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Discrepancies in grading of drug-drug interactions in an elderly HIV population using three different expert databases

P30

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Introduction

Comorbidities and polypharmacy have been associated with adverse drug reactions, misuse and drug-drug interactions (DDI) with an increasing risk in the elderly population living with HIV. Different expert databases can be used to evaluate DDIs with sometimes divergent interpretations that complicate therapeutic management.

Objective

To describe DDIs between antiretrovirals (ARVs) and co-medications in an elderly HIV-population and to compare analyses and interpretations between 3 accessed databases.

Materials and Methods

- **Retrospective multicentric study**
- During a routine visit of a patient living with HIV (PlwHIV) and aged of 65 year-old and more, all the prescriptions (ARV and co-medications) were collected from the electronic medical report Nadis®.
- 6 HIV centers in the COREVIH Pays de la Loire participated : Nantes, Angers, Le Mans, La Roche sur Yon, Laval and Saint Nazaire.
- Two Regional Center of Pharmacovigilance (Nantes and Angers) analyzed the prescriptions and validated the identified DDIs.
- **Three reference database were consulted :**

►Summary of European and National Product Characteristics (SPCs)

►National Thesaurus of DDIs of the French National Agency Medicines Health Products Safety (ANSM) (September 2016 version) (THES)

►Liverpool Drug Interactions Database (LIV) (https://www.hiv-druginteractions.org/)

To identify each interaction and define the DDI, a score was assigned based on the level of DDI in each database (see Table 1).

- DDIs were classified in :
  - "**yellow flag**" interaction (undefined grade in SPC and THES or potential weak interaction in LIV),
  - "**amber flag**" interaction (grade 1 or 2 in SPC and THES and grade 1 in LIV),
  - "**red flag**" interaction (grade 3 or 4 in SPC and THES and grade 2 in LIV).

Results

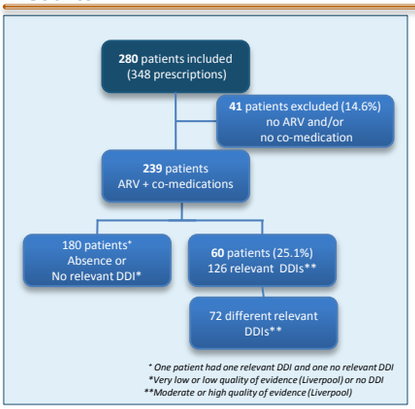

Figure 1 : Flow-chart of the 280 PlwHIV aged of 65 year-old and over included in the study.

Table 1 - DDI level according to the reference database

SPC & THES (ANSM)	LIV	Overall Level	Patients (n)	DDI (n)	DDI type (n)
0 No DDI	0 No DDI		180	181	-
1* Undefined grade	1* Potential weak interaction	"Yellow flag"	9	10	8
1 To be considered 2 Precaution of use	1 Potential Interaction	"Amber flag"	48	86	41
3 Not recommended 4 Contraindication	2 Do not administer	"Red flag"	17	30	23

Among 239 patients included :
- 23 « **red flag** » were identified in 17 patients
- 41 « **amber flag** » DDIs in 48 patients
- 8 « **yellow flag** » DDIs in 9 patients.

23 « red flag » (31.9%) DDIs with at least one contraindication in at least one of the 3 databases (table 3) :
- The metabolic pathway is pharmacokinetic for all these DDIs, included 21 (91.3 %) associated with CYP3A4
- 17 (73.9%) may increase the comedication toxicity (renal, muscular, cardiac ou vascular)
- 7 (30.4%) could modify the comedication or ARV efficacy

Figure 2 presents the total number of DDIs and the grade in the 3 databases for each ART whatever the involved comedication.
The most frequent relevant DDIs involve statins (atorvastatin, pravastatin, rosuvastatin) and boosted inhibitor protease (n=8, 11.1%)
The highest grade DDIs were mostly identified with ritonavir, cobicistat, darunavir, and nevirapine in the 3 expert databases.

Some disparities were highlighted within the 3 databases (table 3) :
- The highest grade was identified concomitantly in the 3 databases in 4/23 cases
- All 23 red flags DDIs have been identified in LIV but only 13/23 (57%) at the highest grade. Respectively THES and SPC missed 6 and 1 "red flags" DDIs

Table 2: Characteristics of the 239 patients on ART and receiving at least one comedication and comparison of subjects with and without DDI

Characteristics median (IQR) or n (%)	Total n=239	No DDI n=179	DDI n=60	p
Age (yr)	69 (67-73)	69 (67-73)	70 (67-74)	0.59
Males	187 (78.2)	137 (76.5)	50 (83.3)	0.27
Risk group				0.98
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 (10.6)	6 (10.0)	
Comorbidities	1 (0-2)	1 (0-2)	2 (1-3)	0.07
At least 1 comorbidity	175 (73.2)	127 (70.9)	48 (80.0)	0.17
Arterial hypertension	82 (34.3)	61 (34.1)	21 (35.0)	0.90
Cardiac disorder	71 (29.7)	49 (27.4)	22 (36.7)	0.17
Stroke	20 (8.4)	16 (8.9)	4 (6.7)	0.58
Dyslipidemia	51 (21.3)	35 (19.6)	16 (26.7)	0.24
Neoplasia	43 (18.0)	31 (17.3)	12 (20.0)	0.64
Diabete	35 (14.6)	20 (11.2)	15 (25.0)	0.01
Depression	26 (10.9)	20 (11.2)	6 (10.0)	0.80
Osteoporosis	21 (8.8)	16 (8.9)	5 (8.3)	0.89
Renal failure	19 (7.9)	12 (6.7)	7 (11.7)	0.22
Hepatic fibrosis	5 (2.1)	3 (1.7)	2 (3.3)	0.44
CDC stage C	76 (31.8)	56 (31.3)	20 (33.3)	0.77
Viral load < 50 copies/ml	213 (89.1)	161 (89.9)	52 (86.7)	0.99
Duration of HIV (yrs)	18.3 (11.9-23.7)	18.3 (12.0-23.8)	18.2 (11.5-23.4)	0.90
CD4/mm3	627 (429-820)	623 (400-810)	654 (436-832)	0.23
Nadir CD4/mm3	205 (105-314)	206 (110-315)	188 (84-306)	0.41
BMI (kg/m2)	24.9 (22.8-27.2)	24.4 (22.2-26.8)	26.4 (23.5-28.3)	0.05
MDRD (ml/min/1.73m2)	74 (61-90)	73 (61-87)	75 (59-95)	0.89
Duration of ART (yrs)	16.7 (9.5-20.5)	16.4 (8.9-20.3)	17.2 (10.8-21.0)	0.24
Number of ARV drugs	3 (3-3)	3 (3-3)	3 (3-4)	0.14
Mono or dual therapy	41 (17.1)	16 (8.9)	25 (41.7)	<0.0001
Tritherapy	193 (80.8)	161 (89.9)	32 (53.3)	<0.0001
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 (50.8)	10 (16.7)	
Others**	11 (4.6)	8 (4.5)	3 (5.0)	
ARV≥4	5 (2.1)	2 (1.1)	3 (5.0)	0.10
Boost-including regimen***	56 (23.4)	24 (13.4)	32 (53.3)	<0.0001
Number of comedications	5 (2-7)	4 (2-6)	6 (3-8.5)	<0.0001
Comedications ≥ 5	124 (51.9)	81 (45.3)	43 (71.7)	0.0004

b=boost, II = integrase inhibitor, INSTI = Integrase Strand Transfert 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+1IE (n=1) ; 1IPb+1II (n=14) ; 1N+1IPb (n=3) ; 1NN+1IPb (n=3) ; 1NN+1IE (n=1) ; 1NN+1II (n=17).
**1N+1IP+1II (n=2) ; 1N+1NN+1II (n=2) ; 1N+1NN+1IPb (n=3) ; 1NN+1IPb+1II (n=3) ; 1NN+2IPb (n=1).
***ritonavir or cobicistat

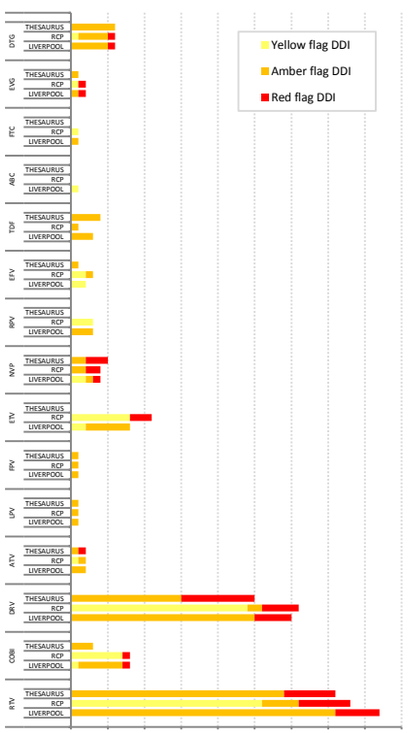

Figure 2 : Total number of DDIs for each antiretroviral according to the grading and the expert database

Table 3 : Detail of the 23 "red flag" DDIs , metabolic pathway, clinical risk and grading in the 3 databases

ARV	Comedication	Metabolic pathway	Clinical risk	RCP	THES	LIV	n
atazanavir	atorvastatin	3A4	Rhabdomyolysysis/myopathy	2	3	1	1
cobicistat	budesonide	3A4	Cushing's syndrome	3	0	2	1
darunavir	alfuzosin	3A4	Hypotension	4	4	2	2
darunavir	amiodarone	3A4	Cardiac arrhythmias	4	0	2	1
darunavir	apixaban	3A4/Pgp	Hemorrhage	3	3	2	1
darunavir	atorvastatin	3A4	Rhabdomyolysysis/myopathy	1*	3	1	2
darunavir	ciclosporin	3A4	Nephrotoxicity	1*	3	1	1
darunavir	colchicine	3A4/Pgp	Gastro-intestinal disorders	1*	3	1	1
darunavir	tamsulosin	3A4/2D6	Decrease tamsulosin efficacy	1*	3	1	2
darunavir	ticagrelor	3A4	Hemorrhage	4	4	2	1
dolutegravir	carbamazepine	3A4	Decrease dolutegravir efficacy	3	2	2	1
elvitegravir/ cobicistat	budesonide	3A4	Cushing's syndrome	3	0	2	1
etravirine	clopidogrel	2C19	Decrease clopidogrel efficacy	3	0	1	3
nevirapine	ketoconazole	3A4	Decrease ketoconazole efficacy and increase nevirapine efficacy	3	4	2	1
nevirapine	mianserin	2D6/3A4	Decrease mianserin efficacy	0	3	1*	1
nevirapine	sertraline	2B6/3A4	Decrease sertraline efficacy	3	3	1*	1
ritonavir	alfuzosin	3A4	Hypotension	4	4	2	2
ritonavir	amiodarone	3A4	Cardiac arrhythmias	4	0	2	1
ritonavir	apixaban	3A4/Pgp	Hemorrhage	3	3	2	1
ritonavir	colchicine	3A4/Pgp	Gastro-intestinal disorders	4	3	1	1
ritonavir	flecainide	2D6	Cardiac arrhythmias	4	0	2	1
ritonavir	tamsulosin	3A4/2D6	Hypotension	1*	3	1	2
ritonavir	ticagrelor	3A4	Hemorrhage	4	4	2	1

Discussion / Conclusion

- **The 239 PlwHIV aged of 65 year-old and more included in the study were receiving a median of 3 ARVs and 4 comedications, 25 % of them had at least one DDI and 7% (17/239) had a "red flag" interaction.**
- Compared to patients with no identified DDI, patients with at least one DDI (whatever the grade), were significantly more often on a boost-including ART (53.3% vs 13.4%), or on dual therapy (41.7% vs 8.9%) and had a diabetes mellitus (25% vs 11.2%) and a higher BMI (26.4% vs 24.4%).
- Our study found a higher rate of contraindications compared with previous published studies : 5% to 6.6% (1-3)
- As reported in previous studies, overall risk of DDIs was associated with high number of comedications (≥5), a boost-including ART (ritonavir or cobicistat) and diabetes (4-5)
- Our study has some limitations : no analysis of DDI between co-medications, no data on DDI-related clinical events, no data on OTC drugs . Referencial books and databases are regularly updated and new DDIs may not have been taken into account in our analysis : for example, the DDI clopidogrel/ritonavir or darunavir has been recently added in the Liverpool Drug Interaction as a contraindication.
- The discrepancies between grading in the 3 databases has some explanations : source of DDI information, method of analysis and date of update are different.
- French SPC and Thesaurus base their recommendations on clinical data with a national approach.
- Liverpool is clinically useful, reliable, comprehensive and available in different languages. The interpretation is mainly based on pharmacological data. The most recent version give clinical advice and implied for alternative medication.
- The disparity of information in the different databases makes the analysis and interpretation of potential DDIs complex.

Our study confirms the high frequency of DDIs between ARV and comedications in the elderly population living with HIV, but highlights the need to find a consensus to optimize the use of the different expert databases to simplify the interpretation of DDIs and the official national recommendations.

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