Polypharmacy in HIV and HCV patients: not only drug interactions

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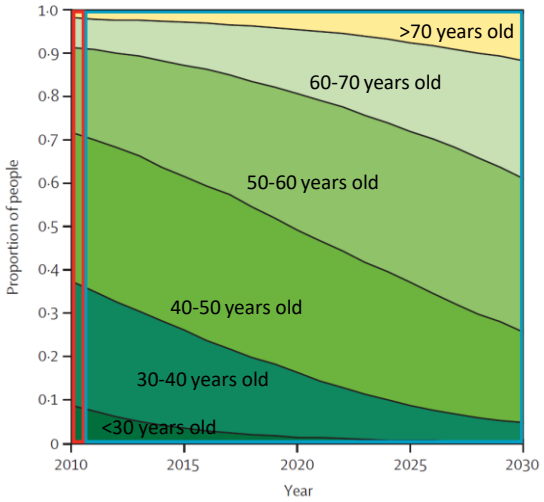
Aging of HIV population: model projections

Age distribution and number of PLWH with ≥ 3 comorbidities

Netherlands

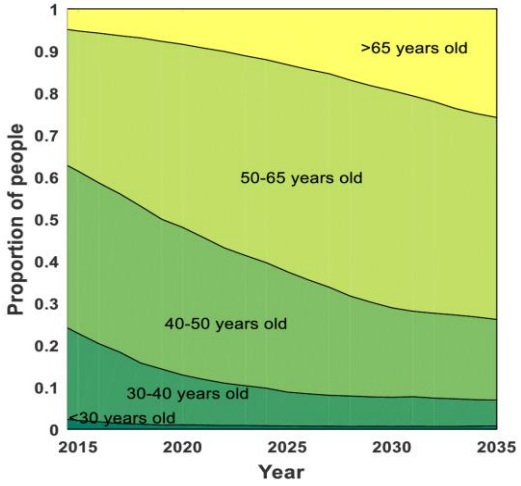


By 2030

39% pts > 60 years old

28% pts ≥ 3 comorbidities

USA

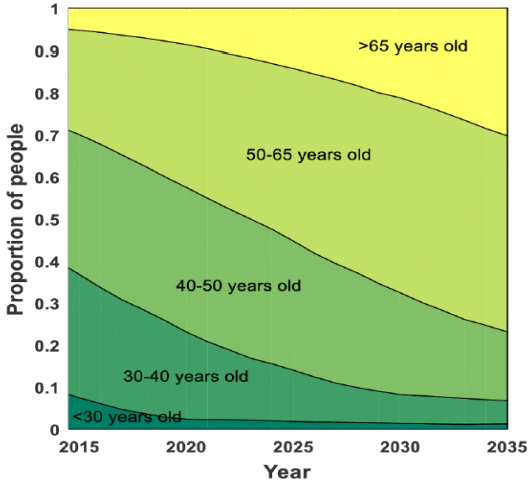


By 2035

27% pts > 65 years old

44% pts ≥ 3 comorbidities

Italy



By 2035

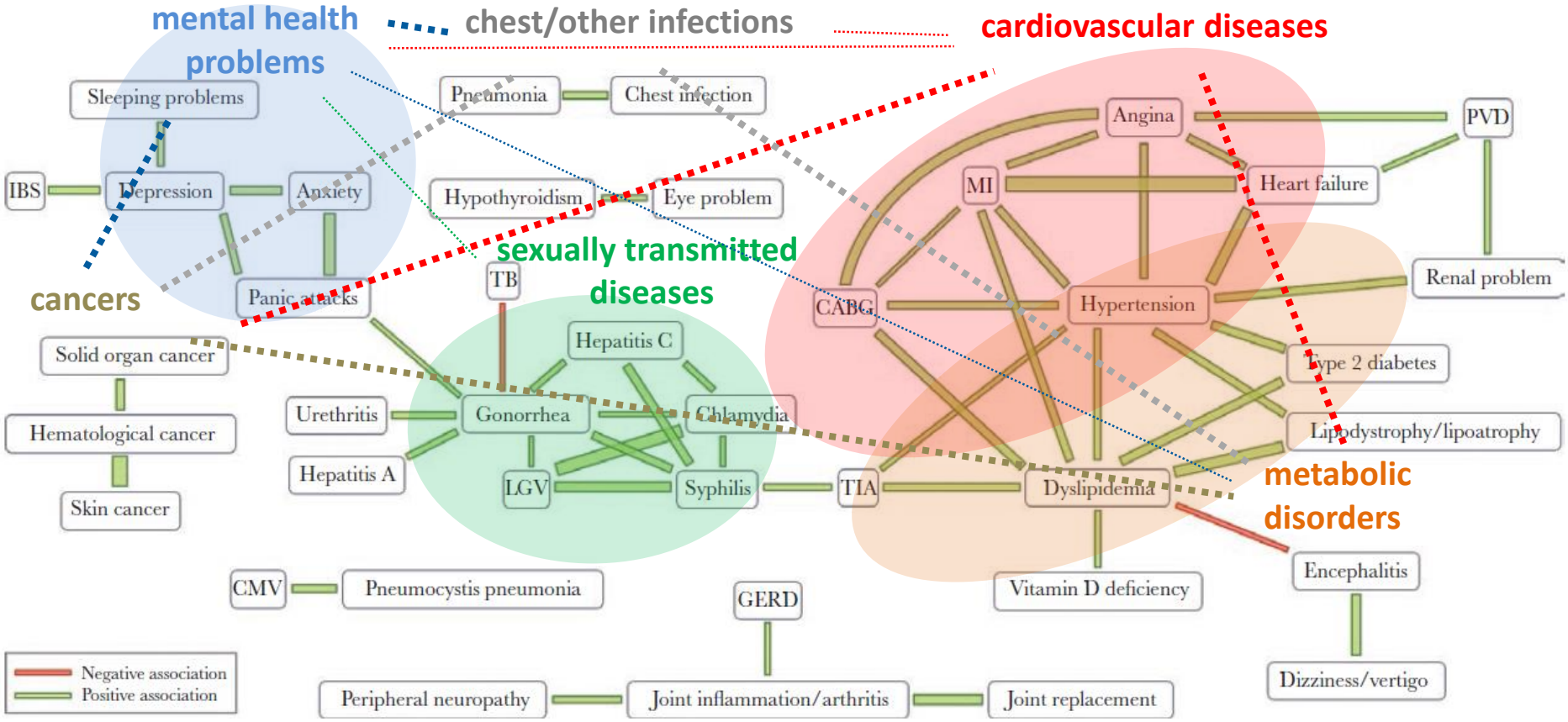
29% pts > 65 years old

29% pts ≥ 3 comorbidities

Smit M et al. Lancet Infect Dis 2015; Smit M et al. PLoS One 2017

Patterns of co-occurring comorbidities in PLWH

Study included 1073 PLWH (mean age 52 years) from the POPPY cohort



- Comorbidities co-occur in specific patterns
- Better understanding how comorbidities cluster together would enable the development of targeted interventions and guidelines addressing specifically the needs of PLWH with multiple comorbidities

De Francesco D et al. Open Forum Infect Dis 2018

Clusters of diseases impact the extent of polypharmacy

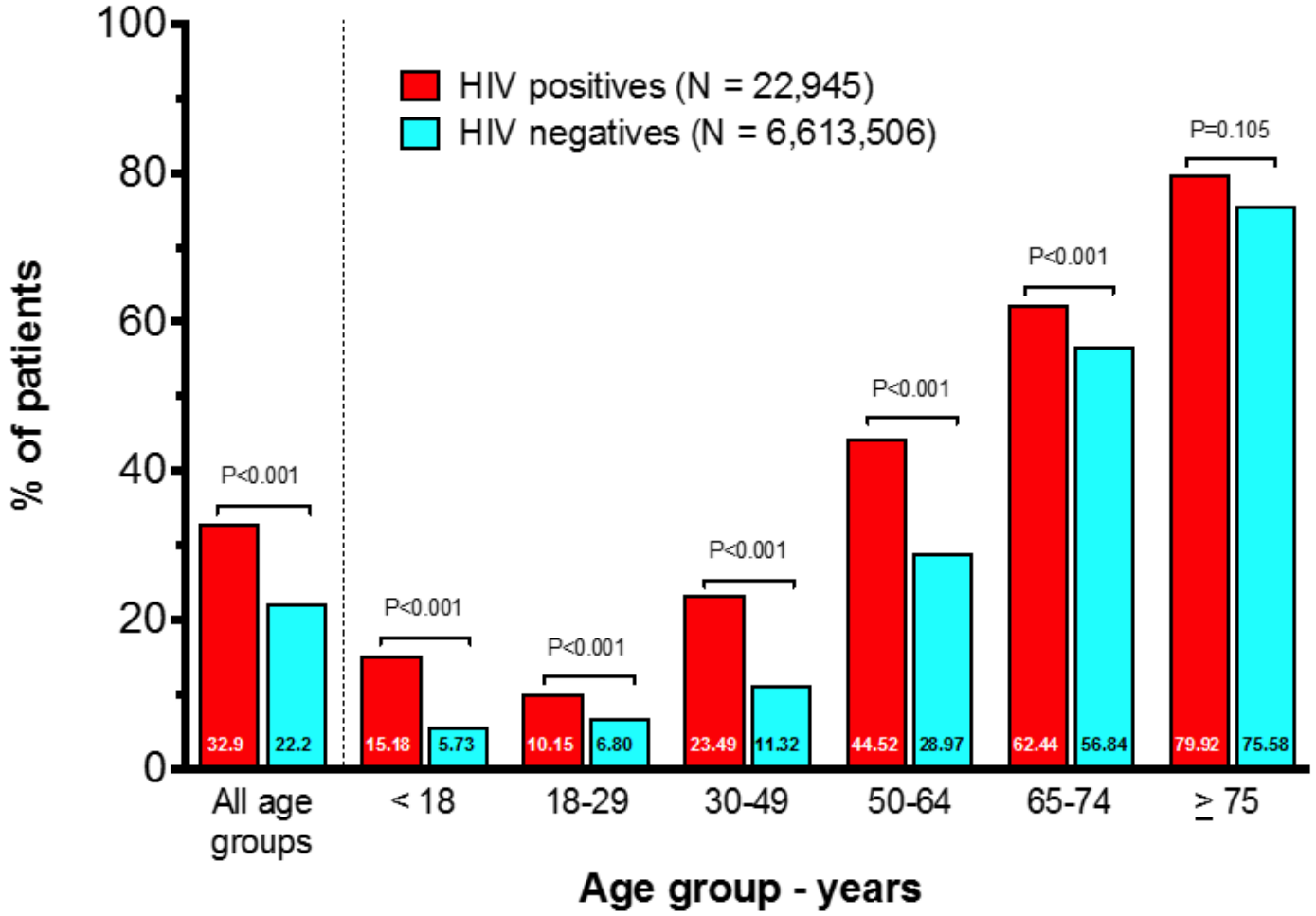
Study included 1155 uninfected individuals aged ≥ 65 years from several Italian hospitals

Clusters of diseases	Mean nb drugs	Odds Ratios for polypharmacy
Diabetes + Coronary heart disease + Cerebrovascular dis.	8.3	9.8
Diabetes + Coronary heart disease	8.7	5.8
Heart failure + Atrial fibrillation	7.6	5.5
Thyroid dysfunction + Atrial fibrillation	7.4	5.0
COPD + Coronary heart disease	8.3	4.1
Hypertension + dyslipidemia	7.1	3.7
Heart failure + COPD	8.7	3.7
Diabetes + Cerebrovascular disease	7.4	3.2
Diabetes + dyslipidemia	7.9	2.8
Diabetes + Chronic renal failure	8.3	2.7
Hypertension + Diabetes	7.7	2.4
Hypertension + Cardiovascular Diseases	6.7	2.3
Heart failure + Chronic renal failure	8.2	2.2
Gastric + Gastro-intestinal diseaes	7.1	1.8
Arthritis + dementia	5.7	0.9

Nobili A et al. Eur J Int Med 2011

Polypharmacy in PLWH and uninfected individuals

Prevalence of polypharmacy (≥ 5 non-HIV drugs) across age groups in a Spanish cohort

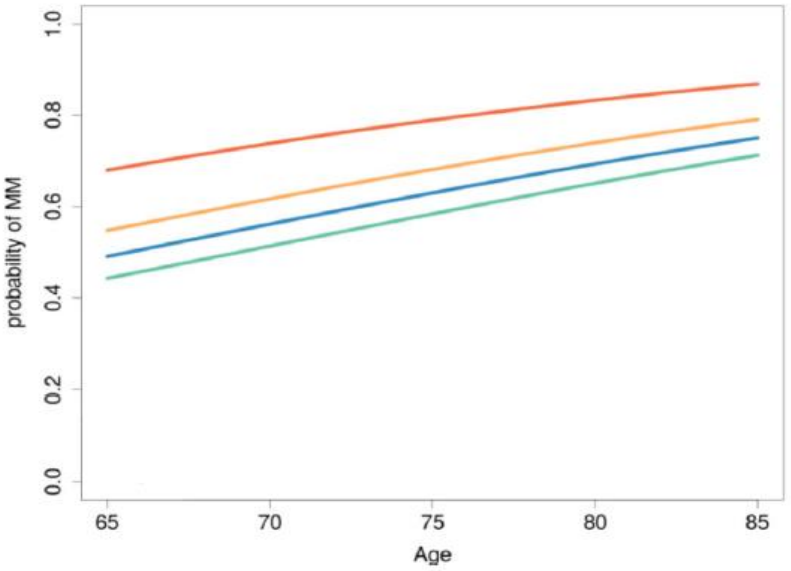


Lopez-Centeno B et al. Glasgow HIV Conference 2018

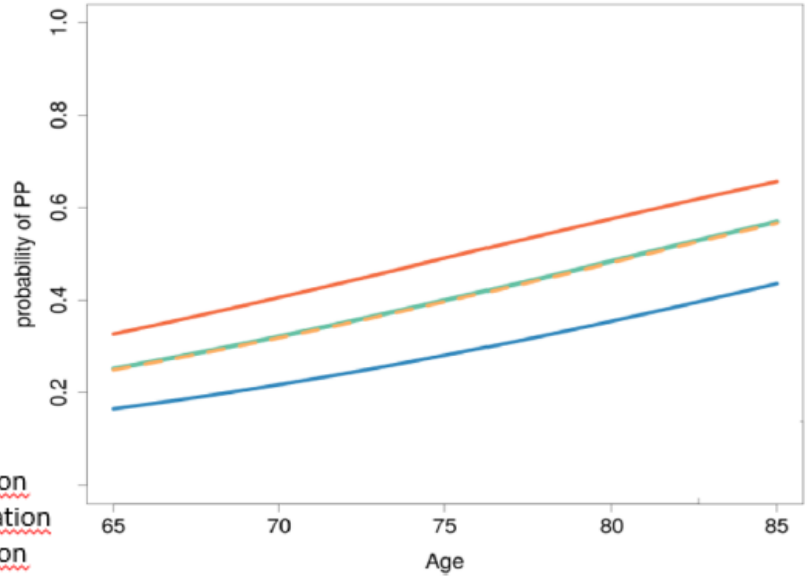
Comorbidities & polypharmacy and duration of HIV infection

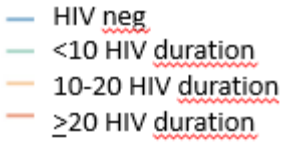
Study included 1158 PLWH aged ≥ 65 years and 315 uninfected elderly from the GEPPO cohort (prospective multicentric italian cohort including elderly individuals)

Risk of multimorbidity



Risk of polypharmacy





Overall, the prevalence of comorbidities in elderly PLWH vs uninfected elderly is comparable. However, individual comorbidities such as dyslipidemia, chronic kidney disease, diabetes were more prevalent in PLWH with a longer duration of HIV infection compared to uninfected individuals which could be attributed to metabolic toxicities of ARV.
Risk of multimorbidity and polypharmacy related to longer duration of HIV infection.

Guaraldi G et al. BMC Geriatrics 2018

Prevalence of polypharmacy in PLWH

Reference	Country	N	Age	Nb comeds / person	Polypharmacy
Livio F et al. Int Work Clin Pharm HIV 2018	Switzerland	111	≥ 75	**5** (3-8)	**60 %**
Guaraldi G et al. BMC Geriatr 2018	Italy	1258	≥ 65	NA	**37 %**
Justice A et al. AIDS 2018	USA	1311	≥ 65	NA	**43 %**
Nunez-Nunez M et al. Farm Hosp 2018	Spain	242	≥ 50	NA	**48 %**
Ssonko M et al. BMC Geriatr 2018	Uganda	411	≥ 50	NA	**15 %**
Mc Nicholl I et al. Pharmacotherapy 2017	USA	248	≥ 50	**11** (± 6)	**94 %**
Krentz H et al. AIDS Pat Care STDS 2016	Canada	386	≥ 50	NA	**43 %**
Greene M et al. J Am Geriatr Soc 2014	USA	89	≥ 60	**8** (4-14)	**74 %**
Holtzman C et al. J Gen Intern Med 2013	USA	1312	≥ 50	NA	**54 %**

Consequences of polypharmacy in elderly PLWH

Adverse drug reactions

Morbidity

Hospitalization

Mortality

Prescribing cascade

Falls

Geriatric syndrome

Cognitive decline

Nonadherence

Limited health literacy

Side effects

High pill burden

Size tablet

Complex dosing regimens

Health belief

Neurocognitive impairment

Drug-drug and drug-disease interactions

Drug toxicity

Lack of efficacy

Aggravation existing condition

Inappropriate prescribing

Errors

Inappropriate medications

Adverse drug reactions

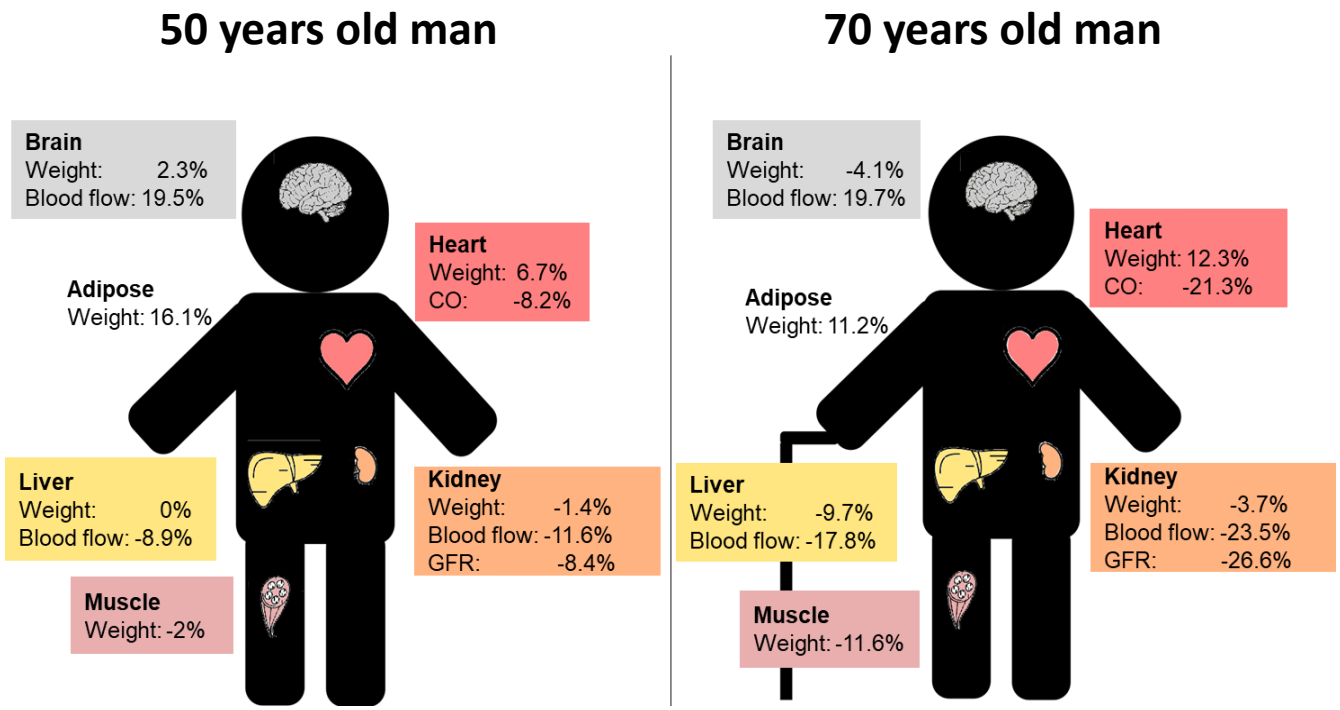
Hospitalization

Prescribing cascade

↑ costs

Shah B et al. Clin Geriatr Med 2012, Gellad WF et al. Am J Geriatr Pharmacother 2011

Age associated physiological changes



all data are relative to 30 years old man

Progressive decline in physiological parameters important for drug disposition is noted with age. The «pharmacological» age cut-off for elderly is difficult to define because it is not known when these changes affect drug pharmacokinetics significantly. Lack of studies correlating changes in physiological parameters to drug pharmacokinetics.

Stader F et al. Clin Pharmacokinet 2018

68-year old woman

Admitted in September 2016 to emergency room: lost balance, fell and broke arm.
Reports repetitive falls since the summer.

At admission: BP: 102/69 mmHg, heartbeat: normal
eGFR: 71 ml/min/1.73m^2
glucose, electrolytes, liver parameters: normal
several recent and old bruises, slight confusion

Medical history	**Treatment**
• 2010: HIV infection	**raltegravir** (400 mg BID) + **FTC** (200 mg QD) + **TDF** (300 mg QD) VL: undetectable, CD4: 467 cells/mm^3
• 2013: hyperlipidemia	**rosuvastatin** (5 mg QD)
• 2015: depression	**amitriptyline** (50 mg QD)
• Jun 2016: hypertension	**amlodipine** (10 mg QD)
• Jul 2016: ankle oedema	**furosemide** (20 mg QD)
• Aug 2016: overactive bladder	**tolterodine** (4 mg QD)
• Sept 2016: xerostomia, constipation	**anetholtrithion** (25 mg TID) and **sterculia** (875 mg BID)

What is the most probable explanation for the recurrent falls?

Drug-drug interactions with antiretroviral therapy

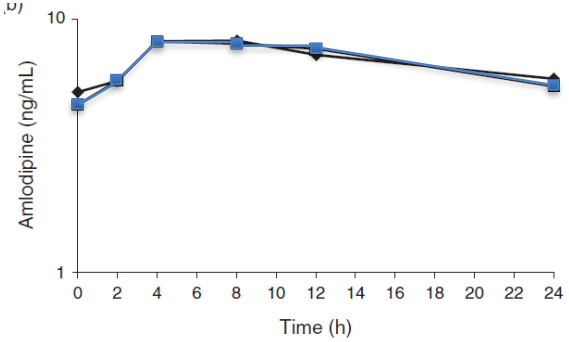
- **Raltegravir:** UGT1A1 metabolism, no inhibitory effects on CYPs or UGTs
- **Emtricitabine** and **tenofovir**: renal elimination, no inhibitory effects on transporters
- **Furosemide**: renal elimination, weak inhibitor of OAT1
- **Amlodipine**: CYP3A4 metabolism

furosemide

No Interaction Expected	No Interaction Expected	Potential Weak Interaction
Raltegravir	Emtricitabine (FTC)	Tenofovir-DF
Furosemide	Furosemide	Furosemide

amlodipine

No Interaction Expected	No Interaction Expected	No Interaction Expected
Raltegravir	Emtricitabine (FTC)	Tenofovir-DF
Amlodipine	Amlodipine	Amlodipine

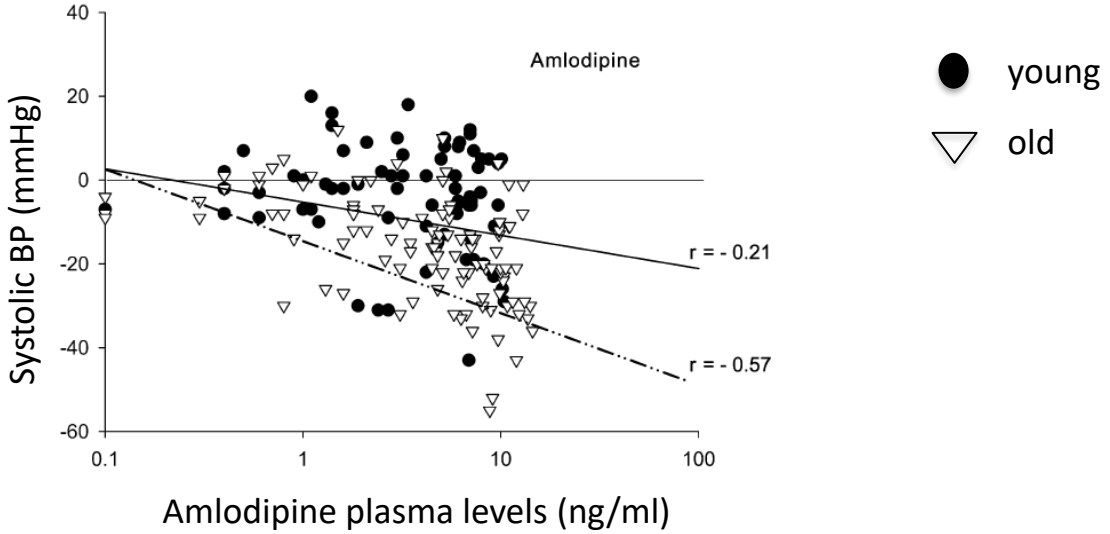


amlodipine + raltegravir
amlodipine alone

Singh G et al. AIDS 2014, www.druginteractions.org

Pharmacodynamics of drugs in elderly

Effect of age on amlodipine pharmacodynamics



- Amlodipine pharmacodynamics significantly impacted by age: more pronounced decrease in systolic BP in elderly compared to young.
- Age affects regulation of physiological processes (arterial baroreflex function), elderly are also more prone to thiazide induced orthostatic changes

there are some other issues….

Leenen FH et al. J Cardiovasc Pharmacol 2010

Drugs with anticholinergic effects and adverse effects in elderly

… the patient is taking several drugs with anticholinergic properties: amitriptyline and tolterodine

- Anticholinergic drugs are considered as inappropriate for use in elderly.
- Elderly are more sensitive to adverse anticholinergic effects due to significant decrease in cholinergic receptors in the brain.
- Drugs with anticholinergic properties can impair cognition ➔ increase risk of falls, cause constipation, xerostomia, dizziness, blurred vision.

Use of Medications with Anticholinergic Activity and Self-Reported Injurious Falls in Older Community-Dwelling Adults

Kathryn Richardson, PhD,[ab] Kathleen Bennett, PhD,[c] Ian D. Maidment, PhD,[de] Chris Fox, MD,[f] David Smithard, MD,[gh] and Rose Anne Kenny, MD[ai]

J Am Geriatr Soc 2015

Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis

Kimberley Ruxton,[1] Richard J. Woodman[2] & Arduino A. Mangoni[1]

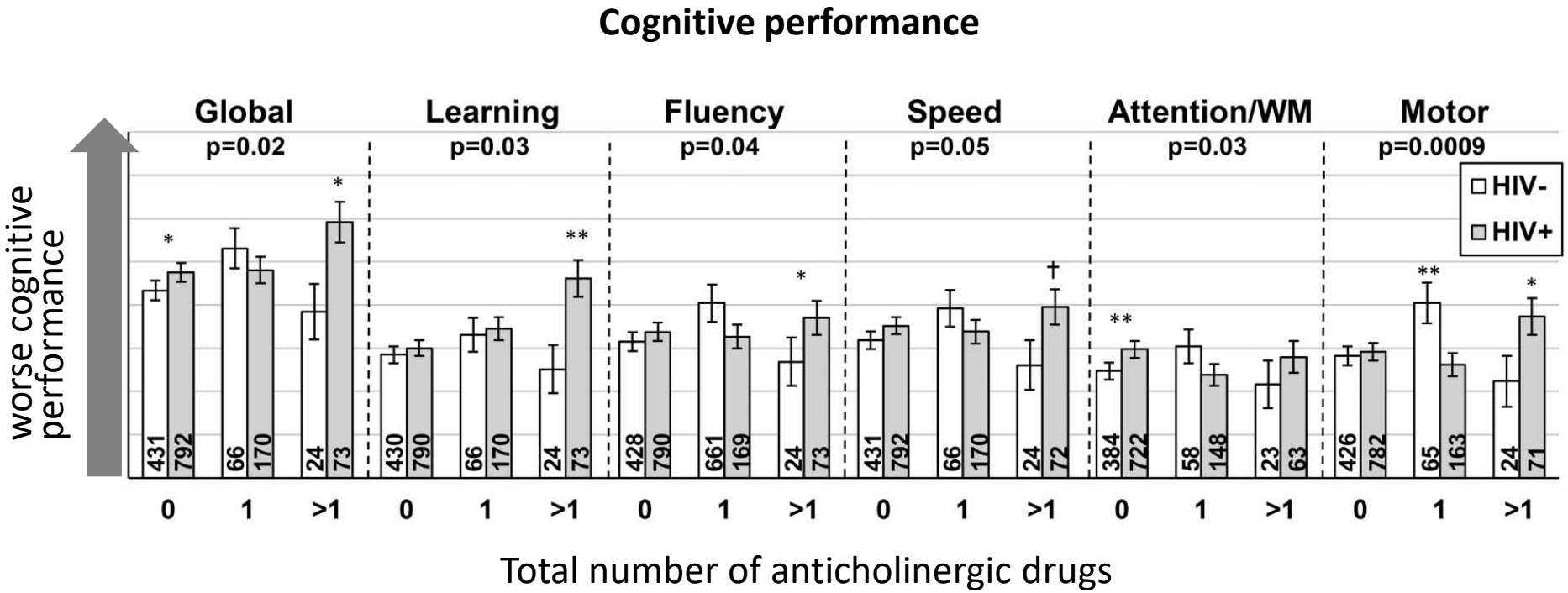
BJCP 2015

Anticholinergic medication use and falls in postmenopausal women: findings from the women's health initiative cohort study

Zachary A. Marcum[1*], Heidi S. Wirtz[2], Mary Pettinger[3], Andrea Z. LaCroix[4], Ryan Carnahan[5], Jane A. Cauley[6], Jennifer W. Bea[7] and Shelly L. Gray[1]

BMC Geriatrics 2016

Drugs with anticholinergic effects and cognitive performance



Rubin L et al. JAIDS 2018

Anticholinergic cognitive burden (ACB) scale

Score 1
Alprazolam
Aripiprazole
Asenapine
Atenolol
Bupropion
Captopril
Cetirizine
Chlorthalidone
Cimetidine
Clidinium
Clorazepate
Codeine
Colchicine
Desloratadine
Diazepam
Digoxin
Dipyridamole
Disopyramide
Fentanyl
Furosemide
Fluvoxamine
Haloperidol
Hydralazine
Hydrocortisone
Iloperidone
Isosorbide
Levocetirizine
Loperamide
Loratadine
Metoprolol
Morphine
Nifedipine
Paliperidone
Prednisone
Quinidine
Ranitidine
Risperidone
Theophylline
Trazodone
Triamterene
Venlafaxine
Warfarin

Score 2
Amantadine
Belladonna
Carbamazepine
Cyclobenzaprine
Cyproheptadine
Loxapine
Meperidine
Methotrimeprazine
Molindone
Nefopam
Oxcarbazepine
Pimozide

Score 3
Amitriptyline
Amoxapine
Atropine
Benztropine
Brompheniramine
Carbinoxamine
Chlorpheniramine
Chlorpromazine
Clemastine
Clomipramine
Clozapine
Darifenacin
Desipramine
Dicyclomine
Dimenhydrinate
Diphenhydramine
Doxepin
Doxylamine
Fesoterodine
Flavoxate
Hydroxyzine
Hyoscyamine
Imipramine
Meclizine
Methocarbamol
Nortriptyline
Olanzapine
Orphenadrine
Oxybutynin
Paroxetine
Perphenazine
Promethazine
Propantheline
Propiverine
Quetiapine
Scopolamine
Solifenacin
Thioridazine
Tolterodine
Trifluoperazine
Trihexyphenidyl
Trimipramine
Trospium

Score 1

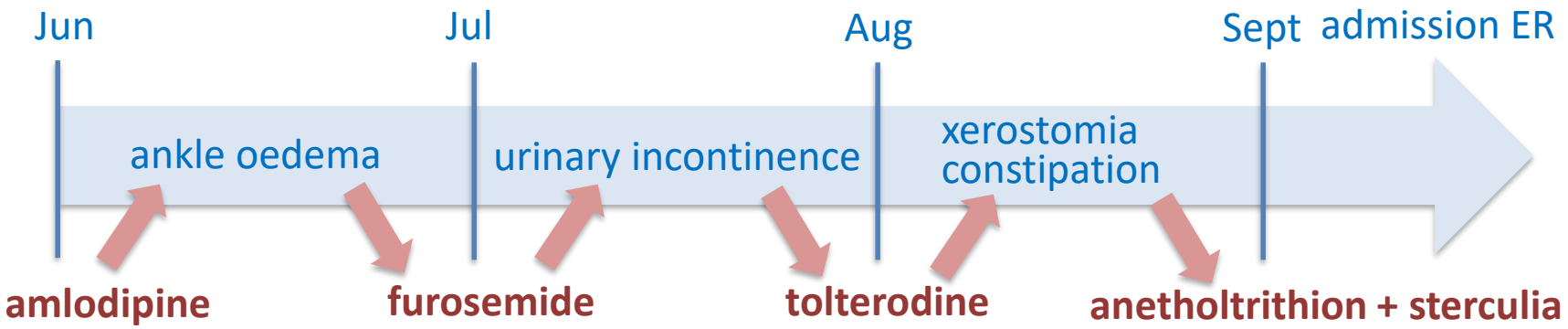
Evidence from in vitro data that drug has antagonist activity at muscarinic receptors but no known clinically relevant cognitive effects

Scores 2 and 3

Drugs with established, clinically relevant cognitive effects. These drugs are considered to have a definitive anticholinergic effect

Boustani M et al. Aging Health 2008

Prescribing cascade



- Ankle oedema recognized adverse effect of amlodipine (risk higher in women, older patients)
- Unlike odema caused by fluid retention, amlodipine induced oedema due to ↑ capillary pressure resulting in fluid loss from the capillaries. Does not respond to diuretic treatment.

Sica D et al. J Clin Hypertens 2011

Treatment

Raltegravir + 3TC + TDF

Rosuvastatin

~~Amitriptyline~~ ➔ escitalopram

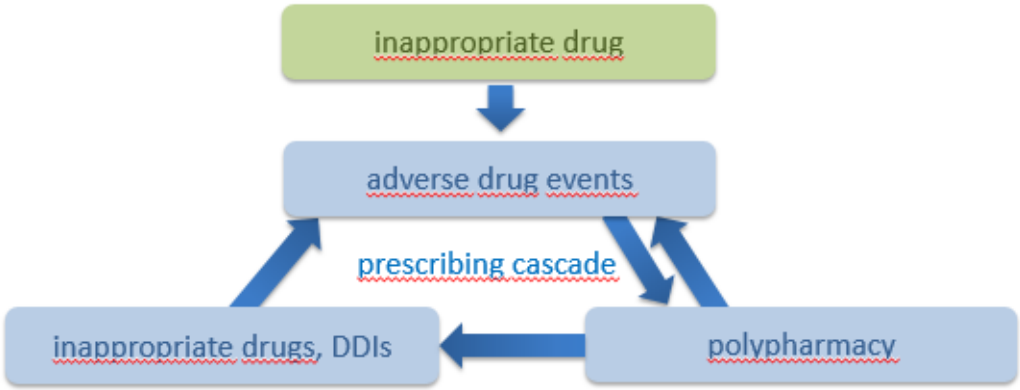
~~Amlodipine~~ ➔ lisinopril

~~Furosemide~~

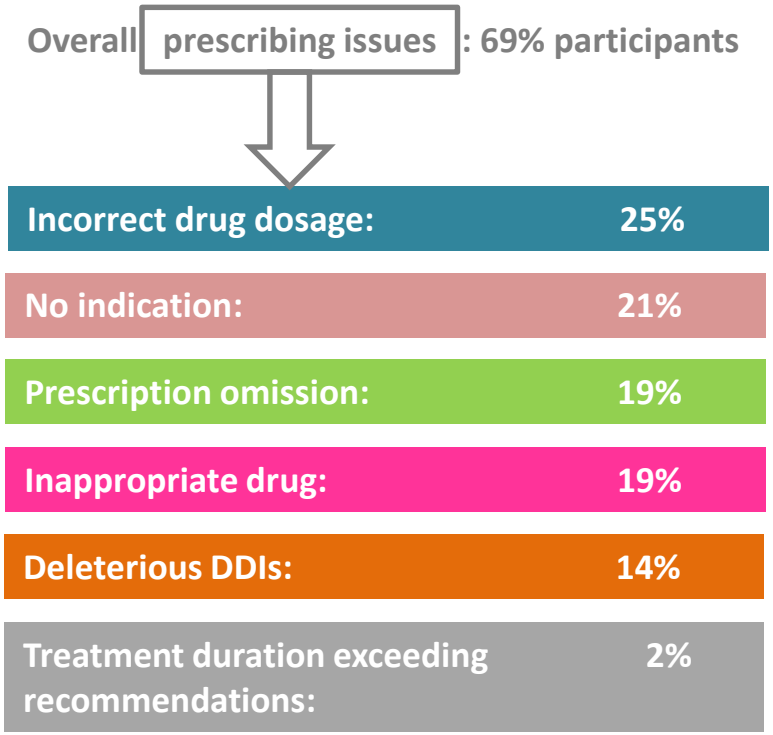
~~Tolterodine~~

~~Anetholtrithion~~

~~Sterculia~~



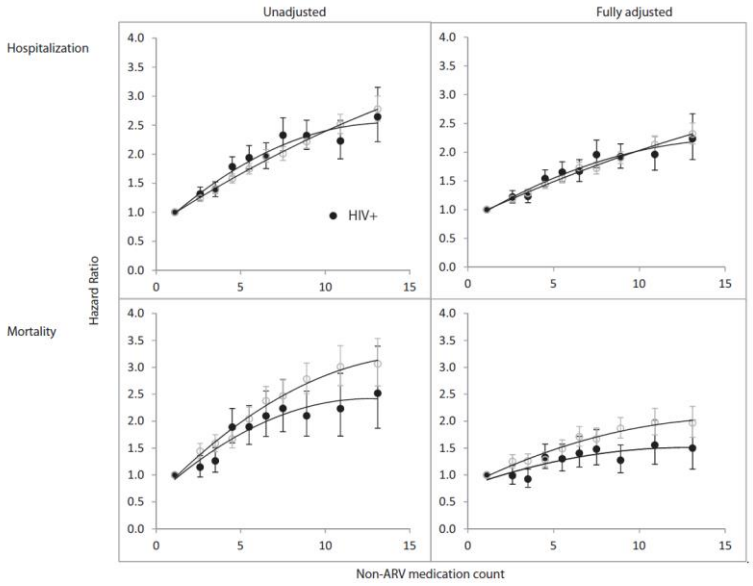
Prevalence of prescribing issues in SHCS patients ≥ 75 years



- 40% of the prescribing issues could possibly lead to deleterious clinical consequences
- Prescribing issues more frequent with non-HIV comeds
- Education on geriatric medicine principles and periodic review of prescriptions could reduce polypharmacy and prescribing errors

Livio F. International Workshop Clin Pharmacol Antivir Ther 2018

Non-HIV polypharmacy and adverse health outcomes



- HIV infected
- HIV uninfected

Association between increased number non-HIV medications and increased risk for **hospitalization** or **mortality** for both PLWH and uninfected individuals.

Justice AC. AIDS 2018

Variable	Falls (+) N=643	No Falls (-) N=1565	Unadjusted p-value	p-value	Adjusted OR (95% CI)
Age (mean ±SD)	59.0 (58.5–59.5)	57.5 (57.2–57.8)	<0.0001	**0.0008**	1.03 (1.01–1.04)
Female Gender (%)	110 (17.1)	161 (10.3)	<0.0001	**0.0016**	1.56 (1.18–2.05)
Total Meds* (mean ±SD)	11.2 (10.6–11.7)	7.5 (7.2–7.7)	<0.0001	**<0.0001**	1.09 (1.07–1.11)

Each additional medication taken increased the odds of a fall by nearly 10%

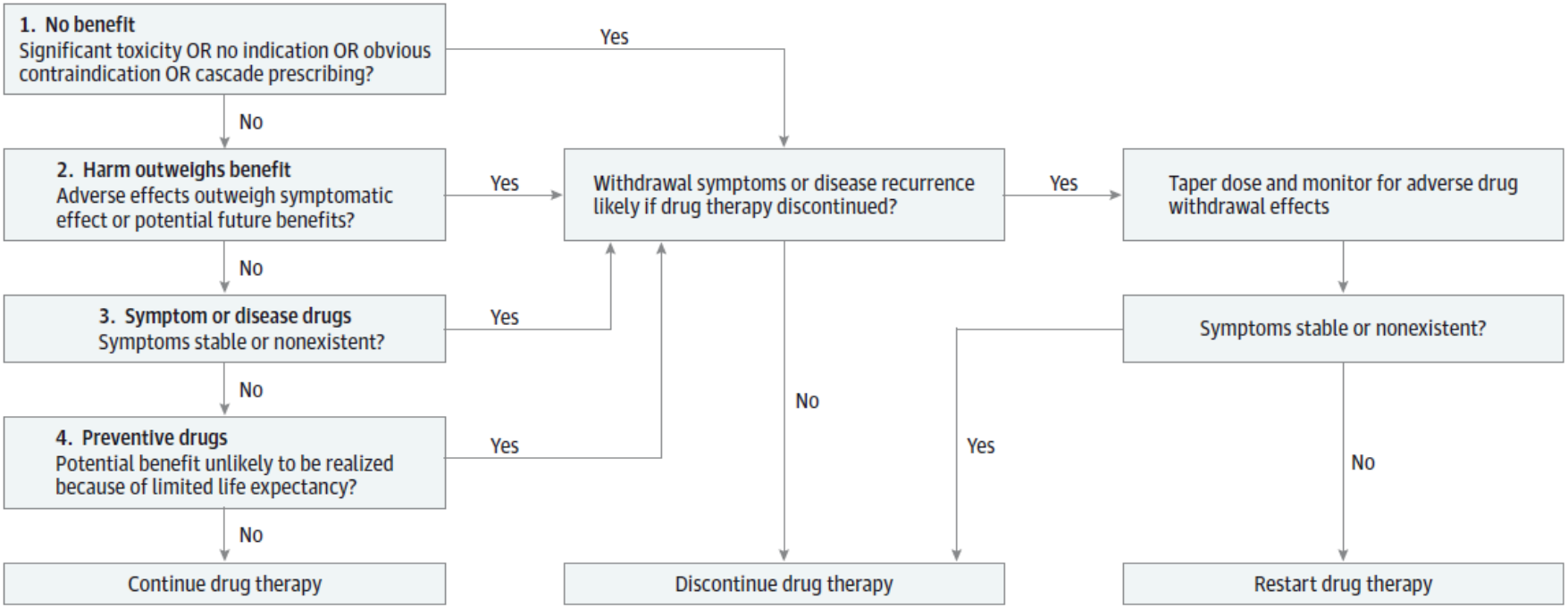
Older age, female gender, total number of non-HIV medications associated with increased risk of having a fall.

➔ both studies conclude that future research is needed to determine the impact of polypharmacy reduction for the prevention of harmful outcomes

Thai L et al. 9th International Workshop on HIV and Aging 2018

Algorithm for drug discontinuation

Deprescribing = planned and supervised process of dose reduction or stopping of medications that may be causing harm or no longer provide benefit



Website for deprescribing of medications: **MedStopper**: http://medstopper.com

http://deprescribing.org website providing algorithms on deprescribing of PPI, BZD and antidiabetics

Scott IA et al. JAMA Intern Med 2015

Interventions to limit polypharmacy and DDIs in elderly PLWH

1) Complete medication reconciliation

- Include over the counter drugs
- Update at each medical visits

2) Review prescription

- Evaluate indication ➔ discontinue unecessary drugs
- Identify medications that are treating adverse effects of other medications ➔ discontinue drug that is causing side effect if possible
- Simplify dosing regimen
- Ensure appropriate dosing of medications
- Ensure duration of treatment is appropriate
- Check for drug-drug interactions ➔ ARV with low DDI potential when possible
- Check for inappropriate drugs in elderly
- Check for any missing medicine

} Beers and STOPP/START criteria

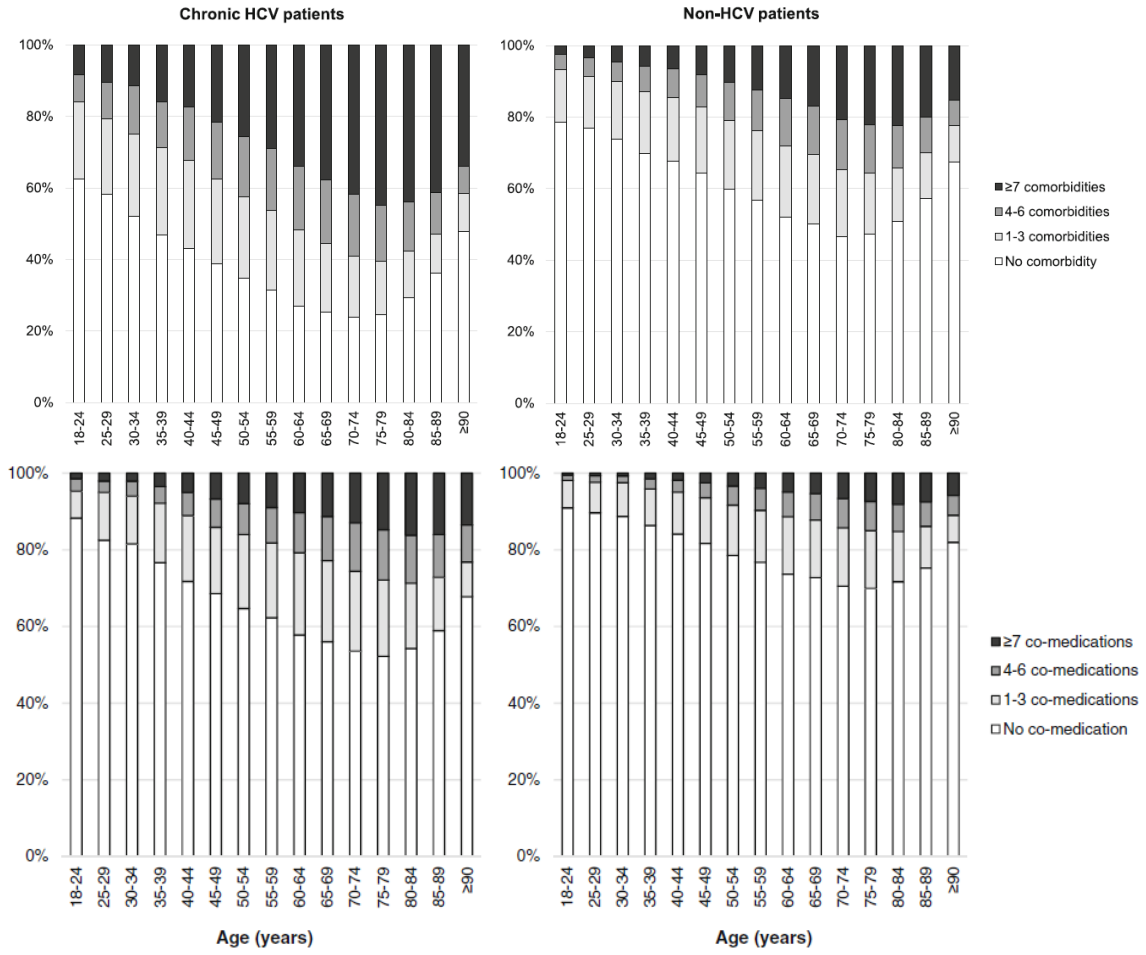
3) Prioritize medications

- Risk and benefit within the context of an individual patient's care goals, current level of functioning, life expectancy and patient preferences

Shah B et al. Clin Geriatr Med 2012, Edelman E et al. Drugs Aging 2013, O'Mahony D et al. Age and Ageing 2015, American Geriatrics Society. J Am Geriatr Soc 2015

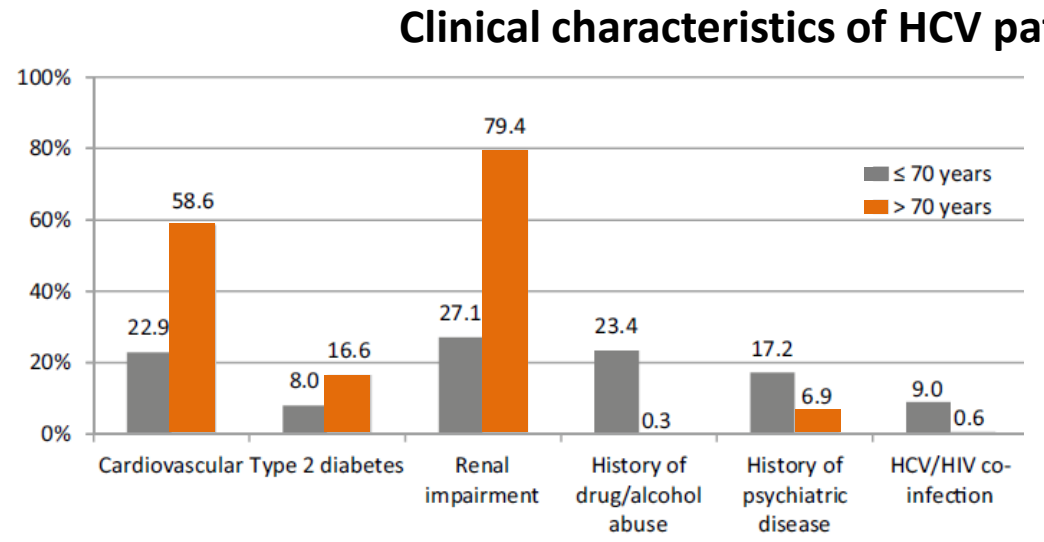
Comorbidities and polypharmacy in HCV infected individuals

Prevalence of comorbidities and polypharmacy in Japanese HCV infected (n = 128’967) **and uninfected** (n = 515’868) **individuals using a hospital-based medical claims database** (period 2015-2016)



Ruzicka D et al. BMC Infect Dis 2018

Comorbididities in elderly vs young HCV infected individuals

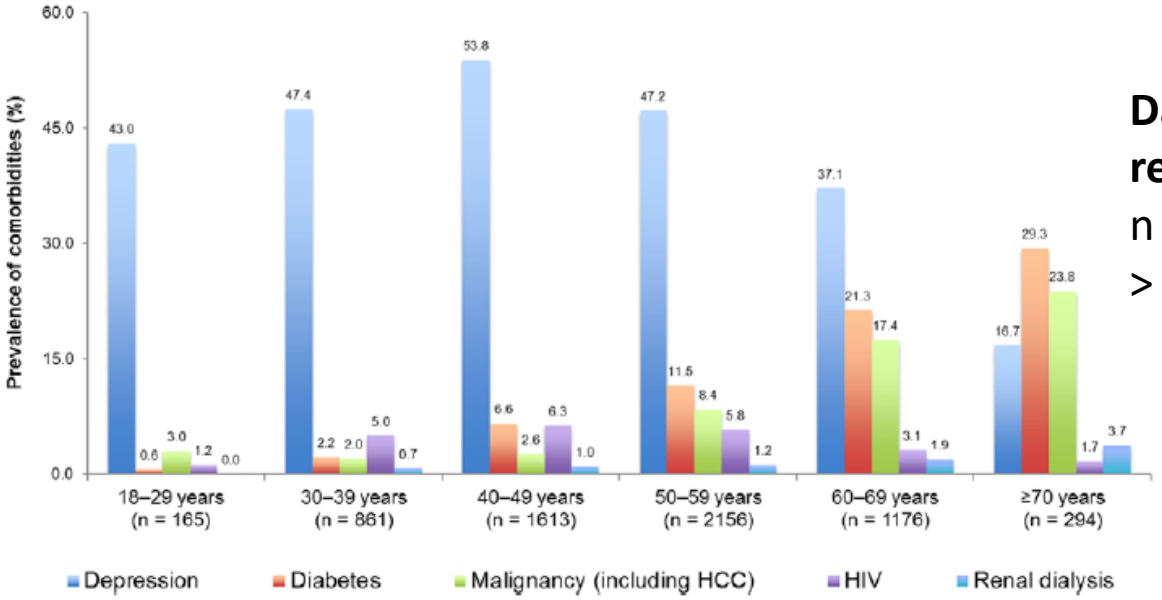


Data from German HCV Registry cohort

n = 7133

> 70 years = 10% overall cohort

Dultz G et al. Drugs Aging 2018



Data from national HCV research UK biobank

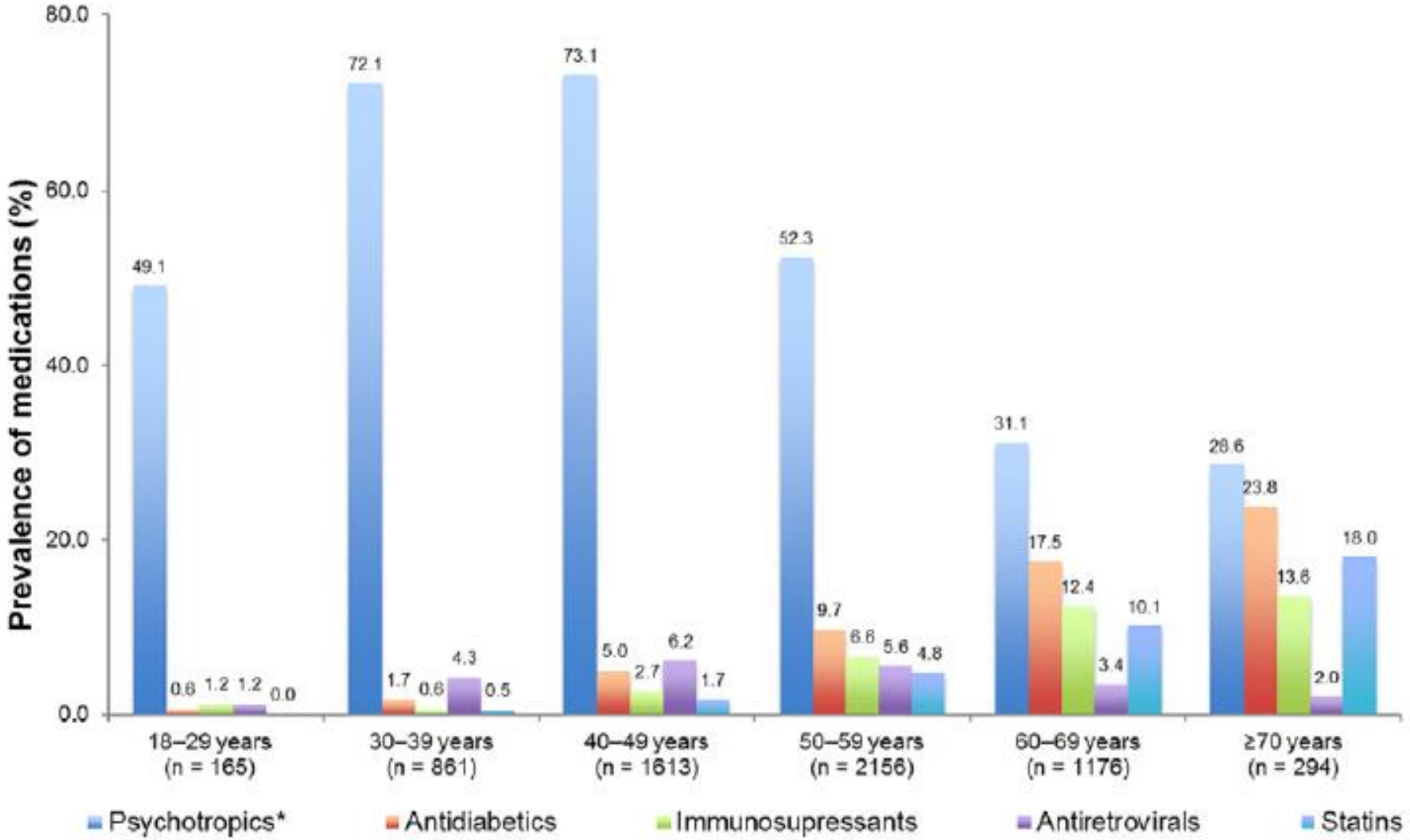
n = 6278

> 60 years = 23% overall cohort

Hudson B et al. J Med Virol 2017

Comedications in elderly vs young HCV infected individuals

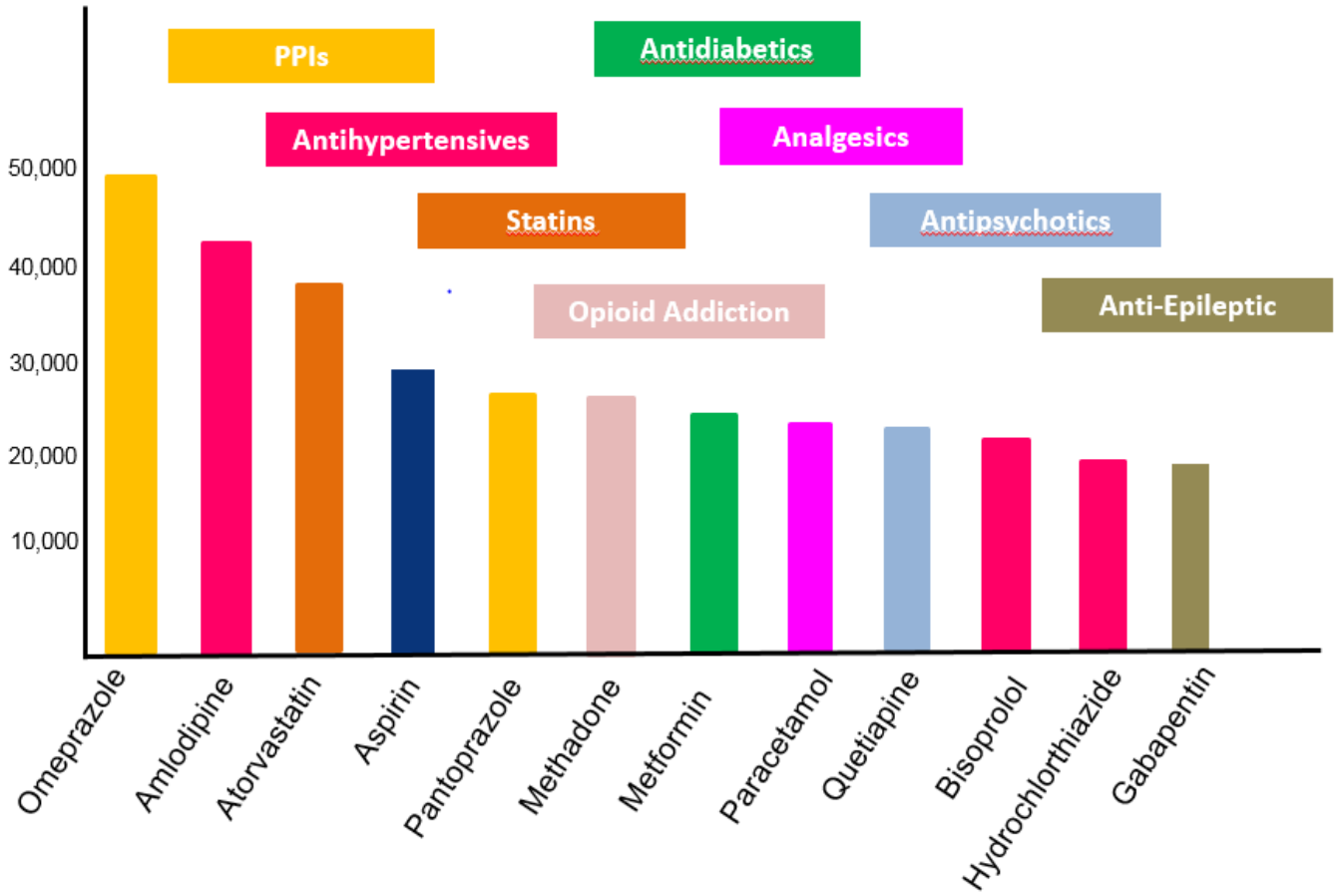
Data from national HCV research UK biobank (n = 6278; > 60 years = 23% overall cohort)



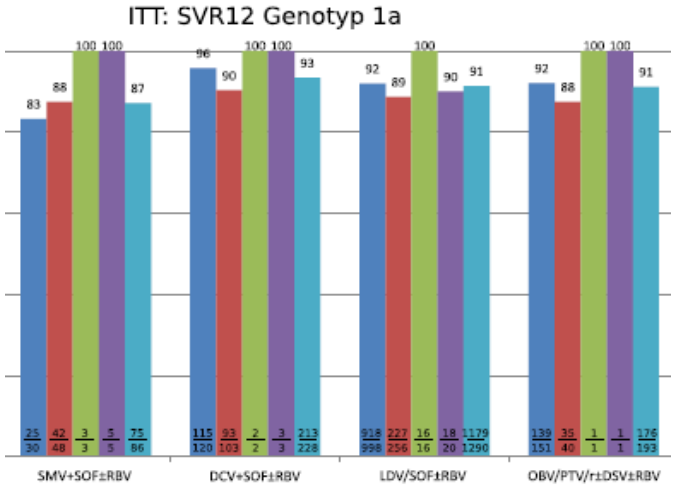
Hudson B et al. J Med Virol 2017

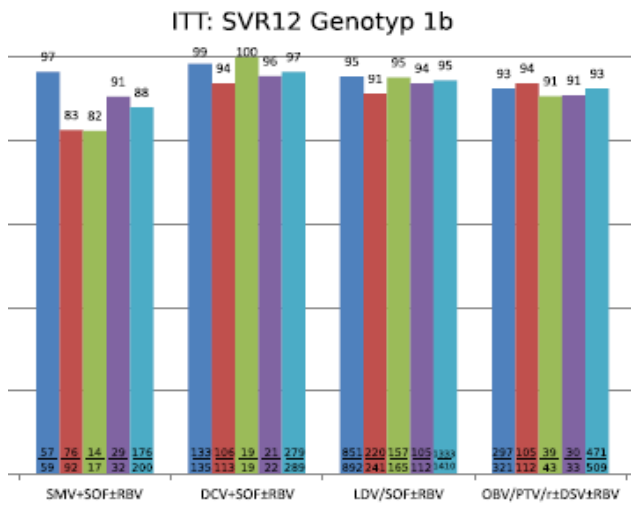
Top global comedications searches in 2018

Top 12 comedications generating the most DDI queries in www.hep-druginteractions.org (MixPanel analytics)

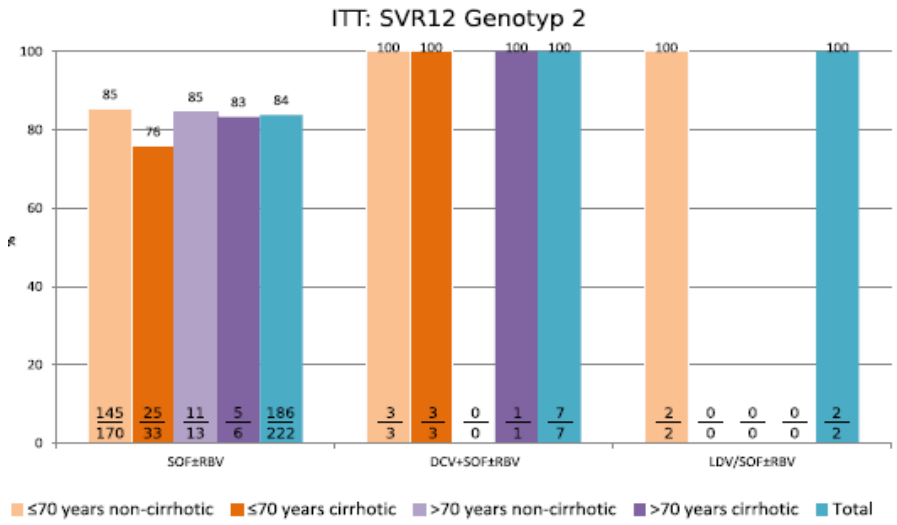


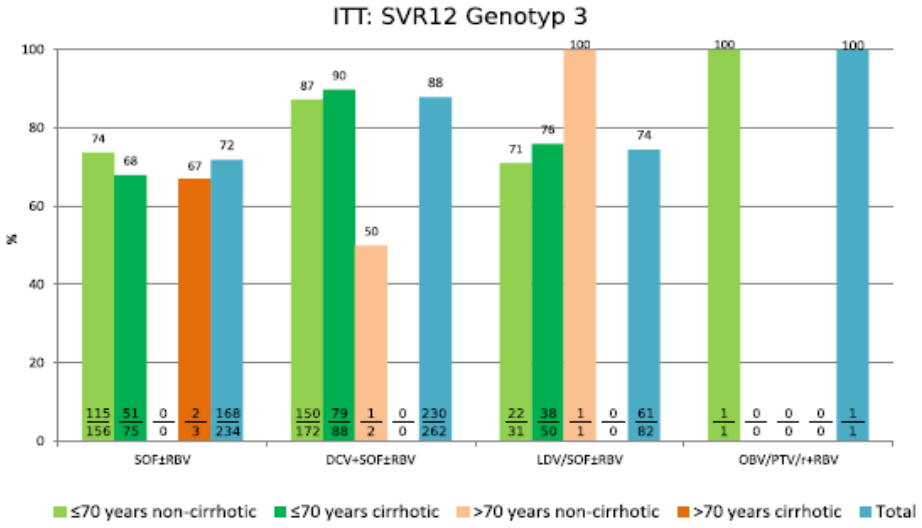
Effectiveness and tolerability of DAAs in elderly





≤70 years non-cirrhotic ≤70 years cirrhotic >70 years non-cirrhotic >70 years cirrhotic Total





≤70 years non-cirrhotic ≤70 years cirrhotic >70 years non-cirrhotic >70 years cirrhotic Total

Adverse drug effects: 54.5% in > 70 years and 53.3% in < 70 years

Dultz G et al. Drugs Aging 2018

DAAs and interactions with drug transporters

	DAAs	P-gp	BCRP	OATP1B1	OATP1B3
Protease inhibitors	Glecaprevir	X	X		
	Grazoprevir		X		
	Paritaprevir	X	X	X	X
	Ritonavir	X	X	X	X
	Simeprevir	x		X	
	Voxilaprevir			X	X
NS5A inhibitors	Daclatasvir	x	x	x	x
	Elbasvir	x	X		
	Ledipasvir	x	x	x	x
	Ombitasvir				
	Pibrentasvir	X	X		
	Velpatasvir	x	X	X	
NS5B	Dasabuvir	X	X		
	Sofosbuvir	x	x		

substrate **X** inhibitor x weak inhibitor

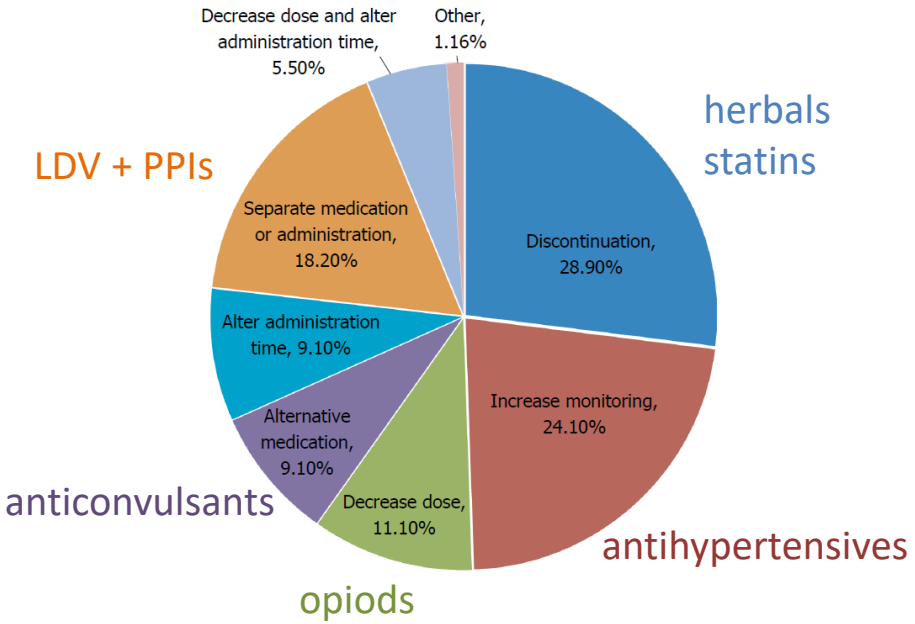
Adapted from Moss D & Marzolini C . In: Drug Interactions in Infectious Diseases 2018

Clinical management of DDIs with DAAs

Retrospective review of management of DDIs in 664 HCV patients from Colorado hospital hepatology clinic

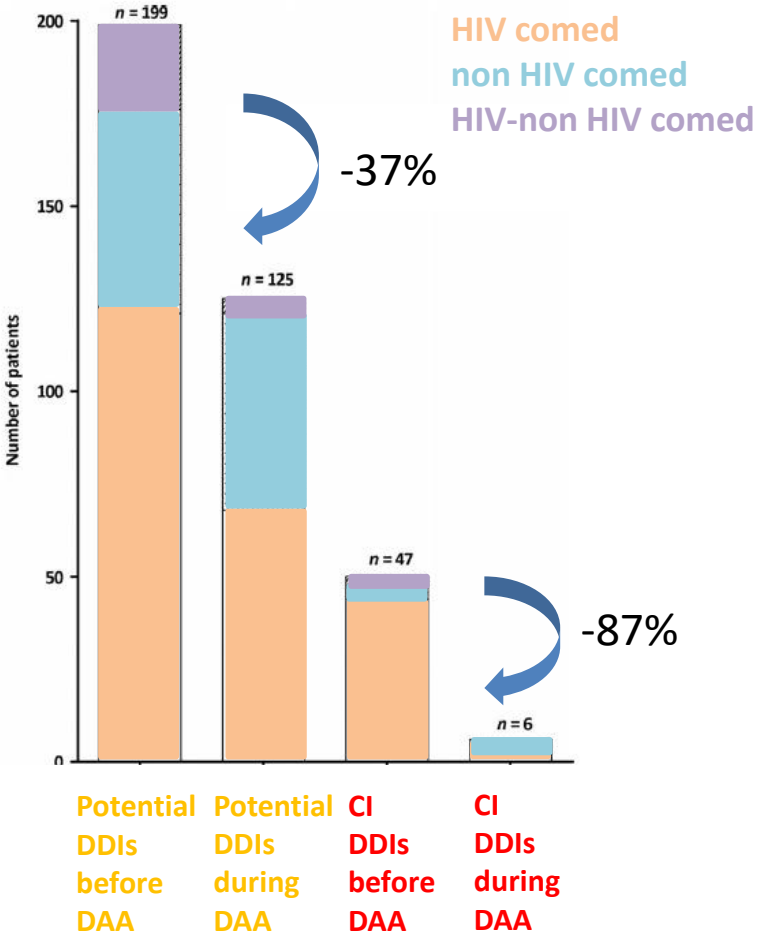
Regimen	*n* = 664	Total number of meds	Total number of interactions, *n* (%)
LDV/SOF	369	2996	472 (15.8)
OBV/PTV/r + DSV	48	312	119 (38.1)
SIM/SOF	114	1002	169 (16.8)
SOF/RBV	133	964	21 (2.2)

Recommendations for management of DDIs



Langness J et al. World J Gastroenterol 2017

Co-medications of 423 HIV/HCV patients from ATHENA cohort analyzed 3 months before starting DAA and during DAA treatment



Smolders E et al. HIV Med 2017

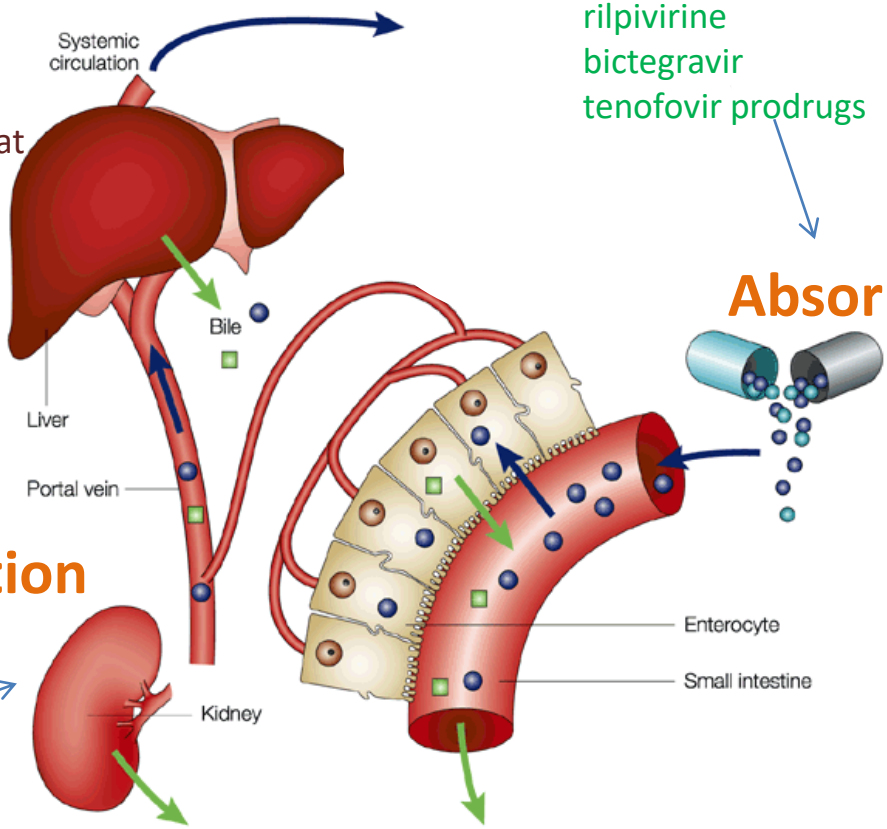
Drug-drug interaction potential of antiretroviral agents

Inhibition/induction of hepatic CYPs glucuronidation, or drug transporters

maraviroc
doravirine
rilpivirine
bictegravir
dolutegravir
raltegravir

PI/ritonavir
PI/cobicistat
EVG/cobicistat
efavirenz
etravirine
nevirapine

Metabolism



Inhibition/induction intestinal CYPs or drug transporters

maraviroc
doravirine
rilpivirine
bictegravir
tenofovir prodrugs

PI/ritonavir
PI/cobicistat
EVG/cobicistat

Change gastric pH

atazanavir
rilpivirine

Absorption

Chelation with mineral supplements

integrase inhibitors

Excretion

Inhibition of renal drug transporters

tenofovir

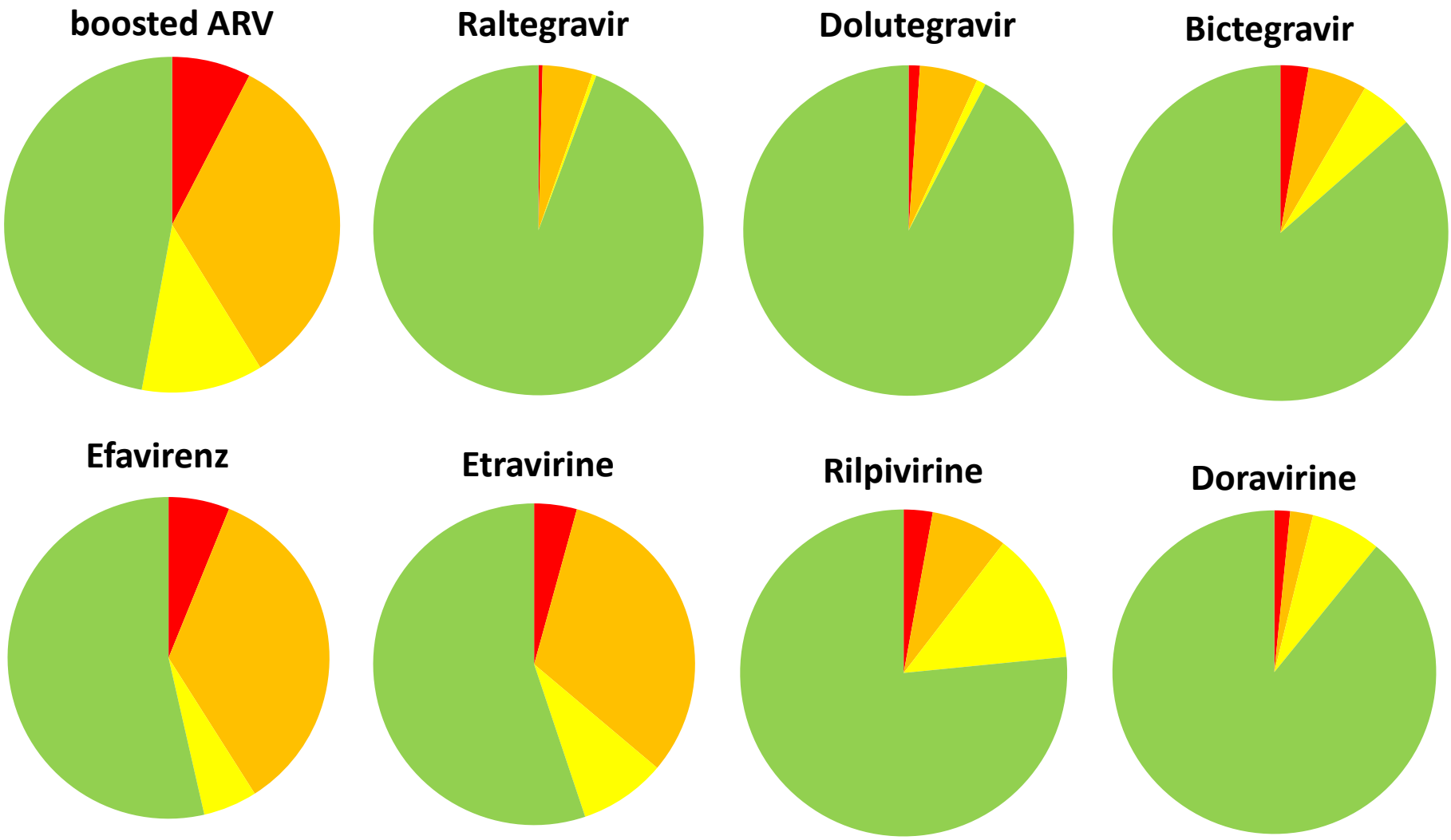
bictegravir
dolutegravir
cobicistat
ritonavir

victim drugs perpetrator drugs

Adapted from Roden DM et al. Nat Rev 2002

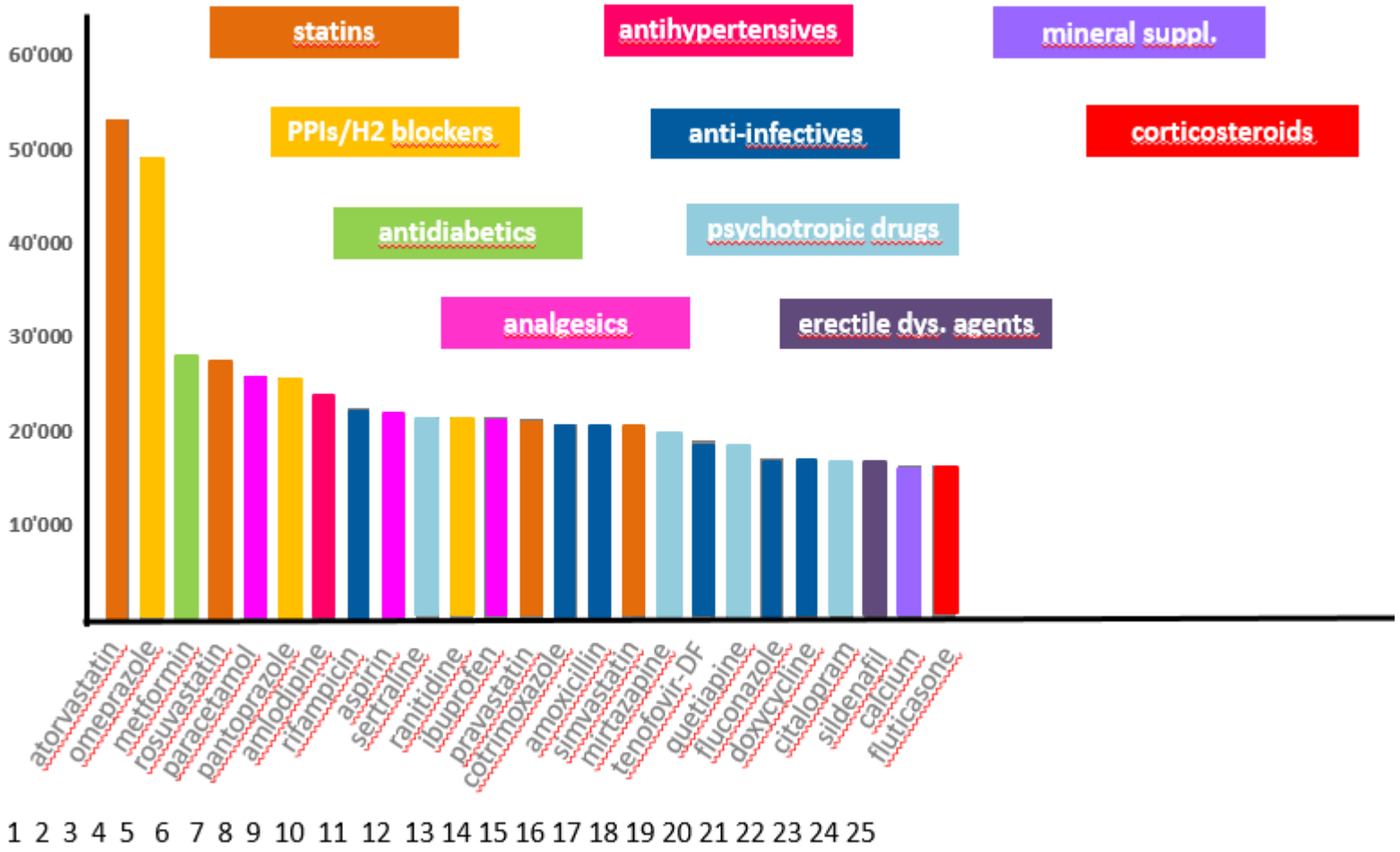
Drug-drug interactions profiles of antiretroviral drugs

n ≈ 700 comedications



Top global comedications searches in 2018

Top 25 comedications generating the most DDI queries in www.hiv-druginteractions.org (MixPanel analytics)



Reg-flag DDIs with antiretroviral drugs

DDI analysis in a large spanish HIV Cohort n = 22'945
Overall 3% (n = 729) of red flag DDIs

ARV class	Co-medication	N (%)
Boosted ARV	**corticosteroids**	**413 (56.7)**
	quetiapine, clozapine	103 (14.1)
	clopidogrel, ticagrelor	61 (12.2)
	domperidone	50 (6.9)
	simvastatin	46 (6.3)
	eplerenone	21 (2.9)
	amiodarone, ivabradine, ranolazine	16 (2.2)
	anticonvulsants, triazolam, rifampicin	11 (1.5)
NNRTI	ketoconazole, itraconazole	61 (8.4)
	contraceptives	11 (1.5)
EFV, NVP, RPV	PPIs	9 (1.2)
	anticonvulsants, triazolam, rifampicin	9 (1.2)

Corticosteroids
mostly CYP3A4 metabolism

+ **PI/r , PI/c** ➔ adrenal insufficiency, Cushing's syndrome
EVG/c (risk with oral, eye, intra-articular, topic admin.)

Lopez-Centeno B et al. Glasgow HIV Conference 2018

Overestimation of DDIs risk and suboptimal treatment

Larger proportion of PLWH with subtherapeutic antidepressants levels compared to uninfected individuals suggesting deliberate lower dosing of antidepressants as clinicians fear DDIs with antiretroviral drugs.

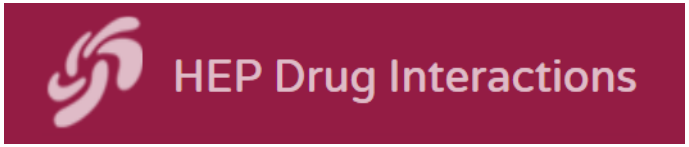
		PLWH treated with ARV (n = 55)		Uninfected individuals (n = 233)	
Drugs	**Reference range (ng/ml)**	**Cmin levels (ng/ml)**	**Subtherapeutic levels**	**Cmin levels (ng/ml)**	**Subtherapeutic levels**
Citalopram	50-110	65 ± 67	**60%**	73 ± 58	**34%**
Duloxetine	30-120	32 ± 35	**63%**	68 ± 41	**32%**
Fluoxetine	120-500	204 ± 190	**50%**	250 ± 160	**21%**
Paroxetine	20-65	22 ± 20	**54%**	150 ± 116	**33%**
Sertraline	10-150	20 ± 12	**20%**	47 ± 43	**6%**
Venlafaxine	100-400	223 ± 52	**0%**	288 ± 239	**23%**

Most antidepressants are metabolized by several CYPs ➔ magnitude of DDI with boosted regimens will be mitigated.
CYP2D6, major CYP in metabolism of antidepressants, only weakly inhibited by RTV or Cobi when used as PK boosters.

Cattaneo D et al. World J Biol Psychiatry 2018

Drug-drug interactions resources

www.hiv-druginteractions.org



www.hep-druginteractions.org

www.cancer-druginteractions.org

Summary

- Polypharmacy ⬆ risk of DDIs (practically unavoidable but most manageable), drug related side effects and medications errors
- Elderly particularly at risk due to ⬆ age related co-morbidities and age related physiological changes which impact the risk-benefit ratio of many drugs
- For an appropriate management of polypharmacy/DDIs:
    - **medication reconciliation**
    - **review prescriptions**
        - **indication ==> stop unecessary treatments**
        - **dose (e.g. adapt to renal function)**
        - **duration of treatment**
        - **drug-drug and drug-diseases interactions**
        - **inappropriate drugs**
        - **missing medication**
    - **prioritize medications according to risk and benefit for an individual patient and considering patient preferences**

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