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Impact of polypharmacy on antiretroviral prescription in people living with HIV

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Objectives: To evaluate the relationship between polypharmacy and ART, delivered as conventional multi-tablet three-drug regimens, single-tablet regimens or less-drug regimens (simplified mono or dual regimens).

Methods: We conducted a cross-sectional analysis of electronic data from the prospective Modena HIV Metabolic Clinic Cohort Study. We included the last clinical observation for each patient from January 2006 to December 2015. Polypharmacy was defined as the use of five or more medications (excluding ART). Multi-morbidity was classified as the presence of two or more non-infectious comorbidities. Factors associated with different ART regimens were analysed using multivariable multinomial logistic regression analyses with multi-tablet three-drug regimens as the reference.

Results: A total of 2944 patients (33.7% females) were included in the analysis. Multinomial logistic regression analysis identified polypharmacy to be negatively associated with single-tablet regimens [relative risk reduction (RRR) = 0.48, 95% CI = 0.28–0.81] independently from frailty (RRR = 0.68, 95% 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 are less likely to be prescribed in patients with polypharmacy. Single-tablet regimens are perceived to be less flexible in patients with multi-morbidity and at higher risk of drug–drug interaction.

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 patients with HIV will have multi-morbidity (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 healthcare 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 may be useful in discriminating whether it is the morbidities themselves or the toxicity of prescribed treatments that contribute more to adverse outcomes.

Frailty reflects a multi-system failure in a vulnerable person with impaired responses to various external stressors.[7] In clinical practice, frailty can be operationalized as an 'index', which counts the number of deficits individuals have accumulated out of various health measures and presents them as a proportion.[8,9] In contrast to the phenotypic approach, any measure can be included in a frailty index (FI) if it is generally related to age and poor health, and if the group of items covers multiple physiological systems. When at least 30 items are included, the proportion of deficits accumulated appears more informative than the specific nature of those deficits.

The FI was able to predict future incidence of MM in a large HIV cohort.[10]

Optimization of ART strategy in patients with MM who are already taking multiple drugs can be challenging, requiring ART regimens to be tailored to minimize pill burden, risk of toxicity and drug–drug interactions. New strategies have been developed alongside conventional triple combination ART administered as multi-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 monotherapy or dual combination therapy.[11]

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

Methods

Setting and sample

This is a cross-sectional analysis of data from the prospective MHMC cohort, whose electronic data collection was initiated in 2003–04 to assess comprehensively the longitudinal metabolic changes among people with HIV.[2,12]

We included last patient visits from 2006 to 2015 to have a decade of observation from the start of contemporary ART regimens. The data included in the cohort study are those used in the clinical care of participants, including disease diagnoses and vital statistics.

Consecutive patients with HIV >18 years old and undergoing ART were included.

Covariates

PP

A complete drug history was collected by physicians at each patient visit and recorded using the Anatomical Therapeutic Chemical 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.[13]

PP was defined as the use of five or more medications identified with the fourth level of the Anatomical Therapeutic Chemical classification system (chemical/pharmacological/therapeutic subgroups) at chronic use, excluding ART.[13]

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 into the following three groups: (i) MTR (triple combination ART administered in two or more pills a day); (ii) STR (co-formulated, fixed-dose triple combination administered once daily); and (iii) LDR (less than three ART compounds administered as either monotherapy or dual combination therapy).

Demographic and clinical data

Demographic and clinical data were collected from electronic patient charts.

HIV-related variables included: current and nadir CD4 T cell counts (categorized into clinically relevant groups as follows: >500, 351–500, 101–350 and ≤100), current HIV-RNA detectability and present and cumulative exposure to ART classes, year of initiation of current ART categorized into three time periods (2006–08, 2009–12 and 2013–15).

MM was classified as the presence of two or more of non-infectious comorbidities, including cardiovascular disease, end-stage kidney disease, cancer, osteoporosis, hypertension, type 2 diabetes mellitus, liver cirrhosis and chronic obstructive pulmonary disease.

Frailty

An FI was calculated based on the deficit accumulation approach,[9] previously applied in the same cohort.[10]

Health variables included in the frailty indices and description of deficit scoring are listed in Table S1 (available as Supplementary data at *JAC* Online).

We assessed the effect of frailty independently from HIV-related variables and non-infectious comorbidities, excluding these variables as items in the index.[10]

Statistical analyses

The cohort was divided into three 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 the χ^2 test.

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

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 $P<0.05$. All statistical analyses have been conducted with STATA 13.1 for Mac (StataCorp Ltd, College Station, TX, USA).

Results

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

The median duration of HIV infection was 19 years (IQR=12.5–23.7), the median CD4 cell count was 638 (IQR=460–830) with a nadir of 192 (IQR=80–290), and 2853 patients had an undetectable HIV viral load (96.9%). The mean age of the entire cohort was 48.6 (SD=8.2).

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

Within the STR group, 350 patients were on efavirenz/emtricitabine/tenofovir, 100 on rilpivirine/emtricitabine/tenofovir and 14 on elvitegravir/cobicistat/emtricitabine/tenofovir.

We analysed the interrelationship between the study covariates, namely MM, PP and FI, which were highly co-linear. The MM and PP result 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 ($n=1523$, 51.7%).

A significant association was found between ART regimens and both FI (STR $\beta=-0.62$, $P<0.001$; LDR $\beta=-0.11$, $P=0.049$; with MTR as the reference) and PP (STR versus MTR OR=0.45, $P=0.001$; LDR versus MTR OR=1.62, $P=0.001$).

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). Factors associated with STR were male gender, younger age, lower HIV duration, year of ART initiation and lower FI; the PP result was negatively associated with STR. The LDR strategy was associated with older age, longer HIV duration and year of ART initiation; FI and PP was not associated with LDR compared with MTR.

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

	MTR (n=2025)		STR (n=464)		LDR (n=455)		P
Women, *n* (%)	737	(36.40)	110	(23.71)	145	(31.87)	<0.001
Age (years), mean (SD)	48.37	(8.03)	47.22	(8.01)	52.13	(7.75)	<0.001
Current smokers, *n* (%)	493	(45.52)	60	(36.81)	76	(35.51)	0.006
Sedentary life, *n* (%)	646	(59.54)	65	(39.88)	91	(42.72)	<0.001
No alcohol, *n* (%)	663	(61.16)	92	(56.79)	134	(62.91)	0.466
<20 g/day of alcohol, *n* (%)	410	(37.82)	69	(42.59)	75	(35.21)	
>20 g/day of alcohol, *n* (%)	11	(1.01)	1	(0.62)	4	(1.88)	
Waist circumference (cm), mean (SD)	86.91	(10.16)	87.46	(9.03)	89.55	(12.03)	0.003
BMI (kg/m^2), mean (SD)	23.54	(3.80)	23.72	(3.27)	24.21	(4.26)	0.064
Fasting glucose (mg/dL), mean (SD)	97.23	(23.20)	98.20	(16.59)	99.48	(29.78)	0.177
HOMA-IR, median (IQR)	2.64	(1.56–4.31)	1.98	(1.25–3.43)	2.26	(1.52–3.60)	<0.001
Triglycerides (mg/dL), mean (SD)	165.29	(120.39)	132.59	(89.38)	182.00	(138.64)	<0.001
Total cholesterol (mg/dL), mean (SD)	189.72	(61.51)	185.51	(37.33)	199.27	(50.60)	0.001
HDL cholesterol (mg/dL), mean (SD)	49.75	(16.88)	50.25	(14.97)	50.77	(17.57)	0.482
LDL cholesterol (mg/dL), mean (SD)	114.77	(35.76)	114.30	(30.67)	121.15	(37.74)	0.002
Metabolic syndrome, *n* (%)	229	(11.31)	37	(7.97)	71	(15.60)	<0.001
CD4 nadir (/μL), median (IQR)	183	(78–280)	222	(114–330)	180	(73.5–269)	<0.001
Current CD4 (/μL), median (IQR)	625	(439–821)	680	(515–854)	663	(484–838)	0.002
Cumulative exposure to ARV (months), median (IQR)	127	(74–185)	112	(62–173)	143	(94–193)	<0.001
Cumulative exposure to NRTIs (months), median (IQR)	127	(74–184)	112	(62–173)	134	(70–186)	0.004
Cumulative exposure to NNRTIs (months), median (IQR)	18	(0–65)	73	(36–120)	28.5	(1–66)	<0.001
Cumulative exposure to PIs (months), median (IQR)	58	(21–101)	0	(0–39)	104.5	(56–154)	<0.001
FI (months), median (IQR)	0.32	(0.25–0.41)	0.26	(0.19–0.33)	0.31	(0.25–0.38)	<0.001
PP, *n* (%)	207	(10.22)	23	(4.96)	71	(15.60)	<0.001
MM, *n* (%)	205	(10.12)	29	(6.25)	79	(17.36)	<0.001

ARV, antiretrovirals.
With the exceptions of female sex and PP, percentages are calculated with respect to the number of available data, not with respect to the overall data.

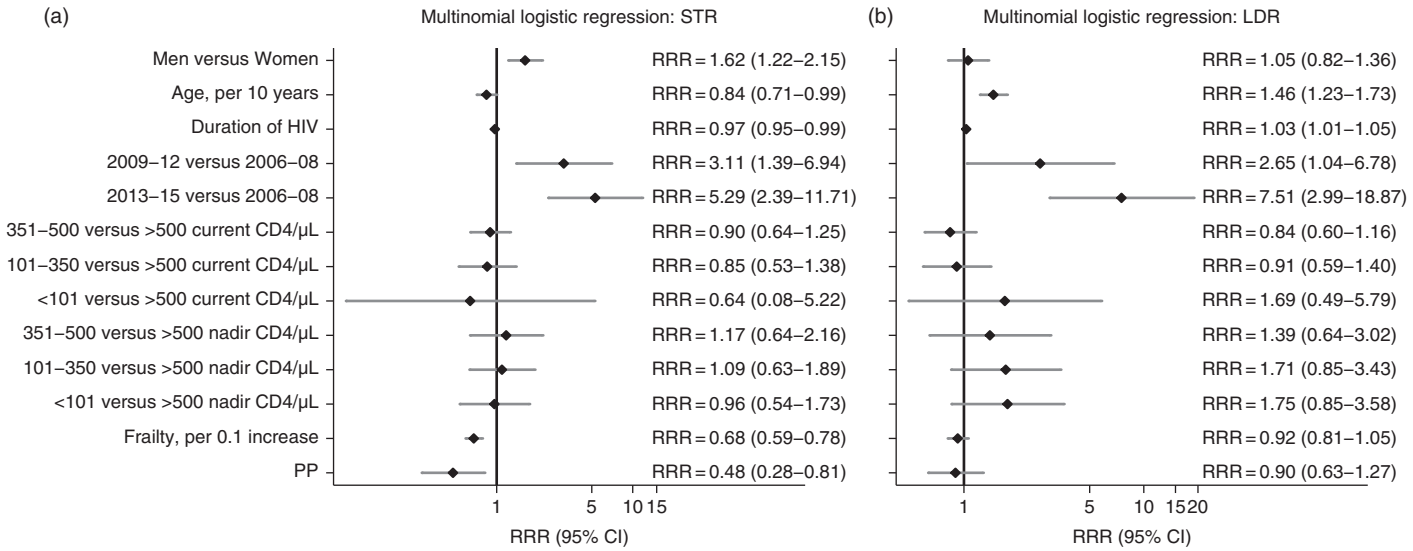

Figure 1. Multinomial logistic regression analysis (more likely, less likely). RRR, relative risk reduction.

Discussion

We observed a striking independent association between PP and FI, and a 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 STR with calendar year. Whilst this might run counter to the notion that the simplicity offered by STR helps to reduce the pill burden in individuals already

taking many tablets, the findings are not necessarily unexpected. Most of the STR 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, the MTR and LDR regimens offer greater flexibility to tailor ART around existing co-medications. The introduction of STR where tenofovir disoproxil fumarate has been substituted with a newer formulation, tenofovir alafenamide may provide some added flexibility to tenofovir-containing STR.

The high rates of MM, frailty and PP observed in our cohort is representative of large cohorts in the industrialized world. The MHMC, like other providers of outpatient HIV care in Italy, offers direct free of charge access to clinics and medications.[2] Although the 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 (mean age was 47.1, SD 7.5) were less likely to receive STR, possibly because 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 patient groups. Individuals with a metabolic syndrome phenotype, as characterized by waist circumference, homeostasis model assessment of insulin resistance (HOMA-IR) and presence of lipodystrophy, were more likely to receive an LDR as metabolic friendly drug associations were needed here.

A novel aspect of our study was to utilize the FI 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 utilize these two clinical variables in the same prediction model and dissect the association between PP and ART strategy.

Knowledge of ART strategies utilized in different groups of individuals receiving ART provides a greater understanding of unmet needs, particularly for older, multi-morbid and frail patients where optimized ART is still not available in a single, fixed-dose formulation. Current treatment guidelines generally fail to reflect this, and continued emphasis on the use of STR to improve adherence needs to be balanced against the limitations of currently available STR for complex individuals with MM.[14]

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Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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