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Patient-reported outcomes of the Treatment and Prevention Study: A real-world community-based trial of direct-acting antivirals for hepatitis C among people who inject drugs

Running title: Community-based DAA treatment and PROs

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Conflicts of Interest Statement

SG, BH, MS and TS have no competing interests to declare. JD, MH, and the Burnet Institute receive investigator-initiated research funding from Gilead Sciences, Merck, AbbVie, and Bristol-Myers Squibb. JD is an advisory board member for Gilead Sciences, AbbVie, Merck. AT is an advisory board member for Gilead Sciences, AbbVie, Bristol-Myers Squibb, Merck, Roche, Eisai and Bayer, and has received speaker fees for Gilead, Bristol-Myers Squibb, AbbVie and Roche. PH has received investigator-initiated research funding to his institution from Gilead Sciences and Abbvie. PD has received investigator-driven funding from Gilead

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Data availability

Research data are not shared.

Abstract:

The impact of hepatitis C cure with direct-acting antivirals (DAAs) on patient-reported outcomes (PROs) in community settings remains unclear. We aimed to assess changes in PROs over time and whether treatment was associated with sustained improved PROs in a cohort of people who inject drugs. This study is a sub-analysis of the Treatment and Prevention Study, a nurse-led trial where people who inject drugs and their injecting partners were recruited in a community setting, in Melbourne, Australia. Three participant groups were characterised; treatment, untreated and non-viremic (hepatitis C RNA negative at screening). PROs included assessment of health-related quality of life using the Short-Form 8

(SF-8) Survey and life satisfaction using Personal Wellbeing Index (PWI). PROs were measured at baseline and every 12 weeks until week 84. Generalised Estimating Equations were used to measure whether treatment was associated with longitudinal PRO change. A total of 215 participants were included in this analysis. PWI scores were significantly higher at week 12 for both the treatment group (p = 0.0309) and non-viremic group (p = 0.0437) compared to baseline. However, treatment was not associated with longitudinal change in PRO scores. In conclusion, we found DAA treatment did not significantly improve PRO scores compared to those not receiving treatment and without hepatitis C. The measures used in this study may not be sensitive enough to capture the hepatitis C specific improvements in quality of life that treatment affords or factors other than treatment may be influencing quality of life scores in this cohort.

Keywords: People Who Inject Drugs, Hepatitis C, Antiviral Agents, Patient Reported Outcomes, Quality of Life

Introduction

Chronic hepatitis C infection is a substantial contributor to mortality and liver-related morbidity worldwide. (1) Irrespective of liver disease stage, living with hepatitis C is also associated with poorer patient-reported outcomes (PROs) compared to those without hepatitis C. (2-5) Until recently, hepatitis C was treated with interferon-based treatments, which were arduous and often accompanied by debilitating side effects. (6) Undertaking interferon treatment was associated with further reductions in PROs including work productivity and quality of life. (7, 8) These impairments were largely credited to intense side effects and negative interactions between treatment and mental health. (3, 6, 9)

The arrival of direct-acting antiviral (DAA) therapy dramatically altered the treatment landscape and PRO trajectory. (1, 10) DAAs are more efficacious, with simpler dosing,

shorter duration and a lower side effect profile than previous interferon-based treatments (11). At a population level, DAAs are cost-effective and if upscaled among people who inject drugs are projected to reduce the liver disease related burden, number of hepatitis C related deaths and hepatitis C incidence. (12-14)

As well as understanding the population-level benefits of DAAs, there is also a need to understand the broader personal benefits of treatment and cure. (15) Alongside treatment outcomes some clinical trials have measured the individual impact of DAAs by reporting on fatigue, work productivity and most frequently, health-related quality of life. (8, 16-18) Health-related quality of life measures the self-reported impact of health status on facets of wellbeing. (9) Clinical trial data of DAA treatment in tertiary health settings consistently describe significant improvements in health-related quality of life throughout treatment, with the greatest improvements relative to treatment-initiation reported at sustained virologic response 12 weeks post treatment (SVR12). (16, 17, 19, 20)

Whilst the existing clinical trial data universally indicate marked improvements in PROs following DAA completion, trial populations from drug registration studies are often not representative of patient populations seeking treatment in the community. (21) Many drug registration clinical trials of DAAs have excluded people who inject drugs. (22) There is a dearth of 'real-world' studies exploring the association between DAA treatment and PROs among people who are actively injecting drugs and beyond the SVR12 time point. We aimed to assess changes in subjective wellbeing and health-related quality of life over time among a cohort of people who inject drugs enrolled in a community based DAA treatment trial.

Methods

Data source

This study is a sub-analysis of PRO data from the Treatment and Prevention (TAP) Study (clinicaltrials.gov NCT02363517). (23) The TAP Study is a community-based nurse-led open-label randomised controlled trial of sofosbuvir/velpatasvir, conducted in Melbourne, Australia, between February 2015 and August 2019. The primary objectives of the TAP Study were to measure the proportion of participants achieving SVR12 and measure the impact of treating injecting networks on rates of infection and reinfection.

TAP Study primary participants were recruited through an existing Burnet Institute study (the SuperMIX study). (24) Eligible primary participants were aged ≥18 years old, hepatitis C

RNA positive and currently injecting drugs (injected any drug at least once in the past six months). Primary participants were asked to invite members of their injecting network to participate in the study, who are described as secondary participants. Secondary participants were not required to be hepatitis C RNA positive. Participants were excluded if they tested positive for Human Immunodeficiency Virus or hepatitis B virus, had cirrhosis of the liver (FibroScan score ≥12.5 Kpa) or were using specified concomitant medications at screening.

Primary participants and their associated secondary participants were originally randomised into one of three groups; non-treatment (group A), treatment for primary participants only (group B), treatment for both primary and secondary participants (group C). The TAP study protocol was amended in 2016 when DAA treatment became universally available in Australia, including for people who inject drugs and it could be prescribed by general practitioners. (25) In 2016 the non-treatment arm was removed and primary participants were re-randomised into either group B or group C. All eligible primary participants were offered treatment. Secondary participants who were hepatitis C RNA positive randomly received either immediate (group C) or delayed (group B) treatment until the end of the study. Participants could remain in the study if they initiated treatment externally to the TAP Study.

Participants received 12 weeks of treatment (sofosbuvir/velpatasvir) through the TAP Study. Clinical and behavioural questionnaires, as well as blood samples were collected at baseline, week 4, week 8, week 12 (end-of-treatment) and every 12 weeks post treatment until week 84. PROs were collected at baseline, week 12 and all subsequent visits. Questionnaires were administered by study nurses on handheld tablet devices in a mobile community clinic.

Patient-Reported Outcome Measures

The Personal Wellbeing Index (PWI) measures subjective wellbeing. The scale contains seven items, each representing a single domain including standard of living, personal health, achieving in life, personal relationships, personal safety, community connectedness and future security. Participants are asked how satisfied they are with each domain, from 0 “not at all” to 10 “completely satisfied”. (26) Domain scores were added to receive an overall score and then converted to a standard summative score out of 100, with a higher score indicating greater wellbeing. (26) The normative range for PWI group mean scores in Australia is 74.2 – 76.7. (27)

The Short Form-8 Survey (SF-8) is an abridged version of the Short Form-36 Survey that measures health-related quality of life. The SF-8 contains eight items, separated into two components physical health (domains: physical functioning, role physical, bodily pain and general health) and mental health (domains: vitality, social functioning, role emotional and mental health). (28, 29) Participants rate how they feel about each domain on a four to six-point scale. Mental and physical component summary scores are derived, with a higher score indicating better quality of life. Component summary scores are standardised t-scores with a general population mean of 50 with a standard deviation of 10. (28)

Covariates

Liver stiffness was measured in kilopascals by transient elastography (FibroScan™, Echosens, Paris) and categorised to represent fibrosis status with the following cut off points; none to mild fibrosis (F0-F1) ≤7 kPa, moderate fibrosis (F2) >7 to ≤9.5 kPa and severe fibrosis (F3-F4) >9.5 kPa. Body Mass Index was calculated by dividing weight (in kilograms) by height (in metres) squared. Body Mass Index was categorised as; underweight <18.5 kg/m^2, normal weight 18.5 to 25 kg/m^2 and overweight to obese >25 kg/m^2. Alcohol consumption in the past month was measured by the Alcohol Use Disorders Identification Test-C, a three-item alcohol screen. (30) Hazardous alcohol consumption was defined as a score of ≥4 in men and ≥3 in women, out of a possible 12. Stable accommodation status included living in a private rental property, community housing or with family. Unstable accommodation included crisis or transitional accommodation, squatting, couch surfing or homelessness. Opioid substitution therapy included methadone, suboxone or naltrexone. Drug used most in the past month was not necessarily injected and 'other' included methadone, other opioids, suboxone, benzodiazepines and a combination of Unisom and morphine. Number of injections in the past week was the total number of times participants reported injecting any drug in the past week.

Study definitions and inclusions

Participants who attended a screening visit only or had no available outcome data for the duration of the study were excluded from this sub-analysis. Three participant groups were devised for this analysis: 1) the treatment group, which included any participants who initiated treatment during the course of the study, either through the TAP Study or externally; 2) the untreated group were participants who were hepatitis C RNA positive at screening but

not treated during the study for any reason and 3) the non-viremic group, which included secondary participants who were hepatitis C RNA negative throughout the study.

For all analyses only post-randomisation data were used for the subset of the cohort that were re-randomised. If participants were missing the re-randomisation baseline time point, data from their preceding interview were used as a proxy for baseline data provided it occurred no more than two months prior. Participants treated external to the TAP Study self-reported treatment initiation. Their treatment start date and DAA regimen were not collected, so only data from their baseline and first negative viral load visits (which we classified as week 24) was used in analyses. A small number of participants (n=4) received treatment twice during the study, either due to returning to the study hepatitis C positive after a period of loss to follow up or because of treatment failure. Only data from participants' first treatment episode were used in analysis.

Statistical analyses

Socio-demographic characteristics were summarised for each participant group at screening. Categorical variables were summarised using the frequency and percentage and compared between participant groups using Chi-squared test. Normally distributed continuous variables were summarised using mean and standard deviation (SD) and compared between participant groups using one-way ANOVA. Non-normally distributed continuous variables were summarised using the median and interquartile range (IQR) and compared between participants groups using Kruskal-Wallis one-way analysis of variance.

PRO scores throughout study follow up were summarised using median and IQR. PRO scores recorded at each post-baseline visit within each group were compared to baseline using the non-parametric Wilcoxon sign rank test. This test assesses 'matched pairs' and so only participants with data at both time-points were compared. Tests were not performed when there were fewer than five participants with matched time-points. Scores at each individual visit were compared between the three participant groups using non-parametric Kruskal-Wallis one-way analysis of variance. If one of the three participant groups had a sample size below five, the Mann-Whitney U test was used to compare scores between two groups.

Generalised Estimating Equations with robust standard errors were used to analyse the association between participant groups and PRO scores over time. The Generalised Estimating Equations approach was used as it accounts for within-participant correlation of

PRO scores throughout follow-up, allows one to specify the correlation structure required and robust standard errors provide accurate and trustworthy confidence intervals. (31, 32) Whilst Generalised Estimating Equations were not used to impute missing data, this approach ensured all relevant reported data was used in the modelling. For each outcome, two sets of models were used. In the first model, longitudinal trends in PROs over time were compared across participant groups, adjusting for liver stiffness (as a continuous variable in kilopascals) and injecting frequency. These variables were selected *a priori* given existing evidence that greater fibrosis and more frequent injecting are associated with poorer quality of life. (33, 34) Given the sample size and similar demographic profiles of each analysis group, analyses were not adjusted for additional demographic variables. Models were also performed stratified by the quartile of baseline PRO scores for each participant group. The second model used time to explore the relationship between treatment and changes in PRO score, stratified by participant group. All Generalised Estimating Equation models were specified using the gaussian family function, an identity link and exchangeable correlation structure. For all models, goodness-of-fit was assessed via analysis of residuals. All available data up to week 84 were used excluding screening data. Participants missing baseline PRO scores were excluded from GEE analysis. The effect sizes are expressed as beta coefficients (β) with 95% confidence interval (95% CI).

All data was analysed using Stata software (Version 16.1; Stata Corporation, College Station, Texas). P-values <0.05 were considered statistically significant.

Ethics statement

Participants were reimbursed for each study visit and primary participants were reimbursed for recruiting secondary participants. Participants provided written informed consent. The TAP Study was approved by the Alfred Human Research Ethics Committee (project no: 257/14).

Results:

Participant demographics

A total of 260 participants were enrolled in the TAP Study, 43 were excluded as they only had a screening visit and two were excluded because they were missing outcome data at all

study visits. A total of 215 participants were included in the current analysis, of whom 149 initiated treatment either through the TAP Study (n=138) or externally (n=11). Twenty-two did not receive treatment and 44 were hepatitis C RNA negative at screening.

Participants characteristics are summarised in Table 1. The mean age of participants at screening was 39.6 years old (±8.1 years). Most participants were male (68%) with no to mild liver fibrosis (75%). Overall, 43% of participants did not consume alcohol but 29% were classified as consuming alcohol at a hazardous level. Most participants (68%) were living in stable accommodation and 42% of participants were currently receiving OST. Nineteen participants (9%) were employed either full-time or part-time at screening. The median number of times participants had injected drugs in the past week was 6 (IQR 2 – 14). The most common drug used most in the past month was heroin (54%). At screening socio-demographics and health indicators were mostly consistent between participant groups, except for incarceration history ($p = 0.004$).

Trends in PROs

Baseline median PRO scores for the analysis cohort were below population norms at baseline. At baseline, the median PWI score was 54.3 (95% CI; 41.4, 70.0), SF-8 Physical Component score was 45.0 (95% CI; 39.1, 50.2) and the Mental Component Score was 45.9 (95% Ci; 34.3, 55.0). There were no significant differences in PRO scores between the groups at baseline. At each time-point after baseline the proportion of participants who missed a study visit or did not complete all three PROs increased.. Of the 215 participants included in analysis the proportion missing outcome data at each time point was: 18.6% baseline, 39.5% at week 24, 50.7% at week 48 and 64.7% at week 84. The highest proportion of missing data occurred in the untreated group (for example 77.3% missing at week 24).

There were no significant differences between participant groups at any time point (Figure 1). For most groups, PROs remained relatively stable throughout study follow up, particularly in SF-8 scores. PWI score was significantly higher at week 12 compared to baseline for the treatment group (61.4 vs 51.4, p = 0.0309). A similar increase in PWI score was observed in the non-viremic group at week 12 compared to baseline (64.3 vs 55.0, p = 0.0437). The non-viremic group also had a significantly higher SF-8 Mental Component Score at week 24 compared to baseline (50.5 vs 43.3, p = 0.006).

Model 1: Association between treatment and PROs

The first model assessed the association between participant group and PRO scores using the non-treated group as the reference group and adjusted for degree of fibrosis and injecting frequency. There were no significant associations between being in the treatment group and PWI score (p = 0.934), SF-8 Physical Health Component (p = 0.582) or SF-8 Mental Health Component score (p = 0.869) (Table 2). Models included 154 participants (159 for PWI) who contributed on average two data points (range: 1 – 3 data points). The same model was performed, stratified based on quartiles of baseline PRO score. There were no significant associations between participant group and PRO score over the study period based on the baseline PRO score quartile (Appendix 1).

Model 2: Association between time and PROs, stratified by participant group.

The second model assessed the association between time and PROs, stratified by participant group (Table 3). For the treatment group, every additional week over the study period was associated with an average 0.27 point increase (95% CI: -0.00, 0.06 points) in PWI score,

however this association was not significant (p = 0.083). Every additional week over the study period was associated with an average 0.01 point decrease (95% CI: -0.03, 0.01 points) in SF-8 Physical Component Score, however this association was not significant (p = 0.327). Every additional week over the study period associated with an average 0.003 unit decrease (95% CI: -0.03, 0.02) in SF-8 mental component score, however this association was not significant (p = 0.812). Each model for the treatment group included 147 participants who contributed on average five data points (range: 1-9 data points).

Discussion

Our study examined the impact of DAA treatment on PROs, comparing people who received DAA treatment, those who were not treated and participants who were hepatitis C RNA negative. We found a significant improvement in PWI score at week 12 compared to baseline among participants who initiated treatment and non-viremic participants. There was also a significant improvement in SF-8 Mental Component Score at week 24 compared to baseline among non-viremic participants. However, Generalised Estimating Equations suggested for participants in this study, hepatitis C treatment was not associated with self-reported improved wellbeing, physical or mental health-related quality of life over the course of the study.

Whilst there is a large body of formal drug registration clinical trial data in the DAA era, there is a paucity of data on PROs, collected among people who inject drugs and in a community or outreach setting. (10) Unlike drug trial data, real-world data do not consistently find improvements in PROs following treatment. (35-37) Further, real-world data reports on a broader range of PRO measures. A recent German study measured health-related quality of life (Short Form-12 Survey) during and following DAA treatment among people on OST (N=328), one third of whom were actively using drugs at baseline. (37) Participants reported mean baseline Physical and Mental Health Component scores (43.7 and 42.4 respectively) that were similar to scores observed in our study (45.0 and 45.9 respectively). (37) The authors also reported no significant improvements in physical health-related quality of life at end of treatment or at SVR12 compared to baseline. Although participants did reported small (approximately three points) but significant improvements in mental health-related quality of life. (37) Contrarily, a study among people co-infected with hepatitis C and HIV, reported significantly improved physical but not mental health-related quality of life at the end of treatment in the sub-group of people who inject drugs, as measured by the Short Form-12 Survey. (35)

Real-world studies often report improvements in some but not all PROs measured. (38-40) For example, a study from Japan reported PROs a year following treatment completion compared to baseline and found significant improvements in cirrhosis-related symptoms, restless leg syndrome, sleepiness, sleep quality and depressive symptoms. (36) However, consistent with our findings, they did not find an improvement in health-related quality of life (as measured by Short-Form 36 Survey). (36) While our study findings are somewhat in line

with the growing body of real-world PRO studies, it is difficult to draw direct comparisons given many of the aforementioned studies are pre- and post-treatment analyses, only include small sub-samples of people who are currently injecting drugs and have been conducted in different settings. Further, there are no published or accepted minimal important differences in PWI or SF-8 Component Scores in people living with hepatitis C.

Although the PRO instruments used in this study did not detect any significant improvements in PROs this does not mean that hepatitis C treatment is not associated with PRO benefits. We suggest two potential explanations for observing no consistent changes in quality of life and wellbeing throughout treatment in a community-based cohort of people who are actively injecting drugs. Firstly, whilst our findings do not indicate an association between treatment and PRO scores, this does not mean participants achieved no improvement in wellbeing. Both the PWI and SF-8 are generic scales, not specific to any single population or disease, each based on a single broad definition of quality of life. Inevitably, these scales may fail to capture the full breadth or nuance of the personal benefits experienced by people who inject drugs who have completed treatment. Qualitative studies conducted in the DAA era have described how hepatitis C treatment affords participants numerous improvements in both psychological and physical wellbeing. Notably, participants report regaining a sense of normality, increased motivation, reduced uncertainty and internalised or experienced stigma. (41-43) Furthermore, the scales used in this study do not capture domains of uncertainty or stigma. Interpreting our findings in the context of qualitative literature, may support the need for a hepatitis C specific-scale to determine the personal impact of DAA treatment on key domains of interest.

Secondly, it is possible participants' baseline PRO scores in this cohort were more heavily influenced by complex social and other health factors evident in participants lives (such as housing, on-going drug use and employment status). This group of participants were injecting drugs multiple times a week and a substantial proportion were experiencing housing instability. A recent study explored trends in PWI scores among people who inject drugs in the SuperMIX cohort (a source of recruitment for our study) over a seven year follow up period. (44) Whilst scores did not significantly differ over the time period, findings suggested increased psychological distress, moving into unstable accommodation or reporting intentional overdose in the past 12 months were associated with decreases in PWI score. (44) This suggests that the PWI is sensitive to change in this cohort and destabilising life events may obscure benefits achieved through hepatitis C treatment. Future studies should explore

the degree to which viral hepatitis C cure and the knowledge of cure directly impact quality of life among people who inject drugs. As well as explore key characteristics of sub-groups who do show improvements in quality of life following treatment.

Our findings should be considered in light of several limitations. Firstly, our study was subject to considerable attrition, which may bias results given it is unlikely patterns of missing data was random and may reduce the accuracy of model estimates. By week 84 only 76 participants contributed outcome data. Secondly, findings may not be generalisable to all people who inject drugs living with hepatitis C in Australia, given participants with HIV co-infection or cirrhosis were excluded. It is possible patterns of PRO change in these sub-groups are different. Further, participants received frequent follow-up, either every four or 12 weeks which may have influenced their quality of life reporting as there may have been a component of 'research fatigue'. It is unclear whether follow-up more closely resembling the clinical pathway, with shorter questionnaires would have altered patterns in quality of life scores. Nevertheless, the inclusion of comparison groups with extended follow-up of a cohort of people who inject drugs receiving treatment in a community setting means our study makes an important and distinct contribution to the limited body of real-world PRO data.

Our study reported on changes in wellbeing and health-related quality of life following DAA treatment in a cohort of people who inject drugs receiving their treatment in an outreach community setting. Treatment was not associated with improved PROs over an 84 week study period. Given the divergence between our findings and existing qualitative literature, we suggest the constructs underpinning the PWI and SF-8 measures may not be the most appropriate for measuring the impacts of hepatitis C treatment specifically. Further, our findings echo the ongoing drive to implement novel community based and people centred health care systems. (45) Whilst treating hepatitis C is undoubtedly efficacious, important for individual liver health and the broader public health, there is a need to address underlying social factors that also contribute to quality of life. It is particularly important to upscale integrated hepatitis C treatment programs, where individuals are offered support for other complex social, physical and mental health concerns alongside hepatitis C treatment.

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Table 1: Screening characteristics of Treatment and Prevention Study sub-analysis participants by treatment status.

Characteristic	**Total cohort**	**Treatment**	**Untreated**	**Non-viremic**
			RNA positive at baseline	**RNA negative at baseline**
Total, n	215	149	22	44
Age, years, mean (SD)	39.6 (±8.1)	40.1 (±8.0)	35.6 (±7.5)	39.6 (±8.2)
Sex				
Female	65 (30.2%)	41 (27.5%)	5 (27.7%)	19 (43.2%)
Male	146 (67.9%)	106 (71.1%)	17 (72.3%)	23 (52.3%)
Missing	4 (1.7%)	2 (1.3%)	0 (0.0%)	2 (4.6%)
Fibrosis status (kPa)				
None to mild (≤7)	161 (74.9%)	106 (71.1%)	17 (77.3%)	38 (86.4%)
Moderate (>7 - ≤9.5)	34 (15.8%)	30 (20.1%)	2 (9.1%)	2 (4.5%)
Severe (>9.5)	7 (3.3%)	4 (2.7%)	3 (13.6%)	0 (0.00%)
Missing	13 (6.0%)	9 (6.0%)	0 (0.0%)	4 (9.1%)
Body Mass Index (kg/m²), median (IQR)	23.4 (21.3 – 26.6)	23.4 (21.3 – 26.9)	22.4 (21.0 – 25.5)	23.6 (21.6 – 27.3)
†**Alcohol consumption**				
Non-drinker	93 (43.3%)	65 (43.6%)	9 (40.9%)	19 (43.2)
Non-hazardous drinker	32 (14.9%)	16 (10.7%)	5 (22.7%)	11 (25.0%)
Hazardous drinker	63 (29.3%)	48 (32.2%)	4 (18.2%)	11 (25.0%)
Missing	27 (12.6%)	20 (13.4%)	4 (18.2%)	3 (6.8%)
On Opioid Substitution Therapy				
No	85 (39.5%)	57 (38.3%)	7 (31.8%)	21 (47.7%)

Yes	91 (42.3%)	64 (43.0%)	9 (40.9%)	18 (40.9%)
Missing	39 (18.1%)	28 (18.8%)	6 (27.3%)	5 (11.4%)
Drug used most in past month				
Heroin	115 (53.5%)	79 (53.0%)	8 (36.4%)	28 (63.6%)
Crystal methamphetamine/ice	23 (10.7%)	19 (12.8%)	2 (9.1%)	2 (4.6%)
Cannabis	44 (20.5%)	26 (17.5%)	8 (36.4%)	10 (22.7%)
‡Other	6 (2.8%)	5 (3.4%)	0 (0.0%)	1 (2.3)
Missing	27 (12.6)	20 (13.4%)	4 (18.2%)	3 (6.8%)
Number of injections in past week, median (IQR)	6 (2 - 14)	6 (2-11)	5 (2-15)	7 (2-14)
Education status				
Completed high school or above	31 (14.4%)	23 (15.4%)	3 (13.6%)	5 (11.4%)
Did not complete high school	152 (70.7%)	103 (69.1%)	15 (68.2%)	34 (77.3%)
Missing	32 (14.9%)	23 (15.4%)	4 (18.2%)	5 (11.4%)
Employment status				
Employed (part time or full time)	19 (8.8%)	14 (9.4%)	2 (9.1%)	3 (6.8%)
Accommodation status				
Stable	146 (67.9%)	102 (68.5%)	13 (59.1%)	31 (70.5%)
Unstable	48 (22.3%)	32 (21.5%)	5 (22.7%)	11 (25.0%)
Missing	21 (9.8%)	15 (10.1%)	4 (18.2%)	2 (4.6%)
*Ever been incarcerated				
No	64 (29.8%)	35 (23.5%)	7 (31.8%)	22 (50.0%)

Yes	124 (57.7%)	95 (63.8%)	11 (50.0%)	18 (40.9%)
Missing	27 (12.6%)	19 (12.8%)	4 (18.2%)	4 (9.1%)

[†]Measured by the brief Alcohol Use Disorders Identification Test (AUDIT-C). [‡] Other incudes: methadone, other opioids, suboxone, benzodiazepines and Unisom + morphine. SD, standard deviation; IQR, interquartile range; [*]represents a significant difference between the three participant groups (p<0.05).

Table 2: Association between participant group and patient-reported outcome scores throughout study follow-up using Generalised Estimating Equations.

	Personal Wellbeing Index			SF-8 Physical Component Score			SF-8 Mental Component Score		
Participant group	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*
Treatment	0.55	-12.45, 13.59	0.934	-1.52	-6.94, 3.90	0.582	-0.64	-8.31, 7.02	0.869
Non-viremic	2.36	-11.89, 16.60	0.745	-1.80	-7.65, 4.05	0.546	-0.12	-8.41, 8.17	0.977

Adjusted for liver stiffness (kPa) and injecting frequency in past week. β: beta coefficient; CI: confidence interval. The non-treated group were used as the reference group

Table 3: Average weekly change in patient-reported outcome scores throughout study follow-up, stratified by participant group.

	Personal Wellbeing Index			SF-8 Physical Component Score			SF-8 Mental Component Score		
Participant group	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*

Treatment	0.27	-0.00 – 0.06	0.083	-0.01	-0.03 – 0.01	0.327	-0.003	-0.03 – 0.02	0.812
Non-viremic	-0.24	-0.09 – 0.04	0.447	0.02	-0.02 – 0.06	0.254	0.02	-0.04 – 0.08	0.470
Non-treated	0.04	-0.12 – 0.20	0.614	0.02	-0.04 – 0.07	0.558	-0.25	-0.11 – 0.06	0.553

β: beta coefficient; CI: confidence interval. The non-treated group were used as the reference group

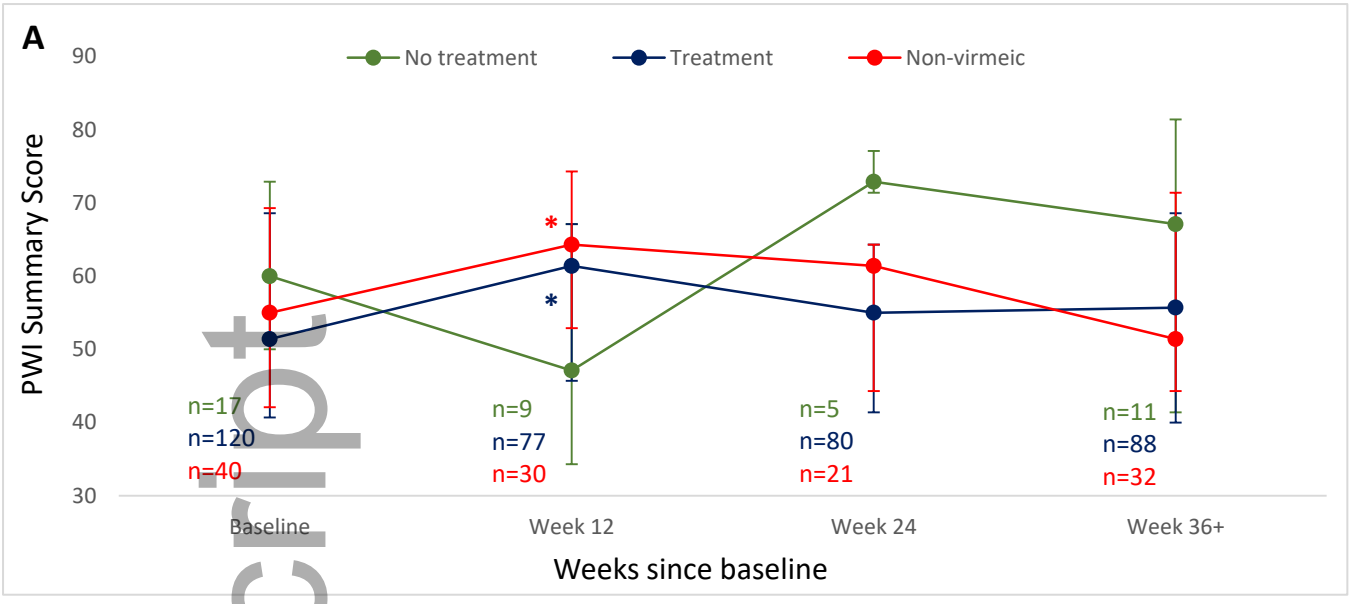
Appendix 1: Association between participant group and patient-reported outcome scores throughout study follow-up using generalised estimating equations, stratified by participants' baseline PRO score quartile.

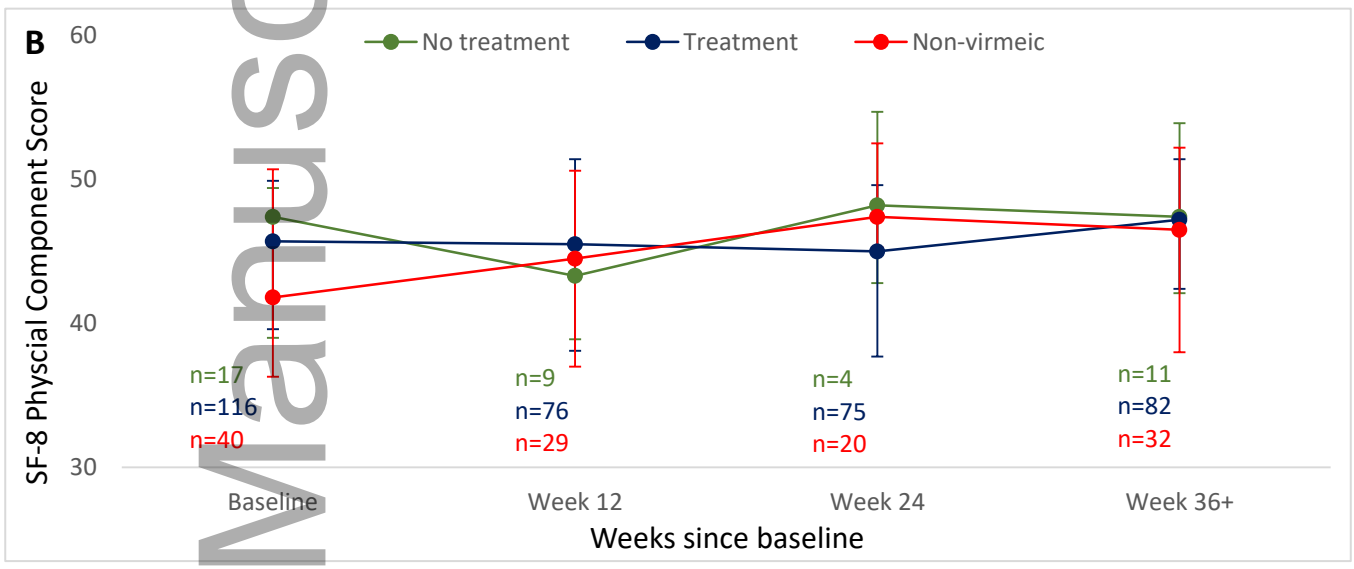
	Personal Wellbeing Index			SF-8 Physical component Score			SF-8 Mental Component Score		
Baseline PRO quartile	β	95% CI	*p*	β	95% CI	*p*	β	95% CI	*p*
Quartile 1									
Treatment	9.46	-33.54, 52.46	0.666	0.93	-12.90, 14.75	0.895	3.94	-10.51, 18.39	0.593
Non-viremic	12.30	-34.23, 58.84	0.604	3.44	-10.73, 17.61	0.634	3.69	-11.89, 19.27	0.643
Quartile 2									
Treatment	19.91	-10.61, 50.44	0.201	-5.24	-12.71, 2.23	0.169	9.19	-4.28, 22.66	0.181
Non-viremic	26.51	-4.76, 57.79	0.097	-4.91	-12.55, 2.74	0.208	11.20	-2.76, 25.15	0.116
Quartile 3									
Treatment	4.42	-11.16, 20.00	0.578	-4.30	-14.73, 6.13	0.419	-2.01	-24.41, 20.40	0.861
Non-viremic	2.80	-14.85, 20.45	0.756	-5.47	-17.30, 6.35	0.364	-3.90	-27.31, 19.50	0.744
Quartile 4									
Treatment	1.22	-13.63, 16.06	0.873	0.02	-8.62, 8.66	0.996	-2.82	-13.07, 7.43	0.590
Non-viremic	3.24	-13.45, 19.97	0.704	1.22	-8.28, 10.71	0.802	0.59	-11.37, 12.55	0.923

Adjusted for liver stiffness (kPa) and injecting frequency in past week. β: beta coefficient; CI: confidence interval. The non-treated group were used as the reference group

Figure legends

Figure 1: Changes in wellbeing (A), physical (B) and mental (C) health-related quality of life throughout the Treatment and Prevention Study, by participant group. Asterisks (*) indicates a significant difference ($p<0.05$) within a group at follow up visit compared to baseline.





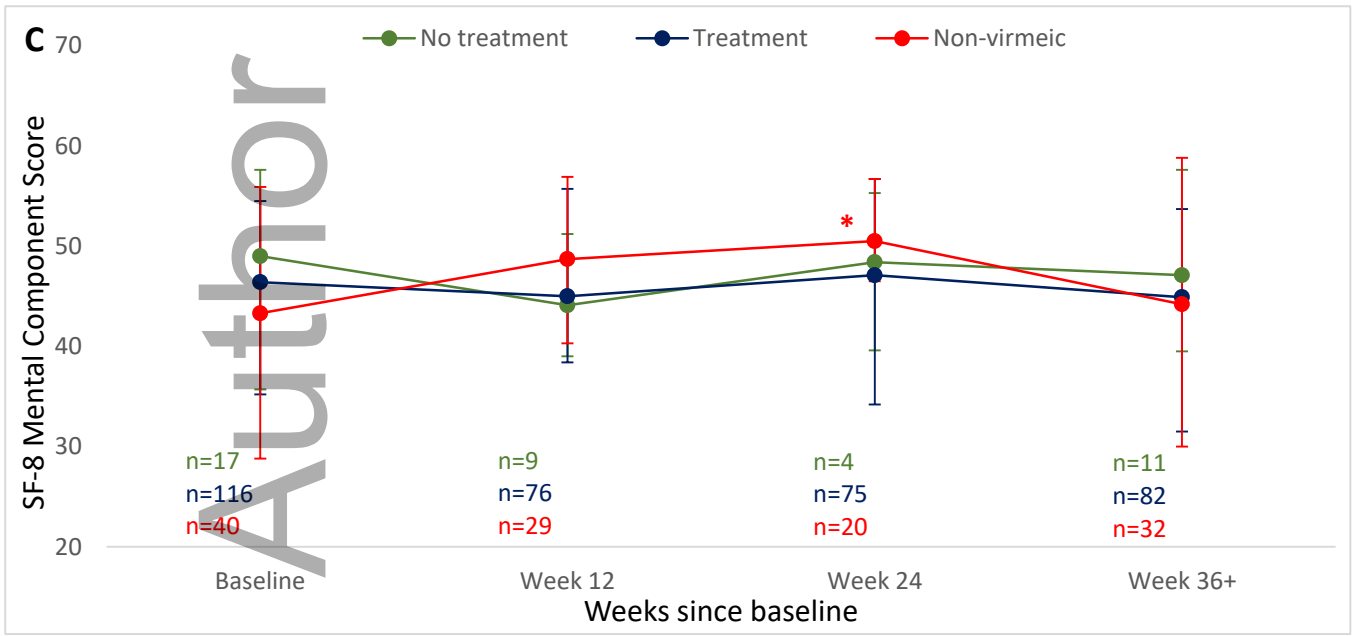


Figure 1: Changes in wellbeing (A), physical (B) and mental (C) health-related quality of life throughout the Treatment and Prevention Study, by participant group. Asterisks (*) indicates a significant difference ($p<0.05$) within a group at follow up visit compared to baseline. Week 36+ represents outcome data from participants' first available visit from week 36 onwards.