Full Title:

**Impact of Polypharmacy on Antiretroviral Prescription in People Living with HIV**

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RunningTitle: **Polypharmacy and Antiretroviral Therapy Prescription**

**Synopsis**

**Objective**

We sought to evaluate the relationship between polypharmacy and antiretroviral therapy, delivered either as conventional multi-tablet three-drug regimens or single tablet regimens or less drug regimens (simplified mono or dual regimens).

**Methods**

Cross sectional analysis of electronic data from the prospective Modena HIV Metabolic Clinic cohort study.We included last clinical observation for each patient from January 2006 to December 2015. polypharmachy was defined as the use of 5 or more medications (excluding antiretroviral therapy).Multy-morbidity was classified as the presence of 2 or more of Non Infectious Comorbidities. Factors associated with different antiretroviral therapy regimens were analysed using multivariable multinomial logistic regression analyses with multi-tablet three-drug regimens therapy as reference.

**Results**

A total of 2944 patients (33.7% females) were included in the analysis.

Multinomial logistic regression analysis identified polypharmachy to be negatively associated with single tablet regimens regimen ($RRR=$0.48, CI:0.28-0.81) independently from frailty ($RRR=$0.68, CI: 0.59-0.78), after correction for age, gender, HIV infection duration, current and nadir CD4 and calendar year. This association was not found comparing multi-tablet three-drug regimens and less drug regimens.

**Conclusions**

Single tablet regimens regimen are less likely prescribed in patients with polypharmacy.

Single tablet regimens is perceived less flexible in patients with multimorbidity and higher risk of drug-drug interaction.

**Keywords**: antivirals; HIV antiviral pharmacology; HIV/AIDS; pharmacy

**Introduction**

The prolonged survival of HIV-infected individuals on combination ART has been accompanied by a marked rise in prevalence of concomitant diseases usually associated with ageing.1 In the Modena HIV Metabolic Clinic (MHMC), 65% of individuals receiving ART are in their fifties.2 The ATHENA investigators estimated that up to 60% of the HIV patients will have multimorbidity (MM) by 2030.3 The major consequence of MM is a corresponding rise in the number of prescribed medications for each individual, also known as polypharmacy (PP).4,5 Whilst PP is not an inevitable consequence of MM, the two are closely linked, and it is difficult to dissect their individual contributions to mortality, disability, functional decline, poor quality of life and high health care costs.6 This is particularly true for ART, which is associated with a high risk for drug-drug interactions and toxicities, which overlap with diseases of ageing such as renal impairment, metabolic syndrome and type II diabetes, bone disease and hyperlipidaemia. The concept of frailty (a measure of biological aging) may be useful in discriminating whether it is the morbidities themselves, or the toxicity of prescribed treatments, which contribute more to adverse outcomes. The Frailty Index (FI) was able to predict future incidence of MM in a large HIV cohort.7

Optimisation of ART strategy in patients with MM who are already taking multiple drugs can be challenging, requiring ART regimens to be tailored to minimise pill burden, risk of toxicity and drug-drug interactions. New strategies have been developed alongside conventional triple combination ART administered as Multiple Tablet Regimens (MTR). They include use of co-formulated, fixed-dose Single Tablet Regimens (STR) administered once-daily, as well as Less Drug Regimens (LDR) which reduce the number of compounds administered to either mono- or dual combination therapy.8

In this study, we sought to evaluate the relationship between MM, frailty, PP and ART strategy in HIV patients.

**Methods**

**Setting and sample**

This is a cross sectional analysis of data from the prospective MHMC cohort, whose electronic data collection was initiated in 2003/2004 to comprehensively assess longitudinal metabolic changes among people with HIV.2,9

We included last patient visits from 2006 to 2015. The data included in the cohort study are those used in the clinical care of participants, including disease diagnoses and vital statistics.

Inclusion Criteria were:

- Age>18 years

- Documented HIV infection

- Undergoing ART regimen.

**Covariates**

*Polypharmacy*

A complete drug history was collected by physicians at each patient visit and recorded using Anatomical Therapeutic Chemical (ATC) classification system, that divides active substances into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.10

Polypharmacy was defined as the use of 5 or more medication identified with 4th levels of ATC classification (chemical/pharmacological/therapeutic subgroups) at chronic use, excluding ART.10

In order to distinguish acute exposure to a drug from chronic use of medication the latter was classified as the consecutive prescription of at least 4 months of medication with the same drug in the study year.

Antiretroviral strategies were categorized in the 3 following groups:

1. Multiple Tablet Regimens (MTR): triple combination ART administered in 2 or more pills a day
2. Single Tablet Regimens (STR): co-formulated, fixed-dose triple combination administered once-daily
3. Less Drug Regimens (LDR) less than 3 ART compounds administered in either mono- or dual combination therapy.

*Demographic and clinical data*

Demographic and clinical data were collected from electronic patient chart.

HIV related variables included: current and nadir CD4+ T-cell counts (categorized into clinically relevant groups as follows: >500, 351-500, 101-350, ≤100), current HIV-RNA detectability and present and cumulative exposure to ART classes, year of initiation of current ART categorized in three time periods 2006-2008, 2009-2012, 2013-2015.

MM was classified as the presence of 2 or more of Non Infectious Comorbidities (NICM), including cardiovascular disease, end-stage kidney disease, cancer, osteoporosis, hypertension, type 2 diabetes mellitus, liver cirrhosis, and chronic obstructive pulmonary disease.

*Frailty*

A Frailty Index was calculated based on the deficit accumulation approach,11 previously applied in the same cohort.7 We assessed the effect of frailty independently from HIV-related variables and NICM, excluding these variables as items in the index.7

**Statistical analyses**

The cohort was divided in 3 ART strategy groups: MTR, STR and LDR. Normally distributed continuous variables were compared among the three groups using ANOVA, while Kruskal-Wallis test was used for non-normally distributed variables. Differences of categorical variables were analysed using Χ2-test.

Factors associated with different ART regimens were analysed using multivariable multinomial logistic regression analyses with MTR therapy as reference.

In order to avoid co-linearity between age and duration of HIV infection, a residual analysis was conducted between these two variables after univariate linear regression. Residuals of HIV duration were included in the multivariable multinomial regression analysis.

Statistical significance level was set for a p-value<0.05. All statistical analyses have been conducted with STATA 13.1 for Mac (StataCorp ltd., College Station, TX, US).

**Results**

A total of 2944 patients (33.7% females) were considered for the analysis.

Median duration of HIV infection was 19 years (IQR 12.5–23.7), median CD4 cell counts was 638 (460–830), with nadir of 192 (80–290) and 2,853 patients had undetectable HIV-VL (96.9%).

Table 1 describes demographic and anthropometric variables of the patients included in the analysis, divided per ART strategy group.

Within the STR group 350 patients were on Atripla®, 100 on Eviplera® and 14 on Stribild®.

We analysed the interrelationship between the study covariates, namely MM, PP and FI, which were highly colinear. MM and PP resulted highly correlated with Pearson’s r coefficient 0.40 (p<0.001). Similar results were found for the analysis of FI and PP r=0.18 (p<0.001). The capacity to discriminate MM and PP is depicted by the lower number of patients with MM with no PP (n=172; 5.84%), versus the higher number of patients with FI above the median and no PP (n=1,523; 51.7%).

A significant association was found between ART regimens and both FI and PP.

To explore their independent contribution to ART strategy we built two different multinomial logistic regression analysis comparing LDR with MTR and STR with MTR (figure 1).

**Discussion**

We observed a striking independent association between PP and FI, and lower likelihood of using an STR. This is despite the increasing median age of our cohort (data not shown) with a corresponding increase in MM, and an increasing tendency to use STRs with calendar year. Whilst this might run counter to the notion that the simplicity offered by STRs helps to reduce the pill burden in individuals already taking many tablets, the findings are not necessarily unexpected. Most of the STRs available during the period of our study contained tenofovir with or without cobicistat, or else abacavir. Prescribers may have chosen to avoid these drugs in a population at greater risk of bone, renal and cardiovascular adverse events, as well as restricted ability to avoid or manage drug interactions. In patients with MM, MTR and LDR regimens offer greater flexibility to tailor ART around existing co-medications. The introduction of STRs where tenofovir diproxil fumarate has been substituted with a newer formulation, tenofovir alafenamide may provide some added flexibility to tenofovir-containing STRs.

The high rates of MM, frailty and PP observed in our cohort is representative of large cohorts in the industrialized world. MHMC, like other providers of outpatient HIV care in Italy, offers direct free of charge access to clinics and medications.2 Although MHMC is a tertiary referral centre, most patients attend from the local catchment population and are representative of the general HIV outpatient setting in Italy. We observed that female patients were less likely to receive STRs, possibly as a result of a previous reluctance to use efavirenz in women planning to conceive, and concerns over tenofovir use in postmenopausal osteoporosis. Conversely, older age was associated with higher use of LDR. This may have been driven by the need to reduce ART toxicities in an age category where MM is highly prevalent. Smoking was highly prevalent in all patients groups. Individuals with a metabolic syndrome phenotype, as characterised by waist circumference, HOMA-IR and presence of lipodystrophy, were more likely to be receiving an LDR. in the need of metabolic friendly drug associations.

A novel aspect of our study was to utilise the Frailty Index as a means of discriminating between MM and PP. Frailty is a measure of clinical complexity and the clinical burden of MM, discriminating vulnerable patients with and without PP. This allowed us to utilise these two clinical variables in the same prediction model and dissect the association between PP and ART strategy.

Knowledge of ART strategies utilised in different groups of individuals receiving ART provides a greater understanding of unmet needs, particularly for older, multimorbid and frail patients where optimised ART is still not available in a single, fixed-dose formulation. Current treatment guidelines generally fail to reflect this, and the continued emphasis on use of STRs to improve adherence needs to be balanced against the limitations of currently available STR for complex individuals with multiple morbidities.12

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All remaining authors have no conflicts of interests to declare.

**References**

1. Schouten J, Wit FW, Stolte IG, *et al.* Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis* 2014; **59**: 1787–97.

2. Guaraldi G, Orlando G, Zona S, *et al.* Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* 2011; **53**: 1120–6.

3. Smit M, Brinkman K, Geerlings S, *et al.* Future challenges for clinical care of an ageing population infected with HIV: a modelling study. *Lancet Infect Dis* 2015; **15**: 810–8.

4. Sinnott C, Bradley CP. Multimorbidity or polypharmacy: two sides of the same coin? *J Comorbidity; Vol 5, No 1* 2015. Available at: http://jcomorbidity.com/index.php/test/article/view/51.

5. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. *BMC Med* 2015; **13**: 74.

6. Marengoni A, Angleman S, Melis R, *et al.* Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev* 2011; **10**: 430–9.

7. Guaraldi G, Brothers TD, Zona S, *et al.* A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. *Aids* 2015; **29**: 1633–41.

8. Clay PG, Nag S, Graham CM, Narayanan S. Meta-Analysis of Studies Comparing Single and Multi-Tablet Fixed Dose Combination HIV Treatment Regimens. *Medicine (Baltimore)* 2015; **94**: e1677.

9. Guaraldi G, Orlando G, Squillace N, *et al.* Multidisciplinary approach to the treatment of metabolic and morphologic alterations of HIV-related lipodystrophy. *HIV Clin Trials* 2006; **7**: 97–106.

10. Ronning M. A historical overview of the ATC/DDD methodology. *WHO Drug Inf* 2002; **16.3**. Available at: http://search.proquest.com/openview/4d3c922f5bec347f7ae0a7fdd73a7407/1?pq-origsite=gscholar.

11. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr* 2008; **8**: 24.

12. Treadwell J. Coping with complexity: working beyond the guidelines for patients with multimorbidities. *J Comorbidity; Vol 5, No 1* 2015.

**Legends**

**Table 1.** Demographic and anthropometric variables of the patients included in the analysis, according to ART strategy group

**Figure 1.** Multinomial logistic regression analysis (more likely, less likely)