Research article

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Patient-reported outcomes with direct-acting antiviral treatment for hepatitis C in West and Central Africa (TAC ANRS 12311 trial)

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Background & Aims: Patient-reported outcomes (PROs) are poorly documented for patients with chronic hepatitis C on direct-acting antiviral (DAA) treatment in low-to-middle-income countries. We documented PROs during and after DAA treatment in participants of the TAC ANRS 12311 trial (West and Central Africa).
Methods: Trial participants received a 12-week regimen containing either sofosbuvir plus ribavirin (HCV genotype 2, n = 40), or sofosbuvir plus ledipasvir (HCV genotypes 1 and 4, n = 80). Health-related quality of life (SF-12), fatigue (Piper Fatigue scale), and self-reported symptoms (35-symptom list) were assessed at enrolment (Week (W) 0), during treatment (W2, W4, W8 and W12) and after treatment (W24 and W36). These PROs were compared between W0 and W36 (Wilcoxon signed-rank or McNemar tests). Mixed-effects linear regression models helped identify correlates of physical and mental quality of life component summaries (PCS and MCS) in a longitudinal analysis.
Results: Most PROs were significantly improved 24 weeks after treatment end (W36), without significant differences between treatment groups. For the post-treatment period, multivariable analysis showed significant increases in PCS for patients with cirrhosis and in MCS for patients in the sofosbuvir plus ribavirin group. A higher number of self-reported symptoms at W0 was associated with lower PCS and MCS, older age and cirrhosis with lower PCS, and male sex and HCV cure with higher PCS.
Conclusions: Sofosbuvir-based DAA therapy was associated with a significant improvement in PROs 6 months after treatment end in patients with chronic HCV infection from Central and West Africa. These findings may guide HCV treatment providers in low-to-middle-income countries to deliver pre-treatment information concerning the benefits of DAAs beyond viral eradication.
ClinicalTrials.gov Identifier: NCT02405013.
Impact and implications: Perceptions and experiences (*i.e.* "patient-reported outcomes") of patients with chronic hepatitis C receiving direct-acting antivirals (DAAs) are poorly documented in the African setting. This study shows significant improvements in health-related quality of life, fatigue, and self-reported symptoms 24 weeks after the end of a 12-week sofosbuvir-based DAA regimen in 120 patients from Central and West Africa. These findings substantially add to the body of knowledge about DAA therapy in the African setting. Treatment providers should be encouraged to inform patients of the benefits of DAAs beyond viral eradication, to increase treatment adherence and retention in care.
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Introduction

The advent of direct-acting antivirals (DAAs) has paved the way for a hepatitis C-free world, an objective set by the World Health Organization (WHO) for 2030.[1] The WHO Global Health Strategy for viral hepatitis 2016-2021[2] identified priority actions, including expanding access to treatment to ensure that 80% of eligible persons with chronic HCV infection are treated by 2030. More recently, the Lancet Gastroenterology and Hepatology Commission highlighted the need to include essential medicines for viral hepatitis in national programs, with a priority given to pan-genotypic DAAs.[3] However, the road to optimal access to

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HCV treatment is still long, with large geographical disparities in treatment coverage rates, the WHO African region showing the lowest rate.[3]

Available data from both clinical trials and observational studies – mainly conducted in high-resource settings – show excellent DAA efficacy in all patient populations,[4–6] including with generic formulations.[7] In this era, when a cure for HCV is possible for most infected individuals receiving treatment, patient-reported outcomes (PROs) – such as health-related quality of life (HRQL), HCV self-reported symptoms, and fatigue – also play a role in the clinical management of hepatitis C.[8] Providing information on patients' experiences with DAAs and on expected improvements in quality of life thanks to HCV cure can help foster adherence and retention in care. The latter may be specifically challenging in low-to-middle income countries (LMICs), where the global cost of care represents a heavy burden for many patients.[9] Documenting PROs in LMICs is therefore a key issue to advocate and facilitate successful scale-up of DAAs there.[10]

Studies performed in high-resource settings show a global improvement of PROs after DAA treatment and HCV cure,[11–14] even though patients' experiences with these new therapies differ.[15] However, data on PROs in LMICs are lacking, as are policy-relevant data on viral hepatitis in sub-Saharan Africa in general.[16]

The non-randomized, international pilot trial ANRS 12311 TAC demonstrated the efficacy and safety of sofosbuvir-based regimens in treatment-naïve patients with chronic HCV infection in Cameroon, Côte d'Ivoire and Senegal.[17] The present study documented PROs during and after DAA treatment in participants in the trial.

Patients and methods

The ANRS 12311 TAC trial

ANRS 12311 TAC is an international, phase IIb, open-label, non-randomized trial conducted in 120 treatment-naïve adults with confirmed genotype 1, 2 or 4 HCV infection. The main eligibility criteria for participation in the trial were being at least 18 years old, having proven chronic HCV infection (third-generation ELISA IgG test) with genotype 1, 2 or 4 and HCV-RNA >12 IU/ml, no previous exposure to HCV treatment, agreement on using a contraceptive method 1-month prior treatment initiation and 7 months after treatment completion, weight between 40 and 125 kg and signed informed consent. The following additional criteria applied for HIV-HCV-coinfected patients: HIV infection confirmed by fourth-generation ELISA and western blot, receiving stable antiretroviral treatment for at least 8 weeks, with two nucleos(t)ide reverse-transcription inhibitors (tenofovir or abacavir, and lamivudine or emtricitabine) and a third agent (raltegravir, lopinavir/ritonavir, atazanavir/ritonavir, darunavir/ritonavir, efavirenz), CD4 T-cell count >100 cells/μl and plasma HIV-RNA <200 copies/ml. Non-inclusion criteria were as follows: positive HBsAg rapid test, known Child-Pugh B or C cirrhosis, pregnancy or breastfeeding, refusal of contraception, history of organ transplantation, comorbidities such as cancer (including hepatocellular carcinoma), epilepsy, drepanocytosis, myocardial infarction, QT elongation ≥20 ms, daily alcohol consumption >20 g (women) or 40 g (men), active drug use, hemoglobin <10 g/ml (women) and 11 g/ml (men), platelet count <50,000/μl, neutrophil count <750/μl, creatinine clearance with Modification of Diet in Renal Disease formula <50 ml/min, history of severe opportunistic infections in the previous 6 months and, for HIV-HCV-coinfected patients, history of non-adherence to antiretroviral treatment, and use of antiretrovirals other than those authorized in the trial. Trial participants were divided into two treatment groups, one administered a 12-week treatment with sofosbuvir plus ledipasvir (for patients infected with genotype 1 or 4: SOF/LDV group, n = 80) and the other sofosbuvir plus weight-based ribavirin (for patients infected with genotype 2: SOF/RBV group, n = 40), and were then followed for 24 weeks (total trial duration: 36 weeks). Following the WHO guidelines

Table 1. Main characteristics of the study population at baseline (W0) (ANRS 12311 TAC trial, N = 120).

Characteristics (no. of missing values)	All patients (n = 120)	Treatment group		*p* value[1]
		SOF/LDV (n = 80)	SOF/RBV (n = 40)	
Male sex (0)	65 (54.2)	40 (50.0)	25 (63.5)	0.271
Age (0) - in years	58.0 [49.0–63.0]	60.0 [53.0–64.0]	52.0 [41.0– 60.0]	0.001
Matrimonial status (0)				0.861
No partner	20 (16.7)	14 (17.5)	6 (15.0)	
Married/common law	90 (75.0)	60 (75.0)	30 (75.0)	
Regular partner, not living together	10 (8.3)	6 (7.5)	4 (10.0)	
Has received income in the previous month (0)	58 (52.7)	36 (48.6)	22 (61.1)	0.305
Cirrhosis (1)	30 (25.2)	20 (25.3)	10 (25.0)	0.989
HIV coinfection (0)	36 (30.0)	24 (30.0)	12 (30.0)	1
AST (IU/L) (0)	48.0 [31.0–68.3]	49.0 [33.0–67.3]	41.5 [28.8–70.0]	0.307
ALT (IU/L) (0)	49.5 [36.0–73.3]	50.5 [38.0–73.0]	42.0 [29.0–82.0]	0.520
Creatinine (mg/L) (0)	9.2 [8.0–12.0]	9.0 [7.0–11.3]	10.4 [9.0–13.1]	0.010
Hemoglobin (g/dl) (0)	13.5 [12.5–14.5]	13.2 [12.4–14.4]	14.1 [12.9–14.7]	0.114
Tobacco smoking (0)				
Never	100 (83.3)	64 (80.0)	36 (90.0)	0.340
Yes, but stopped	12 (10.0)	9 (11.2)	3 (7.5)	
Yes, ongoing	8 (0.7)	7 (8.8)	1 (2.5)	
Alcohol use				0.424
Never	66 (55.0)	42 (52.5)	24 (60.0)	
Yes, but stopped	21 (27.5)	25 (16.3)	8 (20.0)	
Yes, currently (<once a day)	33 (17.5)	13 (31.2)	8 (20.0)	

Data are presented as n (%) or median [IQR].
ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.
[1] Comparison of characteristics between patients in the SOF/RBV group and patients in the SOF/LDV group (Chi-square test for categorical variables, Wilcoxon rank-sum test for continuous variables).

Table2. Distribution of patient-reported outcomes at each follow-up visit and comparison between W0 and W36 (ANRS 12311 TAC trial, N=120).

Visit (in weeks)	W0	W2	W4	W8	W12 (EOT)	W24	W36	*p* value[1]
Patient-reported outcomes (score range)								
HRQL[20] **(0–100)**	**n = 120**	**n = 114**	**n = 115**	**n = 114**	**n = 113**	**n = 118**	**n = 114**	
Physical HRQL (PCS score)	49.3 [38.8–54.8]	50.1 [41.4–54.5]	51.3 [41.7–54.8]	51.8 [43.4–55.7]	51.6 [44.9–54.8]	53.2 [47.2–56.6]	52.3 [46.6–56.2]	0.002
Mental HRQL (MCS score)	48.6 [41.5–52.9]	51.4 [46.9–57.2]	49.9 [45.4–54.7]	48.9 [44.4–54.7]	50.1 [45.3–55.0]	50.6 [45.5–54.7]	51.0 [44.8–54.4]	0.013
Fatigue[21] **(0–10)**	**n = 120**	**n = 119**	**n = 120**	**n = 118**	**n = 118**	**n = 120**	**n = 118**	
Fatigue score	3.5 [2–5]	3 [1–5]	3.5[2–5]	3 [1–5]	3 [1–5]	2.5 [0–5]	2 [0–4.7]	<0.001
Discomforting fatigue	30 (28.3)	22 (21.0)	19 (17.8)	17 (16.1)	22 (21.4)	9 (9.5)	12 (13.5)	<0.001
Self-reported symptoms[22] **(0–35)**	**n = 120**	**n = 120**	**n = 120**	**n = 119**	**n = 118**	**n = 120**	**n = 118**	
Total number of symptoms	6 [3–11]	4 [1–8]	5 [2–8]	4 [2–8]	4 [2–9]	3 [1–7]	3 [0–7]	<0.001
Number of symptoms causing at least little discomfort	5 [2–9]	3 [1–7]	4 [2–7]	3 [1–7]	3 [1–7]	2 [0–6]	2 [0–6]	<0.001
Number of symptoms causing at least medium discomfort	2 [0–5]	1 [0–3]	1 [0–3]	1 [0–3]	1 [0–3]	1 [0–2]	1 [0–2]	0.021
Number of symptoms causing a lot of discomfort	1 [0–3]	0 [0–1]	0 [0–2]	0 [0–1]	0 [0–2]	0 [0–1]	0 [0–2]	0.842

EOT, end of treatment; HRQL, health-related quality of life; MCS, mental component summary; PCS, physical component summary; W, week.
[1] Comparison of patient-reported outcomes between W0 and W36 (Wilcoxon signed-rank test for continuous variables, McNemar test for categorical ones).

that were prevailing at the time the trial was designed, the aspartate aminotransferase-to-platelet ratio index (APRI)[18] was used to assess liver fibrosis, with values above 2 denoting cirrhosis.[19] The trial's primary endpoint was sustained virological response (SVR), assessed 12 weeks after the end of treatment, *i.e.* at week (W) 24. Efficacy results showed an overall SVR rate of 89.2%, with no significant difference according to HCV genotype, and a satisfying tolerance profile, thereby supporting the use of sofosbuvir-based HCV therapy in the African context.[17]

Assessment of patient-reported outcomes

Data on HRQL, perceived fatigue and HCV self-reported symptoms (secondary outcomes) were collected using face-to-face questionnaires administered after each clinical visit, at baseline (*i.e.* at enrolment (W0)), and during treatment follow-up at W2, W4, W8, W12 (end of treatment), and after treatment end at W24 and W36. The questionnaires were administered by trained interviewers, independent from the medical team. They were available in French and in English, which are the languages most used by people living in areas where patients were recruited. In case the participant spoke only a local language (a rare situation), interviewers had been trained to directly translate the questionnaires using the survey guide, which included validated formulations.

HRQL was assessed using the Medical Outcomes Study (MOS) 12-item short-form general health survey (MOS SF-12, version 2),[20] from which two summary scores can be calculated: the physical (PCS) and mental (MCS) component summaries, for physical and mental HRQL, respectively. PCS and MCS scores range from 0 to 100, with higher values denoting better HRQL.

Patients' perceived level of fatigue and associated discomfort were assessed using three items derived from the Piper Fatigue Scale[21] which explores the level of fatigue (using a 10-point numerical rating scale), its duration, and the level of associated concern or discomfort (using a 5-point Likert scale). These items were previously used to assess perceived fatigue in patients treated for HCV infection using sofosbuvir-based therapy.[22]

Self-reported symptoms were assessed using the ANRS AC24 questionnaire which is derived from the AIDS Clinical Trials Group Symptom Distress Module[23] and adapted to the context of HCV infection.[22] This questionnaire asks patients about their experience of 35 symptoms during the previous 4 weeks and the associated discomfort using a 4-point scale ("not at all", "a little", "moderately", or "very" discomforting).

Study population

The study population included trial participants who had at least one measure of PROs between W0 and W36.

Statistical analyses

The main characteristics of the study population at W0 were described and then compared between treatment groups (Chi-square and Wilcoxon rank-sum tests for categorical and continuous variables, respectively). The distribution of PROs was described at each scheduled visit, and then compared between W0 and W36, globally and in each treatment group (Wilcoxon signed-rank and McNemar tests for continuous and categorical variables, respectively). Self-reported symptoms were described at each visit both for the whole study population and for each treatment group. The level of fatigue and the number of self-reported symptoms were compared between treatment groups at each visit during follow-up (Wilcoxon rank-sum test).

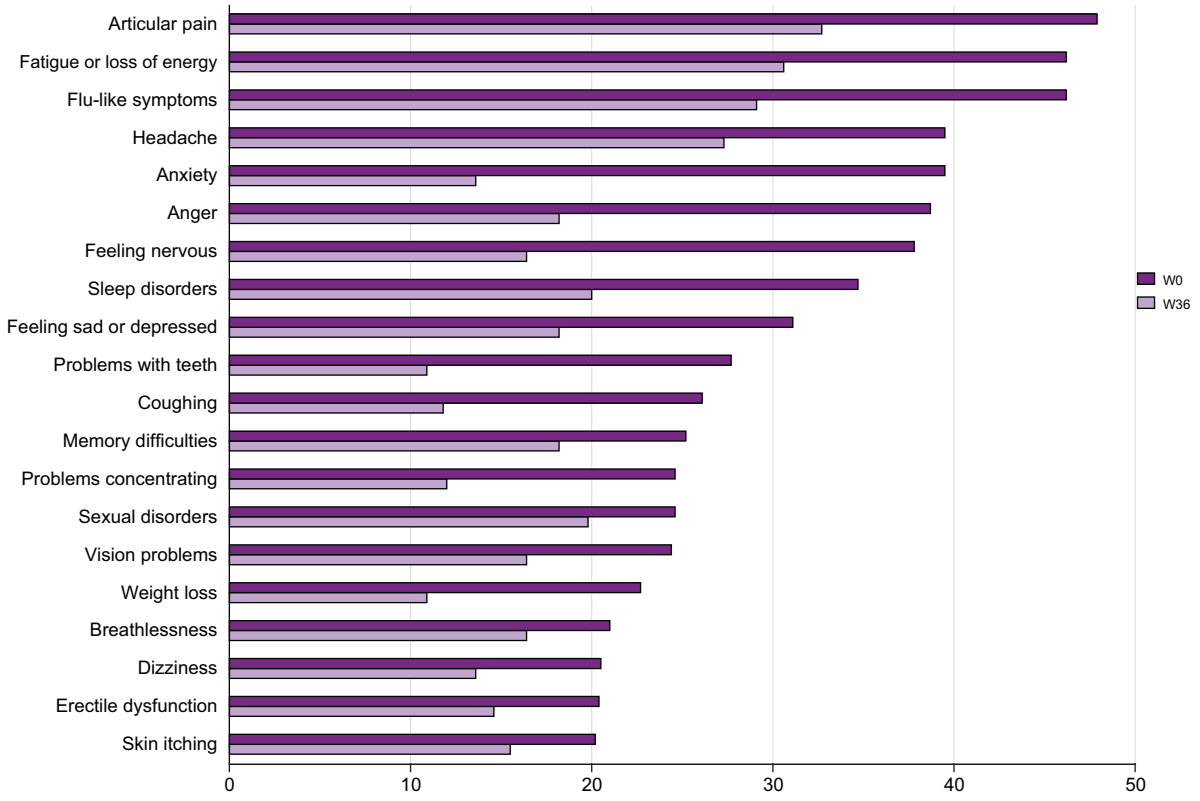

Fig. 1. Symptoms reported by more than 20% of patients at W0: Prevalence rates at W0 and W36 (ANRS 12311 TAC trial, N = 120). W, week.

Mixed-effects linear regression models were used to test the effect, if any, of treatment group on PROs, and to identify correlates of physical (PCS) and mental (MCS) HRQL scores in a longitudinal analysis during the W2–W36 follow-up period. Variables tested in the models included fixed variables, all assessed at W0 (sex, age, presence of cirrhosis, HIV coinfection, treatment group, number of HCV self-reported symptoms, and fatigue score), and time-varying variables (time, with a distinction between on-treatment (W2 to W12) and post-treatment (W24 to W36) periods, and HCV status, defined as being cured

Table 3. Correlates of physical health-related quality of life (PCS score) in the study population (ANRS 12311 TAC trial, N = 120).

	Univariable analyses		Multivariable analysis	
Characteristics	**Coefficient [95% CI]**	***p* value**	**Adjusted coefficient [95% CI]**	***p* value**
Intercept			62.61 [57.33 to 67.89]	<0.001
Time (weeks)◆,[a]				
t1	0.14 [-0.01 to 0.29]	0.074		
t2	0.09 [0.05 to 0.14]	<0.001		
Treatment group				
SOF/RBV *(ref:* SOF/LDV)	2.54 [-0.19 to 5.28]	0.071		
Male sex	2.06 [-0.54 to 4.66]	0.124	2.26 [0.20 to 4.31]	0.027
Age (in years)	-0.20 [-0.31 to -0.10]	<0.001	-0.22 [-0.91 to -0.14]	<0.001
HCV cured◆	4.10 [1.36 to 6.83]	0.003	4.52 [1.95 to 7.14]	<0.001
HIV coinfection	0.807 [-2.05 to 3.66]	0.579		
Cirrhosis	-7.78 [-13.0 to -2.57]	0.004	-6.92 [-11.72 to -2.11]	0.006
Interaction between time and cirrhosis◆				
t1	0.07 [-0.09 to 0.24]	0.374	0.10 [-0.06 to 0.26]	0.218
t2	0.07 [0.02 to 0.11]	0.004	-0.06 [-0.15 to 0.03]	0.162
t1 * cirrhosis	0.44 [-0.06 to 0.93]	0.083	0.46 [-0.02 to 0.95]	0.062
t2 * cirrhosis	0.20 [0.05 to 0.34]	0.008	0.23 [0.08 to 0.37]	0.002
Total number of self-reported symptoms at Week 0	-0.66 [-0.89 to -0.42]	<0.001	-0.74 [-0.93 to -0.53]	<0.001
Fatigue score at Week 0	-1.18 [-1.67 to -0.69]	<0.001		

Mixed-effects linear regression models.
LDV, ledipasvir; PCS, physical component summary; RBV, ribavirin; SOF, sofosbuvir. The symbol * is the standard statistical notation for the interaction term between two variables.
[a] t1 corresponds to the on-treatment period (Week 2 to Week 12), t2 corresponds to the post-treatment period (Week 24 to Week 36).
◆ Time-varying variables.

Table 4. Correlates of mental health-related quality of life (MCS score) in the study population (ANRS 12311 TAC trial, N = 120).

Characteristics	Univariable analyses		Multivariable analysis	
	Coefficient [95% CI]	*p* value	Adjusted coefficient [95% CI]	*p* value
Intercept			53.31 [51.54 to 55.08]	<0.001
Time (weeks)◆,[a]				
t1	-0.10 [-0.25 to 0.06]	0.228		
t2	-0.02 [-0.07 to 0.03]	0.427		
Treatment group				
SOF/RBV (*ref*: SOF/LDV)	-2.58 [-5.40 to 0.23]	0.078	-2.29 [-5.01 to 0.44]	0.100
Interaction between time and treatment group◆				
t1	-0.12 [-0.30 to 0.07]	0.205	-0.12 [-0.30 to 0.07]	0.219
t2	-0.06 [-0.13 to -0.004]	0.038	-0.06 [-0.12 to -0.003]	0.042
t1 * SOF/RBV	0.07 [-0.26 to 0.40]	0.667	0.07 [-0.25 to 0.38]	0.665
t2 * SOF/RBV	0.13 [0.04 to 0.23]	0.011	0.13 [0.03 to 0.24]	0.012
Male sex	0.01 [-1.73 to 1.75]	0.986		
Age (in years)	0.05 [-0.02 to 0.12]	0.178		
HCV cured◆	0.53 [-2.29 to 3.34]	0.714		
HIV coinfection	0.10 [-1.79 to 1.98]	0.918		
Cirrhosis	1.04 [-1.65 to 3.74]	0.450		
Total number of self-reported symptoms at Week 0	-0.44 [-0.60 to -0.29]	<0.001	-0.44 [-0.60 to -0.28]	<0.001
Fatigue score at Week 0	-0.51 [-0.86 to -0.18]	0.004		

Mixed-effects linear regression models.
LDV, ledipasvir; MCS, mental component summary; RBV, ribavirin; SOF, sofosbuvir. The symbol * is the standard statistical notation for the interaction term between two variables.
[a] t1 corresponds to the on-treatment period (Week 2 to Week 12), t2 corresponds to the post-treatment period (Week 24 to Week 36).
◆ Time-varying variables.

of HCV or not). A likelihood ratio test with the backward selection procedure was used to build the two final multivariable models, which comprised variables significant at the 0.05 level. Interactions between variables were also tested for; only those remaining significant after multivariable adjustment were kept in the final models. Statistical analyses were performed using R Statistical Software (version 3.6.3, R Core Team, 2020).

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Baseline characteristics of the study population

The study population included all 120 trial participants (Cameroon: 53; Côte d'Ivoire: 45; and Senegal: 22). A slight majority were men (54.2%), the median [IQR] age at baseline (W0) was 58 [49–63] years, 25.2% of patients had cirrhosis, and 30% were coinfected with HIV. Patients in the SOF/RBV group were significantly younger than those in the SOF/LDV group (Table 1). At inclusion in the trial, four of the 36 HIV-HCV-coinfected patients had a WHO clinical stage 4 (AIDS), six had a plasma HIV viral load above 50 cp/ml, and the median [IQR] CD4 T-cell count was 624 (422–844) cells/μl.

Change in PROs during follow-up

Comparisons of scores between W0 and W36 showed significant improvements in all PROs, except for the number of symptoms causing a lot of discomfort (median [IQR]: 1 [0–3] at W0 *vs.* 0 [0–2] at W36, $p = 0.842$). Among symptoms causing a lot of discomfort, flu-like symptoms, articular pain, sleep disorders, problems with teeth, fatigue or loss of energy, anger, feeling nervous, and anxiety were most cited. A significant increase in physical and mental HRQL (gain of 3 points in median for both PCS and MCS scores) was observed, while significant decreases in the fatigue score (3.5 [2–5] *vs.* 2 [0–4.7], $p < 0.001$), in the percentage of patients reporting discomforting fatigue (28.3% *vs.* 13.5%, $p < 0.001$), and the number of self-reported symptoms were observed (6 [3–11] *vs.* 3 [0–7], $p < 0.001$) (Table 2). Analyses stratified by treatment group showed significant improvements in most PROs between W0 and W36 (Table S1).

No significant effect of treatment group was observed on the total number of self-reported symptoms ($p = 0.868$) or on the fatigue score ($p = 0.640$) in the univariable mixed-effects regression models (data not shown). This was confirmed by between-group comparisons of these scores at each follow-up visit (Table S1).

Types of self-reported symptoms

At W0, the symptoms most reported were articular pain (47.9% of patients), fatigue or loss of energy (46.2%), and flu-like symptoms (46.2%) (Fig. 1). Between 30% and 40% of patients reported the following symptoms: headaches, anxiety, anger, feeling nervous, sleep disorders, and feeling sad or depressed. Furthermore, between 20% and 30% reported the following symptoms: problems with their teeth, coughing, memory difficulties, problems concentrating, sexual disorders (such as loss of libido or dissatisfaction), vision problems, weight loss, breathlessness, dizziness, erectile dysfunction, and skin itching (Fig. 1).

At W36, the symptoms most reported were still articular pain (32.7%), fatigue or loss of energy (30.6%), and flu-like symptoms (29.1%) (Fig. 1). The prevalence of all symptoms reported by more than 20% of patients at baseline was significantly lower at W36 (Fig. 1, Table S2). By contrast, the prevalence of the following symptoms – reported less often – remained stable: change in smell perception (2.5% to 3.6%, $p = 1.0$), change in taste perception (3.4% to 6.4%, $p = 0.248$), diarrhea (8.4% to 13.6%, $p = 0.074$), dry skin (3.4% to 5.5%, $p = 0.480$), hair loss (0.8% to 2.8%, $p = 0.480$), hearing problems (7.6% to 8.2%, $p = 1.0$), tingling around the mouth (0.9% to 1.8%, $p = 1.0$), and change in menstrual cycle (3.1% to 3.3%, $p = 1.0$) (Table S2).

The percentage of patients reporting sexual disorders, such as loss of libido or dissatisfaction, significantly decreased between

W0 and W36 (24.6% *vs.* 19.8%, $p = 0.013$), as did the percentage of male patients reporting erectile dysfunction (20.4% *vs.* 14.6%, $p = 0.023$).

The descriptive analyses stratified by treatment group showed similar results (Table S2), except for a high prevalence of anxiety (51.3%) in the SOF/RBV group at W0.

Correlates of physical HRQL

In the final multivariable model for physical HRQL, older age, cirrhosis, and a higher number of self-reported symptoms at W0 were associated with a lower PCS, denoting impaired physical HRQL (Table 3). By contrast, male sex and HCV cure were associated with a higher PCS. No significant change in PCS over time was found for the on-treatment period (Week 2 to Week 12). However, PCS increased significantly during the post-treatment period (Week 24 to Week 36) in patients with cirrhosis, as shown by the interaction term. No significant effect of treatment group on PCS was observed.

Correlates of mental HRQL

In the final multivariable model for mental HRQL, a higher number of self-reported symptoms at W0 was significantly associated with a lower MCS (Table 4). Moreover, MCS decreased during the post-treatment period for patients in the SOF/LDV group but increased for patients in the SOF/RBV group. No significant change in MCS was observed during the on-treatment period.

Discussion

The TAC clinical trial performed in three African countries – including two (Cameroon and Cote d'Ivoire) from the list of 10 countries with the greatest burden from viral hepatitis[3] – shows a significant improvement in all the PROs studied, including HRQL, fatigue, and self-reported symptoms, 24 weeks after the end of a 12-week sofosbuvir-based treatment program in 120 treatment-naïve adults with confirmed genotype 1, 2 or 4 HCV infection. These findings may help HCV treatment providers inform patients initiating DAA treatment in LMICs about the potential benefits of treatment beyond viral eradication. Expected improvements in both quality of life and the global burden of symptoms may foster adherence and retention in care for these patients. In the meantime, DAA scale-up in Africa remains a priority, especially given the increased incidence of HCV-related hepatocellular carcinoma observed over the last 40 years in this region.[24]

The current literature on DAA in LMICs mainly focuses on-treatment efficacy, effectiveness or cost-effectiveness.[25–30] To our knowledge, only two studies have documented HRQL in DAA-treated patients in such countries. In Rwanda, data from the SHARED clinical trial evaluating a 12-week treatment program with SOF/LDV in 300 HCV-infected adult patients showed significant improvements in physical and mental HRQL (assessed using the MOS-HIV scale[31]) at week 24 compared with baseline.[32] In Egypt, a prospective observational study in 62 patients initiating DAAs showed a deterioration of HRQL (assessed using the Liver Disease Symptom Index[33]) during treatment, a worsening of self-reported symptoms, and increased anxiety and stress in the first weeks of therapy, followed by a return to baseline scores for all PROs at the end of treatment.[34]

Interestingly, in the ANRS 12311 TAC trial, we found no significant change over time in HRQL during the on-treatment period. More particularly, unlike in other studies including ribavirin-based regimens,[8,35] no transient decrease in HRQL was detected in the first weeks after treatment initiation. Overall, significant improvements in physical and mental HRQL were observed 24 weeks after the end of treatment (W36) compared with baseline (W0). In addition, HCV cure was associated with better physical HRQL in both treatment groups. These results confirm those observed in previous studies conducted in various populations of HCV-infected patients in Western[8,12,15,36–38] and Middle Eastern countries.[39] Interestingly, during the post-treatment period, physical HRQL improved significantly only in patients with cirrhosis, which suggests different kinetics of HRQL change after the end of DAA treatment in those with cirrhosis. Further studies with a larger sample size are needed to verify this hypothesis. In addition, unlike the SOF/RBV group, mental HRQL was not found to significantly improve after the end of treatment in the SOF/LDV group. Inter-group differences in age[40] and unobserved confounding factors may explain these contrasting findings more than HCV genotype.

Improvement over time in physical and mental HRQL was observed independently of HIV coinfection. The effect of the latter was not significant, unlike in previous studies which showed a negative effect of HIV coinfection on HRQL before, during, and after DAA treatment,[38] or a smaller benefit of HCV cure on perceived mental health in HIV-HCV-coinfected patients than in their HCV-monoinfected counterparts.[41]

It is also interesting to note that, even though cirrhosis was associated with lower physical HRQL in the TAC trial participants, physical HRQL significantly improved over time in patients with cirrhosis after the end of treatment. This confirms that PROs improve after DAA therapy ends even in patients with advanced stages of liver fibrosis.[42]

We also found that the number of self-reported symptoms was an independent correlate of impaired HRQL. This confirms that symptoms felt – whether related to treatment or to the disease itself – had a substantial impact on patients' overall perceived health.[43] The symptoms most reported were similar to those previously described in high-resource countries[22,41] and, for most of them, their prevalence decreased at the end of follow-up. Interestingly, the percentage of patients reporting sexual disorders and that of male patients reporting erectile dysfunction decreased. These results can be compared with those of a study exploring male sexual dysfunction in HCV-infected men treated with DAAs,[44] which showed a significant improvement in dysfunction after HCV cure. Fatigue was reported by nearly half of the patients in the TAC trial, and one patient in five reported discomforting fatigue at enrolment, which confirms the predominance of fatigue in the symptomatology of HCV infection.[45,46] We observed a statistically significant decline in perceived level of fatigue 24 weeks after the end of treatment. Further research is needed to determine the clinical significance of this decline, and its persistence over the long term.

Changes in PROs observed after DAA treatment in the TAC ANRS 12311 trial are roughly similar to those observed in studies performed in non-low income settings.[12,47] However, the use of different psychometric scales and the differences in PRO assessment schedules make comparisons difficult.

Finally, our results confirm the sex-based effect shown elsewhere for physical HRQL of DAA-treated patients, with men reporting better HRQL than women.[22,34,48] Future research on

PROs in individuals on DAAs should address sex issues to identify the mechanisms at play and to help develop interventions targeted at women initiating HCV treatment.

The main strengths of this study are its international nature in the African context and the longitudinal assessment of a large set of PROs. However, the small sample size per country and the small number of patients with cirrhosis and/or HIV infection limit the generalizability of results. Another limitation of the study is the use of psychometric scales which were initially developed for high-resource settings. However, the MOS SF-12 scale has already been successfully used in the African setting[49–53] where it has been shown to be a valid measure of HRQL.[54,55] Moreover, the self-reported symptoms and fatigue scales we used are easily transposable to the African setting. Importantly, setting up the trial in three different countries facilitated building a network of clinicians, biologists, patient associations, and stakeholders aimed at improving knowledge in recent advances in hepatitis C care and expanding access to DAAs in the region. Finally, further studies are needed to assess if the statistically significant differences found in the before/after treatment comparison of PROs reflect clinically meaningful changes for patients (minimal clinically important difference).[56]

Sofosbuvir-based DAA therapy was associated with a significant improvement of PROs 6 months after treatment end in treatment-naïve patients from Central and West African countries chronically infected with genotype 1, 2 or 4 HCV. These findings add to the body of knowledge concerning chronic HCV-infected patients' experience with DAAs in LMICs and may help foster adherence and retention in care for patients initiating DAAs in these countries. Further research is needed in the African setting to document change in PROs over the long term in DAA-treated patients, including patients with comorbidities such as coinfection with hepatitis B virus.

Abbreviations

DAA, direct-acting antiviral; EOT, end-of-treatment; HRQL, health-related quality of life; LMICs, low-to-middle income countries; MCS, mental component summary; MOS, Medical Outcomes Study; MOS SF-12, Medical Outcomes Study 12-item short-form general health survey; PCS, physical component summary; PROs, patient-reported outcomes; SOF/LDV, sofosbuvir plus ledipasvir; SOF/RBV, sofosbuvir plus ribavirin; SVR, sustained virological response; W, week; WHO, World Health Organization.

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Conflict of interest

KL received personal fees for advisory boards and conferences from MSD, Gilead, Abbvie and ViiV Healthcare. PC received research grants by MSD and Intercept unrelated to this work. The other authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: ML, CK, MS, PC, AA, KL, SB. Methodology: FM, AM, CP. Software: AM. Validation: FM, PC, CP, SB. Formal analysis: AM, CP. Investigation: ML, CK, MS, AA, KL. Resources: FM, AM, ML, CK, MS, PC, AA, CP, KL, SB. Data curation: AM, CP. Writing, original draft: FM, AM. Writing, review and editing: FM, AM, ML, CK, MS, PC, AA, CP, KL, SB. Visualization: FM, AM, CP. Supervision: PC, KL, SB. Project administration: ML, CK, MS, AA, KL, SB. Funding acquisition: ML, CK, MS, AA, KL, SB.

Data availability statement

Data can be accessed upon request to the TAC ANRS 12311 trial scientific committee (contact: karine.lacombe2@aphp.fr).

Ethics

The study protocol has been approved by the national Ethics Committees of each country and by the Ethics Committee of Ile de France XI, France, and recorded in https://www.clinicaltrials.gov/(NCT02405013). Signed informed consent was obtained for all trial participants.

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Supplementary data

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References

[1] WHO. Combating hepatitis B and C to reach elimination by 2030. Advocacy Brief; May 2016. 2016.
[2] WHO. Global health sector strategy on viral hepatitis 2016–2021 - towards ending viral hepatitis. 2016.
[3] Cooke GS, Andrieux-Meyer I, Applegate TL, Atun R, Burry JR, Cheinquer H, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology commission. Lancet Gastroenterol Hepatol 2019;4:135–184.
[4] Zoratti MJ, Siddiqua A, Morassut RE, Zeraatkar D, Chou R, van Holten J, et al. Pangenotypic direct acting antivirals for the treatment of chronic hepatitis C virus infection: a systematic literature review and meta-analysis. EClinicalMedicine 2020;18.
[5] Pol S, Parlati L. Treatment of hepatitis C: the use of the new pangenotypic direct-acting antivirals in "special populations.". Liver Int 2018;38:28–33.
[6] Scotto R, Buonomo AR, Moriello NS, Maraolo AE, Zappulo E, Pinchera B, et al. Real-world efficacy and safety of pangenotypic direct-acting antivirals against hepatitis C virus infection. Rev Recent Clin Trials 2019;14:173–182.
[7] Perazzo H, Castro R, Luz PM, Banholi M, Goldenzon RV, Cardoso SW, et al. Effectiveness of generic direct-acting agents for the treatment of hepatitis C: systematic review and meta-analysis. Bull World Health Organ 2020;98:188–197K.
[8] Marcellin F, Roux P, Protopopescu C, Duracinsky M, Spire B, Carrieri MP. Patient-reported outcomes with direct-acting antivirals for the treatment of chronic hepatitis C: current knowledge and outstanding issues. Expert Rev Gastroenterol Hepatol 2017;11:259–268.
[9] Chabrol F, Noah Noah D, Tchoumi EP, Vidal L, Kuaban C, Carrieri MP, et al. Screening, diagnosis and care cascade for viral hepatitis B and C in Yaoundé, Cameroon: a qualitative study of patients and health providers coping with uncertainty and unbearable costs. BMJ Open 2019;9:e025415.
[10] Goutzamanis S, Doyle J, Higgs P, Hellard M. Improving hepatitis C direct-acting antiviral access and uptake: a role for patient-reported outcomes and lived experience. J Viral Hepat 2019;26:218–223.
[11] Younossi Z, Henry L. The impact of the new antiviral regimens on patient reported outcomes and health economics of patients with chronic hepatitis C. Dig Liver Dis 2014. https://doi.org/10.1016/j.dld.2014.09.025.
[12] Serper M, Evon DM, Amador J, Stewart PW, Sarkar S, Lok AS, et al. Patient-reported outcomes 12 months after hepatitis C treatment with direct-

acting antivirals: results from the PROP UP study. Liver Int 2021;41:692–704.
[13] Ichikawa T, Miyaaki H, Miuma S, Motoyoshi Y, Yamashima M, Yamamichi S, et al. Direct-acting antivirals improved the quality of life, ameliorated disease-related symptoms, and augmented muscle volume three years later in patients with hepatitis C virus. Intern Med 2020;59:2653–2660.
[14] Ouzan D, Larrey D, Guyader D, Remy AJ, Riachi G, Heluwaert F, et al. Evolution of hepatitis C virus treatment during the era of sofosbuvir-based therapies: a real-world experience in France. Dig Dis Sci 2021;66:881–898.
[15] Evon DM, Sarkar S, Amador J, Lok AS, Sterling RK, Stewart PW, et al. Patient-reported symptoms during and after direct-acting antiviral therapies for chronic hepatitis C: the PROP UP study. J Hepatol 2019;71:486–497.
[16] Jaquet A, Muula G, Ekouevi DK, Wandeler G. Elimination of viral hepatitis in low and middle-income countries: epidemiological research gaps. Curr Epidemiol Rep 2021;8:89–96.
[17] Lacombe K, Moh R, Chazallon C, Lecarrou J, Sylla B, Lemoine M, et al. Treatment of chronic hepatitis C GT1, 2, 4 in Africa: final results of ANRS 12311 TAC trial. CROI 2018 - Poster 602 - Boston, MA, USA.
[18] Wai C-T, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatol Baltim Md 2003;38:518–526.
[19] Lin Z-H, Xin Y-N, Dong Q-J, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatol Baltim Md 2011;53:726–736.
[20] Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. SF-12v2: How to score version 2 of the SF-12 health survey. Lincoln, RI: QualityMetric; 2002.
[21] Piper BF, Dibble SL, Dodd MJ, Weiss MC, Slaughter RE, Paul SM. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. Oncol Nurs Forum 1998;25:677–684.
[22] Rosenthal E, Fougerou-Leurent C, Renault A, Carrieri MP, Marcellin F, Garraffo R, et al. Efficacy, safety and patient-reported outcomes of ledipasvir/sofosbuvir in NS3/4A protease inhibitor-experienced individuals with hepatitis C virus genotype 1 and HIV coinfection with and without cirrhosis (ANRS HC31 SOFTRIH study). HIV Med 2018;19:227–237.
[23] Justice AC, Holmes W, Gifford AL, Rabeneck L, Zackin R, Sinclair G, et al. Development and validation of a self-completed HIV symptom index. J Clin Epidemiol 2001;54(Suppl 1):S77–S90.
[24] Dakurah OB, Tamandjou CRT, Zunza M, Preiser W, Maponga TG. Viral hepatitis associated hepatocellular carcinoma on the African continent, the past, present, and future: a systematic review. BMC Cancer 2021;21:715.
[25] Wahsh EA, Hussein AK, Gomaa AA, Baraka MA, Al-deen Abead M. Real life Egyptian experience of daclatasvir plus sofosbuvir with ribavirin in naïve difficult to treat HCV patients. Infect Disord - Drug Targets 2020;20:43–48.
[26] Ibrahim Mohammed Ebid A, Ashraf Ahmed O, Hassan Agwa S, Mohamed Abdel-Motaleb S, Mohamed Elsawy A, Hagag RS. Safety, efficacy and cost of two direct-acting antiviral regimens: a comparative study in chronic hepatitis C Egyptian patients. J Clin Pharm Ther 2020;45:539–546.
[27] Gupta N, Mbituyumuremyi A, Kabahizi J, Ntaganda F, Mambo Muvunyi C, Shumbusho F, et al. Treatment of chronic hepatitis C virus infection in Rwanda with ledipasvir–sofosbuvir (SHARED): a single-arm trial. Lancet Gastroenterol Hepatol 2019;4:119–126.
[28] Mohamed Z, Scott N, Nayagam S, Rwegasha J, Mbwambo J, Thursz MR, et al. Cost effectiveness of simplified HCV screening-and-treatment interventions for people who inject drugs in Dar-es-Salaam, Tanzania. Int J Drug Pol 2022;99:103458.
[29] Kamali I, Barnhart DA, Nyirahabihirwe F, Gakuru JP, Uwase M, Nizeyumuremyi E, et al. Initiation of hepatitis C treatment in two rural Rwandan districts: a mobile clinic approach. BMC Infect Dis 2021;21:220.
[30] Coyer L, Njoya O, Njouom R, Mossus T, Kowo MP, Essomba F, et al. Achieving a high cure rate with direct-acting antivirals for chronic Hepatitis C virus infection in Cameroon: a multi-clinic demonstration project. Trop Med Int Health TM IH 2020;25:1098–1109.
[31] Revicki DA, Sorensen S, Wu AW. Reliability and validity of physical and mental health summary scores from the medical outcomes study HIV health survey. Med Care 1998;36:126–137.
[32] Van Nuil JI, Umutesi G, Shumbusho F, Kateera F, Dushimimana JD, Mambo Muvunyi C, et al. 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). J Viral Hepat 2021;28:112–120.
[33] van der Plas SM, Hansen BE, de Boer JB, Stijnen T, Passchier J, de Man RA, et al. The liver disease symptom index 2.0; validation of a disease-specific questionnaire. Qual Life Res 2004;13:1469–1481.
[34] Youssef NFA, El Kassas M, Farag A, Shepherd A. Health-related quality of Life in patients with chronic hepatitis C receiving Sofosbuvir-based treatment, with and without Interferon: a prospective observational study in Egypt. BMC Gastroenterol 2017;17:18.
[35] Kracht PAM, Lieveld FI, Amelung LM, Verstraete CRJ, Mauser-Bunschoten EP, de Bruijne J, et al. The impact of hepatitis C virus direct-acting antivirals on patient-reported outcomes: a Dutch prospective cohort study. Infect Dis Ther 2018;7:373–385.
[36] Schulte B, Schmidt CS, Manthey J, Strada L, Christensen S, Cimander K, et al. Clinical and patient-reported outcomes of direct-acting antivirals for the treatment of chronic hepatitis C among patients on opioid agonist treatment: a real-world prospective cohort study. Open Forum Infect Dis 2020;7:ofaa317.
[37] Cacoub P, Bourliere M, Asselah T, De Ledinghen V, Mathurin P, Hézode C, et al. French patients with hepatitis C treated with direct-acting antiviral combinations: the effect on patient-reported outcomes. Value Health J Int Soc Pharmacoeconomics Outcomes Res 2018;21:1218–1225.
[38] Fagundes RN, de Castro Ferreira LEVV, de Lima Pace FH. Health-related quality of life and fatigue in patients with chronic hepatitis C with therapy with direct-acting antivirals agents interferon-free. PLoS One 2020;15:e0237005.
[39] Karimi-Sari H, Hosseini MA, Nikjoo N, Bagheri Baghdasht MS, Alavian SM. Patient-reported outcomes of sleep, mood and quality of life after treatment of chronic hepatitis C infection using direct-acting antiviral agents. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2020;26:1093.e5–1093.e8.
[40] Rendas-Baum R, White MK, Kosinski M, Vietri J, Bjorner JB. A cross-national comparison of the effect of age and gender on health-related quality of life (Hrql). Value Health 2016;19:A471.
[41] Marcellin F, Di Beo V, Aumaitre H, Mora M, Wittkop L, Duvivier C, et al. Patient-reported symptoms during direct-acting antiviral treatment: a real-life study in HIV-HCV coinfected patients (ANRS CO13 HEPAVIH). J Hepatol 2020. https://doi.org/10.1016/j.jhep.2019.10.019.
[42] Sung JC, Bosh C, Wyatt B, Miller M, Harty A, Del Bello D, et al. Hepatitis C cure improved patient-reported outcomes in patients with and without liver fibrosis in a prospective study at a large urban medical center. J Viral Hepat 2020;27:350–359.
[43] Marcellin F, Protopopescu C, Esterle L, Wittkop L, Piroth L, Aumaitre H, et al. Short article: anger and quality of life in patients co-infected with HIV and hepatitis C virus: a cross-sectional study (ANRS CO13-HEPAVIH). Eur J Gastroenterol Hepatol 2017;29:786–791.
[44] Elshimi E, Morad W, Mohamad NE. Male sexual dysfunction among Egyptian patients with chronic hepatitis C virus infection before and after direct-acting antiviral drugs. J Sex Med 2019;16:402–409.
[45] Marcellin F, Protopopescu C, Poizot-Martin I, Miailhes P, Esterle L, Wittkop L, et al. Short article: fatigue in the long term after HCV treatment in HIV-HCV-coinfected patients: functional limitations persist despite viral clearance in patients exposed to peg-interferon/ribavirin-containing regimens (ANRS CO13-HEPAVIH cohort). Eur J Gastroenterol Hepatol 2016;28:1003–1007.
[46] Faccioli J, Nardelli S, Gioia S, Riggio O, Ridola L. Neurological and psychiatric effects of hepatitis C virus infection. World J Gastroenterol 2021;27:4846–4861.
[47] Younossi ZM, Stepanova M, Racila A, Afendy A, Lawitz EJ, Schwabe C, et al. Long-term benefits of sustained virologic response for patient-reported outcomes in patients with chronic hepatitis C virus infection. Clin Gastroenterol Hepatol 2020;18:468–476.e11.
[48] Younossi ZM, Stepanova M, Zeuzem S, Dusheiko G, Esteban R, Hezode C, et al. Patient-reported outcomes assessment in chronic hepatitis C treated with sofosbuvir and ribavirin: the VALENCE study. J Hepatol 2014;61:228–234.
[49] Boyer S, Protopopescu C, Marcellin F, Carrieri MP, Koulla-Shiro S, Moatti JP, et al. Performance of HIV care decentralization from the patient's perspective: health-related quality of life and perceived quality of services in Cameroon. Health Policy Plan 2012;27(4):301–315.

[50] Kastien-Hilka T, Rosenkranz B, Schwenkglenks M, Bennett BM, Sinanovic E. Association between health-related quality of life and medication adherence in pulmonary tuberculosis in South Africa. Front Pharmacol 2017;8:919.
[51] Nolens B, van den Akker T, Lule J, Twinomuhangi S, van Roosmalen J, Byamugisha J. Birthing experience and quality of life after vacuum delivery and second-stage caesarean section: a prospective cohort study in Uganda. Trop Med Int Health TM IH 2018;23:914–922.
[52] van der Kop ML, Muhula S, Patel A, Thabane L, Awiti P, Kyomuhangi L, et al. Gender differences in health-related quality of life at the time of a positive HIV test - a cross-sectional study in a resource-poor, high prevalence setting in Nairobi, Kenya. AIDS Care 2018;30:493–499.
[53] Ubuguyu O, Tran OC, Bruce RD, Masao F, Nyandindi C, Sabuni N, et al. Improvements in health-related quality of life among methadone maintenance clients in Dar es Salaam, Tanzania. Int J Drug Pol 2016;30:74–81.
[54] Patel AR, Lester RT, Marra CA, van der Kop ML, Ritvo P, Engel L, et al. The validity of the SF-12 and SF-6D instruments in people living with HIV/AIDS in Kenya. Health Qual Life Outcomes 2017;15:143.
[55] Protopopescu C., Boyer S., Marcellin F., Carrieri M.P., Koulla-Shiro S., Spire B. Validation de l'échelle de qualité de vie SF12 chez des patients infectés par le VIH au Cameroun (enquête EVAL–ANRS 12-116) [in French]. Revue d'Epidémiologie et de Santé Publique 2011; 59 (S1):S9.
[56] Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989;10:407–415.