The Impact of Achieving Sustained Viral Response with Direct Antiviral Agents in HCV/HIV Co-infected Patients

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ABSTRACT **Background:** Co-infection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) affects approximately 2.2 million people globally and is associated with accelerated liver disease progression, increased morbidity, and reduced quality of life (QoL). While direct-acting antivirals (DAAs) have revolutionized HCV treatment with high cure rates, evidence of their long-term impact on liver-related QoL and associated metabolic or immunologic shifts in HIV/HCV co-infected populations remains limited.

Objectives: To evaluate the effect of achieving sustained virologic response (SVR) with DAAs on long-term QoL in HIV/HCV co-infected patients and to examine associated changes in CD4 count, kidney function, and glucose levels.

Methods: This retrospective observational study was conducted at the Rambam Health Care Campus between 2015 and 2019. We collected demographic, clinical, and laboratory data from all patients with HIV/HCV co-infection. QoL was evaluated for at least 6 months after the end of treatment. Metabolic variables were collected before and after treatment to test the effects of treatment.

Results: All 70 patients in the cohort achieved SVR. Successful treatment with DAAs resulted in a significant decrease in liver enzymes and globulin levels, and a substantial increase in CD4. A significant improvement in QoL after treatment was noticed in both sexes, regardless of liver fibrosis stage. FIB-4 calculations 6 months and 1 year after the end of therapy showed improved fibrosis levels after SVR.

Conclusions: The use of DAAs in HCV/HIV co-infected patients has improved the long-term QoL, metabolic factors, and fibrosis stage.

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KEY WORDS: hepatitis C virus (HCV), human immunodeficiency virus (HIV), quality of life, sustained virologic response (SVR), direct-acting antivirals (DAAs), co-infection, hepatic fibrosis

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) co-infection has significant health implications for millions of patients. It raises a major clinical challenge for healthcare providers. In a meta-analysis of over 780 studies evaluating populations with HIV worldwide, the overall prevalence of HCV co-infection was estimated to be approximately 6%, with an estimated 2.2 million cases of co-infection worldwide [1,2]. The consequences of HCV/HIV co-infection are significant and include accelerated liver disease progression and diminished life expectancy after hepatic decompensation [3-6].

In addition to the hepatic morbidities caused by HCV infection, the virus is closely associated with many extrahepatic and metabolic complications, including diabetes mellitus, renal diseases, heart disease, and dysregulated lipid metabolism [7].

Since the introduction of direct-acting antiviral agents (DAAs), significant progress has been made in the treatment of HCV infection. Clinical studies have shown sustained virologic response (SVR) rates above 90% with a good safety profile [8]. High SVR rates in the HCV\HIV co-infected population have been associated with a reduction of morbidity and mortality, reduced incidence of hepatocellular carcinoma, and improvement or delayed progression of fibrosis [9-11]. HCV treatment with DAAs may also benefit the extrahepatic manifestations of HCV infection. Hemoglobin A1C (HbA1C) levels decreased during DAA treatment [12]. However, Sofosbuvir/Simeprevir treatment was associated with a slightly increased risk of chronic kidney disease progression [13].

The effect of DAA treatment on the quality of life (QoL) in HCV mono-infection has been extensively stud-

ied. Mira and colleagues [12] found that viral eradication with DAAs improved QoL, regardless of fibrosis stage, in HCV mono-infected patients. Our previous study concluded that treatment with DAAs significantly improved long-term QoL, irrespective of sex or fibrosis stage [14].

The presence of HIV co-infection has been linked with poor QoL in patients with chronic HCV infection compared with mono-infection [15]. Several studies found that successful treatment with DAAs in the co-infection population was associated with varying degrees of improvement in health-related QoL [16,17]. Health-related QoL in these studies was assessed by asking patients general QoL questions with no specification of liver disease or its complications.

In this study we highlight the relationship between DAAs-associated SVR and long-term liver-disease-related QoL in patients with HCV/HIV co-infection. We also examined the link between QoL changes following DAAs treatment and multiple metabolic variables and laboratory parameters

PATIENTS AND METHODS

The study was conducted at Rambam Health Care Campus between January 2015 and August 2019. The hospital institutional review board approved the study in accordance with the Helsinki Declaration, reference number RMB01-19. Due to the study's retrospective nature, informed consent was waived. All patients with HIV and HCV co-infection were included in the study. Patients with other liver diseases were excluded. Background data, including demographic, clinical, and laboratory data, were collected from the digital profiles before and 6 months after treatment. The Model for End-stage Liver Disease (MELD) score and glomerular filtration rate were calculated for each patient. QoL was estimated by translating and testing the Liver Disease Symptom Index II (LDSI 2.0) score, which includes nine parameters: itch, joint pain, right upper quadrant pain, sleepiness during the day, family worry, decreased appetite, depression, fear of complications, and jaundice. The severity of each symptom may vary from 0 to 5. An HCV-validated QoL questionnaire was chosen over the validated one for multiple reasons. First, chronic HIV is a lifelong infection and will not be eliminated by treatment. Second, HIV treatment can cause chronic diseases and side effects by itself, which obviously will not be improved by HCV treatment. Last, since HCV will be eliminated after treatment, the impact on QoL should be estimated regarding HCV-related symptoms.

The study staff extracted the data for each patient from the records to verify symptom severity before and after treatment. The primary endpoint was the long-term effect of DAAs on LDSI parameters. The secondary endpoints were the effects of DAAs on LDSI 2.0 scores in both sexes and across each fibrosis stage.

STATISTICAL ANALYSIS

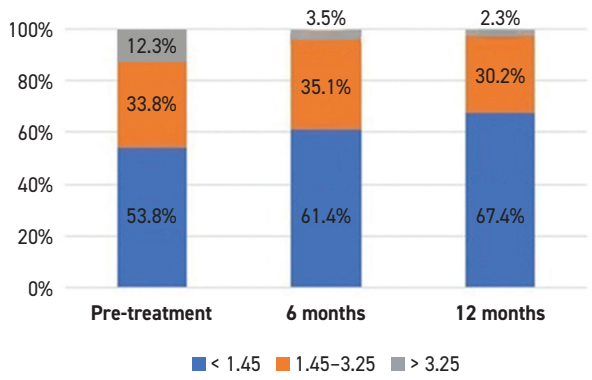
Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). The mean, median, and standard deviations were calculated for continuous variables. The *t*-test and Mann-Whitney tests were used to examine differences in continuous variables between the investigation groups. The chi-square test or Fisher's exact test was used to investigate the categorical parameters. All statistical tests were two-sided. A P-value < 0.05 was considered statistically significant. Data analyses were conducted after data collection ended.

RESULTS

Our study included 70 patients with HCV\HIV co-infection. Demographic data and pre-treatment lab results are shown in Table 1. The most common HCV genotype was 3 (43%), followed by 1B (39%), 1A (14%), 2 (3%), and 4 (1%). Nearly 30% of patients had advanced fibrosis stage (F3/F4) according to the METAVIR score [Table 2]. The list of treatments was also addressed in Table 2.

Fibrosis levels were assessed at three time points (before treatment, 6 months, and 12 months after treatment

Figure 1. The distribution of patients by fibrosis-4 level at three time points



completion) using the FIB-4 formula, which provides a non-invasive method to estimate the fibrosis stage. The distribution of patients by fibrosis level at these three points is shown in Figure 1. The percentage of patients with a low FIB-4 score (< 1.45) increased from 53.8% to 61.4% at 6 months after treatment, indicating that more patients were at low risk of advanced fibrosis. Furthermore, FIB-4 calculations continued to improve even 1 year after treatment, reaching 67.4% of patients with low fibrosis, indicating sustained therapy effects on fibrosis levels.

Lab tests before and after treatment are summarized in Table 3. As expected, hepatocellular liver enzymes were elevated to abnormal levels before treatment and decreased to typical values after achieving SVR. Blood globulins were also reduced. CD4 cells and white blood cells increased slightly but significantly. It is worth noting that other metabolic parameters that may be affected by

Table 1. Demographics and characteristics at baseline

Parameter	Mean ± standard deviation or number (%)
Age (years)	45.2 ± 7.6
Sex (male)	47 (67%)
Body mass index (kg/m^2)	25.7 ± 4.5
Country of birth	
Former Soviet Union	58 (83%)
Israel	4 (6%)
India / Pakistan	4 (6%)
Other	4 (6%)
HBV	2 (3%)
Diabetes mellitus	1 (1%)
Alcohol abuse	1 (1%)
Active / former smoker	28 (40%)
Albumin (g/dl)	4.1 ± 0.44
Bilirubin (mg/dl)	0.67 ± 0.39
INR	1.00 ± 0.07
Platelets (10^3/mcL)	207.8 ± 68.8
Hemoglobin (g/L)	14.5 ± 1.8
WBC (10^3/mcL)	6.4 ± 1.8
Creatinine (mg/dl)	1.03 ± 1.27
ALKP (U/L)	89.2 ± 37.3
ALT (U/L)	110.3 ± 117.2
AST (U/L)	76.7 ± 67.8
GFR (ml/min)	114.4 ± 36.1

ALKP = alkaline phosphatase, ALT = alanine transaminase, AST = aspartate transaminase, GFR = glomerular filtration rate, HBV = hepatitis B virus, INR = international normalized ratio, WBC = white blood cells

Table 2. Liver parameters at baseline and types of treatment

Parameter	Number (%)
HCV genotype	
1A	10 (14%)
1B	27 (39%)
2	2 (3%)
3	30 (43%)
4	1 (1%)
Fibrosis stage	
F0+F1	28 (41%)
F2	20 (29%)
F3	7 (10%)
F4	13 (19%)
Ascites	0
Esophageal varices	1 (1%)
Hepatic encephalopathy	0

Type of HVC treatment	Number (%)
Viekirax (ombitasvir/paritaprevir/ ritonavir) and *Exviera* (dasabuvir)	8 (11%)
Ledipasvir / Sofosbuvir (Harvoni)	2 (3%)
Grazoprevir (Zepatier)	5 (7%)
Sofosbuvir/Velpatasvir (Epclusa)	30 (43%)
Glecaprevir/Pibrentasvir (Maviret)	20 (29%)
Daclatasvir	9 (13%)
Sofosbuvir	9 (13%)
Ribavirin	5 (7%)
Type of HIV treatment	
Emtricitabine / Tenofovir (Truvada)	30 (42%)
Raltegravir (Isentress)	21 (30%)
Dolutegravir (Tivicay)	15 (21%)
Gendevra (Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir)	10 (14%)
Abacavir / Lamivudine (Kivexa)	10 (14%)
Abacavir / Dolutegravir / Lamivudine (Triumeq)	15 (21%)
Darunavir / Cobicistat (Rezolsta)	5 (7%)
Lopinavir / Ritonavir (Kaletra)	1 (1%)
Rilpivirine (Edurant)	1 (1%)
Darunavir (Prezista)	1 (1%)
Ritonavir (Norvir) NORVIR	1 (1%)
Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)	1 (1%)

HCV = hepatitis C virus, HIV = human immunodeficiency virus

HCV infection, such as blood creatinine, glucose, thyroid hormones, and urine protein levels, were normal before and after treatment, as shown in Table 3. The changes in multiple parameters (creatinine clearance, creatinine blood levels, glucose blood levels, CD4 cells, neutrophils, and lymphocytes concentrations) before and after treatment, as measured by lab tests, are depicted in Table 3.

Regarding QoL, we found that three parameters impaired QoL before treatment, including depression, worry about family situations, and fear of HCV complications. All three parameters improved significantly after treatment. The mean value of the nine questions, which may be used as a summary of QoL, was 0.8377 ± 0.5 before treatment (which could be understood as presenting with eight of the nine checked symptoms once a week), median 0.88. After treatment it was reduced to a mean of 0.12 ± 0.17, which could be understood as suffering from one out of the nine checked symptoms once a week, with a median of 0.11 (0–2.78), $P < 0.0001$.

When subdividing the cohort by sex, males reported better QoL than females before treatment. Following successful treatment, QoL improved significantly in both sexes, with comparable post-treatment scores.

No significant correlation was found between patient age and QoL before or after treatment. Still, significant correlations were observed between QoL and changes in white blood cell count, globulin levels, and thyroid-stimulating hormone (TSH) levels before and after treatment [Table 3]. All the fibrosis groups had similar post-treatment QoL.

Table 3. Laboratory parameters pre- and post-treatment

	Pre-treatment, median [range]	Post-treatment, median [range]	*P*-value
ALT (U/L)	110 [38–132]	25 [17–31]	< 0.0001
AST (U/L)	77 [36–104]	27 [22.5–35]	< 0.0001
ALKP (U/L)	76 [63–105]	76 (58–94]	0.47
Bilirubin (mg/dl)	0.63 [0.39–0.78]	0.45 [0.32–0.78]	0.078
WBC (10^3/mcL)	6.4 [5.1–7.6]	6.6 [5.2–8.8]	0.005
Hemoglobin (g/l)	14.6 [13.6–15.7]	14.8 [13.5–15.9]	0.78
Platelets (10^3/mcL)	196 [157–236]	201 [169–241]	0.75
Creatinine (mg/dl)	0.82 [0.77–0.99]	0.85 [0.78–0.94]	0.96
GFR (ml/min)	103.7 [89.8–132.5]	110.0 [91.1–139.8]	0.29
BMI (kg/m^2)	24.5 [22.4–28.2]	25.3 [22.8–28.0]	0.26
HbA1c (n=7)	5.4 [5.0–5.7]	5.1 [4.8–5.6]	0.062
Globulins (g/dL)	3.5 [3.0–4.1]	3.3 [2.9–3.7]	0.001
CD4 (cell/mm)	566 [302–714]	582 [375–892]	0.041
Glucose (mg/dL)	87 [80–93]	87 [79–93]	0.94
Neutrophils (10^3/mcL)	3.25 [2.6–4.5]	3.5 [2.4–5.0]	0.45
Lymphocytes (10^3/mcL)	2.0 [1.5–2.5]	2.0 [1.5–2.7]	0.12
PROTEIN-URINE (mg)	0 [0–20]	0 [0–10]	0.47
TSH (mU/L)	1.7 [1.5–2.5]	1.9 [1.0–2.15]	0.17

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase, GFR = glomerular filtration rate, BMI = body mass index, HbA1c = hemoglobin A1C, HCV = hepatitis C virus, TSH = thyroid-stimulating hormone, WBC = white blood cells

DISCUSSION

The past few years have witnessed significant progress in the treatment of chronic HCV infection. Since the advent of treatment with DAAs, higher SVR rates have been achieved with a more favorable adverse effects profile than with previous treatment regimens containing pegylated-interferon and ribavirin [18,19]. The previous regimen also had adverse effects on patient QoL during treatment. In our previous study, we showed that DAA treatment was associated with improvement in the long-term QoL in patients with HCV mono-infection [14]. In this study, we tested the effects of DAAs-associated SVR on long-term liver-disease-related QoL in the HCV\HIV-co-infected population, along with the demographic and metabolic variables associated with these effects.

In this study, we examined 70 patients with HCV/HIV co-infection and evaluated their QoL at least 6 months after treatment completion. All 70 patients reached SVR. Three parameters–depression, worry about family situation, and fear of HCV complications–were shown to have adverse effects on QoL before treatment. All three parameters, as well as the general QoL, improved significantly at least 6 months after treatment completion. Even though females reported more impaired QoL before the treatment, both The QoL of both sexes improved significantly after treatment, and both sexes reached similar levels of long-term QoL.

We found that QoL improved in the co-infected population regardless of fibrosis stage before treatment, indicating the high efficacy of DAAs treatment in different liver disease stages. QoL was not associated with the patient's age before or after treatment.

We examined the effects of DAA treatment on multiple metabolic variables, as measured by laboratory tests, in the co-infection population before and after treatment. As expected, we observed a reduction in liv-

er enzymes and total globulin levels to normal values. Given the importance of T cell CD4+ levels in HIV infection, multiple studies have investigated the effects of DAA treatment on this cell population, showing no difference in CD4+ cell counts or the CD4/CD8 ratio after treatment [20]. In our study, we found a small but statistically significant increase in total CD4+ cell counts and total white blood cells. Whether this slight change in CD4+ and total white blood cell counts has immunologic or clinical significance remains to be determined in future studies.

Because of the multiple extrahepatic manifestations of HCV infection, such as chronic kidney disease, diabetes mellitus, and thyroiditis, we measured TSH, glucose, creatinine, and other metabolic variables (as shown in Table 3), and they all were within normal limits before and after treatment in our cohort of patients. FIB-4 calculations further indicated a reduction in estimated liver scarring following treatment, with notable improvement observed one year post-treatment. It should be noted that in this cohort, in which FIB-4 was calculated, part of the observed improvement may reflect biochemical normalization rather than definite histologic regression.

The observed improvements in quality of life among HCV/HIV patients offer deeper insights into the complex interplay between liver health, HIV management, and overall well-being. Given that liver disease is a major contributor to morbidity and mortality in HIV-positive individuals, these findings underscore the critical role of liver health in shaping patient outcomes. Effective treatment of HCV not only reduces liver-related complications but may also enhance HIV management by improving immune function and reducing systemic inflammation. Our study has several limitations.

Our study provides valuable insight into the long-term impact of DAA treatment in HIV/HCV co-infected individuals, particularly regarding liver-specific quality of life, which has been underreported in the literature. The use of a validated liver symptom index (LDSI 2.0) enhances the specificity of patient-reported outcomes. The inclusion of laboratory-based fibrosis assessment (FIB-4), immunologic markers (CD4), and metabolic indicators further strengthens the multidimensional nature of our analysis.

The study has limitations, including its retrospective design, lack of a control group, single-center setting, and reliance on patient recall for pre-treatment QoL, which may introduce recall bias. The relatively small, demographically narrow cohort (predominantly of Eastern European origin) may also limit generalizability.

CONCLUSIONS

DAAs treatment in HCV/HIV co-infected patients has shown promising results, significantly improving the long-term quality of life, as well as metabolic factors and fibrosis stage. These positive outcomes provide hope for the future of HCV/HIV co-infected patients.

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The highest exercise of charity is charity towards the uncharitable.

Joseph Stevens Buckminster (1784–1812), influential Unitarian preacher in Boston, Massachusetts, USA, and editor

Capsule

Tumor-derived branched-chain α-keto acids activate Notch signaling in tumor-associated macrophages to limit immunity

Ma et al. uncovered a novel mechanism by which tumors suppress anti-tumor immunity through metabolic signaling. The investigators found that tumor cells release branched-chain α-keto acids, metabolites derived from branched-chain amino acid metabolism, into the tumor microenvironment. These metabolites activated Notch signaling in tumor-associated macrophages, driving the development of an immunosuppressive macrophage phenotype. As a result, T-cell activation and anti-tumor immune responses were diminished, allowing tumors to evade immune surveillance and continue growing. The study establishes a direct link between tumor metabolism and immune suppression and suggests that targeting branched-chain amino acid metabolism or Notch signaling may improve the effectiveness of cancer immunotherapy.

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Eitan Israeli

Capsule

A glycan-based adjuvant expands the breadth and duration of protection of mRNA-based vaccines

Jena and colleagues developed a novel glycan-based adjuvant designed to enhance the efficacy of mRNA vaccines. Although mRNA vaccines have revolutionized infectious disease prevention, concerns remain regarding the breadth and durability of immune protection, particularly against rapidly evolving pathogens. The investigators demonstrated that incorporating a glycan-derived adjuvant into mRNA vaccine formulations significantly enhanced both humoral and cellular immune responses. Vaccinated animals developed broader neutralizing antibody responses against multiple viral variants and maintained protective immunity for longer periods compared with standard mRNA vaccine formulations. The adjuvant also promoted stronger germinal center reactions and improved memory B-cell and T-cell responses. Mechanistically, the glycan-based adjuvant enhanced innate immune activation while avoiding excessive inflammation. The findings suggest a promising strategy to improve next-generation mRNA vaccines against emerging infectious diseases and rapidly mutating viruses.

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