Deprescribing:
The fightback against polypharmacy

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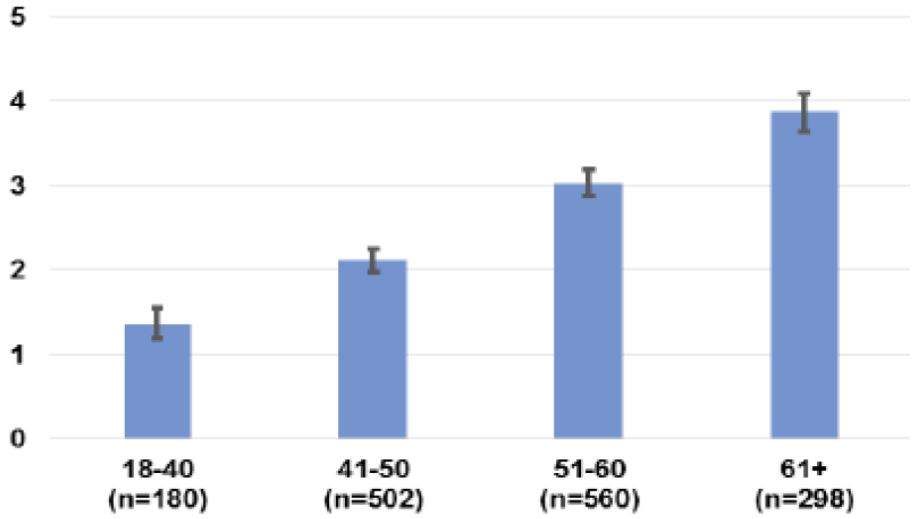
Outline

- Polypharmacy
- Prescribing in elderly
- Deprescribing
- Case presentation

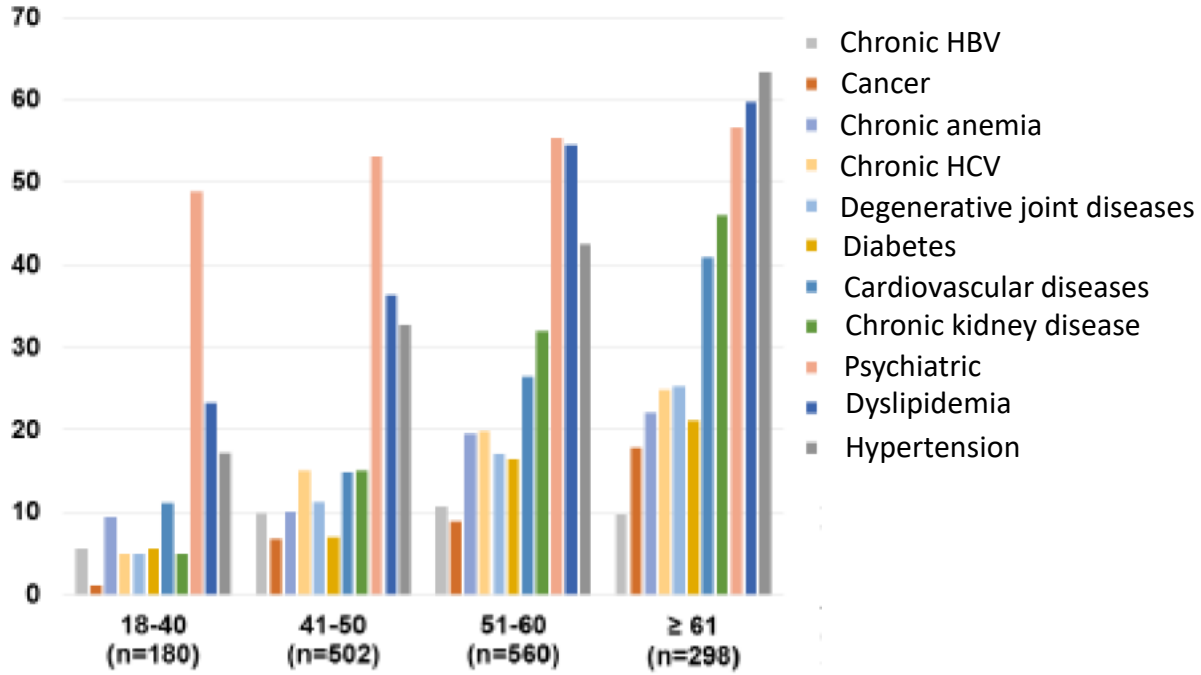
Number and prevalence of comorbidities increase with age

US HIV HOPS cohort

Average number of comorbidities



Prevalence of comorbidities



Similar observations in European/Swiss HIV cohorts:

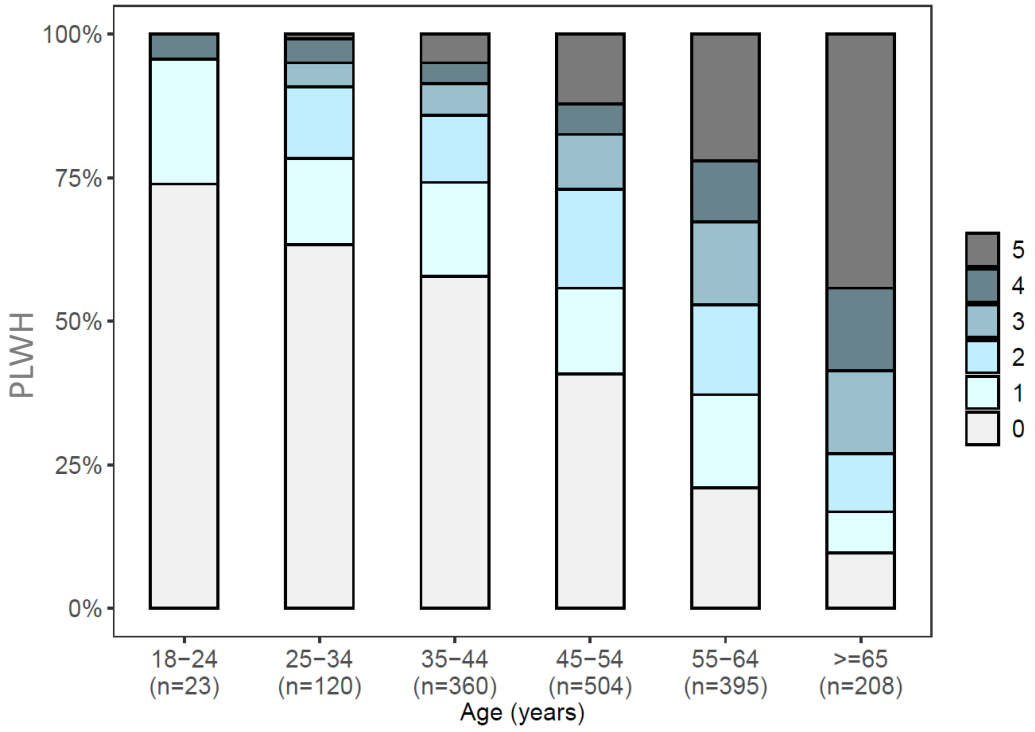
GEPPO cohort (Guaraldi G et al. BMC Geriatr 2018)
EuroSIDA cohort (Pelchen-Matthews A et al. AIDS 2018)
Dat'AIDS cohort (Allavena C et al. PLoS One 2018)
Swiss HIV cohort (Hasse B et al. CID 2011)

Palella FJ et al. AIDS 2019

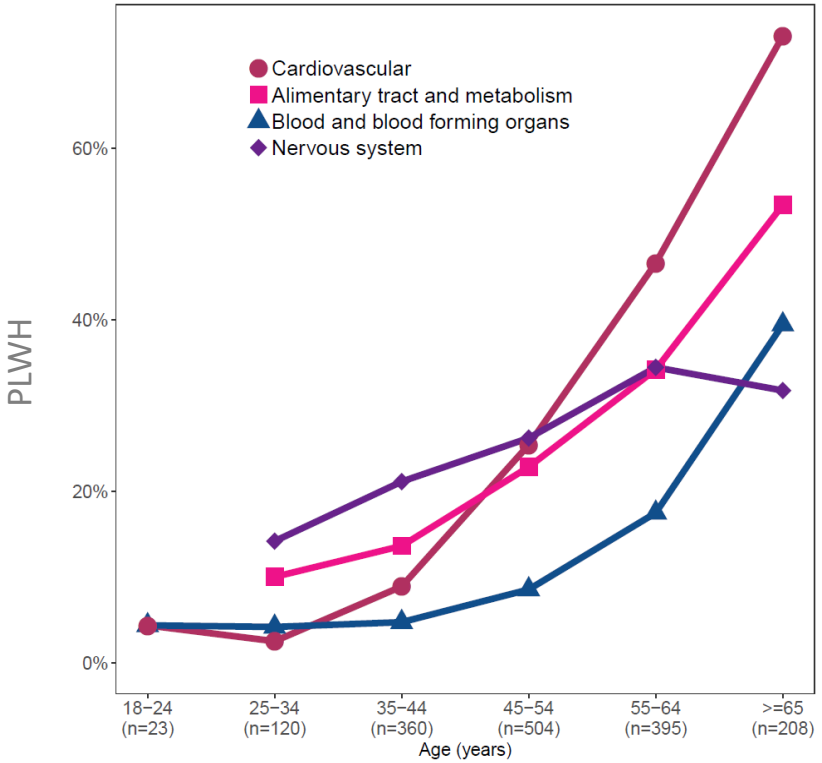
Polypharmacy (≥ 5 non-HIV drugs) increases with age

Swiss HIV Cohort

Number of non- HIV medications



Prevalence of comedications use



Courlet P et al. Open Forum Infect Dis 2020

Polypharmacy is more common in women

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

➔ gender-related biological differences in the occurrence of specific comorbidities (e.g. osteoporosis)

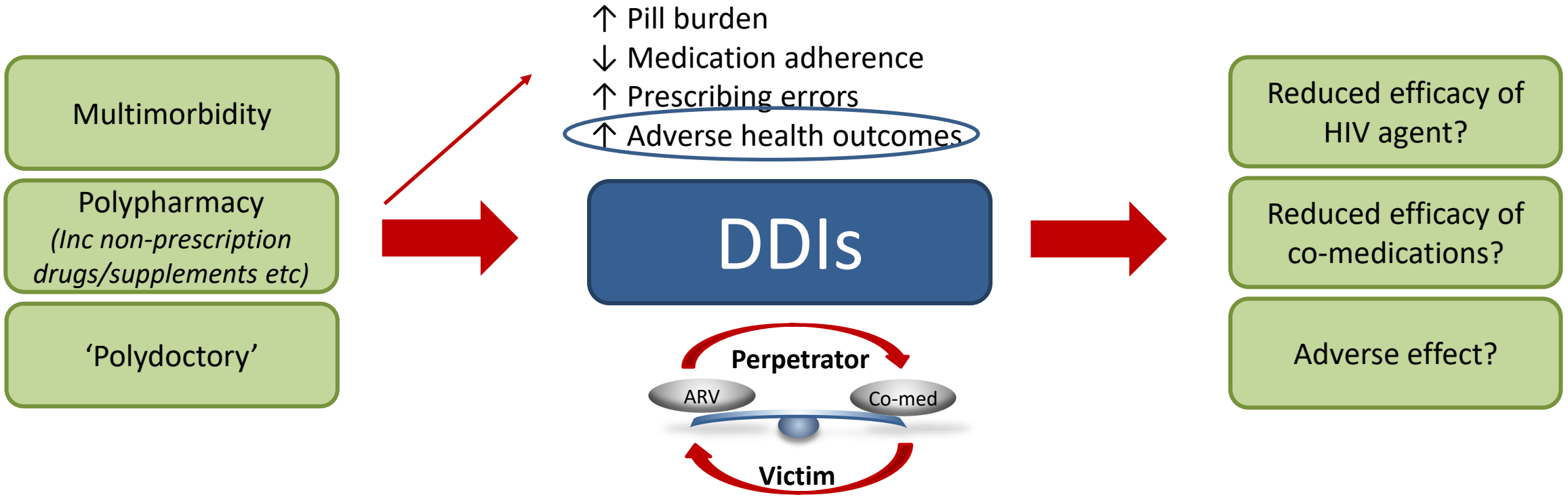
Lopez-Centeno B et al. Clin Infect Dis 2019

Prevalence of polypharmacy in PLWH

Reference	Country	N	Age	Polypharmacy
Livio F et al. Int Work Clin Pharm HIV 2018	Switzerland	111	≥ 75	60 %
Courlet P et al. Open Forum Infect Dis 2020	Switzerland	122	≥ 65	44 %
Guaraldi G et al. BMC Geriatr 2018	Italy	1258	≥ 65	37 %
Justice A et al. AIDS 2018	USA	1311	≥ 65	43 %
Cabanilla G et al. IAS 2019	USA	112	≥ 65	84%
Greene M et al. J Am Geriatr Soc 2014	USA	89	≥ 60	74%
Ware D et al. AIDS Pat Care STDS 2019	USA	1715	≥ 50	36%
Halloran MO et al. Antivir Ther 2019	UK/Ireland	698	≥ 50	30 %
Mazzitelli M et al. AIDS 2020	UK	790	≥ 50	45%
Lopez-Centeno B et al. Clin Infec Dis 2019	Spain	10073	≥ 50	47 %
Nunez-Nunez M et al. Farm Hosp 2018	Spain	242	≥ 50	48 %
Mc Nicholl I et al. Pharmacother 2017	USA	248	≥ 50	94%
Holtzman C et al. J Gen Intern Med 2013	USA	1312	≥ 50	54 %
Krentz H et al. AIDS Pat Care STDS 2016	Canada	386	≥ 50	43 %
Ruzicka DJ et al. BMJ Open 2018	Japan	526	≥ 50	35 %
Ssonko M et al. BMC Geriatr 2018	Uganda	411	≥ 50	15 %

Back D & Marzolini C. J Int AIDS Soc 2020 (in press)

Negative consequences of polypharmacy



Plenary lecture of Prof. D. Back. CROI 2019

Polypharmacy could be a major contributor of frailty

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) **84** 1432–1444 1432

SYSTEMATIC REVIEW AND META–ANALYSIS

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

Polypharmacy more deleterious in prefail & frail individuals

Association between polypharmacy, frailty, health outcome

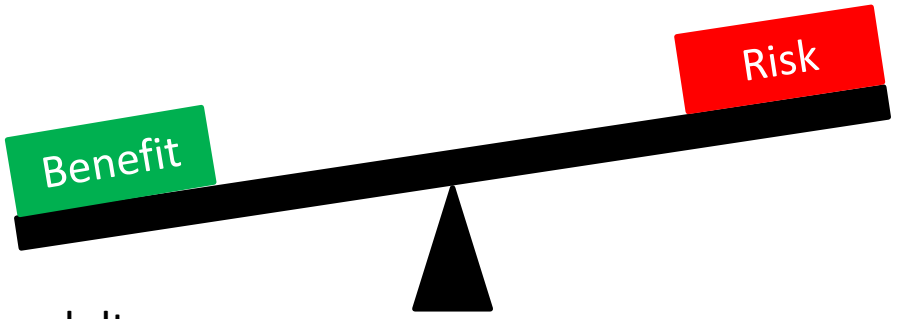
	Mortality or Incident Disability	Incident Disability	Mortality	Hospitalization
G6: Frail-Polypharmacy (n = 118)				
Model 1	27.6 (13.1-58.0)*	24.6 (10.1–60.1)*	13.1 (4.5–38.3)*	3.4 (2.0–6.0)*
Model 2	15.4 (7.0–34.0)*	12.0 (4.7–30.7)*	9.3 (3.0–29.0)*	3.4 (1.8–6.2)*
Model 3	5.3 (2.3–12.5)*	4.7 (1.7–12.8)†	3.8 (1.2–12.5)*,‡	2.3 (1.2–4.4)*
G5: Frail–No Polypharmacy (n = 26)				
Model 1	13.4 (5.0–36.2)*	21.4 (6.6–69.6)*	3.8 (0.8–17.9)	1.4 (0.5–3.5)
Model 2	5.0 (1.7–15.1)†	6.1 (1.7–22.0)†	2.3 (0.4–12.3)	1.3 (0.5–3.7)
Model 3	1.9 (0.6–6.1)	2.1 (0.5–8.5)	1.2 (0.2–6.6)	1.1 (0.4–3.1)
G4: Prefrail-Polypharmacy (n = 273)				
Model 1	8.4 (4.3–16.4)*	8.7 (3.8–19.5)*	5.4 (1.9–15.3)‡	2.1 (1.3–3.4)†
Model 2	5.2 (2.6–10.6)*	4.8 (2.0–11.2)*	4.2 (1.4–12.6)‡	2.2 (1.3–3.7)†
Model 3	3.2 (1.6–6.6)†	3.4 (1.4–8.0)†	2.4 (0.8–7.5)	1.8 (1.1–3.2)*
G3: Prefrail-No Polypharmacy (n = 157)				
Model 1	2.9 (1.4–6.0)†	3.5 (1.5–8.3)†	1.7 (0.5–5.8)	0.8 (0.5–1.5)
Model 2	2.0 (0.9–4.3)	2.2 (0.9–5.4)	1.4 (0.4–4.8)	0.8 (0.5–1.5)
Model 3	1.7 (0.8–3.6)	1.8 (0.7–4.8)	1.2 (0.3–4.1)	0.8 (0.5–1.5)
G2: Nonfrail-Polypharmacy (n = 80)				
Model 1	2.1 (0.9–4.9)	2.8 (1.0–7.5)*	0.7 (0.1–4.1)	1.1 (0.6–2.1)
Model 2	1.6 (0.7–3.9)	2.0 (0.7–5.5)	0.7 (0.1–3.8)	1.2 (0.6–2.3)
Model 3	1.3 (0.5–3.3)	1.8 (0.6–4.9)	0.5 (0.1–3.1)	1.1 (0.5–2.1)

Reference group: nonfrail-no polypharmacy

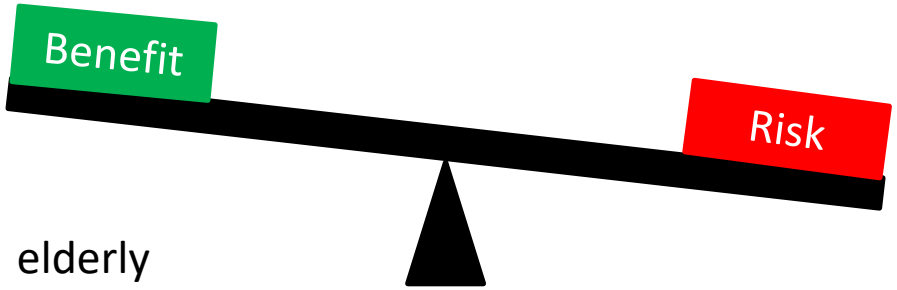
Bonaga B et al. J Am Med Dir Assoc 2018

Prescribing in elderly

Risk/benefit balance of medications



adults



elderly

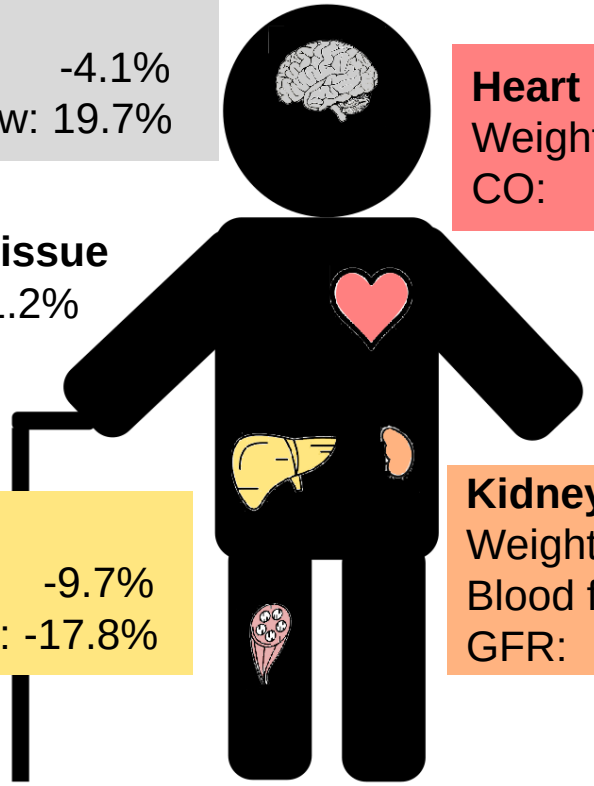
Multiple comorbidities => polypharmacy => ↑DDIs, side effets

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.

Age associated physiological changes in 70 years relative to 30 years old

70 years old man



Brain
Weight: -4.1%
Blood flow: 19.7%

Heart
Weight: 12.3%
CO: -21.3%

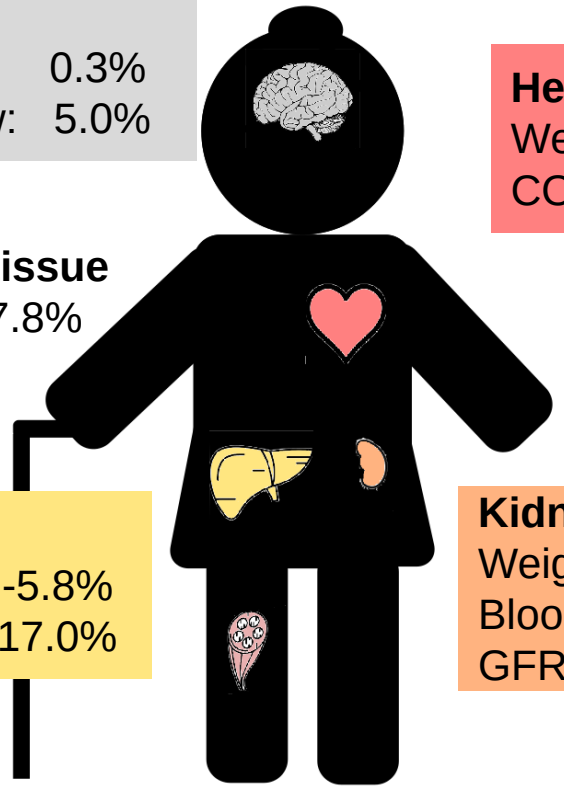
Adipose tissue
Weight: 11.2%

Liver
Weight: -9.7%
Blood flow: -17.8%

Kidney
Weight: -3.7%
Blood flow: -23.5%
GFR: -26.6%

Muscle
Weight: -11.6%

70 years old women



Brain
Weight: 0.3%
Blood flow: 5.0%

Heart
Weight: 19.8%
CO: -21.0%

Adipose tissue
Weight: 27.8%

Liver
Weight: -5.8%
Blood flow: -17.0%

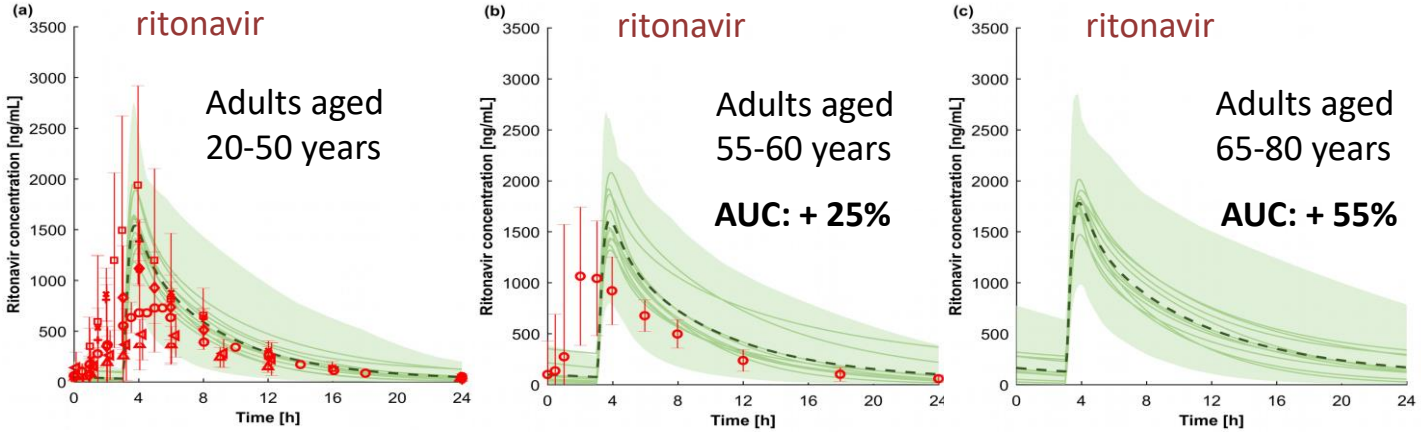
Kidney
Weight: -5.9%
Blood flow: -26.5%
GFR: -24.2%

Muscle
Weight: -13.6%

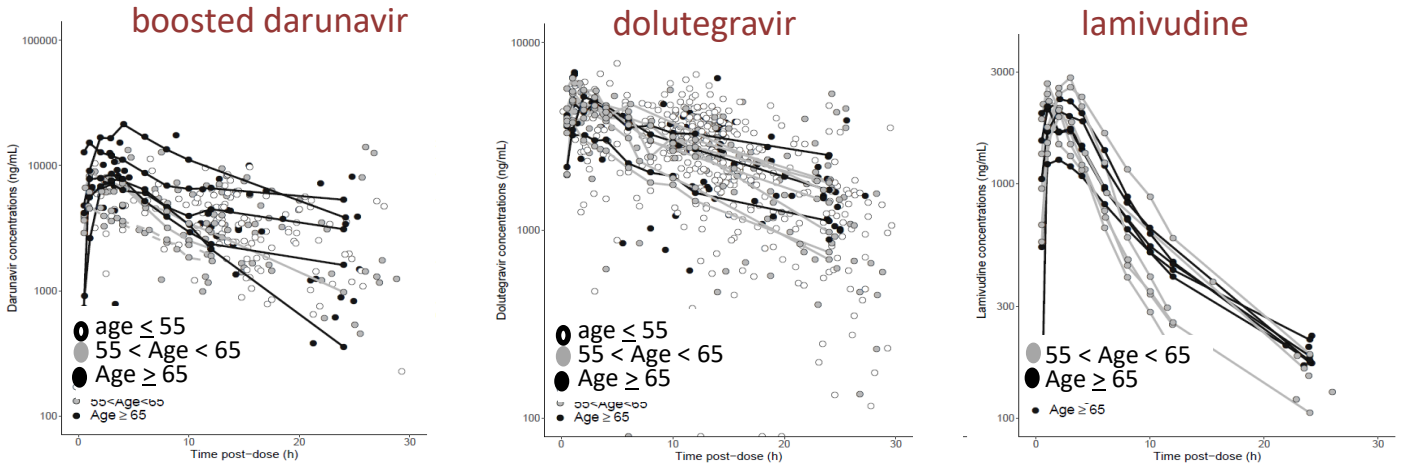
Stader F et al. Clin Pharmacokinet 2019

Aging and effect on the pharmacokinetics of antiretroviral drugs

Pharmacokinetic simulations



Clinical data

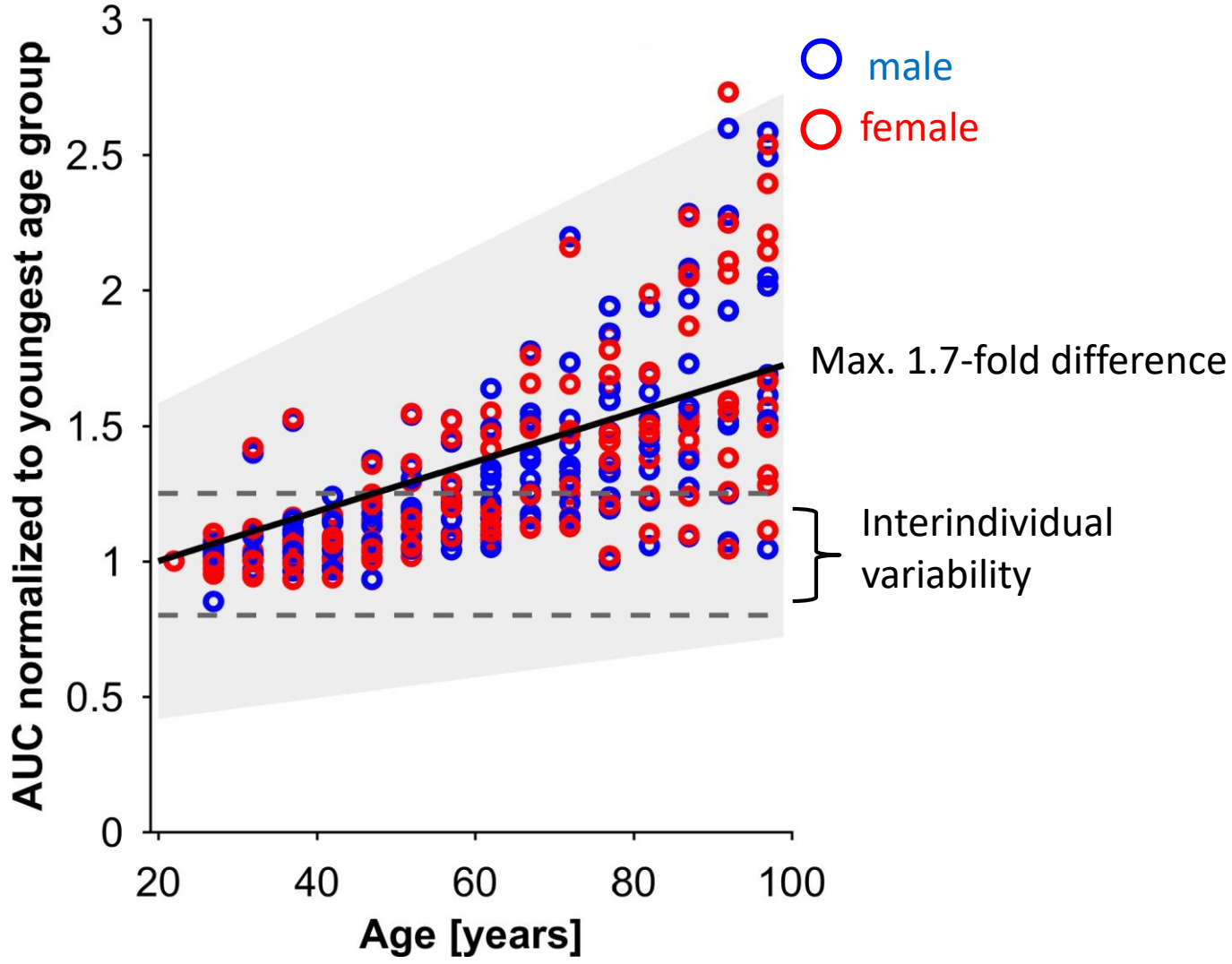


Older age does not impact antiretrovirals pharmacokinetics to a clinically significant extent in absence of severe comorbidities

Courlet P et al. AIDS 2019; Stader F et al. International Workshop Clin Pharmacol Antivir Ther 2019

Aging and effect on the pharmacokinetics of non-HIV drugs

Impact of aging on drug exposure



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

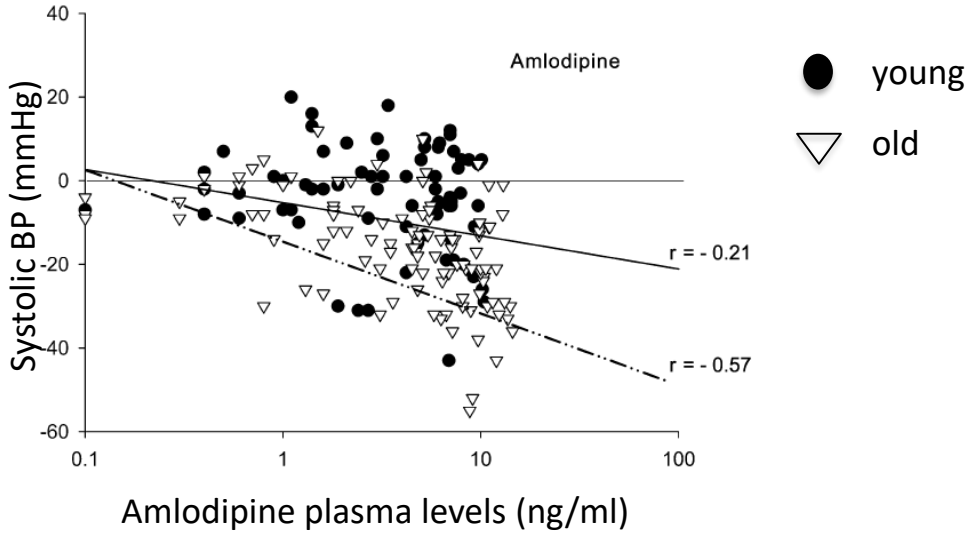
No predicted difference for men and women.

Stader F et al. Clin Pharmacokinet 2019

Age related pharmacodynamic changes

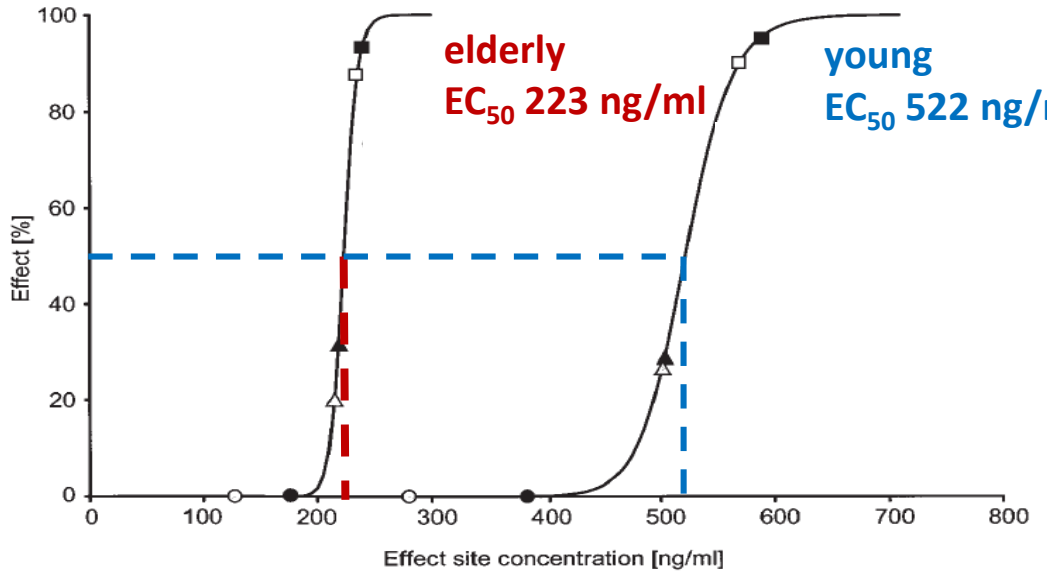
- regulation of some physiological processes (i.e renal hemodynamics) altered with aging
- changes in affinity of some medications to receptor sites or in number of receptors ➔ affect efficacy or increase sensitivity to certain drugs

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



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

Drugs with anticholinergic effects and cognitive performance

- Elderly are more sensitive to drugs with anticholinergic activity due to significant decrease in cholinergic receptors in the brain. Drugs with anticholinergic properties are inappropriate as can impair cognition.

Anticholinergic drugs (AC) use in elderly PLWH

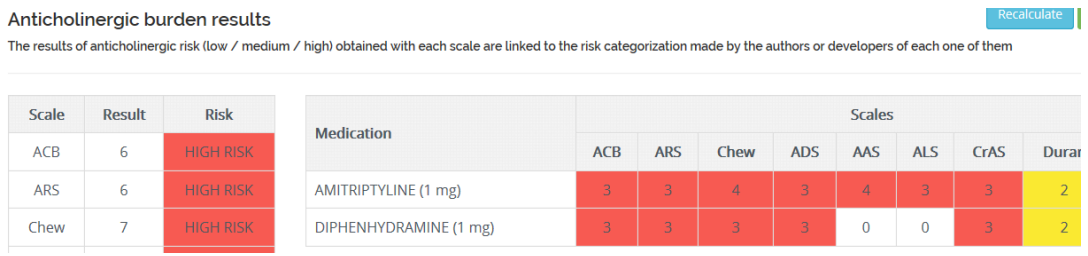
Reference	Age	N	Country	Prevalence AC	AC score ≥ 3
Mazzitelli M et al. AIDS 2019	≥ 50 years	790	UK	14%	3%

Selected anticholinergic drugs

amitriptyline	clozapine	imipramine	promethazine
atropine	darifenacin	nortriptyline	scopolamine
chlorpheniramine	desipramine	olanzapine	thioridazine
chlorpromazine	diphenhydramine	oxybutynin	tolterodine
clomipramine	doxepin	paroxetine	trimipramine

Online calculator

http://anticholinergicscales.es/calculate


Anticholinergic burden results

Recalculate

The results of anticholinergic risk (low / medium / high) obtained with each scale are linked to the risk categorization made by the authors or developers of each one of them

Scale	Result	Risk
ACB	6	HIGH RISK
ARS	6	HIGH RISK
Chew	7	HIGH RISK

Medication	Scales							
	ACB	ARS	Chew	ADS	AAS	ALS	CrAS	Durar
AMITRIPTYLINE (1 mg)	3	3	4	3	4	3	3	2
DIPHENHYDRAMINE (1 mg)	3	3	3	3	0	0	3	2

Boustani M et al. Aging Health 2008

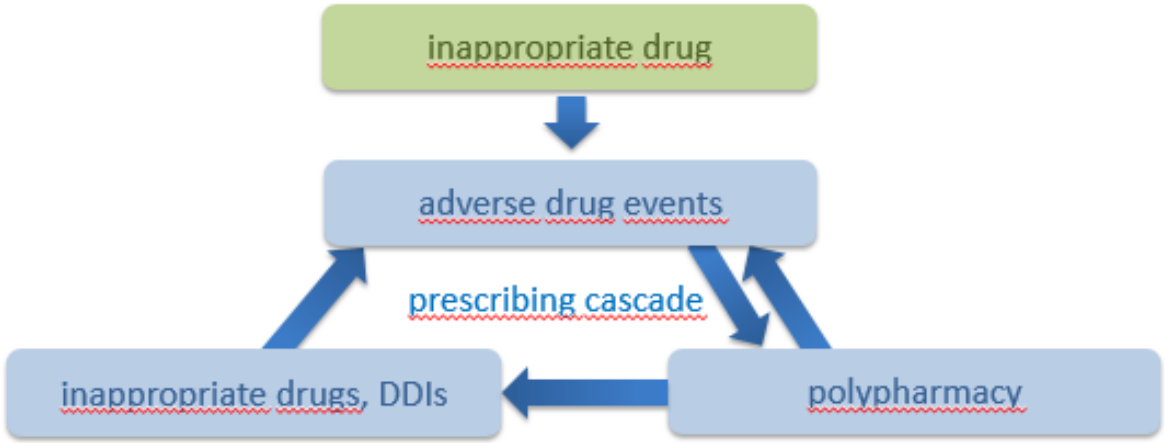
Prescribing cascade

www.hiv-druginteractions.org

Common Prescribing Cascades to Avoid in Elderly PLWH

Produced July 2019

Initial treatment	Adverse drug reaction	Subsequent treatment
ACE inhibitors	Cough	Cough suppressant; antibiotic
Amlodipine	Edema	Diuretics
Antihypertensives	Dizziness	Prochlorperazine
Antipsychotics	Extrapyramidal effect	Antiparkinsonian agents
Beta-blockers	Depression	Antidepressants
Cholinesterase inhibitors	↗ Incontinence	Anticholinergics
	→ Diarrhoea	Bismuth subsalicylate
	↘ Rhinorrhoea	Diphenhydramine
Erythromycin	Arrhythmia	Antiarrhythmics
Lithium	Tremor	Propranolol
Meperidine	Delirium	Antipsychotics*
Metoclopramide	Extrapyramidal effect	Antiparkinsonian agents
NSAIDs	Rise in blood pressure	Antihypertensives
Quinolone	Delirium	Antipsychotics*
SSRI; SNRI	Tremor	Benzodiazepines
Thiazide diuretics	Hyperuricemia; gout	Allopurinol; colchicine
	↗ Decreased cognition	Cholinesterase inhibitors*



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)

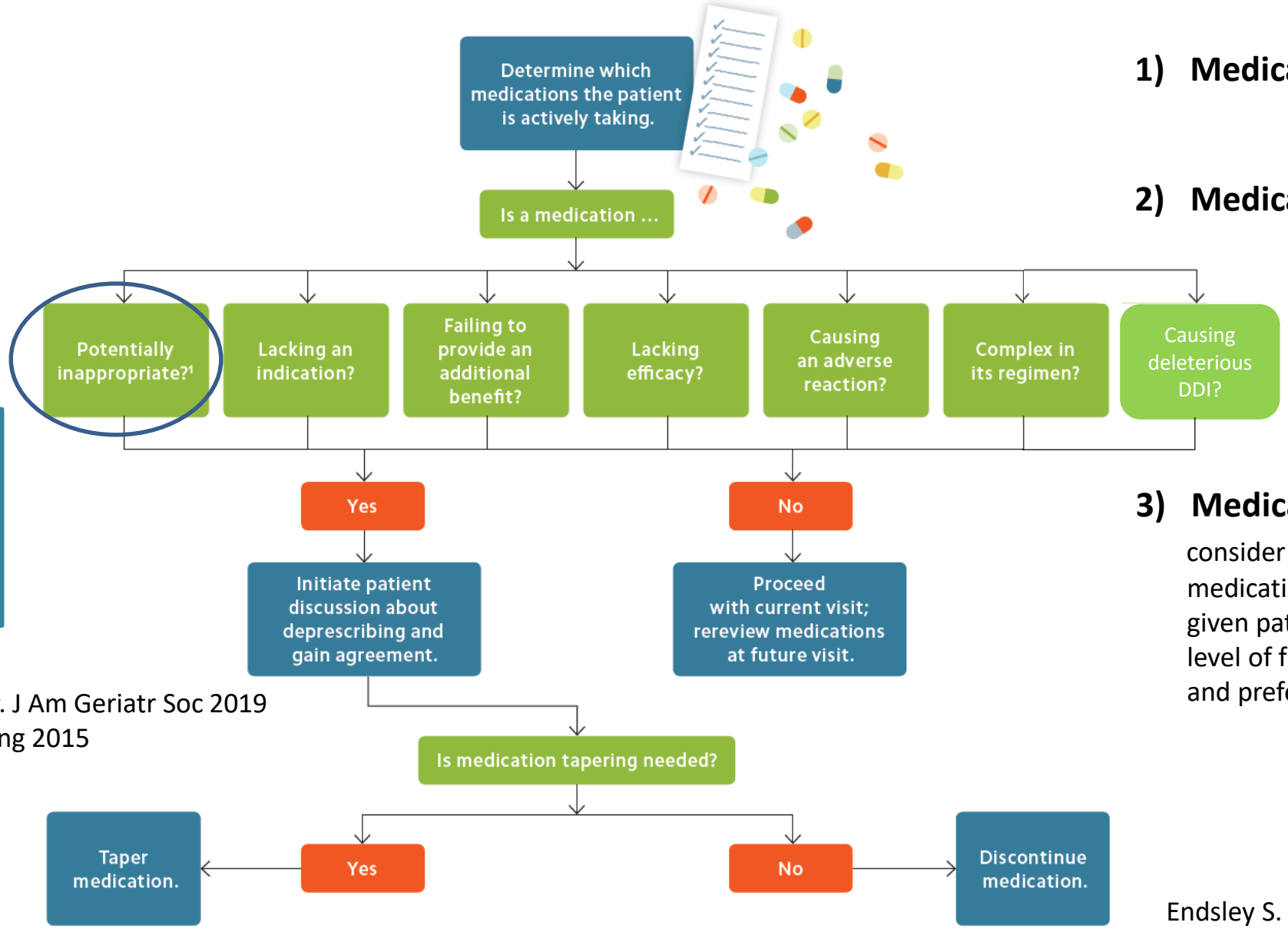
Scott IA et al. JAMA Intern Med 2015; Bain K et al. J Am Geriatr Soc 2008

Deprescribing algorithm

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

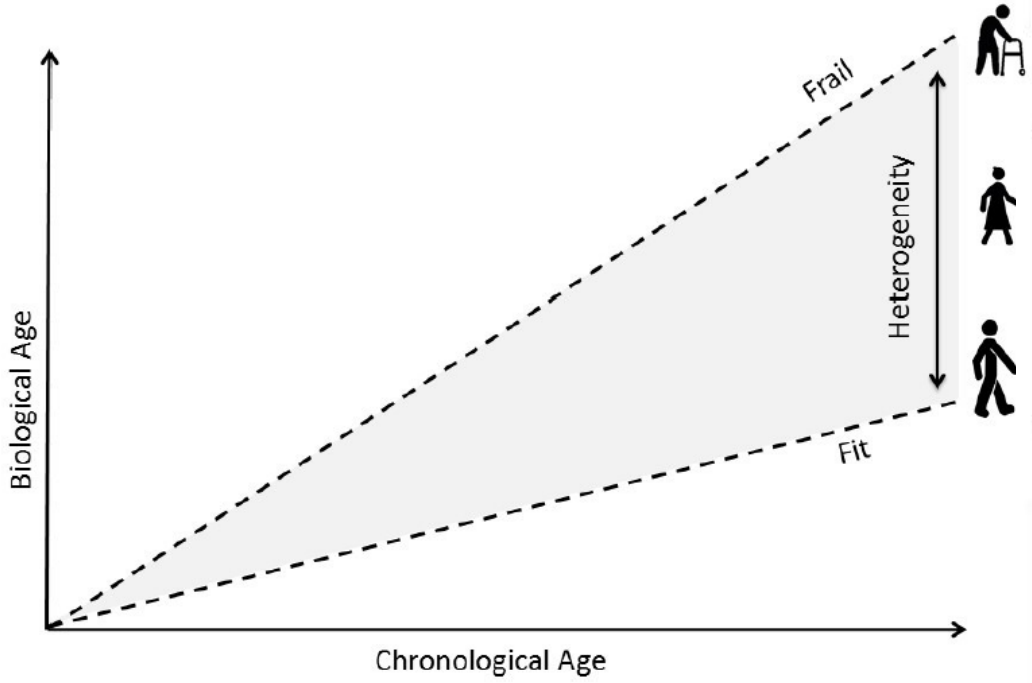
3) Medication prioritization

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

Benefit of medications varies depending on clinical status

Increasing heterogeneity in biological age with increasing chronological age



Patient 3
Male, 75 years
Diabetes, MI, heart failure (NYHA III), cognitive impairment
RR 140/85 mmHg
HDL 1, LDL-c 3.8 mmol/L
Diabetes, total no. drugs 9 (incl. statin)
eGFR 30 mL/min/1.73m²

Life expectancy < 2 years
⇒ Life expectancy does not exceed time until benefit of statin.
Consider deprescribing statin

Patient 2
Female, 75 years
Smoker, osteoporosis, HT
RR 160/90 mmHg
HDL 1.3, LDL-c 3.8 mmol/L
Total no. drugs 6
eGFR 60 mL/min/1.73m²

Life expectancy ± 10 y, 10-y CVD risk 28%
⇒ High risk of CVD, life expectancy is long enough to benefit in terms of gain in CVD-free years.
Consider starting statin

Patient 1
Female, 75 years
Osteoarthritis
RR 140/85 mmHg
HDL 1.3, LDL-c 3.8 mmol/L
Total no. drugs 3
eGFR 60 mL/min/1.73m²

Life expectancy ± 14 y, 10-y CVD risk 10%
⇒ Lifetime absolute risk reduction in CVD-free years would be estimated to be too low.
Do not initiate statin

Kleipool EF et al 2019

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

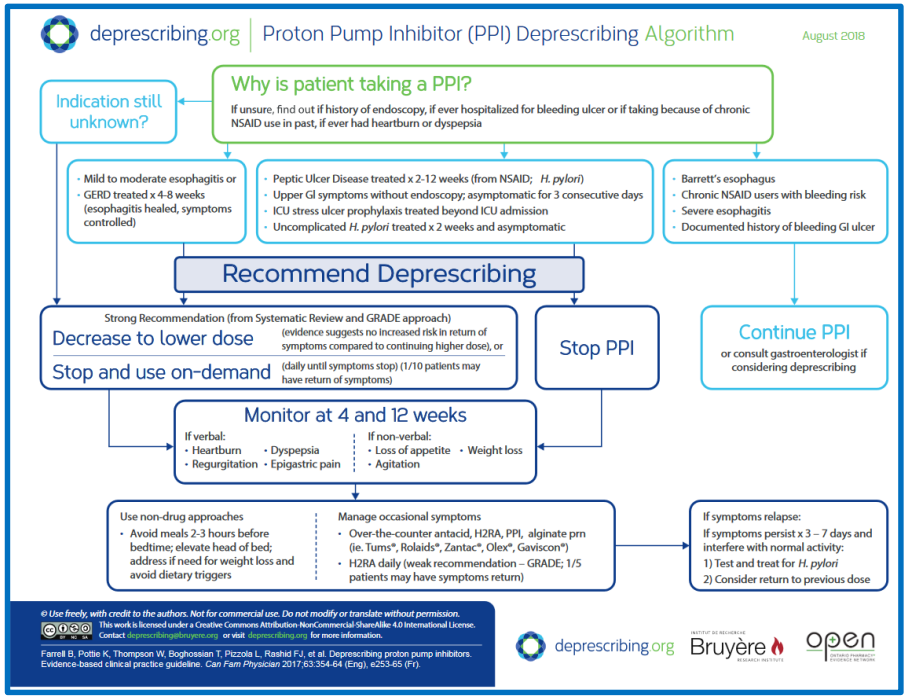
Drug	In favour of deprescribing	Against deprescribing
Antipsychotics	• High risk of falls • Use for symptoms that are unlikely to respond (apathy, antisocial behaviour) • Parkinson's disease or other mouvement disorder • Risk factors for arrhythmias	• Severe behavioural and psychological symptoms of 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

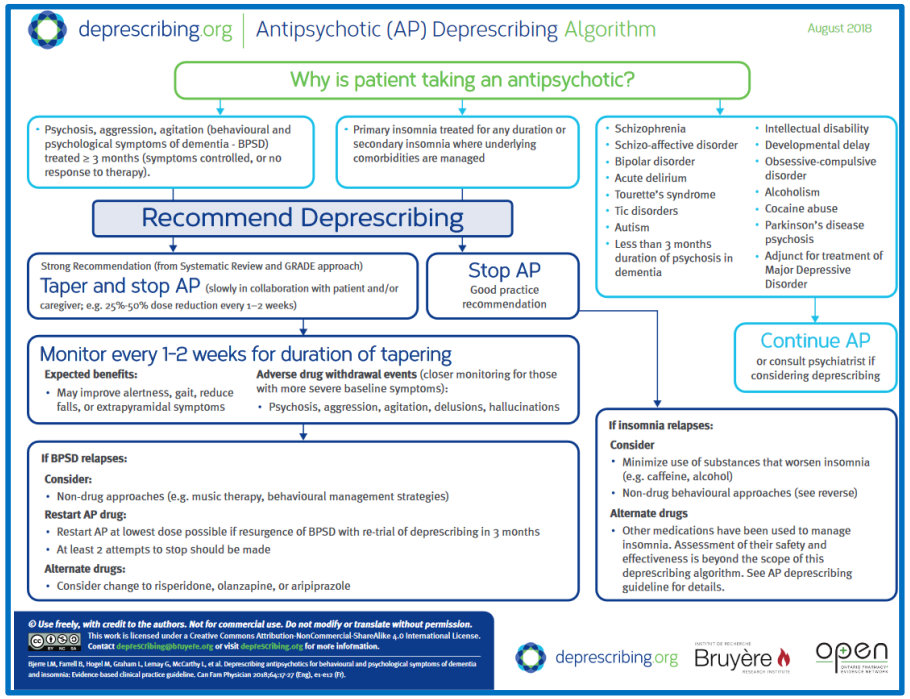
McGrath K et al. J Pharm Pract 2017; Disdier Moulder M et al. Clin Cardiology 2019; www.primaryhealthtas.com.au/resources/deprescribing-resources

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

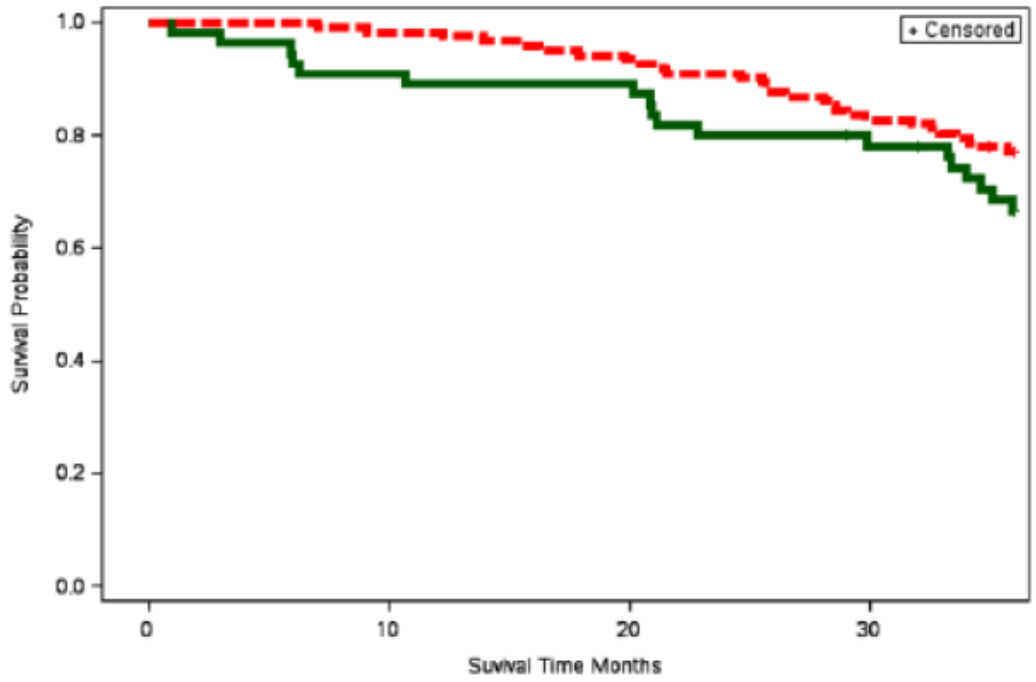
Medication/ Category/ Condition	Suggested Taper Approach	Possible Symptoms when Stopping or Tapering
midazolam (Versed) / Benzodiazepine / **insomnia**	If used daily for more than 3-4 weeks. Reduce dose by 25% every week (i.e. week 1-75%, week 2-50%, week 3-25%) and this can be extended or decreased (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

- 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

- 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

- Reluctance to discontinue medications prescribed by another clinician
- Fear for potential deleterious consequences
- Concern with patients' resistance to change
- Pressure to conform to disease specific treatment guidelines
- Limited time for medication review and discussion with patient

Patients barriers

- Physical dependence to a medication
- Previous negative experience with drug withdrawal
- Fear of consequences of stopping a medication
- 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

Benzodiazepines deprescribing

Risk/benefit of sedative hypnotics is unfavorable: Nb needed to treat (**NNT**) for sleep improvement = **13**

Nb needed to harm (**NNH**) for any adverse event = **6**

➔ adverse events more than twice likely to occur compared to gain in sleep quality

Glass J et al. BMJ 2005

Studies assessing interventions to deprescribe BZD

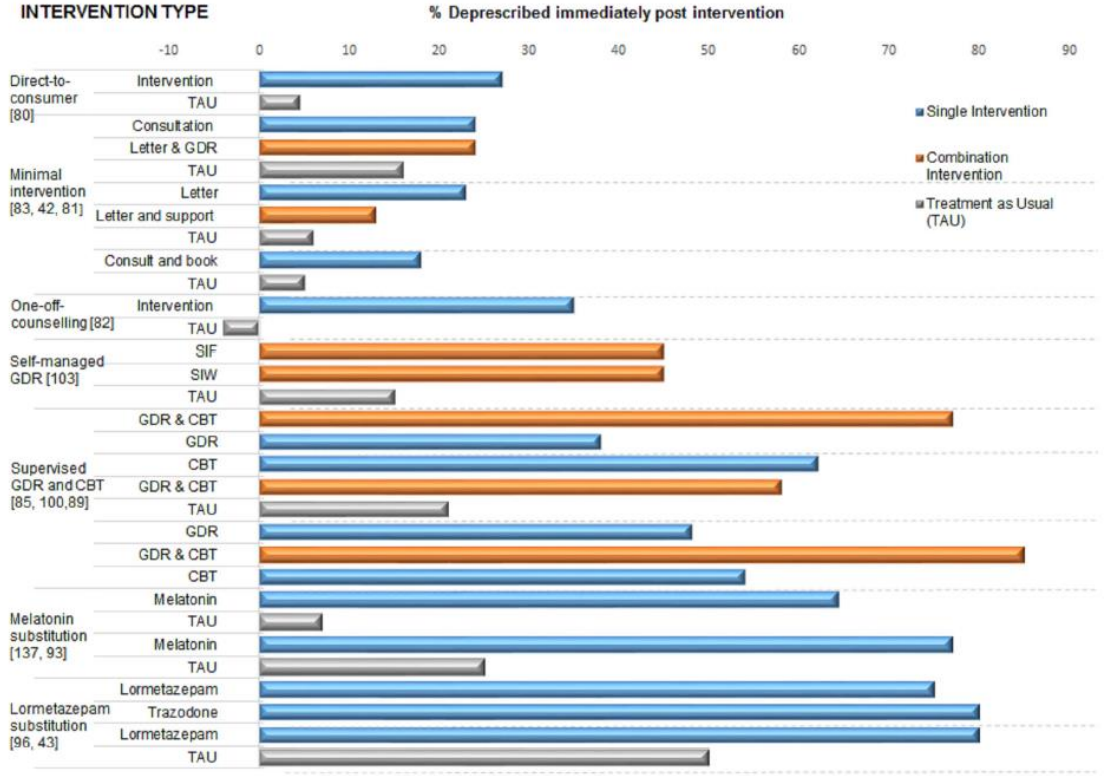


Fig. 1 Rates of successful deprescribing post-study in controlled trials. *TAU* treatment as usual, *SIF* structured interview and follow-up, *SIW* structured interview and written instructions, *GDR* gradual dose reduction, *CBT* cognitive behavioural therapy

Direct to consumer intervention: raise patient awareness of BZD chronic use harm (patient information leaflet)

Minimal intervention: letter from practitioner to patient suggesting cessation or gradual dose reduction

One-off counselling: counselling by geriatrician performed once

GDR: gradual benzodiazepine dose reduction

CBT: cognitive behavioural therapy

Evidence seem to support multistrategic approach

Ng B et al. Drug Aging 2018

62-year old woman

HIV physician note:

Older woman followed-up by several specialists.
Current issue: polypharmacy
Next follow-up visit in January 2020: plan longer consultation time for medication review

HIV infection
(since 2002)

Co-morbidities
Myocardial infarction (10/2019)
Urticaria
Depression
Neucocognitive disorders
Pulmonary embolism (2014)

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

Co-medications
clopidogrel 75 mg QD
aspirin 100 mg QD
metoprolol 25 mg QD
atorvastatin 20 mg QD
clomipramine 75 mg QD
clemastine 1 mg BID
estradiol 1mg QD
dydrogesterone 5 mg QD
esomeprazole 20 mg QD

Immunological/virological parameters
HIV VL: < 20 copies/ml
CD4: 457 cells/mm3

Serum chemistry
eGFR 79 ml/min/1.73
Sodium: 138 mmol/l
Potassium: 3.8 mmol/l
Hepatic enzymes: normal
Glucose: 5 mmol/l
Total cholesterol: 5.1 mmol/l
HDL cholesterol: 1.3 mmol/l
LDL cholesterol: 1.8 mmol/l
TG: 1.5 mmol/l

62-year old woman

HIV infection
(since 2002)

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: 457 cells/mm3

Step 1
Check **indication**

Co-morbidities
Myocardial infarction (10/2019)
Urticaria
Depression
Neucocognitive disorders
Pulmonary embolism (2014)

Co-medications
clopidogrel 75 mg QD
aspirin 100 mg QD
metoprolol 25 mg QD
atorvastatin 20 mg QD
clomipramine 75 mg QD
clemastine 1 mg BID
~~estradiol 1mg QD~~
~~dydrogesterone 5 mg QD~~
~~esomeprazole 20 mg QD~~

Serum chemistry
eGFR 79 ml/min
Sodium: 138 mmol/l
Potassium: 3.8 mmol/l
Hepatic enzymes: normal
Glucose: 5 mmol/l
Total cholesterol: 5.1 mmol/l
HDL cholesterol: 1.3 mmol/l
LDL cholesterol: 1.8 mmol/l
TG: 1.5 mmol/l

- No indication for PPI, patient has no history of reflux or ulcer ➔ stop esomeprazole
- HRT: patient was told that HRT is good for bone health
  ➔ there is clearly no indication to maintain HRT: obviously no benefit in terms of reduction of the risk of coronary heart disease in this patient! Furthermore, the patient has an history of pulmonary embolism! In addition, there are DDIs between hormones and boosted ARV.

DDIs with hormone replacement therapy

antiretrovirals

Boosted ARVs
- RTV exhibit mixed inhibition (CYP) -induction (UGT)
- Cobi inhibits CYP 3A
- ATV inhibits CYP 3A and UGT

NNRTIs
- CYP 3A inducers: EFV > ETV / NVP
- RPV and DOR have no inducing effects

Estradiol
- CYP3A4, CYP1A2, UGT

Progestins:
- Mainly CYP3A4 metabolism
- Provides most of contraceptive effect

Hormones for menopause

The use of hormone replacement therapy is controversial in the general population.

Concerns have been raised about the additive risk of hormone replacement therapy, HIV and ART on cardiovascular disease and stroke, and deep vein thrombophlebitis.[100] If required for management of vasomotor symptoms, hormone replacement therapy should be prescribed early in the menopausal period, for as short a period as possible, and in the lowest dose possible. In addition, clinicians need to consider drug interactions with ART when prescribing hormone replacement therapy,

www.hiv-druginteractions.org — University of Liverpool

HRT Treatment Selector

Charts revised February 2019. Full information available at www.hiv-druginteractions.org

	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC/ F/TAF	DTG	EVG/C/ F/TAF	EVG/C/ F/TDF	RAL	FTC or 3TC	F/TAF	TDF	ZDV
Estrogens																				
Estradiol	↑[a]	↓[b]	↑[a]	↓[b]	↓[b]	↔	↓[b]	↓[b]	↓[b]	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔
Progestins (HRT)																				
Drospirenone	↑[a,c]	↑[a]	↑[a]	↑[a]	↑[a]	↔	↓[b]	↓[b]	↓[b]	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔
Dydrogesterone	↑[a]	↑[a]	↑[a]	↑[a]	↑[a]	↔	↓[b]	↓[b]	↓[b]	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔
Levonorgestrel	↑[a]	↑[a]	↑[a]	↑[a]	↑[a]	↔	↓[b]	↓[b]	↓[b]	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔
Medroxy-progesterone (oral)	↑[a]	↑[a]	↑[a]	↑[a]	↑[a]	↔	↓[b]	↓[b]	↓[b]	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔
Norethisterone (Norethindrone)	↑[a]	↑[a]	↑[a]	↑[a]	↑[a]	↔	↓[b]	↓[b]	↓[b]	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔
Norgestrel	↑[a]	↑[a]	↑[a]	↑[a]	↑[a]	↔	↓[b]	↓[b]	↓[b]	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔

Sundermann E et al. AIDS Res Hum Retroviruses 2019

62-year old woman

HIV infection
(since 2002)

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: 457 cells/mm3

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

(i.e.

10 mg QD

62-year old woman

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(since 2002)

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emtricitabine 200 mg QD
tenofovir alafenamide 10 mg QD

Immunological/virological parameters
HIV VL: < 20 copies/ml
CD4: 457 cells/mm3

Step 3
Check **DDIs/dose**

Co-morbidities
Myocardial infarction (10/2019)
Urticaria
Depression
Neucocognitive disorders
Pulmonary embolism (2014)

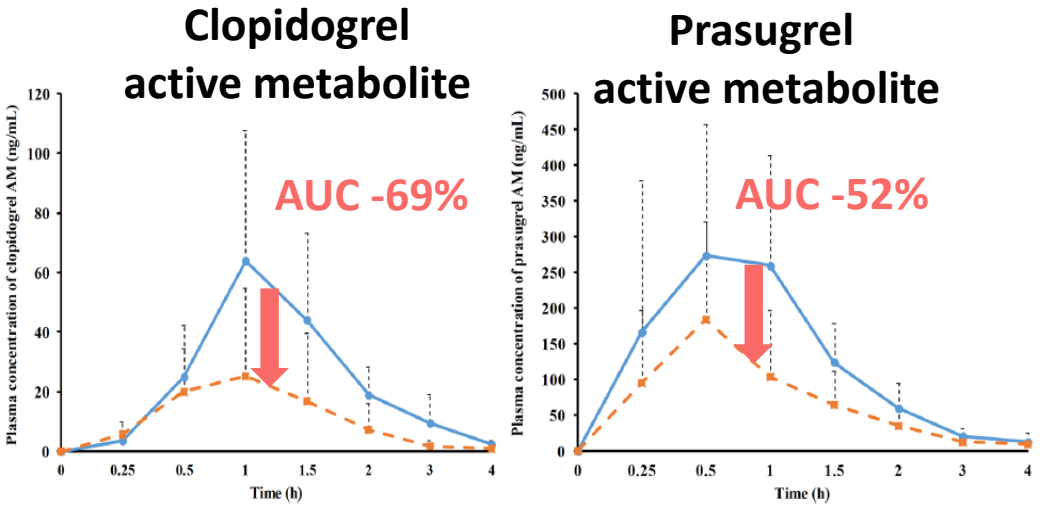
Co-medications
clopidogrel 75 mg QD ✗
aspirin 100 mg QD ✓
metoprolol 25 mg QD ✓
atorvastatin 20 mg QD ✓
escitalopram 20 mg QD ✓
loratadine 10 mg QD ✓
estradiol 1mg QD
dydrogesterone 5 mg QD
esomeprazole 20 mg QD

Serum chemistry
eGFR 79 ml/min
Sodium: 138 mmol/l
Potassium: 3.8 mmol/l
Hepatic enzymes: normal
Glucose: 5 mmol/l
Total cholesterol: 5.1 mmol/l
HDL cholesterol: 1.3 mmol/l
LDL cholesterol: 1.8 mmol/l
TG: 1.5 mmol/l

- I wish the cardiologist would have asked me whether clopidogrel was the best choice considering the current antiretroviral treatment !!!

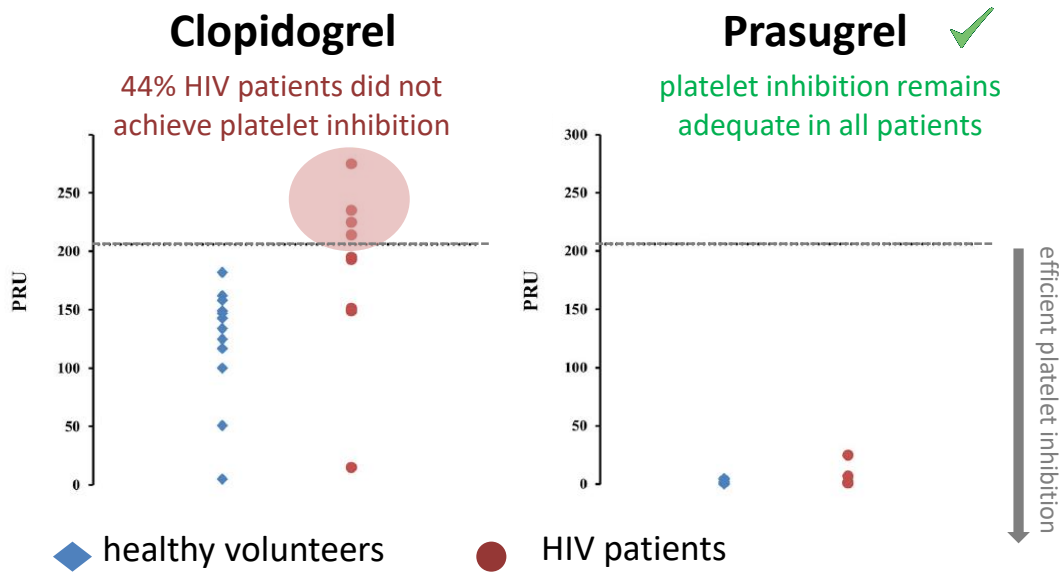
PK/PD DDI between boosted regimens and clopidogrel or prasugrel

PK effect



Second independent clinical study:
clopidogrel + RTV ➔ clopidogrel active met. **AUC -49%**

PD effect (platelet receptor blockade measured with VerifyNow®)



Second independent clinical study:
platelet aggregation inhibition: **51%** (clopidogrel alone) vs **31%** (clopidogrel + RTV)

Cases reports of the deleterious DDI between clopidogrel and boosted regimens start to emerge

- **avoid clopidogrel with boosted HIV regimens**
- use prasugrel unless patient has a clinical condition (e.g. history of stroke or transient ischaemic attack) which contraindicates its use in which case an alternative HIV regimen should be considered
- No DDIs with unboosted ARVs

Marsousi N et al. Clin Pharmacokinet 2018; Itkonen MK et al. Clin Pharmacol Ther 2018, Bravo I et al. BJCP 2018

DDIs with statins

Differences in magnitude of drug-drug interactions with statins explained by different metabolic pathways and affinities to drug transporters.

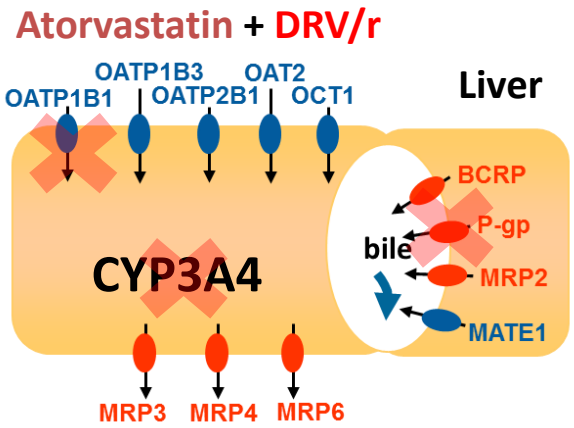
Atorvastatin +
(CYP3A4 + transporters)

ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	EVG/c
↑822%	↑	↑290%	↑	↑490%	↑

OATP1B1 inhibition: ATV > LPV > DRV > RTV, Cobi

Recommendations

	ATV/c	DRV/c
Atorvastatin	NR/lowest dose Max: 10 mg/d	lowest dose Max: 40 mg/d (US label: 20 mg/d)

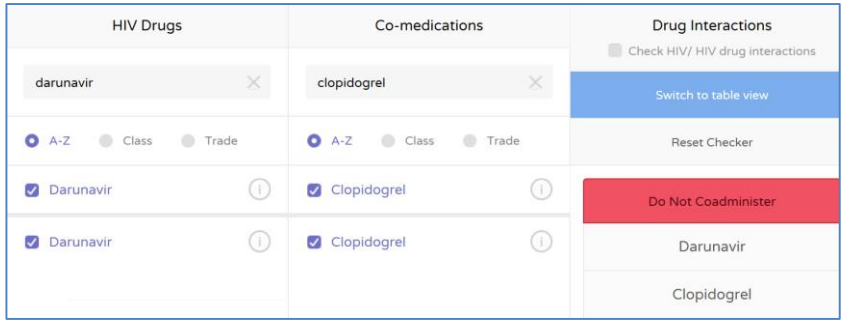


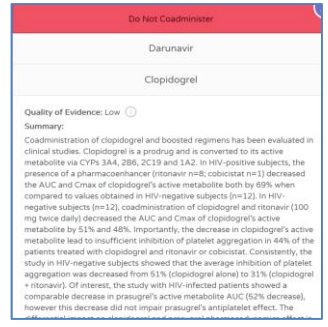
www.hiv-druginteractions.org;

www.hiv-druginteractions.org

Interaction Checker

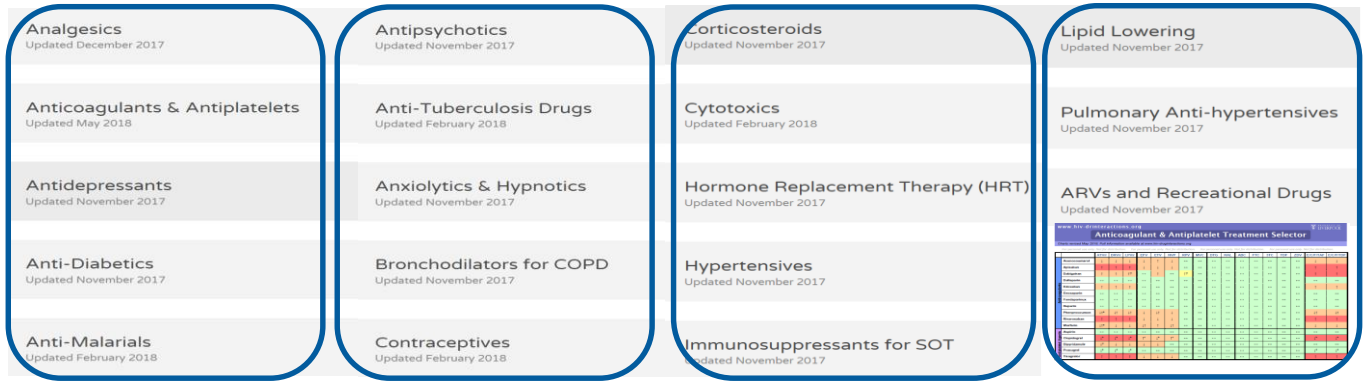
Access our free, comprehensive and user-friendly drug interaction charts





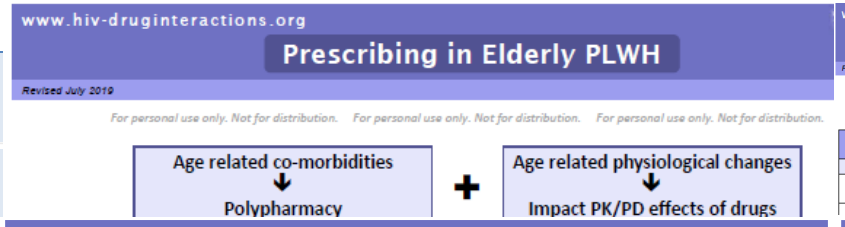
Prescribing Resources

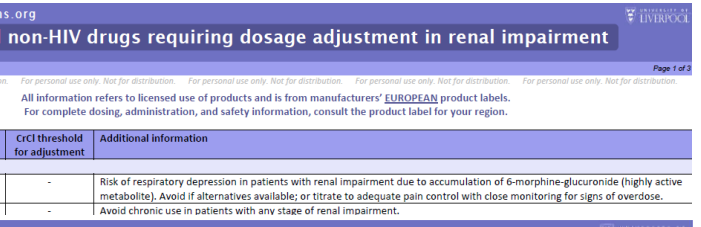
Interaction tables, treatment selectors, clinical prescribing resources, and pharmacokinetic fact sheets

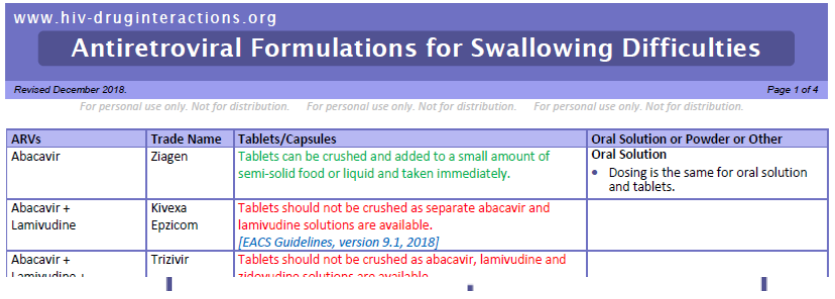


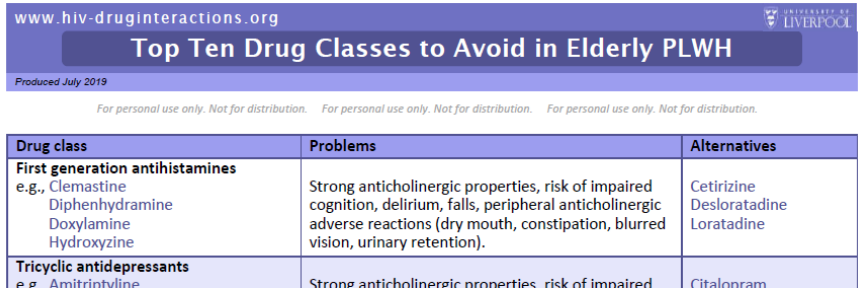
Treatment Selectors (by therapeutic indication)

Treatment Selectors (by patient characteristics)









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

Acknowledgements

University Hospital Basel

Manuel Battegay

Felix Stader

Marcel Stoeckle

CHUV

Matthias Cavassini

Perrine Courlet

Laurent Decosterd

Francoise Livio

University of Liverpool

David Back

Saye Khoo

Hannah Kinvig

Marco Siccardi

Liverpool HIV drug interactions websites team members

Basel Institute ceb for Clinical Epidemiology and Biostatistics

Heiner Bucher

Elisabeth Deutschmann

Giusi Moffa

UNM Health Sciences Clinical & Translational Science Center

Bernadette Jakeman

Swiss HIV Cohort Study

Members of the SHCS
co-workers of all HIV clinics

Funding

FNSNF Swiss National Science Foundation

OPO Stiftung

Isaac Dreyfus Bernheim Foundation/Stiftung