

Association between Direct-Acting Agents Adherence and Health-Related Quality of Life of Patients with Hepatitis C

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ABSTRACT: This observational study included all patients undergoing HCV treatment with direct-acting antiviral (DAA)-based therapy between May 2020 and September 2023 at the Dolj County Hospital, Romania. The aim was to investigate adherence to DAAs among HCV patients and the effect of this treatment on their health-related quality of life (HRQoL). Chronic HCV-infected patients were prospectively evaluated at baseline (T0), before the beginning of treatment, and 12 weeks after completing DAAs treatment (T1). The HCV-AD10 questionnaire was used to measure DAAs adherence, and HRQoL was assessed with the 15D instrument. The 15D questionnaire was administered at two time points: T0 and T1, during which the Sustained Virologic Response (SVR) was also measured. The primary outcome was DAAs adherence, with secondary outcomes including quality of life (QoL), and sustained virologic response (SVR). DAAs based therapy was initiated for 368 patients, all of whom were health insured. HRQoL and psychological state of HCV patients clinically improved. The DAAs adherence was very good (mean±SD, 91.51±8.34), being influenced by age (younger patients were much adherent, rho=-0.112, p-value=0.031) and the severity of the disease (patients with more severe hepatitis were less adherent, rho=-0.167, p-value=0.001). DAAs had a significant effect on improving HRQoL of HCV patients, but did not influence medication adherence.

KEYWORDS: Adherence, hepatitis C, quality of life, protease inhibitors, DAAs.

Introduction

Hepatitis C virus infection (HCV) is still a global health problem, even though in Europe its incidence is reducing.

HCV prevalence varies globally, with certain regions experiencing higher rates due to factors such as unsafe injection practices, inadequate healthcare infrastructure, and limited access to preventative measures [1,2].

Efforts to reduce HCV incidence have included enhancing screening testing strategies, implementing harm reduction programs among high-risk populations, and development of antiviral treatments that can effectively cure the infection [3,4].

Direct-acting antivirals (DAAs) have revolutionized the treatment landscape for HCV [5].

Unlike older regimens that often-involved interferon and had significant side effects, DAAs are a class of highly effective medications specifically designed to target different stages of the HCV replication cycle [6].

These drugs work by inhibiting viral enzymes critical for replication, effectively suppressing viral activity.

DAAs have demonstrated remarkable success in achieving high cure rates, often exceeding 95% [7].

Their effectiveness spans various HCV genotypes, making them a versatile treatment option [8].

The introduction of DAAs has not only increased the likelihood of curing HCV but also shortened treatment duration and minimized adverse effects.

This innovation has significantly transformed HCV management, offering new hope for patients and contributing to global efforts to control and ultimately eliminate HCV as a public health concern [9].

Achieving a sustained virologic response (SVR), which indicates a cure, depends on patients consistently following their prescribed DAAs regimen.

Unlike interferon, DAAs have shorter durations and fewer side effects, making them more tolerable.

However, even with these advantages, maintaining adherence remains important [10].

Skipping doses or not completing the full course can lead to incomplete viral suppression and potential treatment failure.

Healthcare providers play a pivotal role in educating patients about the significance of adherence, addressing any concerns they might have, and offering strategies to overcome the barriers.

Patient support programs, reminders, and easy-to-understand information may contribute to enhancing adherence rates [11-13].

The aim of our study was to evaluate DAAs adherence, assess changes in HRQoL after DAAs treatment, and identify factors that may influence DAAs adherence.

Material and Methods

All patients were >18 years old, with a minimum 6-month history of HCV infection, with detectable HCV-RNA, regardless of value, either HCV treatment-naïve or experienced-previously treated with interferon (INF) or pegylated interferon, with or without ribavirin (RBV), who had at least one visit to the clinic for the assessment of eligibility for treatment, during the mentioned study period.

Patients were thoroughly evaluated for disease status.

Patients were included regardless of fibrosis stage, including patients with compensated or decompensated cirrhosis.

The presence or absence of cirrhosis was established either by imaging methods-Fibroscan or by serological methods-FibroMax.

After obtaining clinical, laboratory and virological data, treatment regimens were selected by gastroenterologists following the National Health Insurance House/Ministry of Health (no. 100 bis/1.II.2020-2023) guidelines and included (1) ledispavir (LDV) and sofosbuvir (SOF) (2) ombitasvir (OBV) and paritaprevir/ritonavir (PTV/R) and dasabuvir (DSV), (3) SOF and velpatasvir (VEL), or (4) glecaprevir (GLE) and pibrentasvir (PIB).

The prescribing doctors chose the treatment regimen based on the clinical experience and the patient's characteristics.

We did not exclude patients who had HBV co-infection, they received concomitant treatment for HBV infection during DAAs treatment plus 12 weeks after completion of HCV therapy.

Patients with HBV infection who met the criteria for treatment continued it according to the protocol.

We excluded patients with cognitive impairments preventing them from completing the questionnaires.

We also excluded patients with HIV co-infection or recently diagnosed with malignant pathologies.

Patients had HCV viral load testing every 4 weeks during treatment and 12 weeks after treatment completion to assess for SVR.

Patients were trained to improve their knowledge of both the disease and DAAs treatment to increase adherence to HCV therapy.

Patients located in rural or remote areas benefited from telemedicine to facilitate collaboration with the medical team.

Written informed consent was obtained from all participants.

Health-related quality of life (HRQoL) was assessed using the 15D instrument, which is a validated generic questionnaire exploring 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity.

A 15D score, representing the overall HRQoL on a 0-1 scale (0=being dead, 1=full health), was calculated.

The translated version of 15D for the Romanian population was applied [14].

An important clinical change in HRQoL was considered to be a minimum important difference of 0.015 in the 15D score from the basis [15], with the following five categories: "much better" (difference greater than 0.035), "slightly better" (difference between 0.015 and 0.035), "much the same (no change)" (difference between -0.015 and 0.015), "slightly worse" (difference between -0.035 and -0.015) and "much worse" (difference less than -0.035).

Statistical analysis was performed using Python.

A descriptive analysis was conducted for each of the study variables.

Continuous data were analyzed using mean, standard deviation (SD), median and interquartile range (IQR).

Qualitative variables were assessed using numbers and percentages.

To visualize the distribution and difference before and after DAAs treatment, violin plots were generated using Seaborn's violin plots function.

Seaborn Heatmap was used to quickly visualize the correlations between the levels of DAAs adherence and changes in QoL (colors range from bright green for a strong positive correlation to bright blue for a strong negative correlation).

A two-sided p-value less than 0.05 was considered statistically significant.

Results

The study included 368 subjects, with predominant female representation (71.5%) and a mean age of 60.8 years, ranging from 22 to 86.

The majority of the participants had a low level of education, as 92.4% had graduated from middle and high school.

Table 1 shows the baseline characteristics of the sample.

Table 1. Characteristics of the patients.

Characteristics	Total (n=368)
Age, years Mean±SD Median (IQR)	60.84±11.6 62 (53-69)
Sex, male Number (%)	105 (28.5%)
Marital status Married Unmarried Divorced Widow	272 (73.9%) 13 (3.5%) 17 (4.6%) 66 (17.9%)
Employment status, number (%) Employed Unemployed Retired	110 (29.9%) 30 (8.2%) 228 (62%)
Education level Middle School High School Faculty	168 (45.7%) 172 (46.7%) 28 (7.6%)
Environmental Urban Rural	150 (40.8%) 218 (59.2%)
Incomes No income <2000 RON 2000-4000 RON 4000-6000 RON >6000 RON	7 (1.9%) 284 (77.2%) 73 (19.8%) 3 (0.8%) 1 (0.3%)
Fibrosis stage, n (%) F0 F0-F1 F1 F1-F2 F2 F2-F3 F3 F3-F4 F4	77 (20.9%) 14 (3.8%) 23 (6.3%) 46 (12.5%) 41 (11.1%) 1 (0.3%) 54 (14.7%) 8 (2.2%) 102 (27.7%)
HCV duration, years Mean±SD Median (IQR)	4.05±6.38 1 (0.3-5.7)
Treatment duration, n (%) 8 weeks 12 weeks 24 weeks	239 (64.9%) 120 (32.6%) 9 (2.4%)
Treatment (1) ledispavir and sofosbuvir (2) ombitasvir and paritaprevir/ritonavir and dasabuvir (3) sofosbuvir and velpatasvir (4) glecaprevir and pibrentasvir	105 (28.5%) 142 (38.6%) 15 (4.1%) 106 (28.8%)
SVR, n (%)	363 (9.6%)
Comorbidities Arterial hypertension Diabetes mellitus Cirrosis	169 (46%) 54 (15%) 103 (28%)

HRQoL was significantly improved after treatment compared to before the DAAs treatment (p -value <0.0001), as shown in Figure 1.

The HCV patients reported much better mental function and vitality, with reduced depression and distress after DAAs treatment.

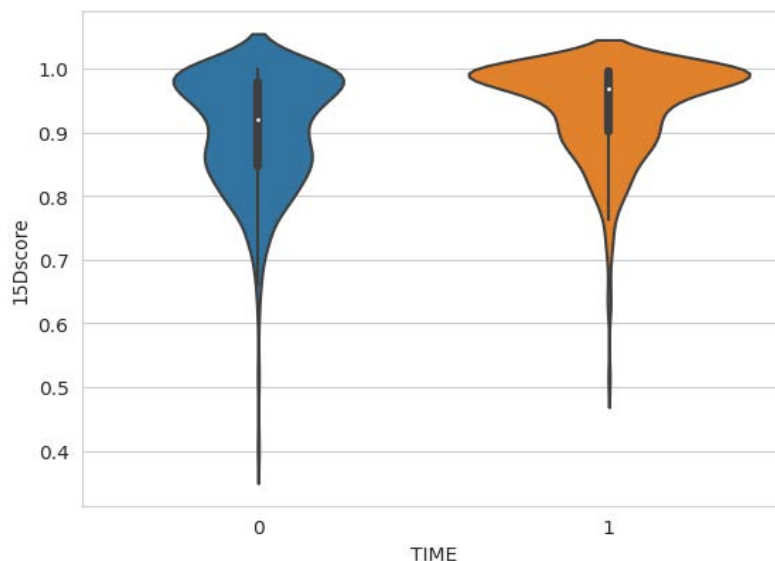


Figure 1. Health-related quality of life before direct-acting antiviral treatment (Time=0) and at 12 weeks after the end of the treatment (Time=1).

According to the responses to the HRQoL related questions, the patients did not declare

significant changes in hearing, eating, speech and excretion, as in Table 2.

Table 2. Comparison of the 15D dimensions between baseline and after the DAAs treatment.

Dimension	Mean difference	Statistical significance	Clinical significance
Mobility	0.0235±0.18	0.015	Slightly better
Vision	0.0334±0.19	0.001	Slightly better
Hearing	-0.0018±0.1	0.532	No change
Breathing	0.0605±0.2	<0.0001	Slightly better
Sleeping	0.0583±0.18	<0.0001	Slightly better
Eating	0.0037±0.06	0.190	No change
Speech	0.0039±0.08	0.437	No change
Excretion	0.0119±0.15	0.113	No change
Usual activities	0.0321±0.19	<0.0001	Slightly better
Mental function	0.0402±0.2	<0.0001	Much better
Discomfort and symptoms	0.0292±0.16	<0.0001	Slightly better
Depression	0.0709±0.18	<0.0001	Much better
Distress	0.079±0.21	<0.0001	Much better
Vitality	0.0863±0.19	<0.0001	Much better
Sexual activity	0.0292±0.17	0.002	Slightly better
15D score	0.0365±0.08	<0.0001	Much better

We observed a significant enhancement in HRQoL for females compared to males (changes in 15D score, mean±SD, female vs. male, 0.0413±0.08 vs. 0.0242±0.09, p -value=0.021).

There were no significant differences regarding mean changes in the HRQoL scores between patients with a treatment duration of 8 weeks vs. 12/24 weeks (p -value=0.169).

The DAAs adherence was very good, with an average of 91.51±8.34, and a median (IQR) of 92.5 (87.8-100).

Out of the 369 HCV patients, a percentage of 9.8% were non-adherent (adherence $<80\%$).

There were no significant differences regarding DAAs adherence between males and females (mean±SD, female vs. male, 91.49±8.41 vs. 91.57±8.21, p -value=0.021 or between patients with treatment duration of 8 weeks vs. 12/24 weeks (p -value=0.056).

Although we observed a higher DAAs adherence for patients with a treatment duration of 8 weeks (mean±SD, 92.21±7.85) compared to

12/24 weeks (mean±SD, 90.23±9.08), the difference was not statistically significant.

The medication adherence was influenced by age (younger patients were much more adherent, rho=-0.112, p-value=0.031) and the severity of

the disease (patients with more severe hepatitis were less adherent, rho=-0.167, p-value=0.001).

As expected, adherent patients showed higher enhancements in dimensions of HRQoL, as shown in Table 3.

Table 3. HRQoL changes reported in adherent and nonadherent HCV patients.

Dimension	Adherence ≥80% (n=332)	Adherence <80% (n=36)	p-value
Mobility	0.0505±0.19	0.0206±0.18	0.191
Vision	-0.0043±0.15	0.0374±0.19	0.305
Hearing	-0.0139±0.08	-0.0005±0.1	0.331
Breathing	0.084±0.23	0.0579±0.19	0.376
Sleeping	0.0703±0.26	0.0570±0.17	0.663
Eating	0.0098±0.06	0.0031±0.06	0.432
Speech	0.0158±0.09	0.0026±0.07	0.467
Excretion	0.0236±0.2	0.0106±0.14	0.929
Usual activities	0.0061±0.27	0.0349±0.18	0.734
Mental function	0.0619±0.21	0.0379±0.2	0.463
Discomfort and symptoms	0.0163±0.14	0.0306±0.16	0.572
Depression	0.0642±0.17	0.1322±0.23	0.023
Distress	0.1053±0.27	0.0761±0.2	0.421
Vitality	0.1507±0.24	0.0793±0.18	0.026
Sexual activity	0.0694±0.24	0.0249±0.15	0.231
15D score	0.0515±0.11	0.0348±0.08	0.25

The magnitude of these increments was statistically significant for depression (p-value=0.023) and vitality (p-value=0.026).

No negative correlations were found between adherence and the changes in dimensions of HRQoL.

However, high adherence was positively correlated with enhancements in vision (rho=0.109, p-value=0.037), hearing (rho=0.129, p-value=0.013), and usual activities (rho=0.103, p-value=0.049).

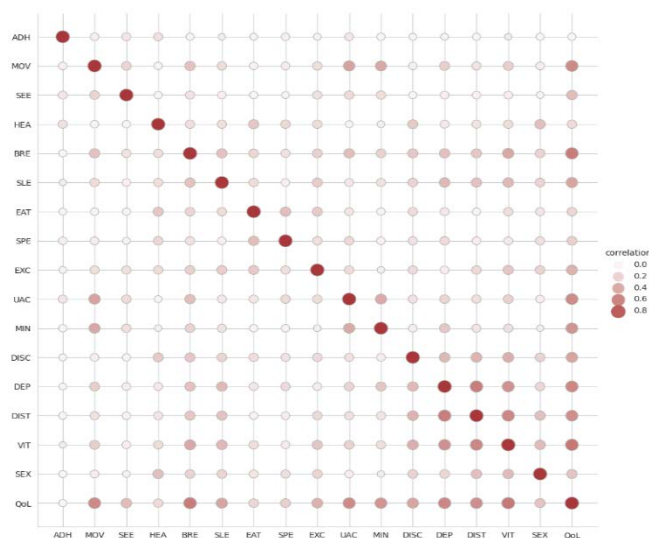


Figure 2. Heatmap of adherence and enhancement of HRQoL dimensions.

Discussion

HCV infections not only pose a substantial threat to liver health but also have wide-range implications for the overall quality of life (QoL) of affected individuals.

The introduction of DAAs has significantly transformed this landscape.

These highly effective medications not only cure HCV but also have a positive impact on patients' QoL.

Traditional HCV treatments often brought about harsh side effects that could severely diminish patients' physical and emotional well-being.

In contrast, DAAs, with their shorter treatment durations and reduced side effects, have made the journey toward viral clearance much more manageable and less disruptive to daily life.

By swiftly and effectively suppressing viral activity, DAAs alleviate the burdens of fatigue, pain, and other symptoms associated with HCV.

This improved health status translates to better emotional well-being, increased energy levels, and improved social functioning, all of which contribute to an enhanced overall QoL.

As such the availability of DAAs not only marks a medical breakthrough in HCV treatment but also signifies a major enhancement in the lives of those grappling with this condition.

As the burden of HCV infection is high, patients infected with HCV may experience a poorer quality of life [16].

Therefore, it is important to understand the effects of DAAs treatment on HCV patients' well-being and HRQoL.

Our findings indicated that HRQoL significantly improved after treatment when compared to the previous stage, with notable improvements in mental function, vitality, and reductions in depression and distress.

Supporting our findings, He et al. conducted a meta-analysis of 8 studies and demonstrated that DAAs therapy clinically improves QoL in HCV patients [17].

These collective findings underscore the positive impact of DAAs treatment on the well-being of HCV patients and highlight the importance of addressing factors that may influence HRQoL in this population.

Moreover, our study also identified significant associations between enhancing HRQoL and several factors, including age (older patients), sex (female), employment (retired), poor family income, low education and long length of disease.

Bertino et al. similarly demonstrated that DAAs treatment improves HRQoL and the psychological state of HCV patients [18].

Understanding the positive impact of DAAs treatment on HRQoL is crucial, given the high burden of HCV infection and its implications for patients' well-being.

Further research and attention to these factors can help in tailoring treatment approaches and support interventions to improve the overall quality of life for HCV patients.

Studies conducted in various European countries [19] have indicated that HCV patients experience a clinically meaningful decrement in HRQoL when compared to control groups.

However, our study focused on Romanian patients and demonstrated not only a statistically significant improvement but also a clinically meaningful enhancement in HRQoL after DAAs treatment.

These findings highlight the effectiveness of HCV treatment in alleviating the work impairment associated with the disease and reducing the burden of healthcare costs.

In our study, we also observed a slight improvement in sleep quality 12 weeks after DAAs treatment compared to before treatment.

This aligns with the results obtained by Karimi-Sari et al., who also reported improved sleep quality after HCV treatment using DAAs [20].

Regarding the DAAs adherence, our study revealed optimal adherence rates among patients with HCV, and we did not find any association between adherence and HRQoL.

These results are consistent with the findings of Younossi et al., who similarly did not find HRQoL to be a predictor of adherence to DAAs treatment [21].

Overall, our study contributes to the growing body of evidence supporting the positive impact of DAAs treatment on HRQoL and reinforces the importance of effective HCV management in improving patients' well-being and reducing the burden of the disease on society.

Indeed, this study has some limitations that need to be acknowledged.

Firstly, the study included patients from a single center, which may limit the generalizability of the findings to a broader population.

Multi-center studies involving diverse patient populations would be beneficial to provide more robust and representative results.

Secondly, while close monitoring during treatment and follow-up is valuable for data accuracy, it may introduce a potential source of bias.

The intensive monitoring could affect patients' behaviour, leading to better adherence and response rates, which might not be reflective of real-world conditions.

Lastly, the study's reliance on self-reported data for some aspects, such as HRQoL and medication adherence, might be subject to recall bias and could affect the accuracy of the findings.

Considering these limitations, future research endeavours could address these issues by conducting multi-center randomized controlled trials with longer follow-up periods and utilizing

objective measures for outcomes whenever possible.

These efforts would contribute to a more comprehensive understanding of the effects of DAAs treatment on HCV patients' well-being and HRQoL.

Conclusion

We found that HCV patients who received DAAs had high adherence rates and high SVR rates regardless of the severity of disease.

More, DAAs treatment clinically improves the HRQoL, especially for mental function and vitality, with reduced depression and distress after DAAs treatment.

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Conflict of interests

None to declare.

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