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Identification of the Medication Regimen Complexity Index as an Associated Factor of Nonadherence to Antiretroviral Treatment in Hiv+Patients

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Abstract

Background: Multiple studies have identified a relationship between the complexity of a medication regimen and non-adherence. However, most studies in people who live with HIV (PLWH) have focused on antiretroviral use and have failed to consider the impact of other medications. **Objective:** The aim of our study is to identify the Medication Regimen Complexity Index (MRCI) as an associated factor for non adherence to antiretroviral treatment (ART). The secondary aim is to analyze the relationship between clinical and pharmacotherapeutical variables and adherence to antiretroviral treatment and to generate an adherence model. **Methods:** A transversal, observational study. Patients included were PLWH over 18 years of age on active antiretroviral therapy. Patients who participated in clinical trials or who did not meet the inclusion criteria were excluded. We had studied HIV transmission mode, viral load, treatment status, number of comorbidities and complexity index as factors associated with adherence to ART. **Results:** We included 619 patients in the study. Number of comorbidities (p = 0.021; OR = 1.038-1.570); viral load (p = 0.023; OR = 1.108-4.505) and MRCI (p < 0.001; OR = 1.138-1.262) (ART and concomitant treatment) were the independent associated factors to ART nonadherence. The value of the Hosmer and Lemeshow test confirmed the validity of this model (P = 0.333). **Conclusion:** A higher MRCI was associated with non-adherence. Therefore, the regimen complexity calculation may be appropriate in daily practice for identifying patients at a higher risk of becoming non-adherent.

Keywords
HIV/AIDS, antiretroviral treatment, adherence, viral infections

Introduction

The introduction of highly active antiretroviral therapy (ART) during the 1990s was crucial to reduce HIV-related morbidity and mortality rates, improving life expectancy among people who live with HIV (PLWH)[1,2] and develop a chronic disease as a result of HIV infection. As a result, a progressive aging of PLWH is observed.[3] The aging of this population worldwide is one of its most significant demographic features. In developed countries, an estimated 50% of PLWH are at an advanced age (people older than 50 years).[4] Because of this change, there has been an increase in the number of comorbidities present in these individuals as well as an increased use of comedications.[5] Polypharmacy, defined as 5 or more prescribed drugs, is common among PLWH.[6] It is worth mentioning that the 55% of patients ≥50 years of age from the Veterans Aging Cohort Study were using 5 or more daily medications.[7] However, the harms of polypharmacy include an increase in adverse events related to medications, geriatric syndromes, mortality, and decreased adherence.[8]

There are multiple reasons for nonadherence: it is known that adverse events related to therapy and drug-drug interactions are typically involved. Multiple studies have also identified a relationship between management complexity

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of a medication regimen and nonadherence in older adults.[9,10] A higher number of medications and complicated schedules or special instructions (time of the day, food interactions) can all contribute to greater patient difficulty or interest in following treatment recommendations.

In this context, Martin et al[11] developed a tool to assess the complexity index of ART. That tool is the first step toward obtaining a better understanding of how the complexity of antiretroviral regimens affects adherence and medical outcomes. However, this tool is limited to the ART regimen, ignoring all other medications to detect comorbidities and symptoms of other health problems. Subsequently, George et al[12] developed the Medication Regimen Complexity Index (MRCI) to estimate the complexity of the treatment regimen taking into account all prescribed drugs in a given patient, even over-the-counter medication. The MRCI consists of a 65-item instrument that can be fed with data from patient records through the use of electronic information in a list of medications. Complexity levels are based on averages weighted by the number of medications, dosage frequency, administration instructions, and prescribed dosage forms.[12] Although a few recent studies have considered the use of specific classes of medications on PLWH,[13,14] most studies have focused on antiretroviral use and have failed to consider the impact of other medications or therapies.[15,16]

The aim of our study was to assess the association between the MRCI and total nonadherence. The secondary aim is to analyze the relationship between clinical and pharmacotherapeutical variables and total adherence and to generate an adherence model.

Materials and Methods

Description of the Population Cohort and Clinical Study

We conducted a transversal, observational study. Patients included in the study met the following inclusion criteria: PLWH >18 years of age, on ART for at least 6 months, and registered as patients in pharmacotherapy follow-up at the pharmaceutical care office of the viral pathologies area in the hospital pharmacy service (PCC) up to February 2015. These patients visit the PCC according to their level of stratification every 1, 2, or 3 months. Patients who participated in clinical trials or who did not meet the inclusion criteria were excluded.

Data collected from the electronic medical record included the following: demographic data (sex and age) and HIV transmission mode (injecting drug user, sexual behavior, or others), clinical end points (plasma viral load (copies/mL; considered detectable if it was >20 copies/mL) and $CD4^+$ T-cell count (cells/μL), immunovirological control (defined as patients who had undetectable viral load and $CD4^+$ T-cell count greater than 200 cells/μL[17]), and Centers for Disease Control and Prevention HIV classification[18] and comorbidities related end points (number and type of comorbidities, particularly liver, central nervous system, diabetes, hyperlipidemias, and cardiovascular disease or high blood pressure).

Pharmacotherapeutic end points were as follows: treatment status (naïve patient or treatment experienced: naïve patient was defined as a patient who did not have modifications or discontinuities since their first ART regimen); type of ART therapy, classified as (*a*) 2 nucleoside reverse transcriptase inhibitors (NRTI) plus a nonnucleoside reverse transcriptase inhibitor (NNRTI), (*b*) 2 NRTIs plus a protease inhibitor, (*c*) 2 NRTIs plus an integrase strand transfer inhibitor, and (*d*) others[17]; number of concomitant medications (was considered only if it was prescribed with a minimum duration of 60 days); polymedicated (defined as a treatment with 5 or more drugs, including ART[19]); antiretroviral strategy treatment, defined as once daily or twice daily (BID) and adherence to ART and the concomitant drugs.

The MRCI was calculated using a web tool of Colorado University available at http://www.ucdenver.edu/academics/colleges/pharmacy/Research/researchareas/Pages/MRCTool.aspx. This web tool is based on an adaptation of the score created by Martin et al.[11] This score takes into account the number of pills per day, the dosing schedule, the dosage form, and any specific instructions related to drug use.

Adherence to ART was measured with the Simplified Medication Adherence Questionnaire (SMAQ)[20] questionnaire and hospital dispensing records[21]. Adherence to concomitant medication was measure with the Morisky-Green questionnaire (MMAS Morisky Medication Adherence Scale)[22] and electronic pharmacy dispensing records. For both types of treatment, the multi-interval adherence index was used for the last 6 months of treatment. A cross section was realised on February 1st 2015 to analyze the medication last 6 months of treatment.

The SMAQ is a 6-item questionnaire that evaluates different aspects of patient adherence: forgetfulness, routine, adverse effects, and missed doses. Patients were considered adherent if ART adherence was > 95% and patients were scored as adherent using the SMAQ MMAS is a questionnaire with 4 items that has been particularly useful in chronic conditions. The scale is scored 1 point for each "no" and 0 points for each "yes." The total score ranges from 0-3 (nonadherent) to 4 (adherent). The adherence questionnaire was carried out in successive visits to the pharmaceutical care office. Patients were considered adherent if ART adherence through dispensing records was > 95%, and the MMAS score was 4.We obtained the number of comorbidities and comedications for other chronic diseases (non-HIV drugs) making use of the information supplied by the medical history and electronic health prescriptions program of Andalusian Public Health System. According to the number

of comorbidities, patients were categorized as having multiple chronic conditions (polypathology) if they had 2 or more chronic diseases[23]. The remaining variables were obtained by consulting analytics, microbiology reports, and from review of the medical history of each patient.

Statistical Analyses

Quantitative variables were expressed as mean and standard deviation or as median and percentile P25 and P75 in case of a skewed distribution. Qualitative variables were expressed as percentages (%).

To compare mean values of quantitative variables among groups, the Student's *t* test was used for independent samples and the Mann-Whitney nonparametric *U* test for nonnormal distributions. If any significant differences were observed, 95% CIs were calculated for differences in mean (or median, if relevant) values. Contingency tables were prepared, and the χ^2 test was used to analyze the relationship between qualitative variables; if not, the Monte Carlo asymptotic method and exact test were used.

To identify independent factors associated with concomitant medication adherence, we performed a univariate logistic regression. We also analyzed the collinearity between the variables. Subsequently, variables that showed statistical significance in the univariate analysis and those with $P < 0.25$ were included in a multivariate model. A 95% CI was used. Validity of the model was evaluated using the Hosmer and Lemeshow test. The sample size was estimated using the Freeman equation, $10 \times (k + 1)$ (Being "k" the number of variables collected). Data analysis was performed using the statistical package SPSS 22.0 for Windows (IBM Corp, Armonk, NY).

This study was conducted according to the principles of the declaration of Helsinki. The local ethics committee approved the collection of data associated with the cohort.

Results

We included 619 patients in the study. Most patients were men (81.4%), and the median age was 48 years (interquartile range [IQR] = 43-53). In addition, we excluded 15 patients because data were not available (n = 12) or because patients were enrolled in clinical trials (n = 3). The baseline demographic, clinical, and lifestyle characteristics of the patients are shown in Table 1.

The type of ART, by drug class, was as follows: 2 NRTIs plus a NNRTI, 47.3%; 2 NRTIs plus a protease inhibitor, 24.7%; 2 NRTIs plus an integrase strand transfer inhibitor, 6.8%; and other combinations, 21.2%. The median of comorbidities per patient was 1 (IQR = 1-2). A total of 56.4% of patients were diagnosed with viral liver diseases, followed by 26.5% with pathologies of the central nervous system, 24.7% with dyslipidemias, 15.8% with cardiovascular disease, 10.9% with hypertension, and 6.2% with diabetes. The percentage of patients with adequate adherence level to the ART was 67.9%, and it was 62% for concomitant medication. Based on the MRCI, the median values of ART and concomitant medications were 5 (IQR = 3-7) and 1 (IQR= 0-5), respectively. The median value of global treatment was 7 (IQR = 4-12).

Table 1. Baseline and Clinical Characteristics of Study Patient Variables (n = 619).

Sex: n (%)	
Female	115 (18.6)
Male	504 (81.4)
Age (years): median (IQR)	48 (43-45)
Average plasma viral load[a]: n (%)	
Detectable	555 (90.0)
Undetectable	62 (10.0)
CD4+ T-cells (cells/mm^3): median (IQR)	583 (380.0-817.8)
Immunovirological control[b]: n (%)	505 (83.7)
HIV exposure categories or acquisition risk factor: n (%)	
Perinatal	1 (0.3)
Injection drug use	140 (42.7)
Sexual	187 (57.0)
AIDS diagnosis: n (%)	288 (63.7)
Treatment status: n (%)	
ART naïve[c]	117 (18.9)
Treatment experienced	502 (81.1)
Regimens	
QD: n (%)	469 (75.8)
BID: n (%)	150 (24.2)
Comorbidities: median (IQR)	1 (1.0-2.0)
Comedications: median (IQR)	0.5 (0.5-2.0)
Polymedicated[d]: n (%)	60 (9.7)

Abbreviations: ART, antiretroviral therapy; BID, twice daily; IQR, interquartile range; QD, once daily.
[a]Considered detectable if it was greater than 20 copies/mL.
[b]Defined as patients who had undetectable viral load and CD4$^+$ T-cell count greater than 200 cells/μL.
[c]Defined as patients who had no modifications or discontinuities since their first ART regimen.
[d]Defined as a treatment with 5 or more drugs, including ART.

Table 2 shows the variables included in the univariate analysis. There was a statistically significant relationship between HIV transmission mode, viral load, age (2 age groups were performed, ≥50 years or <50 years.), treatment status, and number of comorbidities and adherence to ART.

Subsequently, multivariate analysis showed that number of comorbidities, viral load, and global complexity index (ART and concomitant treatment) were independent factors associated with nonadherence to ART (Table 3). This table includes the odds ratio for adherence. The value of the Hosmer and Lemeshow test confirmed the validity of this model ($P = 0.333$).

Table 2. Univariate Analysis of Variables Associated With Total Adherence.

Variable	Adherence	Nonadherence	*P* Value	Odds Ratio (95% CI)
Sex: n (%)				
Female	41 (35.7)	74 (64.3)	0.95	
Male	225 (44.6)	279 (55.4)		
Age (years): n (%)				
<50	180 (46.4)	208 (53.6)	0.029	1.05-2.04
≥50	86 (37.2)	145 (62.8)		
Average plasma viral load[a]: n (%)				
Detectable	16 (25.8)	46 (74.2)	0.004	1.30-4.26
Undetectable	250 (45.0)	305 (55.0)		
HIV exposure categories or acquisition risk factor: n (%)				
Injection drug use	54 (38.6)	86 (61.4)	0.004	1.25-3.05
Sexual	103 (55.1)	84 (44.9)		
Treatment status: n (%)				
ART naïve[b]	64 (54.7)	53 (45.3)	0.005	1.20-2.69
Treatment experienced	202 (40.2)	300 (59.8)		
Comorbidities: median (IQR)	1 (0-1)	2 (1-3)	<0.0001	1.00-1.00

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range.
[a]Considered detectable if it was greater than 20 copies/mL.
[b]Defined as patients who did not have modifications or discontinuities since their first ART regimen.

Table 3. Multivariate Analysis of Variables Associated With Total Adherence.

Variable	*P* Value	Odds Ratio (95% CI)
Sex	0.154	0.880-2.253
Age (years)	0.457	0.575-1.283
Average plasma viral load	0.023	1.108-4.505
Treatment status	0.792	0.585-1.505
Comorbidities	0.021	1.038-1.570
Global Complexity Therapeutic Index	<0.0001	1.138-1.262

Discussion

In our study, we found that MRCI is an independent associated factor for nonadherence to ART among PLWH. Therefore, a higher MRCI value can impair adherence, leading to worse treatment outcomes.

Despite the complexity of ART regimens for PLWH, little is known about the complexity of concomitant medications and their impact on ART adherence. Several studies have examined the impact of MRCI outside the population of people living with HIV.[2-25] In the study carried out by Choudhry et al,[25] the researchers concluded that greater prescribing and filling complexity was associated with lower levels of adherence in patients with cardiovascular disease. However, several authors have studied the relationship between ART complexity index and its impact on ART adherence.[26,27] Stone et al[27] examined the complexity of antiretroviral regimens by assessing administration instructions and dosing frequency. Their results indicated that patients with more complex regimens were also more likely to be nonadherent to those regimens. In contrast, regimen complexity was not a significant predictor of adherence in the study by Gao et al.[28]

In relation to the other variables analyzed in the multivariate analysis, we found that number of comorbidities was an independent associated factor of nonadherence to ART; however, to date, no study has been conducted to evaluate the influence of the number of comorbidities in the adherence to ART. Like many other studies, our study showed a significant associate between detectable VL and nonadherence. A study in a cohort of Brazilian HIV patients showed a reduction of HIV viral load. This viral load was better among adherent patients as compared with nonadherent patients.[29] Other authors have reported too that a reduction in HIV viral load was strongly associated with adherence.[15,30]

The main limitation of our study lies in the unicentric and retrospective design itself. The retrospective nature of the data collection process implies that biases may have influenced our results. In any case, this limitation was compensated by the sample size of our study. This study is limited by the fact that there is no gold standard for adherence measurements. Pharmacy dispensing records are chosen because they are practical and inexpensive. However, this type of method can overestimate adherence. Data from patients with low adherence are reliable, but it is not possible to ensure that patients with perfect dispensation records are taking the medication. To resolve this limitation, ART adherence is measured by a combination of 2 different methods: those based on dispensing records and those based on adherence

questionnaires (MMAS for comedication and SMAQ for ART), as recommended by clinical guidelines.[17]

A common limitation of other published studies is that they only include data on medications of official medical prescriptions; they do not include private health system treatments or alternative medicines. However, this is not seen as a very significant limitation in our study, given the universal coverage of the public health system in Spain, with a small number of patients using alternative medications.

Future studies are needed to validate interventions that will overcome the adherence challenges faced by patients with high MRCI scores. This study suggests that using an MRCI score would help identify those patients in need of multidisciplinary adherence interventions. Additional studies are needed to establish its power and determine possible opportunities for clinical interventions that would reduce the chances of MRCI score being a risk factor for nonadherence and its consequences, in terms of the use of health resources, including hospitalizations.

Conclusion

A higher MRCI was associated with nonadherence. Therefore, regimen complexity calculations may be appropriate in daily practice for identifying patients who are at a higher risk of becoming nonadherent.

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