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Polypharmacy and Drug–Drug Interactions in People Living With Human Immunodeficiency Virus in the Region of Madrid, Spain: A Population-Based Study

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Background. Drug–drug interactions (DDIs) that involve antiretrovirals (ARVs) tend to cause harm if unrecognized, especially in the context of comorbidity and polypharmacy.

Methods. A linkage was established between the drug dispensing registry of Madrid and the Liverpool human immunodeficiency virus (HIV) DDI database (January 2017–June 2017). Polypharmacy was defined as the use of ≥5 non-HIV medications, and DDIs were classified by a traffic-light ranking for severity.

Results. A total of 22 945 people living with HIV (PLWH) and 6 613 506 individuals without HIV had received medications. ARV regimens were predominantly based on integrase inhibitors (51.96%). Polypharmacy was higher in PLWH (32.94%) than individuals without HIV (22.16%; P < .001); this difference was consistently observed across all age strata except for individuals ≥75 years. Polypharmacy was more common in women than men in both PLWH and individuals without HIV. The prevalence of contraindicated combinations involving ARVs was 3.18%. Comedications containing corticosteroids, quetiapine, or antithrombotic agents were associated with the highest risk for red-flag DDI, and the use of raltegravir- or dolutegravir-based antiretroviral therapy was associated with an adjusted odds ratio of 0.72 (95% confidence interval, .60–.88; *P* = .001) for red-flag DDI.

Conclusions. Polypharmacy was more frequent among PLWH across all age groups except those aged ≥75 years and was more common in women. The detection of contraindicated medications in PLWH suggests a likely disconnect between hospital and community prescriptions. Switching to alternative unboosted integrase regimens should be considered for patients with risk of harm from DDIs.

Keywords. HIV; polypharmacy; drug–drug interactions; antiretroviral drugs; population study.

The increased life expectancy of people living with human immunodeficiency virus (PLWH) as a result of combination antiretroviral therapy has led to an aging HIV cohort globally [1–3]. Such individuals develop multiple comorbidities and are at higher risk of harm from polypharmacy as a result of their underlying HIV status, age, and physiologic frailty [4–6]. Potential concerns associated with polypharmacy include increased pill burden, decreased medication adherence, increased risk for drug–drug interactions (DDIs), adverse drug reactions including organ system injury, hospitalization, death, and rising treatment-related costs [7, 8]. DDIs in PLWH with multimorbidity are unavoidable to a large extent, but their safe management is only possible with full knowledge of all medications ingested. Fragmentation that results in treatment silos can increase the risk of harm from DDIs.

The true prevalence of DDIs is unclear since estimates have been derived from hospital or cohort settings [9–13] or have focused on specific groups of patients (eg, older PLWH [13–16]) rather than integrating data across hospital and community settings. Moreover, antiretroviral therapy guidelines have changed significantly with the introduction of newer antiretrovirals (ARVs) in recent years [17–19]. We sought to evaluate the prevalence of polypharmacy in PLWH and individuals without HIV in the region of Madrid through a large prescription-reimbursement database that reconciles hospital and community prescriptions. We also evaluated the risk factors and potential DDIs in people receiving ARVs.

METHODS

Study Design

This cross-sectional population-based study was carried out in the region of Madrid between 31 January 2017 and 30 June

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2017. Prescription drugs in Madrid are covered by the Madrid Health Service (SERMAS [Servicio Madrileño de Salud]). ARVs are dispensed by hospital pharmacies, and non-HIV medications are mainly dispensed by community pharmacies, although some are dispensed by hospital pharmacies (eg, anticancer drugs, anti-hepatitis C virus drugs). Medications are refilled monthly, although for some PLWH, ARVs are refilled every 2 or 3 months.

SERMAS uses unique regional patient identification codes (CIPA [Código de Identificación de Paciente Autonómico]) that allow access to personal information (age, sex, and income status) and all prescription drugs dispensed (ARVs and non-HIV medications). The SERMAS drug database is updated monthly, but the lag time between drug dispensation at pharmacies and recording of this information in the database is 1 month for hospital pharmacies and 2 months for community pharmacies.

Participants

We downloaded the registries from the SERMAS database on an anonymized basis to build a working database with information about all patients who picked up ARVs or non-HIV medications during the study period. The working database was free of fields that contained information that could lead to identification of a patient (ie, CIPA code). Patients were classified as PLWH or people without HIV according to whether or not they received ARVs for indications not including preexposure or postexposure prophylaxis.

Prescription Drugs

ARVs were categorized according to class as nucleoside or nucleotide reverse transcriptase inhibitors (nRTIs), nonnucleoside reverse transcriptase inhibitors (nnRTIs), boosted protease inhibitors (PIs), boosted and unboosted integrase strand transfer inhibitors (INSTIs), and C-C chemokine receptor type 5 (CCR-5) inhibitors. When used as boosting agents, ritonavir and cobicistat were not counted as a separate medication. For this study, all ARVs except nRTIs were also referred to as anchor drugs. Non-HIV medications were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system [20], in which the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological, and chemical properties. Drugs are classified in groups at 5 levels, with the fifth level corresponding to the name of the chemical substance. For combination medications, individual components were counted separately. Nonantiretroviral polypharmacy (referred to as polypharmacy hereafter) was considered as the intake of ≥5 non-HIV medications [21].

Drug–Drug Interactions

We developed a customized application programming interface to link the SERMAS database and the University of Liverpool (UoL) Drug Interactions Database [22], a comprehensive database of >24 000 HIV DDIs that are widely used throughout Europe, to detect potential DDIs between ARVs and non-HIV medications. In brief, medications from the SERMAS database were coded according to ATC criteria and separated into ARVs and non-HIV drugs. All ARV–non-HIV drug pairs were interrogated using the UoL database to generate a comprehensive list of potential DDIs. The Liverpool flag classification was used to categorize the severity of DDIs as follows: a red flag indicates medications that should not be coadministered as they might lead to serious adverse events or profoundly affect antiretroviral therapy efficacy; an orange flag indicates a potential interaction that might require dosage modification or close monitoring to minimize clinical consequences; a yellow flag indicates a potential interaction of weak relevance not requiring additional monitoring or dosage adjustment; a green flag indicates no anticipated risk of interaction; and a gray flag indicates no clear data are available to assess whether a DDI will occur.

Statistical Analyses

For the descriptive study, values were expressed as absolute numbers and percentages and as medians and interquartile ranges (IQRs). Differences between groups were analyzed using the χ^2 test. Logistic regression analysis was used to investigate factors associated with polypharmacy and potential DDIs. IBM SPSS Statistics for Windows version 21.0 was used for all calculations. All statistical tests were 2-sided, and a P value of <.05 was considered statistically significant.

RESULTS

Patients and Polypharmacy

During the study period, 6 636 451 individuals received medications in the region of Madrid. Among them, 22 945 (0.35%) were receiving ARVs. The proportion of females was 21.72% among PLWH and 51.98% among those without HIV ($P < .001$). The median age was 48 years (IQR, 39–54 years) among PLWH and 41 years (24–57 years) among individuals without HIV ($P < .001$).

Overall, polypharmacy was observed in 7557 PLWH (32.94%) and 1 465 552 individuals without HIV (22.16%; odds ratio [OR], 1.73; 95% confidence interval [CI], 1.68–1.77; $P < .001$). Polypharmacy was more common among females than males, increased with age, and was significantly higher among PLWH than individuals without HIV across all age strata except for those aged ≥75 years (Figure 1).

In PLWH, polypharmacy was observed in 17 (15.18%) pediatric patients (aged <18 years) and 7540 (33.02%) adults. Among adults, polypharmacy was more common among older adults (≥50 years) than young adults (≥18 to 50 years) at 47.26% vs 21.78% ($P < .001$). Notably, 2020 (8.85%) adult patients were

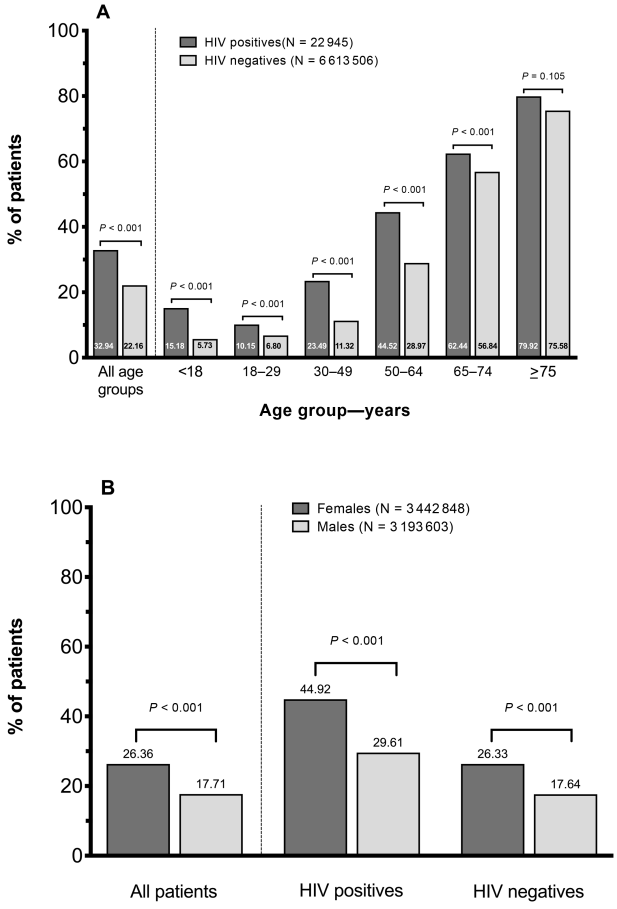

Figure 1. Distribution of polypharmacy among people living with and without HIV according to age (*A*) and gender (*B*). Abbreviation: HIV, human immunodeficiency virus.

taking more than 10 non-HIV medications, which was found in 13.99% of older adults and in 4.79% of young adults ($P < .001$).

Prescription Drugs Among PLWH

Prescription drugs were analyzed for the 22 945 PLWH, of whom 112 (0.49%) were pediatric patients.

Antiretroviral Drugs

A full description of ARV classes broken down by pediatric patients and adults is shown in Supplementary Table 1. In brief, 20 661 (90.05%) patients were treated with at least 1 nRTI. The most frequently used nRTI combinations in children were abacavir/lamivudine (ABC/3TC; 33.93%), followed by tenofovir disoproxil fumarate/emtricitabine (TDF/FTC; 29.46%) and tenofovir alafenamide (TAF)/emtricitabine (FTC; 10.71%). The most frequently used nRTI combination in adults was TDF/FTC (42.62%), followed by 3TC/ABC (37.31%) and TAF/FTC (11.93%).

Overall, the most frequently used anchor ARVs were INSTIs (51.96%), followed by nnRTIs (41.34%) and boosted PIs (23.12%). In pediatric patients, efavirenz (EFV; 20.54%), raltegravir (20.54%), and lopinavir/ritonavir (14.29%) were mostly used. In adults, the most prescribed were dolutegravir (30.92%), rilpivirine (19.41%), and darunavir boosted with cobicistat or ritonavir (17.99%).

Comedications

Among PLWH, 16 402 (71.48%) took at least 1 non-HIV medication overall, 66 (58.93%) among pediatric patients and 16 336 (71.55%) among adults. Figure 2 shows a summary of non-HIV medications classified according to the ATC code categorized into 3 age strata. Among pediatric patients, the most frequently dispensed non-HIV medications were antiinfectives for systemic use (27.68%), nervous system drugs (23.21%), and gastrointestinal and metabolism drugs (16.07%). Among young adults, the most frequently dispensed non-HIV medications were nervous system drugs (35.99%), antiinfectives for systemic use (28.05%), and gastrointestinal and metabolism drugs (26.64%).

Among older adults, the most frequently dispensed non-HIV medications were nervous system drugs (54.22%), gastrointestinal and metabolism drugs (52.26%), and cardiovascular drugs (46.28%). Among adult PLWH, the dispensation of drugs from any of the 14 ATC categories was significantly more common among older adults than young adults, with the exception of antiinfectives and dermatological drugs. A description of non-HIV medications classified by ATC therapeutic subgroup in the 3 age strata is provided in Supplementary Table 2.

Drug–Drug Interactions Among PLWH

The prevalence of the different categories of DDIs among PLWH according to the UoL drug interactions criteria included 729 red flags (3.18%), 4193 orange flags (18.27%), 2363 yellow flags (10.30%), 11 811 green flags (51.48%), and 26 gray flags (0.11%; Figure 3). Potential DDIs according to anchor ARVs and non-HIV medications are shown in Table 1. The prevalence of red-flag DDIs was 2.68% for boosted PIs, 0.39% for nnRTIs, 0.20% for boosted INSTIs, and 0% for unboosted INSTIs. The most frequent red-flag DDIs involved respiratory system drugs (1.37%), followed by dermatological drugs (0.51%), nervous system drugs (0.50%), cardiovascular drugs (0.42%), gastrointestinal and metabolism drugs (0.27%), and blood drugs (0.27%).

A detailed description of the 729 potential red-flag DDIs found among PLWH is provided in Table 2. Overall, the most frequently involved non-HIV medications in red-flag DDIs were corticosteroids, including budesonide, mometasone, fluticasone, and triamcinolone (56.65%), followed by the antipsychotic drug quetiapine (14.54%), antithrombotic agents including clopidogrel and ticagrelor (8.50%), imidazole and triazole derivatives such as ketoconazole and itraconazole (8.37%), domperidone (7.27%), and simvastatin (6.45%).

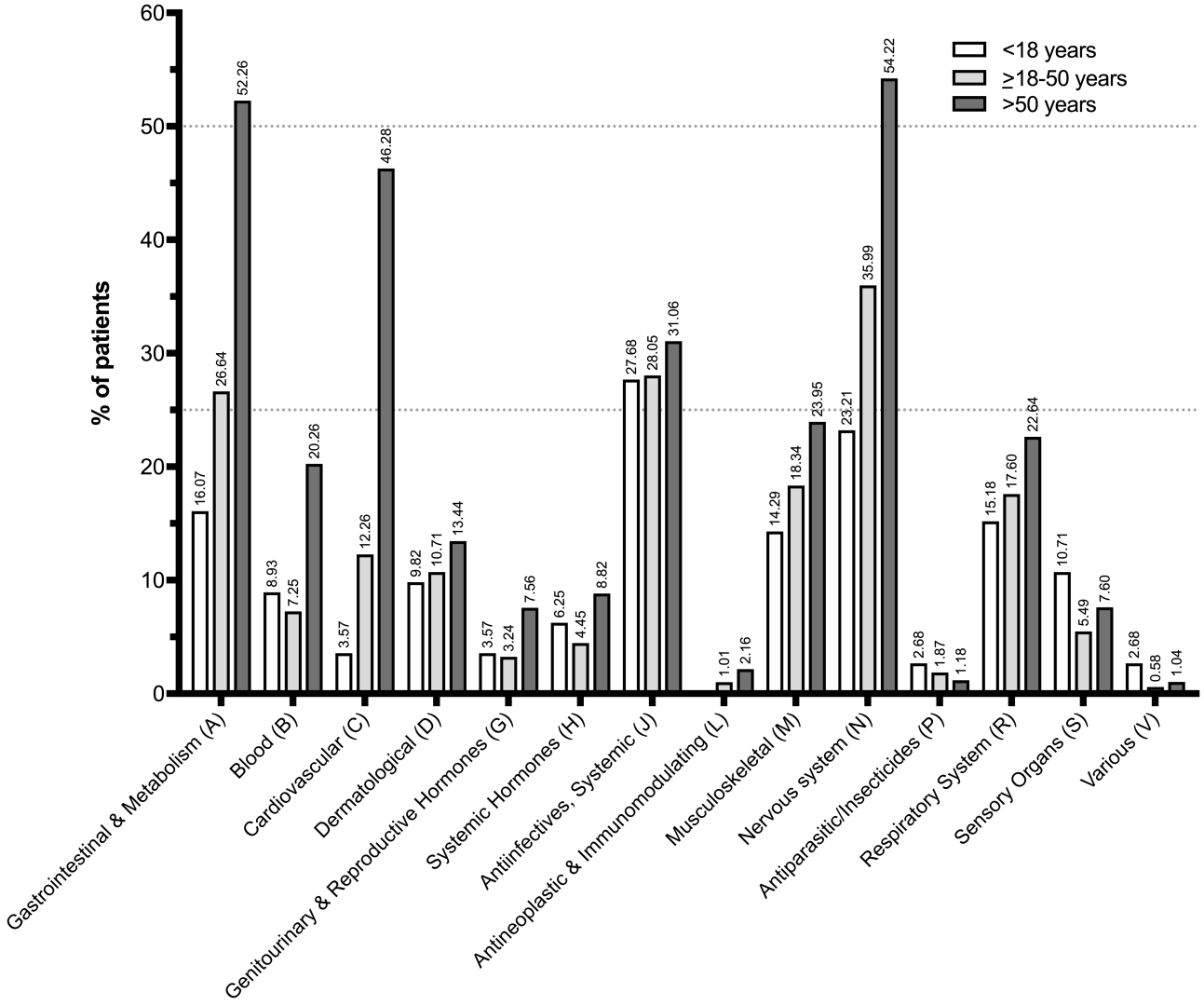

Figure 2. Non–human immunodeficiency virus (HIV) medications used by people living with HIV classified according to the Anatomical Therapeutic Chemical classification system, categorized into 3 age strata.

Ten interactions accounted for 546 (74.90%) of all potential red-flag DDIs (Supplementary Table 3). Boosted DRV was the ARV involved in 7 of these top 10 interactions and accounted for 65.71% of all potential red-flag DDIs. Corticosteroids were the non-HIV medications involved in 4 of these top 10 interactions and accounted for 40.33% of all potential red-flag DDIs.

The ARVs most frequently involved in orange-flag DDIs were boosted PIs (8.50%), followed by nnRTIs (8.33%) and unboosted INSTIs (1.60%). The non-HIV medications most frequently involved in orange-flag DDIs were nervous system drugs (7.99%), followed by cardiovascular drugs (2.94%), musculoskeletal system drugs (2.51%), and systemic hormones (2.03%).

Factors Associated With Drug–Drug Interactions

Table 3 shows the results of multivariable analyses to identify factors associated with DDIs. Factors independently associated with reduced risk of red-flag DDIs included age ≥50 years (adjusted OR [aOR] 0.76; 95% CI, .63–.91, $P = .003$) and treatment with unboosted INSTIs as anchor ARVs (aOR, 0.72; 95% CI, .60–.88; $P = .001$). Factors independently associated with increased risk of red-flag DDIs included treatment with boosted PIs, boosted INSTIs and nnRTIs as anchor ARVs, polypharmacy, and treatment with the following non-HIV medications according to the ATC code: respiratory drugs, dermatological drugs, blood drugs, nervous system drugs, cardiovascular drugs, and systemic hormones. The only factor independently associated with reduced risk of orange-flag DDIs was treatment with unboosted INSTIs as anchor ARVs (aOR, 0.79; 95% CI, .71–.87; $P < .001$). Factors independently associated with increased risk of orange-flag DDI included male gender, treatment with any ARV except unboosted INSTIs, polypharmacy, and treatment with any non-HIV medication with the exception of antineoplastic and immunomodulating drugs and sensory organ drugs.

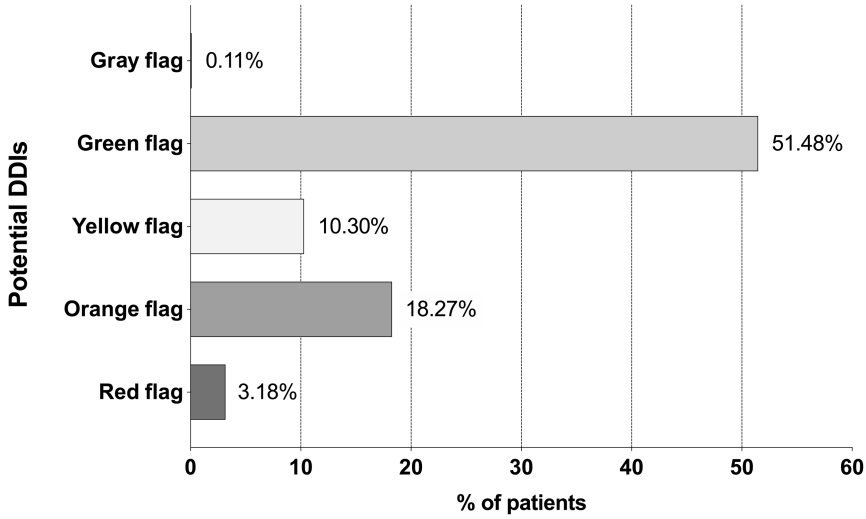

Figure 3. Potential drug–drug interactions among people living with human immunodeficiency virus. Abbreviation: DDI, drug–drug interaction.

DISCUSSION

Our large population-based survey included a comprehensive reconciliation of medicines across multiple prescribers for more than 6.6 million PLWH and individuals without HIV across a broad age range. Approximately 23 000 individuals were receiving HIV medications, and one-third of them experienced polypharmacy. Polypharmacy was more common among females, increased with age, and was more prevalent among

Table 1. Potential Drug–Drug Interactions in 22 945 People Living With Human Immunodeficiency Virus According to Antiretroviral and Nonantiretroviral Medications

	Red Flag		Orange Flag		Yellow Flag		Green Flag		Gray Flag	
Drugs	N	%	N	%	N	%	N	%	N	%
Antiretroviral drug class										
Boosted protease inhibitors	616	2.68	1950	8.50	1263	5.50	2707	11.80	21	0.09
Nonnucleoside reverse transcriptase inhibitors	89	0.39	1911	8.33	789	3.44	4478	19.52	6	0.03
Boosted INSTIs	46	0.20	204	0.89	75	0.33	197	0.86	1	0.00
Nonboosted INSTIs	1	0.00	368	1.60	185	0.81	5912	25.77	0	0.00
Nucleos(t)ide reverse transcriptase inhibitors	0	0.00	127	0.55	265	1.15	6083	26.51	0	0.00
CCR5 inhibitors (maraviroc)	0	0.00	8	0.03	8	0.03	126	0.55	0	0.00
Nonantiretroviral drugs (Anatomical Therapeutic Chemical classification system code)										
Respiratory system (R)	314	1.37	324	1.41	386	1.68	2248	1.68	0	0.00
Dermatological drugs (D)	117	0.51	394	1.72	90	0.39	953	0.39	0	0.00
Nervous system drugs (N)	115	0.50	1833	7.99	1163	5.07	5686	5.07	25	0.11
Cardiovascular drugs (C)	97	0.42	674	2.94	730	3.18	3512	3.18	0	0.00
Gastrointestinal and metabolism drugs (A)	62	0.27	273	1.19	9	0.04	1841	0.04	1	0.00
Blood drugs (B)	61	0.27	368	1.60	0	0.00	1998	0.00	0	0.00
Genitourinary and reproductive hormones (G)	11	0.05	342	1.49	20	0.09	674	0.09	0	0.00
Antiinfectives, systemic (J)	7	0.03	353	1.54	128	0.56	3179	0.56	0	0.00
Systemic hormones (H)	5	0.02	466	2.03	0	0.00	905	0.00	0	0.00
Musculoskeletal system (M)	1	0.00	575	2.51	16	0.07	3208	0.07	0	0.00
Antineoplastic and immunomodulating 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/Insecticides (P)	0	0.00	42	0.18	84	0.37	134	0.37	0	0.00
Various drugs (V)	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Red flag indicates drugs that should not be coadministered as they might lead to serious adverse events or profoundly affect antiretroviral therapy efficacy. Orange flag indicates a potential interaction that might require dosage modification or close monitoring to minimize clinical consequences. Yellow flag indicates weak potential interaction and not requiring additional monitoring or dosage adjustment. Green flag represents no known or anticipated interaction. Gray flag represents when there are no clear data to assess whether a drug–drug interactions will occur.

Abbreviation: INSTI, integrase strand transfer inhibitor.

Table 2. Description of the 729 Potential Red-Flag Drug–Drug Interactions Found Among 22 945 People Living With Human Immunodeficiency Virus

ARV Class	ARV Drugs	Nonantiretroviral Drugs (Anatomical Therapeutic Chemical Classification System Code)	Chemical Substance	Interaction Description	N (%)
Boosted protease inhibitors	bATV, bDRV, lopinavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir, tipranavir/ritonavir, indinavir/ritonavir	Corticosteroids (R01AD, R03BA, R03AK, H02AB, D07AC)[a]	Budesonide, mometasone, fluticasone, triamcinolone	Risk of systemic corticosteroid effects (Cushing's syndrome and adrenal suppression)	375 (51.4)
		Antipsychotic drugs (N05AH)	Quetiapine	Substantial increase of quetiapine exposure	103 (14.1)
		Antithrombotic agents (B01AC)	Clopidogrel	Substantial decrease of clopidogrel exposure	53 (7.3)
		Propulsives (A03FA)	Domperidone	Risk of cardiac adverse effects (QT interval prolongation)	50 (6.9)
		Statins (C10AA)	Simvastatin	Risk of myopathy and rhabdomyolysis	46 (6.3)
		Diuretic drugs (C03DA)	Eplerenone	Risk of hyperkalemia	21 (2.9)
		Cardiac therapy (C01BD, C01EB)	Amiodarone, ranolazine	Substantial increase of cardiac drug exposure	9 (1.2)
		Calcium channel blockers (C08CA)	Lercanidipine	Substantial increase of lercanidipine exposure	9 (1.2)
		Antithrombotic agents (B01AC)	Ticagrelor	Substantial increase of ticagrelor exposure	8 (1.1)
		Cardiac therapy (C01EB)	Ivabradine	Risk of bradycardia	7 (1.0)
		Antiepileptic drugs (N03AB)	Phenytoin	Substantial decrease of bDRV exposure	6 (0.8)
		Proton pump inhibitors (A02BC)	Lansoprazole, esomeprazole, rabeprazole	Substantial decrease of bATV exposure	5 (0.7)
		Psycholeptics drugs (N05CD)	Triazolam	Risk of prolonged sedation or respiratory depression	2 (0.3)
		Psycholeptics drugs (N05AE)	Ziprasidone	Risk of cardiac adverse effects (QT interval prolongation)	1 (0.1)
		Antimycobacterials (J04AB)	Rifampicin	Substantial decrease of bATV exposure	1 (0.1)
Nonnucleoside reverse transcriptase inhibitors	Efavirenz, nevirapine, ETR, RPV	Imidazole and triazole derivatives (D01AC, J02AC)[b]	Ketoconazole, itraconazole	Substantial decrease of imidazole and triazole derivative exposure	61 (8.4)
		Sex hormones and modulators of the genital system (G03AC, G03DC)	Norethisterone [Norethindrone] (POP), desogestrel (POP)	Substantial decrease of hormonal contraceptives exposure	11 (1.5)
		Proton pump inhibitors (A02BC)	Lansoprazole, esomeprazole, rabeprazole	Substantial decrease of RPV exposure	9 (1.2)
		Antiepileptic drugs (N03AB, N03AF)	Phenytoin, oxcarbazepine, carbamazepine	Substantial decrease of ETR and RPV exposure	5 (0.7)
		Psycholeptics drugs (N05AE)	Ziprasidone	Risk of cardiac adverse effects (QT interval prolongation)	2 (0.3)
		Psycholeptics drugs (N05CD)	Triazolam	Risk of prolonged sedation or respiratory depression	1 (0.1)
		Antimycobacterials (J04AB)	Rifampicin	Substantial decrease of ETR exposure	1 (0.1)
Boosted INSTIs	EVG/COBI	Corticosteroids (R01AD, R03BA, H02AB, D07AC)[c]	Budesonide, Mometasone, Fluticasone, Triamcinolone	Risk of systemic corticosteroid effects (Cushing's syndrome and adrenal suppression)	38 (5.2)

Table 2. Continued

ARV Class	ARV Drugs	Nonantiretroviral Drugs (Anatomical Therapeutic Chemical Classification System Code)	Chemical Substance	Interaction Description	N (%)
		Antipsychotic drugs (N05AH)	Quetiapine	Substantial increase of quetiapine exposure	3 (0.4)
		Propulsives (A03FA)	Domperidone	Risk of cardiac adverse effects (QT interval prolongation)	3 (0.4)
		Antiepileptic drugs (N03AA, N03AF)	Phenobarbital, carbamazepine,	Substantial decrease of EVG/COBI exposure	2 (0.3)
		Antithrombotic agents (B01AC)	Clopidogrel	Substantial decrease of clopidogrel exposure	1 (0.1)
		Statins (C10AA)	Simvastatin	Risk of myopathy and rhabdomyolysis	1 (0.1)
		Cardiac therapy (C01EB)	Ivabradine	Risk of bradycardia	1 (0.1)
INSTIs	DTG	Antiepileptic drugs (N03AF)	Oxcarbazepine	Substantial decrease of DTG exposure	1 (0.1)

Abbreviations: ARV, antiretroviral drug; bATV, boosted atazanavir with either ritonavir or cobicistat; bDRV, boosted darunavir with either ritonavir or cobicistat; DTG, dolutegravir; ETR, etravirine; EVG/COBI, elvitegravir/cobicistat; INSTIs, integrase strand transfer inhibitors; POP, progestogen-only pill; QT, the interval between the beginning of the Q wave and the initiation of the T segment; RPV, rilpivirine.

[a]Corticosteroids: R01AD (nasal route), N = 204; R03BA, R03AK (inhalation route), N = 104; H02AB (systemic), N = 5; D07AC (cutaneous route), N = 62.

[b]Imidazole and triazole derivatives: D01AC (cutaneous route), N = 56; J02AC (systemic), N = 5.

[c]Corticosteroids: R01AD (nasal route), N = 28; R03BA (inhalation route), N = 4; H02AB (systemic), N = 1; D07AC (cutaneous route), N = 5.

PLWH than individuals without HIV across all age strata except those aged ≥75 years. The prevalence of contraindicated drug combinations was 3.18%.

The higher prevalence of polypharmacy in women than men is consistent with previous observations in the general population. Gender-related differences in polypharmacy could be explained by several factors, including the more frequent contact with the healthcare system among women, which may provide them with extra opportunity for detecting diseases and receiving prescriptions. Other factors include gender-related biological differences in the occurrence of specific comorbidities associated with a chronic need for medication, as well as the lower propensity to seek preventive healthcare among men in comparison with women [23, 24].

Another interesting observation was that the difference in the prevalence of polypharmacy between PLWH and individuals without HIV tended to become less important and was no longer significant among individuals aged ≥75 years. This was most likely due to the natural occurrence of age-related comorbidities regardless of HIV status. This observation is in line with the results of a large claims-based analysis in the United States, which showed a small difference in the number of non-HIV medications among individuals aged ≥65 years than age-matched individuals without HIV [25].

The literature on DDIs in PLWH is far from comprehensive and reflects the experience of an era in which EFV and boosted PIs were the predominant anchor ARVs and INSTI-based regimens were nonexistent. Two large studies done in sub-Saharan countries showed that antiinfectives, including rifampicin, antifungals, antimalarials, and anthelminthics, were the most frequent non-HIV medications involved in DDIs, [26–28]. To the best of our knowledge, the largest survey to date in a resource-rich setting was carried out within the SHCS, in which the prevalences of red-flag and orange-flag DDIs among 1497 PLWH on ARVs were found to be 1.40% and 39.88%, respectively [12]. In this study, red-flag DDIs mainly involved the coadministration of boosted PIs or EFV with midazolam, and most orange-flag DDIs involved the coadministration EFV and boosted PIs with central nervous system drugs, cardiovascular drugs, and methadone [12].

The prevalence of red-flag DDIs among PLWH in our study was 3.18% and mostly involved the combination of boosted PIs and corticosteroids, quetiapine, or antithrombotic agents. Interestingly, compared to the results reported by Marzolini et al [12], the prevalence of red-flag DDIs was higher in our study population, despite a broader use of unboosted INSTIs, characterized by a more favorable DDI profile. The red-flag DDIs in our study involved corticosteroids, which are used by different routes (topical, inhaled, systemic) across a large variety of medical specialties, including dermatology, pneumology, and rheumatology. Therefore, they are likely to be prescribed by non-HIV specialists who are not aware of DDIs with ARVs or underestimate the risk of DDIs in cases of nonoral administration of corticosteroids.

Table 3. Factors Associated With Potential Drug–Drug Interactions Among 22 945 People Living With Human Immunodeficiency Virus

Characteristic	Red-Flag DDI		Orange-Flag DDI	
	Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Age strata				
Pediatric (<18 years)	1.17 (.35–3.95)	.795	1.20 (.66–2.78)	.541
Older adults (≥50 years)	0.76 (.63–.91)	.003	1.03 (.94–1.13)	.488
Male gender	1.15 (.96–1.40)	.127	1.26 (1.14–1.39)	<.001
Polypharmacy	2.65 (1.98–3.54)	<.001	2.17 (1.90–2.47)	<.001
Antiretroviral drug class				
Boosted protease inhibitors	21.01 (16.60–26.59)	<.001	10.07 (8.95–11.32)	<.001
Nucleos(t)ide reverse transcriptase inhibitors	1.18 (.98–1.40)	.072	2.54 (2.32–2.77)	<.001
Nonnucleoside reverse transcriptase inhibitor	1.31 (1.05–1.65)	.017	5.73 (5.10–6.44)	<.001
Boosted INSTIs	1.96 (1.47–2.61)	<.001	1.94 (1.67–2.26)	<.001
Nonboosted INSTIs	0.72 (.60–.88)	.001	0.79 (.71–0.87)	<.001
CCR5 antagonist (maraviroc)	1.42 (.79–2.55)	.243	2.27 (1.55–3.33)	<.001
Nonantiretroviral drugs (Anatomical Therapeutic Chemical classification system code)				
Gastrointestinal and metabolism drugs (A)	1.10 (.89–1.40)	.355	1.09 (.99–1.21)	.089
Blood drugs (B)	1.52 (1.24–1.86)	<.001	1.49 (1.33–1.67)	<.001
Cardiovascular drugs (C)	1.21 (1.00–1.47)	.048	1.47 (1.33–1.62)	<.001
Dermatological drugs (D)	2.48 (2.05–3.00)	<.001	1.78 (1.59–1.99)	<.001
Genitourinary and reproductive hormones (G)	1.12 (.85–1.49)	.421	2.18 (1.87–2.54)	<.001
Systemic hormones (H)	1.28 (1.00–1.63)	.048	2.58 (2.24–2.98)	<.001
Antiinfectives, systemic (J)	1.00 (.83–1.19)	.974	1.23 (1.12–1.35)	<.001
Antineoplastic and immunomodulating drugs (L)	0.97 (.56–1.68)	.929	0.95 (.72–1.27)	.747
Musculoskeletal system (M)	1.03 (.86–1.24)	.737	1.65 (1.50–1.82)	<.001
Nervous system drugs (N)	1.38 (1.09–1.74)	.006	3.08 (2.78–3.42)	<.001
Antiparasitic/Insecticides (P)	0.56 (.29–1.07)	.081	1.88 (1.42–2.50)	<.001
Respiratory system (R)	3.61 (3.01–4.33)	<.001	1.25 (1.13–1.38)	<.001
Sensory organs (S)	1.20 (.93–1.53)	.155	0.92 (.79–1.01)	.268
Various drugs (V)	0.88 (.48–1.62)	.680	1.76 (1.21–2.56)	.003

Abbreviations: CI, confidence interval; DDI, potential drug–drug interaction; INSTI, integrase strand transfer inhibitor; OR, odds ratio.

The prevalence of orange-flag DDIs in our study was 18.27%, which is substantially lower than the prevalence found in the SHCS [12]. This difference is likely explained by the current broader use of INSTIs and by the use of an updated version of the Liverpool HIV drug interactions database. Previous amber-flag DDIs that are considered to have weak clinical relevance are currently categorized as yellow-flag DDIs.

Factors independently associated with an increased risk of having a red-flag DDI included therapy with boosted PIs, boosted INSTIs and nnRTIs as anchor ARVs, polypharmacy, and treatment with various non-HIV medications categorized as respiratory system drugs, dermatological drugs, blood drugs, nervous system drugs, cardiovascular drugs, and systemic hormones. Treatment with unboosted INSTIs and, surprisingly, age ≥50 years were identified as factors independently associated with a lower risk of having a red-flag DDI. It is possible that increased awareness about comorbidities, fragility, and the potential harms of polypharmacy in older PLWH may have led prescribers to actively manage out significant DDIs. Our findings are consistent with those from previous studies that reported an increased risk of DDIs with PI- or NNRTI-based regimens and in the presence of 2 or more non-HIV comedications [12, 29], and also reduced risk of DDIs with regimens comprising unboosted INSTIs [16].

The limitations of our study include an absence of information about the characteristics of PLWH other than age and sex and a lack of information about medical management and clinical outcomes of those with potentially deleterious DDIs. In addition, since the link between the SERMAS database and the UoL Drug Interactions Database was the ATC code, the prevalence of DDIs found in our study may have been underestimated because not all drugs in the SERMAS database are codified in the Liverpool database.

Another limitation is the lack of information about over-the-counter medications, particularly supplements that contain magnesium or calcium, which may interact with INSTIs and have been reported to account for 3.7% of all the potential DDIs in a recent report [29]. Finally, this analysis did not consider potential dosage adjustments, which might have been performed to overcome a given DDI.

Strengths of our study include its population-based design and the large sample size. In addition, both ARVs and non-HIV medications were automatically retrieved from an official and comprehensive database, and DDIs were analyzed with an

automated cross-checking of the working database with a reliable HIV drug interactions database. Finally, our analysis included contemporary ARV regimens (notably INSTIs), which were lacking in most previous surveys.

The persistent detection of contraindicated medications in PLWH suggests a likely disconnect between hospital and community prescriptions or even among prescribers from different departments within the same hospital. The persistent detection of contraindicated medications also emphasizes the need for implementation of policies to lessen the risks associated with DDIs in an aging population, including medication reconciliation and review at each clinical visit, routine assessment of DDIs with the addition of any new medication, stopping needless medications or harmful combinations, and patient education. Other measures include use of integrated electronic medical records, dispensing records that bridge hospital and community pharmacies, use of comprehensive DDI search tools, and a multidisciplinary team approach that involves an experienced HIV pharmacist [30].

In conclusion, we found that in the region of Madrid, nonantiretroviral polypharmacy was more frequent among PLWH than among individuals without HIV across all age strata except for individuals aged ≥75 years. We also found a prevalence of red-flag DDIs of 3.18%. The medications most frequently involved in red-flag DDIs were combinations of boosted PIs, nnRTIs, and boosted INSTIs with corticosteroids, quetiapine, or antithrombotic agents. The use of unboosted INSTIs as anchor ARVs was independently associated with a decreased risk of having both red-flag and orange-flag DDIs. Switching to alternative unboosted INSTIs regimens should be considered for patients with high risk of harm from DDIs, such as those with multiple comorbidities, organ dysfunction, polypharmacy, and boosted ARVs.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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