Managing special patients with comorbidities

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DI MODENA E REGGIO EMILIA

Menu

- Integration of comorbidities in a total patient care approach
- Polypharmacy

Mr. A: HIV infection detected at an older age (2012)

53 yrs
Heterosexual
Live with family and nephews

HIV diagnosis: 2012
CDC group A
CD4 nadir 320/microL
HIV-1 wild type
HIV VL=46000 c/mL

Antropometry
BMI=25.2
Waist=102 cm
Leg fat%=27%
VAT=256cc

Life style
Sedentary
Non smoker
(pack year=58)

Co-morbidities
- ✓ HTN
- ✓ MS
- ✓ Benign prostatic hyperplasia (BPH)

NEAT Trial
Ranomised in
TDF/FTC+DRV/r

Rx
Lisinopril
Tamsulosin

Aging with HIV: Emerging importance of chronic comorbidities in patients over 75

N(%)	Elderly [50-75[n=12748	Geriatric ≥75 n=430	P. value
Diabetes	1195 (9.4)	96 (22.3)	< 0.001
Hypertension	2685 (21.1)	182 (42.3)	< 0.001
Hyperlipidemia	2700 (21.2)	120 (27.9)	0.001
Cardio-vascular disease	1081 (8.5)	89 (20.7)	< 0.001
Stroke	319 (2.5)	27 (6.3)	< 0.001
Osteoporosis	626 (4.9)	36 (8.4)	0.002
Neoplasia	1526 (12)	97 (22.6)	< 0.001
Renal failure*	594 (4.7)	60 (14)	< 0.001
Depression	2114 (16.6)	65 (15.1)	NS
Liver fibrosis	620 (4.9)	10 (2.3)	0.021
Number of AANC			< 0.001
- 0-1	9058 (71.1)	197 (45.8)	
- 2-3	3147 (24.7)	173 (40.2)	
- ≥4	543 (4.3)	60 (14)	

*eGFR <60 ml/mn/1,73m²

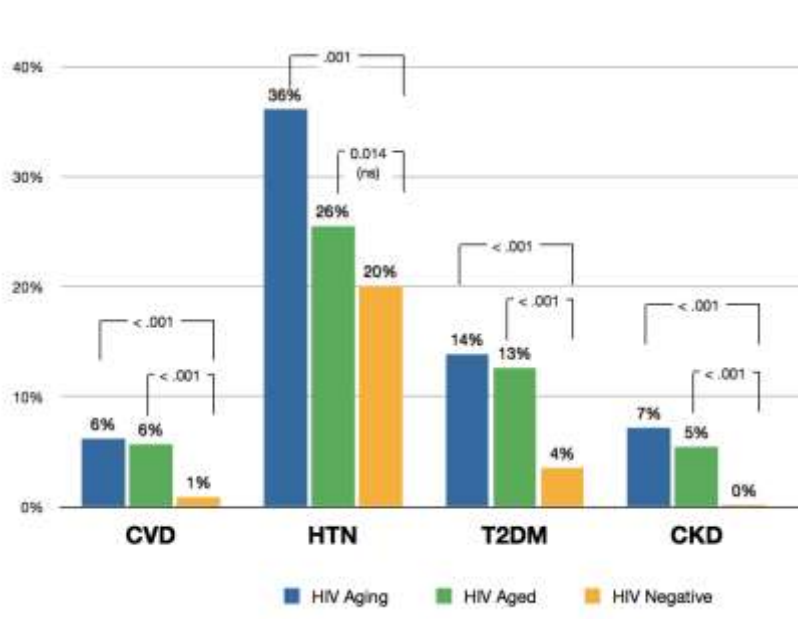
Allavena ,C et at CROI 2016 Feb 22-24 Boston

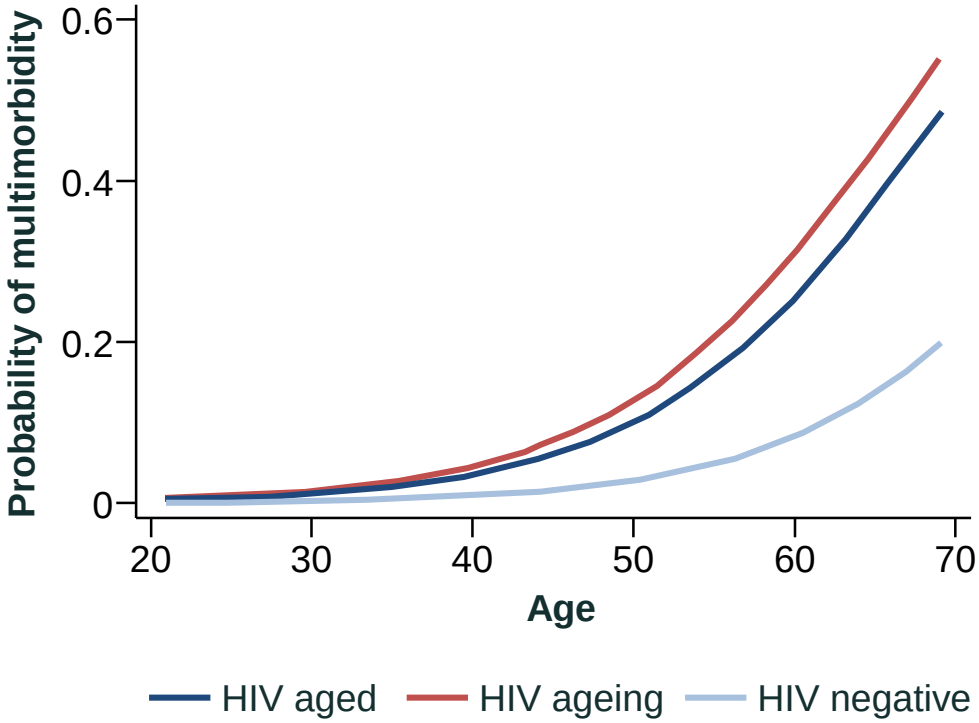
Table 4 Antiretroviral history and current ART regimen

	Elderly [50-75[N=12 748	Geriatric ≥75 N=430	P. value
Age at ART initiation, median [IQR]	44.1 [37.5-50.7]	64.5 [60-70]	**< 0.001**
Age at ART initiation by strata, n (%)			**< 0.001**
<50 year-old	9024 (72.6)	0 (0)	
[50-75[year-old	3409 (27.4)	370 (88.1)	
≥75 year-old	0 (0)	50 (11.9)	
ART Status at last visit, n (%)			NS
ART interruption	124 (1)	3 (0.7)	
on ART	12309 (96.6)	417 (97)	
ART-naïve	315 (2.5)	10 (2.3)	
Number of ART regimen, median [IQR]	5 [3-9]	6 [3-10]	**0.016**
ART at last visit, n (%)			**0.015**
2 NRTIs + INSTI	1234 (9.7)	43 (10)	
2 NRTIs + PI	280 (2.2)	15 (3.5)	
2 NRTIs + bPI	3311 (26)	95 (22.1)	
2 NRTIs + NNRTI	4182 (32.8)	126 (29.3)	
3 NRTIs	140 (1.1)	10 (2.3)	
NRTI-sparing bPI-based regimen	2024 (15.9)	75 (17.4)	
NRTI and bPI-sparing regimen	1262 (9.9)	56 (13)	
Number of ARV, n (%)			NS
1 or 2 ARVs	1355 (11.0)	60 (14)	
3 ARVs	10101 (82.6)	333 (77.6)	
≥ 4 ARVs	962 (7.8)	26 (6.1)	

Allavena C et al CROI 2016 Feb 22-24 Boston

Aging vs aged patients: Prevalence and probability for multimorbidities increases with HIV duration





At any age, long-term infected people (ageing patients) had a 5-fold accentuated risk of multimorbidity than HIV-negative controls, while more recently infected people (aged patients) had an intermediate risk compared with the control group

Guaraldi G, et alPLoS One. 2015 Apr 13;10(4):e0118531

Mr. A (2016)

57 yrs
CD4=770/microL
HIV VL<40 c/mL
TC=165 mg/dL
LDL=91 mg/dL
TG=213 mg/dL
Crea=1.4 mg/dL
Lumbar t-score=-2.3
GGT=60 mg/mL
TDF/FTC+DRV/r

ASCVD=10.5%

CKD-epi=55.4 mg/dL

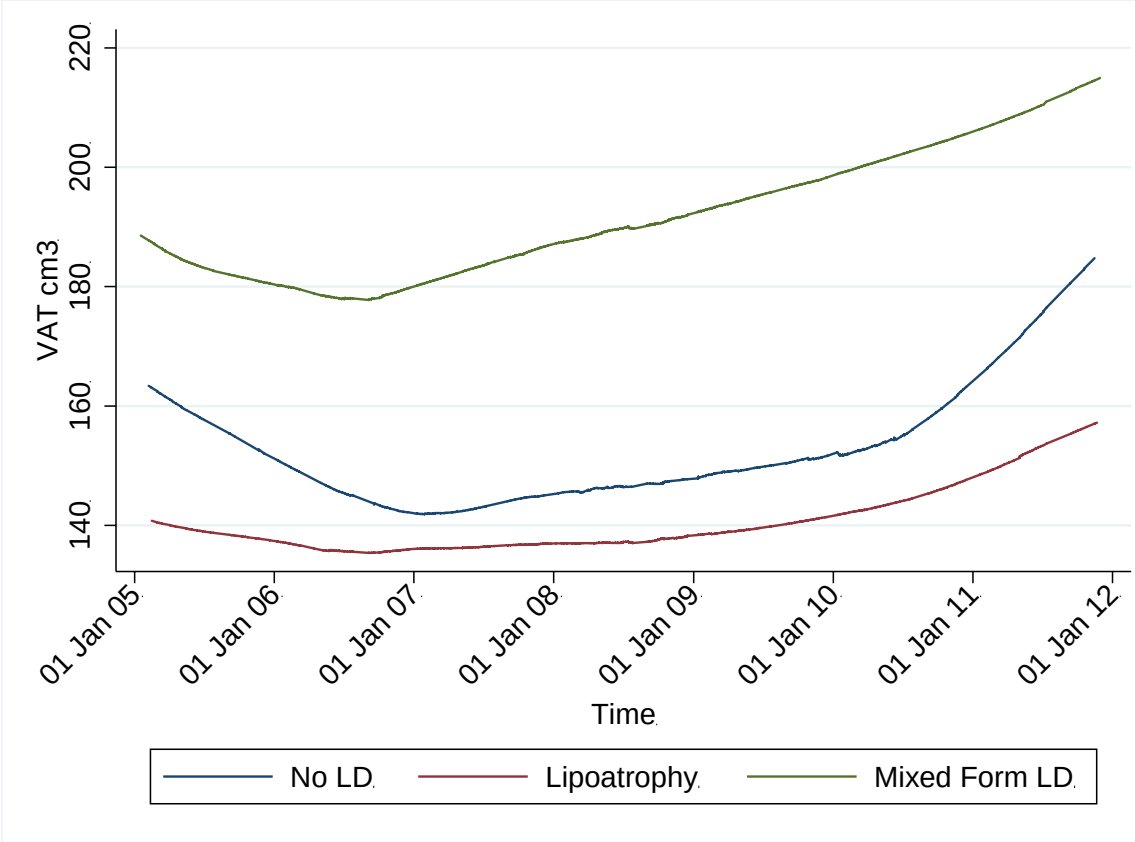
Antropometry
BMI=31
Waist=122 cm
VAT=286cc

Life style
Sedentary
Non smoker
(pack year=58)

Co-morbidities
- ✓ T2DM
- ✓ HTN
- ✓ MS
- ✓ Benign prostatic hyperplasia (BPH)

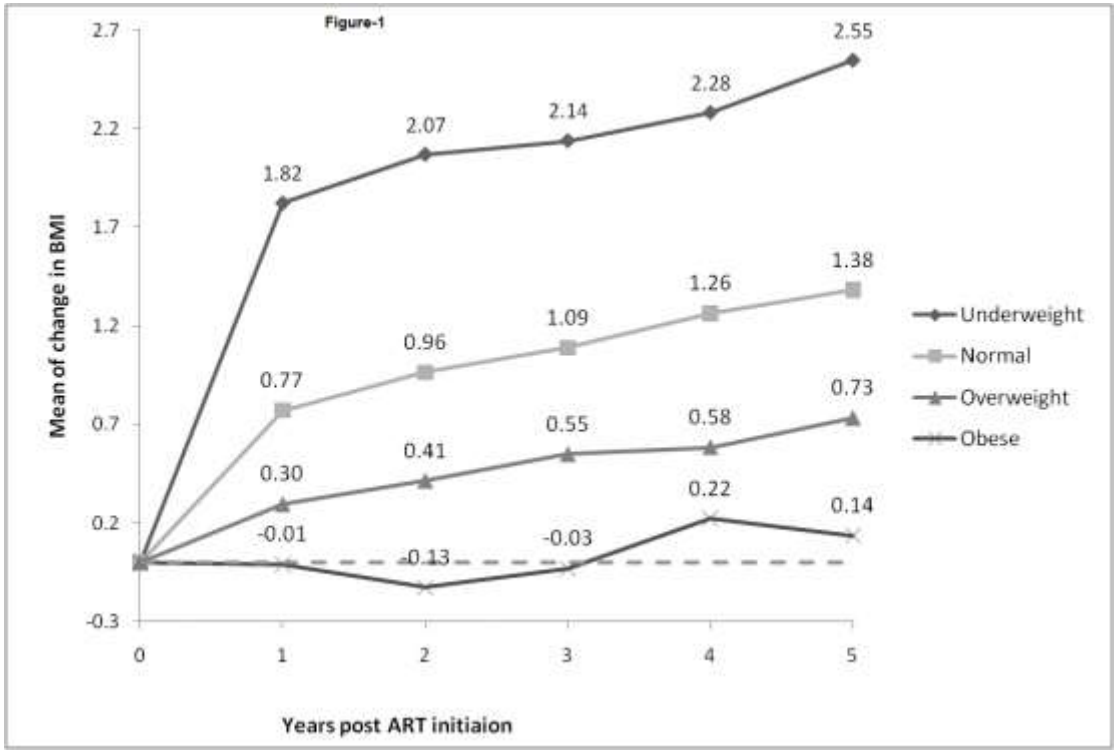
Polifarmacy
ASA 100
Pravastatin
Metformin
Lisinopril
Vit D
Finasteride
Sertraline

Aging Phenotype vs Lipohypertrophy



Guaraldi G, HIV Medicine. 2014

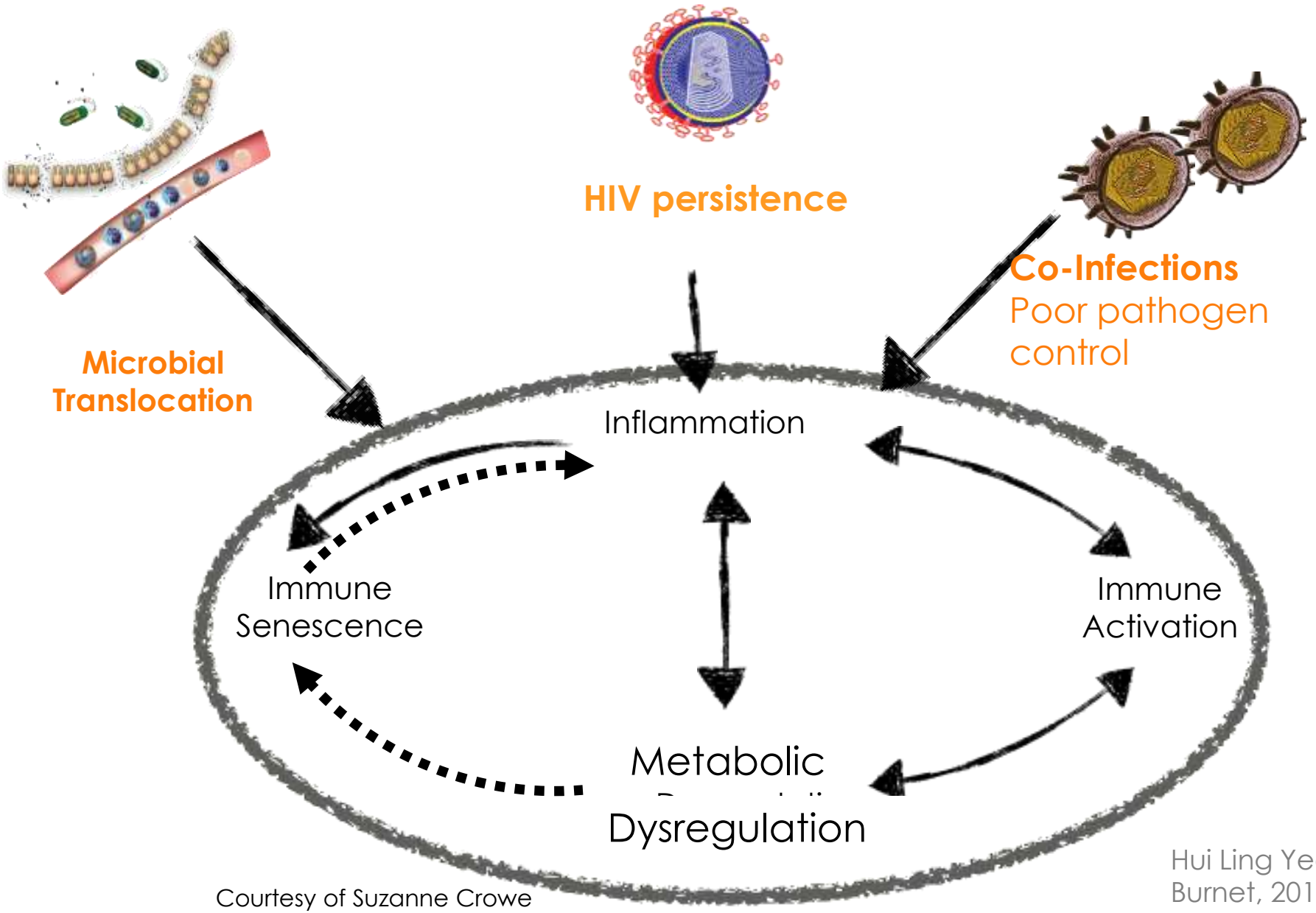
Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study.



Short-term gain in BMI following ART initiation appears to increase the longer term risk of CVD, but only in those with pre-ART BMI in the normal range. It was also associated with increased risk of diabetes regardless of pre-ART BMI.

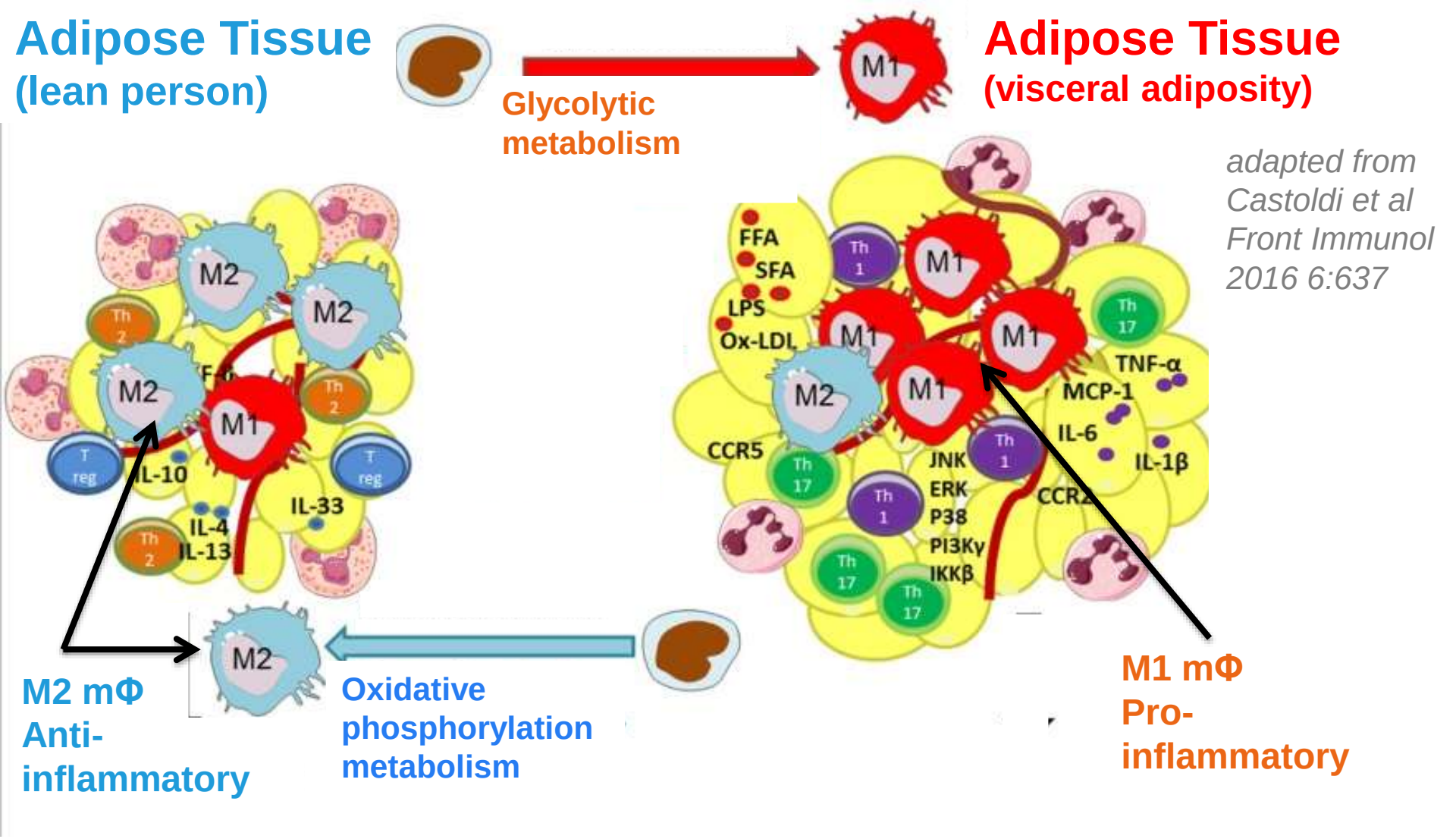
Amit C Achhra et al HIV Med, 2015

Microbial translocation, HIV persistence and coinfections cause persistent innate immune activation



Courtesy of Suzanne Crowe

Hui Ling Yeoh, Burnet, 2016



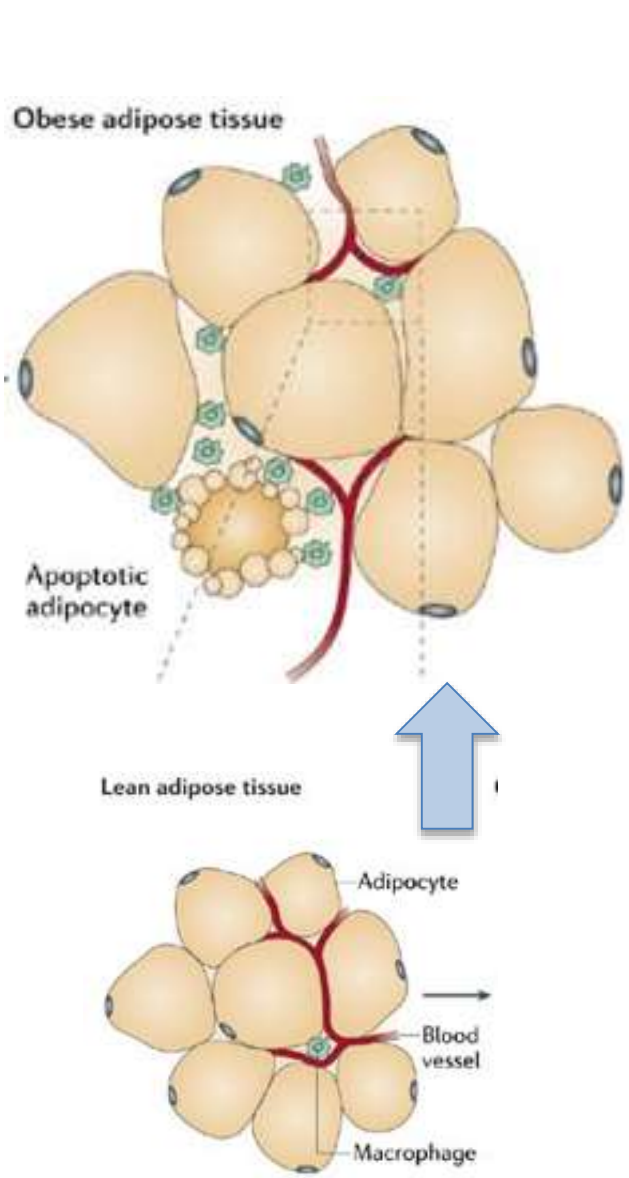
Tissue mΦ and metabolism are critical in adiposity pathogenesis

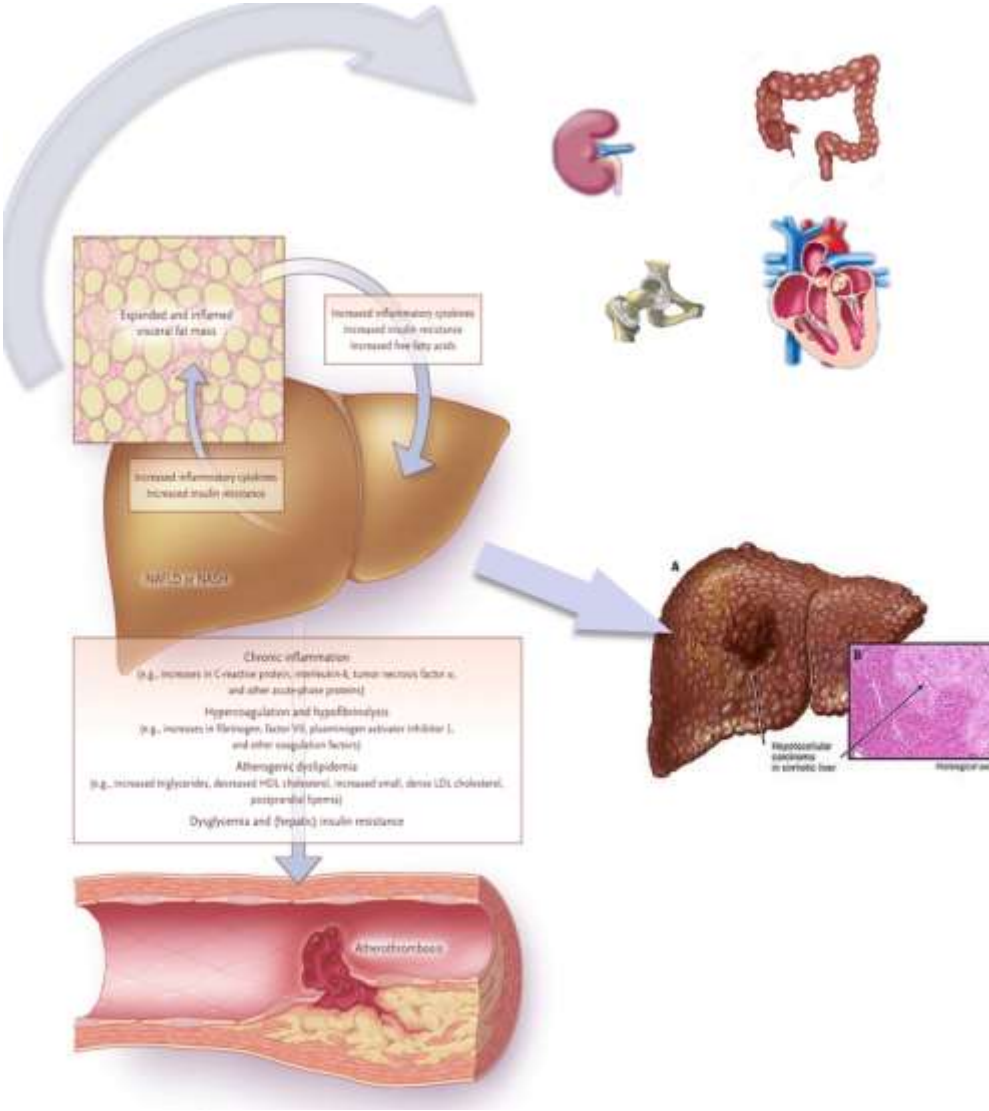
In obese AT, M1mΦ use glycolytic metabolism.

Switch to glycolysis in M1mΦ is central for pro-inflammatory profile

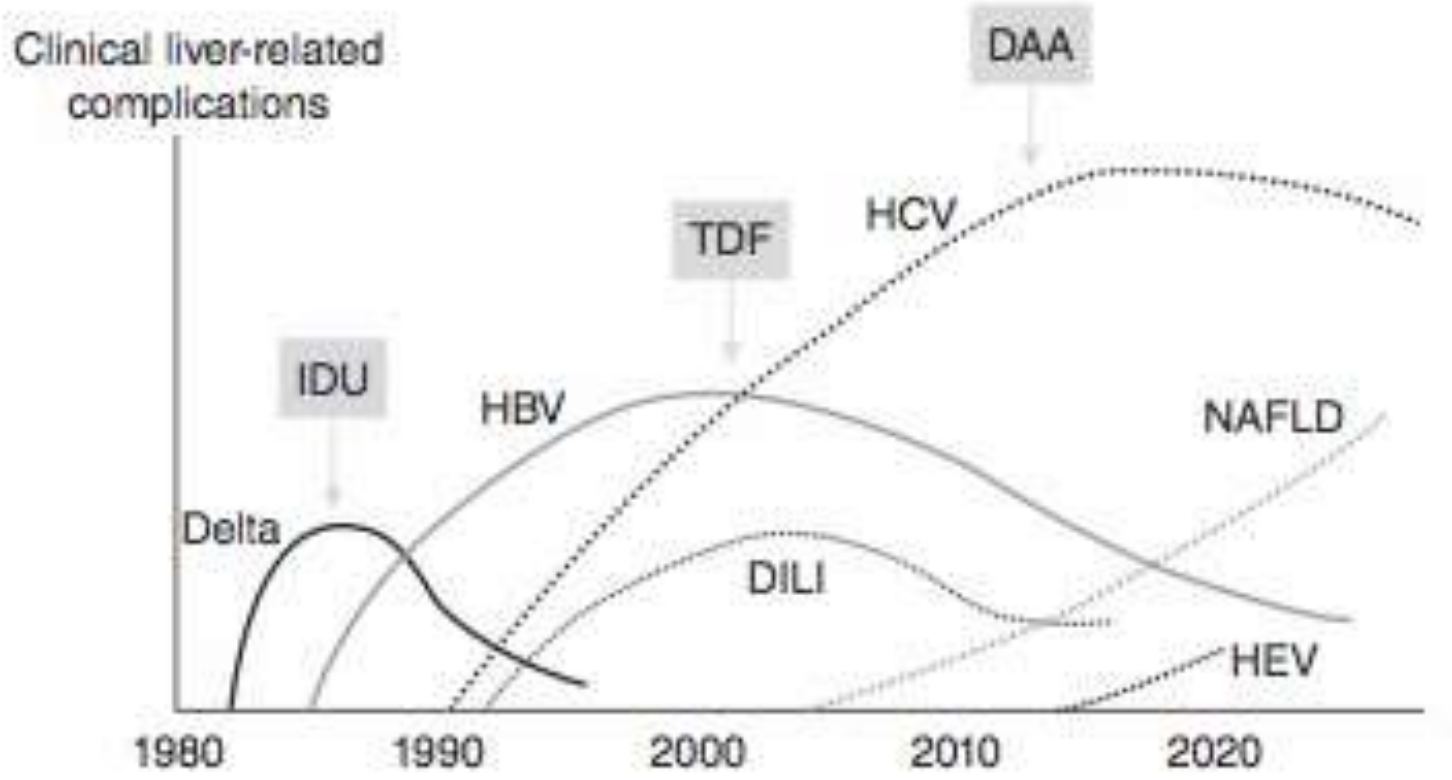
Courtesy of Suzanne Crowe

Metabolic endotoxemia





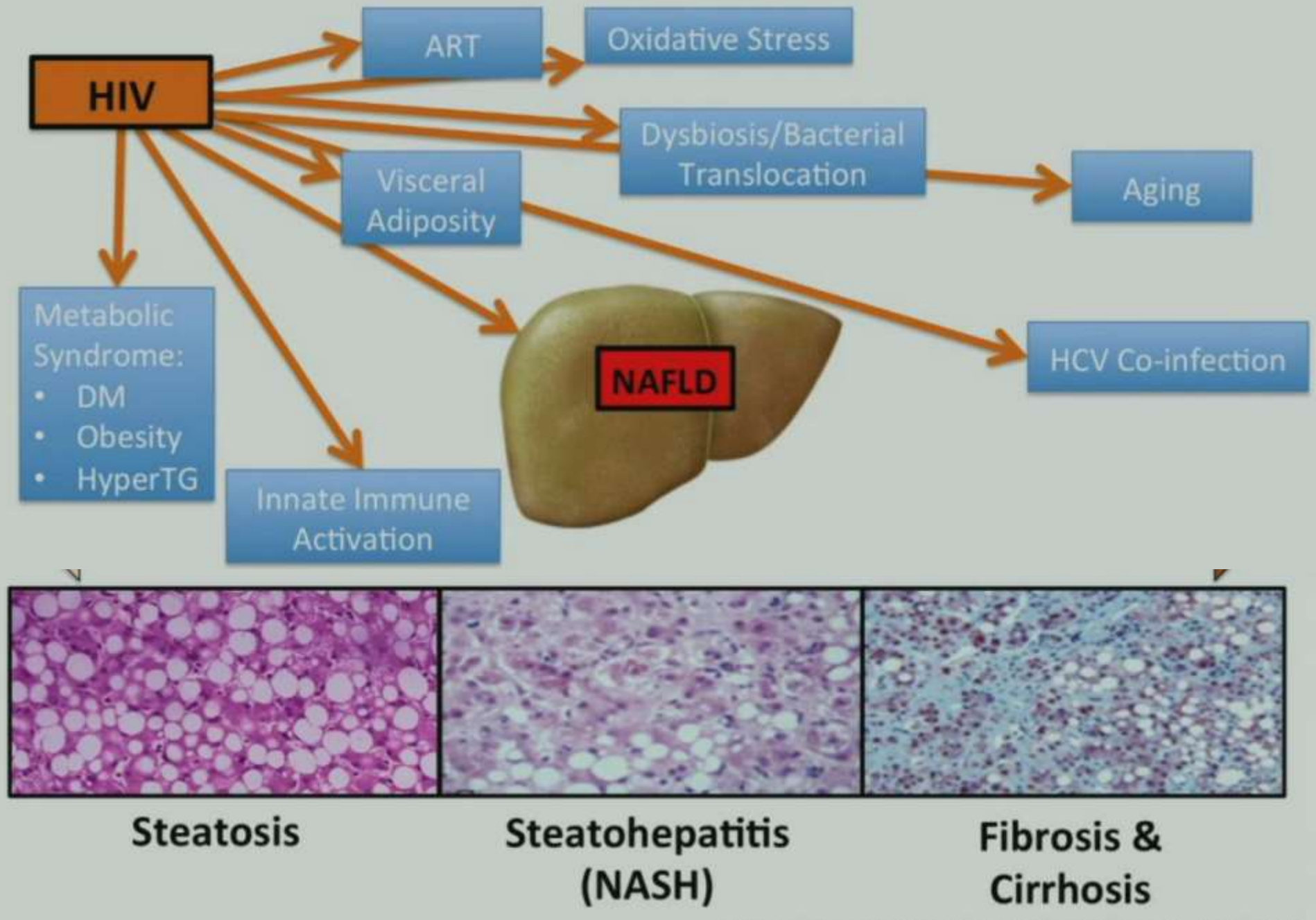
The Changing Epidemiology of Liver Disease in HIV Patients



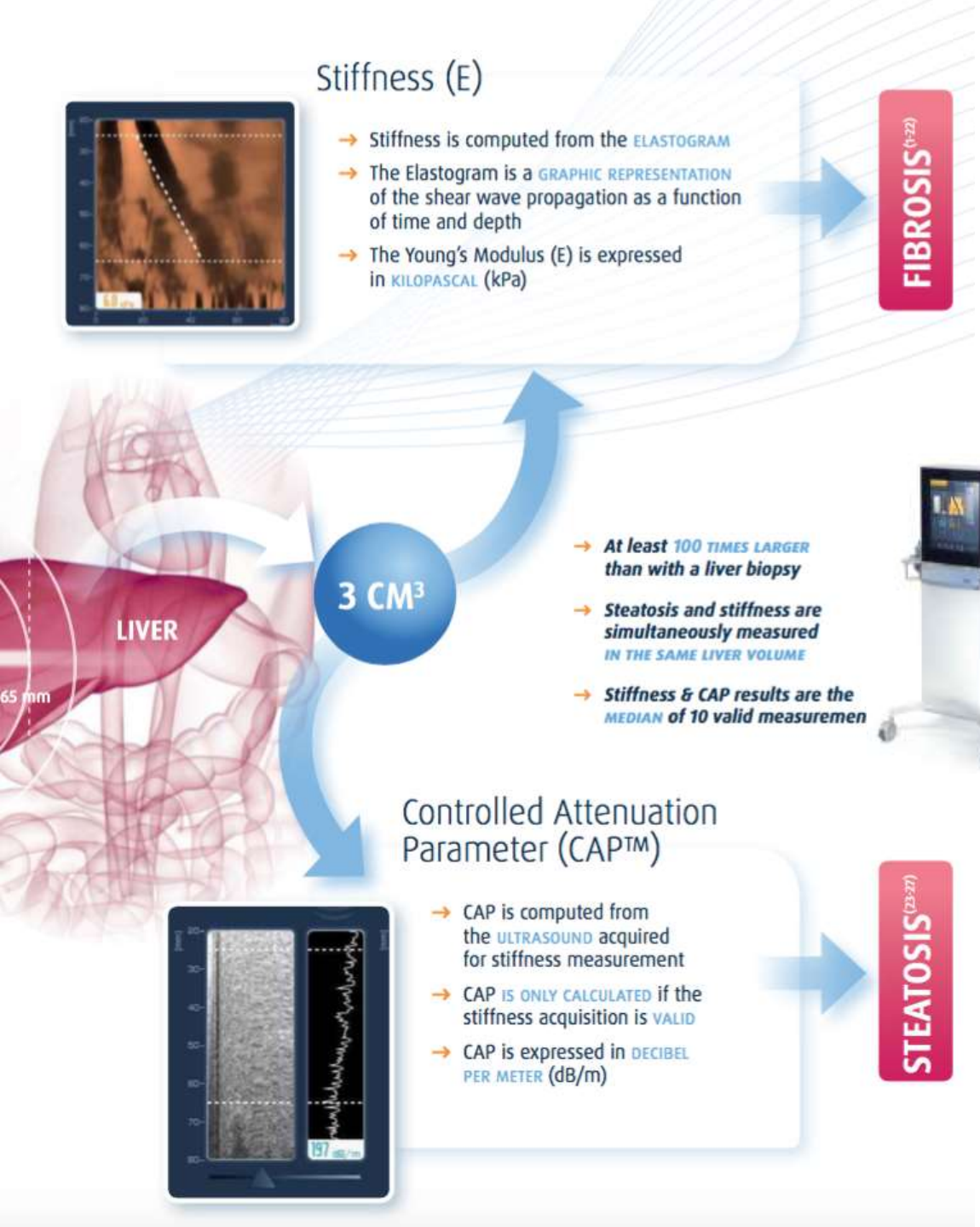
Time trends in liver disease etiologies in HIV patients.

DAA: direct-acting antivirals; TDF: tenofovir; IDU: intravenous drug users; NAFLD: non-alcoholic fatty liver disease; DILI: drug-induced liver injury; HEV: hepatitis E virus.

Soriano v et al **AIDS** Rev. 2013;15:25-31



Chalasani N, et al. AASLD Practice Guideline. Hepatology, 2012



FIBROSIS BIOMARKERS

Surrogate markers of liver fibrosis:

1. AST to ALT Ratio (**AAR**), AST to Platelet Ratio Index (**APRI**)
2. **BARD** score
3. **FIB-4** score
4. NAFLD Fibrosis Score (**NFS**)

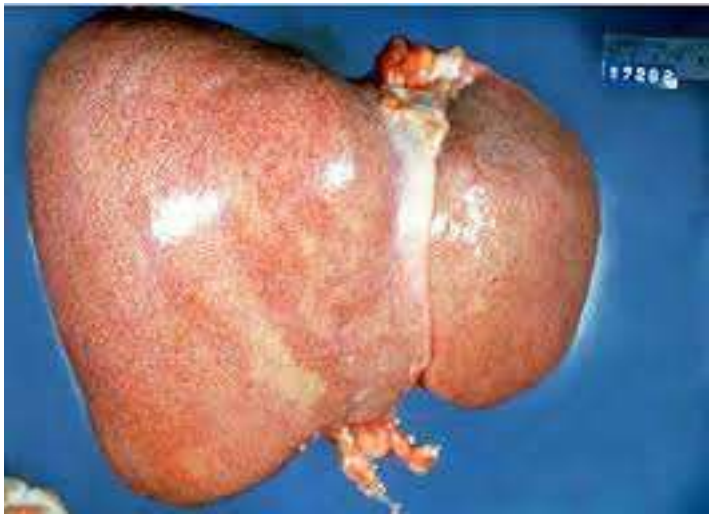
STEATOSIS BIOMARKERS

Surrogate markers of liver steatosis:

1. Fatty Liver Index (**FLI**)
2. Lipid Accumulation Product (**LAP**)
3. NAFLD liver fat score (**NAFLD-LFS**)
4. Hepatic Steatosis Index (**HSI**)
5. Visceral Adiposity Index (**VAI**)
6. Triglycerides and glucose (**TyG**) index.

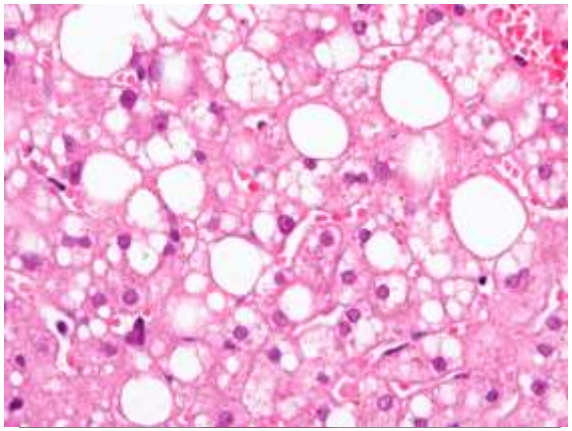
This is metabolism!

Metabolism is an organ disease

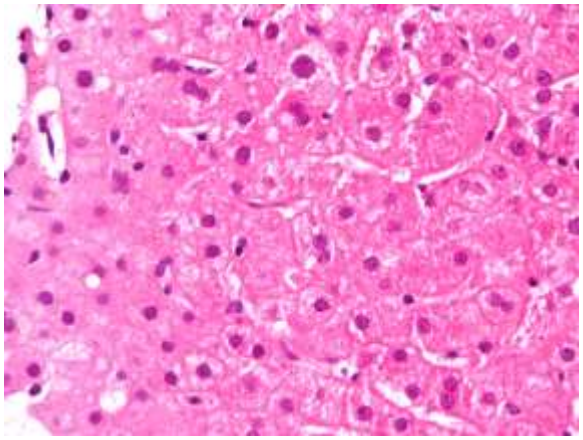


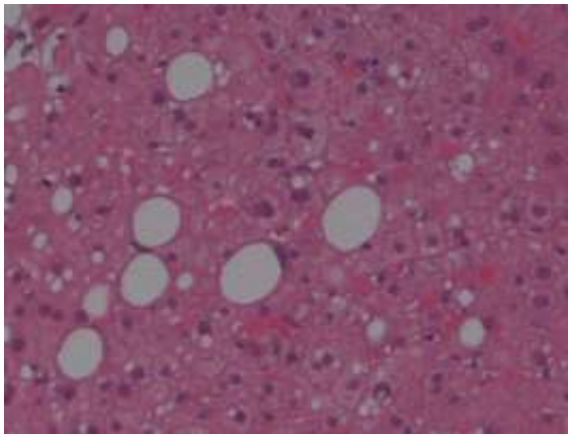
Better drugs, HCV clearance and increased life expectancy will not solve but rather change the metabolic problems of people living with HIV.

NRTI-spearing+ MRV

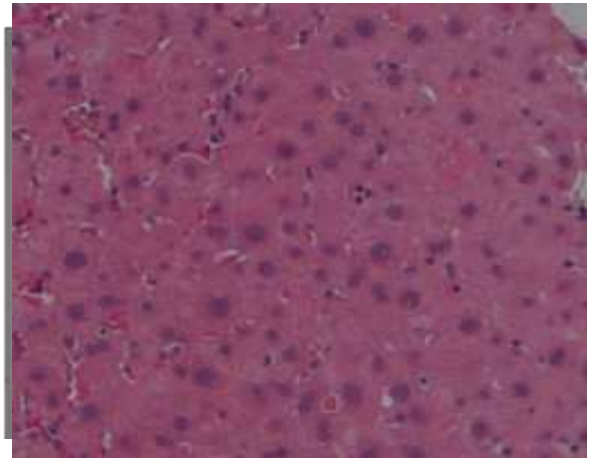


PG, male, 64 years old
287 CD4 402
21.6 BMI 22.8
109 Gly 97
2.5 HOMA-IR 1,38
68 Tg 104
66/152 HDL/LDL 49/141
23/18 ALT/AST 46/44
G1 S0 Brunt GS G1 S0
3 NAS 1
55 LB fat 10
25 RM fat 7
micromacro Steatosis type micromacro
0 Inflammation 0
1 Ballooning 0
0 Fibrosis 0





FE, male, 77 years old
448 CD4 297
23.7 BMI 22.2
83 Gly 81
1.68 HOMA-IR 1.15
207 Tg 146
42/124 HDL/LDL 47/129
27/22 ALT/AST 15/19
G1S2 Brunt GS G1S2
3 NAS 0
15 LB fat 0
9.1 RM fat 6.7
micromacro Steatosis type NA
0 Inflammation 0
1 Ballooning 0
1 Fibrosis 1



Guaraldi G. personal communication 2015

Novel concept in handling of HIV+ persons on stable ART at HIV clinics

- Diversification of type of visits
  - Traditional f2f visit with responsible physician
  - Triage with experienced nurse
  - Community clinic
  - Telemedicine (for most stable patients)
- Enhancing self management
- Focus areas
  - Ensure retainment in care
  - Shared access to electronic systems (lab, medicine) to allow for proactive alert and prompts

HIV specialist physicians have to continue to lead the way to ensure optimization of quality of care for HIV+ persons

Modified by Lundgren J. Glasgow 2014

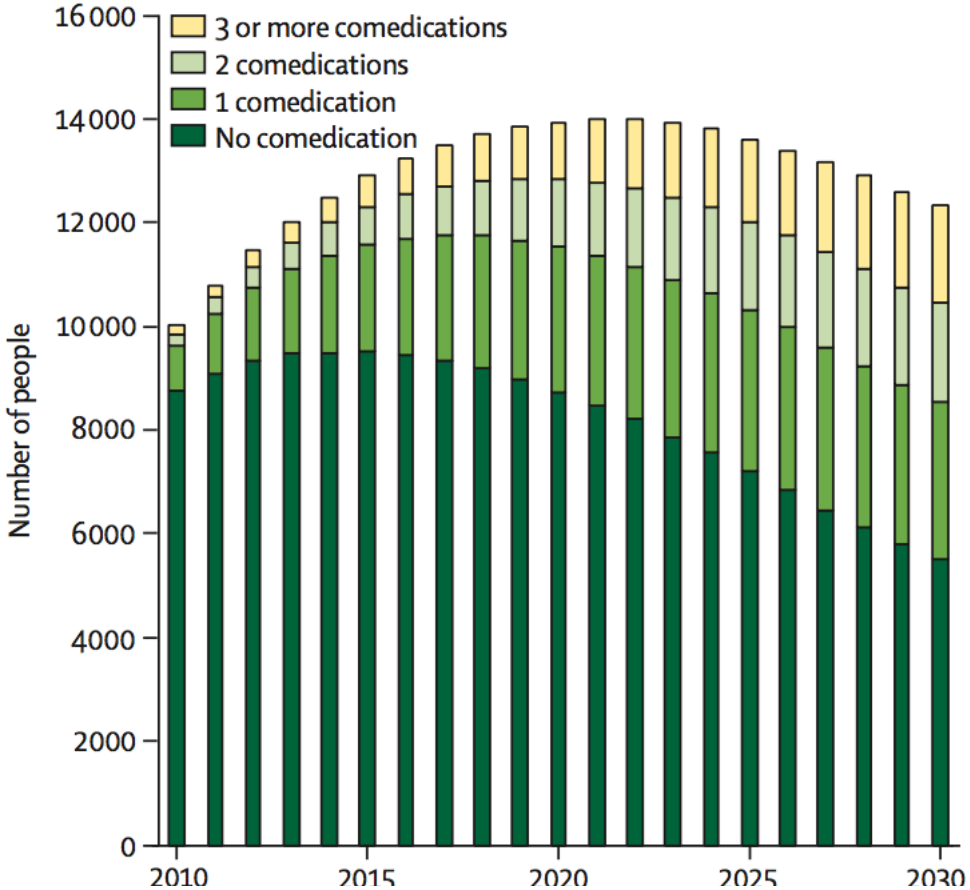
New challenges and unmet needs of PLHIV aged 50+

2000	2005	2010	2013	2015
Drug toxicities	Co-morbidities	Multi-morbidities	Frailty	Disability

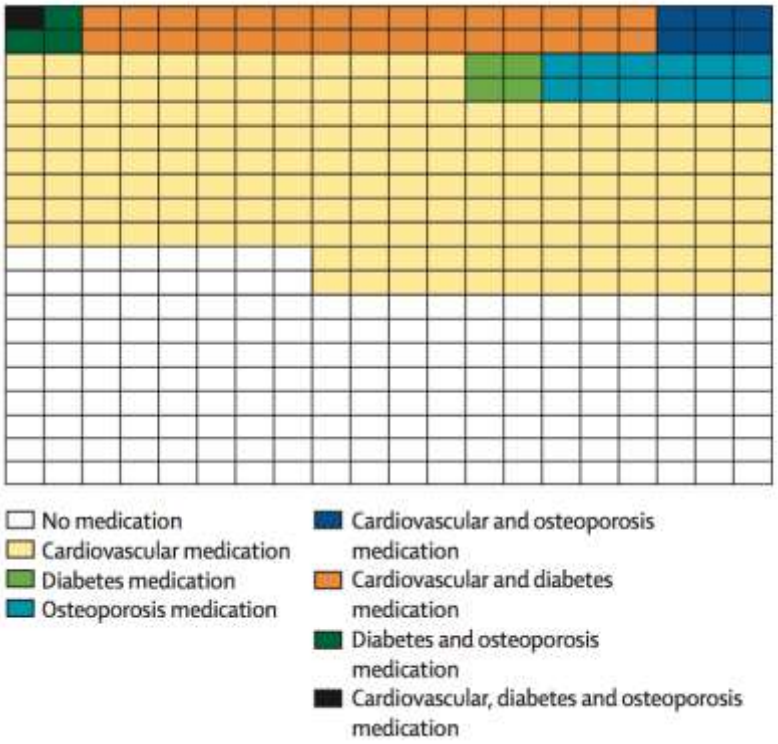
Future challenges for clinical care of an ageing population infected with HIV: a modelling study

Mikaela Smit, Kees Brinkman, Suzanne Geerlings, Colette Smit, Kalyani Thyagarajan, Ard van Sighem, Frank de Wolf, Timothy B Hallett, on behalf of the ATHENA observational cohort

Predicted burden of co-medications in HIV-infected patients between



Predicted prevalence of comedication in 2030 as cross-section of number of patients on the different types of co-medications, based on a representative 400 patients (each square represents a patient). NCD=non-communicable disease.



www.thelancet.com/infection **Published online June 10, 2015 http://dx.doi.org/10.1016/S1473-3099(15)00056-0**

Polypharmacy (PP) in the HIV infected older adult population

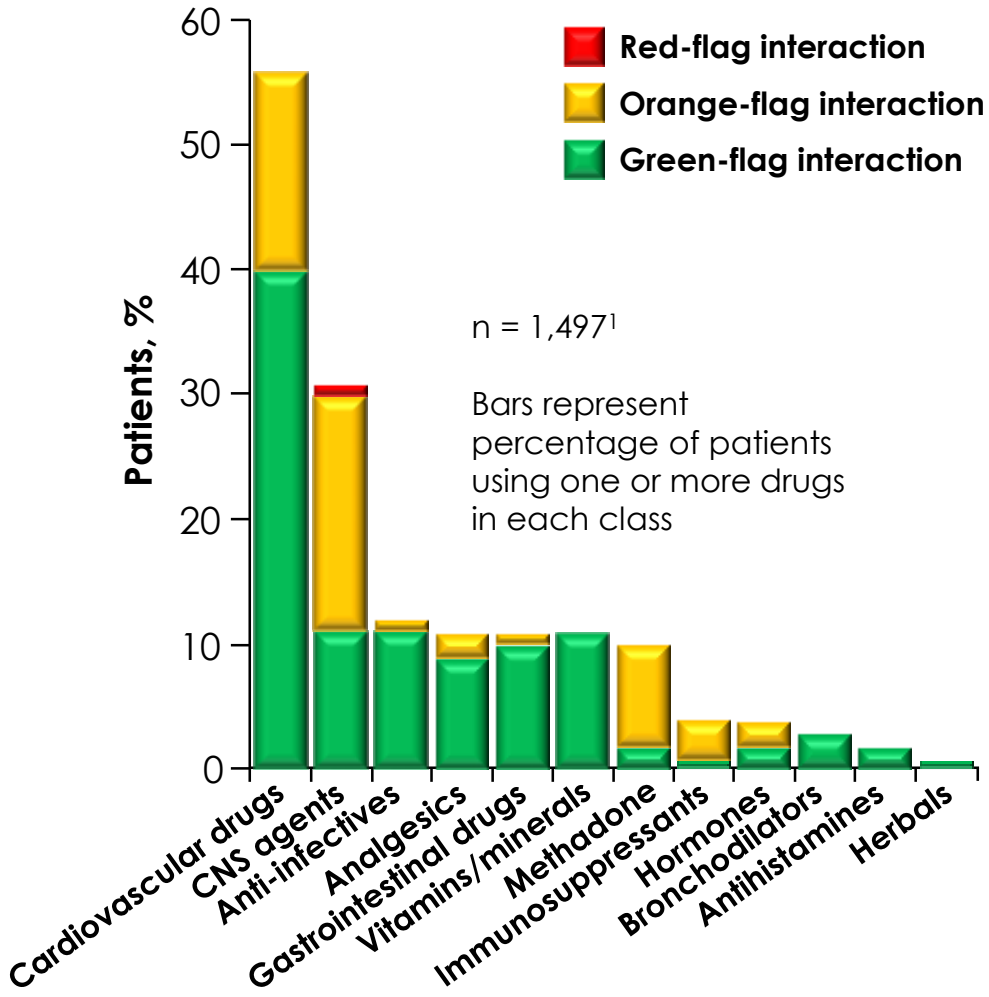
Def: 1. the use of 5 or more medications
2. the use of a potentially inappropriate drug

NEGATIVE CONSEQUENCES OF PP

1. ADE
2. DDIs
3. INCREASED COSTS
4. PILL BURDEN
5. AHDERENCE
6. FALLS
7. MORTALITY

Gleason LG, Clin Interv Aging. Dove Press; 2013;8:749–63.

Potential drug-drug interactions with cART are more likely in older patients



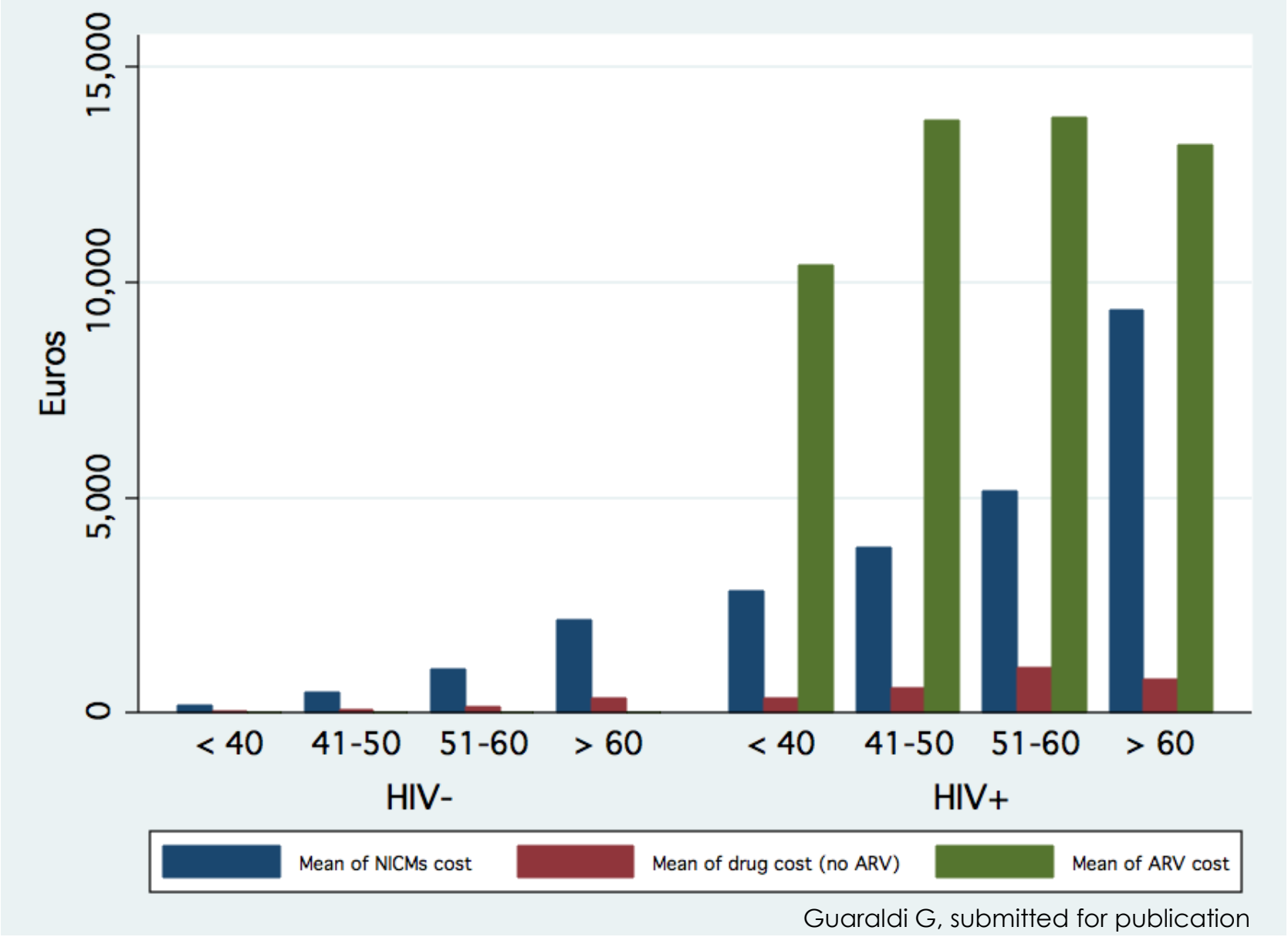
- ARVs may interact with a number of medications, including*[2]
  - Methadone
  - Oral contraceptives
  - Antiepileptics
  - Antidepressants
  - Lipid-lowering agents
  - Acid-reducing agents
  - Antimicrobials
  - Antiarrhythmics
  - Tuberculosis therapy
  - Anti-cancer drugs
  - Immunosuppressants
  - Phosphodiesterase inhibitors
  - Anti-HCV therapies

START LOW
GO SLOW

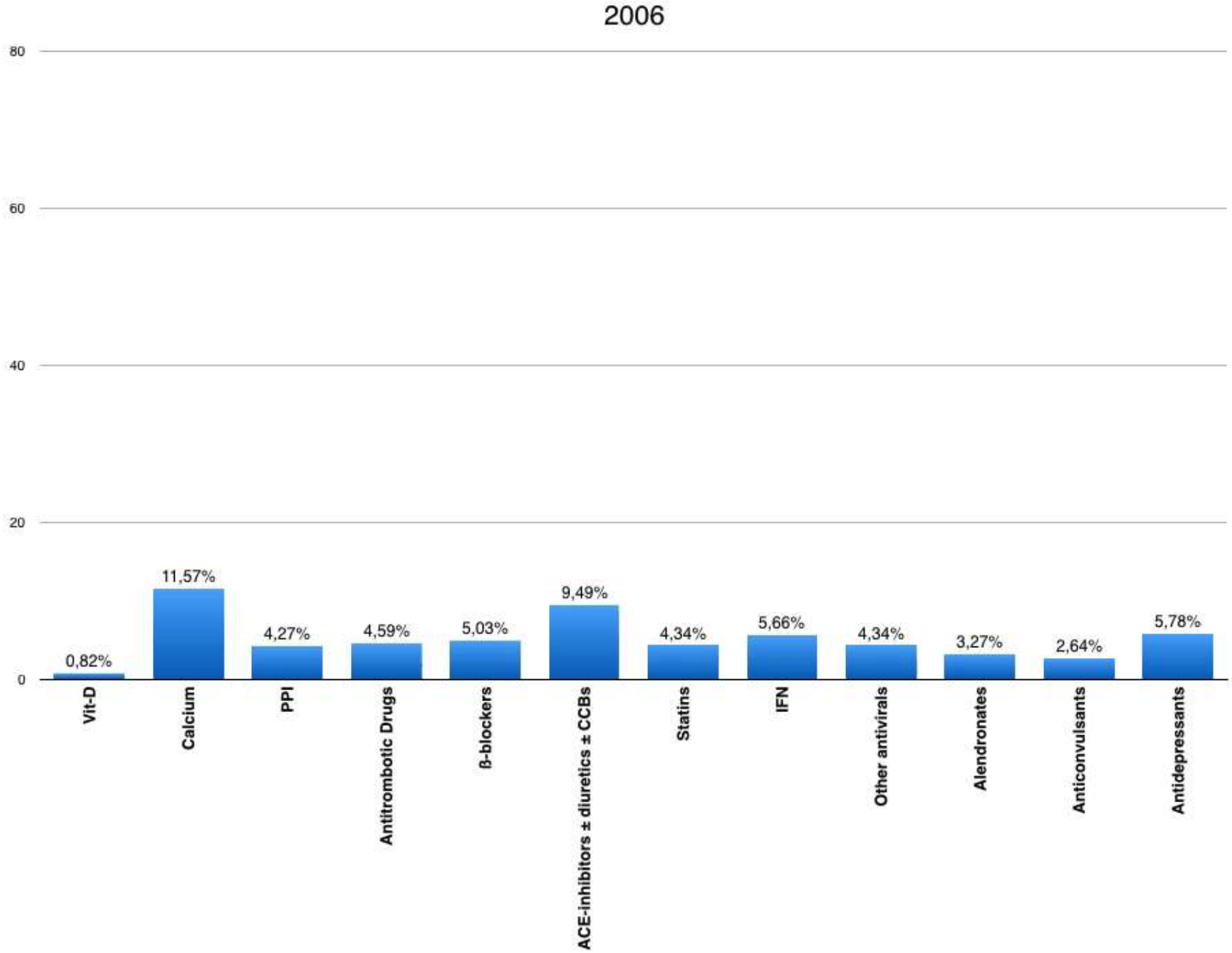
*For further information please visit www.hiv-druginteractions.org

1. Marzolini C, et al. Antivir Ther 2010;15:413-423; 2. BHIVA Draft Guidelines 2012 Available at: www.bhiva.org/documents/Guidelines/Treatment%20Guidelines/2012/formatted__ART_guidelines_04022012_v3_IW.pdf. Accessed Apr 2012.

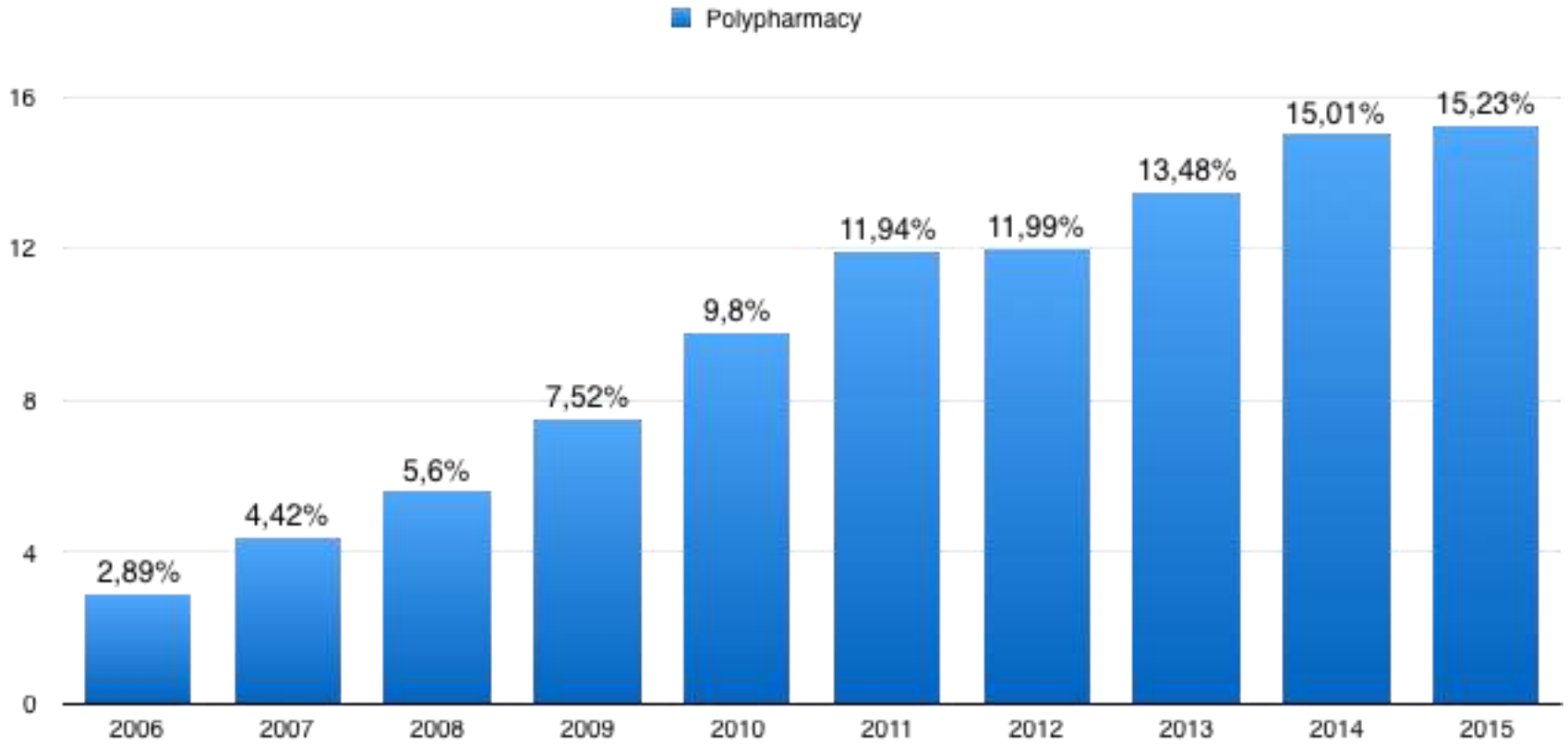
Hospital costs +NICM medication and ARV costs



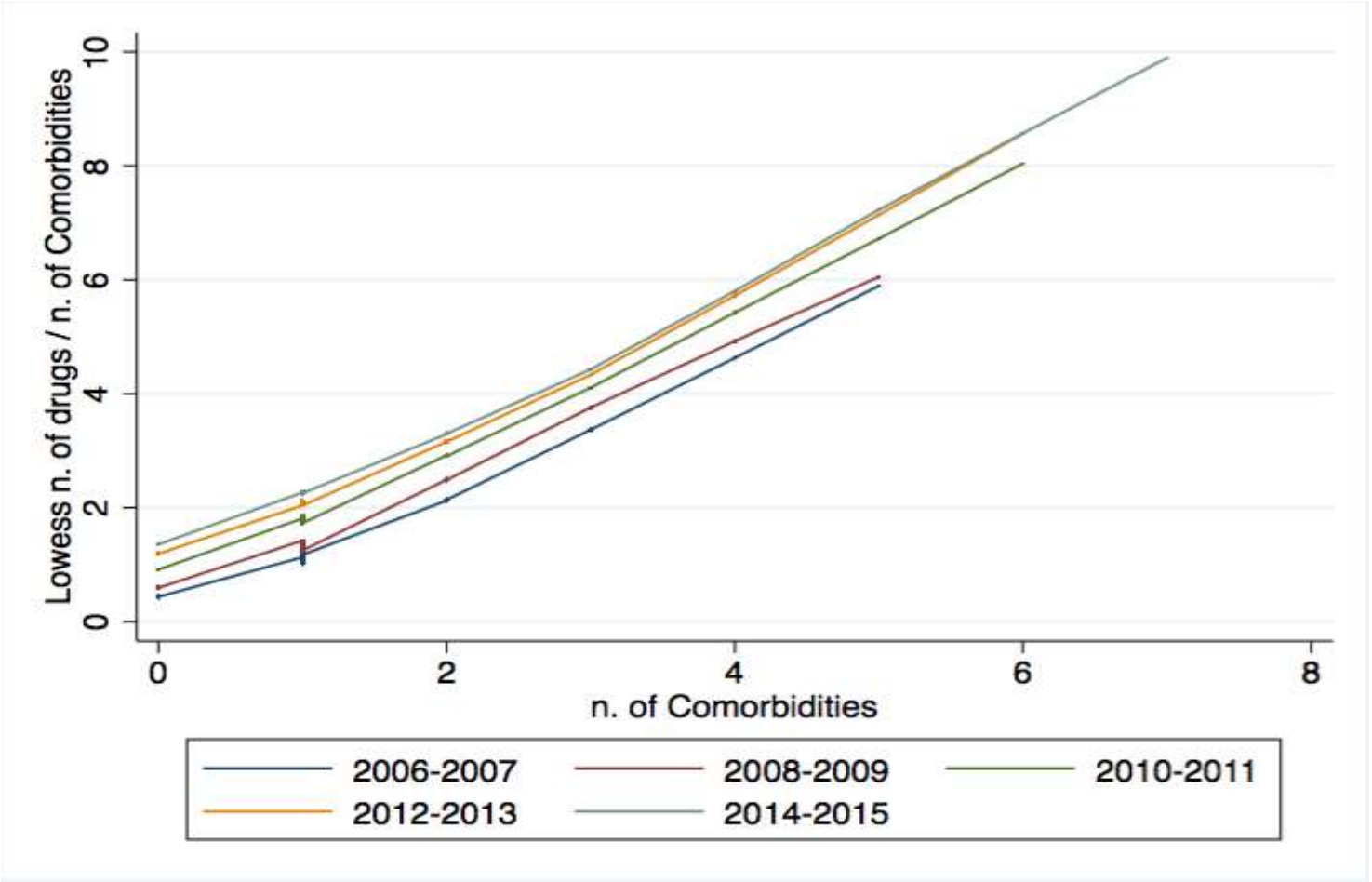
Guaraldi G, submitted for publication


2006
80
60
40
20
0
0,82%
11,57%
4,27%
4,59%
5,03%
9,49%
4,34%
5,66%
4,34%
3,27%
2,64%
5,78%
Vit-D
Calcium
PPI
Antitrombotic Drugs
β-blockers
ACE-inhibitors ± diuretics ± CCBs
Statins
IFN
Other antivirals
Alendronates
Anticonvulsants
Antidepressants

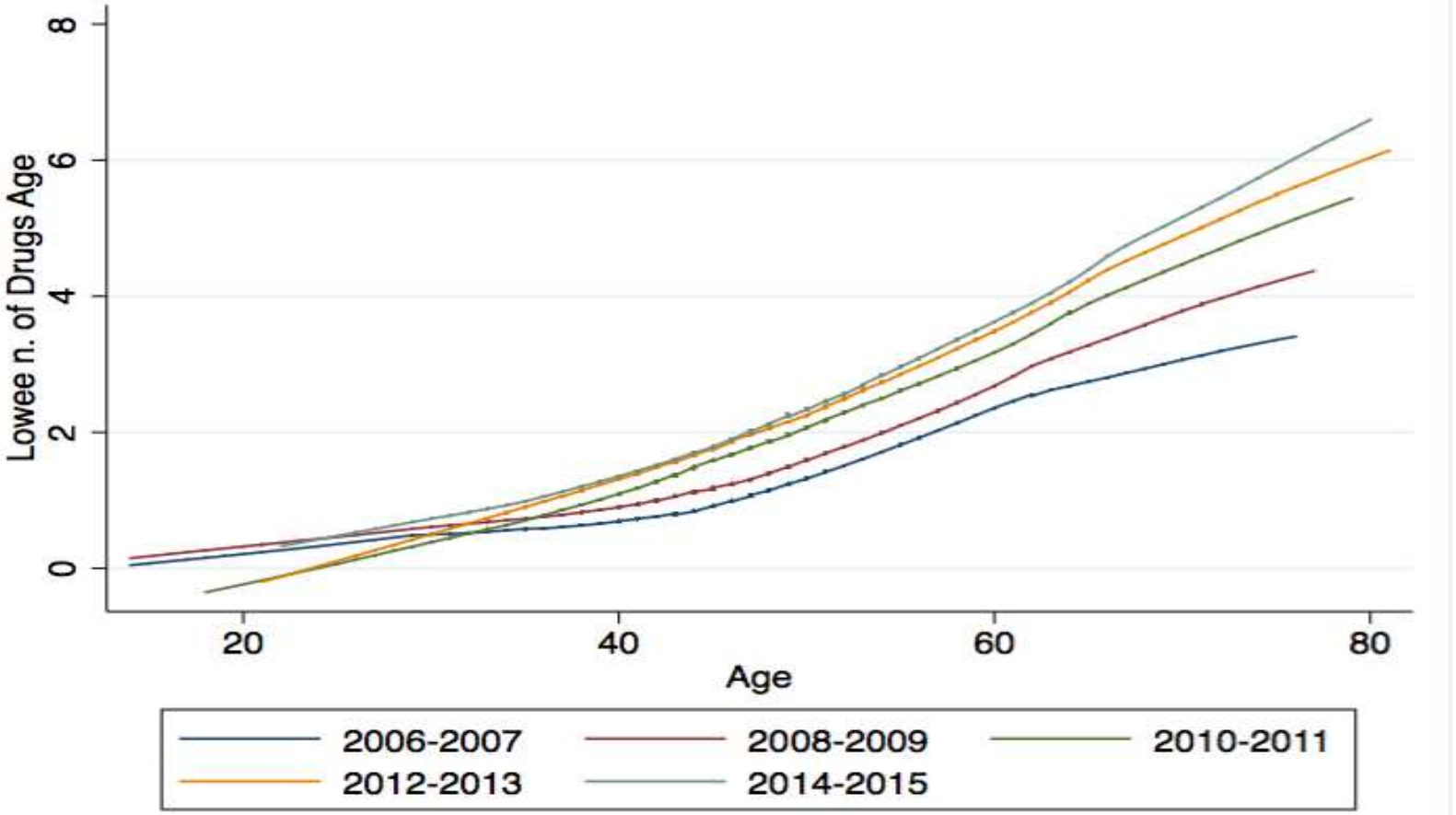
Prevalence of Polypharmacy at MHMC by calendar year



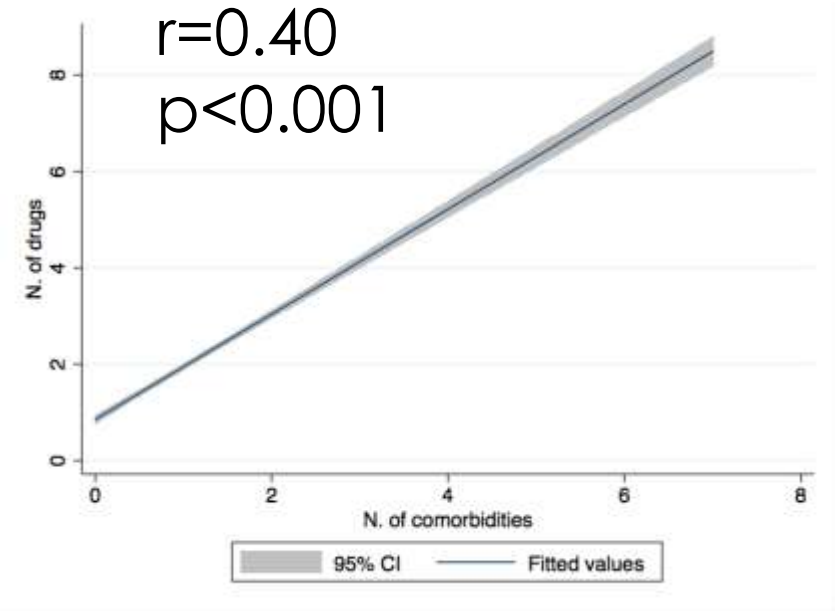
Association between Polypharmacy (PP) and Comorbidity, Age and Frailty by calendar year



Association between Polypharmacy (PP) and Comorbidity, Age and Frailty by calendar year



MM and PP are two face of the same coin



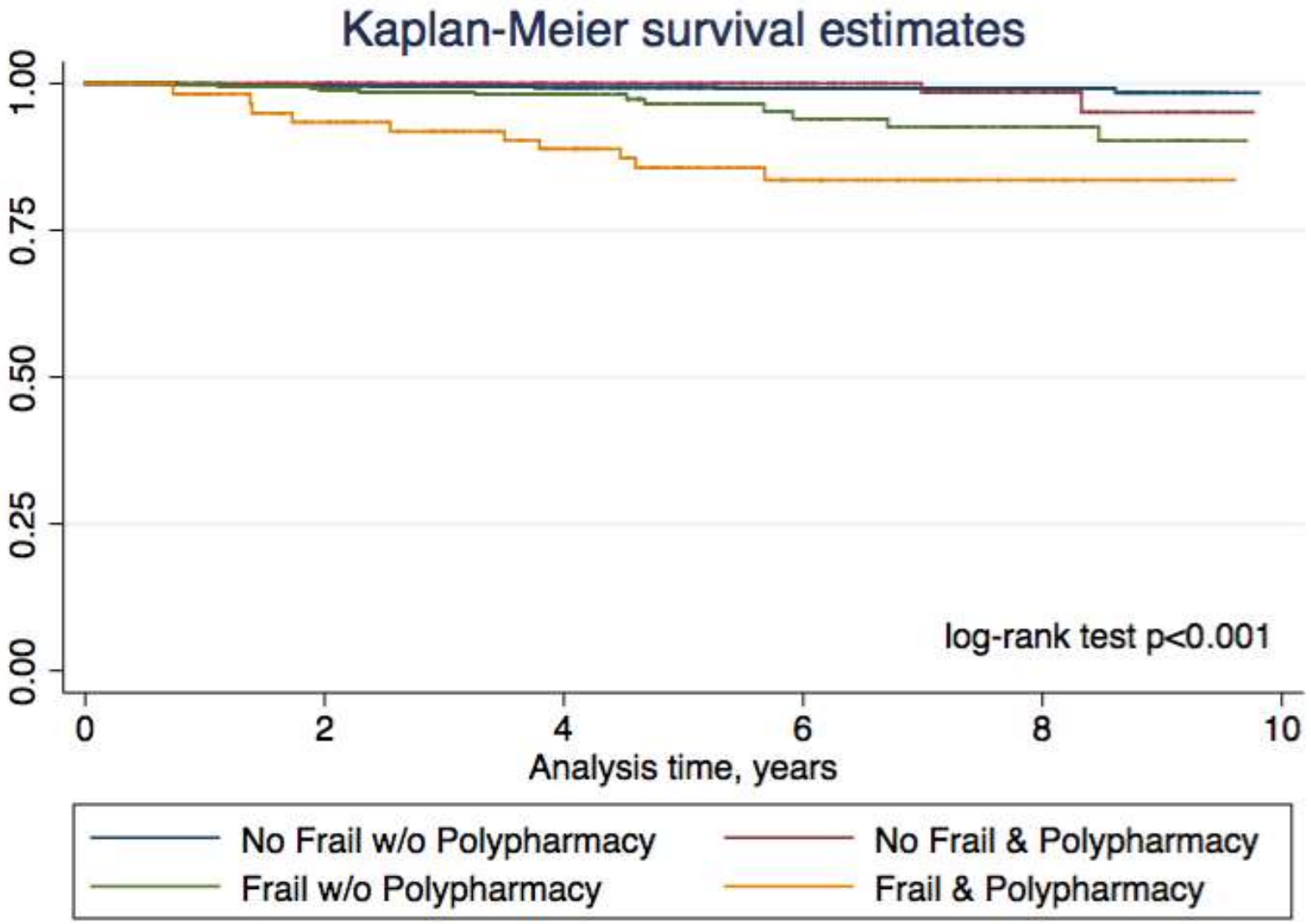
Frailty is a measure of clinical complexity capable to express the clinical burden of MM discriminating vulnerable patients with and without PP.

FI and PP are also co-linear
r=0.18 (p<0.001).

MM(+), PP(-)=172; (5.84%)

FI(+), PP(-)= 1,523; (51.7%).

Polipharmacy in frail patients is a predictor of fall and overall mortality



Special Communication | LESS IS MORE

Reducing Inappropriate Polypharmacy
The Process of Deprescribing

Algorithm for Deciding Order and Mode in Which Drug Use Could Be Discontinued

JAMA Internal Medicine May 2015 Volume 175, Number 5

General considerations for managing polypharmacy in older adults

1. Throughout medication history

"Brown Bag" asking patient to bring in all prescription, OTC, and herbal medications

"Teach-back" method, patient shows how taking medication

2. Determine patient adherence to medication and barriers if not adherent

Is the patient forgetting to take?

Is the pill dif cult to take?

Is the pill costly?

Does the patient believe that the drug is not needed?

3. Is the dosage correct?

- Review drug–drug interactions
- Determine the therapeutic ratio

4. Start low and go slow for titration up

- Good communication with other healthcare providers (physicians and caregivers)

5. Where possible use the same pharmacy

Indications for current medications

6. Determine if medication is on Beers List or Medication Appropriateness Index

Gleason LG, Clin Interv Aging. Dove Press; 2013;8:749–63.

American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel

Table 2. 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

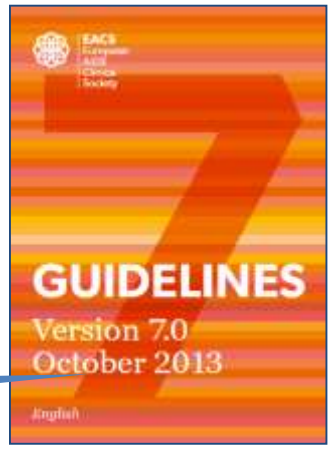
Organ System, Therapeutic Category, Drugs	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Antidepressants, alone or in combination Amitriptyline Amoxapine Clomipramine Desipramine Doxepin >6 mg/d Imipramine Nortriptyline Paroxetine Protriptyline Trimipramine	Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤6 mg/d) comparable with that of placebo	Avoid	High	Strong
Proton-pump inhibitors	Risk of *Clostridium difficile* infection and bone loss and fractures	Avoid scheduled use for >8 weeks unless for high-risk patients (e.g., oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett's esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (e.g., due to failure of drug discontinuation trial or H_2 blockers)	High	Strong
Pain medications				
Meperidine	Not effective oral analgesic in dosages commonly used; may have higher risk of neurotoxicity, including delirium, than other opioids; safer alternatives available	Avoid, especially in individuals with chronic kidney disease	Moderate	Strong

Table 5. 2015 American Geriatrics Society Beers Criteria for Potentially Clinically Important Non-Anti-infective Drug–Drug Interactions That Should Be Avoided in Older Adults

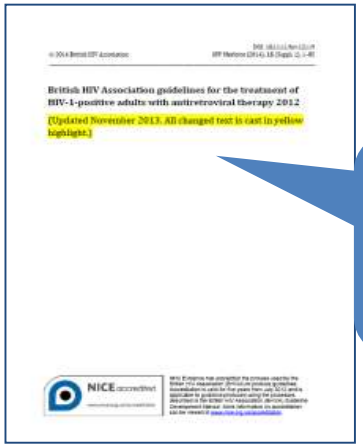
Table 6. 2015 American Geriatrics Society Beers Criteria for Non-Anti-Infective Medications That Should Be Avoided or Have Their Dosage Reduced with Varying Levels of Kidney Function in Older Adults

What do the HIV guidelines recommend for FRAIL patients?

DHHS: no mention



EACS: no mention



BHIVA: no mention

IAS-USA: no mention

CV: cardiovascular; FRAX: WHO Fracture Risk Assessment Tool

1. DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Available at: http://aidsinfo.nih.gov/guidelines/ (accessed May 2014); 2. EACS Guidelines 2013; Available at: http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf. (accessed Mar 2014); 3. British HIV Association guidelines November 2013. HIV Medicine 2014;15:1–85; 4. Thompson MA, et al. JAMA 2012;308:387–402.

Objective

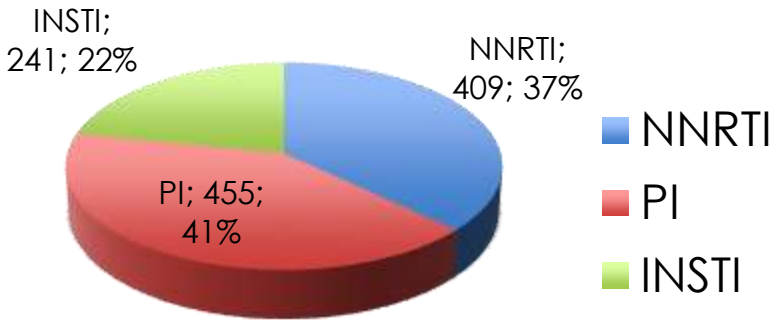
- To describe patterns of ARV use both in terms of drugs class and regimen, in relation to to frailty, age or gender in a clinical setting in patients with well controlled HIV infection.

Patterns of ARV use in relation to to frailty and age

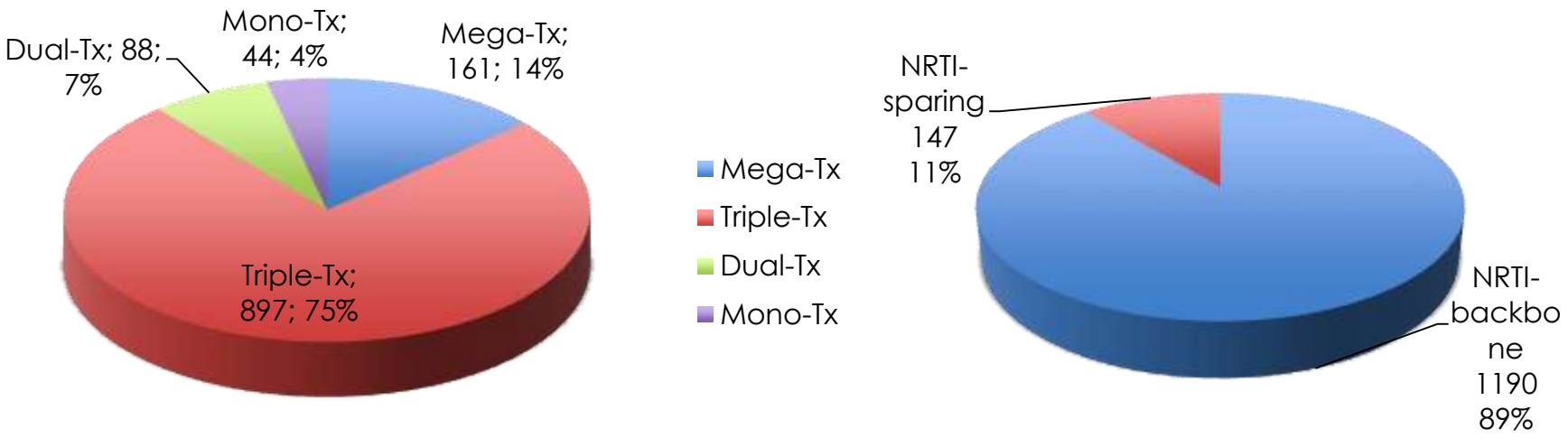
Demographic and HIV characteristics

Patients	1202
Age (Mean±SD)	50 ±7
Women (n [%])	383 (32)
Duration HIV months (Median IQR)	153 (100 – 196)
Nadir CD4 (Median IQR)	209 (101 – 300)
Current CD4 (Median IQR)	721 (610 – 893)
Frailty index (Mean±SD)	0.30 ±0.09
Multi-morbidity (n [%])	357 (30)

ARV drug class exposure (most recent visit)

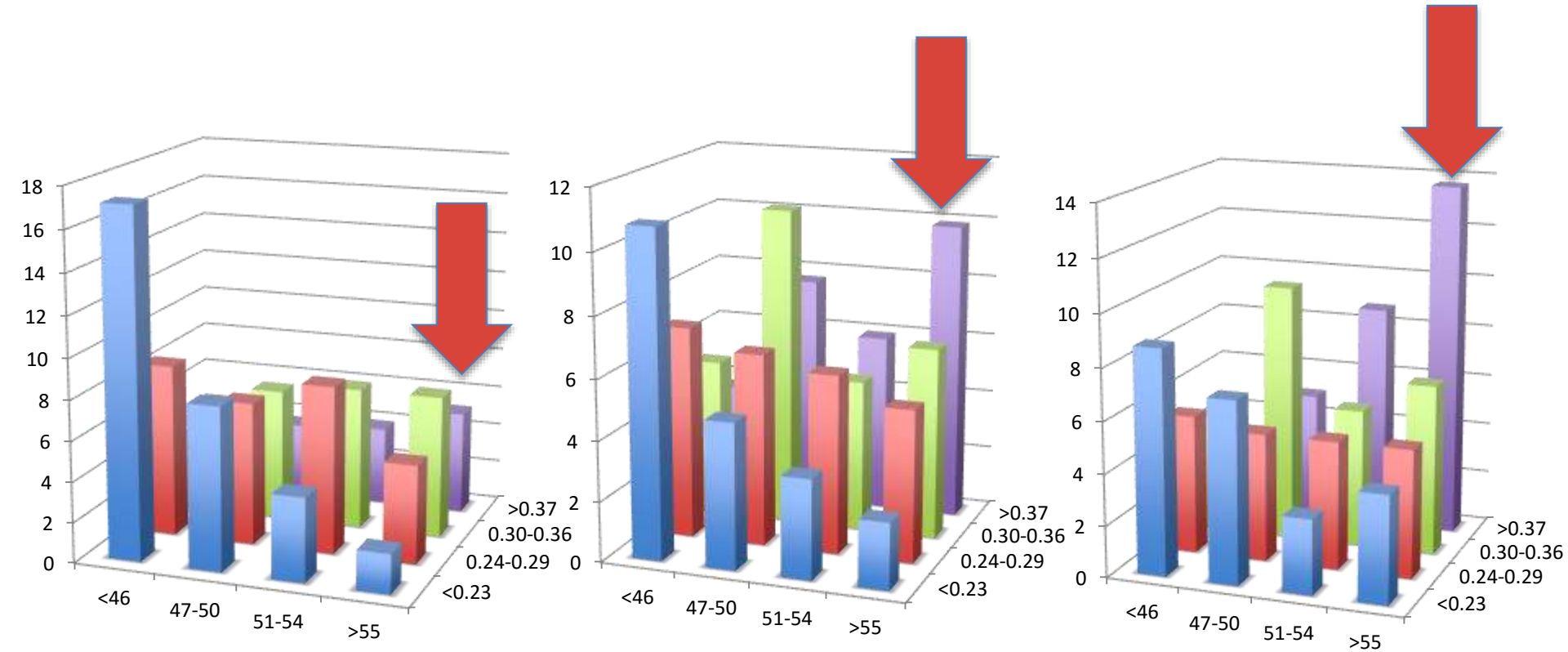


ARV regimen current exposure (most recent visit)



Guaraldi G et al 5° personal comunication

Age and frailty spectrum in different ARV drug classes current exposure



NNRTI-based regimen

292 pts

PI-based regimen

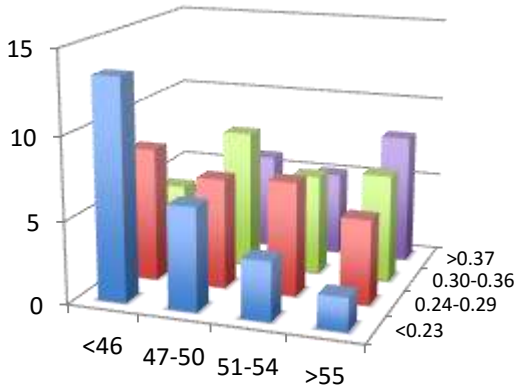
465 pts

INSTI-based regimen

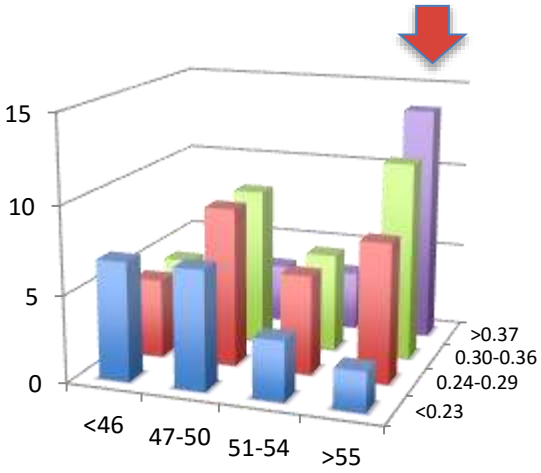
92 pts

Guaraldi G, 5th HIV & Aging workshop, Baltimore 2014

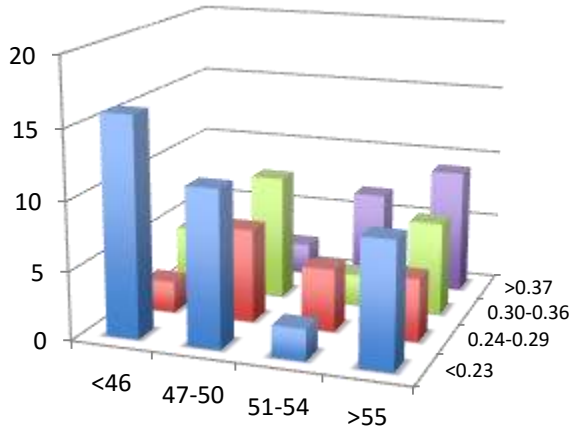
Age and frailty spectrum in different ARV regimen current exposure



Triple-Tp
897 pts



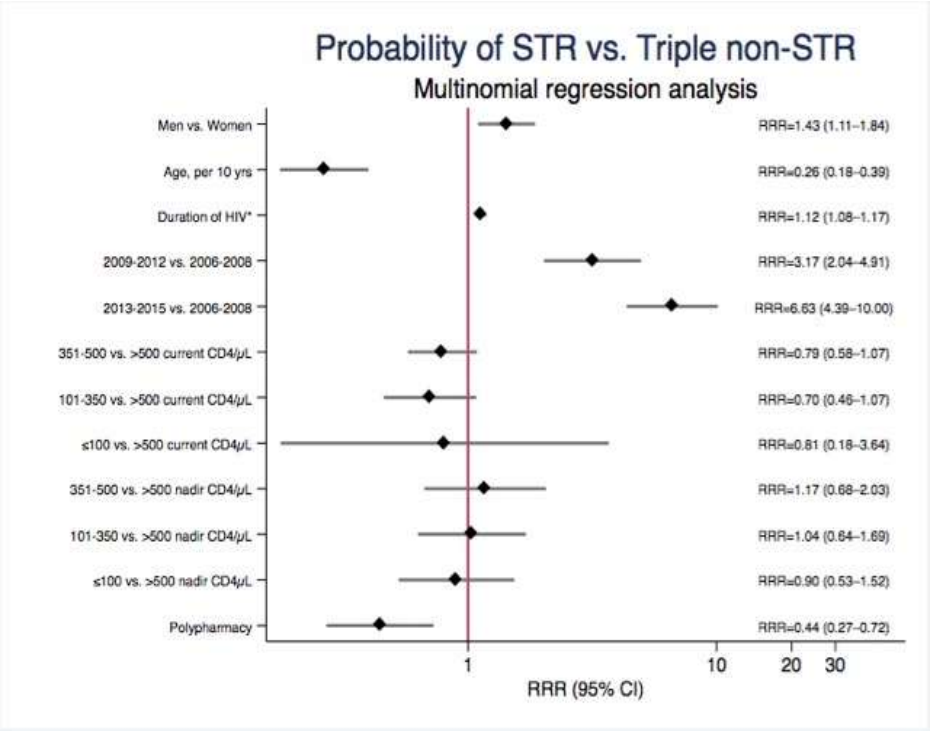
Dual-Tp
88 pts

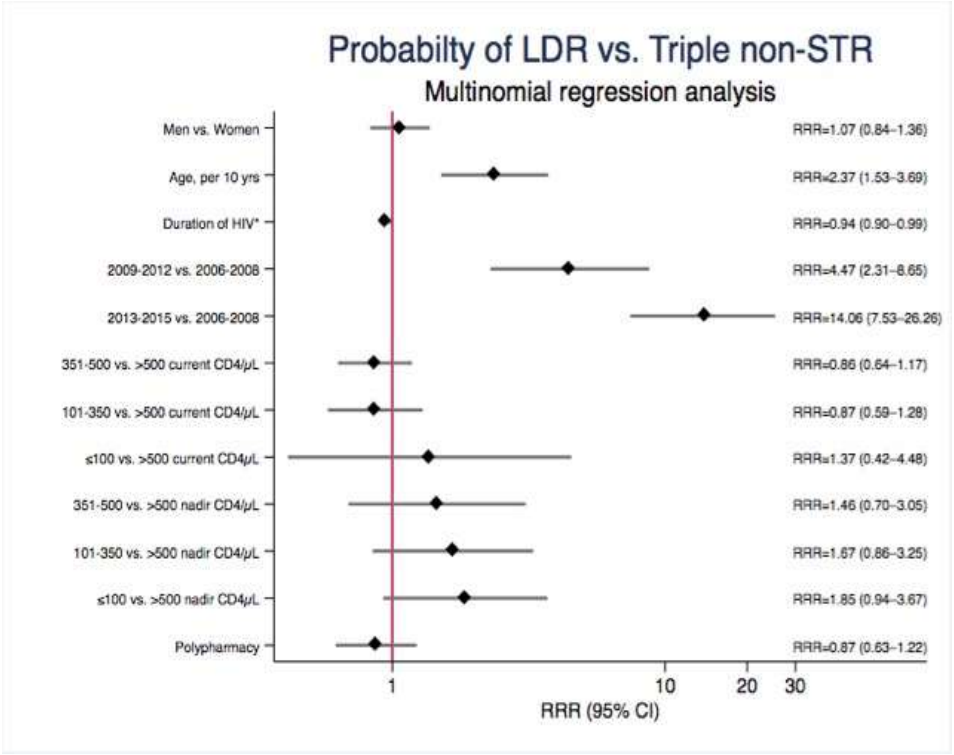


Mono-tp
44 pts

The objective of this study is to analyse the impact of PP on ARV prescription.

On one side PP may be a driver of STR regimen in order to reduce pill burden and, on the other, it may represent a barrier to patient-tailored therapy required by comorbidities





The balance between treatment tailoring, prevention for drug-associated toxicity and reduction in number of pills need to be prospectively studied in order to provide the best approach to ageing HIV-patients.

Considerations in Management of ART in the Older HIV Patient

It is time to move into a proactive approach in ARV management in older HIV patients

			NRTI	NNRTI	PI	INSTI	FI
1.	**Co-morbid conditions**	✓ eg., cardiovascular, hepatic, metabolic ✓ may be exacerbated by effects of HIV or its treatment	✗	✓>✗	✗>✓	✓	✓>✗
2.	**Greater medication use**	– overlapping side effects or potential interactions with ARVs and concomitant medications	✓>✗	✗	✗	✓	✓
3.	**Age-related changes in drug handling (PK) and response (PD)**	– toxicity	✗	✗	✗	✓	✓

Guaraldi G., personal communication

Take home messages

CANGE IN HIV ASSESSMENT:

- ✓ Co-morbidities are an intrinsic characteristic of aging and describe patient complexity

CHANGE IN HIV MANAGEMENT:

- ✓ Care management starts in the recognition of polypharmacy and how to reduce inappropriate prescription

Thank you….
…and stay fit!