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High level of medication regimen complexity index correlate with worse quality of life in people living with HIV

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ABSTRACT

Objectives. People living with HIV (PLWHIV) have now a near-normal life expectancy and thus, a higher risk of polypharmacy. The main objective was to assess the correlation between medication regimen complexity index (MRCI) and quality of life (EQ-5D) and health utilities among PLWHIV patients on ART.

Patients and methods. Observational prospective single-center study including adult PLWHIV on ART from January to March-2020 attended at hospital pharmacy outpatient service according to a Capacity-Motivation-Opportunity (CMO) pharmaceutical care model.

Results. A total of 428 patients were included, mean age of 50 ± 10.9 years, 82.2% males. Negative correlation ($r^2 = -0.147$; $p = 0.0002$) between MRCI and EQ-5D was found. Relationship between the comorbidity pattern and quality of life, was also observed. Regarding MRCI, Anxiety/Depression, Pain/discomfort and Self-Care were the dimensions with the worst assessment.

Conclusions. A new multidimensional revised care plan for PLWHIV focussed on optimising overall patient care, not limited to viral load goal achievement alone but also in their pharmacotherapeutic complexity and quality of life is needed

Keywords: HIV, medication complexity index, quality of life, CMO model.

Correlación entre un alto nivel de complejidad farmacoterapéutica y peor calidad de vida en pacientes con VIH

RESUMEN

Objetivos. Los pacientes VIH tienen ahora una esperanza de vida casi normal y, por tanto, un mayor riesgo de polifarmacia. El objetivo principal fue evaluar la correlación entre el índice de complejidad de la medicación (MRCI) y la calidad de vida (EQ-5D) y su influencia en la salud de los pacientes VIH en tratamiento antirretroviral (TAR).

Pacientes y métodos. Estudio observacional prospectivo en un solo centro que incluyó a pacientes adultos con TAR de enero a marzo de 2020, atendidos en las consultas de farmacia hospitalaria de acuerdo con un modelo CMO de atención farmacéutica.

Resultados. Se incluyeron 428 pacientes, edad media $50 \pm 10,9$ años, 82,2% varones. Se encontró correlación negativa ($r^2 = -0,147$; $p = 0,0002$) entre MRCI y el índice de calidad de vida EQ-5D. También se observó relación entre el patrón de comorbilidad y el EQ-5D. En cuanto al MRCI, Ansiedad / Depresión, Dolor / malestar y Autocuidado fueron las dimensiones con peor valoración.

Conclusiones. Se necesita un nuevo plan de atención multidimensional revisado para pacientes VIH en tratamiento con TAR, centrado en optimizar la atención general del paciente, y no limitado sólo al logro de la meta de carga viral, sino también en su complejidad farmacoterapéutica y calidad de vida.

Palabras clave: VIH, índice de complejidad de la medicación, calidad de vida, CMO model.

INTRODUCTION

As a result of the successful treatment of HIV over the last four decades, people living with HIV (PLWHIV) have now

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a near-normal life expectancy [1]. This challenge, due mainly to the success of the antiretroviral treatment (ART), has resulted in clinical services now seeing an older HIV cohort, with patients experiencing many of the problems of an older HIV-negative cohort such as multiple medical diagnoses, polypharmacy and frailty [2]. All of this leads to a greater attention to PLWHIV population, both young and older, as they are more complex patients than general population [3-5].

The progressive aging of our patients, the higher risk of polypharmacy, the increase of the risk of adverse events due to less functional reserve (hepatic and renal), the chronic inflammation and the impairment of the immune system, contribute to worsening the quality of life (QoL) of these persons [6]. Known as PLWHIV, they develop the same comorbidities as the general population, but at earlier ages, estimating that they occur 10 years earlier than the general population [3,7]. Low-grade chronic inflammatory processes have been described as a risk factor for the development of comorbidities. Low-grade chronic inflammatory processes have been described as a risk factor for the development of comorbidities. In the HIV population, the presence of subclinical chronic inflammation has been observed, finding a relationship with the earlier appearance of the different comorbidity patterns [8]. Indeed, a higher number of medications and complicated schedules or special instructions (time of the day, food interactions) could contribute to a greater patient difficulty or interest in following in a proper way treatment recommendations. In this context, different tools to assess the pharmacotherapy complexity have been developed. Those tools would be the first step toward obtaining a better understanding not only quantitative, but also qualitative, about how the complexity of drug prescribed affects adherence, medical outcomes and QoL [9].

Measuring QoL has become important in clinical research, as it is considered the gold standard to report the patient's experiences with illness and treatment. Changes in QoL from the patient perspective before and after health care interventions can be monitored with instruments like the EQ-5D, a standardized questionnaire that provides a simple, generic measure of health for clinical and economic appraisal [10]. EQ-5D provides health utilities, widely used in cost-effectiveness and decision analyses where different treatments are compared [11].

New ART regimens have changed the landscape of HIV therapy, providing important advantages, including a higher efficacy and optimal safety profile [12]. However, there is scarce data regarding the effect of ART and concomitant drugs, measured by medication regimen complexity index (MRCI) on QoL. Nowadays most of the evidence comes from clinical trials, in which certain subpopulations such as ageing people are underrepresented. It is necessary to establish comprehensive care processes for these patients from all areas, including the pharmacotherapeutic field, always keeping the patient as a priority. Assessment of QoL in real life from PLWHIV patients is needed to evaluate the health impact of overall drugs prescribed.

The main objective of this study was to assess the correlation between MRCI and QoL (EQ-5D) and health utilities

among PLWHIV patients on ART. Another secondary objective was to analyse the influence of treatment in domains of EQ-5D-5L questionnaire.

PATIENTS AND METHODS

Design and study population. This was an observational prospective single-center study. PLWHIV aged 18 years-old or over on ART attending at hospital pharmacy outpatient service from January to March-2020 were included. Those patients received the pharmacotherapeutic follow-up already routinely applied to ambulatory care patients according to a Capacity-Motivation-Opportunity (CMO) pharmaceutical care model [13-15]. CMO (Capacity-Motivation-Opportunity) is a new model whose cornerstones are: capacity, understood as providing individualized pharmaceutical care adapted to each patient, through stratification; Motivation, in order to reach goals with drug therapy, replacing the traditional clinical interview with a motivational interview; and finally, Opportunity, providing follow-up beyond the personal consultation, through information, communication and learning technologies. Patients were excluded if participating in a clinical trial or did not give their written informed consent.

The study fulfilled all the ethical requirements and was approved by the Clinical Research Ethics Committee of Hospital Virgen de Valme (C.I. 0937-N-20).

The following variables were analyzed: demographic (age, sex); analytical data, plasma viral load (copies/mL), CD4 cell count (cells/ μ L); and clinical variables related to comorbidities and pharmacotherapeutics, such as type of ART, concomitant medications and presence of polypharmacy. Only those patients with all variables completed were included in the analysis.

To describe the patterns of multimorbidities, we employed the categorization proposed by Prados-Torres et al who classified the patterns depending on the type of disease they were diagnosed including: cardiometabolic, geriatric-depressive, thyroid mechanic and mixed [16]. Patients were categorized to a specific pattern when they had been diagnosed with at least two diseases included in the pattern.

Polypharmacy was defined as the use of 6 or more different drugs, including antiretroviral medication; major polypharmacy was restricted to the use of ≥ 11 different drugs. To describe the patterns of polypharmacy, we employed the categorization proposed by Calderón-Larrañaga et al. [17] who classified the patterns depending on the type of disease they were intended to treat cardiovascular, depression-anxiety, acute respiratory infection, chronic pulmonary disease, rhinitis-asthma, pain and menopause. After categorizing a drug according to the anatomical therapeutic chemical classification system up to the first three levels, a patient was categorized to a specific pattern when at least three drugs included in the pattern were dispensed.

Finally, pharmaceutical care variables such as the classification of the stratification of patients according to the

risk-stratified model for pharmaceutical care in HIV-patients of Spanish Society of Hospital Pharmacy were recorded.

The MRCI index is a validated 65-item tool that evaluates treatment regimen complexity based on the number of medications, dosage form, dosage frequency, and additional or special instructions. This index score ranges from 1.5 (for someone taking a single tablet or capsule taken once a day) to an undefined maximum since the score increases with the number of medications; greater scores indicate higher complexity [18]. Additionally, according to Morillo-Verdugo et al [19] a cut-off value of 11.25 for MRCI index score was employed for considering complex patient.

All patients were asked to complete the Spanish version of the EQ-5D, an instrument previously used to assess QoL in chronic patients. There are two versions of the EQ-5D, EQ-5D-3L and EQ-5D-5L, the last one was employed because it is more sensitive to changes in health status. EQ-5D-5L provides a simple description of the patient's self-perceived health status covering five health dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with five response options (no problems, slight problems, moderate problems, severe problems and extreme problems). Any response in the items "slight, moderate, severe or extreme" were considered as having "problems", for each dimension. The questionnaire also provides a self-reported Visual Analogue Scale (VAS), which measures the patients' health on a scale from 0 to 100, where 0 reflects the worst imaginable health status and 100 the best imaginable health status. The patient response in the five dimensions results in a five-digit code, which can be transformed to a single measure called EQ-5D index or utility value. It ranges from 0 (reference value assigned to death) to 1 (perfect health), with the possibility of negative values for health states considered worse than death. It is a health summary score used in the clinical and economic evaluation of healthcare as well as in population health surveys. Although the EuroQol Group has already developed a methodology for eliciting value sets for the 5L version in some countries, no EQ-5D-5L value set was available in Spain at the moment of the study. Therefore, following the EuroQol recommendation, an interim mapping method or crosswalk to obtain 5L value sets from the existing 3L values for Spain was used in this study [20].

Regarding the main variable, QoL was measured with the EQ-5D-5L questionnaire, which allowed the 5 dimensions analyzed in each patient to be analyzed separately based on 5 possible responses. In our cases, to facilitate the correlation analysis with the QoL, we have combined the responses in three categories (answer 1: no problems; answer 2: slight-moderate problems; answer 3: severe-extreme problems).

Statistical analysis. Discrete variables were expressed as counts (percentage) and continuous variables as medians and interquartile ranges (IQRs) or means and standard deviation (SD). Differences in categorical variables were calculated using a two-sided likelihood ratio chi-square test or Fisher exact test, and the t-student test or U-Mann-Whitney test were used for

continuous variables, when appropriate. The adjustment or not to normality will be verified by Kolmogorov-Smirnov or Shapiro-Wilk tests, according to the size of the groups.

One-way ANOVA was used to understand if there are statistically significant differences and the effect that the comorbidity pattern has on the QoL of patients. To test whether comorbidities affect differently according to gender and influence on the QoL of patients, we use a multiple comparison approach by Bonferroni adjustment where statistical significance was defined as $p < 0.005$. We used Spearman's or Pearson correlation analysis to test linear association between MRCI and QoL-5D index. The threshold for statistical significance was defined as $p < 0.05$. Data analysis was performed using SPSS for Windows 25.0.0 (SPSS, Chicago, IL, USA). and for the graphic representation, the Microsoft Office package, Excel v2016 software, was used. The trend lines were presented smoothly with logarithmic transformation.

RESULTS

A total of 428 patients were included in this study, mean age of 50 ± 10.9 years, 82.2% males. Baseline characteristics of patients are shown in Table 1. At baseline 396 patients presented an undetectable viral load (< 20 cop/mL) (96.5%) and a $CD4+ > 200$ cell/mm³ count (97.4%). Globally, the number of patients stratified according to the CMO pharmaceutical care model were 369 in level 3 (86.2%), 42 in level 2 (9.8%) and 17 in level 1 (4.0%).

Overall, 25.9% (N=111) of patients presented polypharmacy, 5.4% (N=23) had major polypharmacy.

The MRCI index mean was 6.9 ± 5.5 . Moreover, MRCI index was higher in patients stratified as N1 (12.4 ± 8.4) compared to N2 (9.2 ± 5.9) and N3 (4.7 ± 4.8) ($p = 0.001$). A MRCI value greater than 11.25 (complex patients) was observed in 88 patients (20.6%). The mean value of EQ-5D-5L was 76.1 ± 19.8 points. Additionally, QoL was higher for patients stratified as N3 (74.6 ± 18.7) compared to N2 patients (59.4 ± 22.8) and N1 (66.4 ± 27.3) ($p = 0.0002$).

Spearman's test showed a moderate, negative correlation ($r^2 = -0.147$; $p = 0.0002$) between MRCI and EQ5D from baseline to last evaluation (Figure 1).

ANOVA test showed the existence of a relationship between the comorbidity pattern and QoL, being statistically significant in the geriatric-depressive ($p = 0.003$) and thyroid-mechanic ($p = 0.002$) patterns. The Radar chart demonstrated the most affected dimensions at the time of the MRCI index score calculation (Figure 2). The dimensions with the worst assessment were Anxiety/Depression, Pain/discomfort and Self-Care according to what was obtained in the ANOVA test. Likewise, the multiple comparison table shows how there is a statistically significant influence on the QoL in men with a geriatric-depressive patterns [$F(74,428) = 5.1$; $p = 0.003$] and women with thyroid-mechanic comorbidity patterns [$F(56,428) = 7.1$; $p = 0.002$].

Table 1	Baseline demographics, clinics, pharmacotherapeutics and pharmaceutical care characteristics.
	Total cohort N=428
Demographics	
Age (years); mean \pm SD	50 \pm 10.9
Gender (Male); n, (%)	352 (82.2)
CDC classification (AIDS)	92 (21.5)
Clinics	
CD4 level (>200 cells/ml)	417 (97.4)
Undetectable viral load (<50 c/ml)	396 (96.5)
Comorbidities	
Cardiometabolic	148 (34.6)
Geriatric depressive	44 (10.3)
Thyroid mechanic	28 (6.5)
Pharmacotherapeutics	
ART type	
NRTI + INI	240 (56.1)
NRTI + NNRTI	49 (11.4)
NRTI + IP	86 (20.1)
Concomitant medication (number of drugs); mean \pm SD	3.5 \pm 3.0
Polymedicated; n, (%) ^a	111 (25.9)
Polypharmacy patterns	
Cardiovascular	48 (11.2)
Anxious-depressive	17 (4.0)
CPOD	6 (1.4)
Mixed	40 (9.3)
MRCI (points); mean \pm SD	6.9 \pm 5.5
Pharmaceutical care	
Stratification ^b	
N3	369 (86.2)
N2	42 (9.8)
N1	17 (4)

ART: Antiretroviral therapy; NRTI: Nucleoside reverse transcriptase inhibitors; INI: Integrase inhibitors; NNRTI: Nonnucleoside reverse transcriptase inhibitors; IP: protease inhibitor; MRCI: medication regimen complexity index.

^aDistribution of MRCI according to polymedication status [Polymedicated 13.6 \pm 6.1 vs. 4.5 \pm 2.6 in non polymedicated].

^bDistribution of MRCI according to stratification [N3, 6.6 \pm 4.9; N2, 12.1 \pm 13.2; N1, 12.4 \pm 8.4; ANOVA pintergroups <0.001]

DISCUSSION

Our findings indicate that high MRCI values in PLWHIV are related to worse QoL. The negative statistical correlation shows

how there is an increase in the MRCI value to the detriment of the QoL perceived by the patient.

To our knowledge, this is the first study that clearly correlates pharmacotherapeutic complexity with poorer QoL in

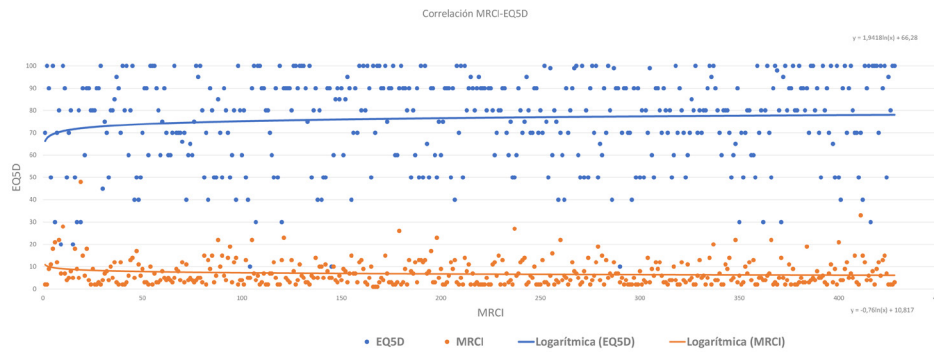


Figure 1 | Curve for Quality of Life (EQ-5D) in relation to the Medication Regimen Complexity Index (MRCI) value.

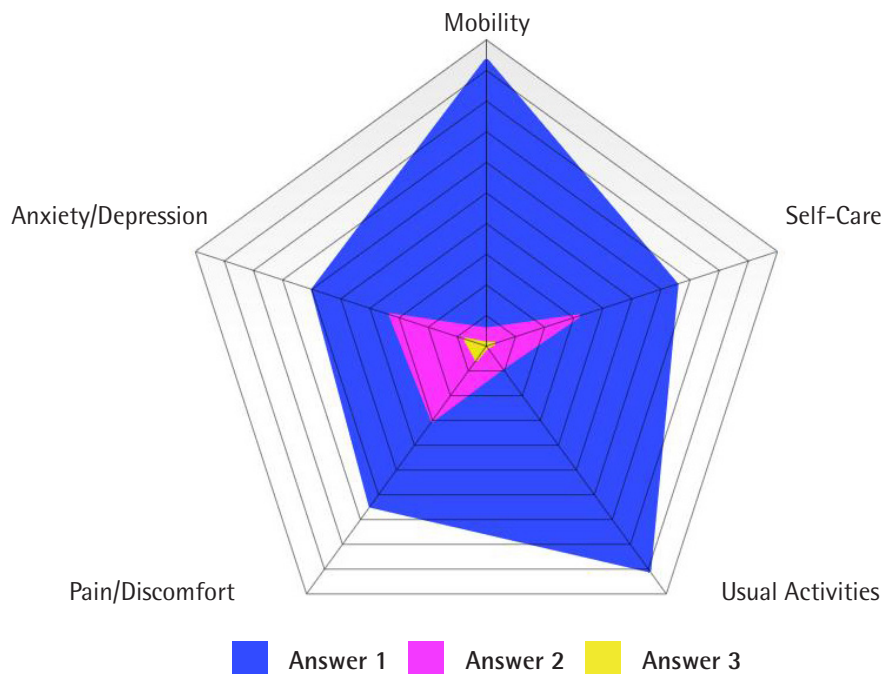


Figure 2 | Radar graph with the characteristics of the 5 dimensions of the EQ-5D-5L questionnaire. Answer 1: no problems; Answer 2: slight-moderate problems; Answer 3: severe-extreme problems.

PLWHIV. Previous studies observed that polypharmacy was strongly associated with a poorer QoL among PLWHIV [21-23]. Furthermore, Keaei et al. [24], showed that the dimensions of pain/discomfort and anxiety/depression were more affected in this kind of patients coinciding with the results of our study. However, the definition of polypharmacy employed by Keaei et al. could be inappropriate to relate the QoL since we can find patients who take the same number of drugs but have different MRCI values. Moreover, MRCI index has been validated as

a tool to analyse the treatment and the complexity associated with this [25].

Nowadays, the WHO strategy calls for person-centred chronic care for PLWHIV, implicitly acknowledging that viral suppression is not the ultimate goal of treatment. Regarding HIV treatment, the strategy puts forth the '90-90-90' target championed by Joint United Nations Programme on HIV/AIDS (UNAIDS). This target is also important from a public health perspective since achieving such a large increase in the num-

ber of virally suppressed people would greatly reduce onward transmission of the disease. According to the proposal of Lazarus et al, it is necessary to add a 'fourth 90' to the treatment target [23]. This new target would be to get 90% of PLWHIV with undetectable viral load to have a good QoL. Furthermore, they suggested that a good health-related QoL for PLWHIV requires attention to two domains: comorbidities and self-perceived QoL. According to our results, the relationship between certain patterns of comorbidity and the worsening of the QoL makes individualized care essential, focusing on its comorbidities [26]. Therefore, it is a field of research to exploit given the greater vulnerability of PLWHIV to age-related conditions because they present a greater number of comorbidities and other age-related conditions at an earlier age than general population.

Knowledge of the domains of health-related QoL that are most affected in patients who are 'controlled' can assist in the development of specific interventions to optimise the health of these individuals, especially undetectable patients. The results of our study indicate the need for monitoring mental health and pain/discomfort at medical and pharmaceutical consultations. The use of specific questionnaires may be recommended. Undertaking a medicines reconciliation evaluation may also be merited to determine primary care prescribing of psychoactive medications or nonsteroidal anti-inflammatory drugs, and the use of over-the-counter medications that may be required by patients to treat underlying comorbidities. This represents an additional facet to the multidisciplinary approach to managing PLWHIV patients in the hospital setting. However, management of high complexity older patients should be included in deprescribing or optimizing strategies, with particular focus on the potential for anxiety/depression interactions, inappropriate drug medication or non-adherence to concomitant drugs at routine healthcare.

Several limitations are worth noting. First, our study was based at a single urban safety net hospital, so generalizability to other settings and patient population would be a priority. However, our study is one of the largest population cohort studying how MRCI may influence over QoL among PLWHIV to date. We had the advantage of being able to extract data from both inpatient and outpatient health information systems to create an important and longitudinal profile of patients and their risk factors. These results may not apply to hospitals lacking MRCI or EQ5D routinely or those without any outpatient care data. Nonetheless, both EQ5D and MRCI tools, are easy to collect and implement, because it includes different elements that would be reasonably available in all kind of hospitals.

Finally, although we used rigorous statistical methods to explore our model, our validation was limited to our internal data set. Due to our hospital system cares for most HIV-infected patients, we believe that this reflects a nowadays real-world setting where a large proportion of HIV-infected patients are engaged in routine HIV care. Anyway, future efforts should validate how MRCI could be used to further profile the interventions and the type of patient that will po-

tentially be a candidate for closer monitoring by the multidisciplinary team.

Despite these potential limitations, this study has successfully identified the correlation between MRCI and QoL. HIV specialist interventions should be carried out more frequently and intensively in current patients, with a methodology that takes into account their needs and individual characteristics and not focused on the prescribed medication, stressing the importance of an effective patient care model to closely monitor high risk-patients. As PLWHIV is becoming increasingly complex, it is increasingly necessary to individualize health care by offering a work system more oriented to their individual needs.

One of the most important pending challenges for the future is to adapt a multidisciplinary methodology to the needs of the multidimensional approach needed on PLWHIV, especially those with greater pharmacotherapeutic complexity, who may have a higher risk of non-adherence, hospital readmissions and worse health outcomes. For this reason, it would be necessary to incorporate new concepts and strategies of joint work to carry out multidimensional interventions.

In conclusion, the results of our study form the basis for a new revised care plan for PLWHIV focussed on optimising overall patient care, not limited to viral load goal achievement alone but also in their pharmacotherapeutic complexity and QoL. No doubt, not only multidisciplinary, but also multidimensionally would be the most successful to approach PLWHIV in the near future.

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None to declare.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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