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Title

Improved quality of life following direct-acting antiviral treatment for chronic hepatitis C infection in Rwanda: Results from a clinical trial in sub-Saharan Africa (the SHARED study)

Running title

Quality of life after hepatitis C treatment

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Abstract (245 words)

Around 71 million people are living with chronic hepatitis C virus (HCV) infection, with approximately 14% residing in Sub-Saharan Africa. Direct acting anti-viral (DAA) therapies offer clear benefits for liver-related morbidity and mortality, and data from high-income settings suggest that DAA treatments also provide significant benefits in terms of health-related quality of life (HRQL). In this study, we assessed the effect of DAA treatment on HRQL for individuals treated for HCV in a clinical trial in Rwanda. We assessed the HRQL of participants using an 83-question composite survey at Day 0 ('baseline') and Week 24 ('endpoint'). Data were analyzed in R.

296 participants were included in this analysis. Their ages ranged from 19-90 and 184 (62.2%) were female. There were significant improvements from baseline to endpoint median scores for all physical and mental quality of life sub-scales. Additionally, a reduction – before and after treatment - in the proportion of those classified as depressed and needing social support was statistically significant (both $p<0.001$). Economic productivity increased after treatment ($p<0.001$) and households classified as food secure increased from baseline to endpoint ($p<0.001$). These results demonstrate that Rwandans with chronic HCV infection experience both clinical and HRQL benefits, including household level benefits like substantial gains in workforce stability, economic productivity, and poverty alleviation, from DAA treatment. A stronger demonstration of accurate and broader household level benefits achieved through treatment of HCV with DAAs will help financing and investment for HCV in resource-constrained settings become an urgent priority.

Keywords

Hepatitis C virus, Rwanda, Quality of life

Word count: 3825/4000

Main text

Introduction

Of the estimated 71.1 million people with chronic hepatitis C virus (HCV) infection globally, 10.1 million (14%) live in Sub-Saharan Africa (SSA).[1,2] The burden of liver cirrhosis in this region doubled from 1990 to 2010[3], and currently, liver cancer is the fourth leading cause of cancer mortality (second most common in men).[4] HCV contributes to roughly half of viral hepatitis related mortality in SSA.[5] In addition to morbidity and mortality due to liver-associated sequelae, extensive extrahepatic conditions attributable to chronic HCV infection include depression, diabetes, and chronic renal disease.[6]

There are clear medical benefits of treatment for HCV infection in terms of liver-related and all-cause mortality and decreased incidence of hepatocellular carcinoma.[7] In addition, there is increasing evidence from high-income settings that treatment with all-oral direct acting antiviral (DAA) regimens also provides significant benefits in terms of health-related quality of life (HRQL).[8–11] Results from clinical trials conducted in the USA and several European countries showed an improvement in HRQL after achievement of sustained virologic response (SVR) for participants who were treated with ledipasvir/sofosbuvir (LDV/SOF) regardless of fibrosis status.[9] Results from a clinical study in Spain that examined changes in HRQL after successful treatment with DAAs also found improvements in HRQL, and those with lower HRQL baseline scores had more pronounced improvements by the end of the treatment.[10] In Japan, researchers found that HRQL improved within four weeks of starting DAA treatment and continued to improve throughout the duration of treatment.[11] In Australia, researchers conducted a qualitative study that demonstrated psychosocial improvements and a feeling of return to "normality" after treatment with all-oral DAA regimens.[12] The HRQL benefits from DAA treatment have been consistently more pronounced than HRQL changes during and after treatment with interferon-based (INF) therapies.[13–16] Previous studies in high-income settings have suggested increased work productivity following HCV treatment with DAAs, including participants with minimal fibrosis.[9]

Although treatment for HCV remains limited in SSA, a growing number of countries have now developed national guidelines and plans for HCV diagnosis and treatment, including DAA regimens as first-line therapy.[17] Given severe resource restrictions in most countries in this region, national programs are challenged with allocating public resources to subsidize the cost of HCV care and treatment, and treatment is largely dependent on out-of-pocket payments that are out of

reach to the majority of patients.[18] In order to include HCV care and treatment in essential health benefits packages, countries in this region are therefore tasked with the challenge to provide accurate and comprehensive information on the costs of diagnosis and treatment, as well as the downstream epidemiologic and economic impacts of treatment on both the individual and population levels. Currently, published studies in LMIC contexts have focused solely on treatment success associated with DAA treatment and have not yet quantified potential secondary benefits of HCV cure with these medications. Here, we aim to assess the effect of DAA treatment related to physical quality of life, mental quality of life, depression, social support, employment and income, and food security for individuals treated in a clinical trial in Rwanda.

Material & Methods

Study Setting

Rwanda is located in the Great Lakes region of East Africa with a population projection of 12.4 million people in 2019.[19] Seventy-one percent of Rwandans work in agricultural occupations and 39.1% of the population live below the poverty line.[20] The prevalence of HCV antibody positivity has been reported as 6.8 – 8.9% in large scale screening campaigns of the general adult population in Rwanda and 4.3 - 4.7% in people living with HIV, though the proportion with chronic infection may be substantially lower.[21–23] Older age and traditional scarification or medical practices were reported as risk factors for HCV acquisition, and the rate of intravenous drug use is extremely low.[21,24] Due to high-level political commitment for the HCV response, robust decentralization and task shifting of HCV care, and central negotiation and procurement of affordable commodities, Rwanda was the first country in SSA to develop an ambitious national elimination goal for HCV by 2024.[25,26]

Study Design & Data Collection

This study was conducted as part of an open-label clinical trial to assess the safety and efficacy of LDV/SOF for adults with genotype 1 or 4 HCV infection in Rwanda ["*Simplifying Hepatitis C Antiviral Therapy in Rwanda for Elsewhere in the Developing World (SHARED)*"; NCT02964091].[27] This study enrolled 300 participants and administered 12 weeks of once daily

LDV/SOF in a fixed-dose combination pill. Individuals with decompensated cirrhosis, hepatitis B co-infection, uncontrolled HIV infection, or other significant co-morbidities limiting study treatment were excluded. Individuals with active drug use or other circumstances limiting ability to comply with study visits or procedures were also excluded. Fibrosis was assessed by aminotransferase platelet ratio index (APRI). All participants were referred from the four major referral hospitals in Rwanda.

All participants were administered an 83-question composite survey at the time of treatment initiation ("baseline") and 12 weeks following the completion of treatment ("endpoint"). The composite survey was comprised of the Medical Outcomes Survey ("MOS-HIV"; 13 questions with 22 sub-items), Hopkins Symptoms Checklist ("HSC-15"; 15 questions), Duke-UNC Functional Social Support Questionnaire ("FSSQ"; 12 questions), Household Food Insecurity Access Scale ("HFIAS"; 9 questions), an expanded stigma index[28] (13 questions), and 21 novel individual questions related to stigma/discrimination, medication and visit adherence, HCV status disclosure, health seeking behaviors and income. All questions in the composite survey were translated into Kinyarwanda and, where relevant, adapted from human immunodeficiency virus (HIV) to HCV. The Kinyarwanda versions of the MOH-HIV, HSC-15, and FSSQ have previously been validated in Rwanda in the local language of Kinyarwanda.[29] Three trained study clinicians (two nurses and one social worker) administered the survey in the Kinyarwanda at baseline and endpoint at the study site.

Questionnaire Components and Statistical Analysis

The MOS-HIV survey contains 24 sub-items related to physical health and 11 sub-items related to mental health.[30] The survey assesses 11 dimensions (or sub-scales), including general health perceptions (5 sub-items), physical functioning (6 sub-items), role functioning (2 sub-items), pain (2 sub-items), social functioning (1 sub-item), mental health (5 sub-items), energy/fatigue (4 sub-items), health distress (4 sub-items), cognitive functioning (4 sub-items), health transition (1 sub-item), and overall quality of life (1 sub-item). We computed the raw score for each dimension and transformed the raw scores to a 0 to 100 scale to allow for comparisons across dimensions. A higher score corresponded with higher quality of life for that specific dimension. Next, we computed two summary scores that represented physical and mental health across 10 dimensions.

The physical health summary (PHS) score was made up of the following dimensions: physical function, pain, role function, vitality, general health, and social function. The mental health summary (MHS) score was made up of the following dimensions: mental health, health distress, quality of life, cognitive function, vitality, general health, and social function. We calculated a z-score transformation for each dimension and then aggregated the summary scores using published scoring co-efficients. Finally, we transformed the scores to a mean of 50 and standard deviation of 10. For each dimension and summary score, we calculated the median score for both baseline and endpoint surveys. We compared the scores for each dimension and summary score from baseline to endpoint using Wilcoxon sign rank test. We stratified PHS and MHS scores by fibrosis (APRI >/= 1.5), sex, HIV status, and SVR12 achievement and used the Wilcoxon-Mann Whitney test to compare the differences among individuals from baseline to endpoint.

The HSC-15 assesses the presence of depressive symptoms over the previous week. Examples of symptoms include "feeling low in energy, slowed down", "worrying too much about things", and "feelings of worthlessness". Respondents were asked to rate how much the symptoms "bothered or distressed you in the last week, including today" on a scale from 1 to 4, with higher scores reflecting greater depressive symptoms. Depression is defined as a mean score of >1.75.[31] We compared the depression scores before and after treatment using the Wilcoxon sign rank test and the differences in proportion of those defined as depressed using the McNemar test. In the FSSQ, respondents were asked to rate perceived social support received in given situations from 1 to 5 with higher scores reflecting higher perceived social support.[32] Examples include "You get help when you are sick in bed" and "Your friends and family visit you." The composite survey also included three questions on topics related to medication and appointment adherence and three questions on HCV status disclosure ("Have you disclosed your HCV status to anyone? If yes, how many people?" If yes, "Have you disclosed to your partner? To other family members? To friends and/or neighbors outside of the home?"). Responses were summed and scores were compared before and after treatment for each participant using the Wilcoxon sign rank test for numeric data and the McNemar test for categorical data. Questions related to stigma and discrimination were not analyzed in this study.

The HFIAS was utilized to assess if a respondent's household had access to enough or a variety of food within the last 30 days. There are four possible responses to each question ("no"=0,

"rarely"=1, "sometimes"=2, "often"=3). An example of a question is, "Did you or any household members eat a limited variety of food due to lack of resources?" The total score ranges from 0-27, with 27 being most severely food insecure. The HFIAS category is determined by the average of all responses and households are categorized according to the following scale: 1=food secure, 2=mildly food insecure access, 3=moderately food insecure access, 4=severely food insecure access. Two additional questions assessed primary water source and travel time to water source. We compared food security before and after treatment using the Wilcoxon sign rank test and the differences in proportion of the FIAS categories using McNemar-Bowker test. Participants were also asked questions related to income ("What was the total monthly income for your family in the last month?"), ability to work ("Are you presently physically able to work? If yes, do you receive cash for your work? If no, why not?"), and six additional questions related to healthcare seeking and access to medical services. Responses for each participant were compared pre-/post- using Wilcoxon sign rank test for numeric data and McNemar test for categorical data.

All responses were recorded on hard copy by the study clinician. Data were entered into a Redcap database by a data officer, and all data points reviewed for accuracy by a separate study staff member. Demographic and clinical information for all study participants were summarized using descriptive statistics. All analyses were conducted using R statistical software.[33]

Ethics

All study participants provided written informed consent prior to study initiation. The study was approved by the Rwanda National Ethics Committee (No. 738/RNEC/2016), Rwanda National Health Research Committee, Partners Human Research Committee (Boston, USA), and Stanford University Institutional Review Board (Palo Alto, USA).

Results

Participant Characteristics

Two hundred ninety-six of the 300 enrolled participants completed both baseline and endpoint surveys and were included in the analysis. For the four participants who were not included in the

analysis, one participant died prior to study completion, one participant withdrew from the study due to a decompensated cirrhosis diagnosis, and two participants declined to complete the endpoint survey. Overall, study participants' ages ranged from 19-90 with a median age of 64, and 184 (62.2%) were female. Almost half (48.0%) of the participants had primary school education or below and 175 (59.1%) were married. Participants were from all provinces of Rwanda with the largest proportion, 111 (37.5%), from the urban center of Kigali. Two hundred and seventy-five of the 296 (92.9%) of the participants had a monthly income of less than 200,000 Rwandan Francs per month ($242 USD) and 263 (88.9%) had community-based health insurance. One hundred and eighty-nine participants (63.9%) were not employed. Median HCV viral load at screening visit was 5.0 $\log_{10}$ IU/ml. Two hundred and fifty-two (85.1%) of participants had an APRI score of < 1.5 and 292 (98.6%) of participants were Child-Turcotte-Pugh class A. Self-reported co-morbid conditions included hypertension (43.2%), diabetes (18.6%), HIV (9.8%), and depression (2.0%) (see Table 1). Two hundred fifty-nine of the 296 (87.5 %) patients achieved SVR12.

Physical Quality of Life

There was significant improvement from baseline to endpoint for all physical quality of life sub-scales, including physical function (p-value<0.001), pain (p<0.001), role function (p<0.001), vitality (p<0.001), general health (p<0.001), and social function (p<0.001) (Figure 1). The PHS scores at endpoint were statistically significantly higher than PHS baseline scores (p<0.001). Participants with advanced fibrosis (APRI score >1.5) had more improvements in physical health after treatment than those with lower APRI scores (p=0.011). There were no statistically significant differences in PHS based on sex, HIV status, or treatment success.

Mental Quality of Life, Depression & Social Support

There was significant improvement from baseline to endpoint for all mental quality of life sub-scales, including mental health (p<0.001), health distress (p<0.001), quality of life (p<0.001), cognitive function (p<0.001), vitality (p<0.001), general health (p<0.001), and social function (p<0.001) (Figure 1). The MHS scores at endpoint were statistically significantly higher than MHS baseline scores (p<0.001). Health transition, though not used in the calculation for either summary score, also improved from 50.0 at baseline to 75.0 at endpoint (p<0.001). There were no

statistically significant differences in the MHS score based on sex, HIV status, advanced fibrosis, or treatment success.

The median depression score reduced from 17 at baseline to 15 at endpoint. The depression scores at endpoint were statistically significantly higher than depression scores baseline depression scores ($p<0.001$). The proportion of participants classified as depressed (i.e. average score >1.75) decreased from 8.1% (24/296) at baseline to 2.0% (6/296) at endpoint after treatment ($p<0.001$) (Figure 2a & b). Social support increased after treatment ($p<0.001$). Overall, at baseline, 98.7% (292/296) of participants had disclosed their HCV status to at least one person and at endpoint all participants had disclosed to at least one person. The proportion of participants disclosing their HCV status to friends/neighbors increased from 65.4% (189/289) to 81.0% (238/294) ($p<0.001$) and to family members from 95.5% (276/289) at baseline to 99.0% (290/293) at endpoint ($p=0.016$). The proportion of participants disclosing HCV status to their partner increased from 92.9% (171/184) to 96.6% (172/178) though these changes were not significant ($p=1.000$).

Employment and Economic Productivity

The proportion of participants reporting physical ability to work increased from 54.1% (160/296) at baseline to 68.6% (203/296) at endpoint ($p<0.001$) and those able to earn cash increased from 29.9% (58/194) at baseline to 36.5% (80/219) at endpoint ($p=0.045$) (Figure 3). Thirty-four participants at baseline and 16 at endpoint reported that they were not physically able to work stated but were able to earn cash. The median income did not change from baseline to endpoint ($p=0.104$). Food security scores at endpoint were statistically significantly higher than scores at baseline ($p<0.001$). The proportion of participants from households classified as food secure increased from 48.6% at baseline to 66.6% at endpoint ($p<0.001$).

Discussion

In this large prospective study of adults treated with DAAs for HCV infection in Rwanda, we found significant improvements in physical, mental, social, and economic aspects of HRQL following treatment. Importantly, there were improvements in all dimensions of physical and mental quality of life on both individual and summary scales. The overall proportion and

magnitude of depression decreased following treatment, and reported social support significantly improved. In addition, the ability to work and earn cash increased after treatment, and food security significantly improved from baseline to endpoint. To our knowledge, this is the first prospective study to directly measure non-clinical outcomes of all-oral DAA treatment in a low-income country setting.

The overall increase across domains of HRQL is similar to that previously reported in clinical trials in high income settings.[8–11,16] Younossi (2015) reported robust improvements in most domains of the MOS Short-Form General Health Survey (SF-36) survey instrument, including physical functioning, role physical, bodily pain, general health, vitality, social functioning, and physical summary score of all fibrosis stages, also treated with LDV/SOF. In contrast to our findings of improvements in mental health and depression, Younossi et al (2018) did not find significant improvements in mental health related domains of the SF-36 or Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) but did report significant improvements in mental health aspects of the Chronic Liver Disease Questionnaire (CLDQ-HCV). The somewhat more robust findings in improvements in mental health quality of life in our study may reflect the overall high rate of mental health impairment and depressive symptoms in Rwanda and lack of previous engagement in care services, both for HCV as well as formal health care more broadly. Participants in our study have previously reported the activation of social support networks through the process of HCV care seeking and treatment.[34] People with active injection drug use or receiving opioid substitution therapy may have lower HRQL overall, especially regarding mental HRQL[35,36] but were not enrolled in this study. In Rwanda, similar improvements in depressive symptoms and depression have been demonstrated in individuals with HIV completing one year of antiretroviral therapy and community-based support.[37] In contrast to findings reported by Younossi et al (2018), participants in our study with advanced fibrosis (APRI>1.5) did have significantly greater improvements in overall physical quality of life. This may reflect a greater extent of baseline impairment and more advanced median age of the cohort, though the different survey instruments utilized in the two studies limit direct comparisons of HRQL impairment between the two groups.

Our findings suggested improvements in physical or mental health summary scores were independent of achievement of SVR12. This is in contrast to recent results from an observational

study in US that found that those who did not achieve SVR after treatment with common DAA regimens had minimal improvements in several elements related to quality of life.[38] In Japan, HRQL were significantly higher for those who achieved SVR than those who did not.[11] One possibility for this finding is that most (86.5%; 32/37) participants who did not achieve SVR12 in our cohort did experience complete suppression of HCV viremia at the end of treatment, and many had significant viral load decreases at endpoint compared to baseline. Rapid improvements in HRQL in patients treated with DAA regimens as compared to IFN-containing regimens has been previously attributed to more rapid suppression or clearance of HCV viremia.[9] Clearance of viremia has been associated with improvement in cerebral inflammation and neurocognitive parameters.[39] Another possibility is the additional impact of formal health care seeking through the clinical trial. A large number of patients were diagnosed for the first time with chronic conditions such as hypertension, diabetes, depression, helicobacter-associated gastritis, migraine headaches, and arthritis, and received concomitant treatment for these conditions outside of the clinical trial.[27]

Our findings of improved ability to work, earn cash, and achievement of household food security following HCV treatment with DAAs are dramatic and important, however, these data are self-reported and participants may have felt more comfortable with study staff about their financial situation by the end of the study. The very low average earnings and high proportion of lack of formal employment among the participants in this study reflects the general population of Rwanda. The Gross Domestic Product (GDP) per capita of Rwanda ($773 USD) approximates the median of low-income countries globally ($721 USD) and SSA countries in general ($1014 USD).[40] In qualitative interviews, participants in this cohort reported lack of household finances as a major barrier to their HCV diagnosis and treatment and overall health care seeking behaviors as well as a primary life stressor.[34] Return to employment and ability to increase household earnings may not only result in improvements in household food security but also in improved financial resiliency, education, and overall poverty alleviation. Large scale investments in large-scale programs for other infectious diseases, such as HIV and TB, have demonstrated long-term gains in economic productivity in highly resource-constrained countries,[41,42] and preliminary modeling of the macroeconomic impact of investment in viral hepatitis programming has been encouraging.[43]

There were several limitations to this study. The clinical or "real-life" significance of change in scores from pre- to post-treatment on several of the survey instruments is difficult to assess. Additionally, survey instruments used in this study are different than those commonly used in high-income clinical trial settings, and individual survey questions were novel for this study, thereby limiting direct comparisons of findings with other study populations. The MOS-HIV was specifically created for HIV and has not been formally endorsed or validated for patients with HCV. However, three of the survey instruments, the MOS-HIV, HSC-15, and FSSQ, have been previously translated in the local language of Kinyarwanda and validated in a Rwandan population, providing essential linguistic accuracy and contextual/cultural appropriateness, which to our knowledge was not available for more commonly used survey instruments in HCV-related studies in high-income settings (i.e., SF-36, CLDQ-HCV, Hepatitis Quality of Life Questionnaire) at the time of initiation of our study. Use of APRI score to determine fibrosis stage in patients with hepatitis in SSA has not been well validated and may be underestimated due to endemic conditions leading to thrombocytopenia. However, in this context, more advanced measures of fibrosis measurement such as liver biopsy and elastography are not routinely available, and therefore non-invasive tests such as APRI are currently recommended by national and international guidelines. Finally, the clinical trial setting may have provided an enhanced standard of clinical care or adherence support for patients in this study compared to other resource-constrained contexts, thereby limiting generalizability in SSA or similar regions. However, the study was conducted at a public-sector referral hospital with a clinical team resembling the standard of referral care in Rwanda. Study staff were able to contact participants by phone in case of missed visits and adverse events, but no additional adherence or psychosocial support measures were provided.

The results from this study demonstrate that Rwandans with chronic HCV infection experience a robust and diverse set of benefits from HCV treatment with DAAs, including improvements in physical quality of life, mental quality of life, depression, social support, perceived ability to work and earn income, and household food security. Overall, these findings support the need for investment and increased scale-up of HCV case finding and treatment in SSA and similar high-burden resource-constrained settings. In addition to the well-established liver-related morbidity and mortality benefits, our findings demonstrate dramatic secondary benefits that when considered on a population scale could result in substantial gains in workforce stability, economic

productivity, and poverty alleviation. Current economic models to inform national programs on the cost-effectiveness of DAA-based HCV treatment do not adequately include these benefits and therefore may significantly underestimate the wide-scale benefits of this simple, low-cost, highly-effective, and time-limited health sector intervention. Further research is needed to more directly quantify household economic and large-scale macroeconomic impacts of HCV treatment with DAAs in various settings in this region, including real-life scenarios. Only with an accurate and expanded picture of the true population level benefits achieved through treatment of HCV with DAAs will financing and investment for the HCV response in resource-constrained settings become an urgent priority.

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Table 1 Baseline demographic and clinical characteristics of study participants

	n (%)
Age, median (IQR)	64 (55 - 72)
Female sex	184 (62.2)
Education	
No formal education	76 (25.7)
Primary school	66 (22.3)
Secondary school	29 (9.8)
Trade school	49 (16.6)
University	28 (9.5)
Unknown	48 (16.2)
Formal employment	
Skilled or non-skilled worker	16 (5.5)
Civil servant	32 (10.8)
Other	59 (19.9)
Not employed	189 (63.9)
Province	
North	33 (11.1)
South	55 (18.6)
East	54 (18.2)
West	43 (14.5)
Kigali	111 (37.5)
Marital Status	
Married	175 (59.1)
Not married	121 (40.9)
Health Insurance	
Community based insurance	263 (88.9)
Public servant	22 (7.4)
Private insurance	4 (1.4)
No insurance	7 (2.4)
Income (1USD=828 RWF)	
<$21.13	123 (41.6)
$21.14 - 42.87	56 (18.9)

$43.48 - 120.77	63 (21.3)
$120.77 - 241.54	33 (11.1)
>$241.55	20 (6.8)
No data	1 (0.3)
Median HCV RNA level (IU/ml)	983,504
Comorbid conditions	
Hypertension	128 (43.2)
Diabetes	55 (18.6)
HIV	29 (9.8)
Depression	6 (2.0)
Treatment Experience	
Treatment naïve	293 (99.0)
Treatment experienced	3 (1.0)
APRI score at enrollment	
APRI < 1.5	252 (85.1)
APRI >= 1.5	44 (14.9)
Child-Turcotte-Pugh Class	
A: (5-6 points)	292 (98.6)
B: (7-9 points)	4 (1.4)
C: (10-15 points)	0 (0.0)

Figure 1. Box plot showing quality of life dimension scores, Mental Health Summary Score (MHS), and Physical Health Summary Score (PHS) at baseline (entry visit) and endpoint (week 24 visit). Box indicates interquartile range, vertical lines indicate range, and bolded horizontal line indicates median.

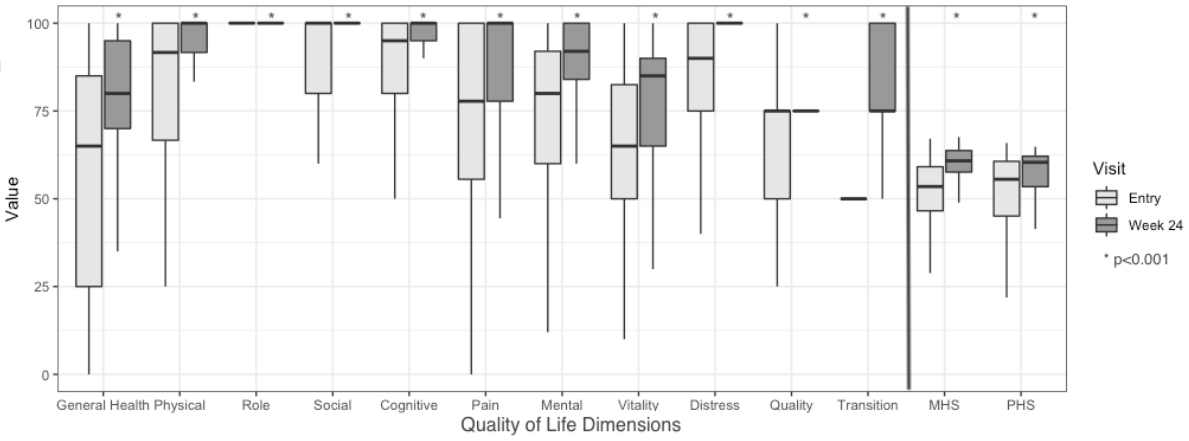

Figure 2a. Total depression score at baseline (entry visit) and endpoint (week 24 visit)

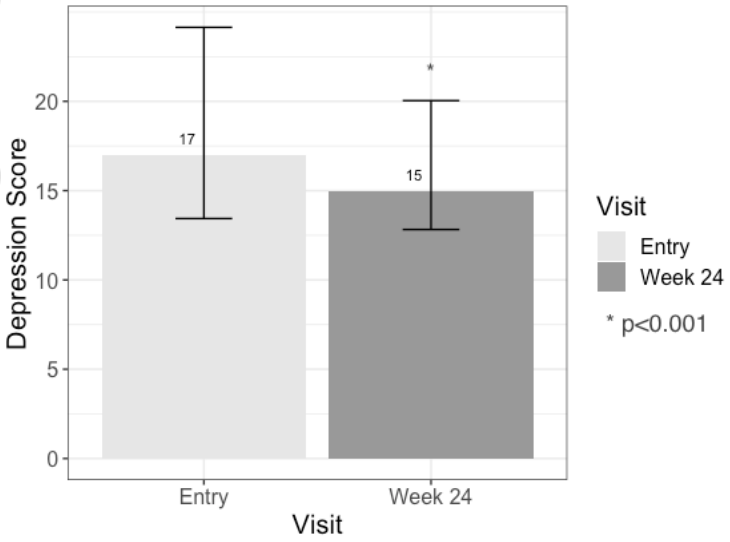

Figure 2b. Percentage of participants classified as depressed (average depression score >1.75) at baseline (entry visit) and endpoint (week 24 visit)

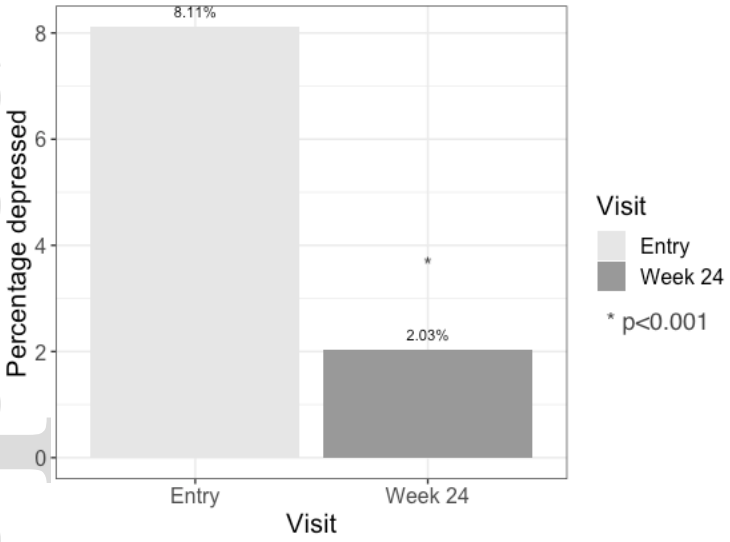

Figure 3. Economic productivity at baseline (entry visit) and endpoint (week 24 visit)