High frequency of polypharmacy and drug-drug interactions in an elderly HIV population on antiretroviral therapy

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Introduction

Co-morbidities and polypharmacy are frequent in the aging population and have been associated with increased risk of adverse drug reactions (ADRs) and drug-drug interactions (DDIs). Few data are available on DDIs between antiretrovirals (ARVs) and co-medications in an elderly HIV population.

Objective

To describe all significative DDIs identified between ARVs and co-medications in the elderly HIV population (≥ 65 years).

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 Departments of Clinical Pharmacology (Nantes and Angers) analyzed all the prescriptions and validated all the identified DDIs.
- **Three reference database were consulted :** the Summary of European and National Product Characteristics (SPCs), the National Thesaurus of DDIs of the French National Agency Medicines and Health Products Safety (ANSM) (September 2016 version) and the Liverpool Drug Interactions Database. To identify each interaction and define the DDI, a score was assigned based on the level of DDI (see Table 1). Significant DDI correspond to all DDIs identified in the SPCs and the Thesaurus, and those within the Liverpool Drug Interactions associated with a moderate or high level of evidence (low and very low evidence levels were not considered significant).

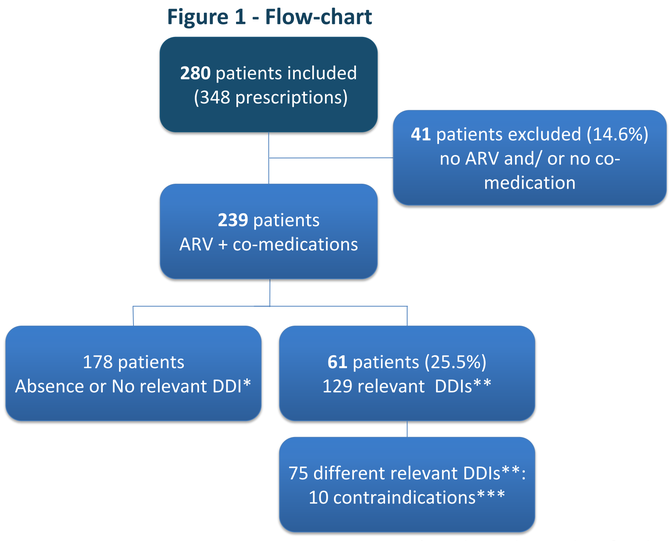
Table 1 - DDI level according to the reference database

	SPC	Thesaurus (ANSM)	Liverpool Drug Interactions	
-1	Undefined grade	Undefined grade	-1	Undefined grade
0	No DDI	No DDI	0	No DDI
1	To be considered	To be considered	1	Potential Interaction
2	Precaution of use	Precaution of use		
3	Not recommended	Not recommended	2	Contraindication
4	Contraindication	Contraindication		

Results

- **From the 1st of January to the 31st of March 2017, 280 PlwHIV aged of 65 year-old and over participated to the study.**
- **41 patients were excluded because of the absence of ARVs and/or co-medication.**
- **Overall 239 prescriptions (ARV + co-medications) were analyzed.**

Figure 1 - Flow-chart



*Very low or low quality of evidence (Liverpool) or no DDI
**Moderate or high quality of evidence (Liverpool)
***Level 4 (RCP/Thesaurus) or 2 (Liverpool)

Table 2 – Characteristics of the 239 patients on ARVs + co-medications

Median or %	Total n=239	No DDI n=178	DDI n=61	p
Male	78.2	77.0	82.0	0.41
Age (years)	69	70	70	0.65
CDC stage C	31.8	30.9	34.4	0.61
HIV Infection duration (years)	18.3	18.4	18.1	0.98
HIV transmission				0.94
Heterosexual	47.3	46.6	49.2	
MSM*	42.3	42.7	41.0	
Others	10.5	10.7	9.8	
HIV VL < 50 copies/ml	96.4	96.4	96.3	0.99
CD4/mm^3	627	625	643	0.35
Nadir CD4/mm^3	205	209	181	0.33
BMI (kg/m^2)	24.9	24.4	26.3	0.07
MDRD (ml/min/1.73m^2)	74	73	76	0.83
Co-medications (n)	5	4	7	**<0.0001**
Comedications ≥ 5	51.8	45.5	70.5	**0.0007**
Co-morbidities	1	1	2	0.06
At least one co-morbidity	74.1	71.9	80.3	0.20
Cardiovascular disease	39.8	37.6	45.9	0.25
High blood pression	34.3	34.3	34.4	0.98
Dyslipidemia	21.3	19.7	26.2	0.28
Neoplasia	18.4	17.4	21.3	0.50
Diabetes	14.6	11.2	24.6	0.01
Depression	10.9	11.2	9.8	0.76
Osteoporosis	8.8	9.0	8.2	**0.04**
Renal Insufficiency	8.0	6.7	11.5	0.24
Hepatic fibrosis	2.1	1.1	4.9	0.11

* Men who have sex with men

Median or %	Total n=239	No DDI n=178	DDI n=61	p
ARV duration (years)	16.7	16.4	16.8	0.29
ARV (n)	3	3	3	0.15
Monotherapy (INSTI, bPI)	0.8	1.1	0	
Bitherapy*	16.3	7.9	41	
Tritherapy	80.8	89.9	54.1	
2NRTIs + PI(b)	8.4	5.6	16.4	
2NRTIs + INSTI(b)	25.5	28.7	16.4	
2NRTIs + NNRTI	42.3	51.1	16.4	
Others**	4.6	4.5	4.9	
ARV ≥ 4	2.1	1.1	4.9	
Boost-including regimen (Ritonavir or cobicistat)	23.5	13.5	52.2	**<0.0001**

* bPI+MVC (n=1) ; bPI+INSTI (n=14) ; NRTI+bPI (n=3) ; NNRTI+bIP (n=3) ; NNRTI+MVC (n=1) ; NNRTI+INSTI (n=17)
** NRTI+bPI+INSTI (n=2) ; NRTI+NNRTI+INSTI (n=2) ; NRTI+NNRTI+bPI (n=3) ; NNRTI+bPI+/-1INSTI (n=4)

- **129 relevant DDIs :**
  - 10 (9%) contraindications (Table 3)
  - 125 (97%) pharmacokinetic DDIs (65.9 % associated with CYP3A4)
  - 85 (66%) affect the comedication efficiency
  - 75 (58%) may cause toxicity (renal, muscular, cardiac ou vascular)
- **The most frequent DDIs :**
  - statins (atorvastatin, pravastatin ou rosuvastatin) and boost (ritonavir/cobicistat) : 34 (26%) (Table 4).

Table 3 - CI and clinical risk : 10 pharmacokinetic DDIs identified in 7 patients.

ARV	Co-medication	n	Clinical risk	DDI	Referential
Ritonavir	Ticagrelor	1	Hemorrhage	CYP3A4	SPC-THES-LIV
	Alfuzosine	2	Severe hypotension	CYP3A4	SPC-THES-LIV
	Amiodarone	1	Cardiac arrythmia	CYP3A4	SPC-LIV
	Flecainide	1	Cardiac arrythmia	CYP2D6	SPC-LIV
Darunavir	Ticagrelor	1	Hemorrhage	CYP3A4	SPC-LIV
	Alfuzosine	2	Severe hypotension	CYP3A4	SPC-LIV
	Amiodarone	1	Cardiac arrythmia	CYP3A4	SPC-LIV
Elvitegravir	Budesonide	1	Cushing Syndrom	CYP3A4	LIV
Cobicistat	Budesonide	1	Cushing Syndrom	CYP3A4	LIV
Nevirapine	Ketoconazole	1	Ketoconazole inefficacy	CYP3A4	THES-LIV

SPC : Summary of Product Characteristics ; LIV : Liverpool Drug Interactions; THES : Thesaurus Drug Interactions; CI : Contraindications

Figure 2 - ARV (a) and co-medications (b) associated with identified relevant DDI among 61 patients (according to ATC system – level 3)

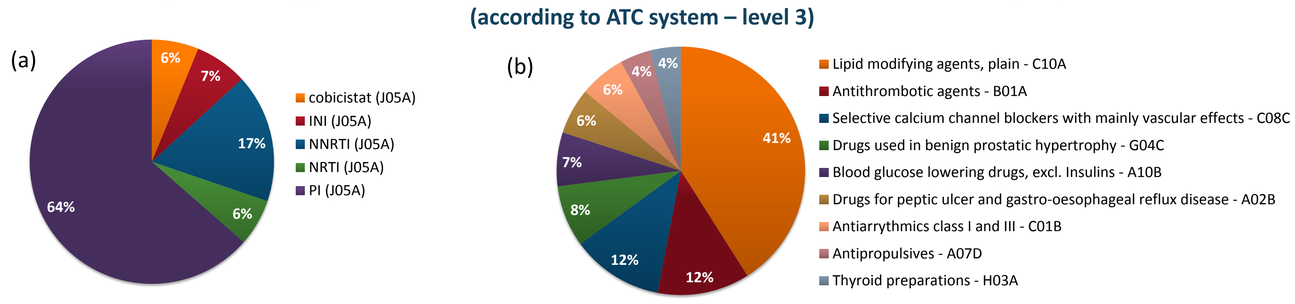


Table 4 – Major relevant DDIs identified in > 1 patient.

ARV	Co-medication	DDI type	Clinical risk	Level OF DDI RCP	THES	LIV
Ritonavir	Rosuvastatine	Pharmacokinetic 3A4	Lactic acidosis	2	2	1 (very low)
	Tamsulosine	Pharmacokinetic 3A4/2D6	Hypotension	3	3	0
	Amlodipine	Pharmacokinetic 3A4	Hypotension	2	2	1 (very low)
	Loperamide	Pharmacokinetic 3A4	QT lengthering	0	0	1 (moderate)
	Levothyroxine	Pharmacokinetic UGT	Decrease efficacy of levothyroxine	2	2	1 (very low)
Darunavir	Alfuzosine	Pharmacokinetic 3A4	Hypotension	4	4	2 (moderate)
	Atorvastatine	Pharmacokinetic 3A4	Rhabdomyolysis/myopathy	3	3	1 (very low)
	Pravastatine	Pharmacokinetic 3A4	Rhabdomyolysis/myopathy	-1	0	1 (very low)
	Alfuzosine	Pharmacokinetic 3A4	Hypotension	4	4	2 (very low)
	Atorvastatine	Pharmacokinetic 3A4	Rhabdomyolysis/myopathy	1	1	1 (moderate)
	Levothyroxine	Pharmacokinetic UGT	Decrease efficacy of levothyroxine	2	2	0
	Tamsulosine	Pharmacokinetic 3A4/2D6	Hypotension	3	3	1 (very low)
	Rosuvastatine	Pharmacokinetic 3A4	Rhabdomyolysis/myopathy	2	2	1 (moderate)
	Amlodipine	Pharmacokinetic 3A4	Hypotension	2	2	1 (very low)
Cobicistat	Verapamil	Pharmacokinetic 3A4	Cardiac arrythmia	2	2	1 (very low)
	Metformine	Pharmacokinetic OCT2/MATE-1	Lactic acidosis	2	0	1 (very low)
Etravirine	Rosuvastatine	Pharmacokinetic 2C9	Decrease efficacy of rosuvastatin	-1	0	0
	Amiodarone	Pharmacokinetic 3A4	Decrease efficacy of amiodarone	2	0	1 (very low)
	Clopidogrel	Pharmacokinetic 2C19	Decrease efficacy of clopidogrel	0	0	1 (very low)
Rilpivirine	Antacids	Pharmacokinetic pH	Decrease efficacy of rilpivirine	2	2	1 (very low)
Tenofovir disoproxil	Valaciclovir	Pharmacodynamic	Increased renal toxicity	2	1	1 (very low)
Dolutegravir	Metformine	Pharmacokinetic OCT2/MATE-1	Lactic acidosis	2	2	1 (very low)

Discussion/Conclusion

- **Of the 239 PlwHIV aged of 65 year-old and more** receiving a median of 3 ARVs and 4 co-medications, **25 % of them had at least one DDI.**
- **75 different relevant DDIs** were identified including 10 contraindications.
- **6 of the 10 contraindications are associated with a boost (ritonavir or cobicistat).**
- Our results are similar with previous published studies (1-5) : high frequency of DDIs with the boost-including ARV regimens, most frequent DDIs are pharmacokinetic DDIs (mostly CYP3A4).
- Our study has some limitations : no analysis of DDI between co-medications, no data on DDI-related clinical events, OTC drugs were not collected
- 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. In our study, 4 patients were treated with clopidogrel and ritonavir and/or darunavir and these prescriptions were not considered as DDIs in our study.
- The disparity of information in the different referentials makes the analysis and interpretation of potential DDIs complex.

Key message

- It is important **to collect all co-medications** in addition to antiretrovirals and **to look for potential DDIs.**
- Some therapeutic classes are more frequently prescribed in the elderly HIV population, such as urological agents (alfuzosin, tamsulosin), and must be considered to be potential DDI with ARV.
- As far as possible, **the prescription of boost (ritonavir/cobicistat) must be avoided in the aging HIV population with comorbidities** to limit the risk of DDIs and subsequent potential related clinical events.

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