Received: 25 March 2020 | Revised: 8 July 2020 | Accepted: 13 July 2020

DOI: 10.1111/bcp.14491

ORIGINAL ARTICLE

Assessment of drug–drug interaction in an elderly human immunodeficiency virus population: Comparison of 3 expert databases

Anne-Lise Ruellan[1] | Delphine Bourneau-Martin[2] | Caroline Joyau[1] | Solène Secher[3] | Pascale Fialaire[5] | Hikombo Hitoto[6] | Sophie Leautez[7] | Christophe Michau[8] | Rémi Vatan[9] | Eric Billaud[3,4] | Marie Briet[2] | Pascale Jolliet[1] | François Raffi[4] | Clotilde Allavena[4]

[1]Department of Clinical Pharmacology. Institute of Biology, University Hospital, Nantes, France

[2]Department of Clinical Pharmacology. Institute of Biology, University Hospital, Angers, France

[3]COREVIH Pays de la Loire

[4]Department of Infectious Diseases, and CIC 1413, INSERM, University Hospital, Nantes, France

[5]Department of Tropical and Infectious Diseases, University Hospital, Angers, France

[6]Department of Tropical and Infectious Diseases, Hospital, Le Mans, France

[7]Department of Post-Emergency, Departmental Hospital, La Roche sur Yon, France

[8]Department of Polyvalent Medicine, Hospital, Saint-Nazaire, France

[9]Department of Polyvalent Medicine, Hospital, Laval, France

Correspondence
Anne-Lise Ruellan, Department of Clinical Pharmacology. Institute of Biology. University Hospital. Nantes, France.
Email: annelise.ruellan@chu-nantes.fr

Aims: Polypharmacy increase the risk of drug–drug interactions (DDIs) in the elderly population living with human immunodeficiency virus (HIV). Several expert databases can be used to evaluate DDIs. The aim of the study was to describe actual DDIs between antiretroviral drugs and comedications in an elderly population and to compare grading of the DDIs in 3 databases.

Methods: All treatments of HIV-infected subjects aged 65 years and older were collected in 6 French HIV centres. Summary of Product Characteristic (SPC), French DDI Thesaurus (THES), and Liverpool HIV DDI website (LIV) were used to define each DDI and specific grade. DDIs were classified in *yellow flag* interaction (undefined grade in SPC and THES or potential weak interaction in LIV), *amber flag* interaction (to be considered/precaution of use in SPC and THES and potential interaction in LIV) and *red flag* interaction (not recommended/contraindication in SPC and THES and do not administer/contraindication in LIV).

Results: Among 239 subjects included, 60 (25.1%) had at least 1 DDI for a total of 126 DDIs: 23/126 *red flag* DDIs were identified in 17 patients. All these 23 DDIs were identified in LIV. THES and SPC missed 6 and 1 *red flag* DDIs, respectively. Seven of 23 *red flag* DDIs were identified in the 3 databases concomitantly.

Conclusion: Polypharmacy is frequent in this elderly HIV population leading to DDI in a quarter of the subjects. The discrepancies between databases can be explained by differences in analysis methods. A consensus between databases would be helpful for clinicians.

KEYWORDS

drug interaction, drug safety, elderly, HIV/AIDS, pharmacovigilance

Anne-Lise Ruellan and Delphine Bourneau-Martin contributed equally

Principal investigator: The authors confirm that the principal investigator for this paper is Dr Clotilde ALLAVENA, she had direct clinical responsibility for patients.

1 | INTRODUCTION

In the general population, the prevalence of comorbidities and the related comedications increase in the ageing population and have been associated with a higher risk of adverse drug reactions, increased hospitalization rates, adherence issues, misuse and drug–drug interactions (DDI).[1–6] Available data from international studies show that the median age of people living with human immunodeficiency virus (HIV) is around 50 year-old with a life expectancy that tends to reach the general population.[7–9] In this context of ageing, comorbidities, such as cardiovascular disease, hyperlipidaemia, hypertension, diabetes, osteoporosis, renal disease and non-HIV-related cancer, are increasingly frequent with a prevalence that can be higher than in a non-HIV population.[4,10,11] Antiretroviral (ARV) drugs combined with comorbidities-associated comedications increases the risk of potentially serious DDIs, which can lead to drug toxicity, low efficacy of the comedication or virological failure.[12,13]

Polypharmacy has been defined as the concurrent use of 5 or more medications. Polypharmacy has been associated with an increased risk of prescribing errors, including, DDIs, the use of potentially inappropriate medications or dosage, the underuse of medications, or therapeutic duplication. Some therapeutic classes are prescribed more often in the elderly population, such as antihyperlipidaemic drugs, β-blockers or analgesic/antipyretics.[10,14] Elderly patients are 2 or 3 times more likely to develop an of adverse drug reaction compared to younger individuals.[15] For people living with HIV, DDIs are more frequent in the elderly population, because of a greater number of non-ARV drugs, in particular cardiovascular agents.[16] Several expert databases are used to evaluate DDI. The Liverpool drug interactions website (LIV) is the most commonly used in the HIV community. Meanwhile, according to countries, others databases are recommended such as French DDI Thesaurus (THES) and the summary of product characteristics (SPC) in France. Less known to the international medical community, THES data are defined by the Drug Interactions working group that was established by the French drug regulatory authorities in 1985.

In the context of the emergent geriatric HIV population at high risk of polypharmacy and related DDIs, the objectives of our study were to describe all relevant DDIs in a geriatric HIV population in 6 French HIV centres and to compare grading of DDIs in 3 different expert databases.

What is already known about this subject

- Comorbidities and polypharmacy increase the risk of drug–drug interactions (DDIs) between antiretrovirals and comedications in the elderly population living with human immunodeficiency virus (HIV).
- Several expert databases are used to evaluate these DDIs but some variations in grading of DDIs are observed in the elderly population living with HIV.

What this study adds

- Discrepancies of drug–drug interactions between antiretroviral drugs and comedications were observed when comparing 3 databases (Summary of Product Characteristic, the French DDI Thesaurus and the Liverpool HIV DDI website).
- Differences in methodologies within databases can explain the discrepancies of drug–drug interactions grades.

2 | METHODS

We carried out a cross-sectional study in the Pays de la Loire region, north-west of France. Between January 2017 and March 2017, patients living with HIV aged 65 years or older going for routine care in 1 of the 6 HIV clinic of Pays de la Loire (Nantes, Angers, La Roche-sur-Yon, Saint-Nazaire, Le Mans, Laval) were included after giving their written informed consent. All prescribed comedications and ARVs as well as the dosing were collected from medical prescriptions, following an update of the prescriptions made the day before the consultation. If patients had several HIV visits in the period, prescription at the first visit was retained. All data were collected from an electronic medical record Nadis® (Fedialis Medica, France. Copyright© 2017 Advanced Biological Laboratories S.A).[17] Prescriptions were analysed in 2 departments of Clinical Pharmacology (Nantes and Angers) using 3 expert databases: SPC, THES and LIV. Comedications and ARVs were classified according to the Anatomic Therapeutic Chemical classification. The analysis was restricted to DDI between ARVs and comedications.

According to SPC and THES, DDIs were classified into 6 grades. When DDI was dose-dependent, the dose of the substance potentially associated with a DDI was taken into account. Overall, we classified DDIs in 4 merged categories: *green flag* for no DDI (grade 0), *yellow flag* for grade 1* in SPC, THES and potential weak interaction in LIV, *amber flag* for grade 1 or 2 in SPC and THES and potential interaction in LIV and *red flag* interaction for grade 3 or 4 in SPC and THES and contraindication in LIV (Table 1). LIV introduces a system that categorizes the quality of evidence from high to very low in order to classify all DDIs. In our analysis, we selected only DDIs with a high or moderate quality of evidence in the LIV, excluding DDIs with a low or very low quality of evidence. The highest level of interactions among the 3 databases were chosen to define the global level of the interaction. All metabolic pathways were conformed to the IUPHAR/BPS Guide to Pharmacology nomenclature classification.[18]

For each patient, the following data were collected at the date of prescription: age, gender, body mass index, mode of HIV transmission, CDC stage C, duration of known HIV infection, duration of antiretroviral therapy (ART), plasma HIV RNA, nadir CD4 cell count and last

TABLE 1 Classification of the drug–drug interactions (DDI) in the 3 databases, number of patients and DDIs in each grade. SPC: Summary of Product Characteristics; THES: French drug–drug interactions; LIV: Liverpool HIV drug–drug interaction website

Grade	SPC	THES	LIV		Overall grade	Patients (n)	Total number of DDI	Number of different DDIS (n)
0	No DD					180	181	
1*	Undefined grade		1*	Potential weak interaction	*Yellow flag*	9	10	8
1	To be considered		1	Potential interaction	*Amber flag*	48	86	41
2	Precaution of use							
3	Not recommended		2	Do not administer contraindication	*Red flag*	17	30	23

CD4 cell count, creatinine clearance), current ART and comorbidities among hypertension, cardiac disorder, stroke, dyslipidaemia, neoplasia, diabetes, depression, osteoporosis, renal disease (defined as confirmed creatinine clearance <60 mL/min) and hepatic fibrosis (Table 2).

Data were analysed using SAS version 9.4. Continuous variables are presented as median and interquartile range and comparison between groups was made using Mann–Whitney test. Categorical variables are presented as frequencies (%) and group differences using χ^2 or Fisher tests with a level of significance at <.05.

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS guide to PHARMACOLOGY.[18]

3 | RESULTS

Of the 4174 patients living with HIV in care at the 6 centres, as of 1 January 2017, 9.7% were 65 years or older. From January to March 2017, 280 subjects aged 65 years and older were included in the study during a routine visit. Among them, 41 subjects were not on ART and/or not receiving comedication. Finally, 239 subjects (85.4%) on ART and receiving at least 1 comedication were selected for the DDI analysis.

Characteristics of the 239 patients are shown in Table 2. Overall, the median age of the subjects was 69 year (interquartile range: 67–73), 78.2% were male, 73.2% had at least 1 comorbidity, and 51.9% were receiving 5 comedications or more. They were on ART for a median duration of 16.7 years with an undetectable plasma HIV RNA in 89.1% of patients.

Compared to patients with no identified DDI, patients with at least 1 DDI, whatever the grade, were significantly more likely to be on a boost-including regimen (53.3 *vs* 13.4%), or on a dual therapy (41.7 *vs* 8.9%), and less likely to be on a triple regimen (53.3 *vs* 89.9%), were receiving more comedications (6 *vs* 4), had type 2 diabetes (25 *vs* 11.2%) and a higher body mass index (26.4 *vs* 24.4), (Table 2). Of these 239 patients, 60 (25.1%) presented a total of 126 ARV-comedication DDI corresponding to 72 different DDIs. Twenty three *red flag* DDIs were identified in 17 patients (31.9%), 41 *amber flag* DDIs (56.9%) in 48 patients and 8 *yellow flag* DDIs (11.1%) in 9 patients, respectively.

Among the 72 DDIs, booster (ritonavir or cobicistat) was involved in 25/72 DDIs (34.7%), protease inhibitor in 20/72 DDIS (27.8%), non-nucleoside reverse transcriptase inhibitor in 16/72 DDIs (22.2%), nucleoside reverse transcriptase inhibitor in 5/72 DDIs (6.9%) and integrase inhibitor in 6 DDIs (8.3%). The most frequent comedications involved in DDIs were lipid modifying agents (18%), antithrombotic agents (13.9%), calcium channel blockers (8.3%), drugs used in benign prostatic hypertrophy (5.5%), antiarrythmics (4.7%), drugs for peptic ulcer and gastro-oesophageal reflux disease (4.2%), and blood glucose lowering drugs (2.8%). Two DDIs corresponding to a potential DDI (*amber flag*) were associated with high doses of the comedication according to the referential data SPC and THES: metformin (1,000 mg twice daily) with dolutegravir; and aspirin (500 mg/d) with tenofovir. On the metabolic pathway, 68 (94.4%) DDIs were pharmacokinetic interactions whose 44 (61.1%) were associated with **cytochrome P450 3A4** (CYP3A4). Forty-six (63.9%) lead to a potential increase in plasma concentration of the comedication with a risk of toxicity and adverse event. Twenty (27.8%) could decrease the comedication efficacy and 6 (8.3%) could affect also the ARV efficacy. The most frequent relevant DDIs (n = 8, 11.1%) involved statins (atorvastatin, pravastatin, rosuvastatin) with boosted PI. The total number of DDIs in the 3 expert databases for each antiretroviral is shown in appendice, and the total number of DDIs for each antiretroviral according to the grading and the expert database is described in Figure 1.

There were no DDIs mentioned by SPC or THES that were not in LIV, 13 *red flag*, 42 *amber flag* and 8 *yellow flag* interactions except 5 DDIs (darunavir/lamotrigine, darunavir/levothyroxine, dolutegravir/sodium bicarbonate, etravirine/rosuvastatine, tenofovir/aspirin). In 6 cases, THES has identified no interaction while SPC and/or LIV identified a *red flag* DDI: cobicistat/budenoside, darunavir/amiodarone, elvitegravir-cobicistat/budenoside, etravirine/clopidogrel, ritonavir/amiodarone and ritonavir/flecainide. In 1 case, SPC identified no interaction while the association nevirapine/mianserine was considered as a *red flag* interaction in THES and *yellow flag* in LIV.

TABLE 2 Characteristics of the 239 patients on antiretroviral therapy (ART) and receiving at least 1 comedication and comparison of subjects with and without drug–drug interaction (DDI)

Characteristics Median (IQR) or *n* (%)	Total *n* = 239		No DDI *n* = 179		DDI*n* = 60		*P*
Age (y)	69	(67–73)	69	(67–73)	70	(67–74)	.59
Male	187	(78.2)	137	(76.5)	50	(83.3)	.27
Risk group							.98
MSM or bisexual	101	(42.3)	76	(42.5)	25	(41.7)	
Heterosexual	113	(47.3)	84	(46.9)	29	(48.3)	
Others/unknown	25	(10.5)	19	(1.6)	6	(10.0)	
Number of comorbidities	1	(0–2)	1	(0–2)	2	(1-3)	.07
At least 1 comorbidity	175	(73.2)	127	(7.9)	48	(80.0)	.17
Hypertension	82	(34.3)	61	(34.1)	21	(35.0)	.90
Cardiac disorder	71	(29.7)	49	(27.4)	22	(36.7)	.17
Stroke	20	(8.4)	16	(8.9)	4	(6.7)	.58
Dyslipidaemia	51	(21.3)	35	(19.6)	16	(26.7)	.24
Neoplasia	43	(18.0)	31	(17.3)	12	(20.0)	.64
Diabetes	35	(14.6)	20	(11.2)	15	(25.0)	.01
Depression	26	(10.9)	20	(11.2)	6	(10.0)	.80
Osteoporosis	21	(8.8)	16	(8.9)	5	(8.3)	.89
Renal disease	19	(7.9)	12	(6.7)	7	(11.7)	.22
Hepatic fibrosis	5	(2.1)	3	(1.7)	2	(3.3)	.44
CDC stage C	76	(31.8)	56	(31.3)	20	(33.3)	.77
Viral load < 50 copies/mL	213	(89.1)	161	(89.9)	52	(86.7)	.99
Duration of HIV infection (y)	18.3	(11.9–23.7)	18.3	(12.0–23.8)	18.2	(11.5–23.4)	.90
CD4/μL	627	(429–820)	623	(400–810)	654	(436–832)	.23
Nadir CD4/μL	205	(105–314)	206	(110–315)	188	(84–306)	.41
Body mass index (kg/m^2)	24.9	(22.8–27.2)	24.4	(22.2–26.8)	26.4	(23.5–28.3)	.05
Creatinine clearance (mL/min/1.73 m^2)	74	(61–90)	73	(61–87)	75	(59–95)	.89
Duration of ART (y)	16.7	(9.5–20.5)	16.4	(8.9–2.3)	17.2	(10.8–21.0)	.24
Number of ARV drugs	3	(3-3)	3	(3-3)	3	(3-4)	.14
Mono or dual therapy*	41	(17.1)	16	(8.9)	25	(41.7)	<.0001
Tritherapy	193	(80.8)	161	(89.9)	32	(53.3)	<.0001
2NRTIs + PI(b)	20	(8.4)	11	(6.1)	9	(15.0)	
2NRTIs + INSTI(b)	61	(25.5)	51	(28.5)	10	(16.7)	
2NRTIs + NNRTI(b)	101	(42.3)	91	(5.8)	10	(16.7)	
Others**	11	(4.6)	8	(4.5)	3	(5.0)	
ARV ≥ 4	5	(2.1)	2	(1.1)	3	(5.0)	.10
Boost-including regimen***	56	(23.4)	24	(13.4)	32	(53.3)	<.0001
Number of comedications	5	(2-7)	4	(2-6)	6	(3–8.5)	<.0001
Comedications ≥ 5	124	(51.9)	81	(45.3)	43	(71.7)	.0004

b = boost; IP = inhibitor protease; INSTI = integrase strand transfer inhibitor; IQR = interquartile range; MSM = men who have sex with men; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

*1IPb + 1 IE (*n* = 1); 1IPb + 1II (*n* = 14); 1 N + 1IPb (*n* = 3); 1NN + 1IPb (*n* = 3); 1NN + 1 IE (*n* = 1); 1NN + 1II (*n* = 17).

**1N + 1IP + 1II (*n* = 2); 1 N + 1NN + 1II (*n* = 2); 1 N + 1NN + 1IPb (*n* = 3); 1NN + 1IPb + 1II (*n* = 3); 1NN + 2IPb (*n* = 1).

***ritonavir or cobicistat.

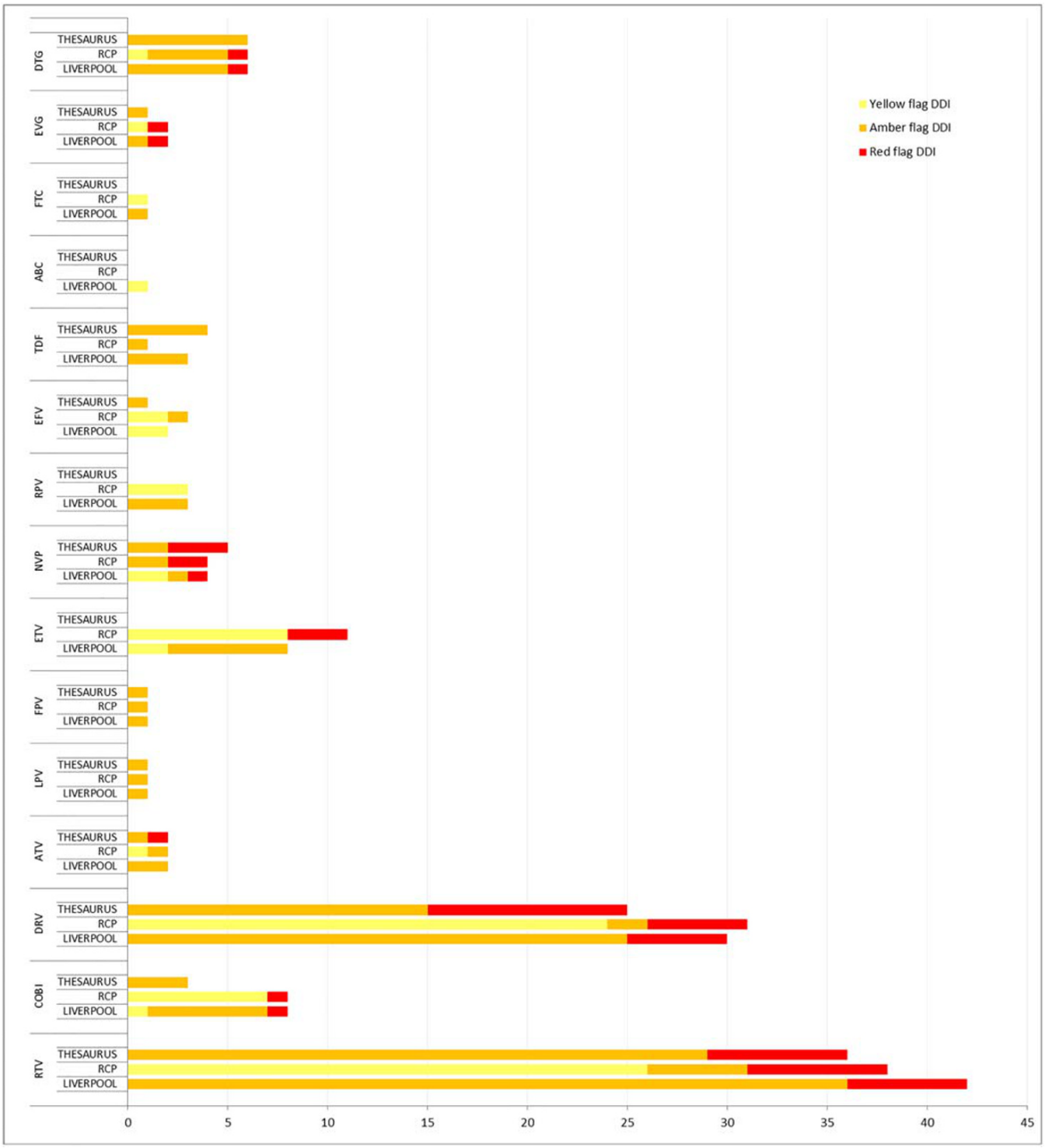

FIGURE 1 Total number of drug–drug interactions (DDIs) for each antiretroviral according to the grading and the expert database. DTG: dolutegravir; EVG: elvitegravir; FTC: lamivudine; ABC: abacavir; TDF: tenofovir disoproxil; EFV: efavirenz; RPV: rilpivirine; NVP: nevirapine; ETV: etravirine; FPV: fosamprenavir; LPV: lopinavir; ATV: atazanavir; DRV: darunavir; COBI: cobicistat; RTV: ritonavir

The 23 *red flag* interactions detected in at least 1 of the 3 databases are detailed in Table 3. The highest level of interaction was concomitantly identified in the 3 databases in only 4/23 cases: darunavir/alfuzosine; darunavir/ticagrelor; ritonavir/alfuzosine; and ritonavir/ticagrelor.

4 | DISCUSSION

In our study, which evaluated 239 HIV-infected patients aged of 65 years and older, a quarter of them (n = 60) had at least 1 identified DDI and almost a third (17/60) included a *red flag* DDI, which means a

TABLE 3 Detail of the 23 *red flag* drug–drug interactions, metabolic pathway, clinical risk and grading in the 3 databases. SPC: summary of product characteristics; THES: French drug–drug interactions; LIV: Liverpool HIV drug–drug interaction website. Metabolic pathways conform to the IUPHAR/BPS guide to PHARMACOLOGY nomenclature classification[18] (CYP: cytochrome P450 family; P-gp: P-glycoprotein)

ARV	Comedication	Metabolic pathway	Clinical risk	RCP	THES	LIV	*n*
Atazanavir	Atorvastatin	CYP3A4	Rhabdomyolysis/myopathy	2	3	1	1
Cobicistat	Budesonide	CYP3A4	Cushing syndrome	3	0	2	1
Darunavir	Alfuzosin	CYP3A4	Hypotension	4	4	2	2
Darunavir	Amiodarone	CYP3A4	Cardiac arrhythmias	4	0	2	1
Darunavir	Apixaban	CYP3A4/ P-gp	Haemorrhage	3	3	2	1
Darunavir	Atorvastatin	CYP3A4	Rhabdomyolysis/myopathy	1*	3	1	2
Darunavir	Ciclosporin	CYP3A4	Nephrotoxicity	1*	3	1	1
Darunavir	Colchicine	CYP3A4/ /P-gp	Gastrointestinal disorders	1*	3	1	1
Darunavir	Tamsulosin	CYP3A4/ CYP2D6	Decrease in tamsulosin efficacy	1*	3	1	2
Darunavir	Ticagrelor	CYP3A4	Haemorrhage	4	4	2	1
Dolutegravir	Carbamazepine	CYP3A4	Decrease in dolutegravir efficacy	3	2	2	1
Elvitegravir/cobicistat	Budesonide	CYP3A4	Cushing syndrome	3	0	2	1
Etravirine	Clopidogrel	CYP2C19	Decrease in clopidogrel efficacy	3	0	1	3
névirapine	Ketoconazole	CYP3A4	Decrease in ketoconazole efficacy and increase in nevirapine efficacy	3	4	2	1
Nevirapine	Mianserin	CYP2D6/ CYP3A4	Decrease in mianserin efficacy	0	3	1*	1
Nevirapine	Sertraline	CYP2B6/ CYP3A4	Decrease in sertraline efficacy	3	3	1*	1
Ritonavir	Alfuzosin	CYP3A4	Hypotension	4	4	2	2
Ritonavir	Amiodarone	CYP3A4	Cardiac arrhythmias	4	0	2	1
Ritonavir	Apixaban	CYP3A4/P-gp	Haemorrhage	3	3	2	1
Ritonavir	Colchicine	CYP3A4/P-gp	Gastrointestinal disorders	4	3	1	1
Ritonavir	Flecainide	CYP2D6	Cardiac arrhythmias	4	0	2	1
Ritonavir	Tamsulosin	CYP3A4/ CYP2D6	Hypotension	1*	3	1	2
Ritonavir	Ticagrelor	CYP3A4	Haemorrhage	4	4	2	1

contraindication. Our study found a higher rate of contraindications compared with studies focused on ageing population living with HIV, for which the rate varies from 3 to 8%, which can be partly explain by the high frequency of polypharmacy. As reported in previous studies, overall risk of DDIs was associated with receiving 5 comedications or more, being on a boost-including antiretroviral regimen, diabetes.[19,20] The most frequent antiretroviral-associated DDIs involved statins, antithrombotic agents, antihypertensives, drugs used in benign prostatic hypertrophy, blood glucose-lowering drugs, PPIs and antiarrythmics.[20,21] DDIs with antidepressant, hypnotic or sedative were not identified in our study, contrary to other studies.[18,22–24] Since higher number of DDIs was reported in the presence of a boost, main DDI concerned pharmacokinetic mechanism, including CYP3A4, which can affect the efficacy of comedication and increase its toxicity. The prescribed doses were known and checked in relation to the context of risk of potential DDI, allowing us to identify in 2 cases doses potentially at risk for such comedications: aspirin and metformin. According to our results, pravastatin, finasteride or aspirin should be the preferred drugs within their class, given their favourable safety data (not metabolized by **P450 cytochrome**), in the management of the elderly patient.

We conducted this study according to a rigorous method, taking into account the different grades of the 2 French reference databases, and those of the University of Liverpool website. This approach has allowed us to highlight some disparities for some of the identified DDIs that were not uniformly categorized across the 3 guidelines.

Several studies evaluating DDI in HIV infected population have recently been published but to our knowledge, few have compared different databases. Molas *et al*. previously reported out some discrepancies in grading of DDIs between the website of the University of Liverpool, the Food and Drug Administration and Toronto database and showed, for example, that quetiapine administered with PIs is contraindicated in the LIV, whereas it requires strict monitoring in the Food and Drug Administration product insert and Toronto database.[22] Similar observations were discussed in other studies, 1 comparing 100 drug interaction pairs involving psychiatric drugs, using

6 commercial DDI databases (3 requiring subscription and 3 open access)[23] and another comparing 2 DDI databases (Micromedex and Drugs.com), in a referral hospital for infectious diseases in Rio de Janeiro, showing that the agreement between the databases regarding the severity rating was only 68.3%.[24] Despite efforts to improve the basis or criteria for DDI evidence selection of DDI evidence, there is no broadly accepted standard for defining DDI risk.[23] When assessment of DDIs is compared between electronic database and clinician' assessment, there is a large discrepancy in number and relevance of detected DDIs, with overlap as low as 11% in some cases .[25]

In our study, all *red flag* DDIs were identified in LIV, but only 13/23 (56.5%) at the highest grade, among which THES missed 6/23 (26.1%) DDIs. Only 4 contraindications were identified in the 3 databases concomitantly at the highest grade. The discrepancies between grading in the 3 databases might be challenging from a clinical point of view and for patient's management. This could have several explanations: sources of DDIs information, analysis method and the date of update, that differ within the 3 databases. The date of update is not precisely known for the LIV and the SPC. THES recommendations and associated arguments are established and updated twice a year by the experts of the Drug interaction working group. Clinical pharmacologists evaluate data from in vitro, pharmacokinetic, pharmacodynamic, clinical and epidemiological studies as well as isolated cases published or extracted from the National Pharmacovigilance Database. They set the grade of contraindication according to specific characteristics, such as significant, described or potentially serious clinical events, i.e. those that are likely to cause or increase adverse reactions, or lead, by reducing activity, to less effective treatment. Since 1985, SPC has been an official document in France and has become an opposable standard with regard to a 3-step argumentation: the ethical cascade, the validation by the administrative authority in charge of public health, and finally the fact that the SPC is an annex to the Marketing Authorization, being the subject of a publication in the official journal of the French Republic, giving it an enforceable character. French SPC and THES base their recommendations on clinical data and a national approach. However, LIV is used by clinicians all over the world, is clinically relevant, reliable, comprehensive and available in several languages among them a French version. The site is regularly and frequently updated and uses evidence-based DDI resource. Information relates only to known or suspected effects of interacting medications and is based on relevant data in the public area, but interpretation is in some cases based only on pharmacological data. Recently clinical advice was added to provide or suggest alternative treatment in case of contraindicated association. THES systematically offers advice associated with the interaction, whereas this is rarely the case in the European SPC. Finally, these observations could disturb clinicians if they search potential DDIs in several databases with more or less discordant interpretation when they face therapeutic choices that can potentially lead to toxicity or loss of efficacy. As recently mentioned by Back[26] and Burger *et al.*,[27] a single reference system or a consensus would be helpful and facilitate the interpretation of specific data to consider DDIs. A multidisciplinary approach should be considered to collect the different practices on potential DDI identification. Since recent data were obtained with LIV, our results raise a new issue of data interpretation by using 2 additional reference databases that can be opposable to date in France.[28]

Our study has some strengths and limitations. Limitations are the small size of our population and the cross-sectional design in which data were analysed from 3 databases over a period given. Reference databases could have been updated with identification of new DDI that have not been taken into account in the analysis. For example, a new DDI between clopidogrel and ritonavir or darunavir has recently been added to LIV (risk of decreased clopidogrel response and considered as a contraindication). This interaction was experienced in 4 patients in our study. Another example is the combination cobicistat/budesonide, in 1 patient, whose DDI has recently been added in the new version of THES (May 2018). Furthermore, we did not analyse interactions between non-ARV comedications and we did not collect over-the-counter medication/dietary supplement/phytotherapy that may be involved in significant interactions. The number of DDIs is probably underestimated, as with other studies.[15,19,20,29,30] In addition, our study was based on drug prescription and we are not certain whether drugs were actually taken by patients. At least, even if none of these interactions was clinically significant, clinical adverse events were not collected in our study. Despite these limitations, a strength of the study is that the analysis of the DDIs was done by substance, allowing us to give details on the type and level of the interaction, unlike previous studies, which were analysed by Anatomic Therapeutic Chemical classification. Our study is among the first highlighting the potential discrepancies between the different available reference databases to identify DDI in a vulnerable population, the elderly HIV population.

In conclusion, our study confirms the frequency of interactions between ARVs and comedications in this elderly population. The comparison of 3 expert databases showed discrepancies and highlights the need to find a consensus between the different databases to facilitate drug prescriptions, to simplify interpretation of DDI and the related therapeutic recommendations for physicians caring for ageing individuals living with HIV.

ACKNOWLEDGEMENTS

The authors are grateful for patients who accepted to participate to the study, all members of Corevih Pays de La Loire (E. Billaud, A. Boumier; Nantes: F. Raffi, O. Aubry, C. Bernaud, M. Besnier, C. Biron, B. Bonnet, S. Bouchez, D. Boutoille, C. Brunet, C. Deschanvres, B. Gaborit, O. Grossi, N. Hall, T. Jovelin, M. Lefebvre, P. Morineau-Le Houssine, S. Pineau, P. Point, V. Reliquet, F. Sauser, H. Hue, A. Soria, M. Cavellec; Angers: P. Abgueguen, V. Delbos, V. Rabier, J.-M. Turmel, Y.-M. Vandamme, S. Rehaiem; Le Mans: S. Blanchi, N. Crochette, L. Perez, N. Qatib; La Roche sur Yon: O. Bollengier-Stragier, J.-L. Esnault, T. Guimard, D. Merrien, M. Morrier, P. Perré, L. Laine; Saint Nazaire: J. Brochard, C. Grand-Courault); pharmacy students (R. Balestra, C. Chas, B. Morin, C. Dorleans, L. Pommier, S. Dauve, C. Pepion, A. Perpoil, and P. Chapron); and B. Saint Salvi, member of DDI expert group of the National Agency for the Safety of Medicines and Health Products.

COMPETING INTERESTS

there are no competing interests to declare.

CONTRIBUTORS

Anne-Lise Ruellan, Delphine Bourneau-Martin, Caroline Joyau: study design, data analysis, pharmacological expertise and writing. Solène Secher: data analysis and writing. Pascale Fialaire, Hikombo Hitoto, Sophie Leautez, Christophe Michau, Rémi Vatan, Eric Billaud: patient inclusion. Marie Briet: pharmacological expertise. Pascale Jolliet: pharmacological expertise. François Raffi: infectious disease expertise. Clotilde Allavena: study design, data analysis, infectious disease expertise and writing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Anne-Lise Ruellan https://orcid.org/0000-0003-4036-1882
Marie Briet https://orcid.org/0000-0003-3738-5998

REFERENCES

1. Nozza S, Malagoli A, Maia L, et al. Antiretroviral therapy in geriatric HIV patients: the GEPPO cohort study. *J Antimicrob Chemother*. 2017; 72(10):2879-2886.
2. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis*. 2011;53(11):1120-1126.
3. Hentzien M, Dramé M, Allavena C, et al. Impact of age-related comorbidities on five-year overall mortality among elderly HIV-infected patients in the late HAART era--role of chronic renal disease. *J Nutr Health Aging*. 2016;20(4):408-414.
4. Guaraldi G, Malagoli A, Calcagno A, et al. The increasing burden and complexity of multi-morbidity and polypharmacy in geriatric HIV patients: a cross sectional study of people aged 65–74 years and more than 75 years. *BMC Geriatr [Internet]*. 2018;18(1):99. https://doi.org/10.1186/s12877-018-0789-0
5. Livio F, Marzolini C. Prescribing issues in older adults living with HIV: thinking beyond drug-drug interactions with antiretroviral drugs. *Ther Adv Drug Saf*. 2019;10. https://doi.org/10.1177/2042098619880122
6. Greene M, Steinman MA, McNicholl IR, Valcour V. Polypharmacy, drug-drug interactions, and potentially inappropriate medications in older adults with human immunodeficiency virus infection. *J Am Geriatr Soc*. 2014;62(3):447-453.
7. Morillo-Verdugo R, Blanco Ramos JR, Abdel-Kader Martín L, Álvarez de Sotomayor M. The challenge of aging and pharmacoterapeutic complexity in the HIV + patient. *Farm Hosp Organo Expresion Cient Soc Espanola Farm Hosp*. 2018;42(3):120-127.
8. Gueler A, Moser A, Calmy A, et al. Life expectancy in HIV-positive persons in Switzerland: matched comparison with general population. *AIDS Lond Engl*. 2017;31(3):427-436.
9. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS ONE*. 2013;8(12):e81355.
10. Kong AM, Pozen A, Anastos K, Kelvin EA, Nash D. Non-HIV comorbid conditions and polypharmacy among people living with HIV age 65 or older compared with HIV-negative individuals age 65 or older in the United States: a retrospective claims-based analysis. *AIDS Patient Care STDS*. 2019;33(3):93-103.
11. Allavena C, Hanf M, Rey D, et al. Antiretroviral exposure and comorbidities in an aging HIV-infected population: the challenge of geriatric patients. *PLoS ONE*. 2018;13(9):e0203895.
12. Marzolini C, Back D, Weber R, et al. Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother*. 1 sept 2011;66(9):2107-2111.
13. Nachega JB, Hsu AJ, Uthman OA, Spinewine A, Pham PA. Antiretroviral therapy adherence and drug–drug interactions in the aging HIV population. *AIDS*. 2012;26:S39-S53.
14. Gimeno-Gracia M, Crusells-Canales MJ, Armesto-Gómez FJ, Compaired-Turlán V, Rabanaque-Hernández MJ. Polypharmacy in older adults with human immunodeficiency virus infection compared with the general population. *Clin Interv Aging*. 2016;11:1149-1157.
15. Nolan L, O'Malley K. Prescribing for the elderly. Part I: sensitivity of the elderly to adverse drug reactions. *J Am Geriatr Soc*. 1988;36(2): 142-149.
16. Tseng A, Szadkowski L, Walmsley S, Salit I, Raboud J. Association of age with Polypharmacy and Risk of drug interactions with antiretroviral medications in HIV-positive patients. *Ann Pharmacother*. 2013; 47(11):1429-1439.
17. Nadis® Fedialis Medica, France. Copyright© 2017 Advanced Biological Laboratories S.A.
18. Alexander SP, Kelly E, Marrion N. The concise guide to PHARMACOLOGY 2015/16: overview: the concise guide to PHARMACOLOGY 2015/16: overview. *Br J Pharmacol*. et al., 2015;172(24): 5729-5743.
19. Jakeman B, Nasiri M, Ruth L, Morse C, Mahatme S, Patel N. Comparing the frequencies of contraindicated drug-drug interactions between differing antiretroviral regimens in HIV-infected patients. *Ann Pharmacother*. 2017;51(5):365-372.
20. Iniesta-Navalón C, Franco-Miguel JJ, Gascón-Cánovas JJ, Rentero-Redondo L. Identification of potential clinically significant drug interactions in HIV-infected patients: a comprehensive therapeutic approach. *HIV Med*. 2015;16(5):273-279.
21. Bastida C, Grau A, Márquez M, et al. Polypharmacy and potential drug-drug interactions in an HIV-infected elderly population. *Farm Hosp Organo Expresion Cient Soc Espanola Farm Hosp*. 1 sept 2017; 41(5):618-624.
22. Molas E, Luque S, Retamero A, et al. Frequency and severity of potential drug interactions in a cohort of HIV-infected patients identified through a multidisciplinary team. *HIV Clin Trials*. 2018;19(1):1-7.
23. Monteith S, Glenn T. A comparison of potential psychiatric drug interactions from six drug interaction database programs. *Psychiatry Res*. 2019;275:366-372.
24. Ramos GV, Guaraldo L, Japiassú AM, Bozza FA. Comparison of two databases to detect potential drug-drug interactions between prescriptions of HIV/AIDS patients in critical care. *J Clin Pharm Ther*. 2015;40(1):63-67.
25. Roblek T, Vaupotic T, Mrhar A, Lainscak M. Drug-drug interaction software in clinical practice: a systematic review. *Eur J Clin Pharmacol*. 2015;71(2):131-142.
26. Back D. 21st international workshop on co-morbidities and adverse drug reactions in HIV. *Antivir Ther*. 2019;24(Suppl 1):A1-A112.
27. Burger DM, Smolders EJ, Schapiro J, Drenth JPH, Back DJ. A call for a consortium for optimal Management of Drug–Drug Interactions in patient care. *Clin Pharmacol Ther*. 2017;102(3):391-394.
28. Naves O, Deysson M, Buxeraud J. Le résumé des caractéristiques du produit au cours du temps. Wwwem-Premiumcomdatarevues05153700v55i553S0515370015005029 [Internet]. 4 févr 2016 [cité 30 sept 2019]; Disponible sur: https://www.em-premium.com/article/1029942?redirectTo=EM
29. López-Centeno B, Badenes-Olmedo C, Mataix-Sanjuan Á, et al. Polypharmacy and drug–drug interactions in people living with human immunodeficiency virus in the region of Madrid, Spain: a population-

based study. *Clin Infect Dis*. 2020;71(2):353-362. https://doi.org/10.1093/cid/ciz811

30. Ranzani A, Oreni L, Agrò M, et al. Burden of exposure to potential interactions between antiretroviral and non-antiretroviral medications in a population of HIV-positive patients aged 50 years or older. *JAIDS J Acquir Immune Defic Syndr*. 2018;78(2):193-201.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Ruellan A-L, Bourneau-Martin D, Joyau C, et al. Assessment of drug–drug interaction in an elderly human immunodeficiency virus population: Comparison of 3 expert databases. *Br J Clin Pharmacol*. 2020; 1–9. https://doi.org/10.1111/bcp.14491