez [1] , A. Cuadra-Grande[2] , M.Á. Casado[2] , A. Cabello Úbeda[1] , A.W. Al-Hayani[1] , I. Carrillo Acosta[1] , I. Mahillo-Fernández[3] , M. Górgolas Hernández-Mora[1] , J. Benito[4,5] , N. Rallón[4,5]

[1]Division of Infectious Diseases, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [2]Pharmacoeconomics & Outcomes Research Iberia (PORIB), Madrid, Spain; [3]Biostatistics and Epidemiology Unit, Instituto de Investigación Sanitaria, Hospital Universitario Fundación Jiménez Díaz, Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain; [4]HIV and Viral Hepatitis Research Laboratory, Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain; [5]Hospital Universitario Rey Juan Carlos, Móstoles, Spain.

I. Background

- Despite advances in antiretroviral treatment, the life expectancy of people living with HIV (PLWH) remains lower than that of uninfected people largely due to comorbidities such as hepatitis C coinfection.
- Previous studies have shown a higher incidence of different comorbidities and non-AIDS events in PLWH coinfected with HCV. However, most of these studies have been biased by the use of interferon-α-based anti-HCV therapy.
- Fortunately, the arrival of direct-acting antivirals (DAAs) allow to study the real impact of HCV eradication on the evolution of HIV infection, regarding the development of different comorbidities, without the bias of previous anti-HCV regimens including the immunomodulatory effect of the interferon-α.
- The objective of this study is to determine whether individuals with HIV/HCV coinfection versus HIV-infected individuals, in the era of interferon-free therapies, exhibit an increased incidence of comorbidities and non-AIDS-related events.

II. Methods

- A retrospective analysis was conducted by collecting data from clinical records of spanish patients at a tertiary hospital involving HIV/HCV-coinfected and HIV-infected patients, all with effectively controlled HIV.
- Coinfected patients underwent HCV clearance using direct-acting antivirals (DAAs) and had no history of interferon-α treatment.
- The incidences of hypertension, diabetes mellitus, cardiovascular disease, kidney disease, liver disease, non-AIDS cancer, and death were compared between the groups.
- Multivariate adjustments for all factors potentially impacting outcomes were used to assess the risk of clinical event onset. Propensity Score (PS) analyses were also conducted to support the multivariate model results.

III. Results

Table 1 shows the different baseline characteristics of the two cohorts: 229 HIV/HCV-coinfected patients and 229 HIV-infected patients.

Table 1. Baseline characteristics of the cohorts

		HIV/HCV Group (N = 229)	HIV Group (N = 229)	*p*-Value
Demographics				
Age	Mean (SD)	49.1 (10.8)	49.6 (10.4)	0.627 [1]
Gender				1.000 [2]
Male	N (%)	218 (95.2%)	218 (95.2%)	
Female	N (%)	11 (4.8%)	10 (4.4%)	
Transgender	N (%)	0 (0.0%)	1 (0.4%)	
Ethnicity				0.934 [2]
African	N (%)	0 (0.0%)	1 (0.4%)	
Arab	N (%)	1 (0.4%)	0 (0.0%)	
Asian	N (%)	1 (0.4%)	1 (0.4%)	
Caucasian	N (%)	174 (76.0%)	176 (76.9%)	
Latino	N (%)	53 (23.1%)	51 (22.3%)	
Sexual orientation				<0.001 [2]
Heterosexual	N (%)	51 (22.3%)	17 (7.4%)	
Homosexual	N (%)	173 (75.5%)	212 (92.6%)	
Bisexual	N (%)	5 (2.2%)	0 (0.0%)	
Lifestyle habits				
Smoking habit				0.001 [2]
No	N (%)	97 (42.9%)	122 (53.3%)	
Yes	N (%)	126 (55.8%)	93 (40.6%)	
Former smoker	N (%)	3 (1.3%)	14 (6.1%)	
Alcohol consumption				<0.001 [2]
No	N (%)	120 (53.1%)	167 (72.9%)	
Yes	N (%)	106 (46.9%)	62 (27.1%)	
Drug consumption (ever)				<0.001 [2]
No	N (%)	54 (25.5%)	203 (89.0%)	
Yes	N (%)	157 (74.1%)	25 (11.0%)	
Former consumer	N (%)	1 (0.5%)	0 (0.0%)	
Purpose of parenteral drugs' use				<0.001 [2]
Nonconsumer	N (%)	117 (55.2%)	226 (98.7%)	
Conventional use	N (%)	48 (22.6%)	2 (0.9%)	
ChemSex	N (%)	47 (22.2%)	1 (0.4%)	
HIV infection				
Time since diagnosis (years)	Median (IQR)	14.0 (9.0–20.0)	13.0 (9.0–18.0)	0.092 [3]
HIV route of transmission				<0.001 [2]
Parenteral	N (%)	50 (21.8%)	7 (3.1%)	
Sexual	N (%)	179 (78.2%)	222 (96.9%)	
HIV clinical stage				<0.001 [2]
Stage A	N (%)	140 (61.1%)	163 (71.2%)	
Stage B	N (%)	42 (18.3%)	36 (15.7%)	
Stage C	N (%)	47 (20.5%)	30 (13.1%)	
CD4+ cell count at ART initiation (cells/μL)	Median (IQR)	306.0 (180.0–472.0)	314.0 (216.0–440.0)	0.845 [3]
CD4+ cell count at ART initiation (range)				0.012 [2]
1–199 cells/μL	N (%)	61 (30.0%)	44 (20.2%)	
200–499 cells/μL	N (%)	98 (48.3%)	136 (62.4%)	
≥500 cells/μL	N (%)	44 (21.7%)	38 (17.4%)	
CD4+/CD8+ ratio at ART initiation	Median (IQR)	0.28 (0.14–0.47)	0.30 (0.18–0.45)	0.313 [3]
Baseline HIV-1 VL (copies/mL)	Median (IQR)	107.730 (31.960–271.000)	86.743 (23.147–258.250)	0.282 [3]
Baseline HIV-1VL (range)				0.102 [2]
<100.000 copies/mL	N (%)	93 (48.2%)	114 (54.0%)	
100.000–500.000 copies/mL	N (%)	67 (34.7%)	76 (36.0%)	
<500.000 copies/mL	N (%)	33 (17.1%)	21 (10.0%)	
History of AIDS	N (%)	48 (21.0%)	29 (12.7%)	0.025 [2]
HIV treatment				
Time since HIV diagnosis to treatment (years)	Median (IQR)	1.0 (0.0–4.0)	1.0 (0.0–3.0)	0.155 [3]
Time on HIV treatment (years)	Median (IQR)	11.0 (7.0–15.0)	11.0 (7.0–15.0)	0.573 [3]
Ever exposed to rilpivirine	N (%)	65 (28.4%)	54 (23.6%)	0.287 [2]
Poor previous ART adherence	N (%)	29 (12.7%)	9 (3.9%)	0.001 [2]
HCV infection				
HCV route of transmission				-
Parenteral	N (%)	51 (22.3%)	-	
Sexual	N (%)	178 (77.7%)	-	
HCV clinical stage at diagnosis				-
Acute	N (%)	150 (65.5%)	-	
Chronic	N (%)	79 (34.5%)	-	
Time since HCV diagnosis to successful treatment (years)	Mean (SD) / Median (IQR)	5.66 (9.13) / 1.0 (0.0–6.0)	-	
HCV genotypes				-
1a/b	N (%)	159 (69.5%)	-	
2/3	N (%)	13 (5.6%)	-	
4	N (%)	57 (24.9%)	-	
HCV viral load at DAA initiation (IU/mL)				-
<800.000	N (%)	88 (38.4%)	-	
≥800.000	N (%)	141 (61.6%)	-	
Achieved SVR12	N (%)	225 (98.2%)	-	-
Transient elastography (FibroScan) LS before DAAs (kPa)	Mean (SD)	7.13 (5.32)	-	-
Transient elastography (FibroScan) LS before DAAs (Metavir fibrosis score stages)				-
F0–F1 (<7.1 kPa)	N (%)	153 (66.8%)	-	
F2 (7.1–9.4 kPa)	N (%)	33 (14.4%)	-	
F3 (9.5–12.4 kPa)	N (%)	20 (8.7%)	-	
F4 (≥12.5 kPa)	N (%)	13 (5.7%)	-	
No data	N (%)	10 (4.4%)	-	
HCV reinfections (number)				-
2 HCV infections	N (%)	25 (10.9%)	-	
3 HCV infections	N (%)	5 (2.2%)	-	
Baseline biochemistry results				
AST (IU/L)	Median (IQR)	48.0 (35.0–74.0)	21.0 (17.0–27.0)	<0.001 [3]
ALT (IU/L)	Median (IQR)	69.0 (45.0–123.0)	21.0 (16.0–30.0)	<0.001 [3]
GGT (IU/L)	Median (IQR)	60.5 (32.8–114.0)	21.0 (15.0–32.0)	<0.001 [3]
Total cholesterol (mg/dL)	Mean (SD)	159.0 (33.2)	181.0 (35.5)	<0.001 [1]
LDL-cholesterol (mg/dL)	Mean (SD)	90.4 (27.5)	110.0 (34.1)	<0.001 [1]
HDL-cholesterol (mg/dL)	Mean (SD)	47.3 (13.7)	49.8 (15.2)	0.063 [1]
Triglycerides (mg/dL)	Median (IQR)	101.0 (74.0–138.0)	106.0 (83.0–151.0)	0.136 [3]
GFR (mL/min/1.73 m²)	Mean (SD)	94.0 (15.1)	83.0 (17.8)	<0.001 [3]
Platelet (x10³ μL)	Mean (SD)	231.0 (66.6)	251.0 (62.7)	0.001 [1]
CD4+ (cells/μL)	Mean (SD)	703.0 (350.)	812.0 (328.0)	0.001 [1]
CD8+ (cells/μL)	Mean (SD)	1074.0 (510.0)	968.0 (442.0)	0.018 [1]
CD4+/CD8+	Mean (SD)	0.73 (0.37)	0.96 (0.49)	<0.001 [1]
APRI score	Median (IQR)	0.55 (0.35–0.90)	0.09 (0.05–0.13)	<0.001 [3]
APRI fibrosis stage				<0.001 [2]
No fibrosis	N (%)	102 (44.5%)	226 (98.7%)	
Moderate fibrosis	N (%)	94 (41.0%)	3 (1.3%)	
Cirrhosis	N (%)	33 (14.4%)	0 (0.0%)	
FIB-4 score	Median (IQR)	1.12 (0.78–1.57)	0.33 (0.22–0.57)	<0.001 [3]
FIB-4 fibrosis stage				<0.001 [2]
No fibrosis	N (%)	159 (69.4%)	224 (97.8%)	
Moderate fibrosis	N (%)	53 (23.2%)	5 (2.2%)	
Cirrhosis	N (%)	17 (7.4%)	0 (0.0%)	
Baseline comorbidities				
Number of previous comorbidities	Mean (SD)	0.30 (0.70)	0.10 (0.30)	<0.001 [1]
Number of documented STIs	Mean (SD)	4.20 (3.60)	2.60 (2.40)	<0.001 [1]
Hepatitis A test (Positive)	N (%)	163 (74.4%)	155 (76.4%)	0.730 [2]
HBsAg (Positive)	N (%)	9 (3.9%)	6 (2.7%)	0.662 [2]
HBsAb (Positive)	N (%)	136 (59.4%)	147 (66.8%)	0.125 [2]
HBcAb (Positive)	N (%)	97 (42.4%)	81 (37.0%)	0.287 [2]
Obesity (BMI > 30 kg/m²)	N (%)	19 (8.3%)	21 (10.8%)	0.483 [2]
Hypertension at diagnosis	N (%)	18 (7.9%)	3 (1.3%)	0.002 [2]
DM at diagnosis	N (%)	18 (7.9%)	3 (1.3%)	0.040 [2]
Dyslipidemia at diagnosis	N (%)	15 (6.6%)	12 (5.2%)	0.692 [2]
CVD at diagnosis	N (%)	7 (3.1%)	1 (0.4%)	0.075 [2]
Kidney disease at diagnosis	N (%)	6 (2.6%)	0 (0.0%)	0.040 [2]
Hepatic disease at diagnosis	N (%)	15 (6.6%)	0 (0.0%)	<0.001 [2]
Non-AIDS cancer at diagnosis	N (%)	9 (3.9%)	0 (0.0%)	0.007 [2]

Abbreviations. AIDS: Acquired Immunodeficiency Syndrome; ALT: Alanine amino Transferase; ART: Antiretroviral Treatment; AST: Aspartate amino Transferase; BMI: Body Mass Index; CVD: Cardiovascular Disease; GGT: Gamma Glutamyl Transferase; HBcAb: Hepatitis B core antibody; DAA: Direct Acting Antiviral; DM: Diabetes mellitus; Hepatitis B core Antibodies; HBsAb: Hepatitis B surface Antibodies; HBsAg: Hepatitis B surface Antigen; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; IQR: Interquartile Range; LS: Liver Stiffness; SD: Standard Deviation; STI: Sexually Transmitted Infection; SVR12: Sustained Viral Response 12 months; VL: Viral Load. **Clarifications:** [1] Student's t test was used to determine differences between the HIV/HCV and HIV groups. [2] Differences between the HIV/HCV and HIV groups according to the chi-square test or Fisher's exact test. [3] Differences between the HIV/HCV and HIV groups according to the Mann—Whitney U test.

Multivariate models and PS showed that previous exposure to HCV was not associated with the onset of any clinical events studied **(Figure 1).**

Variable	OR	(95%CI)	P
Hypertension	0.92	(0.42−2.04)	0.841
DM	1.48	(0.45−4.84)	0.515
Dyslipidemia	1.27	(0.67−2.42)	0.459
CVD	2.11	(0.85−5.25)	0.106
Kidney disease	1.74	(0.49−6.16)	0.388
Hepatic disease	0.52	(0.02−15.4)	0.706
Non-AIDS cancer	1.60	(0.53−4.84)	0.407
Death	0.34	(0.06−1.77)	0.199

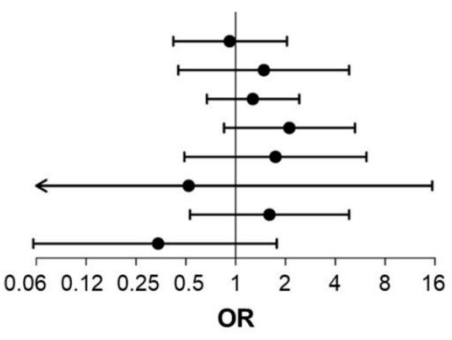

Figure 1. PS analysis results for the risk of comorbidities development and mortality: HIV vs. HIV/HCV cohorts. Abbreviations. AIDS: Acquired Immunodeficiency Syndrome; CI: Confidence Interval; CVD: Cardiovascular Disease; DM: Diabetes Mellitus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; OR: Odds Ratio; PS: Propensity Score. **Results interpretation**. OR < 1 represents a higher risk for the clinical event development in HIV/HCV-coinfected patients (lower risk for HIV-monoinfected patients); OR > 1 represents a lower risk for the clinical event development in HIV/HCV-coinfected patients (higher risk for HIV-monoinfected patients); 95% CI including 1 indicate no statistically significant association between group and clinical event onset (p-value > 0.05).

Furthermore, the survival analysis did not find significant differences between HIV/HCV-coinfected and HIV-infected for survival (comorbidities development and death) according to the log-rank test (p = 0.402) (**Figure 2).**

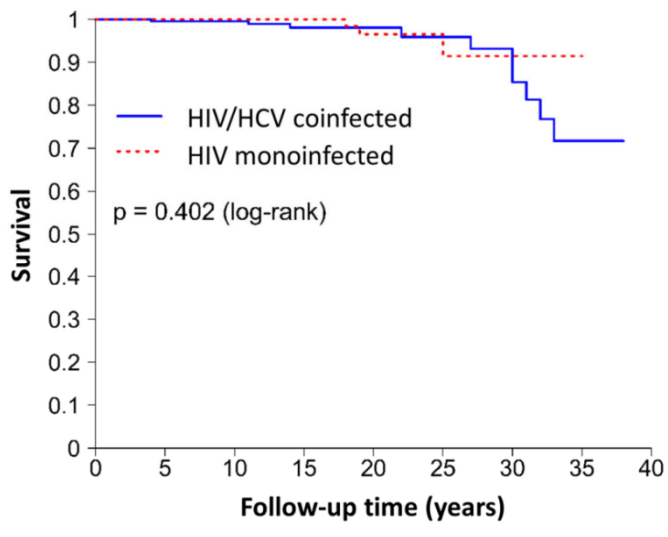

Figure 2. Kaplan-Meier survival curves showing the probability of comorbidities development and mortality: HIV/HCV vs. HIV cohorts. **Abbreviations**. HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus.

IV. Conclusions

- Successful HCV elimination using DAAs improved the outlook regarding comorbidities and survival across HIV/HCV-coinfected cohort.
- In HIV/HCV-coinfected patients, the eradication of HCV could enhance the effectiveness of immune recovery, which follows the control of HIV replication.
- These findings provide an optimistic perspective for those living with HIV/HCV coinfection and underscore the importance of continuing efforts toward early HCV detection and DAA treatment initiation.