The efficacy of integrated hepatitis C virus treatment in relieving fatigue in people who inject drugs: A randomized controlled trial

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Abstract

Background

Most people who inject drugs (PWIDs) suffer from severe fatigue, and chronic hepatitis C virus (HCV) infection may play a role in this. However, there is scarce evidence about interventions that alleviate fatigue among PWIDs. The present study investigated the effect of integrated HCV treatment on fatigue in this population compared to the effect of standard HCV treatment.

Methods

This multi-center, randomized controlled trial evaluated fatigue as a secondary outcome of integrated HCV treatment (the INTRO-HCV trial). From May 2017 to June 2019, 276 participants in Bergen and Stavanger, Norway, were randomly assigned to receive integrated and standard HCV treatment. Integrated treatment was delivered in eight decentralized outpatient opioid agonist therapy clinics and two community care centers; standard treatment was delivered in specialized infectious disease outpatient clinics at referral hospitals. Fatigue was assessed prior to treatment and 12 weeks after treatment using the nine-item Fatigue Severity Scale (FSS-9). We applied a linear mixed model to evaluate the impact of integrated HCV treatment on changes in FSS-9 (ΔFSS-9) sum scores.

Results

At baseline, the mean FSS-9 sum score was 46 for participants on integrated HCV treatment and 41 for those on standard treatment. In the intention-to-treat analysis, integrated HCV treatment reduced the FSS-9 scores significantly better than standard treatment (ΔFSS-9: −2.7, 95% confidence interval (CI): −5.0;−0.4). No similar effect was found in the per-protocol analysis (ΔFSS-9: −1.0, 95% CI: −3.8;1.7).

Conclusion

Fatigue is a common symptom among PWIDs. Integrated HCV treatment is superior, or at least equal to standard HCV treatment in improving fatigue.

Trial registration: ClinicalTrials.gov.no NCT03155906, 16/05/2017.

1. Background

Fatigue is a debilitating symptom that affects as many as 50 to 80% of people with chronic hepatitis C virus (HCV) infection [1–3]. This contributes, in part, to extensive demotivation, non-restorative sleep, disinterest, lack of energy, and impaired quality of life, even among people in the early stages of HCV infection and those who achieve viral clearance [2, 4–6]. Among people who inject drugs (PWIDs), three out of four suffer from severe fatigue symptoms [7], which is comparable to those affected by stroke or major depressive disorder [8–10]. Multifactorial medical and psychosocial challenges––debt difficulties, hard drug use, mental disorders, and nutritional deficiency––dominate among these people and are

associated with severe fatigue symptoms [7, 11, 12]. Additionally, HCV infection, which affects nearly half of PWIDs [13], is likely an essential cause of fatigue symptoms. Thus, investigating treatment approaches that might alleviate fatigue among PWIDs, particularly those infected with HCV is warranted.

In this regard, some studies have suggested that HCV treatment may reduce fatigue [14–17]. However, these mainly observational studies are encumbered substantially by a range of biases. Reaching PWIDs with HCV treatment may initiate other interventions concomitantly, such as addiction treatment and psychosocial support for debt, income, and housing stress, which are associated with changes in fatigue [7]. Thus, a randomized design is needed to disentangle the effect of HCV treatment from other confounding medical and psychosocial factors. Trials evaluating treatment models may be essential to explore the potential benefits of HCV treatment on fatigue among PWIDs. In a previous study from the INTRO-HCV trial, integrated HCV and addiction treatments involving decentralized outpatient clinics with multidisciplinary teams and close follow-up improved the sustained virological response (SVR) by 27% compared to standard HCV treatment for PWIDs [18]. Furthermore, the INTRO-HCV trial showed that the treatment initiation rate was 98% among patients who received integrated HCV treatment, compared to 77% among those who received standard HCV treatment. Thus, integrated HCV treatment may be preferable for reducing fatigue symptoms in this population.

This randomized controlled trial investigated the impact of integrated HCV infection treatment on fatigue using the nine-item fatigue severity scale (FSS-9) among PWIDs receiving oral direct-acting antivirals (DAAs) in western Norway. More specifically, we compared the impact of integrated HCV treatment to standard HCV treatment on changes of FSS-9 sum scores.

2. Methods

Study design and setting

The original study, the INTRO-HCV trial, was designed as a multi-center, randomized controlled trial [19]. This study evaluated fatigue as a secondary outcome of the INTRO-HCV trial. We recruited PWIDs with chronic HCV infection who were eligible for HCV treatment with DAAs in accordance with Norwegian HCV treatment guidelines (Additional File 1). Participants were recruited from eight outpatient clinics providing opioid agonist therapy (OAT) in Bergen and Stavanger, Norway, as well as two community care centers (CCCs) in Bergen providing primary healthcare to PWIDs. Enrollment was conducted from May 2017 to June 2019. For a more comprehensive description, a published protocol is available [19].

Study sample

A total of 148 participants were randomized into the integrated HCV treatment group and 150 into the standard HCV treatment group (Figure 1). Ultimately, seven participants in the integrated treatment group and 15 in the standard treatment group were excluded due to death or lack of FSS-9 assessments. In total, 276 participants were included in the study – 141 in the integrated treatment group and 135 in the standard treatment group.

Inclusion and exclusion criteria

Inclusion criteria were defined as follows: 1) receiving OAT opioids in the OAT outpatient clinics or people injecting drugs receiving healthcare from the two CCCs; 2) having chronic HCV infection defined as detecting HCV with HCV polymerase chain reaction in two separate blood samples drawn with an interval of at least six months; 3) eligibility for treatment according to the Norwegian HCV treatment guidelines; and 4) willingness to sign a written informed consent to participate in the trial. We excluded people who 1) currently received treatment for HCV; 2) were co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (positive surface antigen) at the time of inclusion; 3) had severe extrahepatic manifestations (e.g., cryoglobulinemia or membranoproliferative glomerulonephritis); 4) had chronic renal disease stages 4–5 (glomerular filtration rate < 30 ml/min/1.73 m^2); and 5) had decompensated liver disease (Child-Pugh class B or C). Additionally, people who did not complete the FSS-9 questionnaire during the study period were excluded. For details on demographic and clinical variables, see Table 1.

Randomization and masking

Selected participants were randomized at a 1:1 ratio using blocks of 10 stratified by city and assigned into integrated (*n* = 148) or standard treatment (*n* = 150) for the trial. Complete blinding was considered impractical and would have reduced external validity [20], although some masking measures were taken [19]. In short, randomization was disclosed to clinical staff providing treatment and follow-up. Participants were informed of key elements in the delivery of the respective intervention and follow-up to which they were assigned, but no information was shared on treatment and follow-up alternatives or the hypotheses for the study.

Ethics approval and consent to participate

The present study was reviewed and approved by the Regional Ethical Committee for Health Research (REC) West, Norway (reference number: 2017/51/REK Vest, dated 29.03.2017/20.04.2017). All recruited participants were fully informed about the study, and their written informed consent was provided before their inclusion and randomization. All methods were carried out in accordance with relevant guidelines and regulations.

Data collection

Participants were evaluated prior to HCV treatment and 12 weeks after the end of treatment (EOT12) to record their health status, including fatigue level according to the FSS-9 score, sociodemographic data, current drug use, blood samples, transient elastography, and clinical examination. The health assessments were conducted by specialized research nurses in close collaboration with the clinics' consultants in addiction medicine and infectious diseases. A medical team followed up with those who did not meet the criteria for inclusion in the study. Data from the health assessments prior to and after HCV treatment were defined as the study's baseline and EOT12 (endpoint), respectively.

Measuring fatigue and drawing blood samples

We assessed fatigue using the FSS-9, including items considering mental and physical functioning, motivation, carrying out duties, and interfering with work, family, or social life. The FSS-9 is a well-known questionnaire to quantify fatigue during the week prior to the assessment [21-26], with high validity and reliability in people undergoing HCV treatment [27]. The FSS-9 items are answered on a Likert scale ranging from 1, no fatigue, to 7, worst fatigue, demonstrating the fatigue level. A high FSS-9 score indicates a high level of fatigue; a mean score greater than 4.0 reveals severe fatigue [26]. The FSS-9 employed had been translated and back-translated from US-English into Norwegian by qualified native Norwegian-speaking translators (Additional File 2) [28].

We drew blood samples, including hepatitis B virus surface antigen, HIV antigen/antibodies, thrombocytes, and aspartate aminotransferase, as well as HCV antibodies and HCV polymerase chain reactions. Liver stiffness was measured by calculating the aspartate aminotransferase to platelet ratio index and performing transient elastography at baseline (Additional File 3). Transient elastography calculates liver stiffness using the median value of ten repeated measurements on an empty stomach [29, 30].

Intervention – standard HCV treatment

Participants in the standard HCV treatment group were referred to the centralized outpatient infectious disease clinic at the collaborating referral hospital for HCV treatment. Their clinical assessment could involve additional blood samples and imaging before initiating HCV treatment. In the first year of the study, HCV consultation with a consultant in infectious diseases was mandatory, but with increasing clinical experience and growing evidence, the primary assessment became voluntary. Participants were offered follow-up assessments, including blood samples, during treatment in the infectious disease outpatient clinic every four weeks. They were responsible for retrieving and adhering to their prescriptions, and attending assessment appointments. At EOT12, blood samples, including HCV polymerase chain reaction, were drawn at infectious disease outpatient clinics, OAT clinics, and CCCs. In addition, participants met at OAT clinics or CCCs to assess their FSS-9 levels.

Intervention – integrated HCV treatment

All assessments and medications for participants in the integrated treatment groups were provided onsite at the OAT clinics or CCCs, including DAAs, blood samples, and FSS-9 assessments. The OAT clinics differed from the CCCs by offering OAT medications in addition to psychosocial approaches. In both settings, nurses and social workers, in cooperation with peer counselors, provided most of the participants' daily follow-ups. For those eligible for HCV treatment, DAAs were administered by a nurse at OAT clinics/CCCs after a prescription from a consultant in infectious diseases. All HCV treatment and scheduled follow-up during treatment were given in parallel with the observed intake of OAT medications and other care, in line with the study protocol. The number of deliveries of OAT and DAA medications per

week was adapted to the level of functioning of each participant. The multidisciplinary team planned assessments with participants, or drop-in approaches were applied.

Statistical analyses

We used Stata SE version 17 (StataCorp, TX, USA) for descriptive analyses and linear mixed model analyses, and IBM SPSS version 26.0 for expectation-maximization calculation. The threshold for statistical significance was set to $p < 0.05$ for all analyses unless otherwise stated. All statistical analyses were conducted following CONSORT and SPIRIT guidelines [31, 32]. The sample size was calculated for the primary outcome of SVR, defined as undetectable HCV RNA 12 weeks after HCV treatment completion, in the INTRO-HCV trial [19].

We dealt with any missing values in FSS-9 scores at baseline and EOT12 as “missing at random” when running expectation-maximization algorithm [33, 34]. We identified missing values in 1.4% of FSS-9 scores at baseline and 29% at EOT12, and all were replaced with estimated values. The expectation–maximization algorithm for computing data iteratively performs maximum likelihood estimation in the presence of latent variables [35], recommended for optimizing the mixed models. Sensitivity analyses without estimated values were conducted in all regression models.

The FSS-9 sum scores at baseline and EOT12 were calculated by summarizing the points generated by the nine items. We created Pen’s parades in which the FSS-9 sum score at baseline were listed chronologically per participant and spikes were performed to express changes in FSS-9 scores from baseline to EOT12 in the integrated and standard HCV treatment groups. Additionally, linear mixed models were applied to investigate changes in FSS-9 sum scores (outcome variable) from baseline to EOT12, with the interaction between treatment groups (dichotomized as standard (0) versus integrated (1)) and time (dichotomized as baseline (0) and EOT12 (1)) as a predictor variable. The linear mixed models were random intercept fixed slope regression models. The restricted maximum likelihood was set as the estimator [36, 37]. The full information of maximum likelihood ensured that all available FSS-9 sum score were used. The LMM analysis was run as intention-to-treat and per-protocol analyses and as a sensitivity analysis without computed data.

3. Results

Characteristics at baseline

The median age was 44 years (interquartile range (IQR): 36–52) in the integrated HCV treatment group (Table 1). Of those, 73% were male, and 58 % had injected drugs recently. In the standard HCV treatment group, the median age was 42 years (IQR 34–49), 81% were male, and 64% had injected drugs recently. HCV genotype 3 was most prevalent, representing 65% of participants in the integrated HCV treatment group and 61% in the standard HCV treatment group.

FSS-9 sum scores at baseline and EOT12

At baseline, the mean FSS-9 sum score for participants on receiving integrated treatment was 46 (Standard deviation (SD) 15) and 41 (SD 16) for those on standard treatment. The mean FSS-9 sum score in both groups was slightly left-skewed and tended toward a flattened distribution at baseline (Additional File 4). At EOT12, the mean FSS-9 sum score for participants receiving integrated treatment was 42 (SD 15) and 40 (SD 14) for those receiving standard treatment. For detailed information on the FSS-9 sum scores at baseline and EOT12, see Additional File 5.

The impact of integrated HCV treatment on change in the FSS-9 sum score

Integrated HCV treatment reduced the FSS-9 sum score from baseline to EOT12 more than standard HCV treatment (ΔFSS-9 sum score: −2.7, 95 % confidence interval (CI): −5.0; −0.4) (Table 2, Figure 2) (intention to treat). Moreover, substantial intraindividual variations in FSS-9 sum scores over time were observed in both groups (Figure 3). In the per-protocol analysis, no significant effect of integrated HCV treatment compared to standard HCV treatment was observed (per-protocol: ΔFSS-9 sum score: −1.0, 95 % CI: −3.8;1.7) (Additional Files 6-8). Likewise, sensitivity analyses without computed data showed similar results (Additional Files 9-10).

4. Discussion

The present RCT demonstrated that, compared to standard HCV treatment, integrated HCV treatment reduced fatigue from baseline to EOT12 among PWIDs; however, the per-protocol analysis and sensitivity analyses did not reveal a similar alleviation of fatigue. The fatigue level was high in both the integrated and the standard HCV treatment groups, with substantial intraindividual variation from baseline to EOT12.

To our knowledge, this was the first trial conducted in outpatient OAT clinics and CCCs to investigate the impact of integrated HCV treatment on fatigue among PWIDs. Although per-protocol and sensitivity analyses showed no significant improvement in integrated HCV treatment compared to standard treatment, the intention-to-treat analysis revealed an almost three-point improvement in FSS-9 scores with integrated HCV treatment. This implies that an integrated approach is at least equal to or possibly more effective than standard HCV treatment in reducing fatigue symptoms in this population. Achieving SVR representing 85% and 64% of participants in integrated and standard HCV treatments, respectively, according to the INTRO-HCV trial [18], probably contributed to the improved fatigue level. Two cohort studies in which people co-infected with HIV and HCV recruited showed that DAA treatment may reduce fatigue symptoms [14, 15]. However, liver cirrhosis, representing up to 45% of these participants, and co-infection with HIV could have influenced the results of those studies [16, 17]. Liver cirrhosis caused by HCV infection is associated with fatigue [38], and mono-infection by HCV is associated with more fatigue than co-infection of HCV and HIV [17], arguably due to closer follow-ups of co-infected people. In our PWID population, few participants had liver cirrhosis, no participants were co-infected with HIV, and most patients achieved SVR, which could explain our results, particularly in the analyses showing no improvement in fatigue in this population.

The present study demonstrated that integrated HCV treatment was more likely to relieve fatigue symptoms among PWIDs than standard HCV treatment. The results align with existing literature on this topic [39, 40]. Although the impact of integrated HCV treatment on fatigue was equivocal in the present study, the integrated HCV treatment approach improved medical treatment among PWIDs significantly, as demonstrated in the INTRO-HCV trial [18]. Due to the usually chaotic life situations of these people, close follow-ups and decentralized treatment are essential to provide healthcare and improve their medical and psychosocial conditions [18]. In a cohort study in which fatigue was evaluated in people with drug use disorders, benzodiazepine, cocaine, or amphetamine use, debt difficulties, and female sex were significantly associated with fatigue [7]. Otherwise, people with a higher HCV viral load (≥ 800,000 IU/ml) had more fatigue than those with a lower HCV viral load (< 800,000 IU/ml) prior to HCV infection treatment; however, other studies did not find a similar association based on clinical and histological features [41-44]. These results imply that underlying medical and psychosocial challenges impact fatigue among PWIDs. Thus, aside from alleviating fatigue, integrated HCV treatment may be conceptually better suited to reach PWIDs with other interventions, such as adequate addiction treatment, which is associated with changes in fatigue levels [7, 45].

The integrated and standard treatment groups demonstrated substantial intraindividual variation in fatigue levels over time. This corresponds with the results detected in another fatigue study of people infected with HCV [46]. The large intraindividual variation in the present study is likely attributable to changes in multiple drug use, housing- and debt stress, OAT medication, and drug overdoses and withdrawals that necessitate hospitalizations, which are significantly associated with fatigue [7]. Although the fatigue assessments were performed under medically and psychosocially stable conditions, it was hard to eliminate the various influencing factors; and thus, some intraindividual variations in fatigue level are expected [18]. This reflects the complexity of interpreting the impact of interventions on fatigue among PWIDs, even with targeted HCV treatment interventions.

5. Strengths And Limitations

A major strength of this study is its trial design of individual randomization with balanced groups, which minimizes potential confounding. Furthermore, we included PWIDs who usually struggle with adherence to standard HCV treatment and have frequently discontinued previous HCV assessment and treatment in centralized infectious disease outpatient clinics. A limitation of this study is in the selection of outpatient clinics, where most participants received OAT to recover from opioid dependence, affecting the generalizability of our results to non-OAT populations. Another limitation is the 30% loss-to-follow-up of FSS-9 assessment at EOT12 and the exclusion of 18 randomized participants due to missing FSS-9 assessments during the period. This may explain the four-point higher FSS-9 sum score in the intervention group than in the control group at baseline. Furthermore, due to system and individual delays and changes in national guidelines for HCV treatment throughout the study period, the FSS-9 assessments were not conducted in exact concurrence with HCV treatment initiation and EOT12. This could affect the interpretation of the predicted fatigue changes from baseline. Moreover, in the per-protocol analyses, one out of five participants was excluded because they had predominantly integrated

HCV treatment while enrolled in standard HCV treatment. In these cases, the standard HCV treatment involved a multidisciplinary team consisting of a consultant in addiction medicine, a psychologist, nurses, and social workers who facilitated HCV treatment beyond the approved standard treatment protocol. When adjusted for this bias in the per-protocol analysis, the integrated HCV treatment was equal to the standard HCV treatment in changing fatigue symptoms.

6. Conclusion

The present trial documented that fatigue is a common symptom among PWIDs. Integrated HCV treatment was superior to or at least equal to standard HCV treatment in alleviating fatigue. It is reasonable to implement integrated HCV treatment in other medical and psychosocial care, considering the challenges related to drug use behavior and life situations in this population.

7. Abbreviations

CCC
Community care centers
CI
Confidence interval
DAA
Direct-acting antiviral agent
EOT12
12 weeks after the end of treatment
FSS-9
Nine-item fatigue severity scale
HCV
Hepatitis C virus
HIV
Human immunodeficiency virus
IQR
Interquartile range
OAT
Opioid agonist therapy
PWID
People who inject drugs
SD
Standard deviation
SVR
Sustained virological response

8. Declarations

Ethics approval and consent to participate

The present study was reviewed and approved by the Regional Ethical Committee for Health Research (REC) West, Norway (reference number: 2017/51/REK Vest, dated 29.03.2017/20.04.2017). All recruited participants were fully informed about the study, and their written informed consent was provided before their inclusion and randomization. All methods were carried out in accordance with relevant guidelines and regulations.

Consent of publication

Not applicable

Availability of data and material

The datasets analyzed during the current study are not publicly available due data protection requirements but are available from the corresponding author on reasonable request.

Competing interests

Not applicable

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Authors' contributions

JHV has led the study design, analysis, and writing the article preparation. FC, EML, CFA, AL, PV, KAJ, and LTF have contributed to the study design, analysis, and article preparation. All authors have read and approved the final article.

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9. References

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Tables

Table 1
Characteristics at baseline

	Integrated treatment (N = 141)	Standard treatment (N = 135)
Age (years), n (%)		
18–29	14 (10)	16 (12)
30–39	41 (29)	43 (32)
40–49	44 (31)	45 (33)
≥ 50	42 (30)	31 (23)
Median (IQR)	44 (36–52)	42 (34–49)
Sex, n (%)		
Male	103 (73)	109 (81)
Highest level of education, n (%)		
Not completed primary school	7 (5)	12 (9)
Completed primary school (9 years)	67 (48)	66 (49)
Completed high school (12 years)	52 (37)	44 (31)
Completed college or university	13 (9)	14 (10)
Opioid agonist therapy, n (%)	120 (85)	120 (88)
Unstable housing past 30 days[1)]*, n (%)*	21 (14)	18 (13)
Injected drug use past 12 months, n (%)	81 (58)	83 (64)
Frequent drug use past 12 months, n (%)[2)]		
Alcohol	35 (25)	32 (25)
Benzodiazepines	55 (40)	52 (41)

Legends: FSS-9: Nine-item fatigue severity scale; IQR: Interquartile range; kPa: Kilopascal;

[1)] Unstable housing was defined as living in a homeless shelter, with family or friends, or on the street during the 30 days leading up to the first health assessment (baseline);

[2)] Frequent drug use was defined as using substance at least weekly during the 12 months leading up to the first health assessment (baseline).

The table displays the sociodemographic and clinical characteristics of participants randomly assigned to integrated and standard HCV treatment groups.

	Integrated treatment (N = 141)	Standard treatment (N = 135)
Cannabis	75 (54)	72 (56)
Opioids	17 (12)	15 (12)
Stimulants (amphetamines and cocaine)	48 (35)	39 (30)
Infectious diseases, n (%)		
Hepatitis C virus genotypes	47 (34)	44 (33)
1	< 5 (1)	6 (4)
2	91 (65)	80 (61)
3	< 5 (0)	< 5 (1)
4	< 5 (0)	< 5 (1)
6	< 5 (0)	< 5 (0)
Hepatitis B virus infection		
Human immunodeficiency virus	< 5 (0)	< 5 (0)
Liver stiffness, n (%)		
Transient elastography (≥ 12.5 kPa)	19 (13)	14 (11)
Aspartate transaminase to platelets ratio index (≥ 1.5)	16 (12)	17 (12)
Legends: FSS-9: Nine-item fatigue severity scale; IQR: Interquartile range; kPa: Kilopascal;		
[1)] Unstable housing was defined as living in a homeless shelter, with family or friends, or on the street during the 30 days leading up to the first health assessment (baseline);		
[2)] Frequent drug use was defined as using substance at least weekly during the 12 months leading up to the first health assessment (baseline).		
The table displays the sociodemographic and clinical characteristics of participants randomly assigned to integrated and standard HCV treatment groups.		

Table 2
Linear mixed model of ΔFSS-9 sum scores from baseline to EOT12 for integrated HCV treatment (intention-to-treat) (N = 276)

	Effect estimates	
	Coefficient (95% CI)	p**-value**
Time trend	−0.8 (−2.8;1.3)	0.457
ΔFSS-9 sum score from baseline to EOT12		
Standard HCV treatment	0.0 (ref.)	-
Integrated HCV treatment	−2.7 (-5.0;−0.4)	0.022
Legends: EOT12: 12 weeks after the end of HCV treatment; FSS-9: Nine-item fatigue severity scale.		
The table displays a linear mixed model analysis (Restricted Maximum Likelihood) regression of the impact of integrated HCV treatment on changes in FSS-9 sum scores (ΔFSS-9 sum score) from baseline to EOT12 (intention-to-treat analysis). The FSS-9 sum score ranges from 9 points, no fatigue, to 63 points, worst fatigue.		

Figures

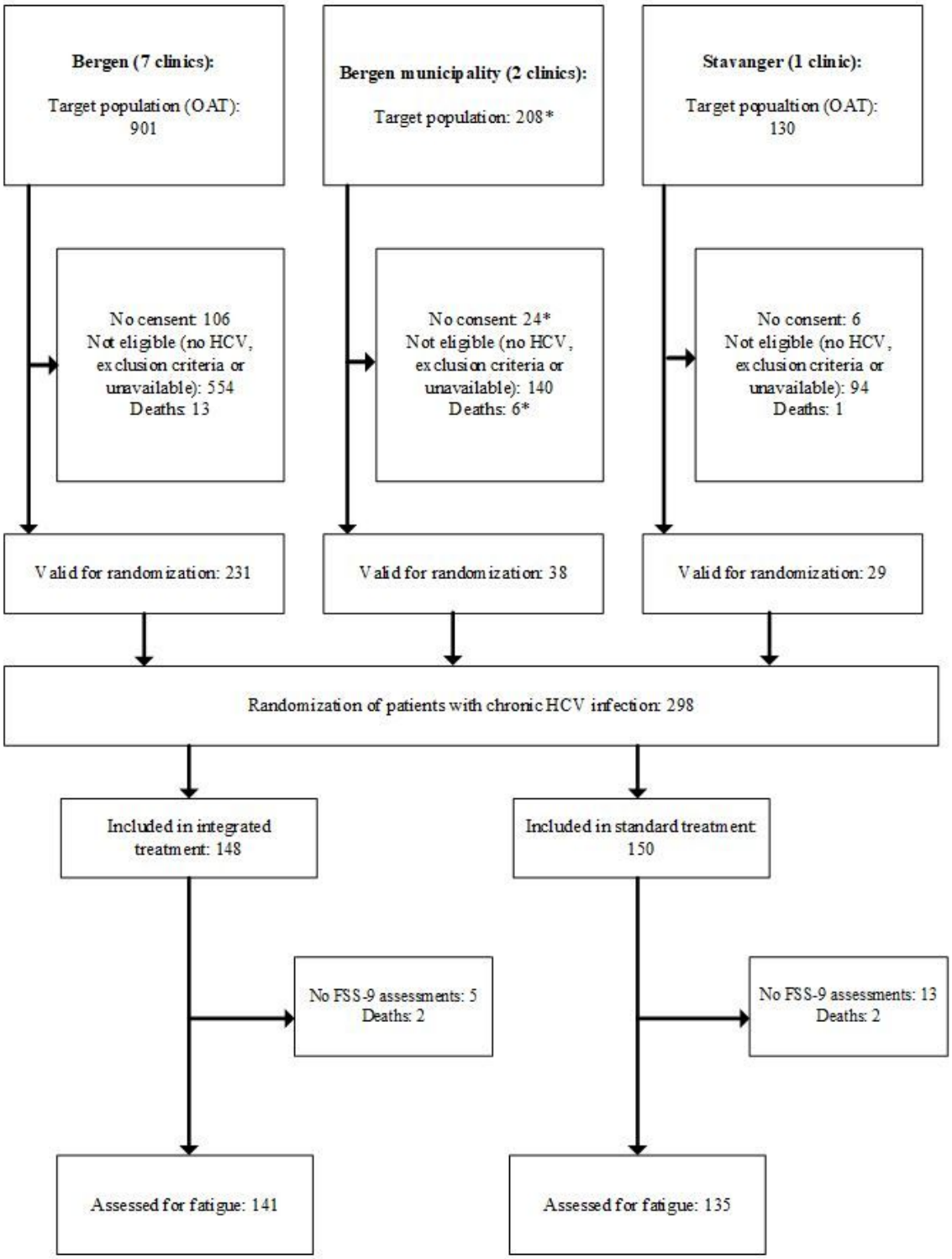

Figure 1

Title: Trial profile for the study.

Legends: * Estimated numbers. FSS-9: Nine-item Fatigue Severity Scale; HCV: hepatitis C virus; OAT: opioid agonist therapy.

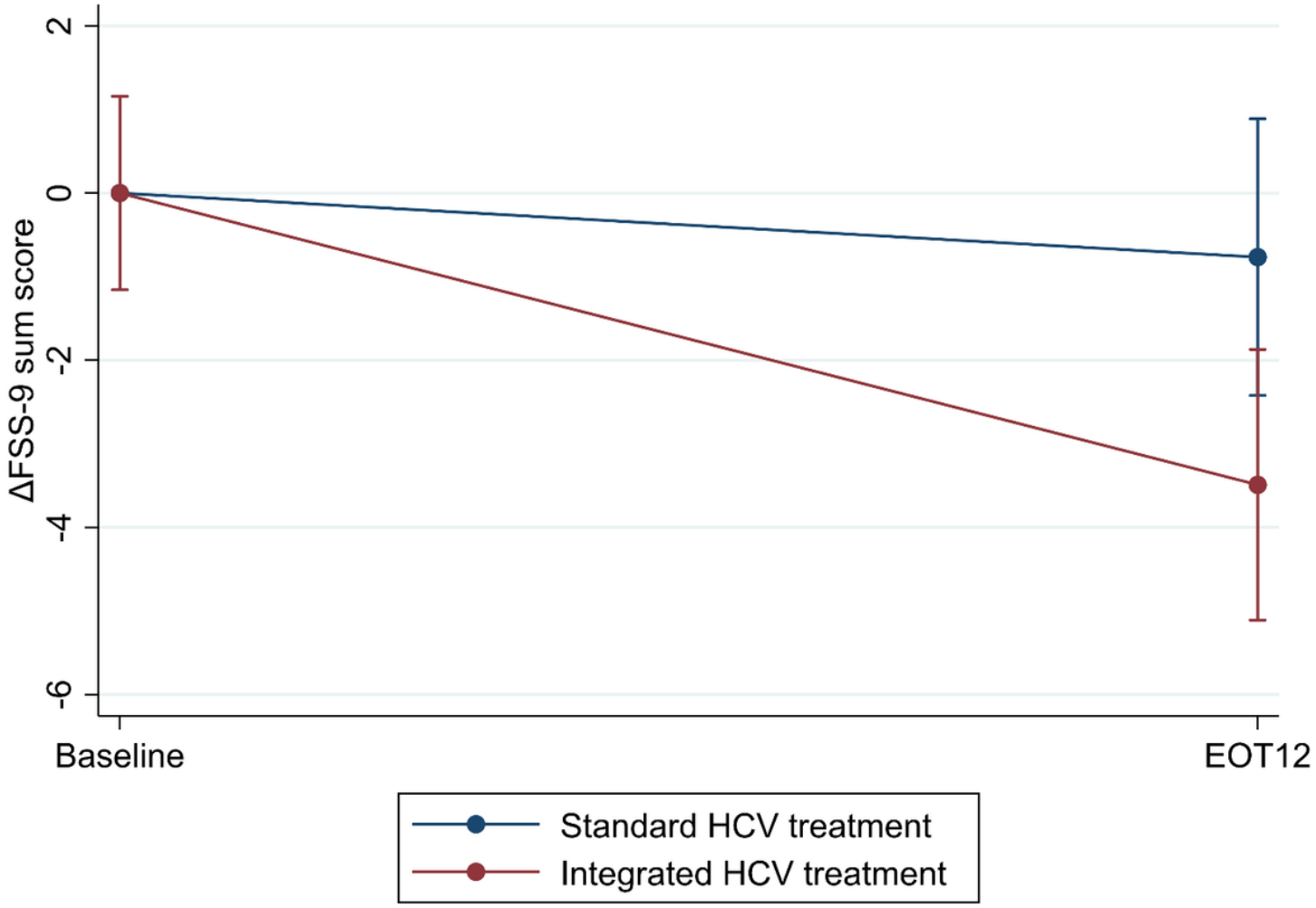

Figure 2

Title: A linear prediction of changes in FSS-9 sum scores from baseline to EOT12 (intention-to-treat analysis) (N = 276).

Legends: The figure displays the linear prediction (fixed portion) including 95 % confidence intervals of changes in FSS-9 sum score (ΔFSS-9 sum score) from baseline to EOT12 for integrated and standard HCV treatment groups. EOT12: 12 weeks after the end of HCV treatment; FSS-9: Nine-item fatigue severity scale; HCV: Hepatitis C virus.

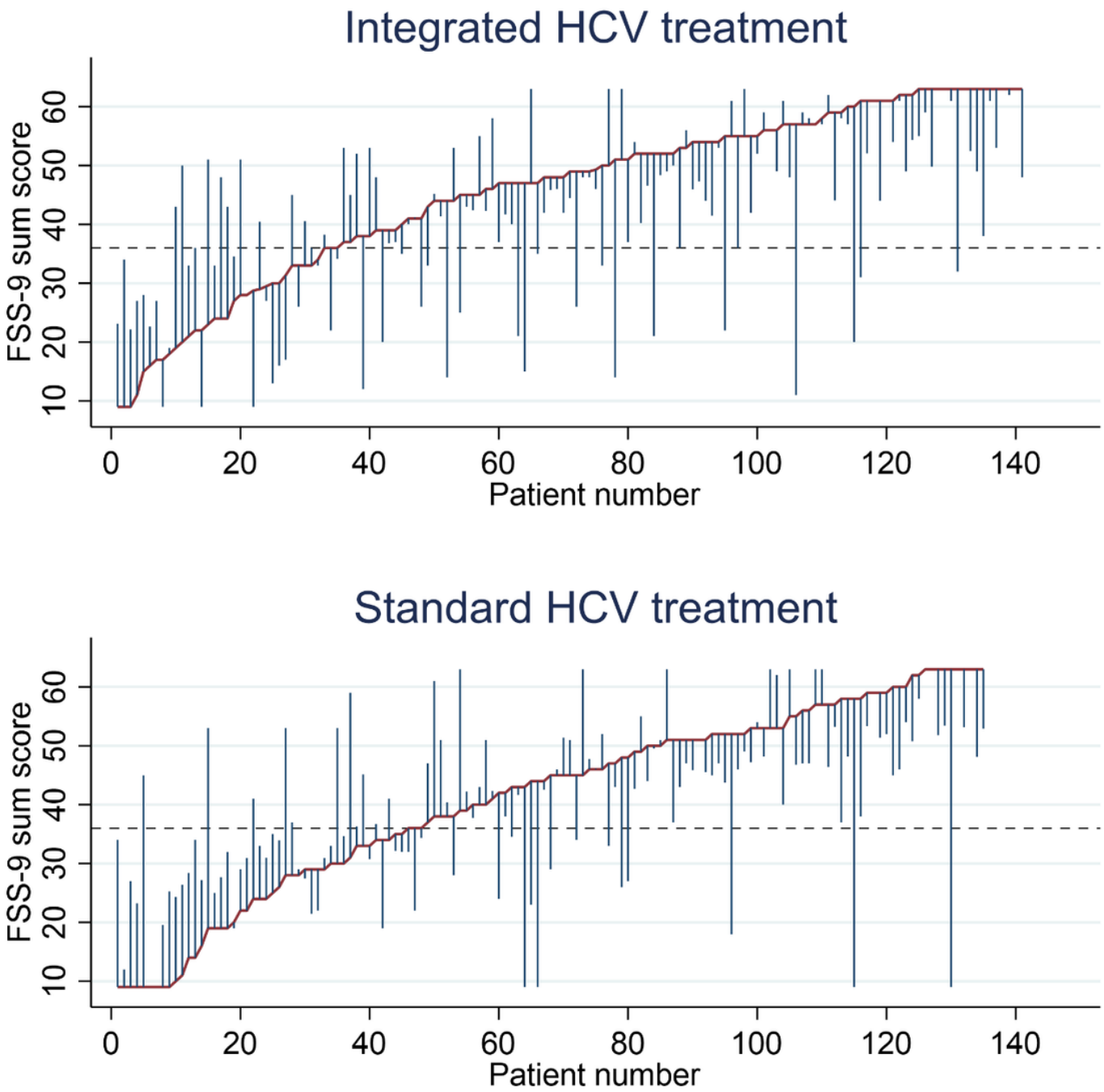

Figure 3

Title: Pen's parades of FSS-9 sum scores at baseline and EOT12 (N = 276).

Legends: The figures display participants who received integrated and standard HCV treatment and were included in the intention-to-treat analysis. The graphs demonstrate the FSS-9 sum scores at the first health assessment (baseline/before HCV treatment) and EOT12 when the FSS-9 sum scores are listed chronologically per participant. The red line represents the FSS-9 sum scores at baseline and the blue

spikes mark changes in the FSS-9 score between baseline and EOT12. Participants without spikes did not conduct FSS-9 assessment at EOT12. The spikes' endpoints (furthest from the red line) demonstrate the FSS-9 sum score at the EOT12. The dotted line demonstrates the cut-off value for severe fatigue (36 points). EOT12: 12 weeks after the end of treatment; FSS-9: Nine-item Fatigue Severity Scale.

Supplementary Files

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