La persona che invecchia con l'HIV: personalizzazione della terapia

Numeri dell'Azienda
REGIONE DEL VENETO
Azienda Ospedale Università Padova

Dott.ssa Maria Mazzitelli, MD, PhD

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Agenda

- Who is our target population?
  - *Defining and sizing the burden of people aging with HIV*
- Main issue in elderly people living with HIV
  - *Multimorbidity, polypharmacy, DDIs*
  - *Acceptability, tolerability and adherence to treatment*
  - *Expectations and QOL*
- Long-term management and follow-up
  - Treatment option dual, triple or injectables?
  - *Should we reshape models of care?*

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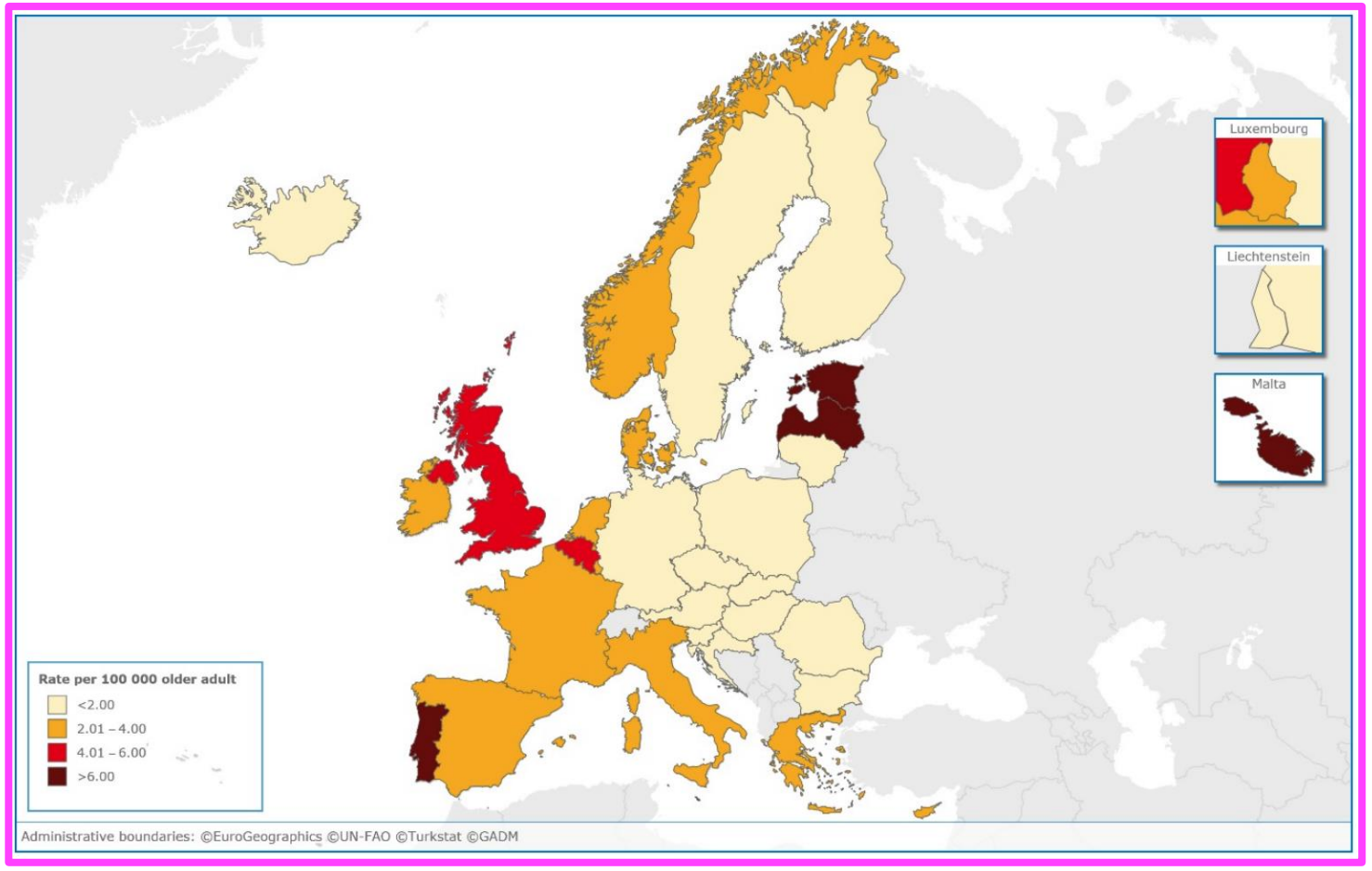
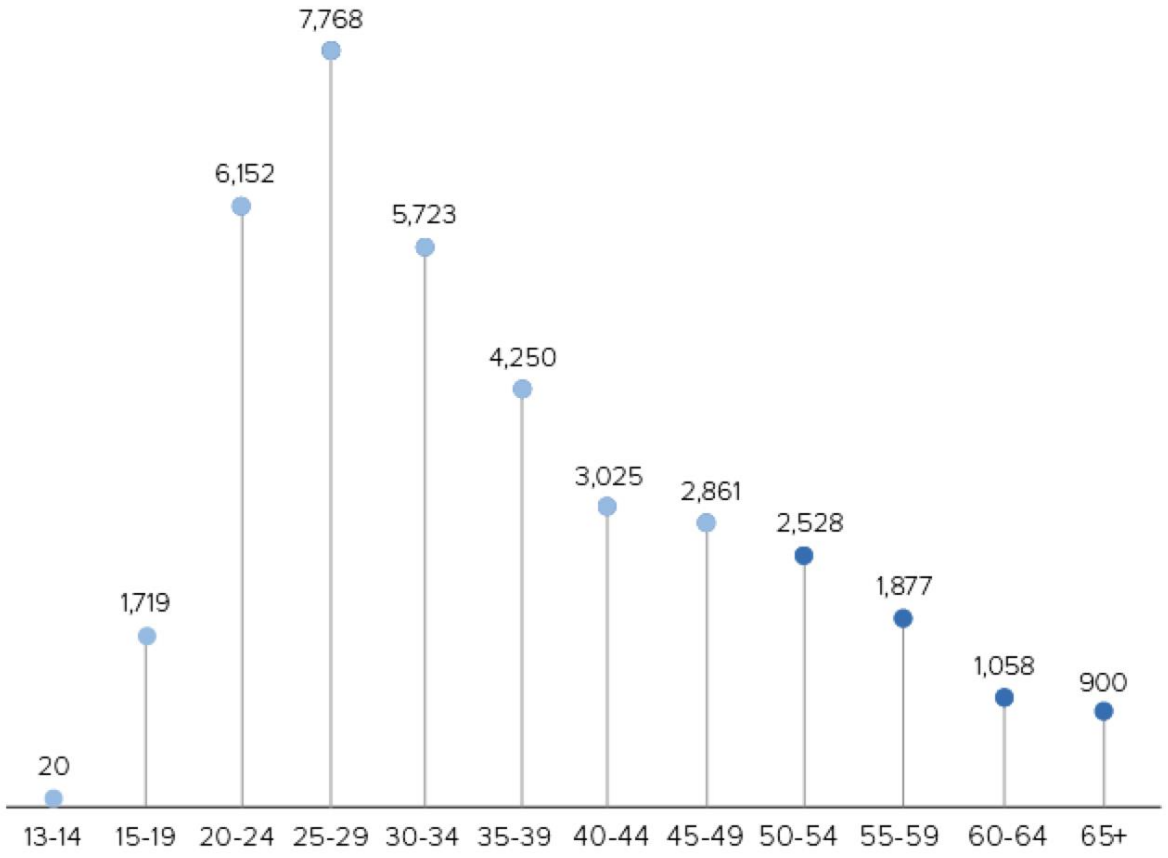
New HIV diagnoses among adults aged 50 years and over per 100 000 persons in EU/EEA



https://www.ecdc.europa.eu/sites/portal/files/documents/new-HIV-diagnoses-among-older-adults-in-europe-analysis-surveillance-data-2004-2015.pdf

New HIV diagnoses by age in the US

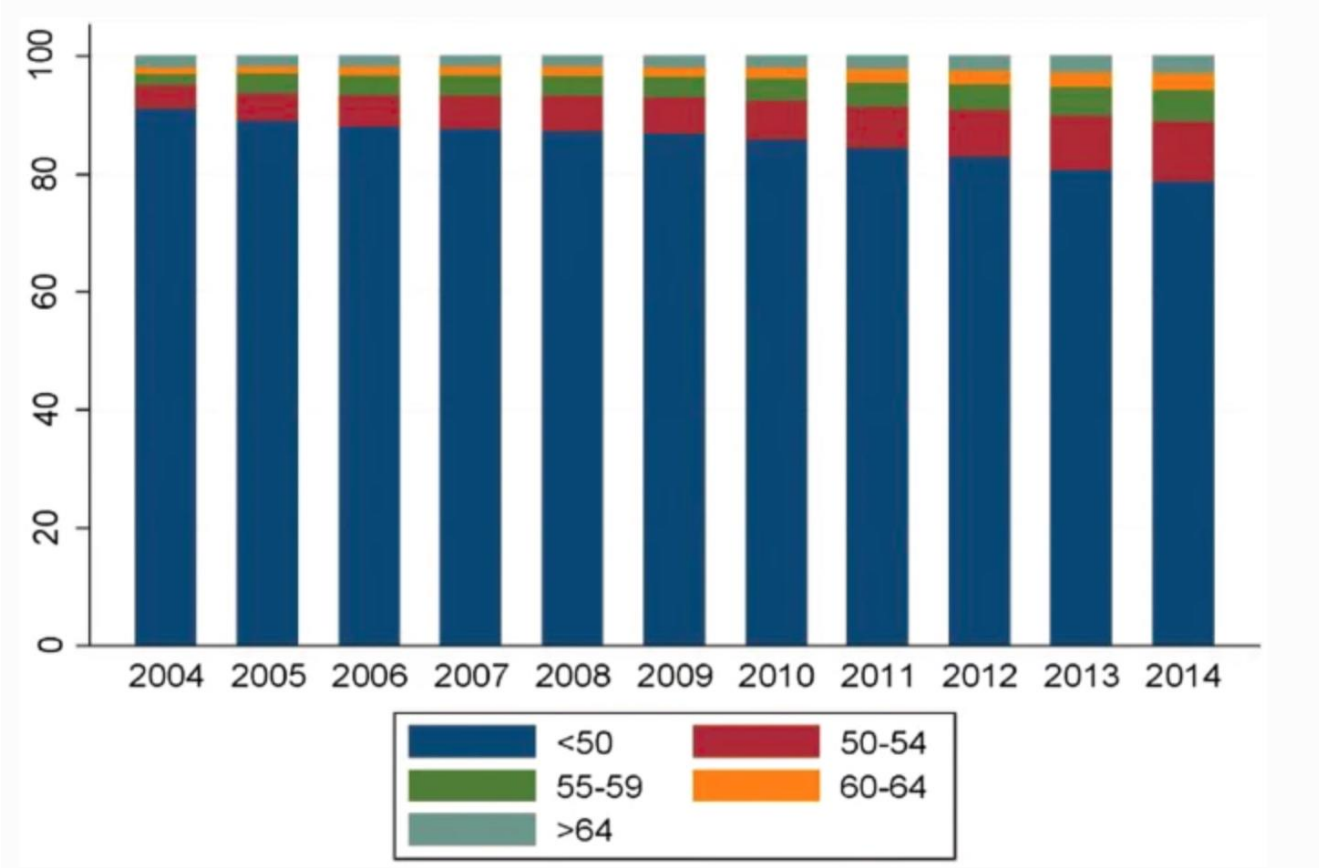
1 in 6 new HIV diagnoses were among people aged 50 and older.



https://www.cdc.gov/hiv/group/age/olderamericans/index.html

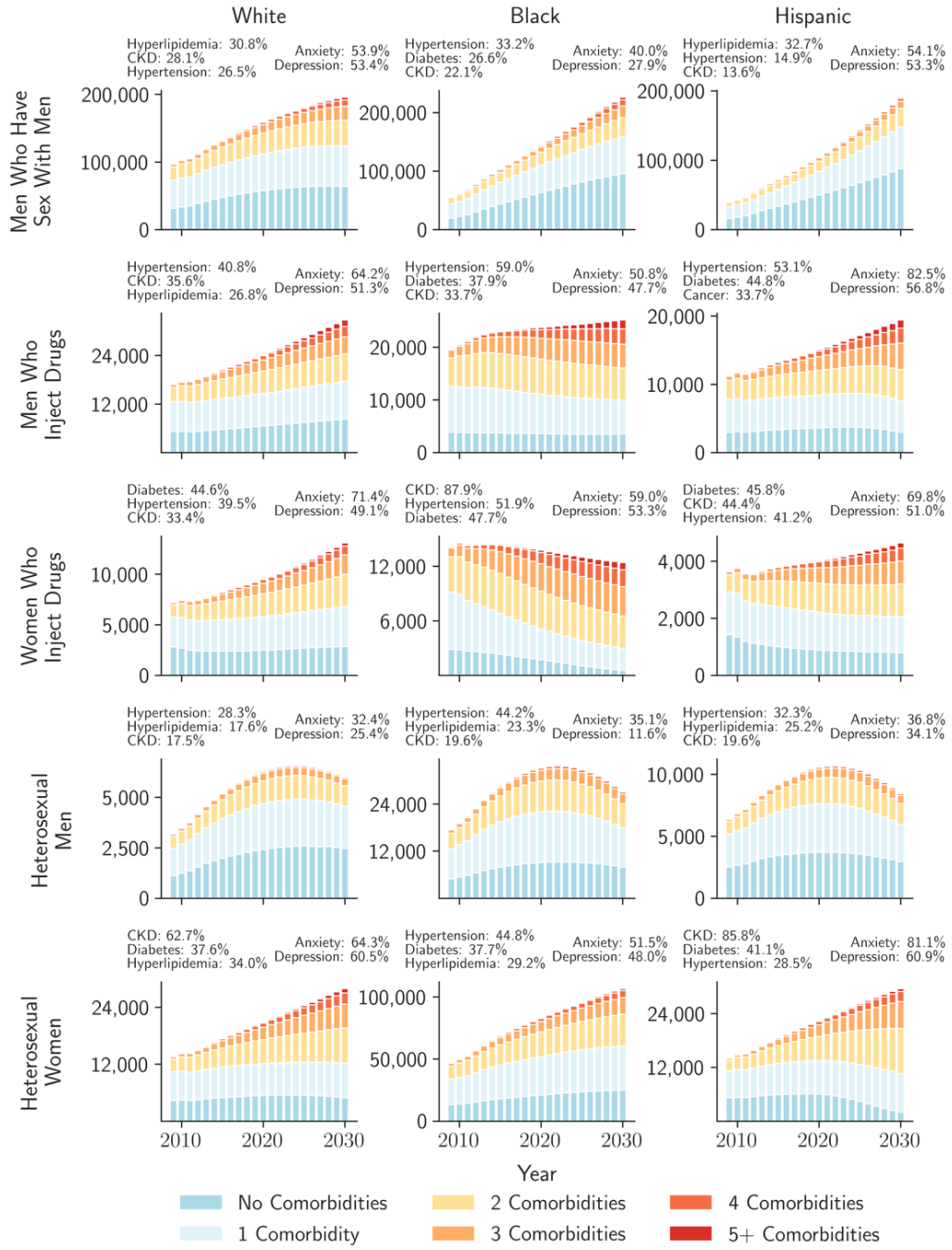
Number are obviously expected to increase

Thanks to effective **HIV treatment**, the number of **older adults** living with HIV is **increasing**.



Vivancos et al, Eur Geriatr Med, 2018

ProjEcting Age, MultimoRbidity, and PoLypharmacy (PEARL) is an agent-based simulation of HIV and comorbidities among PWH receiving ART in the US (2009–2030).



CROI
Conference on Retroviruses and Opportunistic Infections

Kasaje et al, Oral Comm-03

ITALY: Who is our target population?

ODOACRE 12 centres– 4200 patients – mean age 50.5 years
Ciccullo et al, BMJ Open, 2019

geppo cohort

More than 1500 patients – 10 centres – Mean age 68.2

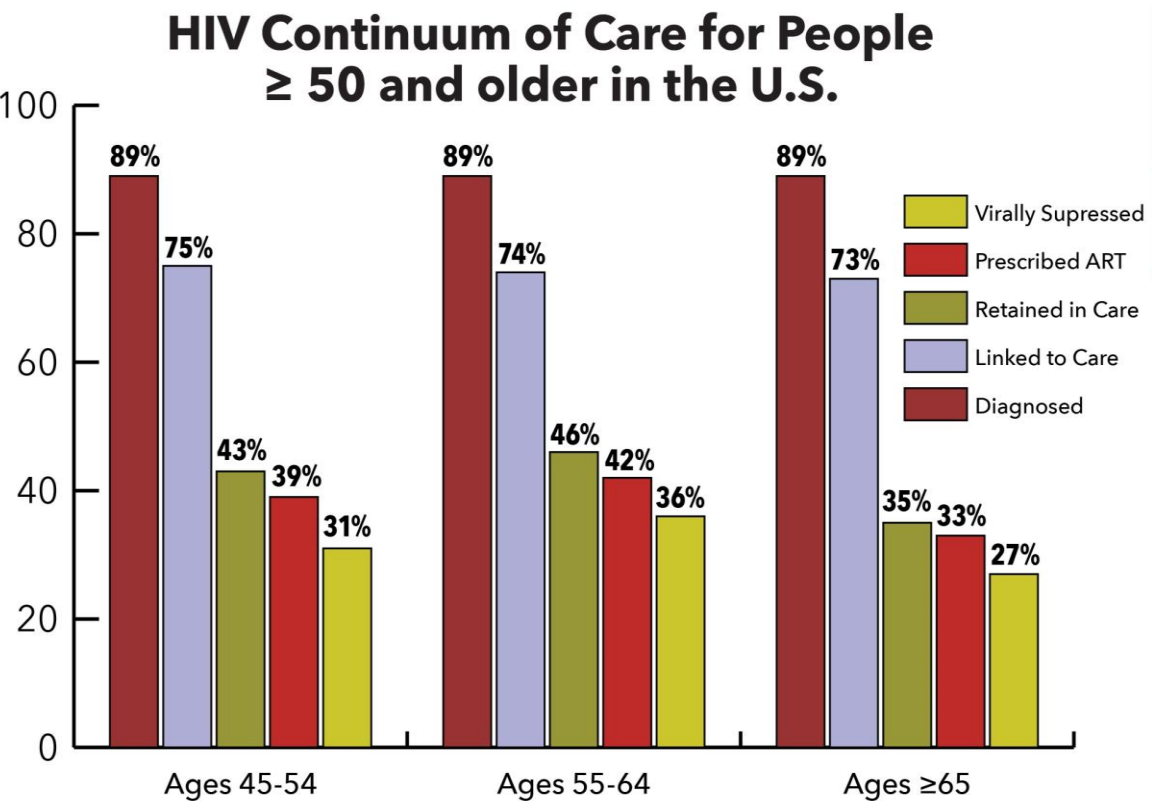
Italian Cohort I. C O. N A. Naive Antiretrovirals
Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS
Conceived by Professor Mauro Moroni

More than 4000 patients from more than 40 centres,
45% over 50's
https://www.fondazioneicona.org

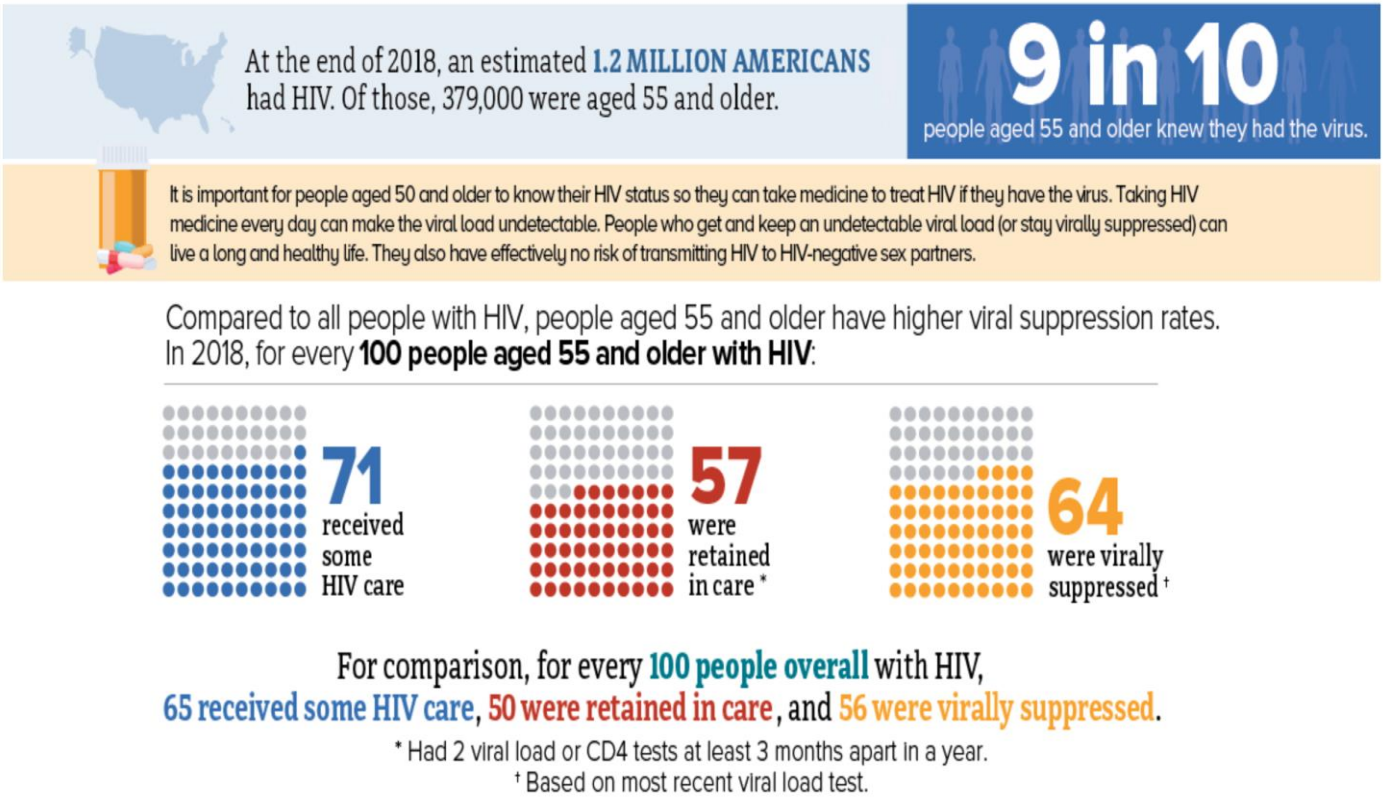
PROGETTO MASTER
Management standardizzato di terapia anti-retrovirale

3000 patients, 10% over 55's
Torti et al. Int J Epidemiol, 2017

HIV Continuum of Care for People Aged ≥ 50 in U.S.



Reference: http://www.cdc.gov/hiv/risk/age/olderamericans/
Disclaimer: The original version of this bar graph was taken from the CDC website and modified to display data for the 45 years and older population only.



This gap should be taked into account in selecting antiretroviral treatment

https://www.cdc.gov/hiv/images/group/age/olderamericans/2020/cdc-hiv-older-infographic

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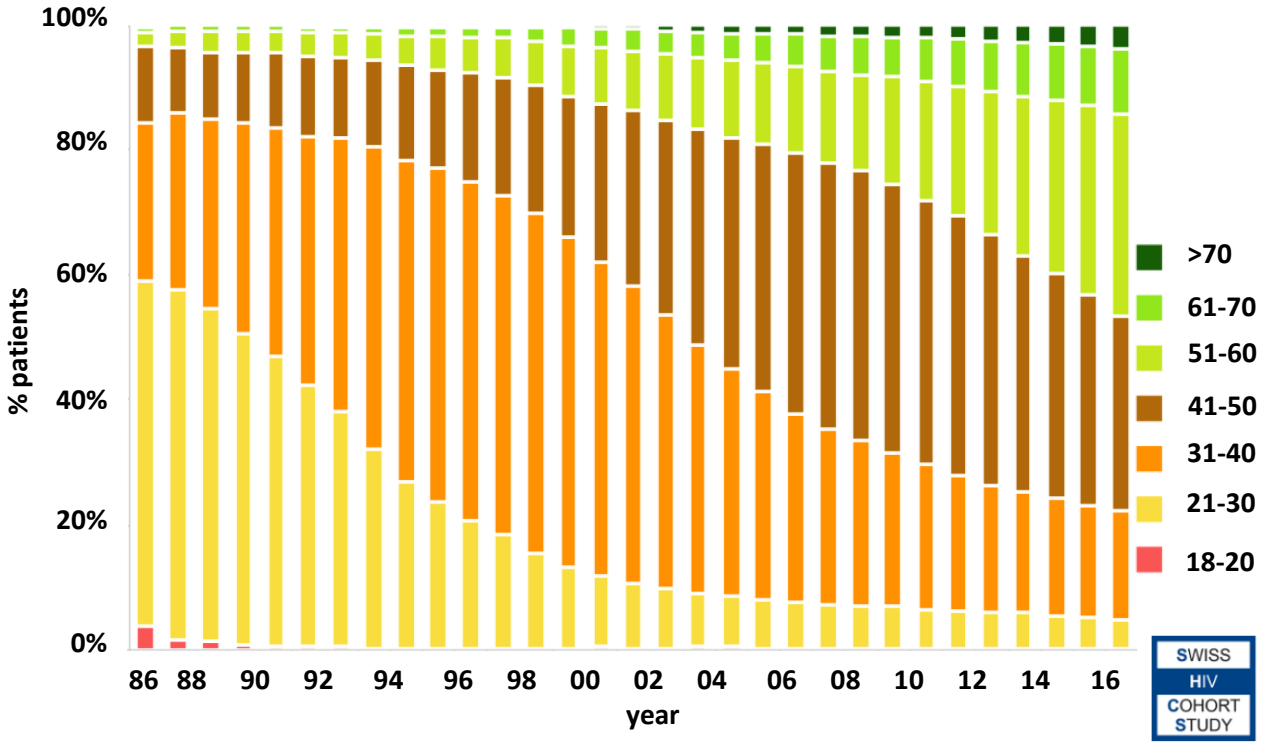
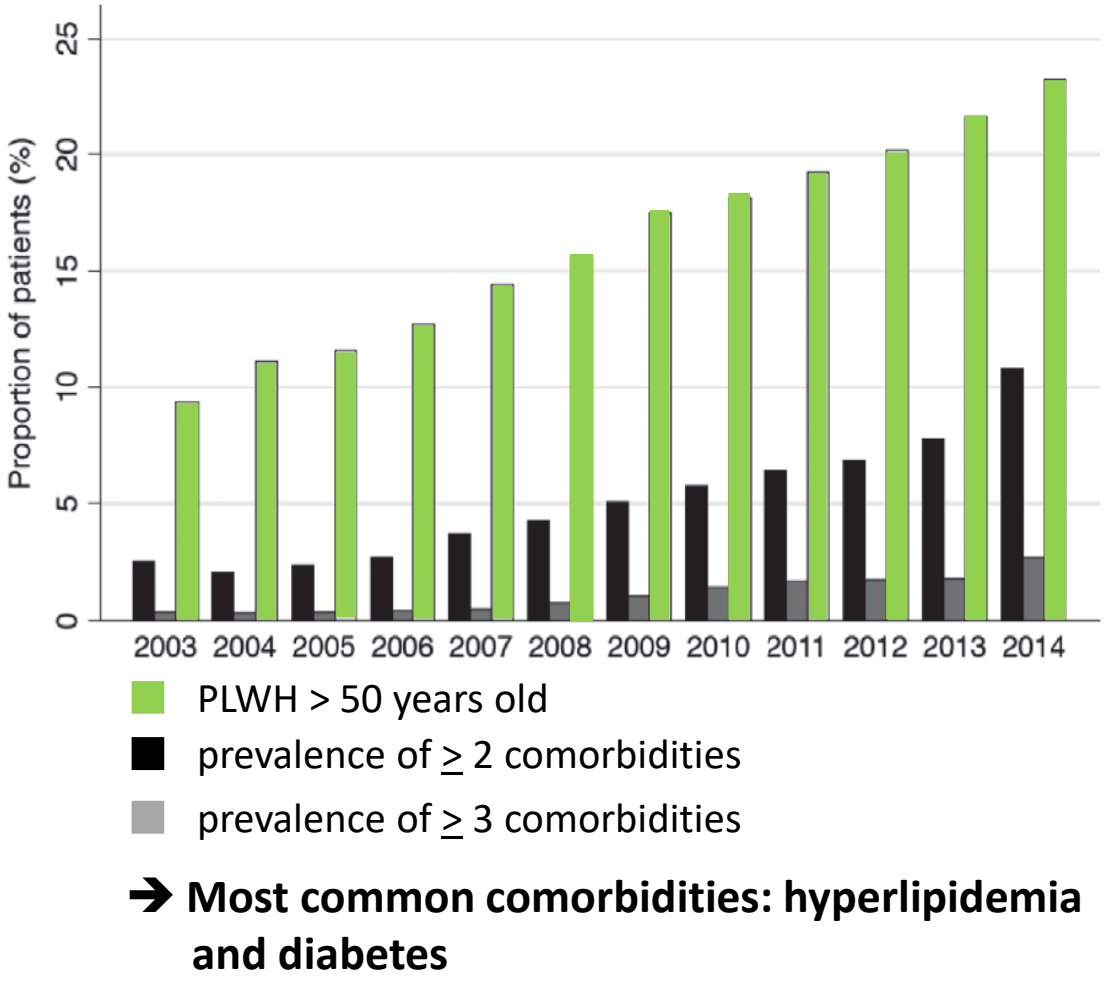
Aging of HIV population

Age distribution of PLWH in the SHCS



Proportion of ≥ 50 years old PLWH in a multi-site cohort in Brazil



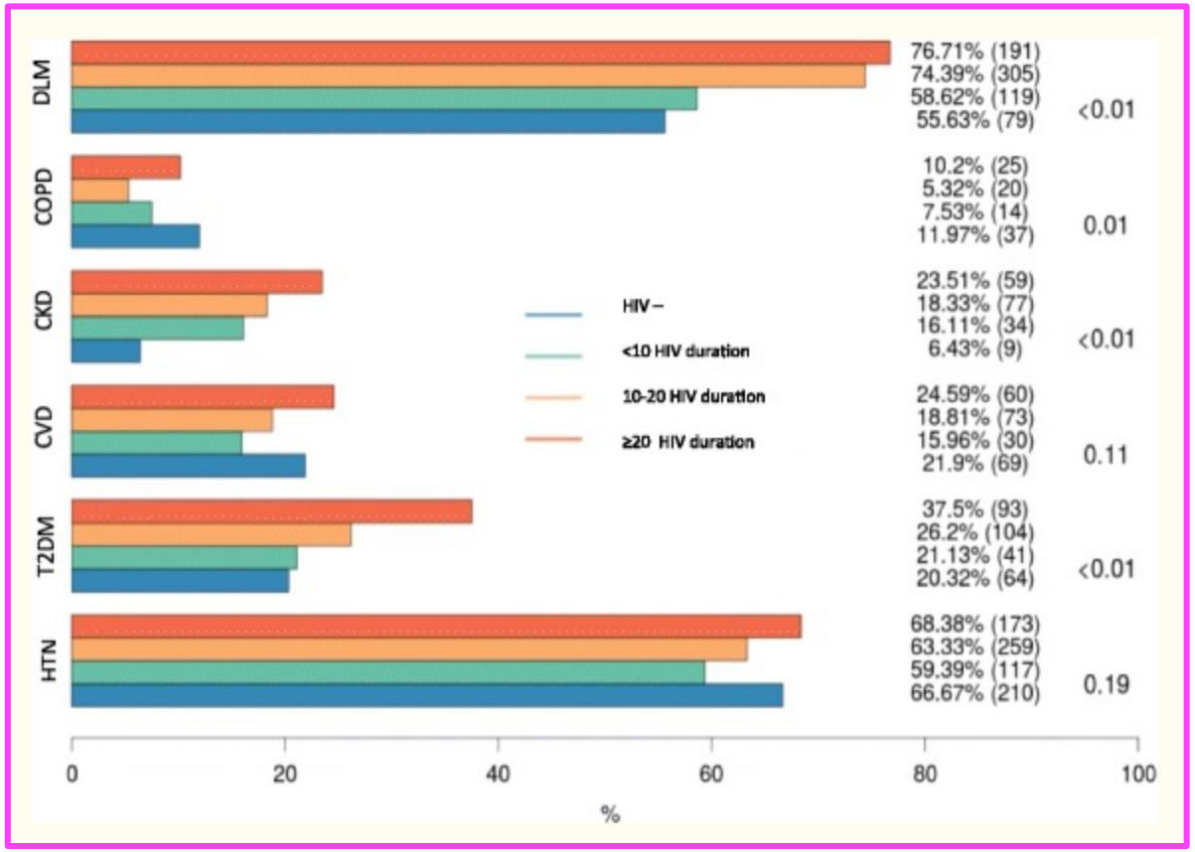
Mathematical models using data from US, Italian and Dutch HIV Cohort project that 30-40% of PLWH will be > 60-65 years with ≥ 3 comorbidities by 2030-2035.

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

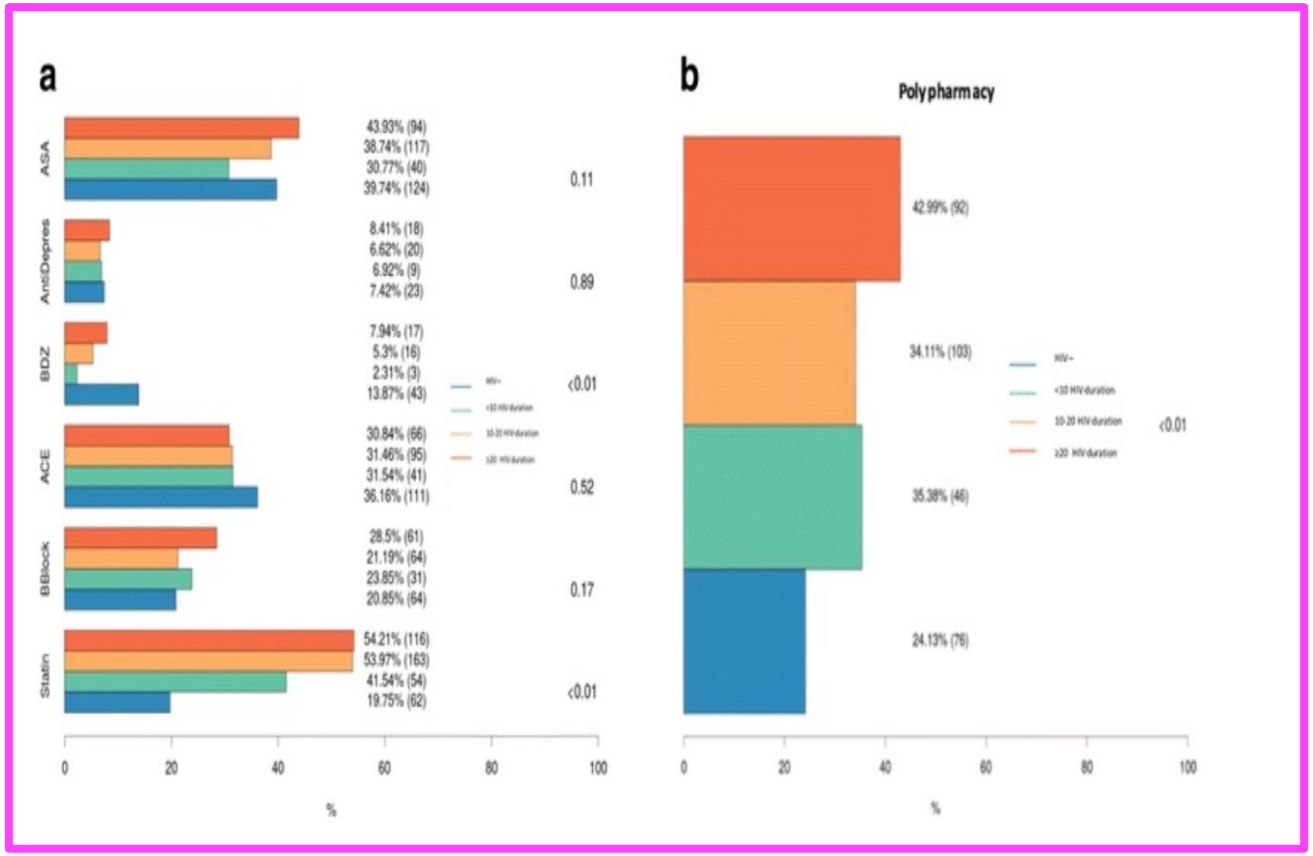
➔ **Most common comorbidities: hyperlipidemia and diabetes**

Castilho JL et al. J Int AIDS Soc 2019

Comorbidities by age in PLWH in the GEPPO Cohort



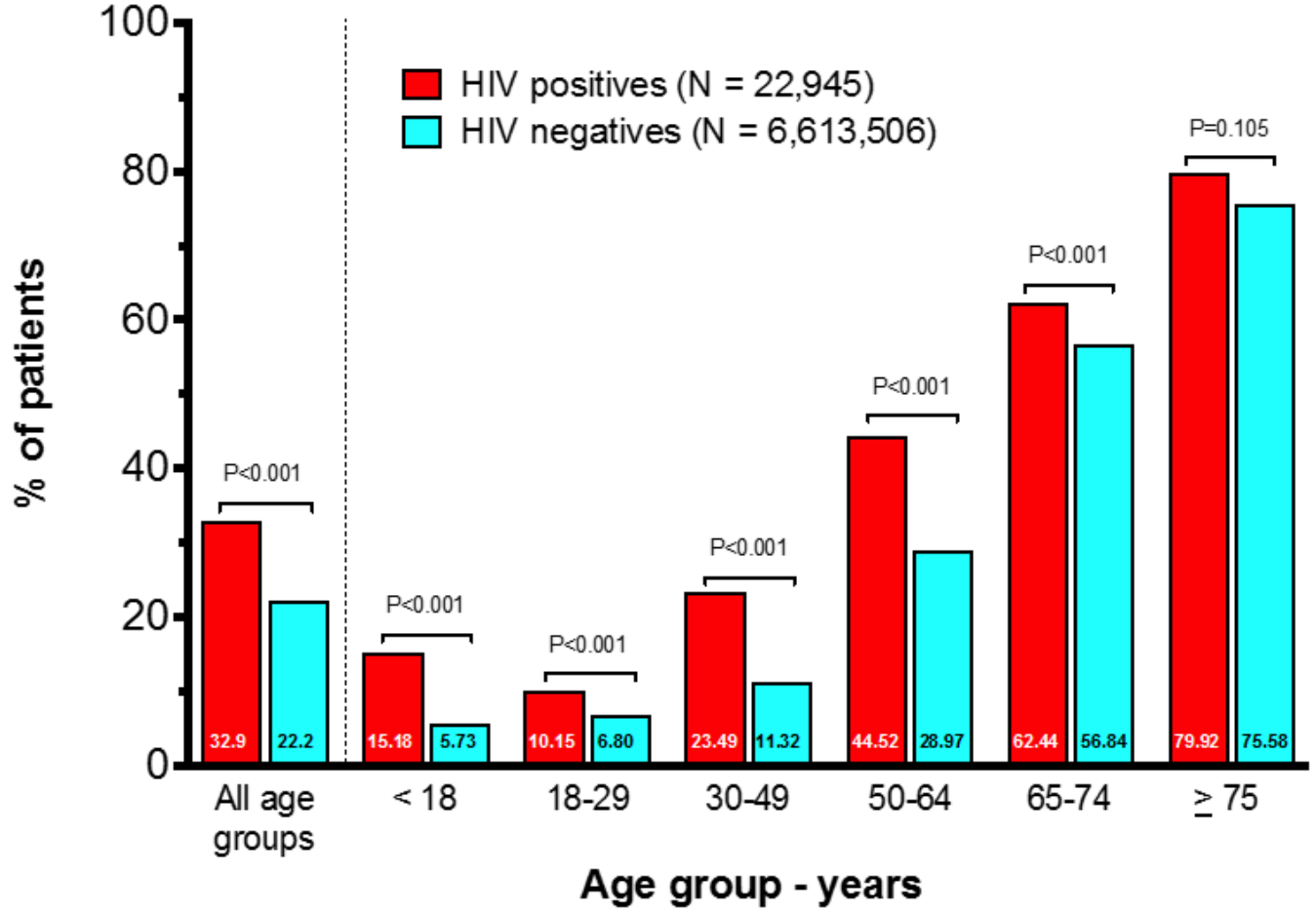
Prescription by drug classes and PP by age classes



Guaraldi et al. BMC Geriatrics, 2018

Polypharmacy in PLWH and uninfected individuals

Prevalence of polypharmacy (≥ 5 non-HIV drugs) in PLWH and uninfected individuals who picked up prescription drugs in hospital and community pharmacies in the region of Madrid



P values refer to comparisons of proportions of patients with polypharmacy (≥ 5 Co-meds) between groups

Lopez-Centeno B et al. Glasgow HIV Conference 2018

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. CROI 2019	Switzerland	131	≥ 65	46 %
Guaraldi G et al. BMC Geriatr 2018	Italy	1258	≥ 65	37 %
Justice A et al. AIDS 2018	USA	1311	≥ 65	43 %
Halloran MO et al. Antivir Ther 2019	UK/Ireland	698	≥ 50	30 %
Lopez-Centeno B et al. HIV Drug Ther, Glasgow 2018	Spain	10073	≥ 50	47 %
Nunez-Nunez M et al. Farm Hosp 2018	Spain	242	≥ 50	48 %
Ruzicka DJ et al. BMJ Open 2018	Japan	526	≥ 50	35%
Ssonko M et al. BMC Geriatr 2018	Uganda	411	≥ 50	15 %
Krentz H et al. AIDS Pat Care STDS 2016	Canada	386	≥ 50	43 %
Holtzman C et al. J Gen Intern Med 2013	USA	1312	≥ 50	54 %

Consequences of polypharmacy

Polypharmacy
≥ 5 medications

Nonadherence

Possible causes:

- **Side effets**
- **High pill burden**
- **Complex dosing regimens**
- **Depression**
- **Neurocognitive impairment**
- **Size of tablets**
- **Limited health literacy** (misunderstanding of instructions)
- **Health beliefs** (being unconvinced about necessity of medication)

Adverse drug reactions

Most common drug classes associated with ADR in elderly:

- **Cardiovascular drugs**
- **Diuretics**
- **Anticoagulants**
- **NSAIDs**
- **Antidiabetics**

Geriatric syndromes

- **Falls**
- **Cognitive decline**
- **Orthostatic hypotension**

Drug-drug interactions

	PLWH ≥ 50 years (n= 698)	PLWH < 50 years (n= 374)
Median nb medications	6 (0-27)	4 (0-17)
DDIs **HIV/non-HIV** drugs	400 (57.3)	121 (32.4)
DDIs **non-HIV/non-HIV** drugs	252 (36.1)	76 (20.3)

Older PLWH receive more medications and therefore are at > risk for DDIs between HIV/non-HIV drugs and between non-HIV/non-HIV drugs

Shah B et al. Clin Geriatr Med 2012, Gellad WF et al. Am J Geriatr Pharmacother 2011, Halloran MO et al. Antivir Ther 2019

Aging & comorbidities pose additional therapeutic challenges

- **Drug-disease interactions**

Examples

Disease	Drug	Potential adverse reaction
Diabetes	corticosteroids	increase in blood glucose level
Parkinson	antipsychotics	aggravation of movement disorder
Renal failure	NSAIDs	decrease of glomerular filtration rate

- **Age associated changes in pharmacokinetics**

PK parameter	Altered physiology with aging	Comments
Absorption	↑ gastric pH	modification of drug absorption
Distribution	↓ albumin ↑ body fat ↓ lean muscle and total body water	↑ free fraction of drugs ↑ Vd of lipophilic drugs ↑ plasma concentration of hydrophilic drugs
Metabolism	↓ hepatic mass ↓ hepatic blood flow	↓ reduced hepatic clearance
Elimination	↓ kidney mass ↓ glomerular filtration rate ↓ renal blood flow	↓ reduced renal clearance

Wooten JM. South Med J 2012, Marzolini C et al. Expert Rev Clin Pharmacol 2019

Aging & comorbidities pose additional therapeutic challenges

- **Age associated changes in pharmacodynamics:**

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

Examples

Drug class	Potential PD issues	Comments
Antihypertensives	orthostatic hypotension	start with lower dose
Benzodiazepines	↑ sensitivity (sedation, confusion…)	use with caution and for short period of time, use lowest dose
Opioids	↑ sensitivity	use with caution, use lowest dose
β-blockers	↓ β-receptors function	may require ↑ β-blocker dose
Diuretics	↑ sensitivity drug effect	monitor blood pressure and electrolytes
Vitamin K antagonists	↑ sensitivity (inhibition synthesis of vitamin K dependent clotting factors)	start with lower dose and adjust based on INR
Anticholinergic agents	↑ sensitivity (delirium, dry mouth, constipation, urinary retention, cognitive impairment, falls…)	avoid

Wooten JM. South Med J 2012, Marzolini C et al. Expert Rev Clin Pharmacol 2019

Interventions to limit/manage polypharmacy

1) Medication reconciliation

- Establish list of current prescription & over-the-counter drugs to be updated at each medical visit

2) Periodic medication review

- Check indication ➔ discontinuation of unecessary drugs
- Identify medications treating adverse effects of other medications ➔ discontinue drug that is causing side effect if possible
- Check dosing of medications ➔ simplification of dosing regimen when possible
- 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 STOP/START criteria

3) Medication prioritization

- Consider risk/benefit of each medication within the context of a given patient's care goals, current level of functioning, life expectancy and preference

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

Mechanisms of DDis Oral vs. Parenteral ART

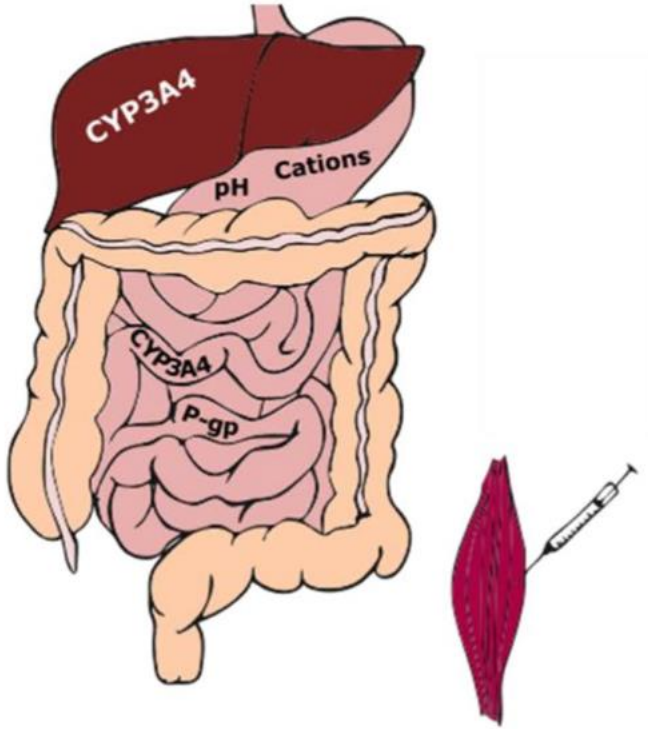
ORAL administration

Stomach/intestine
Change gastric pH
e.g. proton pump inhibitor

Chelation divalent cations
e.g. magnesium, iron, calcium

Inhibition/induction of CYP3A4, drug transporters
e.g. ritonavir, rifampicin

Liver
Inhibition/induction of CYP3A4, UGTs, drug transporters
e.g. ritonavir, rifampicin

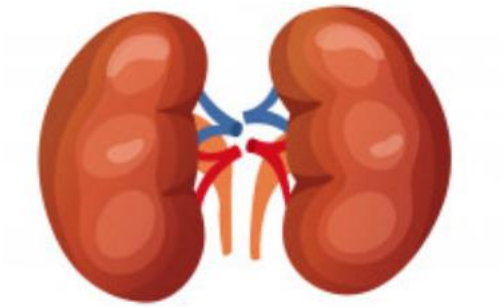


INTRAMUSCULAR administration

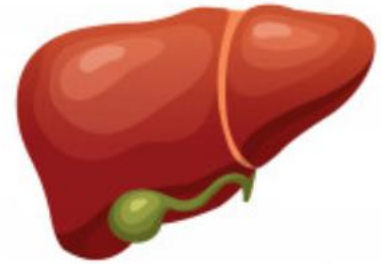
Stomach/intestine
Bypassed

Liver
Inhibition/induction of CYP3A4, UGTs, drug transporters
e.g. ritonavir, rifampicin

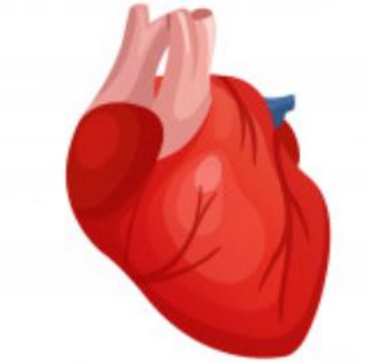
PK of CAB-RPV in special populations



- Renal disease:
  - No diff obserbed between health subjects with or without severe renal disease
  - No data on CAB in HD or ESKD



- Liver disease:
  -Caution!



- Cardiac and rythm disorders:
  - Caution!

https://www.ema.europa.eu/en/documents/product-information/vocabria-epar-product-information_en.pdf

Cabotegravir/rilpivirine [long acting] (CAB/RPV LA)

Do Not Coadminister

Rifabutin
Rifampicin
Rifapentin
Carbamazepine
Eslicarbazepine
Oxacarbazepine
Phenobarbital
Phenytoin
Primidone
Griseofulvin
Thioridazine
Ziprasidone
Some antiretrovirals
Bexarotene
Enzalutamide
Ifosfamide
Vinblastine
St John's Wort
Bosentan
Modafinil
Bethametasone
Dexamethasone

Potential Interaction

Propofol
Sevoflurane
Methadone
Amiodarone
Bepridil
Disopyramide
Dofetilide
Flecainide
Quinidine
Azithromycin
Ciprofloxacin
Clarithromycin
Erythromycine
Flucloxacillin
Levofloxacin
Moxifloxacin
Citalopram
Escitalopram
Fluconazole
Astemizole
Terfenadine
Artemisinin
Chloroquine
Halofantine
Hydroxychloroquine
Meglumine antim.
Pentamidine
Quinine
Stibogluconate
Chlorpromazine
Haloperidol
Levomepromazine
Pimozide
Sulpiride
Some antiretrovirals
Ombit./Paritapr.
Ombit/Paritapr/r/Das.
Clobazam
Docetaxel
Doxorubicin
Imatinib
Methothrexate
Oxalipratin
Paclitaxel
Tamoxifen
Topotecan
Toremifene
Cisapride
Domperidone
Ondansetron
African potato
Echinacea
Guggulsterone
Hops
Liquorice
Malabar nut tree
Quercetin
Cocaine
Ursodeoxycholic acid

Polypharmacy and evaluation of anticholinergic risk in a cohort of elderly people living with HIV

Maria Mazzitelli [1], Ana Milinkovic, Branca Pereira, James Palmer, Timothy Tong, David Asboe, Marta Boffito

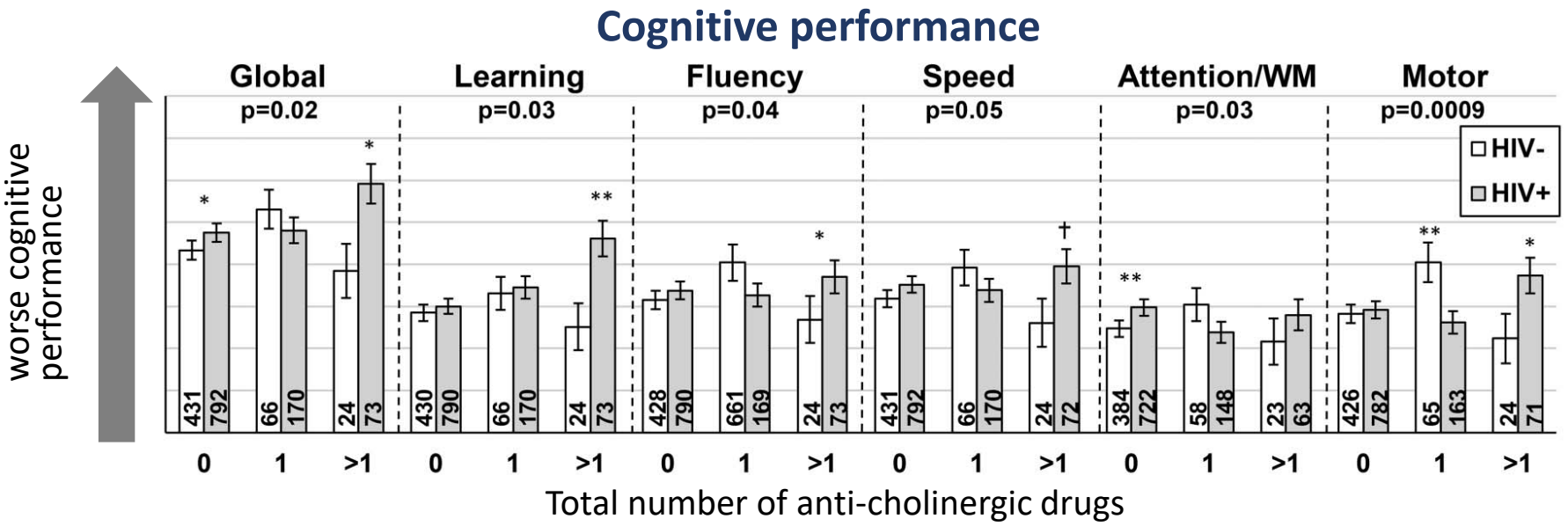
Table 1. Anticholinergic risk results for the two scales.

Level of anticholinergic risk	Anticholinergic burden scale *n* (%)	Anticholinergic risk score *n* (%)
0 (no risk)	697 (88.2)	711 (90)
1–2 (intermediate)	68 (8.6)	57 (7.2)
>0 = 3 (high)	25 (3.2)	22 (2.8)

Increased anticholinergic exposure, due to DDis, may escalate the risk of side effects such as falls and cognitive impairment. This is particularly true for anti-epyleptic drugs, antipsychotics, PPis, and steroids

AIDS, 2019

Drugs with anticholinergic effects and cognitive performance



Rubin L et al. JAIDS 2018

Selected anticholinergic drugs

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

Boustani M et al. Aging Health 2008

Top Ten Drug Classes to Avoid in Elderly PLWH

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
Benzodiazepines Long and short acting benzodiazepines e.g., Clonazepam Diazepam Midazolam Non-benzodiazepines hypnotics e.g., Zolpidem Zopiclone	Elderly are more sensitive to their effect, risk of falls, fractures, delirium, cognitive impairment, drug dependency. Use with caution, at the lowest dose, and for a short duration.	Non-pharmacological treatment of sleep disturbance/sleep hygiene
Atypical antipsychotics e.g., Clozapine, Olanzapine, Quetiapine	Anticholinergic adverse reactions, increased risk of stroke and mortality (all antipsychotics).	Aripiprazole Ziprasidone
Urological spasmolytic agents e.g., Oxybutynin, Solifenacin, Tolterodine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention).	Non-pharmacological treatment (pelvic floor exercices)

Prevalence of prescribing issues in patients ≥ 75 years

Overall prescribing issues : 69% participants

Incorrect drug dosage:	25%
No indication:	21%
Prescription omission:	19%
Inappropriate drug:	19%
Deleterious DDIs:	14%
Treatment duration exceeding recommendations:	2%

www.hiv-druginteractions.org

Selected non-HIV drugs requiring dosage adjustment in renal insufficiency

Antiretroviral Dosing in Adults with Renal Impairment

- 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

IAS 2019

WEPEB314 Cabanilla G et al. Risk of polypharmacy and inappropriate prescribing in persons living with HIV > 65 years of age

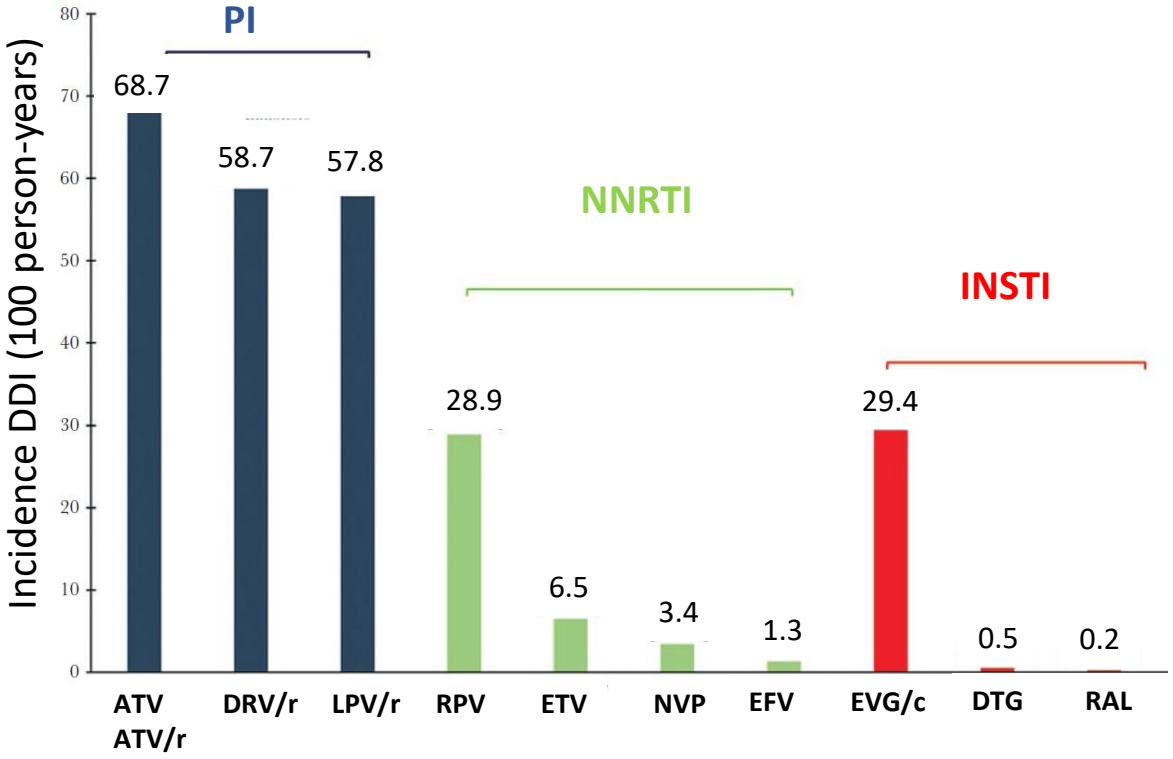
Livio F. International Workshop Clin Pharmacol Antivir Ther 2018

Risk and cost associated with DDIs in elderly PLWH

Frequency, risks and costs attributable to «red flag DDIs» (Liverpool database) using French nationwide health e-records for 2016:

- 9076 PLWH, mean age: 71 ± 5 years, median non-HIV comeds (IQR): 14 (9-21)
- **16.8%** ≥ 1 DDI, unboosted INI associated with lower risk for DDI (OR: 0.02), boosted PIs increased risk for DDI (OR: 4.12)
- **Presence of DDIs associated with additional 2693 USD/year**

Incidence of DDI per 100 person-years



10 most frequent encountered DDIs

	DNCIs, No. (%)	Risk
PI or boost/inhaled glucocorticoids[b]	739 (29)	Cushing syndrome
Atazanavir or rilpivirine/proton pump inhibitors[c]	676 (27)	↓ ARV efficacy
PI or boost/lercanidipine	285 (11)	hypotension & cardiac disorders
PI or boost/alfuzosin	233 (9)	severe hypotension
PI or boost/domperidone	136 (5)	QT prolongation
PI or boost/amiodarone	82 (3)	QT prolongation
PI or boost/simvastatin	79 (3)	rhabdomyolysis
PI or boost/apixaban or rivaroxaban	67 (3)	bleeding
PI or boost/piroxicam	51 (2)	respiratory depression & hematologic abnorm.
Darunavir/injectable lidocaine	38 (2)	QT prolongation

Desmessine L et al. Open Forum Infect Dis 2019

Outcomes of drug-drug interactions in real-life

clinical cases DDIs

www.clinicalcasesDDIs.com

The page can be used for:

- **Reporting** new clinical cases on drug combinations
- **Searching** for information on specific combinations.
- **Share information on real-life experience** about drug combinations that may be used in the clinic.

Tolerability: what side effects may LA cause?

- **Injection site reactions** (bumps, swellings, pain) that go away in most people within a week.

  Injection site reactions are most common with the first injection and decrease over time.

  FLAIR/ATLAS 83%, ATLAS-2M 76%

  1% participants discontinued treatment because of injections site reactions
- **Headache**, dizziness
- Depression, anxiety, difficulty in sleeping (insomnia), abnormal dreams
- **Raised temperature, feeling hot**
- Aches and pains, muscle pain
- Tiredness, feeling weak
- Nausea (feeling sick), vomiting, abdominal pain, diarrhoea
- Rash

Patients' satisfaction and qualitative data:

HIVTSQ

Item no.	Item label [Suffix *(c)* denotes item label in the change version]	Item wording	The following questions are concerned with your anti-HIV medicine therapy for HIV infection and your experience over the past few weeks. Please answer each question by circling a number on each of the scales. Response options 6-0	The following questions are concerned with your present anti-HIV medicine therapy compared with your experience of medicine therapy used just before you started in the current study. We are interested to know how, if at all, your experience of medicine therapy has changed. Please answer each question by circling a number on each of the scales to indicate the extent to which you have experienced changes. If you have experienced no change, circle '0'. Response options 6-0
1	*current treatment*	How satisfied are you with your current treatment?	very satisfied 6 to 0 very dissatisfied	much more satisfied now 3 to -3 much less satisfied now
2	*control*	How well controlled do you feel your HIV has been recently?	very well controlled 6 to 0 very poorly controlled	much better controlled now 3 to -3 much worse controlled now
3	*side effects*	How satisfied are you with any side-effects of your present treatment?	very satisfied 6 to 0 very dissatisfied	much more satisfied now 3 to -3 much less satisfied now
4	*demands*	How satisfied are you with the demands made by your current treatment?	very satisfied 6 to 0 very dissatisfied	much more satisfied now 3 to -3 much less satisfied now
5	*convenience*	How convenient have you been finding your treatment to be recently?	very convenient 6 to 0 very inconvenient	much more convenient now 3 to -3 much less convenient now
6	*flexibility*	How flexible have you been finding your treatment to be recently?	very flexible 6 to 0 very inflexible	much more flexible now 3 to -3 much less flexible now
7	*understanding*	How satisfied are you with your understanding of your HIV?	very satisfied 6 to 0 very dissatisfied	much more satisfied now 3 to -3 much less satisfied now
8	*lifestyle*	How satisfied are you with the extent to which the treatment fits in with your life-style?	very satisfied 6 to 0 very dissatisfied	much more satisfied now 3 to -3 much less satisfied now
9	*recommend to others*	Would you recommend your present treatment to someone else with HIV?	Yes I would definitely recommend the treatment 6 to 0 No I would definitely not recommend the treatment	much more satisfied now 3 to -3 much less satisfied now
10	*continue*	How satisfied would you be to continue with your present form of treatment?	very satisfied 6 to 0 very dissatisfied	much more likely to recommend the treatment now 3 to -3 much less likely to recommend the treatment now

Fernandez et al. HIV/AIDS - Research and Palliative Care, 2019

LA drugs

PROs

- LATTE-2: High levels of satisfaction 98% and 99% in injectable arms at week 48, compared with 88% in the oral arm.
- ATLAS and FLAIR have also demonstrated markedly higher levels of satisfaction with LA regimens compared to oral therapy. In those participants who switched from oral to injectable therapy in both studies, the vast majority of responding participants (99% in FLAIR and 97% in ATLAS) preferred injectables.
- Emotional advantage of reduced risk of inadvertent disclosure and eliminating the daily reminder of living with HIV.
- Benefits in terms of stigma and discrimination were cited, with reduced concern about travel to countries where laws still discriminate on the basis of HIV status.

«It might be painful, but it is better than pills»

CONS

- Increased frequency of clinic visits, and many hoped for less frequent injec-tions to be available.
- Participant views were largely posi-tive, albeit among those choosing to participate in the trial, experiencing virological suppression on LA therapy and then agreeing to participate in a qualitative sub-study.
- Providers of injectable therapy were not so selected and had some concerns about the characteristics of PLWH who would most benefit from injectables and the fact that injectable therapy does not completely obviate the need for adherence to a medication schedule.
- Other con-cerns included emergent resistance if injections are missed and issues with switching if necessitated by new concomitant medications.

Fernandez et al. HIV/AIDS - Research and Palliative Care, 2019

Agenda

- Who is our target population?
  - *Defining and sizing the burden of people ageing with HIV*
- Main issue in elderly people living with HIV
  - *Multimorbidity, polypharmacy, DD(s*
  - *Acceptability, tolerability and adherence to treatment*
  - *Expectations and QOL*
- **Long-term management and follow-up**
  - *Treatment option dual, triple or injectables?*
  - *Should we reshape models of care?*

Experiences of simplification to different dual therapies in elderly populations

- Doravirine+Dolutegravir
- Dolutegravir+Lamivudine
- Cabotegravir+Rilpivirine

Observational Study

Medicine®

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Real life use of dolutegravir doravirine dual regimen in experienced elderly PLWH with multiple comorbidities and on polypharmacy

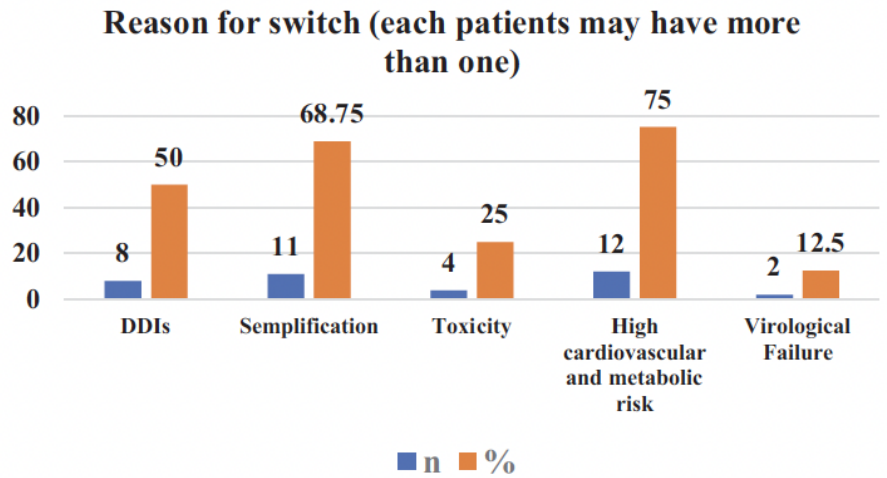
A retrospective analysis

Maria Mazzitelli, MD[a,b,*], Lolita Sasset, MD[a], Davide Leoni, MD[a], Cristina Putaggio, MD[a], Anna Maria Cattelan, MD[a]

A

Comorbidity *each patient had more than 1	Overall 18 n (%)
Dyslipidaemia	16 (88.8)
Hypertension	14 (77.7)
Depression	7 (38.9)
COPD	6 (33.3)
Diabetes	5 (27.8)
Osteoporosis	5 (27.8)
Obesity	3 (16.7)
Cirrhosis	2 (1.1)
Ischaemic heart disease	2 (1.1)

B



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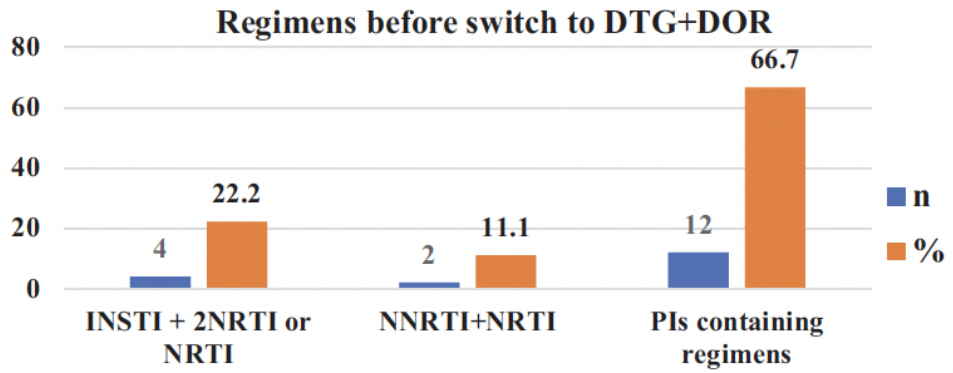

D

Parameter	Before switch, n(%)	After switch n (%)	p value
Undetectable HIV-RNA (Yes)	15 (88.2)	17 (100)	-
CD4+, cell/mm^3, mean (SD)	607 (240)	629 (232)	0.37
Cholesterol, mmol/L, mean (SD)	5.1 (3.3)	4.8 (1.4)	0.1
HDL, mmol/L, mean (SD)	1.5 (0.7)	1.1 (0.4)	0.75
LDL, mmol/L, mean (SD)	3.1 (1)	2.9 (1.1)	0.49
Triglycerides, mmol/L, mean (SD)	1.41 (0.7)	1.5 (0.7)	0.2
Fasting glucose, mmol/L, mean (SD)	6.2 (1.7)	5.5 (1.4)	0.08
BMI, kg/m^2, mean (SD)	25.4 (3.2)	24.7 (3.3)	<0.01
Body weight, kg, mean (SD)	75.2 (11.6)	73.1 (11.6)	<0.01
Waist circumference, cm, mean (SD)	98.1 (10)	95.9 (9.8)	<0.01
Creatinine, umol/L	86.1 (22)	90.7 (23.4)	**0.04**
eGFR, ml/min, mean (SD)	79.4 (21)	75.2 (20.9)	**0.03**

Observational Study

Medicine

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Real-life use of Doravirine in treatment-experienced people living with HIV

A multicenter Italian study

Maria Mazzitelli, MD, PhD[a*], Melania Degli Antoni, MD[b], Francesco Castelli, MD[b], Diego Ripamonti, MD[c], Gianluca Zuglian, MD[c], Giuseppe Lapadula, MD[d], Massimiliano Fabbiani, MD[e], Alice Ferraresi, MD[f], Cristina Putaggio, MD[a], Anna Maria Cattelan, MD[a], Eugenia Quiros-Roldan, MD[b]

Table 1

Main clinical and biochemical parameters at baseline.

Characteristics	Overall, n = 132, n (%)
Gender, male	91 (68.9)
Age, y, median (IQR)	56 (51–61)
Years since HIV diagnosis, median, (IQR)	22 (12–30)
CD4+ T-cell count, cells/mm^3, median (IQR)	654 (400–890)
CD4/CD8 ratio*	0.75 (0.5–1.1)
HIV-RNA	
<50 copies/mL	107 (81.1)
50–200 copies/mL	9 (6.8)
>200 copies/mL	16 (12.1)
Resistance test	
Genotype not available	34 (25.7)
Genotypic major mutations	
INI	5 (3.8)
PI	6 (4.5)
NRTI	29 (21.9)
NNRTI	28 (21.2)
No mutations	37 (28)
In 2 antiretroviral classes	20 (15.1)
In 3 antiretroviral classes	11 (8.3)
In 4 antiretroviral classes	2 (2.3)
Antiretroviral regimen before switch	
2NRTI + INI	30 (22.7)
2NRTI + NNRTI	19 (14.4)
2NRTI + PI	18 (13.6)
NNRTI + INI	3 (2.3)
NRTI + INI	10 (7.6)
INI + PI	27 (10.5)
NRTI + PI	4 (3)
Other	21 (15.9)
Reason for switching	
Drug–drug interaction	17 (12.9)
Ongoing toxicity	9 (6.8)
Dyslipidemia	24 (18.2)
Weight gain	7 (5.3)
Proactive switch	52 (39.4)
Virological failure	23 (17.4)
Agents associated to DOR at switching	
INI	[illegible]
Dolutegravir	45 (34)
Raltegravir	9 (6.9)
PI	4 (3)
Atazanavir/cobicistat	1 (0.7)
Darunavir/ritonavir	3 (2.3)
Abacavir/lamivudine	3 (2.3)
Tenofovir alafenamide/emitricitabine	25 (18.9)
Tenofovir disoproxil fumarate/emtricitabine	4 (3)
Tenofovir disoproxil fumarate/lamivudine	25 (18.9)
PI+INI (boosted darunavir+dolutegravir)	8 (6.1)
Other regimes	9 (6.8)

*(Available only for 121 patients).

DOR = doravirine, INI = integrase inhibitors, PI = protease inhibitors, NRTI = nucleoside reverse-transcriptase inhibitors, NNRTI = nonnucleoside reverse-transcriptase inhibitors, IQR = interquartile range.

Table 2

Change from baseline to week 24 of main clinical characteristics for 52 patients who reached the follow-up point.

Parameter	Baseline, n (%)	Week 24 after switch n (%)	*P* value
Detectable HIV-RNA (Yes)	4/52 (7.6)	3/52 (5.7)	.695
CD4+, cell/mm^3, median (IQR)*	612 (423–783)	625 (440–835)	.708
CD4/CD8 ratio	0.73 (0.5–1.2)	0.72 (0.5–1.2)	.160
Cholesterol, mg/dL, median (IQR)	205 (171–232)	193 (155–214)	.008
Triglycerides, mmol/L, median (IQR)	116 (89–172)	114 (82–156)	.01
Body weight, kg, median (IQR)*	78.5 (67–84)	76.5 (67–83)	.093
Creatinine, mg/dL, median (IQR)	0.99 (0.8–1.2)	1 (0.8–1.2)	.323

*Available for 38 patients.

The DoDo experience: an alternative antiretroviral 2-drug regimen of doravirine and dolutegravir

Stefanie Sammet[1] · Veronique Touzeau-Römer[2] · Eva Wolf[3] · Pia Schenk-Westkamp[1] · Birgit Romano[2] · Elke Gersbacher[3] · Ulrich Kastenbauer[4] · Christoph Boesecke[5] · Jürgen Rockstroh[5] · Stefan Scholten[6] · Stephan Schneeweiss[6] · Julia Roider[7,8] · Ulrich Seybold[7,8]

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Characteristic	Total $N=85$	n	(%)
Gender			
	Female	18	21%
	Male	67	79%
Age [years]			
	(median (range))	57	(19–81)
Medical history			
	HIV-associated condition	24	28%
	AIDS	32	38%
	CD4-T-cell-count nadir < 200 cells/µl	55	65%
CD4-T-cell count nadir [cells/µl]	(median (range))	173 (0–922)	
Years on ART	(median (range))	21 (0–34)	
Number of previous ART regimens	(median (range))	6 (1–22)	
ART experience			
	NRTI	85	100%
	NNRTI	75	88%
	INSTI	73	86%
	PI	70	82%
	Maraviroc	6	7%
	Enfuvirtide	2	2%
Switch from			
	Nucleos/tide sparing regimen	52	61%
	INSTI-containing regimen	70	82%
	Including dolutegravir	53	62%
	Rilpivirine/dolutegravir	22	26%
	Dolutegravir + darunavir	10	12%
	Lamivudine/dolutegravir	4	5%
	Including raltegravir	9	11%
	Including bictegravir	5	6%
	Including elvitegravir/cobicistat	2	2%
	Including cabotegravir	1	1%
	NNRTI-containing regimen	40	47%
	Including rilpivirine	24	28%
	Including etravirine	7	8%
	Including nevirapine	5	6%
	Including efavirenz	2	2%
	Including doravirine	2	2%
	PI-containing regimen	31	36%
	Including darunavir	27	32%
	Including atazanavir	3	4%
	Including lopinavir/ritonavir	1	1%
Main reason for switch (multiple selection)			
	Drug – drug interactions	25	29%
	Gastric-acid reducing agents	18	21%
	Side-effects of previous regimen	21	25%
	Cardiovascular risk reduction	18	21%
	Convenience/pill burden	10	12%
	Renal function	8	9%

ART antiretroviral therapy, *NRTI* nucleoside/nucleotide reverse transcriptase inhibitors, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *PI* protease inhibitors, *INSTI* integrase strand transferase inhibitors

Table 2 Information on cumulative genotypic resistance testing among 85 people living with HIV/AIDS at the time of switch to a 2-drug-regimen consisting of DOR + DTG (doravirine + dolutegravir, "DoDo")

Total $N=85$	n	(%)
Resistance testing information		
Results available	66	77.6%
Testing never performed	9	10.6%
No information available	10	11.8%
Reverse transcriptase		
Any mutation documented	57	67%
RAM affecting currently approved NRTI	43	51%
RAM affecting currently approved NNRTI	30	35%
DOR-RAM: algrothm-specific interpretation		
GRADE 01/2023[a]		
Flagged mutation(s) (S)	21	25%
Resistance (R)	1	1%
ANRS 33_10/2022[a]		
Possible resistance (I)	4	5%
Resistance (R)	2	2%
HIVDB 9.4[a]		
Low level/intermediate resistance (score 15–40) (I)	9	11%
High level resistance (score ≥ 60) (R)	2	2%
Integrase		
Any mutation documented	4	5%
RAM affecting DTG	2	2%
N155H (algorithm-specific interpretation:)	1	1%
GRADE 01/2023[a]	DTG qd: Intermediate (I), DTG bid: Flagged mutation (S)	
ANRS 33_10/2022[a]	DTG qd: Resistance (R), DTG bid: Susceptible (S)	
HIVDB 9.4[a]	Potential Low-Level Resistance (Score: 10) (S)	
Rega 10.0.0[a]	Susceptible GSS 1 (Score: 0.5) (S)	
L74I, T97A (algorithm-specific interpretation:)	1	1%
GRADE 01/2023[a]	Flagged mutations (S)	
ANRS 33_10/2022[a]	Susceptible (S)	
HIVDB 9.4[a]	Susceptible (S)	
Rega 10.0.0[a]	Susceptible GSS 1 (Score: 0.25) (S)	
Protease		
Any mutation reported	48	56%
RAM affecting currently approved PI	43	51%
Tropism testing		
Test results available	$N=16$	(%)[b]
CCR5	9	56%
Dual/mixed	1	6%
CXCR4	6	38%

RAM resistance associated mutation, *NRTI* nucleoside/nucleotide reverse transcriptase inhibitors, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *DOR* doravirine, *GRADE* Genotypic Resistance-Algorithm Deutschland [17]. (S), susceptible, (*R*) resistance, *ANRS* Agence Nationale de Recherche sur le Sida resistance algorithm, (*I*) intermediate, *HIVDB* Stanford HIV drug resistance database, *DTG* dolutegravir, *qd* once daily, *bid* twice daily, *Rega* Rega institute HIV-1 subtyping tool, *PI* protease inhibitors, *CCR5* C–C-motif chemokine receptor type 5, *CXCR4* C-X-C-motif chemokine receptor type 4

[a] All genotypic resistance interpretation algorithms were accessed via the GRADE website[17]

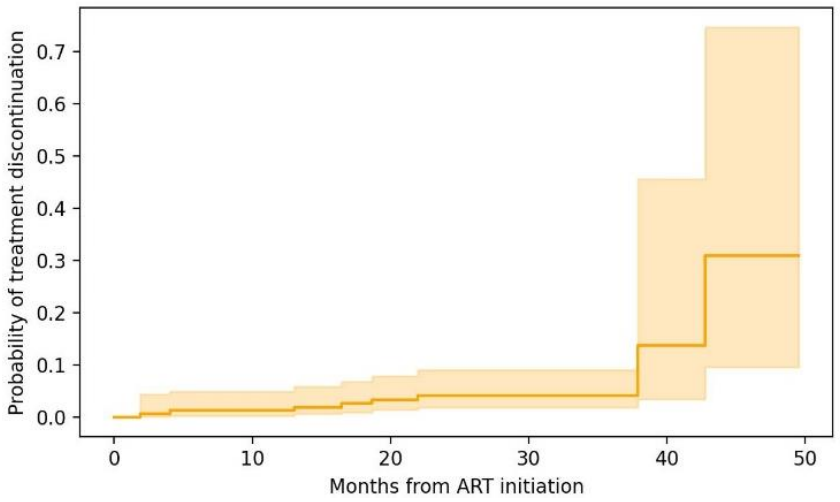
[b] Based on the observed data

Discontinuation after 1 year (IQR: 20-1300 d)
10, 12%

1.Long- acting
1. Discontinuation for RM in historical genotype
2 .Persistent viremia
5. persistent side effects
1. with to have STR (DTG/RPV)

During the follow-up, ART was again changed from DOR + DTG to another regimen in 10 participants (12%) after a median of 265 days (range 20–1390): 5 patients continued to experience potentially ART-associated side effects despite the switch to DOR + DTG, one wished to return to a single tablet regimen of RPV/DTG after stopping pantoprazole, and one wished to switch to long acting injectable ART. For one participant the identification of the DOR-RAM V106A in an historic genotypic resistance test led to the recommendation to switch off DOR + DTG despite a continuously undetectable VL. In 2 participants persisting low-level viremia of < 100 copies/ml led to the add-on of lamivudine. The other 75 participants (88%) have remained on DOR + DTG for a median of 947 days (range 43–1543) with no occurrence of virologic failure. While on DOR + DTG, 4 male participants died from non-AIDS comorbidities at age 62, 63, 66, and 82, respectively.

Unpublished data



7 cases of discontinuation

Characteristics	Population, n = 157
Age, years, median (IQR)	59.00 [55.00;63.97]
Gender, male, n (%)	96 (61.1%)
Risk factor for HIV acquisition, n (%)	
Sex between men	50 (31.8%)
Heterosexuals	73 (46.5%)
Intravenous drug use	27 (17.2%)
Other, unknown	7 (4.5%)
Smoker status, n (%)	83 (52.9%)
Years living with HIV, median (IQR)	26.00 [18.00;31.00]
Past AIDS events, n (%)	45 (28.7%)
Baseline antiretroviral regimen, n (%)	
2NRTI + PI	16 (10.2%)
2NRTI+INI	29 (18.5%)
2NRTI+NNRTI	8 (5.1%)
INI NNRTI	24 (15.3%)
INI PI	65 (41.4%)
NNRTI+PI	4 (2.5%)
Complex	11 (7.0%)
N tablet at the baseline, median (IQR)	2.00 [2.00;3.00]
Undetectable HIV RNA, n (%)	143 (91.1%)
CD4+T cell count, median (IQR)	543.50 [41.60;832.50]
Reasons to initiate DODO, n (%)	
Virological failure	6 (3.8%)
Drug interactions	40 (25.5%)
High cardiovascular and metabolic risk	81 (51.6%)
Toxicity of the ongoing regimen	24 (15.3%)
Simplification	83 (52.9%)
People with more than one reason to initiate DODO, n (%)	68 (43.3%)
Comorbidities, n (%)	
Chronic Kidney disease	34 (21.7%)
COPD	12 (7.6%)
Diabetes	34 (21.7%)
Dyslipidemia	100 (63.7%)
Hypertension	78 (49.7%)
Ischemic heart disease	30 (19.1%)
Malignancies	32 (20.4%)
Neurological diseases	16 (10.2%)
Obesity (BMI > 30)	31 (19.7%)
Osteoporosis	37 (23.6%)
Other cardiovascular disease	22 (14.0%)
Psychiatric diseases	20 (12.7%)
Multimorbidity, n (%)	118 (75.2%)
Polypharmacy, n (%)	61 (38.9%)
N non-art comedications, median (IQR)	3.00 [2.00;6.00]

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Viruses. 2023 Aug; 15(8): 1740.
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PMCID: PMC10459453
PMID: 37632082

Real-Life Experience on Dolutegravir and Lamivudine as Initial or Switch Therapy in a Silver Population Living with HIV

Maria Mazzitelli,[1,*] Lolita Sasset,[1] Samuele Gardin,[1] Davide Leoni,[1] Mattia Trunfio,[2,3] Vincenzo Scaglione,[1] Daniele Mengato,[4] Elena Agostini,[1] Eleonora Vania,[1,5] Cristina Putaggio,[1] and Annamaria Cattelan[1,6]

Table 1

Cohort description.

Characteristics	Study Population (n = 112)
Age, years, median (IQR)	66 (65–70)
Male gender, n (%)	87 (77.6)
White race, n (%)	109 (97.3)
Length of HIV infection, years, median (IQR)	25 (20–29)
CD4+ T cell count nadir, cells/mm^3	233 (122–345)
Past AIDS episodes, n (%)	27 (24.1)
HCV coinfection, n (%)	21 (18.7)
HIV acquisition route, n (%)	
MSM	61 (54.5)
Heterosexual	34 (30.3)
IVDU	15 (13.4)
Blood products	2 (1.8)
Previous antiretroviral, n (%)	
Naïve	6 (5.4)
Mono/dual regimen	25 (22.3)
2NRTI+PI	4 (3.6)
2NRTI+NNRTI	11 (9.8)
2NRTI+INSTI	58 (51.8)
Reason to switch, n (%)	
ABC discontinuation	41 (38.7)
PI discontinuation	22 (28.2)
Simplification	35 (33.1)
Comorbidities, n (%)	
Malignancy	27 (24.1)
Chronic renal disease	27 (24.1)
Dyslipidemia	54 (48.2)
Ischemic heart disease	19 (17.0)
Hypertension	57 (50.9)
Obesity	25 (22.3)
Cirrhosis	3 (2.7)
Diabetes	21 (18.8)
Osteoporosis	30 (26.8)
COPD	12 (10.7)
Mood disorders	26 (23.2)
Neurological disorders	24 (21.4)
N of comorbidities per participant, median (IQR)	4 (2–6)
Multimorbidity, n (%)	95 (84.8)
N of comedications per participant, median (IQR)	4 (2–5)
Polypharmacy, n (%)	39 (34.8%)

The median durability of follow-up of the DTG+3TC was 6.0 (5.4–7.0) years.

n. discontinuation=8

2 deaths
2 VF with no RAMs
2 NP intolerance (1 naive)
1 weight gain
1 LA switch

Table 2

Evolution of the study parameters.

Parameter	Baseline (n = 104)	End of Follow-Up (n = 104)	p
HIV-RNA, cp/mL, median (IQR)	0 (0–0)	0 (0–0)	-
HIV-RNA *, cp/mL, median (IQR)	74.100 (63.000–86.700)	0 (0–0)	-
CD4+ T cell count, cells/mmc, median (IQR)	663 (419–775)	614 (490–799)	0.537
CD4+ T cell count, cells/mmc *, median (IQR)	451 (240–748)	780 (625–836)	0.042
CD4/CD8 ratio, median (IQR)	0.91 (0.60–1.31)	0.92 (0.52–1.40)	0.632
CD4/CD8 ratio *, median (IQR)	0.5 (0.47–0.48)	1.1 (0.91–1.5)	0.003
Total cholesterol, mmol/dL, median (IQR)	4.8 (4.0–5.4)	4.7 (3.7–5.3)	0.091
HDL, mmol/dL, median (IQR)	1.3 (1.1–1.6)	1.2 (1.1–1.6)	0.957
LDL, mmol/dL, median (IQR)	2.9 (2.3–3.7)	2.9 (2.3–3.6)	0.412
Triglycerides, mmol/dL, median (IQR)	1.2 (0.91–1.8)	1.2 (0.82–1.6)	0.069
Glucose, mmol/dL, median (IQR)	5.4 (4.9–6.1)	5.3 (4.7–6.2)	0.239
eGFR, mL/min, median (IQR)	74 (62–89)	73 (60–88)	0.105
ALT, IU/mL, median (IQR)	23 (17–29)	22 (17–31)	0.700
AST, IU/mL, median (IQR)	24 (17–30)	25 (20–31)	0.609
Albumin, mmol/dL, median (IQR)	41 (39–44)	40 (39–43)	0.638
NAFLD, median (IQR)	−0.84 (−1.32; −0.075)	−0.73 (−1.41; −0.0097)	0.110
Framingham, median (IQR)	30.0 (18.4–30.0)	30.0 (18.4–30.0)	0.673
FIB-4, median (IQR)	0.036 (0.017–0.56)	0 (0–0.0086)	<0.001
APRI score, median (IQR)	0.31 (0.24–0.44)	0.31 (0.21–0.44)	0.877
BMI, median (IQR)	25.9 (24.0–29.6)	25.9 (23.9–29.4)	0.360

Considerations for long-acting antiretroviral therapy in older persons with HIV

Jesse G. O'Shea[a,*], Preetam Cholli[a,*], Emily L. Heil[b] and Kate Buchacz[a]

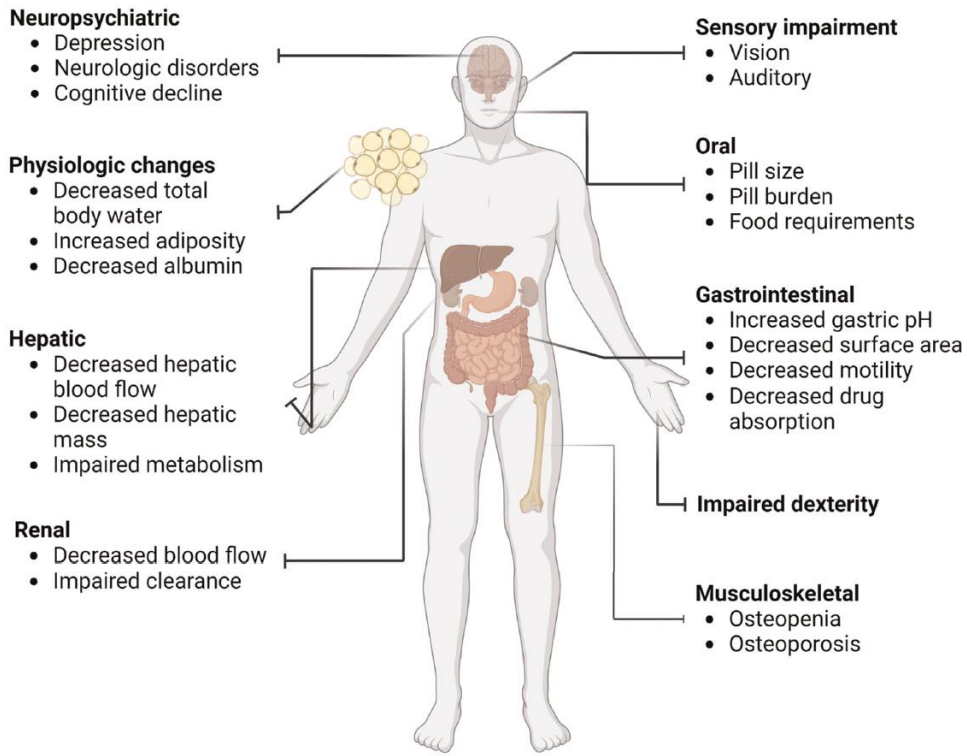

Fig. 1. Age-related changes affecting oral ART adherence and pharmacology.

AIDS 2023, **37**:2271–2286

Open Forum Infectious Diseases

MAJOR ARTICLE

Drug Exposure of Long-Acting Cabotegravir and Rilpivirine in Older People With Human Immunodeficiency Virus: A Pharmacokinetic Modeling Study

Sara Bettonte,[1,2] Mattia Berton,[1,2] Felix Stader,[3] Manuel Battegay,[1,2] and Catia Marzolini[1,2,4,5]

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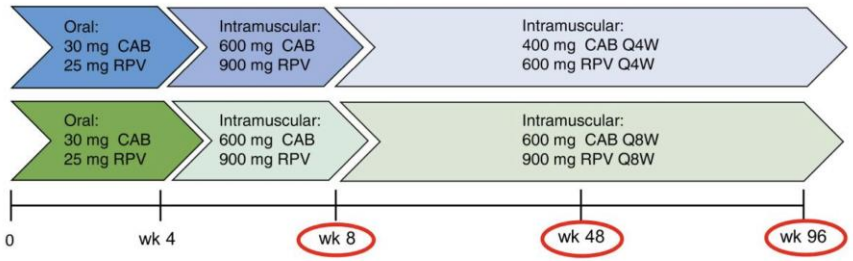

Figure 1. Schematic study design used to determine the exposure of long-acting (LA) cabotegravir (CAB) and rilpivirine (RPV) in young (aged 20–50 years), middle-aged (50–65 years), and older (65–85 years) virtual adults. Physiologically based pharmacokinetic (PBPK) modeling was applied to conduct virtual trials. The design of the phase III registrational studies (ie, FLAIR, ATLAS and ATLAS-2M studies) and of the label dosing recommendations were applied, which consisted of administering an oral lead-in 30 mg for CAB and 25 mg for RPV) for 4 weeks. At week 4, the first intramuscular loading dose was injected (600 mg for CAB and 900 mg for RPV). From week 8 on, the maintenance doses of LA CAB and LA RPV were administered either monthly (every 4 weeks [Q4W]) (400 mg for CAB and 600 mg for RPV) or bimonthly (every 8 weeks [Q8W]) (600 mg for CAB and 900 mg for RPV). Red ovals represent the time points at which the CAB and RPV concentrations were determined at the end of the dosing interval (trough concentrations) for the different age groups.

Table 1. Predicted Pharmacokinetic Values for Oral Cabotegravir and Rilpivirine in Young and Older Individuals (Both 50% Female))

Parameter	Geometric Mean (CV) by Age Group		Ratio Older/ Young Adults
	Young (Aged 20–50 y; 50% Female)	Older (Aged 65–85 y; 50% Female)	
Cabotegravir			
C_{max}, ng/mL	8526 (49)	9918 (45)	1.16
AUC_{τ}, ng · h/mL	168 700 (57	202 384 (51)	1.20
C_{min}, ng/mL	5493 (67)	6904 (59)	1.26
Rilpivirine			
C_{max}, ng/mL	198 (28)	238 (25)	1.20
AUC_{τ}, ng · h/mL	3158 (34)	3946 (28)	1.25
C_{min}, ng/mL	98 (43)	132 (33)	1.35

Abbreviations: AUC_{τ}, area under the concentration-time curve to tau; C_{max}, peak concentration; C_{min}, trough concentration; CV, coefficient of variation.

https://doi.org/10.1093/ofid/ofae171

Chronic care model: possible obstacles?

- Services issues
- Stigma or privacy overprotection risk
- Heterogeneity of istitutional approaches (regional plans for HIV management, «PDTA»)
- Lacking of staff (primary care) e tools (information technology)

Long-term management and follow-up

- Dedicated staffs
- Plan and manage population data to facilitate efficient and effective care
- What about missed injections visits?
- Implementing home services for patients with disabilities and/or reduced mobility, istitutionalised

Take home messages for simplified treatment in elderly

- Safe and durable data on dual oral regimens
- Selection of elderly PLWH who can have LA should be very carefull conducted
- Good acceptation in trial populations, but new real life data is necessary
- Some DDis, even with LA, are practically unavoidable, but mostly manageable
- Active surveillance for DDis should be perfomed, de-prescribing approach with multidisciplinary team
- New therapeutic approaches require new pathway/services for care delivery
- PK/PD to monitor over-exposure

- Multidimensional clinics with one-shot multidimensional assessment
- Home care/service delivery
- Long term implants

Thanks for your attention!

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