

Polypharmacy and Drug-drug Interactions in HIV-infected Subjects in the Region of Madrid (Spain): a Population-based Study

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Background

- The life expectancy of HIV-infected individuals has dramatically increased since combination ART has been available, and continues to improve¹.
- As a consequence of improved survival, HIV-infected individuals in developed countries are growing older², meaning that they may be at higher risk of both comorbid diseases and harm from polypharmacy, risks that likely increase with age and physiologic frailty^{3,4}.
- Concerns associated with polypharmacy include increased pill burden, decreased medication adherence, potential clinically significant drug-drug interactions (DDIs), adverse drug reactions including organ system injury, hospitalization, death, and rising treatment-related costs⁵.

Objetive

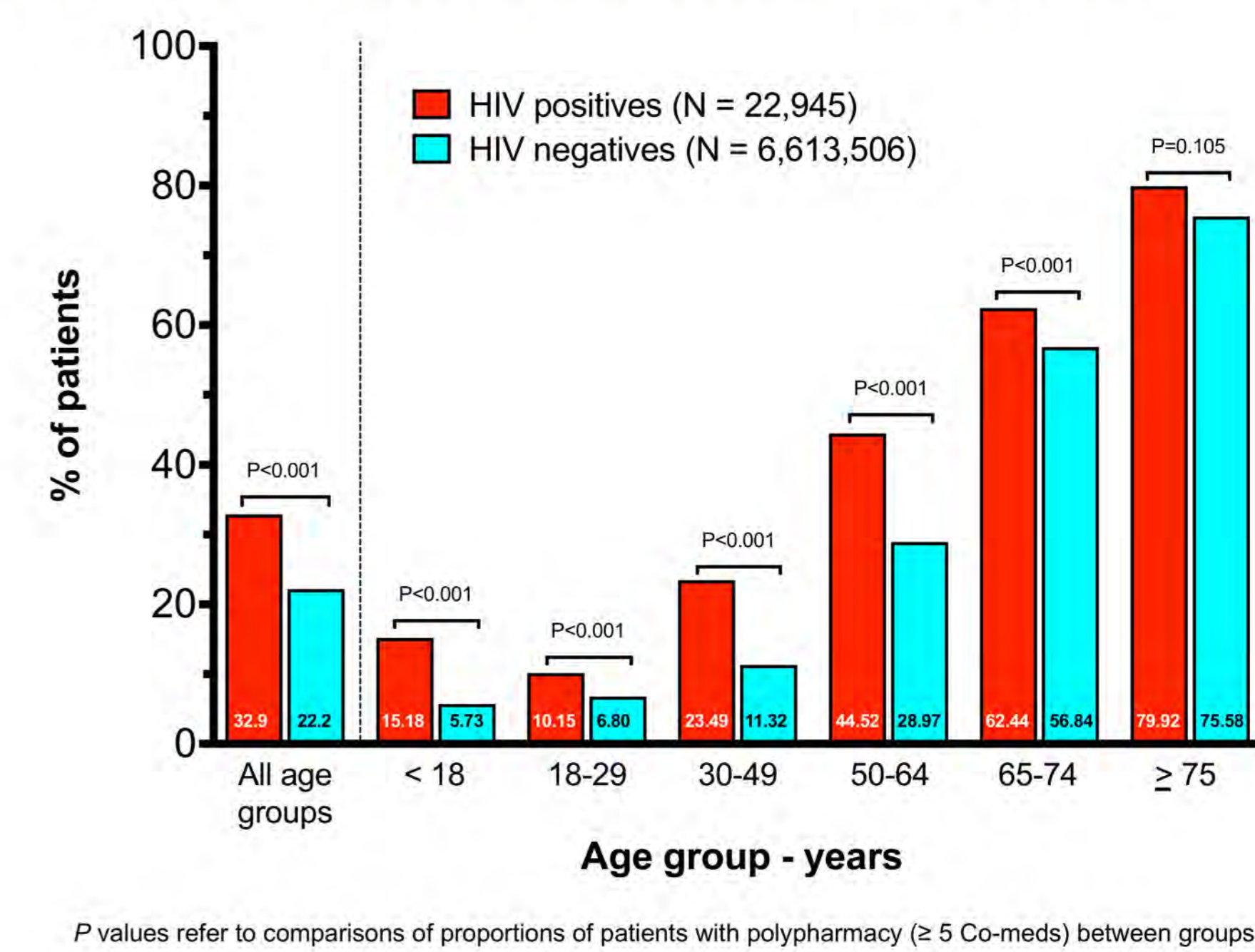
We assessed polypharmacy in HIV-infected and HIV-uninfected subjects in the region of Madrid and analyzed DDIs in HIV-infected subjects who received antiretrovirals (ARVs).

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2. Justice AC. *Current HIV/AIDS reports* 2010;7:69-76.
3. Greene M, et al. *JAMA* 2013;309:1397-405.
4. Edelman EJ, et al. *Drugs Aging* 2013;30:613-26.
5. Moore NH, et al. *AIDS Care* 2015;27:1443-6.

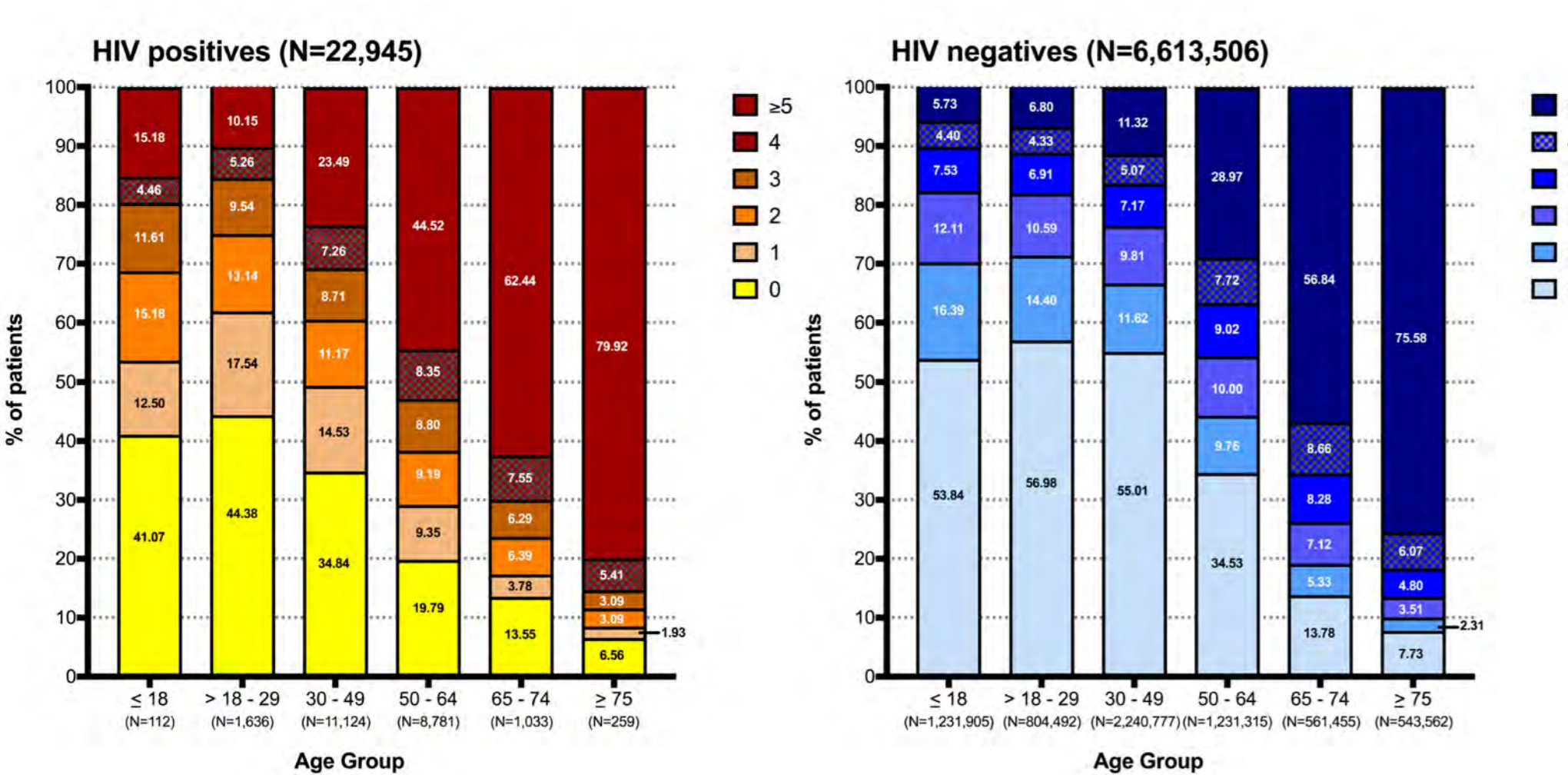
Methods

Study Design	Cross-sectional population-based study. Setting: region of Madrid. Study period: January 1 to June 30, 2017
Participants	All HIV-infected and HIV-uninfected individuals who picked-up prescription drugs in hospital and community pharmacies in the region of Madrid. The Madrid Regional Health Service (SERMAS) has a unique regional patient identification code (CIPA), that permits the access to personal information (age, sex, income) and also to all prescription drugs dispensed.
Prescription drugs	ARVs were dispensed in hospital pharmacies and categorized according to class. Non-ARV medications (Co-meds) were dispensed mainly by community pharmacies and classified according to the Anatomical Therapeutic Chemical (ATC) classification system.
Definitions	Polypharmacy was defined as the intake of ≥ 5 Co-meds. Patients were classified as HIV-infected or HIV-uninfected according to whether or not they received ARVs.
Screening for DDIs	Customized Application Programming Interface connecting the SERMAS database and the University of Liverpool (UoL) drug interactions database.
Classification of DDIs	UoL criteria (summarized with a traffic light method).

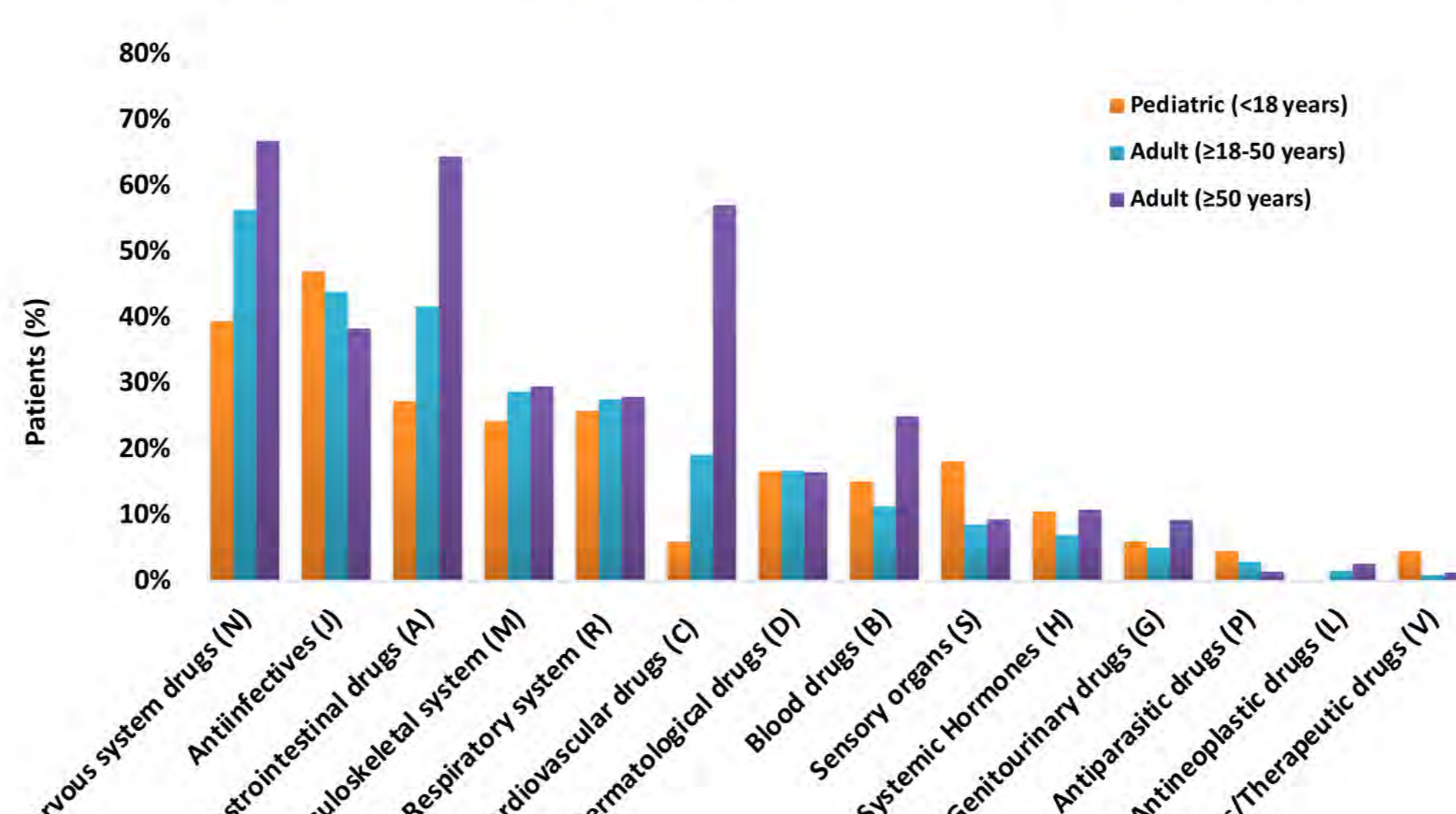
Polypharmacy among the study population (N = 6,636,451)



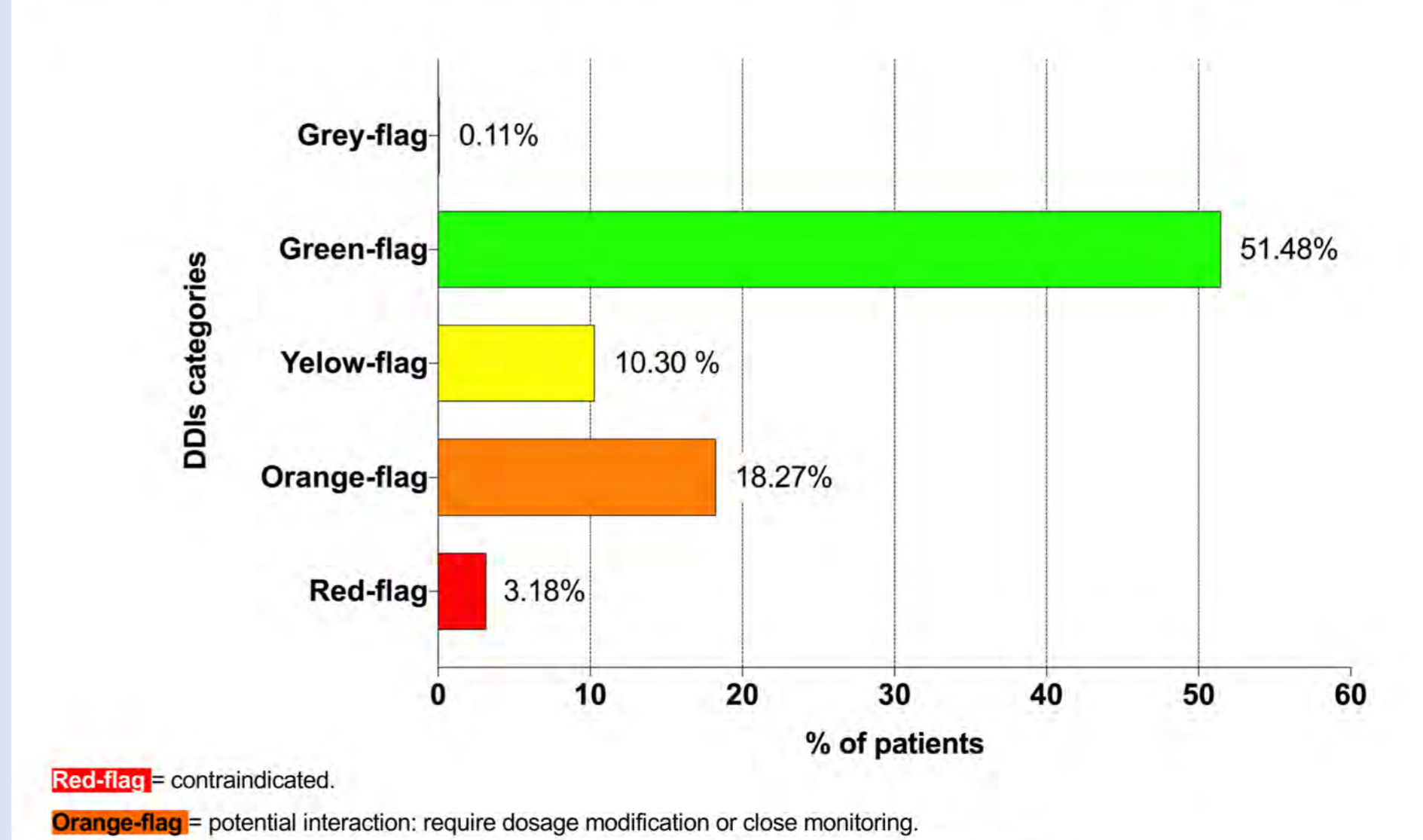
Co-meds categorized by HIV serostatus and age



Co-meds in HIV-infected individuals according to ATC code



Prevalence of DDIs in HIV-infected individuals (N = 22,945)



Red-flag DDIs (N=729) among HIV-infected individuals

ARVs Class	ARVs	Co-meds (ATC Code)	Chemical substance	N° (%)
Boosted PIs (RTV or COBI)	bATV, ddRV, LPV/r, FPV/r, SQV/r, TPV/r, IDV/r	Corticosteroids (R01AD, R03BA, R03AK, H02AB, D07AC)	Budesonide, Mometasone, Fluticasone, Triamcinolone	375 (51.4)
		Antipsychotic drugs (N05AH)	Quetiapine, Clozapine	103 (14.1)
		Antithrombotic agents (B01AC)	Clopidogrel, Ticagrelor	61 (12.2)
		Propulsives (A03FA)	Domperidone	50 (6.9)
		Statins (C10AA)	Simvastatin	46 (6.3)
		Diuretic drugs (C03DA)	Eplerenone	21 (2.9)
		Cardiac therapy (C01BD, C01EB)	Amiodarone, Ivabradine, Ranolazine	16 (2.2)
		Calcium channel blockers (C08CA)	Lercanidipine	9 (1.2)
		Other Co-meds (N03/N05/N06, J04)		11 (1.5)
		Proton pump inhibitors (A02BC)	Lansoprazol, Esomeprazole, Rabeprazole	5 (0.7)
Boosted INSTIs	EVG/COBI	Corticosteroids (R01AD, R03BA, H02AB, D07AC)	Budesonide, Mometasone, Fluticasone, Triamcinolone	38 (5.2)
		Other Co-meds (A03, B01, C01/C10, N03/N05)	Domperidone, Clopidogrel, Ivabradine, Simvastatin, Phenobarbital, Carbamazepine, Quetiapine	11 (1.5)
nnRTIs	EFV, NVP, RPV	Imidazole and triazole derivatives (D01AC, J02AC)	Ketoconazole, Itraconazole	61 (8.4)
		Sex hormones and modulators of the genital system (G03AC, G03DC)	Norethisterone [Norethindrone] (POP), Desogestrel (POP)	11 (1.5)
		Proton pump inhibitors (A02BC)	Lansoprazol, Esomeprazole, Rabeprazole	9 (1.2)
Non boosted INSTIs	DTG	Other Co-meds (N03/N05, J04)	Oxcarbazepine, Carbamazepine, Phenytoin, Ziprasidone, Triazolam, Rifampicin	9 (1.2)
Non boosted INSTIs	DTG	Antiepileptic drugs (N03AF)	Oxcarbazepine	1 (0.1)

Red-flag = contraindicated.
Orange-flag = potential interaction: require dosage modification or close monitoring.
Yellow-flag = weak potential interaction: no require additional monitoring or dosage adjustment.
Green-flag = non clinically significant interaction.
Grey-flag = no data to indicate interaction.

DDIs in HIV-infected individuals (N=22,945) according to Co-meds

Co-meds (ATC Code)	Red-flag		Orange-flag		Yellow-flag		Green-flag		Grey-flag	
	N°	%	N°	%	N°	%	N°	%	N°	%
Nervous system drugs (N)	115	0.50	1,833	7.99	1,163	5.07	5,886	5.07	25	0.11
Cardiovascular drugs (C)	97	0.42	674	2.94	730	3.18	3,512	3.18	0	0.00
Musculoskeletal system (M)	1	0.00	575	2.51	16	0.07	3,208	0.07	0	0.00
Antifectives (J)	7	0.03	353	1.54	128	0.56	3,179	0.56	0	0.00
Respiratory system (R)	314	1.37	324	1.41	386	1.68	2,248	1.68	0	0.00
Blood drugs (B)	61	0.27	368	1.60	0	0.00	1,998	0.00	0	0.00
Gastrointestinal drugs (A)	62	0.27	273	1.19	9	0.04	1,841	0.04	1	0.00
Dermatological drugs (D)	117	0.51	394	1.72	90	0.39	953	0.39	0	0.00
Systemic Hormones (H)	5	0.02	466	2.03	0	0.00	905	0.00	0	0.00
Genitourinary drugs (G)	11	0.05	342	1.49	20	0.09	674	0.09	0	0.00
Antineoplastic drugs (L)	0	0.00	15	0.07	0	0.00	230	0.00	0	0.00
Sensory organs (S)	0	0.00	23	0.10	31	0.14	179	0.14	0	0.00
Antiparasitic drugs (P)	0	0.00	42	0.18	84	0.37	134	0.37	0	0.00
Various/Therapeutic drugs (V)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

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DDIs in HIV-infected individuals (N=22,945) according to ARVs

ARV class	Red-flag		Orange-flag		Yellow-flag		Green-flag		Grey-flag	
	N°	%	N°	%	N°	%	N°	%	N°	%
Boosted PIs	616	2.68	1,950	8.50	1,263	5.50	2,707	11.80	21	0.09
nnRTIs	89	0.39	1,911	8.33	789	3.44	4,478	19.52	6	0.03
Boosted INSTIs	46	0.20	204	0.89	75	0.33	197	0.86	1	0.00
Non-boosted INSTIs	1	0.00	368	1.60	185	0.81	5,912	25.77	0	0.00
nRTIs	0	0.00	127	0.55	265	1.15	6,083	26.51	0	0.00
CCR5 antagonist	0	0.00	8	0.03	8	0.03	126	0.55	0	0.00

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Top-Ten Red-flag DDIs among HIV-infected individuals

Total Red-flag DDIs = 729

#	ARVs	Co-meds (ATC Code)	Chemical substance	N° (%)
1	boosted-Darunavir	Corticosteroids [R01AD05 (nasal), R03BA02 (inhalants)]	Budesonide	137 (18.8)
2	boosted-Darunavir	Corticosteroids [R01AD09 (nasal), D07AC13 (dermatological)]	Mometasone	114 (15.6)
3	boosted-Darunavir	Antipsychotic drugs (N05AH04)	Quetiapine	85 (11.7)
4	boosted-Darunavir	Propulsives (A03FA03)	Domperidone	44 (6.0)
5	boosted-Darunavir	Antithrombotic agents (B01AC04)	Clopidogrel	43 (5.9)
6	boosted-Darunavir	Statins (C10AA)	Simvastatin	31 (4.3)
7	Efavirenz	Imidazole and triazole derivatives (D01AC08)	Ketoconazole	25 (3.4)
8	boosted-Darunavir	Corticosteroids [R03AK06 (inhalants)]	Fluticasone	25 (3.4)
9	Nevirapine	Imidazole and triazole derivatives (D01AC08)	Ketoconazole	24 (3.3)
10	Elvitegravir/Cobicistat	Corticosteroids [R01AD05 (nasal)]	Budesonide	18 (2.5)

Conclusions

- Nervous system drugs followed by gastrointestinal drugs and anti-infectives were the most frequently prescribed Co-meds among HIV-infected subjects.
- Polypharmacy was significantly more frequent among HIV-infected individuals in comparison with HIV-noninfected individuals across all age strata, except for those aged ≥ 75 years.
- The prevalence of red-flag DDIs among HIV-infected individuals was 3.2%.
- The most frequent involved ARVs in red-flag DDIs were boosted PIs, followed by nnRTIs, and boosted INSTIs.
- The most frequently involved Co-meds in red-flag DDIs were corticosteroids (51.4%), followed by antipsychotic drugs, statins, and imidazole and triazole derivatives.

