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Evolution of Drug Interactions With Antiretroviral Medication in People With HIV

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Background. Polypharmacy and drug interactions are important issues for HIV-infected individuals. The number and nature of those interactions are continuously evolving with the use of new antiretroviral drugs and the aging of HIV-infected individuals. We aimed to analyze this evolution over time.

Methods. This retrospective cohort study was conducted in the University Hospital of Liège (Belgium). Treatments of HIV-infected outpatients attending Liège University Hospital were collected and analyzed in 2012 and 2016. The University of Liverpool HIV drug interactions database was used to determine drug interactions.

Results. We included 1038 patients in 2016, of whom 78% had 1 comedication. Polypharmacy was seen in 20% of the cohort. Four percent of the patients presented red flag interactions, and 38% had orange flag interactions. Nonantiretroviral (non-ARV) therapeutic classes involved in drug interactions were mostly cardiovascular and central nervous system drugs. They were followed by hormone drugs and dietary supplements for orange flag interactions. Two factors significantly contributed to both red and orange flag interactions: the number of non-ARV comedications and protease inhibitor–based ARV regimens. The proportion of patients with red or orange flag interactions remained stable from 2012 to 2016.

Conclusions. This study highlights the persistence of an alarming number of contraindicated drug interactions and a high prevalence of potential drug interactions over time. Identification, prevention, and management of drug interactions remain a key priority in HIV care.

Keywords: antiretroviral therapy; drug interactions; HIV.

Since the advent of combination antiretroviral therapy (ARV) in 1996, the lifespan of HIV-infected patients has been extended significantly. The disease has become a chronic condition requiring lifelong treatment.

Hence, the average age of HIV-infected patients is steadily increasing. In Belgium, 36% of all HIV-infected patients were aged 50 years or older in 2017, compared with 19% in 2006 [1]. This aging of the affected population leads to a paradigm shift for medical management. This shift must now be holistic, taking into account age-associated comorbidities (including, among others, cardiovascular diseases, kidney disease, liver disease, bone disorders, neurocognitive impairment, and non-AIDS-related cancers) [2]. It is all the more true that these comorbidities are highly prevalent in HIV-infected individuals compared with general population [3, 4]. Because of these comorbidities, many drugs are prescribed along with ARV therapy. It is well known that concomitant medication use is more prevalent in HIV-infected people than in the general population [5, 6].

As a result, these patients are more and more exposed to polypharmacy (generally defined as the use of 5 or more medications) and consequently to potential drug–drug interactions (PDDIs), which could lead to clinically significant events [7].

The incidence rate of PDDIs in HIV-infected patients may vary according to the ARV regimens used. For instance, ARVs can be substrates (eg, rilpivirine, maraviroc, bictegravir), inhibitors (eg, ritonavir, cobicistat), or inducers (eg, efavirenz, nevirapine) of cytochrome P450 3A enzymes (CYP450), which constitute the major mechanism of drug metabolism. Drug interactions with ARV can also occur through the alteration of other mechanisms including uridine 5'-diphosphoglucuronosyltransferase, drug transporters (eg, P-glycoprotein), nuclear receptor activation, pH-dependent drug absorption, and drug chelation [8].

PDDIs can lead to both reduction and increase in ARV drug concentrations, resulting in suboptimal disease or symptom management, development of ARV resistance, serious adverse

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reactions, and drug toxicity, which could lead to nonadherence to treatment [7].

Polypharmacy and PDDIs are thus persistent and evolving challenges faced by clinicians. However, little is known regarding the evolution of the number and the nature of PDDIs in the recent years, although important modifications could be predicted due to a major increase in the use of integrase inhibitors (INIs) and the aging of HIV-infected individuals.

The aim of this study was to retrospectively investigate the prevalence of drug interactions with ARV in 2016, to compare their evolution between 2012 and 2016, and finally to identify risk factors precipitating them.

METHODS

We performed a retrospective cohort study of individuals aged 18 years and older who were infected with HIV and were attending the University Hospital of Liège (Belgium) during 2012 and 2016 in an outpatient setting. The observation period for each year extended from January to December.

Demographic variables included age (categorized as <50 years, 50–64 years, and 65 years), gender, and ethnicity. Clinical variables included mode of transmission, comorbidities, coinfections, current $CD4^+$ T-lymphocyte (CD4) count, HIV plasma viral load, ARV regimen, number of days on therapy, delayed diagnosis, duration of HIV infection, delayed initiation of treatment, and number of comedications.

Non-ARV medication data were collected at every visit to a specialist in infectious diseases and were categorized according to the Belgian Center for Pharmacotherapeutic Information classification (CBIP) [9]. Comedications were listed for each patient, and polypharmacy was defined as the use of ≥5 concomitant medications [6, 11, 14].

The University of Liverpool HIV drug interactions database [10] was used to determine interactions between ARV and non-ARV medications and classify them into red flag (contraindicated) and orange flag (potential dose adjustment and/or timing of administration and/or close monitoring required) interactions. The Liverpool Drug Interaction website provides reliable information that is regularly updated about drug interactions with ARV. To validate the occurrence of a red flag interaction, a medical report from an infectious diseases specialist mentioning the implicated medications had to be identified to ensure the concomitant use of the drugs.

Descriptive analyses are reported using means, standard deviations, medians, interquartile ranges (IQRs; 25th to 75th quartile), and extreme values. We compared patient characteristics between age groups using chi-square tests for categorical variables and analysis of variance or the Kruskal-Wallis test for continuous variables. We used McNemar's test to compare drug interactions between 2012 and 2016. A multiple logistic regression analysis was performed to determine independent risk factors of drug interactions. Variables for which the significance level was <.1 were included in the model. The results are presented as *P* values, adjusted odds ratios (ORs), and 95% confidence intervals. Differences were considered statistically significant if the *P* value was <.05. All statistical analyses were performed with SAS Statistical Software, version 9.4 (SAS Institute Inc, Cary, NC, USA), graphs were built using R, version 3.6.1.

RESULTS

Patient Baseline Characteristics

A total of 1220 HIV-infected patients were enrolled in the study over 2 periods: 911 patients were followed in 2012 and 1038 patients in 2016; among these, 729 patients (60%) were followed during both years.

The baseline characteristics of the patients are presented in Supplementary Tables 1–3 according the year of follow-up (2016, 2012, and both).

In 2016, 1038 patients aged 18–81 years were under follow-up at our university hospital, of whom 62.6% were aged <50 years. Older HIV-infected individuals were more likely to be male and Caucasian (Supplementary Table 1). Conversely, 57.7% of younger patients were coming from Sub-Saharan Africa. Logically, older patients tended to have more comorbidities. The median $CD4^+$ T-cell count (IQR) was 683 (495–915) cells/mm^3, and 81% of the patients (838/1038) had a controlled HIV plasma viral load (≤200 copies/mL) on every blood sample collected during the year. The most prescribed ARV combination was an INI-based regimen, independent of age group. In particular, the association dolutegravir/abacavir/lamivudine was the most frequently reported ARV regimen. More than 90% of patients were on ARV treatment throughout the year (Supplementary Table 1).

In 2012, 911 patients aged 18–80 years were under follow-up at our hospital, of whom 71% were aged <50 years (Supplementary Table 2). The median CD4+ T-cell count (IQR) was 574 (420–780) cells/mm^3, and 56.0% (505/911) had a controlled HIV plasma viral load on every blood sample. Importantly, the most frequently used ARV drug combination was a protease inhibitor (PI)–based regimen (Supplementary Table 2).

Among 729 patients followed in 2012 and 2016, 625 patients (85.7%) were taking at least 1 non-ARV comedication in 2016 compared with 565 patients (77.5%) in 2012 ($P < .0001$) with a median of 2 drugs for both years (Table 1). Polypharmacy was observed in 164 patients (22.5%) in 2016 compared with 129 patients (17.7%) in 2012. Older patients had a higher median number of comedications (IQR): 1 (0–3) for <50 years, 3 (1–6) for 50–64 years, 4 (3–7) for ≥65 years ($P < .0001$) in the population of patients followed in 2016 (n = 1038 patients) (Table 1).

Table 1. Comedications and Drug Interactions

Patients Followed in 2016 (n = 1038 Patients)					
	All	Age <50 y	Age 50–64 y	Age ≥65 y	
	n = 1038	n = 650	n = 320	n = 68	
Variables	No. (%)	No. (%)	No. (%)	No. (%)	*P* Value
Number of comedications					
None	228 (22.0)	188 (28.9)	38 (11.9)	2 (2.9)	<.0001[a]
≥1	810 (78.0)	462 (71.1)	282 (88.1)	66 (97.1)	
1–4	601	382	184	*35*	
≥5	209	80	98	*31*	
Total	1038 (100.0)	650 (100.0)	320 (100.0)	68 (100.0)	
Mean ± SD	2.7 ± 2.9	2.0 ± 2.4	3.7 ± 3.2	4.8 ± 3.1	<.0001[b]
Median (IQR)	2 (1–4)	1 (0–3)	3 (1–6)	4 (3–7)	
Extreme values	0–19	0–19	0–16	0–12	
Number of interactions					
Red flag	85				
Orange flag	1337				
Number of patients with at least 1 drug interaction					
Red flag	45 (4.3)				
Orange flag	396 (38.1)				
Evolution: patients followed both in 2012 and 2016 (n = 729 patients)					
Variables	2012	2016	*P* Value		
Number of comedications					
None	164 (22.5)	104 (14.3)	<.0001[c]		
≥1	565 (77.5)	625 (85.7)			
1–4	436	461			
≥5	129	164			
Total	729 (100.0)	729 (100.0)			
Mean ± SD	2.4 ± 2.5	3.0 ± 2.9			
Median (IQR)	2 (1–3)	2 (1–4)			
Extreme values	0–15	0–19			
Number of interactions					
Red flag	63	69			
Orange flag	915	940			
Number of patients with at least 1 drug interaction					
Red flag	34 (4.7)	35 (4.8)	.88[c]		
Orange flag	300 (41.1)	310 (42.5)	.50[c]		

Abbreviation: IQR, interquartile range.

[a]Chi-square test.

[b]Kruskal-Wallis test.

[c]McNemar test for repeated measurements.

Drug Interactions in 2012

Based on the Liverpool HIV Drug Interactions website, 68 red flag interactions were identified in 37 patients, meaning that 4.1% (37/911) of patients had at least 1 red flag interaction. The most frequent non-ARV medications involved were cardiovascular drugs, followed by gastrointestinal (27.9%), respiratory (16.5%), otolaryngology (ENT) (8.8%), osteo-articular (2.9%), and central nervous system (CNS) agents (2.9%) (Table 2). The majority of ARV medications involved were PIs, except for 1 drug interaction with a non-nucleoside reverse transcriptase inhibitor (NNRTI; rilpivirine). Red flag interactions occurred mainly between atazanavir with proton pump inhibitor (omeprazole), ritonavir with antihypertensive calcium channel blocker (lercanidipine), and inhaled corticosteroids (budesonide). Coadministration of atazanavir or rilpivirine with proton pump inhibitor (PPI) may have decreased the plasma concentration of the ARV by reducing the solubility of the ARV, as intragastric pH increases with PPI.

A total of 1070 orange flag interactions were reported in 349 patients corresponding to 38.3% (349/911) of patients. Most of these interactions involved CNS agents (28.5%) with mainly anxiolytic drugs, followed by cardiovascular (23.4%), hormone (13%), and anti-infective (7.7%) agents (Table 2). The ARV medications involved were mainly PIs (62.8%), followed by NNRTIs (21.2%), NRTIs (6.9%), CCR5 receptor antagonists (5.4%), and INIs (3.8%). The most common individual orange

Table 2. Number of ARV and Non-ARV Treatments Affected by a Drug Interaction in 2016 and 2012

Treatment	2016		2012	
	Red Flag Interactions (n = 85), No. (%)	Orange Flag Interactions (n = 1412), No. (%)	Red Flag Interactions (n = 68), No. (%)	Orange Flag Interactions (n = 1070), No. (%)
ARV				
Atazanavir	9 (10.6)	63 (5.5)	25 (36.8)	169 (15.8)
Darunavir	17 (20.0)	128 (11.3)	3 (4.4)	76 (7.1)
Ritonavir	23 (27.1)	177 (15.6)	30 (44.1)	314 (29.3)
Lopinavir	5 (5.9)	21 (1.9)	9 (13.2)	90 (8.4)
Fosamprenavir	-	2 (0.2)	-	22 (2.1)
Saquinarir	-	-	-	1 (0.1)
Darunavir/cobicistat	6 (7.1)	45 (4.0)	-	-
Etravirine	1 (1.2)	42 (3.7)	-	39 (3.6)
Efavirenz	-	72 (6.3)	-	93 (8.7)
Zidovudine	-	1 (0.1)	-	12 (1.2)
Rilpivirine	9 (10.6)	23 (2.0)	1 (1.5)	-
Nevirapine	-	111 (9.8)	-	82 (7.7)
Abacavir	-	11 (1.0)	-	3 (0.3)
Didanosine	-	-	-	1 (0.1)
Emtricitabine	-	13 (1.1)	-	44 (4.1)
Lamivudine	-	33 (2.9)	-	26 (2.4)
Tenofovir	-	51 (4.5)	-	58 (5.4)
Maraviroc	-	9 (0.8)	-	4 (0.4)
Dolutegravir	-	140 (12.3)	-	-
Raltegravir	-	31 (1.7)	-	36 (3.4)
Emtricitabine/tenofovir alafenamide fumarate/elvitegravir/cobicistat	6 (7.1)	54 (4.8)	-	-
Emtricitabine/tenofovir disoproxil fumarate/elvitegravir/cobicistat	9 (10.6)	110 (9.7)	-	-
Non-ARV				
Ear, nose, and throat drugs	5 (5.9)	5 (0.4)	6 (8.8)	5 (0.5)
Osteoarticular drugs	1 (1.2)	57 (5.0)	2 (2.9)	48 (4.5)
Cardiovascular drugs	35 (41.2)	272 (23.9)	21 (30.9)	250 (23.4)
Gastrointestinal drugs	17 (20.0)	21 (1.9)	19 (27.9)	18 (1.7)
Respiratory drugs	24 (28.2)	21 (1.9)	18 (16.5)	33 (3.1)
Hemostasis drugs	1 (1.2)	46 (4.0)	-	43 (4.0)
CNS agents	2 (2.4)	255 (22.4)	2 (2.9)	305 (28.5)
Analgesics	-	34 (3.0)	-	46 (4.3)
Obstetrics & gynecology	-	27 (2.4)	-	41 (3.8)
Immunity	-	19 (1.7)	-	10 (0.9)
Anti-infectives	-	58 (5.1)	-	82 (7.7)
Antineoplastic agents	-	2 (0.2)	-	1 (0.1)
Others drugs	-	8 (0.7)	-	5 (0.5)
Genitourinary drugs	-	3 (0.3)	-	12 (1.1)
Dietary supplements	-	153 (13.5)	-	32 (3.0)
Hormone drugs	-	156 (13.7)	-	139 (13.0)

Abbreviations: ARV, antiretroviral; CNS, central nervous system.

flag interactions were ritonavir with levothyroxin, emtricitabine with trimethoprim/sulfamethoxazone, ritonavir with alprazolam, and ritonavir with rosuvastatin.

Drug Interactions in 2016

A total of 85 red flag interactions were found in 45 patients, meaning that 4.3% (45/1038) of patients had at least 1 red flag interaction, with a maximum of 6 contraindicated interactions per patient. The non-ARV medication classes involved included cardiovascular (41.2%), respiratory (28.2%), gastrointestinal (20%), ENT (5.9%), CNS (2.4%), osteo-articular (1.2%), and hemostasis (1.2%) drugs (Table 2). Regarding ARV medications, PIs were by far the most frequently involved ARV (70.7% of red flag interactions), followed by NNRTIs (11.8%) (Table 2). Overall, red flag interactions arose mainly between ritonavir with lercanidipine and budesonide.

Concerning orange flag interactions, 1137 interactions were identified in 396 patients in 2016. Thereby, 38.1% (396/1038) of patients had at least 1 orange flag interaction, which corresponds to 48.0% (396/810) of patients with at least 1 comedication. There were 1, 2, and 3 interactions in 38.6%, 21.7%, and 11.6% of cases, respectively, with a maximum of 34 interactions per patient (Table 1). The non-ARV medications involved included mainly cardiovascular agents (23.9%) and CNS agents (22.4%), followed by hormone drugs (13.7%) and dietary supplements (13.5%) (Table 2). Regarding ARV medications, these interactions most frequently involved PIs (38.5%), followed by NNRTIs (21.9%) and INIs (14%) (Table 2). Overall, individual orange flag interactions occurred mainly between dolutegravir and metformine followed by ritonavir and levothyroxine and dolutegravir and calcium. Calcium alone, with cholecalciferol or in multivitamin preparations, represented the most common drug of the dietary supplements therapeutic class.

Predictors of Drug Interactions in 2016

In 2016, multiple logistic regression analysis identified the use of PIs (OR, 7.5; 95% CI, 4.5–12.5), NNRTIs (OR, 2.4; 95% CI, 1.5–4.0) or INIs (OR, 1.6; 95% CI, 1.03–2.6), the duration of HIV infection (OR, 1.03; 95% CI, 1.001–1.05), the occurrence of osteoporosis or fracture (OR, 1.9; 95% CI, 1.03–3.6), and the number of non-ARV comedications (OR, 1.8; 95% CI, 1.6–2.0) as independent risk factors for orange flag interactions (Figure 1B). Among patients with red flag interactions, only the use of PIs (OR, 7.9; 95% CI, 3.2–19.5) and the number of non-ARV comedications (OR, 1.4; 95% CI, 1.3–1.6) were noted as independent risk factors (Figure 1A). The mode of HIV transmission had no impact on the risk of red flag ($P = .58$) or orange flag ($P = .93$) interactions.

Analysis of Individuals Followed Both in 2012 and 2016

A total of 729 patients were followed during both 2012 and 2016 (Supplementary Table 3). In this population, 63 red flag and 915 orange flag interactions were reported in 2012 compared with 69 red flag and 940 orange flag interactions in 2016 (Table 1).

The rate of patients with at least 1 drug interaction was similar between 2012 and 2016: 4.7% vs 4.8% of patients for red flag interactions and 41.1% vs 42.5% for orange flag interactions (Table 1).

Among patients with red flag interactions, in 2012 the non-ARV medications involved were mainly gastrointestinal drugs, while the non-ARV medications involved were mostly cardiovascular drugs in 2016 (Table 4). About 30% of the patients with red flag interactions in both 2012 and 2016 presented at least 1 drug interaction, which could have reduced ARV plasma concentrations and thereby might have compromised the ARV's efficacy. The implicated drug interactions were PPI with PI (atazanavir) or NNRTI (rilpivirine) and carbamazepine with NNRTI (etravirine). However, we found no correlation with the occurrence of a detectable viral load.

Orange flag interactions involving dietary supplements were found in 6.7% (49/729) of the patients in 2016, whereas only 2.1% (15/729) were found in 2012 ($P < .0001$) (Table 4). On the other hand, the rate of patients with orange flag interactions

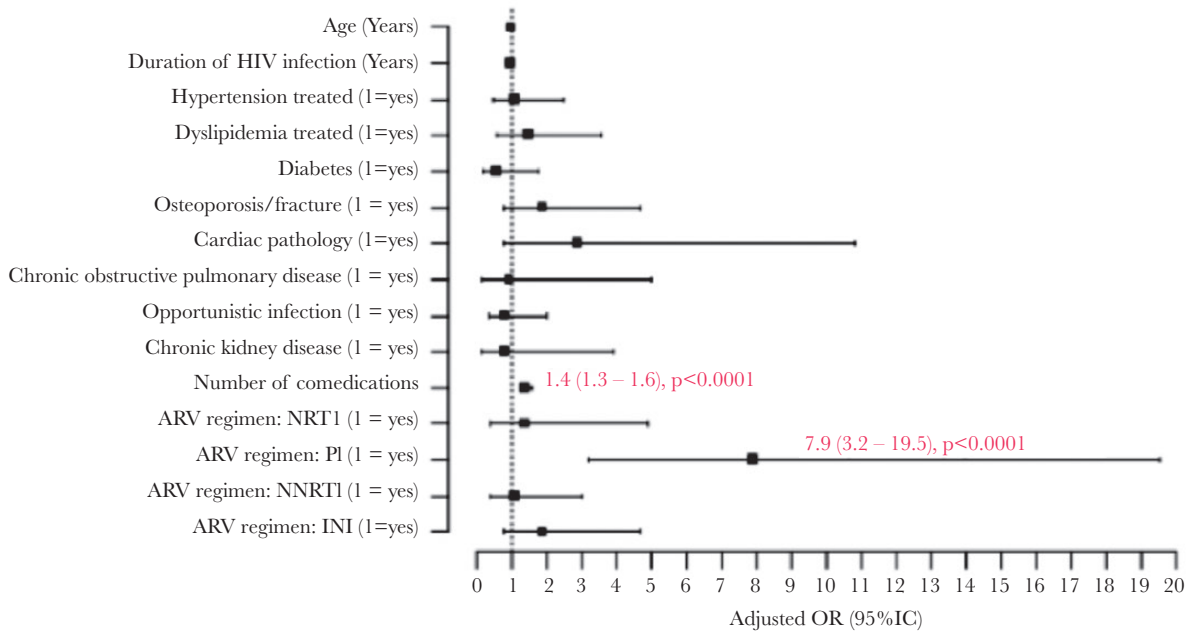

Figure 1. Independent risk factors for drug interactions in 2016. A, Red flag interactions. B, Orange flag interactions. Abbreviations: ARV, antiretroviral; INI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor.

Table 3. Comparison of the Proportion of Patients With at Least 1 Drug Interaction by Type of ARV Treatment Between 2012 and 2016 (n = 729), McNemar Test

ARV treatment	2012, No. (%)	2016, No. (%)	*P* Value
Orange flag interactions			
Atazanavir	84 (11.5)	33 (4.5)	<.0001
Darunavir	37 (5.1)	57 (7.8)	.0055
Ritonavir	156 (21.4)	86 (11.8)	<.0001
Lopinavir	46 (6.3)	11 (1.5)	<.0001
Fosamprenavir	9 (1.2)	1 (0.1)	.0047
Darunavir/cobicistat	0 (0.0)	20 (2.7)	-
Saquinavir	1 (0.1)	0 (0.0)	-
Etravirine	20 (2.7)	13 (1.8)	.035
Efavirenz	49 (6.7)	37 (5.1)	.077
Rilpivirine	0 (0.0)	11 (1.5)	-
Nevirapine	41 (5.6)	47 (6.5)	.30
Abacavir	3 (0.4)	7 (1.0)	.16
Emtricitabine	26 (3.6)	7 (1.0)	.0001
Lamivudine	18 (2.5)	13 (1.8)	.32
Tenofovir	44 (6.0)	36 (4.9)	.24
Zidovudine	8 (1.1)	1 (0.1)	.020
Maraviroc	4 (0.6)	6 (0.8)	.16
Dolutegravir	0 (0.0)	68 (9.3)	-
Raltegravir	18 (2.5)	9 (1.2)	.020
Emtricitabine/tenofovir alafenamide fumarate/elvitegravir/cobicistat	0 (0.0)	24 (3.3)	-
Emtricitabine/tenofovir disoproxil fumarate/elvitegravir/cobicistat	0 (0.0)	41 (5.2)	-
Red flag interactions			
Atazanavir	19 (2.6)	2 (0.3)	<.0001
Darunavir	3 (0.4)	2 (0.3)	.66
Ritonavir	26 (3.6)	2 (0.3)	<.0001
Lopinavir	8 (1.1)	2 (0.3)	.058
Darunavir/cobicistat	0 (0.0)	2 (0.3)	-
Etravirine	0 (0.0)	2 (0.3)	-
Rilpivirine	1 (0.1)	2 (0.3)	.56
Emtricitabine/tenofovir alafenamide fumarate/elvitegravir/cobicistat	0 (0.0)	2 (0.3)	-

Abbreviation: ARV, antiretroviral.

related to anti-infective agents showed a significant decrease (5.5% vs 2.9% of patients; $P = .0056$) (Table 3).

DISCUSSION

PDDIs between ARVs and non-ARVs in HIV-infected individuals were common in our study, both in 2012 and in 2016. The percentages of individuals receiving medications causing at least 1 red flag interaction were similar over time: 4.7% in 2012 compared with 4.8% in 2016. However, these alarmingly high rates are in the line with previous studies showing results ranging from 1% to 7% [7, 11–15]. The same evolution was observed with orange flag interactions, represented by 41.1% of patients with at least 1 drug interaction in 2012 and 42.5% in 2016.

All orange flag interactions are not equal, but they can usually be managed by dosage or timing administration adjustment or close monitoring. On the other hand, red flag interactions generally require a major shift in treatment [10].

Recognition of the risk factors for PPDI may help clinicians prevent it. Risk factors that were independently associated with red flag interactions included the number of non-ARV comedications, as expected, and PI intake. Logistic regression analysis showed that the use of PIs was an important independent risk factor for both orange flag and red flag interactions, in concordance with the literature [7, 11–15]. We observed a significant decrease of drug interactions involving PIs from 2012 to 2016. This is easily explained by the lower use of PIs in 2016. However, PIs are still drugs we must monitor because individuals on PIs were at higher risk (6.7 times) of having a red flag interaction in 2016. Ritonavir, especially, may be involved in interactions with numerous medications because of its potent inhibition of CYP3A4 and P-glycoprotein and potent induction of glucuronyl transferases, CYPP1A2, CYP2B6, CYP2C9, and CYP2C19 [16]. Coadministration of PIs with certain non-ARV drugs may increase the non-ARV concentration in plasma, resulting in adverse clinical outcomes. For example, PIs with inhaled corticosteroids, calcium channel blockers, and

Table 4. Comparison of the Proportion of Patients With at Least 1 Drug Interaction by Therapeutic Class Between 2012 and 2016 (n = 729), McNemar Test

Non-ARV Treatment Class (CBIP)	2012, No. (%)	2016, No. (%)	*P* Value
Orange flag interactions			
Ear, nose, and throat drugs	5 (0.5)	3 (0.4)	.71
Osteoarticular drugs	19 (2.6)	17 (2.3)	.67
Cardiovascular drugs	109 (15)	92 (12.6)	.081
Gastrointestinal drugs	6 (0.8)	6 (0.8)	1.00
Respiratory drugs	10 (3.2)	6 (0.8)	.21
Hemostasis drugs	23 (3.2)	25 (3.4)	.70
CNS agents	57 (7.8)	47 (6.4)	.20
Analgesics	20 (2.7)	20 (2.7)	1.00
Obstetrics & gynecology	11 (1.5)	13 (1.8)	.62
Immunity	7 (1.0)	7 (1.0)	1.00
Anti-infectives	40 (5.5)	21 (2.9)	.0056
Antineoplastic agents	1 (0.1)	2 (0.3)	.32
Others drugs	2 (0.3)	4 (0.6)	.16
Genitourinary drugs	1 (0.1)	1 (0.1)	1.0
Dietary supplements	15 (2.1)	49 (6.7)	<.0001
Hormone drugs	39 (5.4)	46 (6.3)	.32
Red flag interactions			
Ear, nose, and throat drugs	4 (0.5)	2 (0.3)	.32
Osteoarticular drugs	2 (0.3)	1 (0.1)	.32
Cardiovascular drugs	9 (1.2)	16 (2.2)	.090
Gastrointestinal drugs	13 (1.8)	11 (1.5)	.62
Respiratory drugs	8 (1.1)	7 (1.0)	.71
Hemostasis drugs	0 (0.0)	1 (0.1)	.32
CNS agents	0 (0.0)	2 (0.3)	.16

Abbreviations: ARV, antiretroviral; CBIP, Belgian Center for Pharmacotherapeutic Information; CNS, central nervous system.

statins may lead to potential systemic corticosteroid effects including Cushing's syndrome, arterial hypotension, and myopathy with rhabdomyolysis, respectively.

We also reported some red flag interactions that could lead to a decrease in ARV plasma concentrations. These interactions concerned some PIs or rilpivirine (NNRTI) with a PPI, which are frequently used treatments, and etravirine (NNRTI) with carbamazepine.

The non-ARV medications mainly involved in red flag interactions in 2012 were gastrointestinal drugs, while these were mostly cardiovascular drugs in 2016 [17–19]. This can be explained by a specific shift in the use of PIs over the time. In fact, between 2012 and 2016, we reported a significant decrease of orange flag interactions with atazanavir, which interacts in particular with PPIs, and a significant increase of orange flag interactions with darunavir, which had no interaction with PPIs.

In many studies, the use of an INI is associated with a decreased risk of drug interactions [14–16, 20, 21]. In the presented study, we reported a few red flag interactions involving INI (elvitegravir boosted) in 2016. This is explained by the fact that elvitegravir is metabolized predominantly by CYP450 enzymes with a minor pathway involving UGT1A1/3-glucuronidation and requires boosting with cobicistat (an inhibitor of the CYP3A isozyme family of proteins) to reach therapeutic concentrations [22]. As such, elvitegravir/cobicistat has a drug interaction profile similar to ritonavir-boosted PI and was thus the only INI reported to cause a red flag interaction in our study.

Our study showed a high rate of orange flag interactions from 2012 to 2016. These orange flag interactions involved disproportionally more cardiovascular drugs than other therapeutic classes, followed by CNS agents, as in the Swiss HIV Cohort Study [7]. The second most frequent therapeutic class associated with orange flag interactions was dietary supplements in 2016, which showed a significant increase compared with 2012. These interactions occurred mainly between INIs and calcium. Calcium and cholecalciferol supplements are commonly used in HIV-infected individuals because of the increased risk of osteoporosis directly linked to the disease and some ARVs (eg, tenofovir fumarate) [23]. Moreover, HIV-infected individuals face the significant challenge of coping with an incurable disease, leading to the frequent use of complementary and alternative medicine (CAM) as a way to manage their illness, with up to 60% of HIV-infected individuals using CAMs according to the literature [11, 24–27]. Indeed, divalent and trivalent metal cations (as calcium supplements) in co-administration with INI can lead to chelation-type drug interactions. Many oral multivitamin supplements also contain polyvalent cations. This drug interaction may result in reduced solubility and, consequently, a reduced oral absorption of INIs. Several studies have found

clinically significant effects of concomitant administration of INIs with mineral supplements or antacids (that contain aluminium and magnesium) [28–31]. If known, these interactions could be managed easily by administering the INI 2 hours before or 6 hours after taking mineral supplements or with a meal [31].

Unlike elvitegravir, raltegravir and dolutegravir are options to consider in order to decrease the risk of red flag interactions with non-ARV medication because of their different metabolism. Raltegravir does not exhibit any effects on the CYP450 system, and dolutegravir is predominantly metabolized by UGTA1A-mediated glucuronidation with a minor pathway involving CYP450 enzymes [32]. However, our study underlines their potential for chelation-type drug interactions. Other studies have often underestimated the number of orange flag interactions with INI because dietary supplements were not or were incompletely reported [14]. In fact, physicians are often unaware of their patient's use of CAM. The increase of interactions involving dietary supplements reported in 2016 compared with 2012 could be explained by an improvement of the listing of these drugs in medical reports and probably a greater attention given to dietary supplements in 2016.

Some limitations of our study should be acknowledged. First, drug interactions could be underestimated because we did not include interactions between ARV medications among themselves, and we probably did not report all over-the-counter drugs like herbal therapies, which are not always reported in the medical report. Furthermore, we have mentioned some drug interactions without considering if the dose or timing of administration adjustment had or had not already been carried out.

In response to these alarming rates of drug interactions, we developed a flag indicator in our medical program to inform the clinicians of potential drug interactions with an ARV. This interaction alert program might help clinicians prevent drug interactions and improve patient management in our hospital.

CONCLUSIONS

In conclusion, drug interactions are still common in the HIV-infected population. Indeed, although the type of interactions has changed overtime, with different ARV and comedications involved, the number of PDDIs remains an important concern. This is likely going to get worse as the HIV-infected population ages, implying an increase in use of comedications. Our study also highlights the importance of reporting and considering complementary and alternative medicine as a potential source of PDDIs, notably with INIs, which now often constitute the basis of therapy.

Following the alarming results of this study, we have implemented an informatics program to detect PDDIs. Together, thanks to an optimization of comedications report, the number of PPDIs will hopefully decrease in the coming years.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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Patient consent. The design of the work has been approved by local ethical committees.

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