Medication Burden and Clustering in People Living with HIV Undergoing Therapeutic Drug Monitoring

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Running Head: Medication Burden in PLWH

Type of article: Original article

Key words: HIV; polypharmacy, co-medications, clusters, drug-to-drug interactions.

Word count: total 1952 (abstract 247)

Figures: 3 (+1 supplementary)

Tables: 1 (+1 supplementary)

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What is already known about this subject:

- Multimorbidity and polypharmacy (PP) are highly prevalent in people living with HIV (PLWH)
- Apart from age and number of co-morbidities factors associated with PP are poorly characterized in PLWH
- Co-morbidities in elderly PLWH and matched controls seem to cluster in several groups

What this study adds:

- Female gender was significantly associated with the presence of more co-medications (and specific patterns) in PLWH
- PLWH receiving oral drug for type-2-diabetes have a high probability of receiving several other drugs;
- Cluster of co-medications have been identified for the first time in PLWH and the largest include opioids, diuretics and central nervous system affecting drugs.

Abstract

Aim People living with HIV (PLWH) have a high burden of comorbidities and concomitant medication use. Aim of this study was to analyze the prevalence, predictors and patterns of polypharmacy (PP) in a large therapeutic drug monitoring (TDM) registry.

Methods We searched our TDM registry and categorized co-medications into 26 drug classes. We included patients with at least one medication recorded: PP and severe PP (sPP) were defined as the concomitant use of 5 or 7 non-antiretroviral/non-antitubercular drugs. Multivariable binary logistic analysis were conducted for identifying PP/sPP predictors. A hierarchical average-linkage cluster analysis was performed among drug classes.

Results We included 2432 participants (1158 PLWH) aged 49.6 years (± 14.4) in the 2016-2020 period. A higher number of concomitant medications were recorded in controls (4 vs. 3.1, $p<0.001$), yet PP was more common in PLWH (21.8% vs. 17.1%, $p=0.003$). At multivariable binary logistic analysis older age, female gender and HIV-positive serostatus ($p=0.009$) were independent predictors of PP; older age and female gender were independent predictors of sPP. Cluster analysis showed that patients receiving oral drug for type-2-diabetes have a high probability of receiving several other drugs; a cluster of co-medications was observed with opioids, diuretics and central nervous system affecting drugs.

Conclusion We observed a moderately high prevalence of polypharmacy in middle-aged PLWH: advanced age and female gender were associated with the greatest prevalence. The observation of co-medication clusters suggests groups of comorbidities but also identifies groups of patients at risk of similar drug to drug interactions.

Funding The paper has been supported by an unrestricted grant from Gilead Sciences.

Introduction

People living with HIV (PLWH) have a high prevalence of co-morbidities as a consequence of risk factors, chronic inflammation and side effects associated with long-term use of antiretroviral drugs (ARVs).[1] Apart from exposing patients to the cumulative effects of concomitant disorders, a higher number of comorbidities increases the probability of receiving co-medications and, eventually, of being affected by polypharmacy (PP, or the use of >5 concomitant drugs apart from ARVs).[2] PP is increasingly common in elderly PLWH and has been associated with several unfavourable conditions including frailty, falls and even death.[3] The association between PP and frailty components may be even more frequent in PLWH, according to a recent study in US veteran participants.[4] Additionally using more drugs may expose patients to drug to drug interactions (DDIs) with potentially serious health hazards.[5] While DDIs seem less common with modern ARVs there are some manageable but unavoidable interactions and some patients require boosting agents; the latter ones have been associated with a higher risk of DDI due to the cytochromes and transporters inhibition.[6]

While the clustering of co-morbidities has already been studied few is known on how co-medications cluster in PLWH and controls.[7] This issue may be useful for identifying patients at risk of multiple DDIs and for selecting subgroups having the larger benefit from deprescription of concomitant medications.

Aim of this study was to analyze the prevalence, risk factors and clustering of co-medications in patients for whom a therapeutic drug monitoring of antibiotics/antifungal/antitubercular/antiretroviral drugs was requested.

Methods

The Therapeutic Drug Monitoring (TDM) service of the University of Torino performs the analysis of concentrations of several drugs following clinicians' requests of study protocols. Before blood withdrawal patients sign an informed consent for anonymous data use and publication. The TDM registry includes age, body mass index, HIV status, anti-infectious drugs and dosages and concomitant medications. We searched the 2016-2020 (January to January) database co-medications fields for either active ingredients or commercial names and they were categorized into selected drug classes (the list is in Supplementary table 1); polypharmacy (PP) and severe-polypharmacy (sPP) were defined as receiving 5 and 7 non-antiretroviral and non-antitubercular drugs among participant with at least one concomitant medication. This selection criteria (>=1 non-antiretroviral medication) was applied in order to exclude patients' unrecorded co-medications. Antitubercular drugs were excluded from the PP/sPP definition since five drugs are usually contemporary administered (for a

limited amount of time) thus artificially increasing the number of co-medications. Age was stratified in decades.

Data were described with number (percentage) and average (± standard deviation) and analysed through parametric tests. A binary logistic regression analysis was performed for establishing factors associated with PP and sPP: adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) have been reported. Among participants receiving at least two co-medication classes, for each pair of drug classes the prevalence of co-medications was computed calculating conditional probabilities (proportion of subjects treated with one drug among those treated with the other drug). The results are displayed as heat plots. To further understand the relationship between the 26 drug classes, a hierarchical average-linkage cluster analysis was performed on the dissimilarity matrix produced using the Jaccard measure for binary data. Results from this analysis are presented using dendrograms.

Drug class	Used strings
STATINS	Simvastatina, Sivastin, Sinvacor, Atorvastatina, Totalip, Torvast, Rosuvastatina, Crestor, Provisacor, Rosuvastatina, Crestor, Provisacor, Lovastatina, Lovinacor, Tavacor, Pravastatina, Pravaselect, Selectin, Fluvastatina, Lescol, Lipaxan
CALCIUM CHANNEL BLOCKERS	Verapamil, Isoptin, Isoptin R, Isoptin Press, Diltiazem, Altiazem, Altiazem R, Diltazem Rk, Tildiem, Tildiem R, Nifedipina, Adalat, Adalat Crono, Amlodipina, Norvasc, Felodipina, Plendil, Nicardipina, Perdipina, Perdipina R, Barnidipina, Vasexten
BETA BLOCKERS	Propranololo, Inderal, Timololo, Pindololo, Visken, Nadololo, Atenololo, Tenormin, Acebutololo, Secral, Metoprololo, Lopresor, Seloken, Esmololo, Brevibloc, Bisoprololo, Concor, Congescor, Cardicor, Sequacor, Carvedilolo, Dilatrend, Labetalolo, Trandate, Celiprololo, Cordiax, Betaxololo, Betoptic
ACE INHIBITORS	Captopril, Capoten, Enalapril, Enapren, Lisinopril, Zestril, Zestoretic, Ramipril, Triatec, Perindopril, Procaptan, Quinapril, Quinazil, Fosinopril, Fosicombit, Benazepril, Cibadrex,
ARBs	Losartan, Forzaar, Lortaan, Losaprex, Losazid, Valsartan, Combisartan, Cotareg, Tareg, Valpression, Candesartan, Blopress, Ratacand, Eprosartan, Tiartan, Irbesartan, Aprovel, Coaprovel, Karvea, Karvezide, Olmesartan, Olpress, Olprezide, Telmisartan, Micardis, Pritor
ANTI-PLATELET	Ticlopidina, Tiklid, Clopidogrel, Plavix, Ticagrelor, Brilique, Prasugrel, Efient, Aspirina, ASA, Cardioasa, Cardirene
ANTICOAGULANTS	Warfarin, Coumadin, Sintrom, TAO, Eparina, Enoxaparina, Parnaparina, Clexane, Fluxum, Apixaban, Eliquis, Dabigatran, Lixiana, Edoxaban, Pradaxa, Idarucizumab, Praxbind, Rivaroxaban, Xarelto
INSULIN	Humalog, Lantus, Actrapid, Humulin, Protaphane, Levemir
ORAL ANTI T2DM	Glibenclamide, Daonil, Euglucon, Gliben, Gliconorm, Glibomet, Gliclazide, Diabrezide, Diamicron, Dramion, Glipizide, Minidiab, Gliquidone, Glurenor, Glimepiride, Amaryl
ANTIDEPRESSANTS	Paroxetina, Daparox, Dapagut, Dropaxin, Eutimil, Sereupin, Seroxat, Stiliden, Sertralina, Zoloft, Tatig, Tralisen, Citalopram: Seropram, Elopram, Felipram, Frimaind, Feliximir, Frimaind, Kaidor, Marpram, Percitale, Return, Ricap, Sintopram, Verisan, Escitalopram, Cipralex, Entact, Fluoxetina, Prozac, Fluoxeren, Azur, Clexiclor, Cloriflox, Diesan, Flotina, Ipsumor, Xeredien, Fluvoxamina, Dumirox, Fevarin, Maveral, Dapoxetina, Priligy
ANXYOLITICS	Benzodiazepine, Tavor, Xanax, Rivotril, Valium, Ansiolin, En, Frontal, Lexotan, Prazene, Control, Lorans, Dalmadorm, Felison, Halcion, Minias, Roipnol, Nottem, Stilnox, Buspar, Alprazolam, Lorazepam, Diazepam, Delorazepam, Zolpidem,
ANTI-PSICOTICS	Clorpromazina, Dixirazina, Flufenazina, Flufenazina, Levomepromazina, Promazina, Perfenazina, Propericiazina, Tioridazina, Trifluoperazina, Aloperidolo, Dipiperone, Droperidolo, Amisulpride, Levosulpride, Sulpiride, Sultopride, Tiapride, Clozapina, Olanzapina, Quetiapina, Risperidone, Largactil,Prozin, Esucos, Anatensol, Moditen, Nozinan,Trilafon, Trilafon, Talofen, Neuleptil, Melleril, Modalina, Haldol, Serenase, Haldol, Decanoas, Impromen, Piperonil, Sintodian, Deniban, Solian, Sulamid, Levobren, Levopraid, Championil, Dobren, Equilid, Barnotil, Italpride, Sereprile, Leponex, Zyprexa, Seroquel, Belivon, Risperdal
CATIONS	Magnesio, Calcio, Ferro
PPIs	Omeprazolo, Antra, Mepral, Omeprazen, Lansoprazolo, Lansox, Limpidex, Esomeprazolo, Nexium, Lucen, Pantoprazolo, Pantorc, Pantopan, Rabeprazolo, Pariet

OPIOID SUBSTITUTIVE TREATMENT	Metadone, Buprenorfina
ANTI-EPILEPTICS	Fenobarbital, Fenobarbitale, Luminale, Gardenale, Clobazam, Frisium, Valproato, Acido Valproico, Depakin, Progabide, Gabapentin, Neurontin, Fenitoina, Dintoina, Carbamazepina, Tegretol, Oxcarbamazepina, Tolep, Lamotrigina, Lamictal, Levetiracetam, Keppra
ANTI-ARRHYTMICS	Chinidina, Disopiramide, Procainamide, Lidocaina, Flecainide, Propafenone, Propranololo, Sotalolo, Nadololo, Atenololo, Acebutololo, Pindololo, Amiodarone, Cordarone, Verapamil, Diltiazem, Digossina, Digitale
ALPHA-BLOCKERS	Silodosina, Urorec, Doxazosina, Cardura, Prazosina, Minipress, Fenossibenzamina, Fentolamina, Regitine, Tamsulosin, Tamsulosina, Omnic, Alfuzosina, Uroxatral, Terazosina, Hytrin, Unoprost
SEXUAL HORMONS	Estroprogestinici, Pillola, Tibolone, Livial, Estradiolo, Estriolo, Estrogeni
DIURETICS	Furosemide, Lasix, Lasitone, Megalasix, Idroclorotiazide, HCT, Esidrex, Bumetadone, Bidien, Etacrinico, Reomax, Torasemide, Diuresix, ZAROXOLIN, TORADIUR, DIURESIX, Spironolattone, Canrenone, Canreonato, Aldactone, Luvion, Amiloride, Moduretic
NSAIDS	Apranax, Naprossene, Arthrotec, Diclofenac, Aulin, Nimesulide, Brufen, Ibuprofene, Moment, Felden, Piroxicam, Froben, Diclofenac, Flurbiprofene, Indometacina, Paracetamolo, Tachipirina
OPPIOIDS	Buprenorfina, Codeina, Diidrocodeina, Fentanyl, Idrocodone, Idromorfone, Metadone, Morfina, Ossicodone, Ossimorfone, Tapentadolo, Sufentanil
CORTICOSTEROIDS	Cortisone, Cortone, Prednisone, Deltacortone, Metilprednisolone, Medrol, Solumedrol, Beclometasone, Clenil, Flunisolide, Forbest, Betametasone, Bentelan, Desametasone, Decadron, Idrocortisone, Flebocortid
INHALED DRUGS	Salbutamolo, Ventolin, Salmeterolo, Fenoterolo, Ipratropio, Beclometasone, Flunisolide, Ciclesonide, Fluticasone, Vilanterolo, Olodaterolo, Formeterolo, Budesonide, Indacaterolo, Glicopirronio, Aclidinio, Atem, Breva, Onbrex, Foster, Seretide, Aliflus, Symbicort
IMMUNE-SUPPRESSANTS	Ciclosporina, Tacrolimus, Everolimus, Sandimmun, Advagraf, Afinitor, Methotrexate, Metotressato, Reumaflex, Rituximab, Infliximab, Mabthera, Remicade
DRUGS USED IN THYROID DISORDERS	Levotiroxina, Eutirox, Tirosint, Tapazole, Tiamazolo

Supplementary Table 1. Drug categories and single compounds (active principle and trade names) used in the database search.

Results

Out of 11126 cases (6901 PWH and 4225 controls) in the TDM registry we included in this analysis 2432 participants with average age and body weight of 49.6 (± 14.4) years and 72.2 (± 14.8) Kg. Participants were similarly distributed among years 2016 to 2019 with only 20 subjects included in 2020. An average of 3.6 (± 2.8) co-medications were recorded with the most used classes being proton pump inhibitors (PPIs, 24.2%), diuretics (17.3%) and anxyolitics (15.1%). PP and sPP were recorded in 471 (19.4%) and 253 (10.4%) subjects.

We included 1158 PLWH (47.6%) and 1274 controls. Table 1 summarizes participants' characteristics according to HIV serostatus and bi-variate comparisons (t-test, chi-square or Fisher's analysis). Despite a higher average age in PLWH most elderly (age >=65 years) participants were included among controls (27.9% vs. 7.9%, $p<0.001$): a higher number of concomitant medications were recorded in controls, yet PP was more common in PLWH (21.8% vs. 17.1%, $p=0.003$). Co-administered drugs were different in the two groups with opioids (19.3% vs. 4.9%, $p<0.001$), diuretics (20.2% vs. 14.6%, $p<0.001$) and anti-platelet agents (12% vs. 6.3%,

p<0.001) being more common in PLWH and PPIs (30.4% vs. 17.4%, p<0.001), corticosteroids (13.8% vs. 5.9%, p<0.001) and anti-coagulant drugs (9.1% vs. 3.2%, p<0.001) in controls.

Variables		PLWH	Controls	p-Values
n		1158	1274	-
Age (years)		**51.6 (±9.9)**	**47.7 (±15.1)**	**<0.001**
Age >65 Years		**91 (7.9%)**	**226 (27.9%)**	**<0.001**
Male gender		808 (69.8%)	877 (68.8%)	0.628
Weight (Kg)		**71.8 (±15.4)**	**68.6 (±15.6)**	**<0.001**
Body Mass Index (Kg/m^2)		**24.2 (±4.4)**	**22.8 (±4.7)**	**<0.001**
Year of inclusion	**2016**	235 (20.3%)	193 (15.1%)	**0.015**
	2017	291 (25.1%)	351 (27.6%)	
	2018	329 (28.4 %)	360 (28.3%)	
	2019	294 (25.4 %)	359 (28.2%)	
	2020	9 (0.8 %)	11 (0.9%)	
Number of Comedications		**3.1 (±2.5)**	**4.0 (±2.9)**	**<0.001**
PP		**253 (21.8%)**	**218 (17.1%)**	**0.003**
sPP		132 (11.4%)	121 (9.5%)	0.127
Class	**Statins**	**138 (11.9%)**	**47 (3.7%)**	**<0.001**
	Ca-blockers	**44 (3.8%)**	**91 (7.1%)**	**<0.001**
	Beta-blockers	124 (10.7%)	135 (10.6%)	0.948
	ACE-i	**122 (10.5%)**	**74 (5.8%)**	**<0.001**
	ARBs	56 (4.8%)	45 (3.5%)	0.127
	alpha-blockers	**36 (3.1%)**	**67 (5.3%)**	**0.009**
	diuretics	**234 (20.2%)**	**186 (14.6%)**	**<0.001**
	anti-arrythmics	**31 (2.7%)**	**53 (4.2%)**	**0.046**
	anti-platelet	**139 (12%)**	**80 (6.3%)**	**<0.001**
	anticoagulant	**37 (3.2%)**	**116 (9.1%)**	**<0.001**
	insulin	**28 (2.4%)**	**50 (3.9%)**	**0.038**
	oral antiT2DM	9 (0.8%)	17 (1.3%)	0.236
	antidepressants	**106 (9.2%)**	**60 (4.7%)**	**<0.001**
	anxiolytics	176 (15.2%)	191 (15%)	0.910
	anti-psychotics	100 (8.6%)	93 (7.3%)	0.230
	cations	**36 (3.1%)**	**19 (1.5%)**	**0.009**
	PPIs	**202 (17.4%)**	**387 (30.4%)**	**<0.001**
	opioid substitutive treatment	**208 (18%)**	**41 (3.2%)**	**<0.001**
	opioids	**223 (19.3%)**	**62 (4.9%)**	**<0.001**
	anti-epileptic	101 (8.7%)	126 (9.9%)	0.329
	sexual hormons	20 (1.7%)	27 (2.1%)	0.556
	corticosteroids	**68 (5.9%)**	**176 (13.8%)**	**<0.001**
	NSAIDs	**40 (3.5%)**	**113 (8.9%)**	**<0.001**
	immune suppressants	10 (0.9%)	19 (1.5%)	0.191
	inhaled drugs	32 (2.8%)	40 (3.1%)	0.633
	thyroid	**67 (5.8%)**	**35 (2.7%)**	**<0.001**

Table 1. Participants' characteristics according to HIV serostatus. "PP", polypharmacy; "sPP", severe polypharmacy; "ACE-i", Angiotensin-converting-enzyme inhibitors; "ARBs", Angiotensin II receptor blockers, "PPIs", proton pump inhibitors; "NSAIDs", non-steroidal anti-inflammatory drugs. Bold lines indicate a statistically significant difference between the two groups; green boxes are used to highlight the highest variable.

At univariate analysis PP was associated with older age (p<0.001), higher BMI (p<0.001) and HIV-positive serostatus (p<0.001). At multivariable binary logistic analysis (after correcting for BMI and year of inclusion) more advanced age (p<0.001, aOR for 10 year increase 1.436, 95%CI 1.327-1.554), female gender (p=0.001, aOR 1.443, 95%CI 1.151-1.808) and HIV-positive serostatus (p=0.009, aOR 1.337, 95%CI 1.075-1.663) were independent predictors of PP. When stratified according to HIV serostatus predictors of PP in PLWH were age (p<0.001, aOR 1.303, 95%CI 1.129-1.505) and female gender (p=0.001; aOR 1.683, 95%CI 1.240-2.283) while only age was independently associated with PP in controls (p<0.001, aOR 1.515, 95%CI 1.373-1.672). Figure 1 depicts the prevalence of PP according to age (decades), gender and HIV-serostatus.

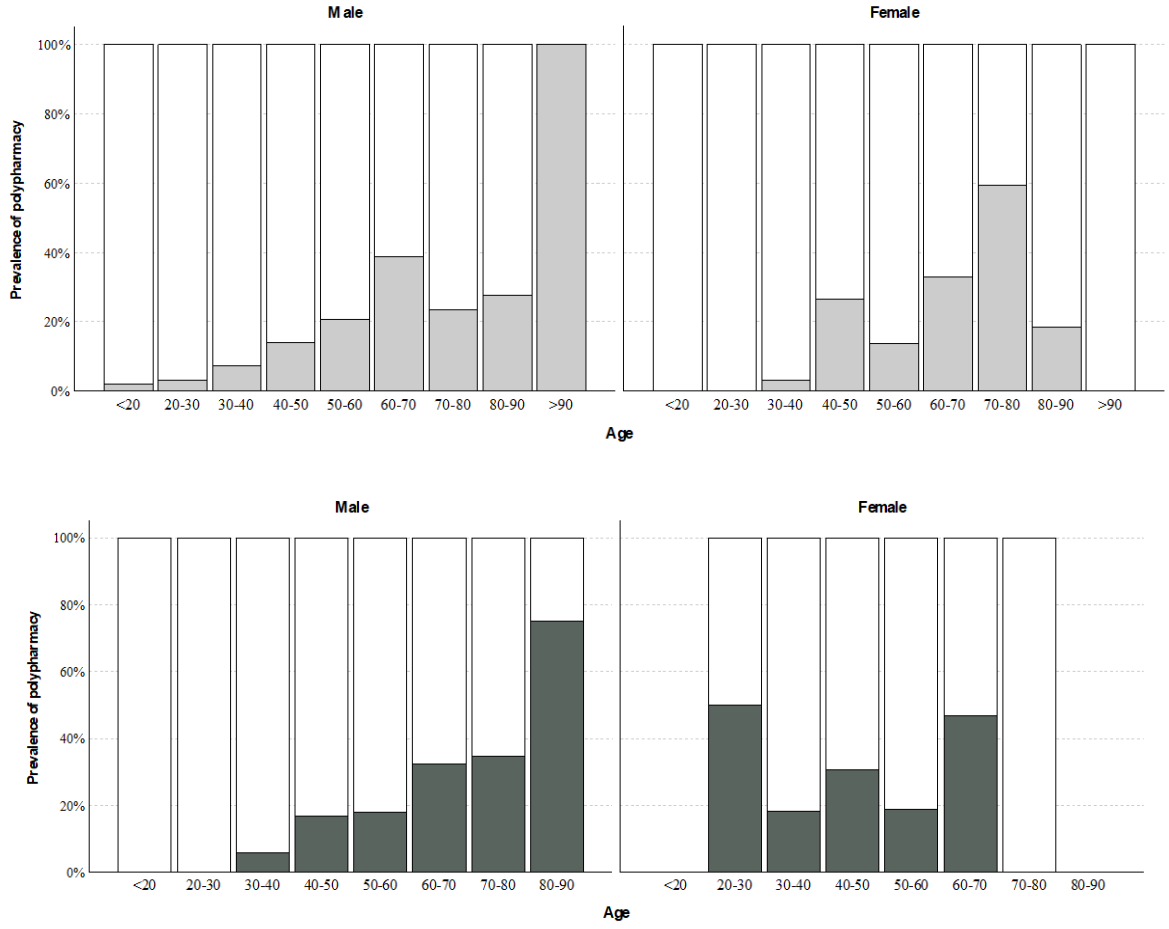
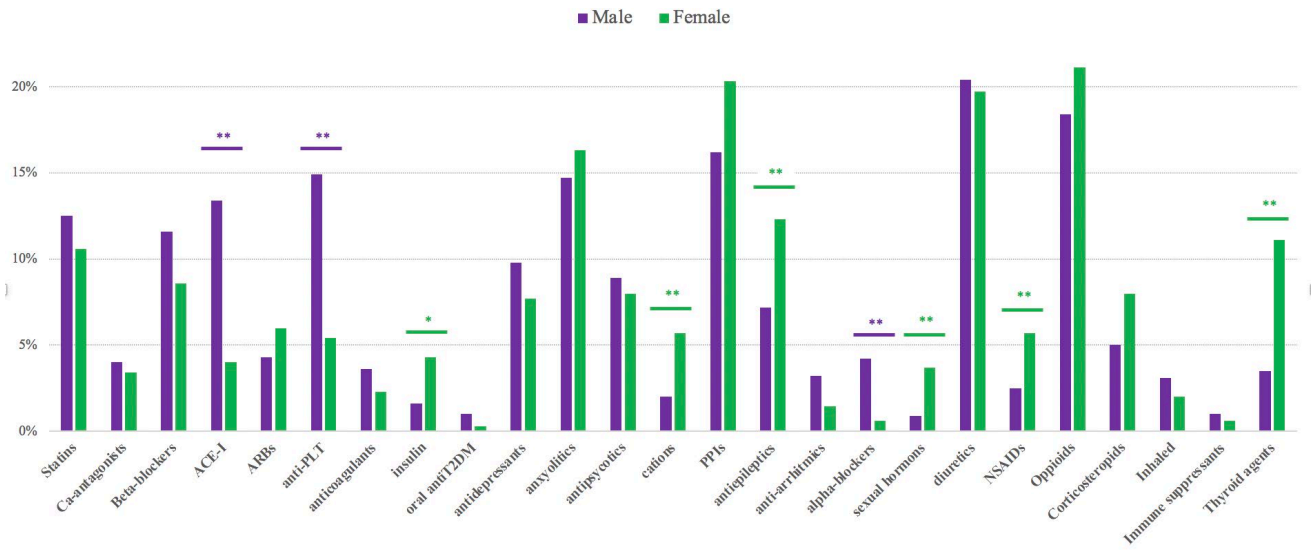


Figure 1. Prevalence of polypharmacy according to age (x axis), gender (male participants in left panels) and HIV serostatus (HIV-negative top panels with bars in light grey).

At univariate analysis sPP was associated with age (p<0.001) and BMI (p<0.001). At multivariable binary logistic analysis (after correcting for BMI, year of inclusion and HIV-serostatus) more advanced age (p<0.001, aOR for 10 year increase 1.440, 95%CI 1.307-1.586) and female gender (p=0.001, aOR 1.637, 95%CI 1.239-2.162) were independent predictors of sPP. When stratified according to HIV serostatus predictors of sPP in PLWH were age (p<0.001, aOR 1.225, 95%CI 1.016-1.475) and female gender (p=0.001; aOR 1.936, 95%CI 1.318-2.844); age (p<0.001, aOR 1.562, 95%CI 1.385-1.760) and body mass index (p=0.013, aOR for 5 Kg/m^2 increase 1.268, 95%CI 1.051-1.531) were independently associated with sPP in controls.

Supplementary Figure 1 represents the prevalence of concomitant drug class use according to gender in PLWH. Female living with HIV more often were on treatment with insulin (4.3% vs. 1.6%, p=0.011), cations (5.7% vs. 2%, p<0.001), anti-epilectics (12.3% vs. 7.2%, p=0.006), sexual hormons (3.7% vs. 0.9%, p=0.002), NSAIDs (5.7% vs. 2.5%, p=0.008) and agents for thyroid disorders (11.1% vs. 3.5%, p<0.001) and less often with ACE-i (4% vs. 13.4%, p<0.001), anti-platelets (5.4% vs. 14.9%, p<0.001) and alpha-blockers (0.6% vs. 4.2%, p<0.001).



Supplementary Figure 1. Prevalence of drug class use in people living with HIV according to gender. Statistically significant differences with p values <0.05 and <0.001 are marked by * and **, respectively. The colour of asterisks and horizontal lines represent the group with the highest prevalence (green female, purple male).

In PLWH the most used ARV classes were integrase strand transfer inhibitors (INSTI, 858, 74.1%), nucleot(s)ide reverse transcriptase inhibitors (NRTIs, 847, 73.1%) and protease inhibitors (PIs, 284, 24.5%) followed by non-nucleotide reverse transcriptase inhibitors (NNRTIs, 207, 17.9%) and entry inhibitors (EI, 74, 6.4%). PLWH with PP were less likely to receive boosting agents (25.3% vs.

32.5%, p=0.031) and NRTIs (66% vs. 75.1%, p=0.005); PLWH with sPP were less likely to receive NRTIs (64.4% vs. 74.3%, p=0.021) and more likely to receive EIs (12.1% vs. 5.7%, p=0.008).

In order to understand the relationships between drug classes use we included participants receiving at least two co-medication classes (n=1102, 592 PLWH) in the following analysis. In Figure 2 the matrixes including the column percentages of co-medications for each pair of drug classes are shown as heat plots. The results of the hierarchical cluster analysis are displayed in Figure 3 (dendrograms). In both groups patients receiving oral drug for type 2 diabetes have a high probability of receiving several other drugs (estroprogestinic and drugs for chronic obstructive pulmonary disorders in controls and estroprogestinic and anticoagulants in PLWH). In PLWH a cluster of co-medications was observed in those receiving opioid substitutive treatment: these subjects were often treated with diuretics and central nervous system affecting drugs (antidepressants, anxyolitics, antipsicotics and antiepileptics).

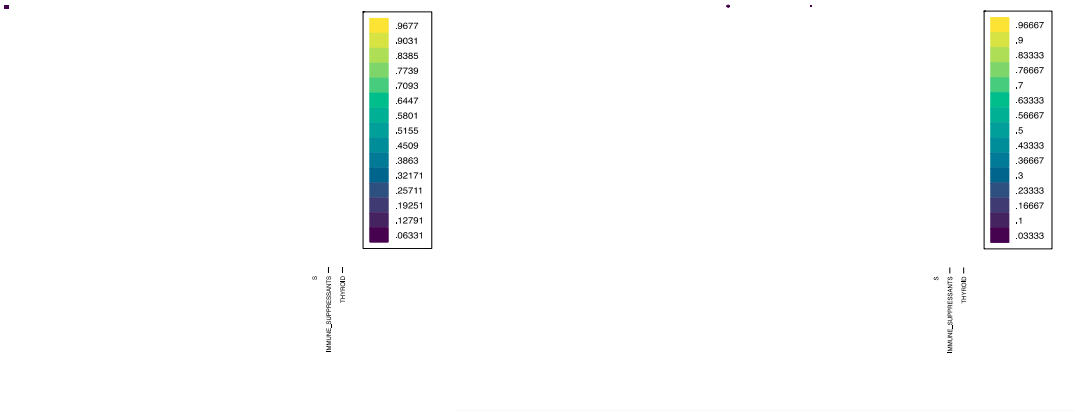


Figure 2. Heat plots showing the prevalence of co-medications for each pair of drug classes (controls left panel, PLWH right panel). Each cell includes the proportion of subjects treated with the drug on the y-axis among those treated with the drug on the x-axis (column percentages).

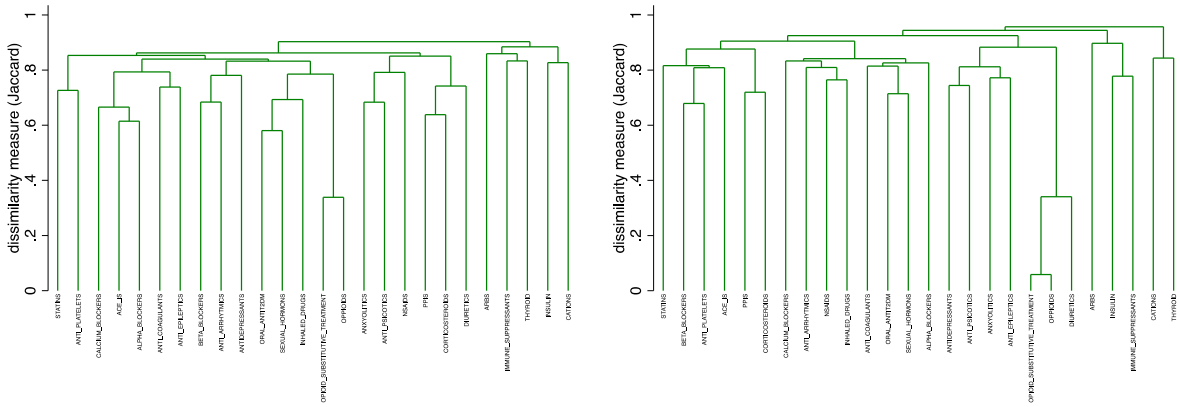


Figure 3. Dendrograms from hierarchical cluster analysis with average linkage performed using the Jaccard dissimilarity method in controls (left panel) and PLWH participants (right panel). Examining the dendrogram from bottom to top, drug classes (the clusters) that are more similar to each other are grouped together earlier. The horizontal lines represent the grouping of clusters; as the drug classes being joined become less homogeneous, the horizontal lines will be located farther to the top side of the plot. The distance between two joining drug classes is reported in the y axis; the longer the vertical lines the larger the difference.

Discussion

In this analysis from a TDM registry we studied the prevalence, determinants and features of co-medications in PLWH and controls.

Before discussing the results we want to acknowledge the limitations of this work: the inclusion of participants whose physician requested a TDM could be a proxy of clinical (renal or hepatic impairment) or pharmacological (drug to drug interactions) characteristics potentially associated with PP. Additionally the lack of detailed information on comorbidities and laboratory tests limit our ability to better characterize comedications clusters. Yet the sample size is reasonably large and this is the first analysis, to the best of our knowledge, of this kind.

In a sample of middle-aged PLWH (average age 51.6 years) we recorded polypharmacy in 21.8% participants with a higher prevalence in advanced age and female subjects. The prevalence of PP we reported is similar to what observed in other cohorts of PLWH[2] but lower than what a US and a Spanish group recently published (32.4%).[8,9] Conversely PP prevalence in PLWH aged above 65 years was above 40% and significantly higher than what observed in the Italian geriatric GEPPO cohort (approximately 20%).[10,11]

While age has constantly been reported as a major risk factor for PP, female gender is not usually recognized as such.[12–15] In our sample female participants living with HIV were treated with drug

classes usually associated with comorbidities more prevalent in women such as thyroid disorders and, not surprisingly, less with drugs used for ischemic cardiac disease (such as anti-platelet agents) or hypertrophic prostate (such as alpha-blockers).[16] Yet the larger use of cations, anti-epileptics and insulin in female participants do not have obvious explanations and require a thorough correlation with participants' comorbidities.

We arbitrarily defined severe polypharmacy as the use of more than 7 concomitant medications: the prevalence was similar between PLWH and controls and this may be explained by a significant higher proportion of controls falling in the definition of elderly subjects (i.e. 65 years old or more). In PLWH advanced age and female gender were associated with sPP while higher body mass index (along with age) were independent predictors of sPP in HIV-negative controls. Higher BMI may identify patients with metabolic syndrome and, often, type 2 diabetes: both conditions are treated with several drugs for controlling metabolic abnormalities and decreasing cardiovascular risk.

The concomitant drugs that were more commonly administered to PLWH were opioids, diuretics and anti-platelet agents: these ones were significantly different from what other cohorts reported. In the US Veteran study antihypertensives, antilipemic agents and antidepressants while in a large Spanish study central nervous system, anti-infective and gastrointestinal agents were recorded as the commonest co-medications.[8,9] Heterogeneity in inclusion criteria, local prescription and caring habits may explain these differences and may account for distinct DDIs and unwanted outcomes potential.[17]

Finally we observed that certain drugs were more commonly administered together. Our heatmaps highlighted that oral antidiabetic medications were often co-administered with several other compounds and that beta-blockers/antiarrhythmics and opioids/diuretics were co-administered in a relatively high proportion of our HIV-positive participants receiving at least 2 drugs beyond ARVs. Dendrograms showed additional hierarchical clusters of co-medications that may be relevant for potential DDIs and inappropriate prescribing. The association of beta-blockers, anti-platelet, statins and ACE-I identifies a cluster of co-medications that may be affected by cytochrome and transporter inhibitors and that requires close evaluation of risk-benefits. Furthermore opioid use has been associated with negative long-term outcomes in PLWH: the finding of clustering of this drug classes with CNS-active molecules may also prioritize this group of patients for medication review.[18] In this setting anticholinergic burden is an emerging issue in ageing HIV-positive participant and may be studied in detail in the setting of clustered polypharmacy.[19,20]

In conclusion we observed a moderately high prevalence of polypharmacy in middle-aged PLWH: advanced age and female gender were associated with the greatest prevalence and identify elderly women living with HIV as a group for prioritizing appropriate prescribing. The observation of co-medication clusters suggests groups of comorbidities but also identifies groups of patients at risk of

similar drug to drug interactions. These data will be useful for fine-tuning protocols of treatment simplification in these co-administration clusters, potentially reducing the prevalence of PP and sPP.

Conflicts of Interest Statement:

Prof. CALCAGNO reports grants from VIIV, GILEAD, personal fees from VIIV, GILEAD, JANSSEN-CILAG, INSMED, MSD, outside the submitted work. Prof. D'AVOLIO reports grants from Correvio, CoQua Lab, personal fees from GILEAD, outside the submitted work. Prof. BONORA and Prof. Di Perri report grants from VIIV, GILEAD, personal fees from VIIV, GILEAD, JANSSEN-CILAG, MSD, outside the submitted work. The remaining authors have no conflict of interest to declare.

Funding source statement

The paper has been supported by an unrestricted grant from Gilead Sciences.

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