Influence of the type of antiretroviral treatment on the time to reach high pharmacotherapy complexity in people living with HIV

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Research Article

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Abstract

**Background:** The primary objective was to assess the impact of antiretroviral treatment (ARV) on the duration required to achieve a high medication regimen complexity index (MRCI) in people living with HIV (PLWH).

**Methods:** A single-centre observational analytical research study was conducted, including adult PLWH on ARV from January 2010 to December 2022, who were treated in the hospital pharmacy. An analysis of the time to reach the MRCI value \( \geq 11.25 \) was performed, followed by a Cox regression model to determine the influence of ARV on high pharmacotherapeutic complexity.

**Results:** A total of 789 PLWH were included, with a medium age of 52 years (interquartile range: 45-58 years). Overall, 195 patients had an MRCI value \( \geq 11.25 \) with a mean time to reach it of 181.86 months (95%CI: 176.24 - 187.49 months). Significant differences were observed in sex, advanced age, AIDS stage, presence of comorbidities, polypharmacy, and ARV-related variables. A multivariate Cox proportional hazards model showed that INSTI-containing regimens (HR: 1.83; 95CI: 1.08-3.10) and NNRTI-based regimens (HR: 0.72; 95CI: 0.52-0.98) influenced the time until high pharmacotherapeutic complexity was reached.

**Conclusions:** In summary, regimens composed of 2 NRTI + NNRTI showed a protective effect in the development of high pharmacotherapeutic complexity compared to 2 NRTI + INSTI, which is identified as a risk factor. These conclusions were derived from the patient profile that included advanced age and high prevalence of both comorbidities and polypharmacy. Therefore, identifying high complexity allows us to implement pharmacotherapeutic optimization strategies to improve health outcomes.

Background

The development of effective antiretroviral therapy (ARV), combined with socioeconomic advances, has significantly improved the survival rates of people living with HIV (PLWH). Consequently, the proportion of older PLWH, defined as individuals aged \( \geq 50 \) years, has experienced a substantial increase. In 2016, there were 5.7 million older PLWHs, representing 16% of the global HIV population [1]. This trend is expected to persist, as evidenced by the ATHENA cohort study, which estimates that by 2030 approximately 73% of HIV patients will be older PLWH [2].

The ageing of PLWH presents a series of challenges, including the development of age-related comorbidities [3]. Older PLWH, despite achieving viral suppression, exhibits higher rates of multimorbidity at an earlier age compared to their HIV-uninfected counterparts of the same age [4, 5]. The most common comorbidities in older PLWH include metabolic disorders such as hypertension and hyperlipidemia, cardiovascular disease, and age-related conditions such as cognitive impairment and frailty [6]. The simultaneous presence of comorbidities in these patients increases the likelihood of polypharmacy. Research indicates that in older PLWH, the burden of multimorbidity and polypharmacy is more closely related to the duration of HIV infection than to advanced age itself [7, 8].
The concept of polypharmacy is commonly used to identify those patients with a higher probability of experiencing negative health outcomes due to medication use. However, polypharmacy has its limitation, primarily its purely quantitative nature, which only considers the number of drugs prescribed to each patient. Medication regimens with similar quantities of drugs can vary significantly in complexity due to multiple factors such as dosage forms, dosing frequencies, and additional usage directions. Therefore, it is essential to employ tools that consider both quantitative and qualitative aspects, such as the Medication Regimen Complexity Index (MRCI) [9]. Furthermore, the MRCI value of 11.25 has been defined as the cut-off point to identify patients with high pharmacotherapeutic complexity [10].

Data within our population already showed a high prevalence of polypharmacy and high complexity in elderly PLWH. This is associated with an elevated risk of developing negative health outcomes related to treatment, such as drug-drug interactions (DDIs) or lack of adherence, which can negatively impact the control of HIV infection and its comorbidities [11]. Since 2011, American consensus has that pharmacotherapeutic follow-ups should be based on pharmacotherapeutic complexity [12, 13]. Furthermore, studies have demonstrated the validity of MRCI as a tool for identifying patients who may benefit from pharmacotherapeutic optimisation strategies, including interventions such as prescribing adjustments [14, 15].

Different studies have analysed the evolution of the pharmacotherapeutic complexity of ARVs, showing a decreasing trend as ARV regimens are optimised and simplified [16]. However, there is a gap in the literature concerning the influence of ARVs on the duration required to reach high pharmacotherapeutic complexity. Therefore, the main objective is to determine the impact of ARVs on the timeframe for reaching high pharmacotherapeutic complexity in PLWH.

Methods

Study design and participants

Single-centre prospective observational study conducted at the hospital pharmacy outpatient service. We include PLWH attended from January 2010 to December 2021, were over 18 years old, and were on active ARV. Patients were followed up until December 31, 2023. Exclusion criteria included loss to follow-up and participation in clinical trials.

Data were collected during outpatient visits to the hospital pharmacy throughout the follow-up period. The following variables were analysed: demographic (age, sex); analytical data, plasma viral load (copies/ml), CD4 cell count (cells/µL); and clinical variables related to comorbidities and pharmacotherapeutics, such as type of ARV, number of drugs in the ARV regimen, presence of comorbidities, patterns of multimorbidity, concomitant medications, polypharmacy, patterns of polypharmacy, and MRCI. Only patients with complete data for all variables were included in the analysis.

Definition of the endpoint
The primary endpoint was global high pharmacotherapeutic complexity measured using the MRCI tool, with the threshold value defined according to the study by Morillo-Verdugo et al [10]. Global pharmacotherapeutic complexity is defined as the aggregate of the MRCI values obtained for antiretroviral (ARV) and concomitant medications.

The MRCI index is a validated tool consisting of 65 items designed to evaluate the complexity of treatment regimens. It considers variables such as the quantity of medications, form of administration, dosing frequency, and supplementary instructions [17]. Scores of the index range from 2 (representing individuals who take a single tablet or capsule once daily) to an undetermined upper limit, as the score increases proportionally with the number of medications. This tool has been adapted and validated for use in Spanish [18].

Definitions

ARV regimens were classified according to their classes as follows: a combination of 2 nucleoside analogue reverse transcriptase inhibitors (NRTI) together with a third drug, which could be a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI / b) or an integrase inhibitor (INSTI). ARV regimens that incorporate alternative approaches not following the triple therapy schemes referenced above were included within the broader category of "others". Additionally, ARV regimens were classified according to the number of drugs comprising ARV schemes: triple therapy, dual therapy, or monotherapy.

Comorbidity was defined as the presence of any chronic diseases present in the patient at the beginning of the study or those that emerged during the study period. Specific types of comorbidities were recorded in addition to documenting their presence or absence. Comorbidity patterns were further classified according to the study published by De Francesco et al. [19].

Polypharmacy was defined as the use of six or more different drugs, including antiretroviral medication, while major polypharmacy was limited to the use of 11 or more different drugs. To describe polypharmacy patterns, we adopted the categorisation proposed by Calderón-Larranaga et al., which classifies patterns based on the intended treatment for specific diseases. A patient was classified into a particular polypharmacy pattern if prescribed at least three drugs included in that pattern [20].

Statistical analyses

Baseline characteristics of included patients were reported as absolute numbers with percentages and medians with interquartile ranges (IQR), as appropriate. Comparison between subgroups generated by the variables was performed using either the chi-square test or the Mann-Whitney U test, as deemed suitable.

We evaluated the time to reach high pharmacotherapeutic complexity for each ARV regimen and scheme. This was analysed using the Kaplan-Meier method to identify independent associated factors. Differences between subgroups were evaluated using the log-rank test. To identify factors associated
with the development of high pharmacotherapeutic complexity, a multivariate Cox regression model was used. All variables demonstrating an association were included in the bivariate analysis using the Cox model ($p < 0.20$) were included. Backward selection was used to eliminate variables until the final Cox model was reached. Hazard ratios (HR) with 95% confidence intervals (CI) were reported to assess the strength and association between variables.

Results

A total of 789 PLWH were included in the study, with males comprising the majority (81.5%). The median age was 52 years (IQR: 45–58 years). Most patients had an optimal immunovirological control of HIV infection. The baseline characteristics of patients are shown in Table 1.
<table>
<thead>
<tr>
<th></th>
<th>Total, n (%)</th>
<th>PLWH with MRCI value &lt; 11.25</th>
<th>PLWH with MRCI value ≥ 11.25</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>789</td>
<td>594</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>643 (81.5)</td>
<td>477 (80.3)</td>
<td>166 (85.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>Age, years; median (Q1,Q3)</td>
<td>52 (45–58)</td>
<td>54 (46–58)</td>
<td>49 (44–55)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>273 (34.6)</td>
<td>151 (25.4)</td>
<td>122 (62.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HIV acquisition route</td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Sexual</td>
<td>609 (77.2)</td>
<td>469 (78.9)</td>
<td>140 (71.8)</td>
<td></td>
</tr>
<tr>
<td>Injecting drug users</td>
<td>175 (22.2)</td>
<td>120 (20.2)</td>
<td>55 (28.2)</td>
<td></td>
</tr>
<tr>
<td>Vertical</td>
<td>5 (0.6)</td>
<td>5 (0.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Undetectable viral load; (&lt; 50 cop/mL)</td>
<td>669 (84.8)</td>
<td>506 (85.2)</td>
<td>163 (83.6)</td>
<td>0.59</td>
</tr>
<tr>
<td>CD4 Cell count ≥ 200 cels/µL</td>
<td>714 (90.5)</td>
<td>537 (90.4)</td>
<td>177 (90.8)</td>
<td>0.88</td>
</tr>
<tr>
<td>Previous AIDS events</td>
<td>250 (31.7)</td>
<td>173 (29.1)</td>
<td>77 (39.5)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>91 (11.5)</td>
<td>2 (0.3)</td>
<td>89 (45.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>399 (50.6)</td>
<td>233 (39.2)</td>
<td>166 (85.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ARV Regimen</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>2 NRTIs + NNRTIs</td>
<td>354 (44.9)</td>
<td>286 (48.1)</td>
<td>68 (34.9)</td>
<td></td>
</tr>
<tr>
<td>2 NRTIs + PI/b</td>
<td>284 (36)</td>
<td>204 (34.3)</td>
<td>80 (41.0)</td>
<td></td>
</tr>
<tr>
<td>2 NRTIs + INSTI</td>
<td>64 (8.1)</td>
<td>47 (7.9)</td>
<td>17 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>87 (11)</td>
<td>57 (9.6)</td>
<td>30 (15.4)</td>
<td></td>
</tr>
<tr>
<td>ARV Scheme</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>736 (93.3)</td>
<td>563 (94.8)</td>
<td>173 (88.7)</td>
<td></td>
</tr>
<tr>
<td>Dual therapy</td>
<td>27 (3.4)</td>
<td>16 (2.7)</td>
<td>11 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>26 (3.3)</td>
<td>15 (2.5)</td>
<td>11 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Single-Tablet Regimen</td>
<td>572 (72.5)</td>
<td>522 (87.9)</td>
<td>50 (25.8)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

MRCI: Medication Regimen Complexity Index; ARV: antiretroviral treatment; NRTI: nucleoside analogue reverse transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI/b: boosted protease inhibitor; INSTI: integrase inhibitor.
Approximately half of the PLWH included in the study had comorbidities, with cardiovascular disease being the most common (61.9%), followed by neuropsychiatric pathologies (29.6%). This correlates with the prevalence of polypharmacy patterns, where the mixed type pattern was the most common (42.2%), incorporating drugs from various specific patterns, followed by psychogeriatric (28.9%) and cardiometabolic (23.3%) polypharmacy patterns.

Regarding the ARV regimen complexity, a higher percentage of patients with high complexity was found among those with ARV treatments categorized as "other" (34.5%), followed by those composed of 2 NRTIs + PI/b (28.2%), 2 NRTIs + INSTI (26.6%), and 2 NRTIs + NNRTI (19.2%). When considering the number of drugs comprising the regimens, a higher prevalence of high complexity was observed in patients receiving monotherapy (42.3%) and dual therapy (40.7%) compared to triple therapy regimens (23.5%). This is related to the higher percentage of single-tablet regimen schemes among patients on triple therapy (37.7%).

At the beginning of the study, 93 PLWH (11.8%) exhibited high pharmacotherapeutic complexity. Throughout the follow-up period, high MRCI was observed in 195 PLWH (24.7%), with a mean time to reach it of 181.86 months (95% CI: 176.24–187.49 months). Regarding ARV regimens, the longest period of time to reach high pharmacotherapeutic complexity was observed for regimens containing NNRTI, followed by regimens with PI/b and other regimens. Analysing the number of drugs comprising ARV, triple therapy regimens showed the longest period to reach high pharmacotherapeutic complexity. Figure 1 shows risk graphs illustrating the time to reach a high MRCI based on the regimen and ARV scheme used.

The Log-Rank test revealed significant differences for several variables, including gender (p = 0.04), advanced age (p = 0.04), AIDS stage (p < 0.01), presence of comorbidities (p < 0.01), and polypharmacy (p < 0.01). Focusing on ARV-related variables, statistical significance was found for single-tablet regimens (p < 0.01), ARV regimens based on both NNRTIs (p < 0.01) and INSTIs (p < 0.01), as well as for triple therapy (p < 0.01) and dual therapy (p = 0.01) schemes.

A multivariable Cox proportional hazards model that included variables related to ARV demonstrated the influence of different ARV regimens, identifying INSTI-containing regimens as a risk factor compared to the protective effect of NNRTI-based regimens. Table 2 displays the Cox proportional hazards model developed in the study.
Table 2
Multivariable Cox proportional hazards model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-Tablet regimen</td>
<td>0.86</td>
<td>0.67–1.12</td>
<td>0.09</td>
</tr>
<tr>
<td>NNRTI-based regimens</td>
<td>0.72</td>
<td>0.52–0.98</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>INSTI-based regimens</td>
<td>1.83</td>
<td>1.08–3.10</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Triple therapy</td>
<td>0.64</td>
<td>0.33–1.23</td>
<td>0.18</td>
</tr>
<tr>
<td>Dual therapy</td>
<td>1.27</td>
<td>0.54–2.98</td>
<td>0.59</td>
</tr>
</tbody>
</table>

CI: confidence interval; NNRTI: non-nucleoside reverse transcriptase inhibitor INSTI: integrase inhibitor.

The ROC curve was constructed (Fig. 2), indicating that the model predicted the risk of reaching high pharmacotherapeutic complexity in PLWH based on variables related to ARV (area under curve = 0.82; 95%CI, 0.78–0.85)

Discussion

ARV regimens based on INSTIs have a higher risk of reaching high pharmacotherapeutic complexity earlier compared to other regimens, with those containing NNRTIs even identified as protective factors in the development of high pharmacotherapeutic complexity.

The development of new drugs within the various families of antiretrovirals has facilitated the simplification of ARV regimens through the creation of coformulations, single-tablet regimens, and scheme optimisation, resulting in a reduction of the pharmacotherapeutic complexity associated with ARV. However, to date, highly complex ARVs can still be found in patients with multidrug failure who are rescued with regimens containing more than two families of antiretrovirals [21]. Therefore, currently, the high complexity of pharmacotherapy in PLWH is mainly due to the concomitant medication prescribed to manage comorbidities, as demonstrated by various studies such as the one conducted by Hirsch et al. [22]. In our study, this phenomenon follows the same trend, as evidenced by the high rates of comorbidities and polypharmacy in the high pharmacotherapeutic complexity group compared to patients with an MRCI < 11.25 [23]. It must be acknowledged that although ARVs currently does not exert a significant influence on the calculation of MRCI in most PLWH, the various regimens and therapeutic schemes used can be associated with a high level of pharmacotherapeutic complexity. This association arises from the inherent characteristics of the various drugs used, such as their pharmacological interactions with concomitant medication and the potential adverse effects associated with ARVs.

ARV regimens based on INSTIs exhibit an optimal DDI profile with various medications used to manage the most common comorbidities compared to NNRTI-based regimens. Several studies confirm these findings, identifying treatments containing NNRTIs as risk factors for the development of DDI, while also noting a reduction in the rate of DDI as the prescription of ARVs based on INSTI increases [24, 25]. All of
this is evident in our study, where we observe a reduction in the rate of ARV regimens prescribed based on NNRTI in patients with an MRCI value equal to or greater than 11.25, as INSTI-based regimens increase in this group with a higher prevalence of polypharmacy and, consequently, the need for pharmacotherapeutic optimisation to minimise DDI.

The MRCI value allows us to undertake a prescription approach considering both quantitative and qualitative aspects, which is essential for quality pharmaceutical care in older PLWH where there is not only a higher prevalence of comorbidities but also of frailty and geriatric syndrome [26]. Therefore, it is crucial to include these aspects in pharmaceutical care for these patients, who have shown a reduction in negative health outcomes involving various phenomena such as the PIMDINAC and 3-HIT criteria [27, 28].

Based on the results presented, there are several future lines of research that could be explored in the field of prescribing ARVs. First, investigating strategies to simplify ARVs regimens based on INSTI and NNRTI, aiming to reduce complexity of pharmacotherapy, especially in patients with comorbidities, would be valuable. Additionally, conducting long-term analysis to investigate the sustained efficacy, tolerance, adherence, and quality of life of PLWH treated with INSTI and NNRTI would provide important insights. Furthermore, exploring personalised treatment approaches for PLWH, considering individual patient characteristics and factors, could lead to improve treatment outcomes. Lastly, conducting studies to better understand the needs and challenges of PLWH with high MRCI values and how to adjust their treatments to improve their health and quality of life would be beneficial. It is crucial to carry out multidimensional pharmaceutical care strategies that go beyond polypharmacy and consider concepts such as pharmacotherapeutic complexity, given the potential negative consequences it may have on patients' health outcomes. These negative consequences may be related to clinical aspects such as nonadherence to medications, which can lead to virological failure or exacerbation of comorbidities [29, 30]. Furthermore, nonclinical aspects, such as quality of life, are impacted by high pharmacotherapeutic complexity, as evidenced by worse outcomes in patients with an MRCI value equal to or greater than 11.25 [31]. Therefore, it is interesting to use high pharmacotherapeutic complexity to identify patients who may benefit from pharmacotherapeutic optimisation strategies, including deprescription, which could lead to reduced complexity and improved health outcomes.

Despite these results, it is essential to highlight one of the main limitations, which was its unicentric nature and the potential influence favouring certain guidelines over others, thereby creating a selection bias. However, this bias was mitigated because infectious disease consultations at our centre adhered to national and international clinical practice guidelines, which standardised care practices with other national centres following the same working documents.

**Conclusions**

The influence of ARV on pharmacotherapeutic complexity has been reduced thanks to the simplification and optimisation of various ARV regimens. However, our study revealed that ARV regimens influence the
time it takes for the high pharmacotherapeutic complexity to develop. The results of this study indicate that patients with an MRCI value greater than or equal to 11.25 have a higher prevalence of comorbidities and polypharmacy. This highlights the need for pharmacotherapeutic optimisation in this population to minimise negative effects related to drugs, such as DDIs with concomitant medication. In this regard, INSTI-based ARVs have been identified to have a better safety profile compared to other treatment regimens, which leads to an increase in their prescription compared to patients with low pharmacotherapeutic complexity.

**Abbreviations**

ARV  
antiretroviral treatment

DDI  
drug-drug interaction

INSTI  
integrase inhibitor

MRCI  
medication regimen complexity index

NNRTI  
non-nucleoside reverse transcriptase inhibitor

NRTI  
nucleoside analogue reverse transcriptase inhibitors

PI/b  
boosted protease inhibitor

PLWH  
people living with HIV

**Declarations**

**Ethics approval and consent to participate**

Data collected from the study cohort were generated during routine care. The study met all the ethical requirements and was approved by the Sevilla-Sur Clinical Research Ethics Committee of Sevilla-Sur (C.I. 0174-N-20). This study was carried out according to the Declaration of Helsinki guidelines for biomedical research.

**Consent for publication**

Not applicable

**Availability of data and materials**
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

Authors declare no have conflict of interest.

**Funding**

Not applicable

**Authors' contributions**

ECM, MARC, JRBR, RMV conceived the study, involved in the study design, data analysis, drafting the manuscript and critically reviewing the manuscript. ECM are involved in data analysis. MARC, JRBR, RMV are involved in critically reviewing the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

Not applicable

**References**


**Figures**

**Figure 1**

Kaplan-Meier curves of transitioning to high pharmacotherapeutic complexity

1a. Antiretroviral regimen risk plot. 1b. Antiretroviral scheme risk plot.
Figure 2

Receiver operating characteristic curve for Cox model.

<table>
<thead>
<tr>
<th>AUC</th>
<th>SE</th>
<th>Signif</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.82</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>0.78 - 0.85</td>
</tr>
</tbody>
</table>

AUC: Area Under Curve; SE: Sensitivity; Signif: P-value; CI: Confidence Interval