Deprescribing:
The fightback against polypharmacy

Catia Marzolini

University Hospital & University of Basel
University of Liverpool

University Hospital Basel

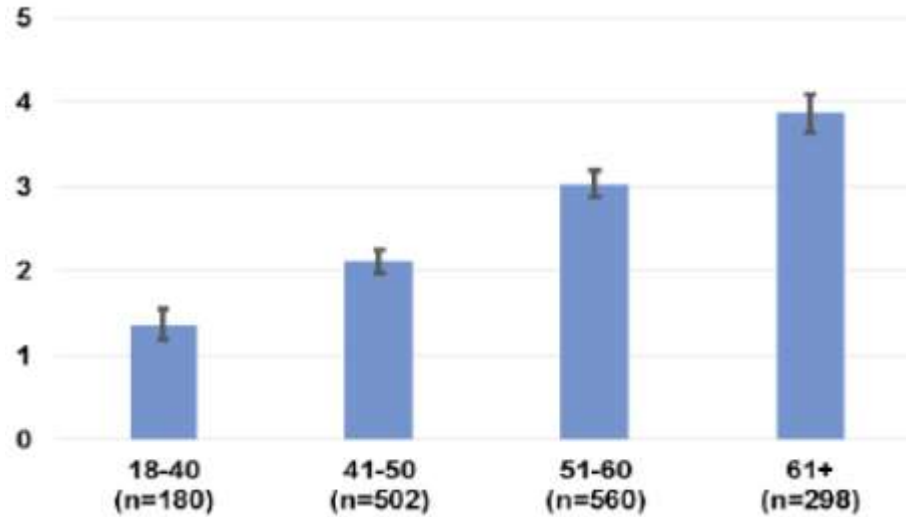University of Basel

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Outline

- Polypharmacy

- Prescribing in elderly
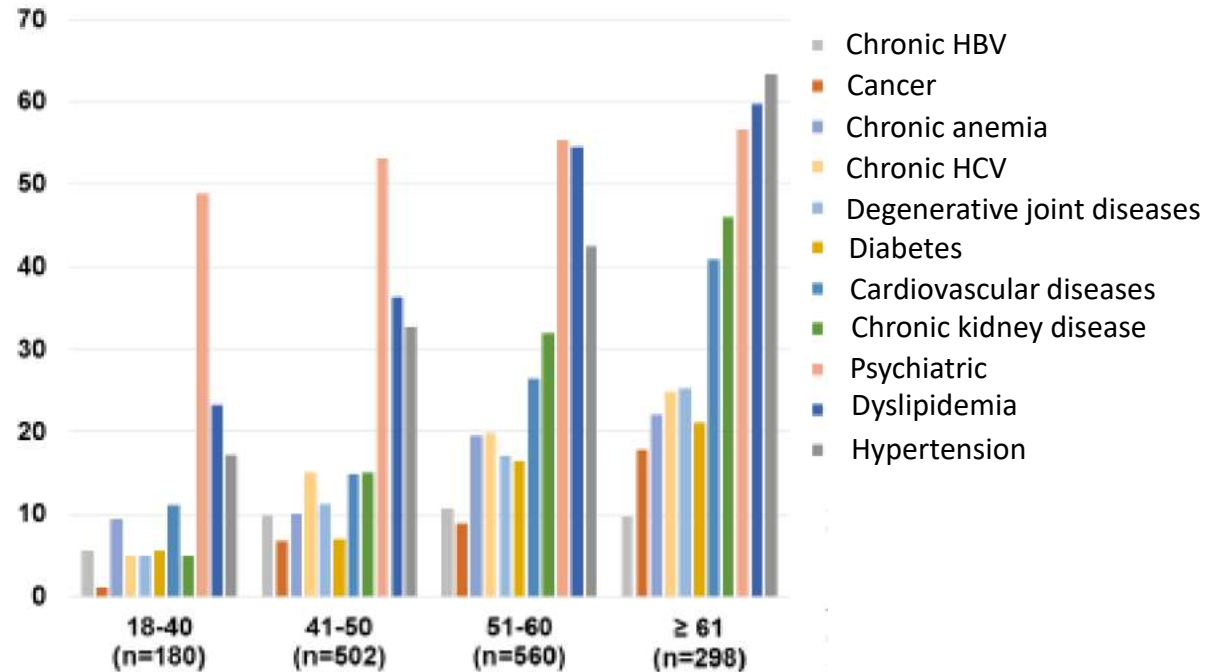
- Deprescribing

- Case presentation

Number and prevalence of comorbidities increase with age

US HIV HOPS cohort

Average number of comorbidities

Prevalence of comorbidities

Similar observations in European/Swiss HIV cohorts:

GEPPO cohort (Guaraldi G et al. BMC Geriatr 2018)
EuroSIDA cohort (Pelchen-Matthews A et al. AIDS 2018)
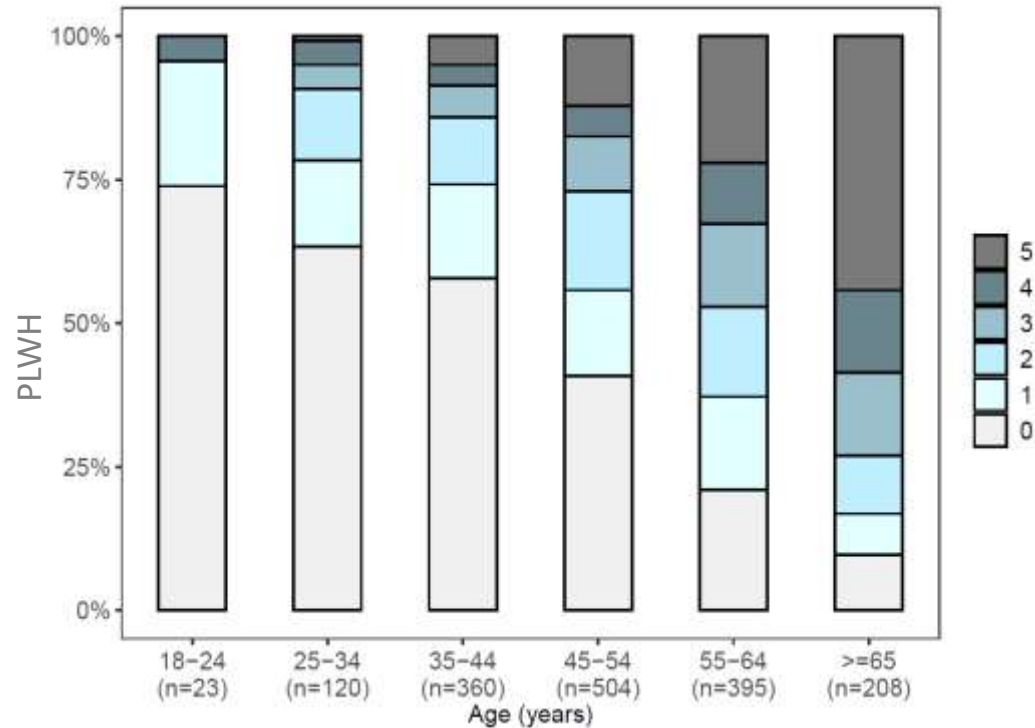**Dat'AIDS cohort** (Allavena C et al. PLoS One 2018)
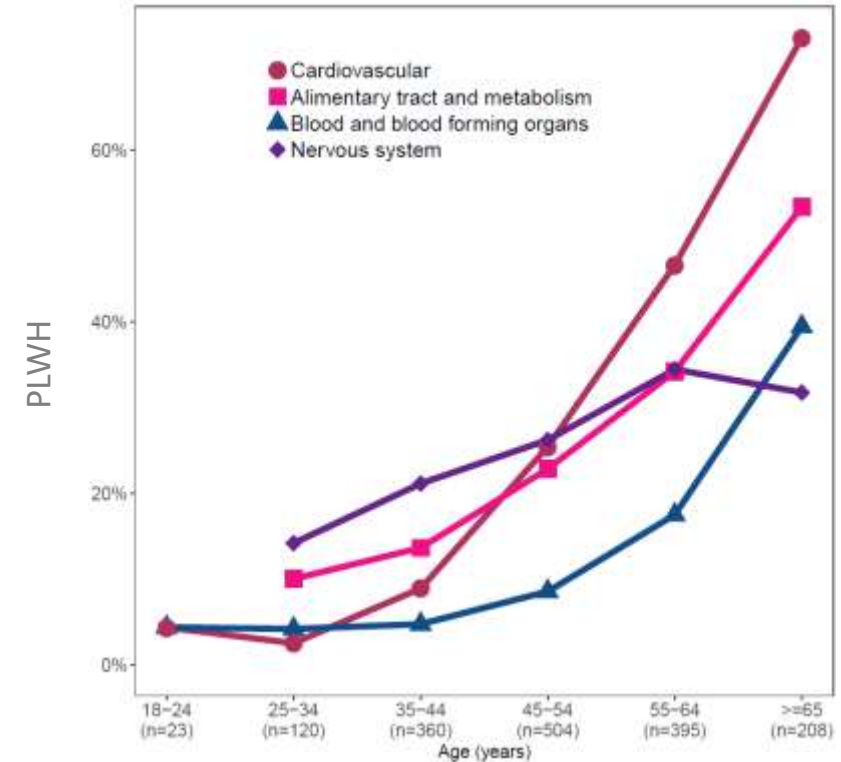**Swiss HIV cohort** (Hasse B et al. CID 2011)

Palella FJ et al. AIDS 2019

Polypharmacy (≥ 5 non-HIV drugs) increases with age

Swiss HIV Cohort

Number of non- HIV medications

Prevalence of comedications use

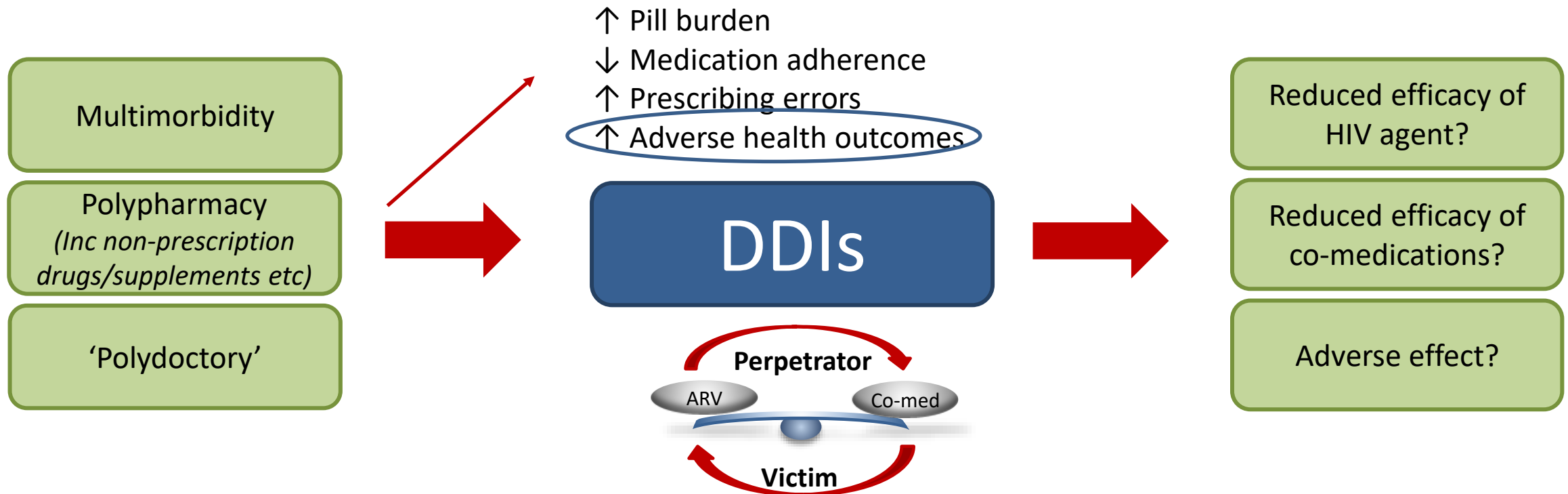Courlet P et al. Open Forum Infect Dis 2019

Polypharmacy is more common in women

➔ consult more often physicians which may provide extra opportunity to detect diseases and receive medications

Lopez-Centeno B et al. Clin Infect Dis 2020

Negative consequences of polypharmacy

Multimorbidity

Polypharmacy
(Inc non-prescription drugs/supplements etc)

'Polydoctory'

↑ Pill burden
↓ Medication adherence
↑ Prescribing errors
↑ Adverse health outcomes

DDIs

Perpetrator

ARV   Co-med

Victim

Reduced efficacy of HIV agent?

Reduced efficacy of co-medications?

Adverse effect?

Polypharmacy could be a major contributor of frailty
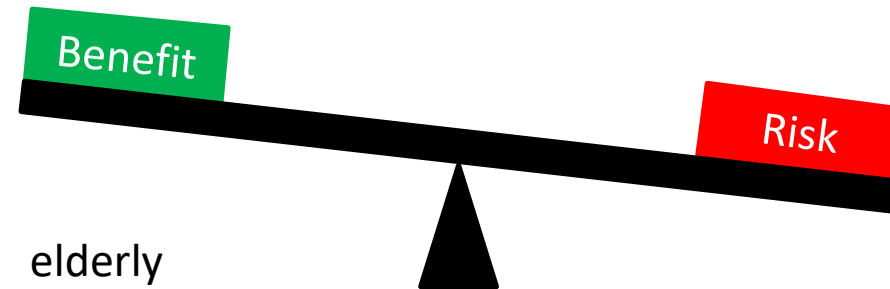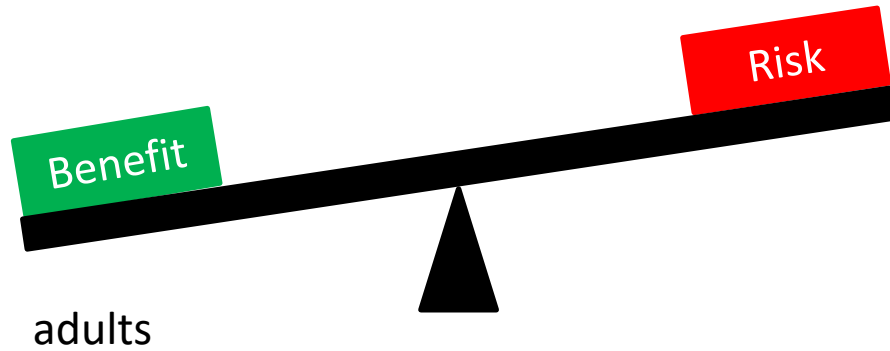
SYSTEMATIC REVIEW AND META–ANALYSIS

The relationship between frailty and polypharmacy in older people: A systematic review

Prescribing in elderly

Risk/benefit balance of medications

adults

elderly

Multiple comorbidities => polypharmacy => ↑DDIs, side effets

Age-related physiological changes which can impact PK/PD

Poor representation of elderly individuals in clinical trials which leads to inadequate treatment evidence and knowledge regarding drug therapy in elderly.
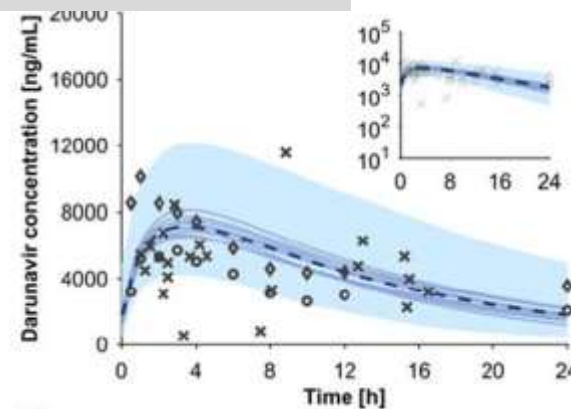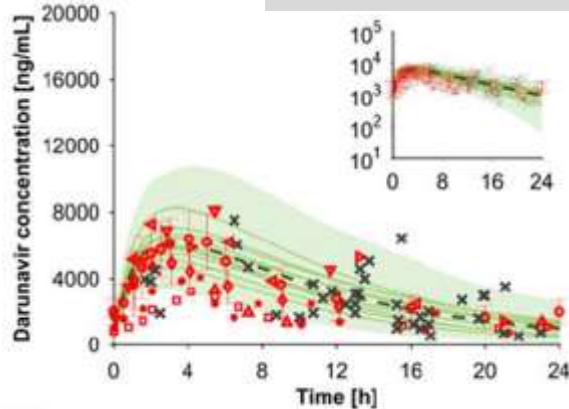
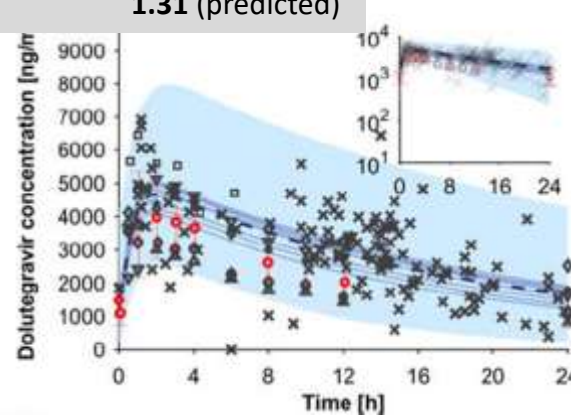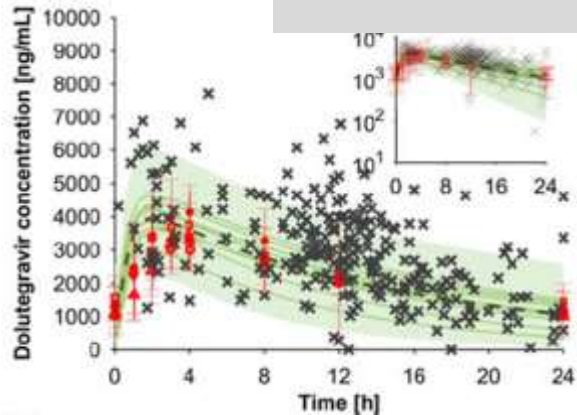# Effect of aging on antiretroviral drug pharmacokinetics

Young adults (20-50 years)   **Elderly adults (55-85 years)**   **Impact of aging on ARVs drug exposure**
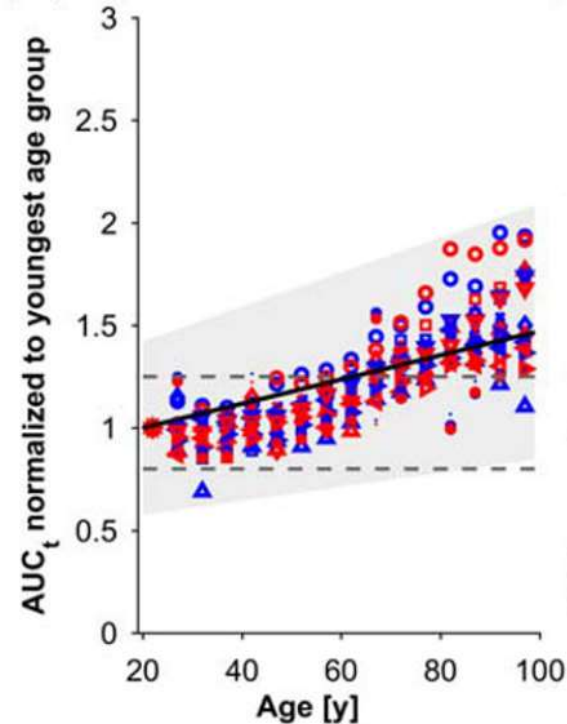
Darunavir/r AUC elderly/young: **1.27** (observed)
1.33 (predicted)

Dolutegravir AUC elderly/young: **1.16** (observed)
1.31 (predicted)

○ male
○ female

Max. 70% increase
in ARV exposure across
adulthood

Drug exposure increases progressively due to a decrease
in CL as a result of decreased hepatic blood flow and
glomerular filtration rate with aging.

**Simulations combined with clinical data indicate that older age does not impact antiretroviral PK to a clinically
significant extent. No a priori dose adjustment is needed in elderly individuals in absence of severe comorbidities.**

Stader F et al. Br J Clin Pharmacol 2020; Courlet P et al. AIDS 2020

Effect of aging on dolutegravir exposure in plasma and CSF

Dolutegravir Ctrough in plasma
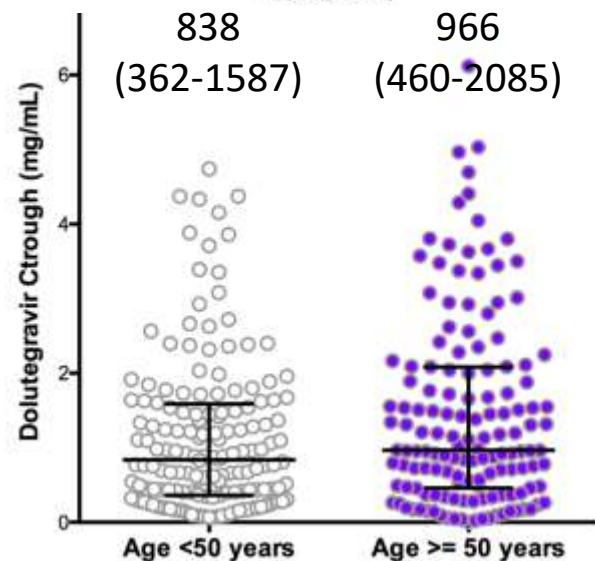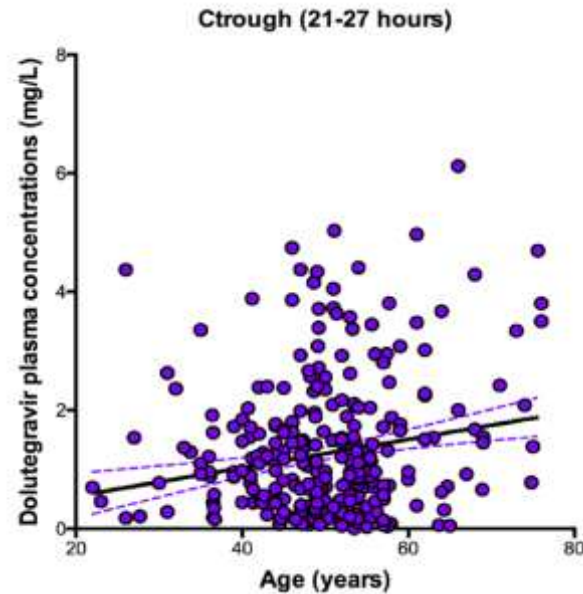
Dolutegravir concentrations in CSF

Calcagno A et al. Clin Pharmacokinet 2020

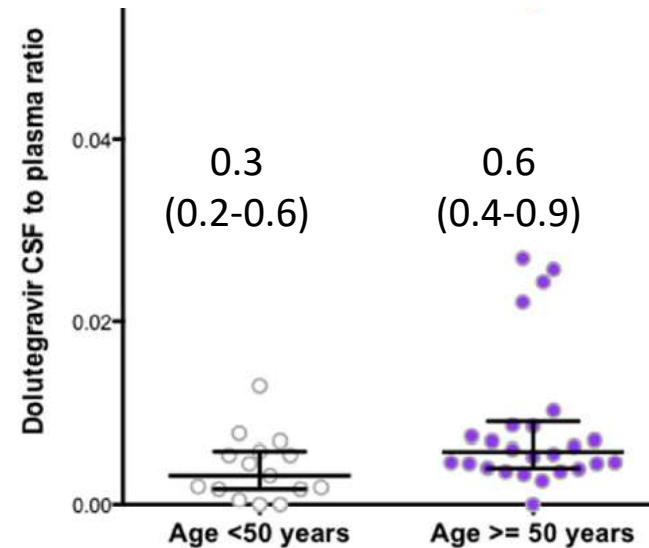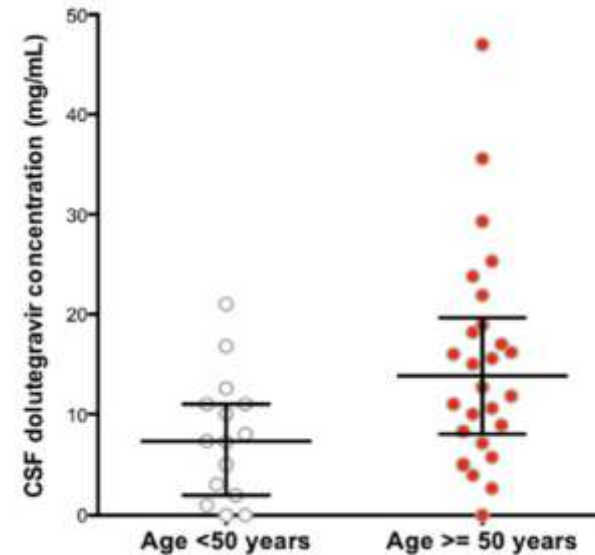# Effect of aging on magnitude of DDIs

Young adults (20-50 years) **Elderly adults (55-85 years)**

Dolutegravir + darunavir/r : AUC **-31%** (obs); **-21%** (pred)   AUC **-15%** (obs); **-28%** (pred)
Dolutegravir alone
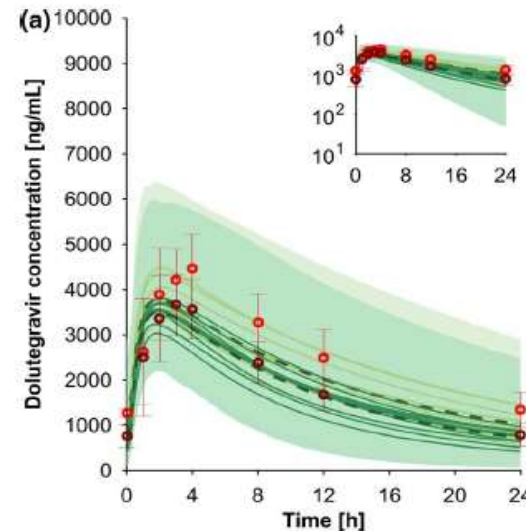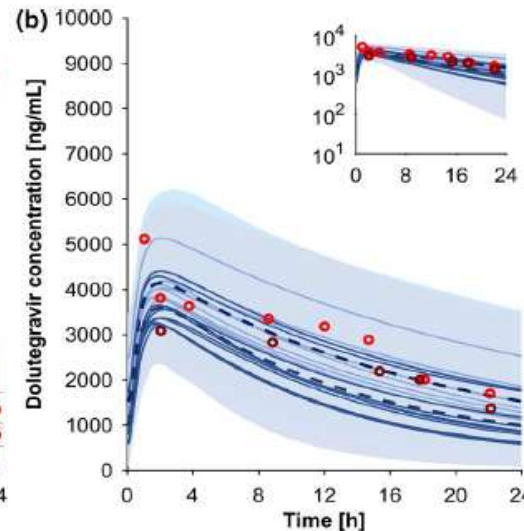
Some more examples of unchanged DDI magnitudes:

Amlodipine + darunavir/r : AUC **+111**% (obs); **+113**% (pred)   AUC **+110%** (obs); **+101%** (pred)
Amlodipine alone

Rosuvastatin + darunavir/r : AUC **+50%** (obs); **+50%** (pred)   AUC **+60%** (obs); **+66%** (pred)
Rosuvastatin alone

Simulations combined with clinical data indicate that magnitude of DDI is comparable in elderly and young adults.

Age related pharmacodynamic changes

❖ regulation of some physiological processes (i.e renal hemodynamics) altered with aging

❖ changes in affinity of some medications to receptor sites or in number of receptors ➜ affect efficacy or increase sensitivity to certain drugs
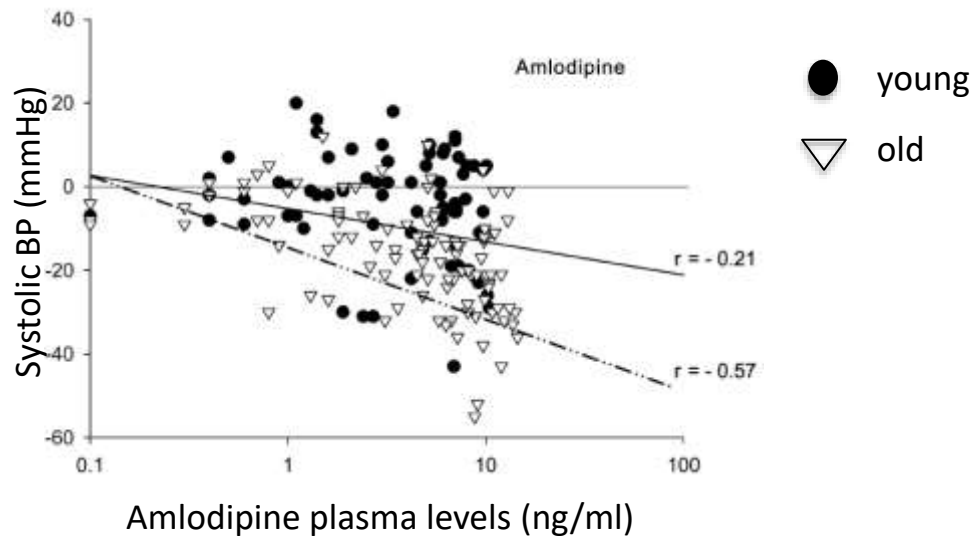
Amlodipine effect in elderly vs young adults

More pronounced decrease in systolic BP in elderly. Start with lower dose in elderly and titrate.

Midazolam effect in elderly vs young adults

elderly
EC_{50} 223 ng/ml

young
EC_{50} 522 ng/ml
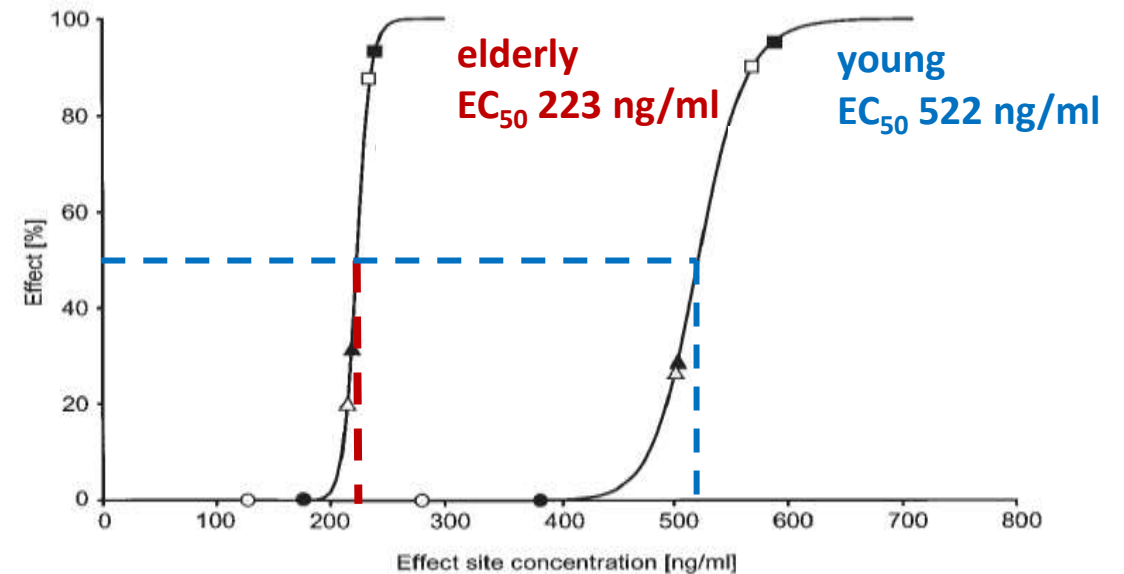
Total dose of midazolam needed to reach effect is half in elderly. Use BZD with caution, at a low dose and for a short period of time.

Leenen FH et al. J Cardiovasc Pharmacol 2010; Albrecht S et al. Clin Pharmacol Ther 1999

Prescribing errors in SHCS patients $\geq$ 75 years

Overall | prescribing issues | : 67% participants

Incorrect drug dosage:	26%
No indication:	21%
Prescription omission:	17%
Inappropriate drug:	18%
Deleterious DDIs:	17%
Treatment duration exceeding recommendations:	1%

Common inappropriate drugs:
- Benzodiazepines
- NSAIDs
- First generation antihistamine drugs

Loste C et al. BJCP 2020; Lopez-Centeno B et al. HIV Med 2020

- 40% of the prescribing issues could possibly lead to deleterious clinical consequences
- Prescribing issues more frequent with non-HIV comeds

Livio F et al. J Antimicrob Chemother 2020

Risk factors for inappropriate prescribing

Factors	OR	95% CI
Age	1.03	0.97-1.08
Duration of HIV infection	1.02	0.98-1.06
Polypharmacy	**2.50**	1.34-4.65
Renal impairment	**2.68**	1.42-5.05
HIV treatment containing TDF	1.38	0.77-2.49
Treatment with CNS drug	**2.09**	1.14-3.82
Female sex	**8.28**	2.44-28.08

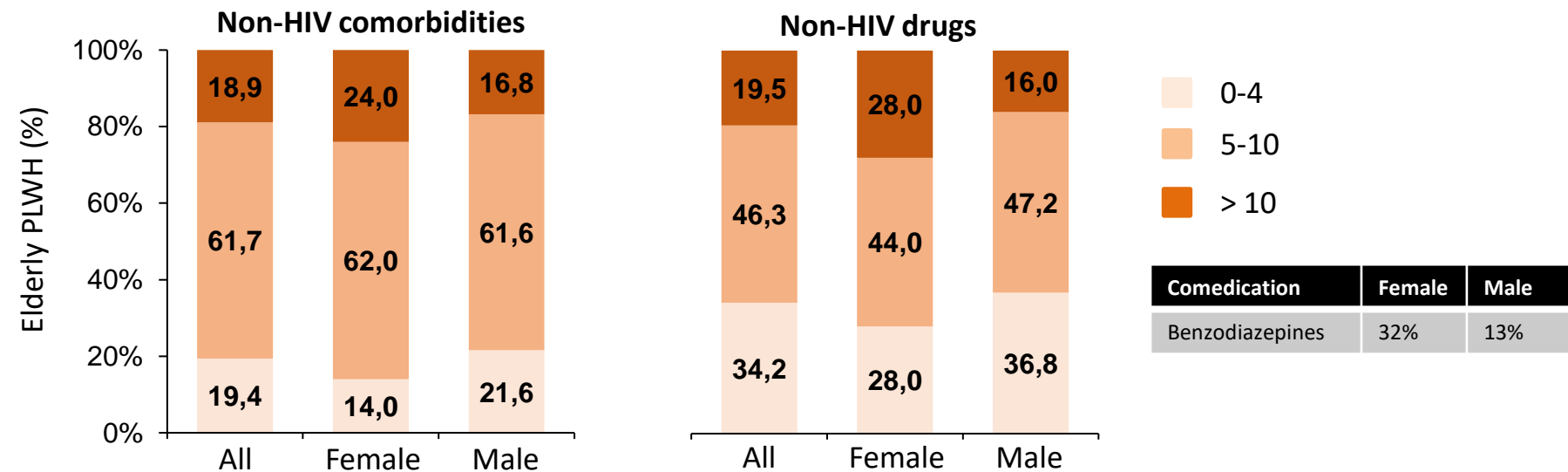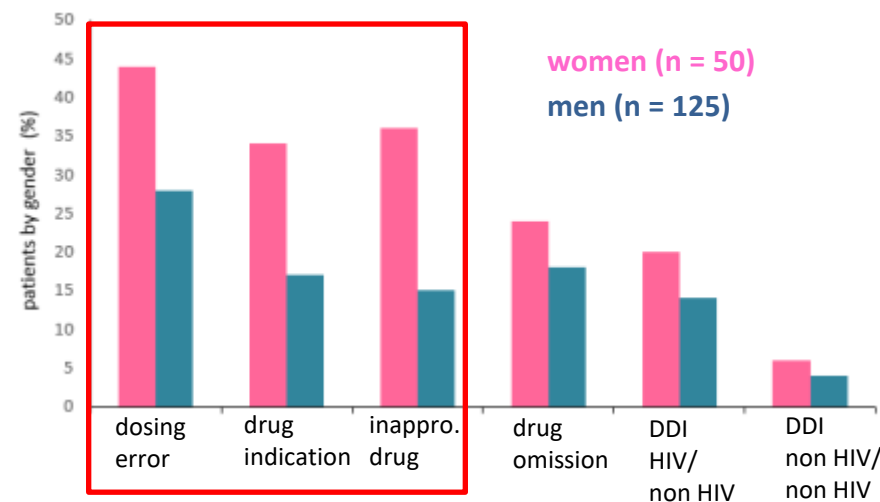Livio F et al. J Antimicrob Chemother 2020
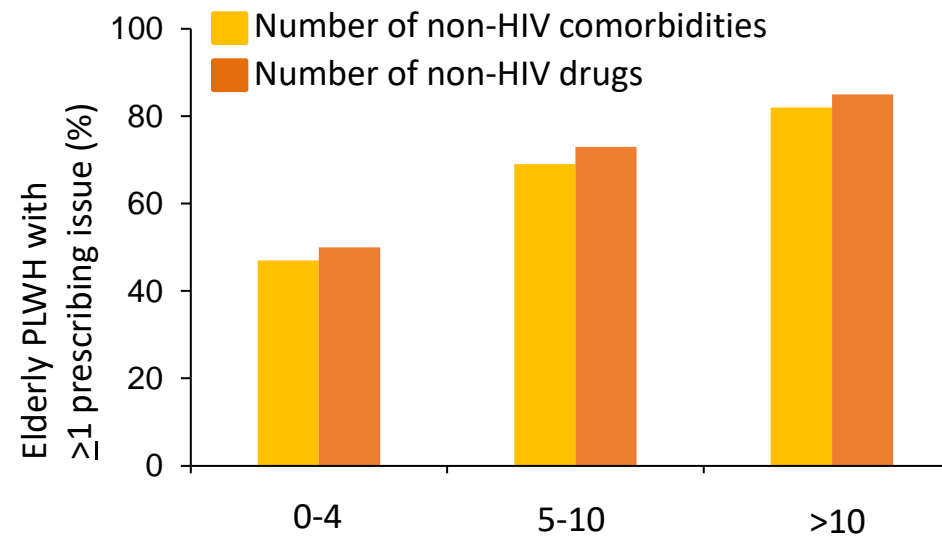
Sex differences in prevalence of comorbidities, medications use and prescribing errors

Distribution of elderly PLWH by number of non-HIV comorbidities and non-HIV drugs

Non-HIV comorbidities

Comorbidity	Female	Male
CNS disorder	62%	45%
Renal impairment	62%	54%
Musculo-skeletal disorder	72%	61%

Non-HIV comorbidities (Elderly PLWH %)

- All: 0-4 = 19,4; 5-10 = 61,7; > 10 = 18,9
- Female: 0-4 = 14,0; 5-10 = 62,0; > 10 = 24,0
- Male: 0-4 = 21,6; 5-10 = 61,6; > 10 = 16,8

Non-HIV drugs (Elderly PLWH %)

- All: 0-4 = 34,2; 5-10 = 46,3; > 10 = 19,5
- Female: 0-4 = 28,0; 5-10 = 44,0; > 10 = 28,0
- Male: 0-4 = 36,8; 5-10 = 47,2; > 10 = 16,0

Legend:
- 0-4
- 5-10
- > 10

Comedication	Female	Male
Benzodiazepines	32%	13%

Prevalence of prescribing issues according to sex

women (n = 50)
men (n = 125)

Categories: dosing error, drug indication, inappro. drug, drug omission, DDI HIV/ non HIV, DDI non HIV/ non HIV

Livio F et al. J Antimicrob Chemother 2020

Possible explanations for sex differences in risk of prescribing errors

➢ **biological factor**: sex difference in occurrence of comorbidities ➔ different patterns of health service use including number of healthcare providers.

➢ **social factor**: sex difference in care. For instance, psychotropic drugs have been shown to be more often prescribed to female than male with similar problems and diagnoses. Female tend to consult more and talk more about their symptoms leading to higher prescription rate. Healthcare providers tend to diagnose more disorders and prescribe more in female than male.

➢ **socio-economic factor**: socio-economic disparities may affect access to care and self-rated health.

Deprescribing

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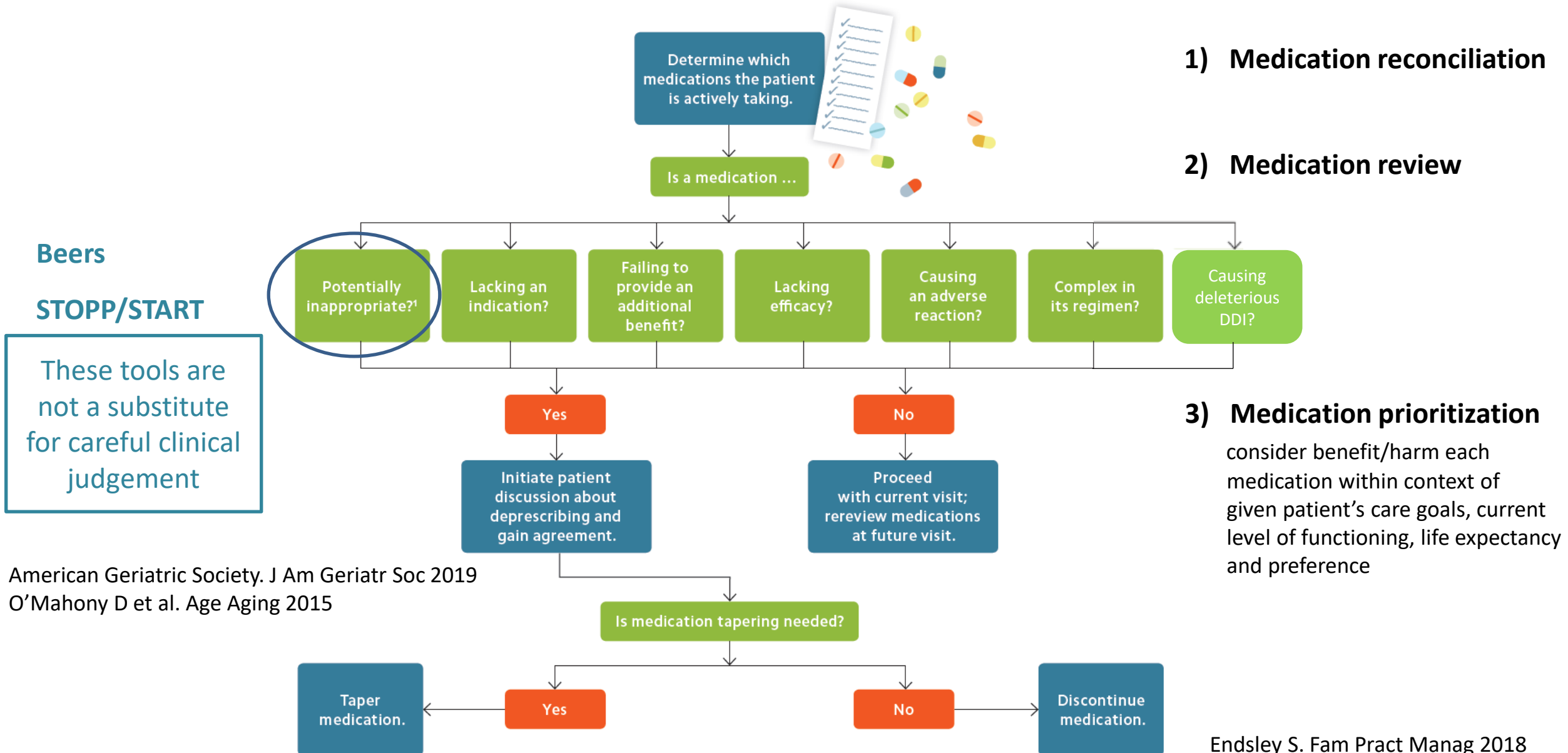
When should deprescribing be considered?

- No valid indication for the medicine
- Adverse drug reaction
- Risk of cumulative toxicity
- Lack of effectiveness
- Drug-drug interactions
- Inappropriate medications
- Short remaining life expectancy
- Drugs that patient is reluctant to take (toxicity, difficulty taking medication, cost)

Scott IA et al. JAMA Intern Med 2015; Bain K et al. J Am Geriatr Soc 2008

Deprescribing algorithm

Determine which medications the patient is actively taking.

Is a medication …

Potentially inappropriate?[1]

Lacking an indication?

Failing to provide an additional benefit?

Lacking efficacy?

Causing an adverse reaction?

Complex in its regimen?

Causing deleterious DDI?

Yes

No

Initiate patient discussion about deprescribing and gain agreement.

Proceed with current visit; rereview medications at future visit.

Is medication tapering needed?

Yes

No

Taper medication.

Discontinue medication.

Beers

STOPP/START

These tools are not a substitute for careful clinical judgement

American Geriatric Society. J Am Geriatr Soc 2019
O'Mahony D et al. Age Aging 2015

1) **Medication reconciliation**

2) **Medication review**

3) **Medication prioritization**
   consider benefit/harm each medication within context of given patient's care goals, current level of functioning, life expectancy and preference

Endsley S. Fam Pract Manag 2018

Arguments in favor/against deprescribing in elderly individuals

Drug	In favour of deprescribing	Against deprescribing
Proton pump inhibitors	• Disappearance of GERD symptoms after initial treatment period of 4-8 weeks • Potential ulcerogenic medications are stopped • Continous use for mild oesophagitis or intermittent symptoms	• Ongoing symptoms for GERD requiring treatment • Ongoing use of GI irritant (e.g. anticoagulants, antiplatelets, NSAIDs) • Presence of Barrett's oesophagus, severe oesophagitis • Previous bleeding gastric ulcers. Risk exacerbated by some medications (antiplatelets, anticoagulants, NSAIDs)
Biphosphonates	• Five or more years of continuous treatment with current low fracture risk	• High fracture risk, recurrent fractures
Antihypertensives	• Confirmed postural hypotension • High risk of falls • Benefit of treating HT in patients > 85 y is unclear, treatment should be reassessed in case of poor prognosis, frailty and depending on comorbidities	• Multiple cardiovascular risk factors • Prior vascular disease • Agents with HT effect may have other benefits in patients with other comorbidities (i.e. B-blockers for heart failure, AF) , cessation may worsen underlying condition
NSAIDs	• Concurrent use of GI irritants (anticoagulants, antiplatelets) • Prior gastrointestinal bleeding • Presence of renal dysfunction • Articular arthritis which may be managed by local strategies	• Short term use for pain from inflammatory cause or injury

McGrath K et al. J Pharm Pract 2017; Disdier Moulder M et al. Clin Cardiology 2019; www.primaryhealthtas.com.au/resources/deprescribing-resources

Arguments in favor/against deprescribing in elderly individuals

Drug	In favour of deprescribing	Against deprescribing
Antipsychotics	• High risk of falls • Use for symptoms that are unlikely to respond (apathy, antisocial behaviour) • Parkinson's disease or other mouvement disorder • Risk factors for arrhythmias	• Severe behavioural and psychological symptoms of dementia (BPSD)
Benzodiazepines	• Long term treatment of insomnia • Adverse effects (cognitive impairment, falls, daytime sedation • Concurrent use of central depressant agents (opiods, antipsychotics, alcohol) • Patient willingness to change	• Short term use
Statins	• Primary prevention • Patients > 80 y (benefit unclear)	• Secondary prevention of CVD events
Aspirin	• High risk of bleeding • Low cardiovascular risk • Dual antiplatelet therapy should have one of these drugs ceased within 12 months of the acute event. For patients where bleeding risk is higher, earlier cessation may be appropriate • Limited life expectancy	• Secondary prevention of CVD events

McGrath K et al. J Pharm Pract 2017; Disdier Moulder M et al. Clin Cardiology 2019; www.primaryhealthtas.com.au/resources/deprescribing-resources

Drug specific deprescribing guidelines

Resources where to find deprescribing guidelines:

http://deprescribing.org
https://www.primaryhealthtas.com.au/resources/deprescribing-resources/

Common targets for deprescribing*
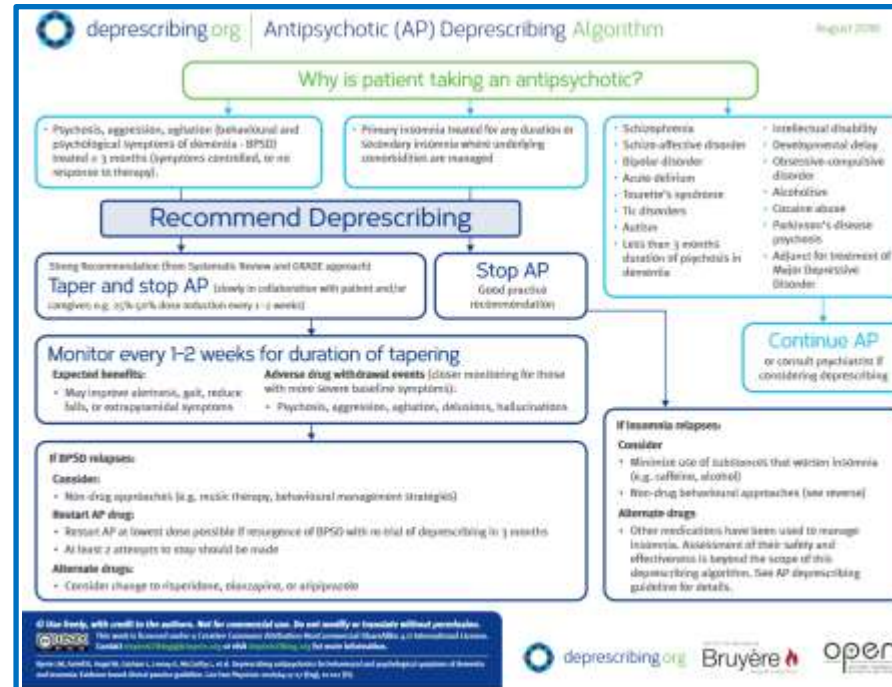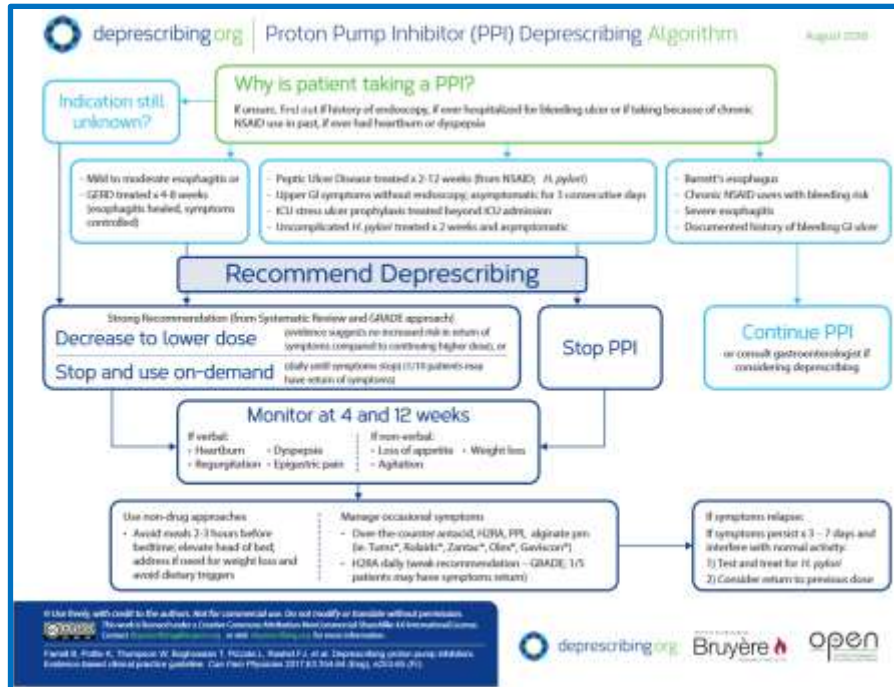
- ☑ ANTIHYPERGLYCAEMICS
- ☑ ANTIHYPERTENSIVES *
- ☑ ANTIPSYCHOTICS *
- ☑ ASPIRIN *
- ☑ BENZODIAZEPINES *
- ☑ BISPHOSPHONATES
- ☑ CHOLINESTERASE INHIBITORS
- ☑ GLAUCOMA EYE DROPS
- ☑ NSAIDS *
- ☑ OPIOIDS
- ☑ PROTON PUMP INHIBITORS *
- ☑ STATINS *
- ☑ VITAMIN D AND CALCIUM

Medications commonly associated with adverse drug withdrawal reactions

Drug	Withdrawal event
Alpha antagonist antihypertensives	Agitation, headache, hypertension, palpitations
ACE inhibitors	Heart failure, hypertension
Anticonvulsants	Anxiety, depression, seizures
Antidepressants	Anxiety, insomnia, reccurrence depression
Antiparkinson	Hypotension, psychosis, tremor
Antipsychotics	Insomnia, nausea, dykinesia
Baclofen	Agitation, confusion, hallucinations, seizures
Benzodiazepines	Anxiety, delirium, insomnia

Drug	Withdrawal event
B-blockers	Anxiety, hypertension, tachycardia, angina
Corticosteroids	Adrenal insufficiency (tapering too rapid)
Digoxin	Heart failure, palpitations
Diuretics	Heart failure, hypertension
H2 blockers	Recurrence of esophagitis and indigestion symptoms
Narcotic analg.	Anxiety, diarrhea, insomnia, chills
NSAID	Recurrence of arthritis, gout symptoms
Sedative/ hyp.	Anxiety, dizziness, tremor

Withdrawal symptoms/disease reccurrence due to:

- Physiological withdrawal reactions
- Exacerbation of underlying condition
- New set of symptoms

Bain K et al. J Am Geriatr Soc 2008

Guidance on how to taper medicicines

http://medstopper.com

Medication/ Category/ Condition	Suggested Taper Approach	Possible Symptoms when Stopping or Tapering
midazolam (Versed) / Benzodiazepine / **insomnia**	If used daily for more than 3-4 weeks. Reduce dose by 25% every week (i.e. week 1-75%, week 2-50%, week 3-25%) and this can be extended or decreased (10% dose reductions) if needed. If intolerable withdrawal symptoms occur (usually 1-3 days after a dose change), go back to the previously tolerated dose until symptoms resolve and plan for a more gradual taper with the patient. Dose reduction may need to slow down as one gets to smaller doses (i.e. 25% of the original dose). Overall, the rate of discontinuation needs to be controlled by the person taking the medication.	rebound insomnia, tremor, anxiety, as well as more serious, rare manifestations including hallucinations, seizures, and delirium
lisinopril (Prinivil, Zestril) / ACE inhibitor / **blood pressure**	If used daily for more than 3-4 weeks. Reduce dose by 50% every 1 to 2 weeks. Once at 25% of the original dose and no withdrawal symptoms have been seen, stop the drug. If any withdrawal symptoms occur, go back to approximately 75% of the previously tolerated dose.	chest pain, pounding heart, heart rate, blood pressure (re-measure for up to 6 months), anxiety, tremor

Deprescribing trials

o Systematic reviews of deprescribing trials in older people concluded that drug classes like antihypertensives, BZD, and psychotropic drugs can be withdrawn successfully without causing harm.

Iyer S et al. Drug Aging 2008; Page AT et al. BJCP 2016

o Longitudinal, prospective, nonrandomized study elderly participants who received a deprescribing intervention and participants receiving usual care.
Trend for better survival in deprescribing group as well as improvements in cognitive function and appetite.

Deprescribing group (122 elderly)
Median nb drugs: 4

Standard of care (55 elderly)
Median nb drugs: 11

Garfinkel D. Ther Adv Drug Saf 2018
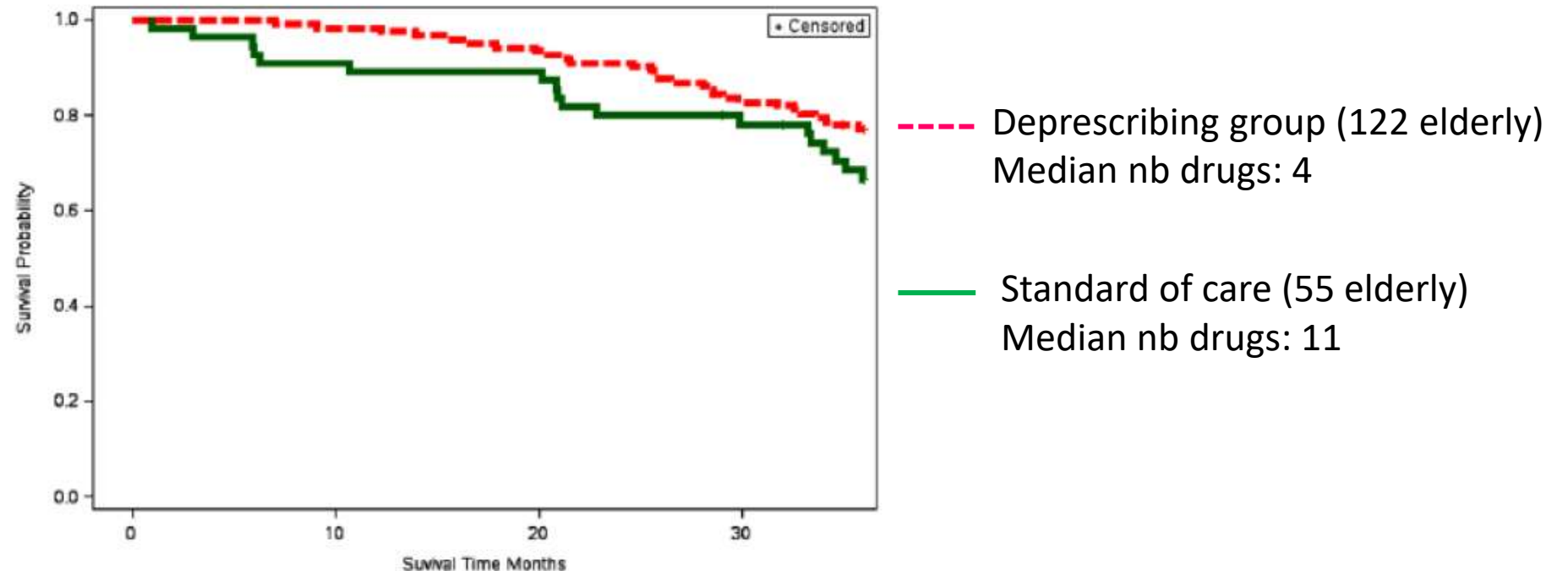
Barriers to deprescribing

Clinicians barriers

o Reluctance to discontinue medications
   prescribed by another clinician

o Fear for potential deleterious consequences

o Concern with patients' resistance to change

o Pressure to conform to disease specific
   treatment guidelines

o Limited time for medication review and
   discussion with patient

Patients barriers

o Physical dependence to a medication

o Previous negative experience with drug withdrawal

o Fear of consequences of stopping a medication

o Discontinuation of medication can be interpreted
   as «giving up» care

⇒ Informing the patient of the rationale for deprescribing
   improves success rates in deprescribing

Bain K et al. J Am Geriatr Soc 2008; Wallis K et al. Ann Fam Med 2017

Older PLWH beliefs towards their medications and deprescribing

Serrano Gimenez R et al. Rev Esp Quimioter 2020

72-year old man

HIV infection
(since 2004)

HIV medications
darunavir/r 800/100 mg QD
emtricitabine 200 mg QD
tenofovir alafenamide 10 mg QD

Immunological/virological parameters
HIV VL: < 20 copies/ml
CD4: 519 cells/mm3

Co-morbidities
Myocardial infarction (2010)
Neurocognitive disorders
Depression
Gout
Gastro-eosophageal reflux
Urticaria
Dyslipidemia

Co-medications
hydrochlorothiazide 25 mg QD
aspirin cardio 100 mg QD
escitalopram 10 mg QD
allopurinol 300 mg QD
pantoprazole 20 mg QD
clemastine 1 mg BID
pitavastatin 4 mg QD

Serum chemistry
eGFR 70 ml/min/1.73
Potassium: 3.8 mmol/l
Sodium: 137 mmol/l
Hepatic enzymes: normal
Glucose: 5 mmol/l
Total cholesterol: 5.2 mmol/l
HDL cholesterol: 1.6 mmol/l
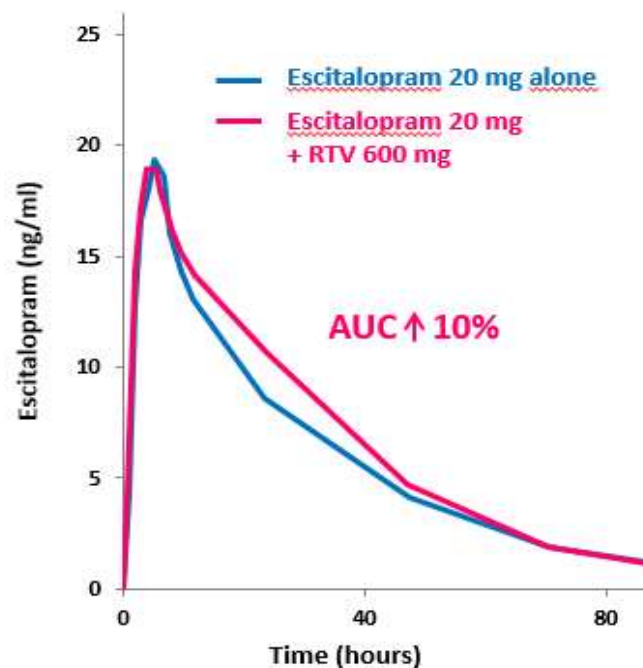LDL cholesterol: 3.0 mmol/l

Blood pressure: 120/80 mmHg

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(since 2004)

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Co-medications
hydrochlorothiazide 25 mg QD

aspirin cardio 100 mg QD
escitalopram 10 mg QD
allopurinol 300 mg QD
pantoprazole 20 mg QD
clemastine 1 mg BID
pitavastatin 4 mg QD

Serum chemistry
eGFR 70 ml/min/1.73
Potassium: 3.8 mmol/l
Sodium: 137 mmol/l
Hepatic enzymes: normal
Glucose: 5 mmol/l

Total cholesterol: 5.2 mmol/l
HDL cholesterol: 1.6 mmol/l
LDL cholesterol: 3.0 mmol/l

Blood pressure: 120/80 mmHg

- No indication for hydrochlorothiazide, patient has no hypertension
- Hydrochlorothiazide can increase uric acid levels

Interaction between hydrochlorothiazide and uric acid

Hydrochlorothiazide recognized as organic acid and serves as substrate for moving uric acid intracellularly from renal filtrate
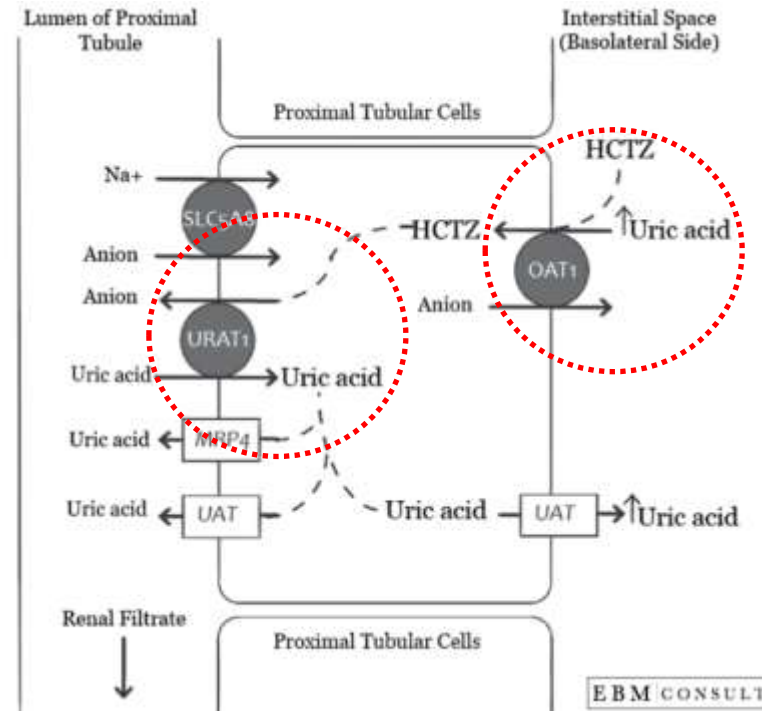
competition between hydrochlorothiazide and uric acid for renal elimination via OAT1

www.hiv-druginteractions.org

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Common Prescribing Cascades to Avoid in Elderly PLWH

Produced July 2019

| Thiazide diuretics | → | Hyperuricemia; gout | → | Allopurinol; colchicine |

www.hiv-druginteractions.org

72-year old man

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(since 2004)

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darunavir/r 800/100 mg QD
emtricitabine 200 mg QD
tenofovir alafenamide 10 mg QD

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Step 2
Check
Inappropriate drug

www.hiv-druginteractions.org   UNIVERSITY OF LIVERPOOL

Top Ten Drug Classes to Avoid in Elderly PLWH

Produced July 2019

Drug class	Problems	Alternatives
First generation antihistamines e.g., Clemastine Diphenhydramine Doxylamine Hydroxyzine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention).	Cetirizine Desloratadine Loratadine
Tricyclic antidepressants e.g., Amitriptyline Clomipramine Doxepin Imipramine Trimipramine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention).	Citalopram Escitalopram Mirtazapine Venlafaxine

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(since 2004)

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darunavir/r 800/100 mg QD
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Co-morbidities
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Depression
Gout
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Urticaria
Dyslipidemia

Co-medications
hydrochlorothiazide 25 mg QD

aspirin cardio 100 mg QD ✓
escitalopram 10 mg QD ✓
allopurinol 300 mg QD ? ✓
pantoprazole 20 mg QD ✓
loratadine 10 mg QD ✓
pitavastatin 4 mg QD ✓

Serum chemistry
eGFR 70 ml/min/1.73
Potassium: 3.8 mmol/l
Sodium: 137 mmol/l
Hepatic enzymes: normal
Glucose: 5 mmol/l
Total cholesterol: 5.2 mmol/l
HDL cholesterol: 1.6 mmol/l
LDL cholesterol: 3.0 mmol/l

Blood pressure: 120/80 mmHg

Interaction escitalopram - ritonavir

Antidepressants are metabolized by several CYPs

➜ mitigate DDIs magnitude

Magnitude of drug-drug interaction depends on:

- **Fraction of metabolism via given CYP (DPI)**

Drug	DPI $_{CYP3A4}$
simvastatin	1.0
zolpidem	0.26

exclusively metabolized by CYP3A4

CYP3A4 contributes to 26% of the overall metabolism

Gutierrez MM et al. Clin Ther 2003; Stader F et al. Antimicrob Agent Chemother 2018
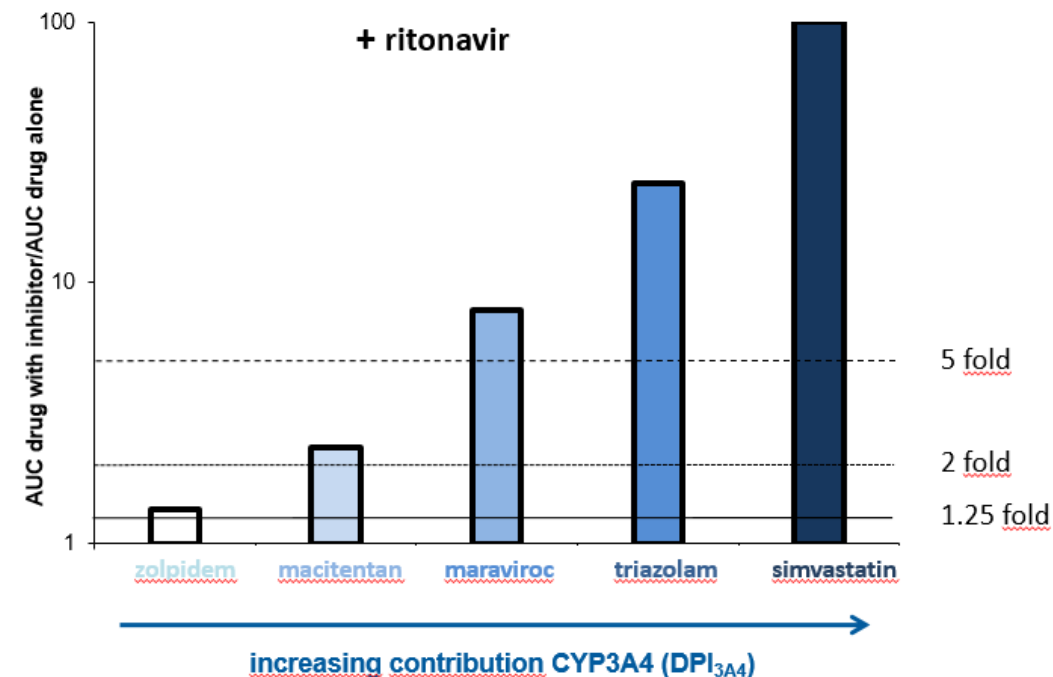
Interaction pitavastatin – darunavir/ritonavir
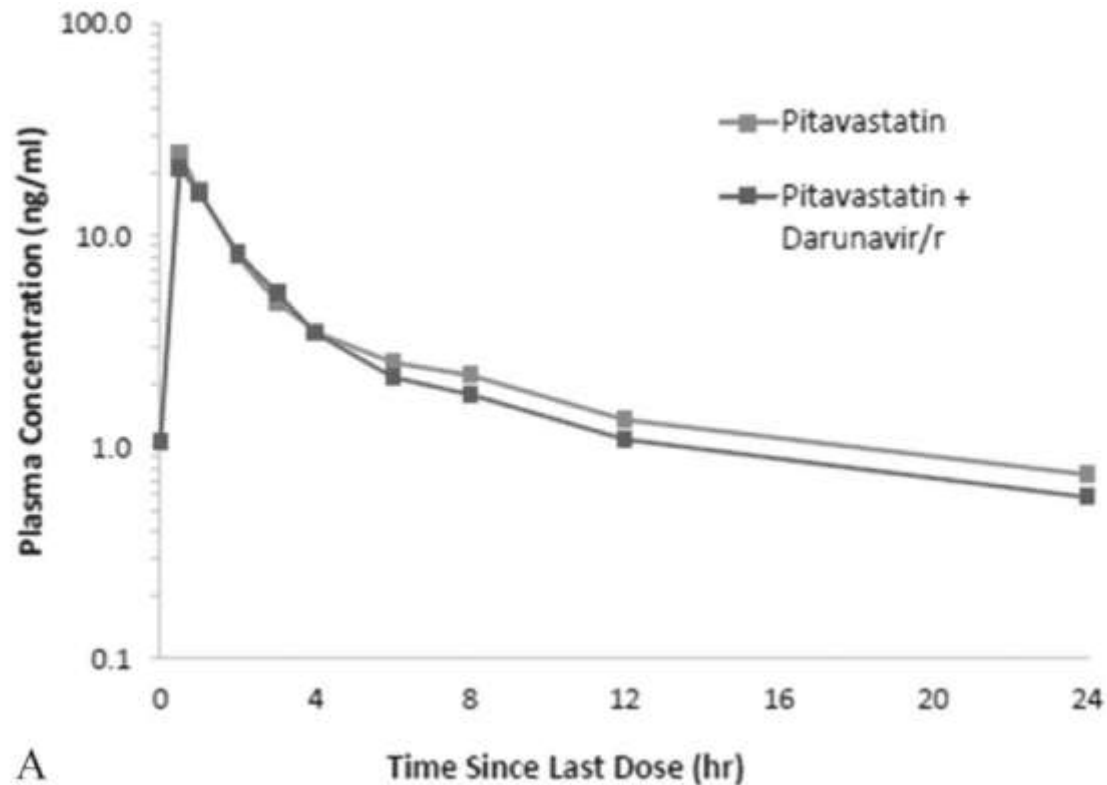
No Interaction Expected

Darunavir + ritonavir (DRV/r)

Pitavastatin

Quality of evidence: Moderate ⓘ

Summary:

Pitavastatin is metabolised by UGTs 1A3 and 2B7 with minimal metabolism by CYPs 2C9 and 2C8. Data from pharmacokinetic studies suggest no clinically significant interaction between darunavir/ritonavir and pravastatin. Coadministration of darunavir/ritonavir (800/100 mg once daily) and pitavastatin (2 or 4 mg once daily) was investigated in two studies in HIV-negative subjects. Coadministration with 2 mg pitavastatin decreased pitavastatin AUC and Cmax by 9% and 7% (n=10) and increased darunavir AUC and Cmax by 8% and 3% (n=14). Coadministration with 4 mg pitavastatin decreased pitavastatin AUC and Cmax by 26% and 4% (n=27) and increased darunavir and ritonavir exposure (darunavir AUC and Cmax increased by 3% and 6%; ritonavir AUC and Cmax increased by 8% and 2%).

www.hiv-druginteractions.org; Malvestutto CD et al. JAIDS 2014

Achievement of lipid targets in patients of the SHCS

- Inclusion of 175 SHCS patients on ARV and receiving a statin
- Individual non-HDL and total cholesterol target values were set using the Framingham score and EACS recommendations
- Achievement of lipid targets based on statin dosing recommendations considering the co-administered ARV

University of Michigan statin dose intensity and equivalence chart

Courlet P et al. J Antimicrob Chemother 2020

www.med.umich.edu/1info/FHP/practiceguides/lipids/lipidsupdate.pdf

www.hiv-druginteractions.org

Interaction Checker

Access our free, comprehensive and user-friendly drug interaction charts

Prescribing Resources

Interaction tables, treatment selectors, clinical prescribing resources, and pharmacokinetic fact sheets

Treatment Selectors (by therapeutic indication)

Summary

- Management HIV infection more challenging in elderly PLWH: comorbitidities, organ dysfunction, age-related physiological changes

- Polypharmacy often unavoidable, avoid unnecessary/inappropriate polypharmacy

- Medication reconciliation, regular medication review, medication prioritization

- Multidisciplinary team approach recommended for care of elderly PLWH

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Liverpool HIV drug interactions websites team members

Basel Institute for Clinical Epidemiology and Biostatistics

Elisabeth Deutschmann

Giusi Moffa