Challenges of managing ageing HIV patients

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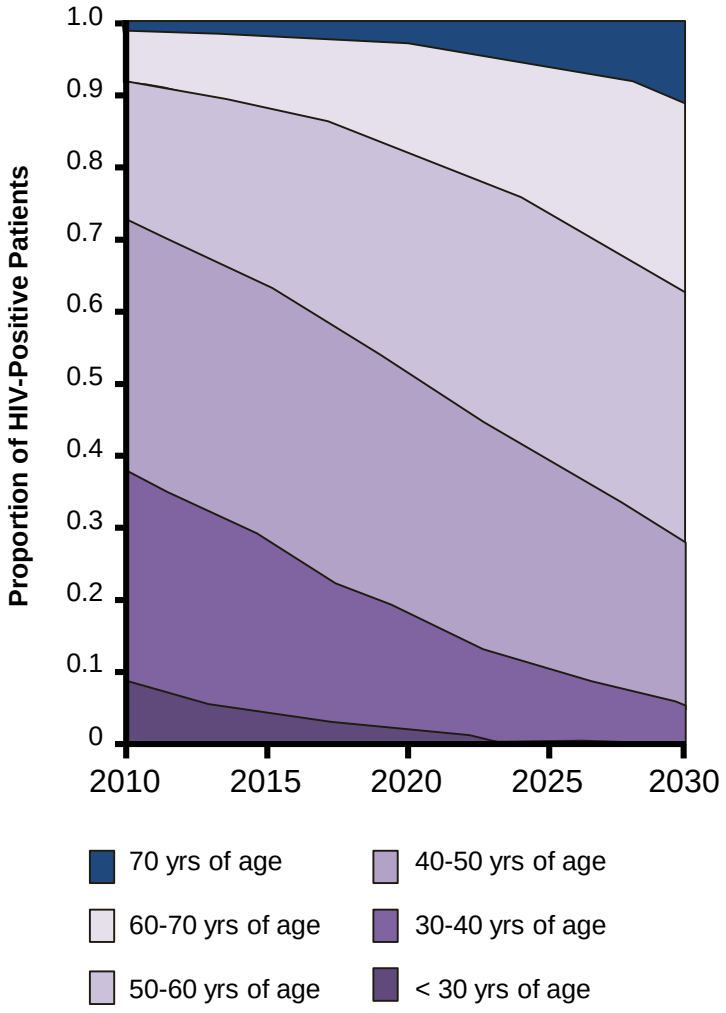
ATHENA: Older patients more prevalent in the HIV-population

- Observational cohort of 10,278 HIV-infected patients in the Netherlands
- Modeling study projections:
  - Proportion of HIV-positive patients ≥ 50 yrs of age to increase from 28% in 2010 to 73% in 2030
  - Median age of HIV-positive patients on combination ART to increase from 43.9 yrs in 2010 to 56.6 yrs in 2030

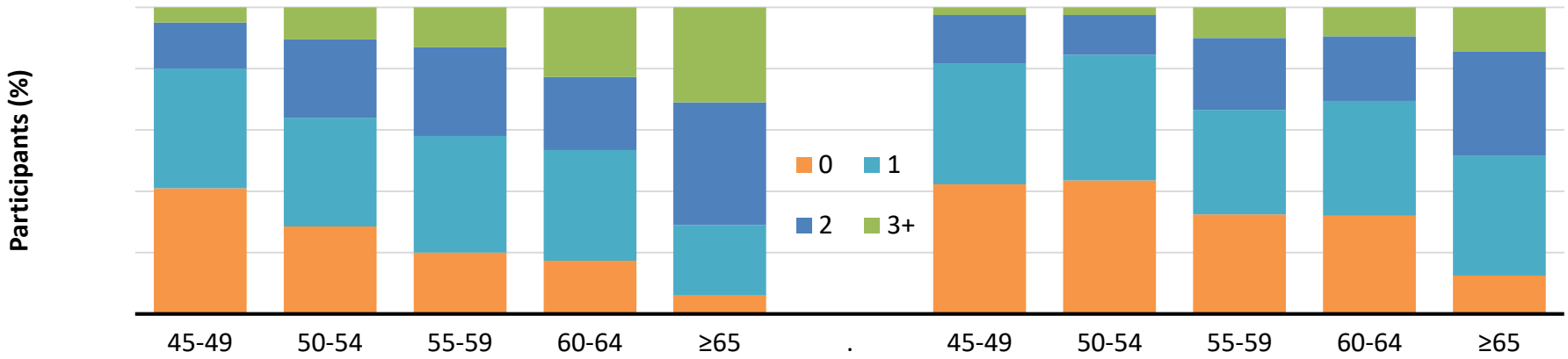


Smit et al. Lancet Infect Dis. 2015

Incidence of co-morbidities is higher in PLWH

HIV-infected (N=540)
Mean AANCC/person = 1.3 (SD 1.14)

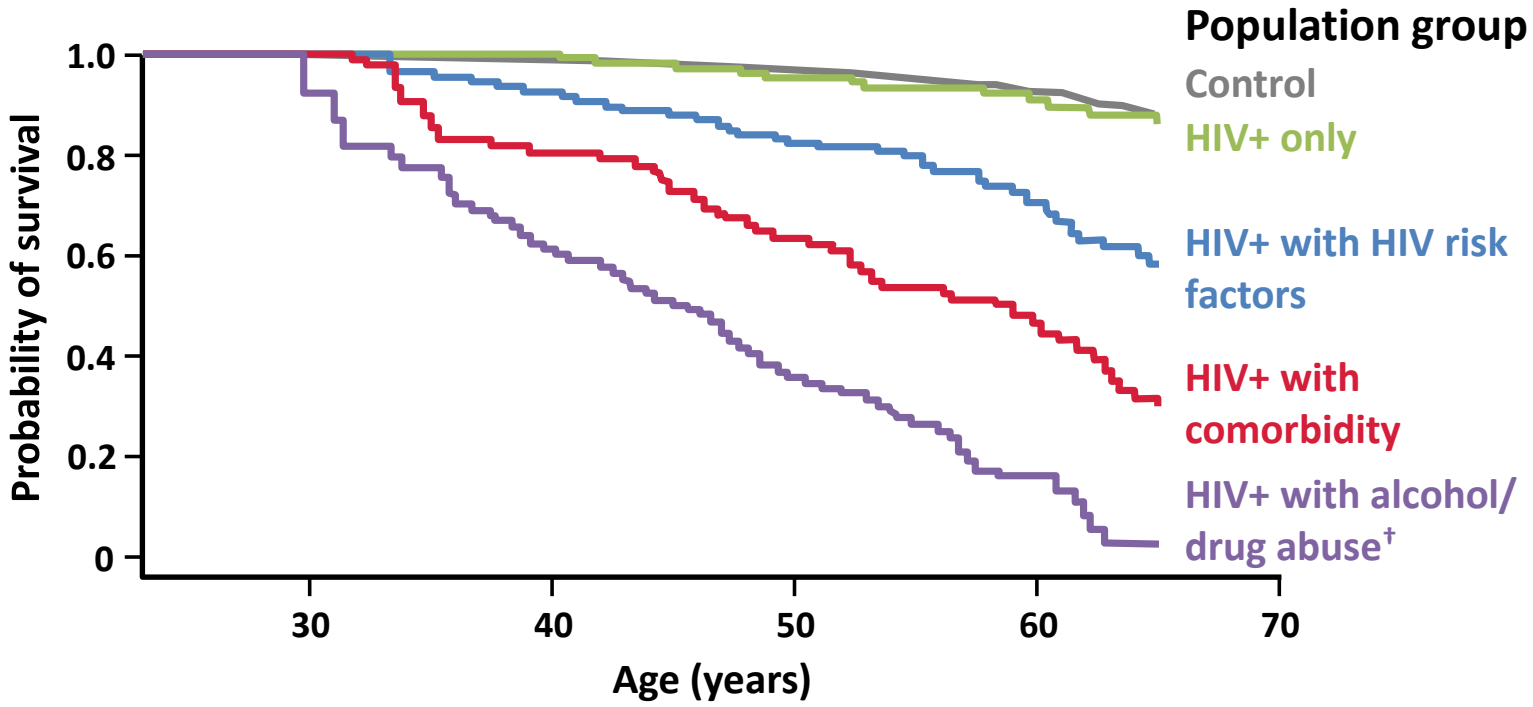
HIV-uninfected controls (N=524)
Mean AANCC/person = 1.0 (SD 0.96)



Schouten et al. Clin Infect Dis 2014

Impact of co-morbidities

Cumulative survival for HIV-infected patients starting HAART and persons from the general population

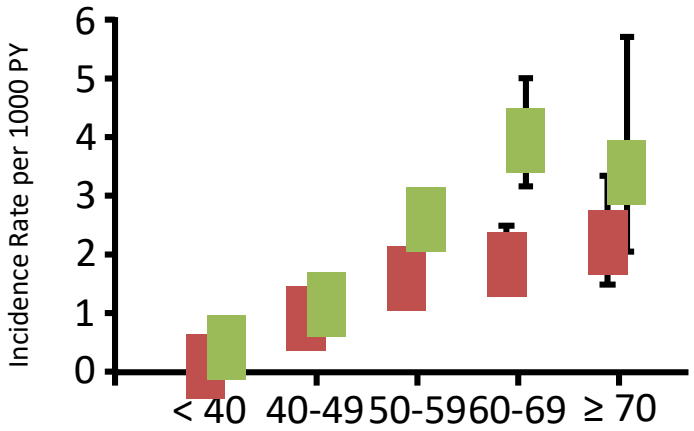


Obel et al. PLoS ONE 2011

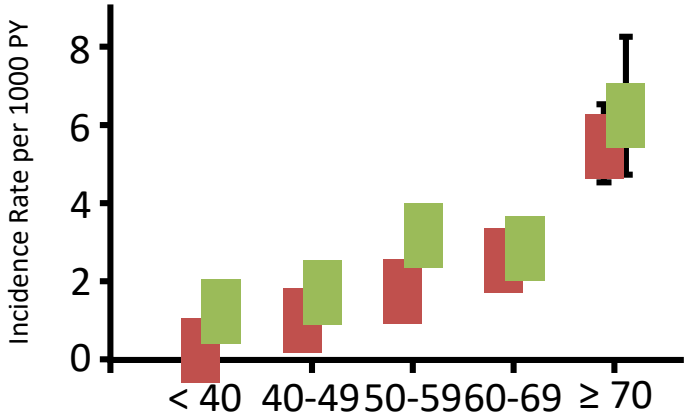
HIV-
HIV+

Events are more frequent

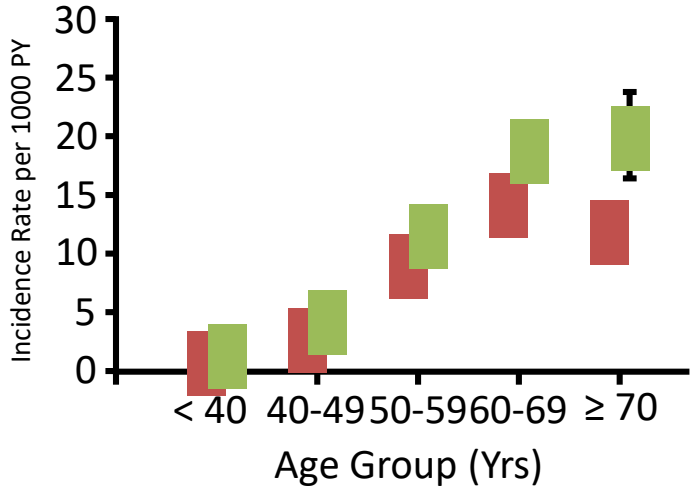
MI



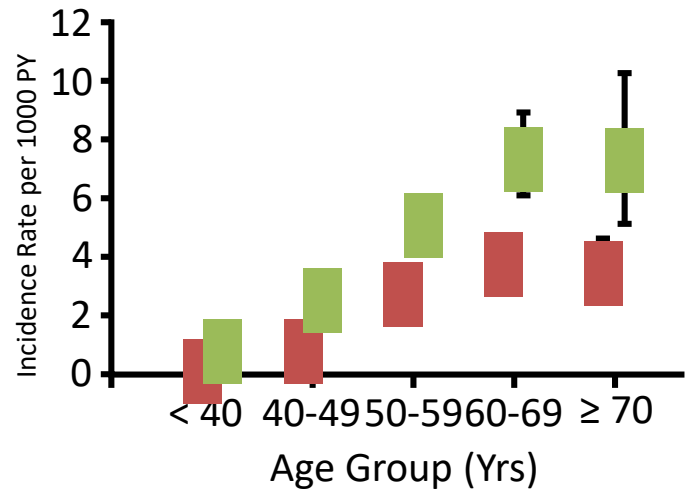
ESRD



NADC

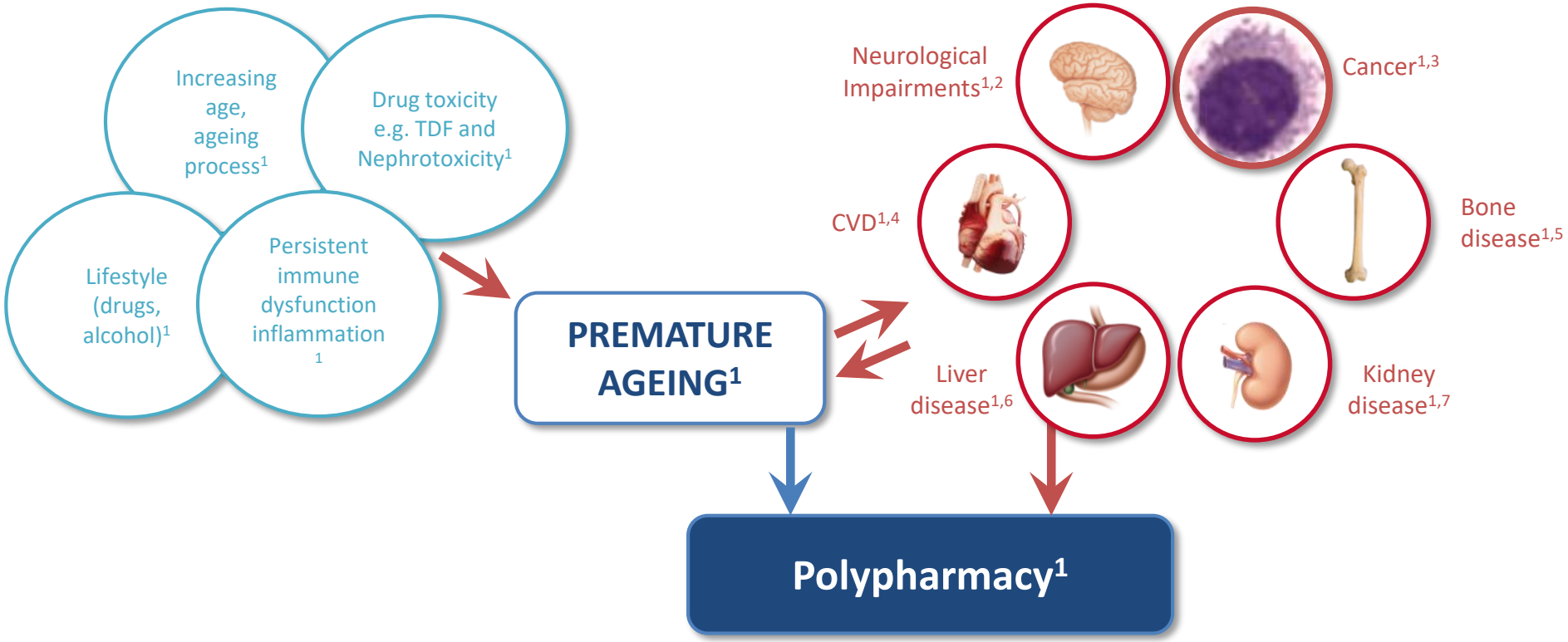


HIV-assoc. cancers



Althoff et al. Clin Infect Dis. 2014

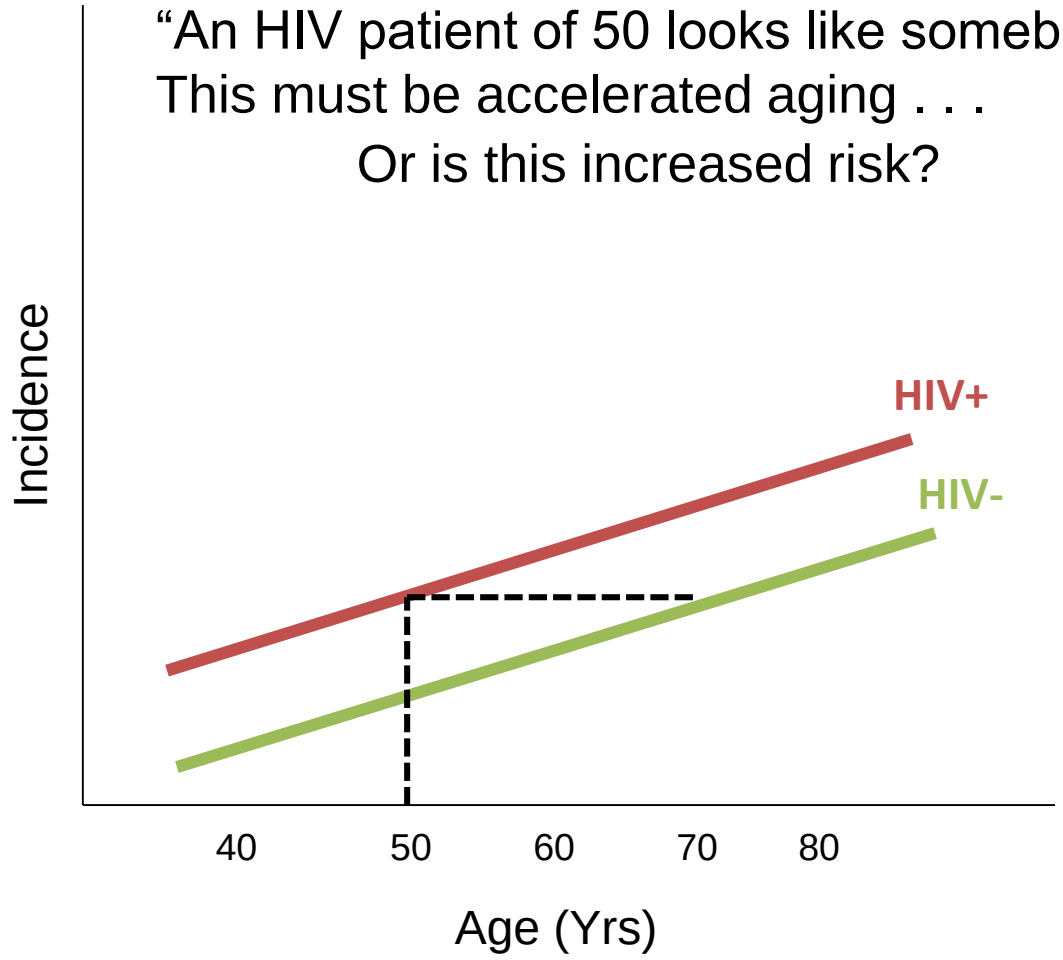
Do patients with HIV age prematurely?



1. Deeks et al. BMJ 2009
2. McArthur et al. Ann Neurol 2010
3. Nguyen et al. 18th IAC. Vienna, Austria 2010
4. Freiberg et al. JAMA Intern Med 2013
5. Brown et al. AIDS 2006
6. Towner et al. JAIDS 2012
7. Lucas et al. Clin Infect Dis 2014

Accelerated aging or increased risk?

"An HIV patient of 50 looks like somebody of 70"
This must be accelerated aging . . .
Or is this increased risk?



Lifestyle factors

POPPY
Pharmacokinetic and clinical observations in people over 50

		PLWH>50	PLWH<50	HIV-ve >50
Smoking status	Current (%)	23.9	26.5	21.4
	Ex-smoker (%)	36.9	27.2	37.8
	Never (%)	38.6	42.7	39.8
Alcohol	Current consumption (%)	77.8	73.5	84.7
	Previous consumption only (%)	13.1	11.0	7.1
	Units per week (if current or previous; median (range))	7 (0, 75)	3 (0, 45)	10 (0, 63)
Recreational drugs in past 6 months	Any (%)	27.5	26.5	13.3
	Marijuana (%) *	14.7	12.5	1.0
	Methadone (%) *	2.6	10.3	1.0
	Mephedrone (%) *	9.2	13.2	5.1
	Amphetamine (%) *	5.2	7.4	0
	Crystal Meth (%) *	3.3	8.1	5.1

*** Recreational drugs with >5% use in a study group**

Winston et al. BHIVA 2016

Non-AIDS medical events

POPPY
Pharmacokinetic and clinical observations in people over 50

		PLWH>50	PLWH<50	HIV-ve >50
Cardiovascular events	MI, angina, narrowed blood vessels, TIA, CABG. *P=0.002*	**25%** (76)	**10%** (14)	**18%** (18)
Nervous system diseases	Parkinson's, vertigo, loss of consciousness, epilepsy, encephalitis. *P=0.14*	**11%** (35)	**8%** (11)	**5%** (5)
Respiratory diseases	Asthma, bronchitis, emphysema or COPD. *P=0.004*	**42%** (127)	**26%** (35)	**29%** (29)

Winston et al. BHIVA 2016

Knowledge on aging with HIV

Majority of clinical trial populations include people under the age of 50 years and very few (if any?) above 60 years

Our knowledge limited to

- Cohort studies (e.g. AGEhiv, POPPY, etc)
- Clinical experience

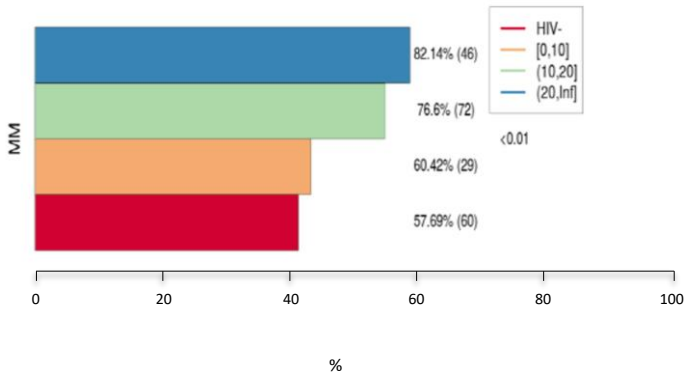
Trial	Drug(s)	Study population	Median age
GS - 104&111[1]	ECFTAF vs ECFTDF	Naïve	33
ARTEMIS[2]	DRV/r vs LPV/r	Naïve	36
SPRING-2[3]	DTG vs RAL	Naïve	37
STAR[4]	EFV vs RPV	Naïve	37
FLAMINGO[5]	DTG vs DRV/r	Naïve	34
GS-US-292-0112[6]	***ECFTAF***	***Switch***	***58***
GS-US-292-1826*	***TDF based regimen to ECFTAF***	***Switch***	***>60***

*recruiting

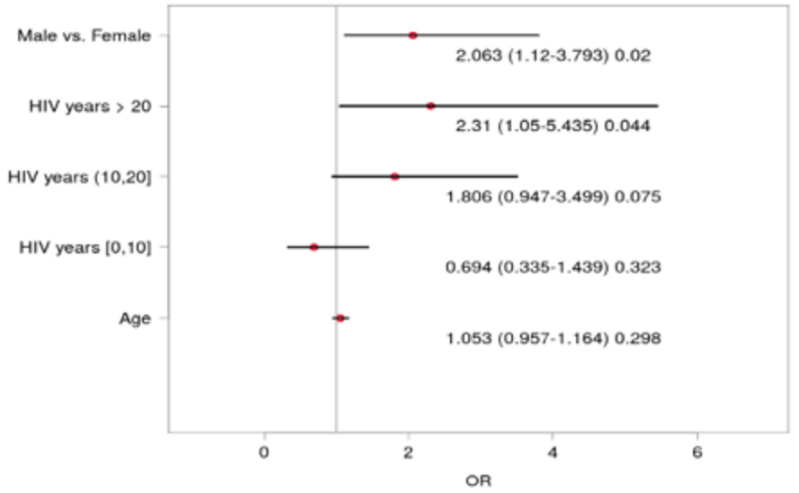
1 Wohl et al, Lancet 2015. 2 Orkin et al, HIV Med. 2013. 3 Raffi et al, Lancet 2013. 4 Cohen et al, Journal of the International AIDS Society 2012. 5 Cloet et al, Lancet 2014. 6 Pozniak et al, JAIDS 2015

GEPPO cohort (GEriatricPatients living with HIV/AIDS): HIV duration of 20 years in 75 year old pts doubles multimorbidities & polypharmacy

Prevalence of MM in HIV- and HIV+ pts, stratified by duration of HIV infection

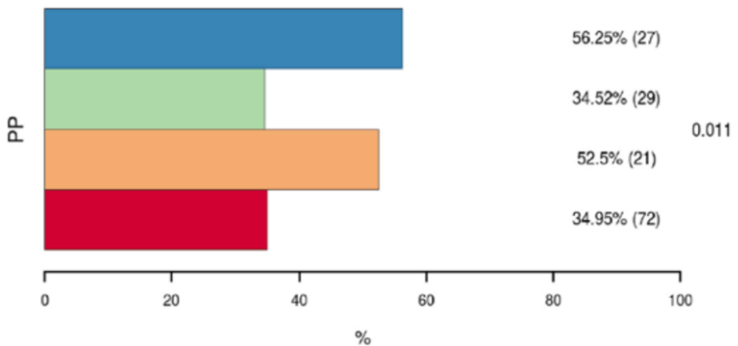


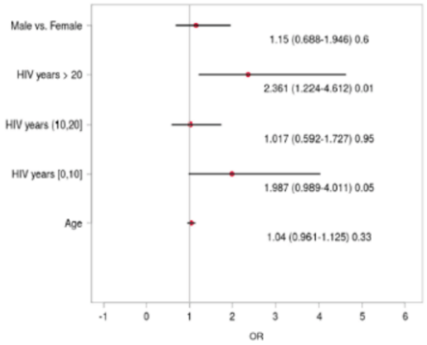
Predictors of MM: multivariable logistic regression



Prevalence of PP in HIV- and HIV+ pts, stratified by duration of HIV infection

Predictors of PP: multivariable logistic regression





Guaraldi et al. 18th IWCADRH 2016

A dedicated clinic for the over 50's at CWH


A dedicated clinic for HIV-positive individuals over 50 years of age: a multidisciplinary experience

L Waters MRCP, B Patterson BNurs RGN, A Scourfield MRCP, A Hughes MRCP, S de Silva MRCP, B Gazzard MD FRCP, S Barton FRCOG FRCP, D Asboe FRCP, A Pozniak MD FRCP and M Boffito MD PhD

Department of GU/HIV Medicine, Chelsea & Westminster Hospital, London, UK

Summary: The HIV-infected population is ageing. Issues including polypharmacy and co-morbidities led us to develop a dedicated clinic for HIV-infected individuals over 50. We describe our ... two years. The over 50 clinic commenced in January 2009. The team comprises a registrar, consultant ... supported by a pharmacist and mental health services. Patients undergo a full medication and drug ... assessment, adherence self-assessment and investigations including therapeutic drug monitoring ... scores (CACS) and bone mineral density. Over two years of activity, 180 patients attended the ... –88), all were on combined antiretroviral therapy and 38% (57/150) were on ≥3 non-HIV drug ... Thirty-eight percent had osteopaenia and 18% had osteoporosis requiring treatment. ... prostate specific antigen, four were diagnosed with prostate cancer. Drug interaction, ... useful for several patients. Asymptomatic patients over 50 in long-term follow-up ... gh targeted screening. The clinic has improved general practitioner (GP) liaison and fast-track ... other specialities. Patients have reacted positively to the clinic, particularly as many do not routinely ...

Keywords: HIV infection, ageing with HIV, multidisciplinary ...

INTRODUCTION

Since the advent of combination antiretroviral therapy (cART) in the mid-1990s, HIV-infected individuals have enjoyed progressive reductions in HIV-associated morbidity and mortality. Recent studies show marked improvements in life-expectancy for patients with HIV and patients experiencing sustained immune reconstitution on cART have a risk of mortality similar to that of the general population.[1] There has been a shift from HIV-related to 'non-HIV-related' morbidities and in life-expectancy, but, in addition, patients are becoming ageing population. This is partly due to marked improvements in infected with HIV at an older age.[2] Indeed, the Centers for Disease Control and Prevention (CDC) have predicted that by 2015, 50% of HIV-infected individuals in the US will be older than 50 years of age.[3] Older age is not a barrier to successful ... patients demonstrate ... response rates but lower CD4 ... aged-related changes in drug ... and excretion may render older ... eligible to drug-related adverse ...

Correspondence to: Dr Laura Waters ... Centre – Chelsea & Westminster ... London SW10 9NH, UK ... Email: laura.waters@nhs.net

International Journal of STD & AIDS 2012; 23: 546–552 ... 10.1258/ijsa.2012.011412

...full medication and drug interactions review, neurocognitive assessment, adherence self-assessment and investigations, including TDM, CACS and BMD.

...osteoporosis…
…prostate cancer…
The clinic has improved general practitioner (GP) liaison…

HIV=human immunodeficiency virus; TDM=therapeutic drug monitoring; CACS=coronary artery calcium scores; BMD=bone mineral density

Waters et al. Int J STD AIDS 2012

1 – Drug history

- N of drugs
- Type of drugs
  - Prescribed
  - OTC
  - Herbals
  - Recreational
  - Alcohol
- Drug interactions

C&W over 50s clinic – Examples

67 yo Caucasian gentleman
HIV+ since 1990,
mild chronic renal failure,
diabetes TII, hypertension,
benign prostatic hypertrophy,
pancreatic insufficiency,
and hyperlipidaemia

- **Truvada** 1 tab once daily (TDF 245mg/FTC 250mg)*
- **Darunavir** 600 mg twice daily *
- **Ritonavir** 100 mg twice daily *

- **Diltiazem** 200 mg SR once daily
  - monitor for AEs *
- **Metformin** 500 mg twice daily *
- **Lisinopril** 2.5 mg once daily
- **Tolterodine** 4 mg MR once daily
- **Tamsulosin** 400 mcg MR once daily
  - monitor for AEs *
- **Aciclovir** 400 mg twice daily
- **Omeprazole** 20 mg od *
- **Pravastatin** 20 mg nocte *
- **Bezafibrate** 400 mg MR once daily *
- **Pancreatin** 10 000 u ii twice daily
- **Echinacea** herbal supplement 2 tabs daily *

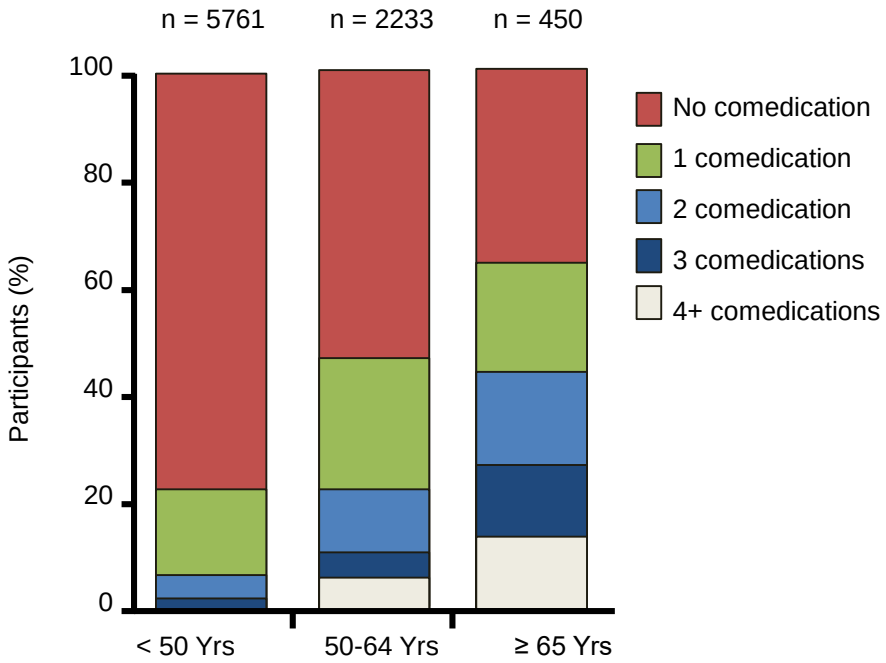
59 yo Caucasian gentleman,
HIV+ since 1994,
Hx of stroke, hypertension,
low vitamin D/osteopenia,
heartburn, chronic back pain
and hyperlipidaemia

- **Truvada** 1 tab once daily (TDF 245mg/FTC 250mg)
- **Darunavir** 800 mg once daily
- **Ritonavir** 100 mg once daily

- **Omeprazole** 40 mg once daily
- **Calchichew** D3 Forte 1 tab twice daily
- **Ramipril** 5 mg once daily
- **Bendroflumethiazide** 5 mg once daily
- **Amlodipine** 10 mg OD
- **Aspirine** 75 mg once daily
- **Dipyridamol** 200 mg twice daily
- **Bisoprolol fumarate** 10 mg once daily
- **Atorvastatin** 20 mg OD
- **Rosuvastatin** 10 mg OD
- **Ibuprofen** 400 mg twice daily
- **Tramadol** 50 mg PRN
- **Nicotine patch**

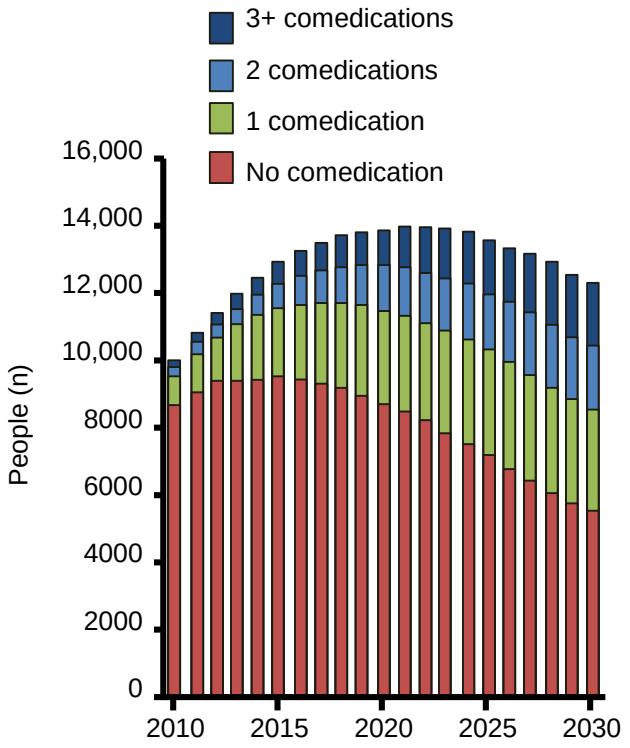
Beware of interactions: polypharmacy among PLWH on ART

Swiss HIV Cohort Study (N = 8444)[1]
Prospective Observational Study



5.2% of patients 50-64 yrs of age and 14.2% of patients ≥ 65 yrs of age received ≥ 4 meds other than ART

ATHENA Modeling Study[2]



Predicts that 20% of patients will be receiving ≥ 3 meds other than ART in 2030

1. Hasse et al. Clin Infect Dis. 2011. 2. Smit et al. Lancet Infect Dis. 2015.

Key DDI: boosted PI or NNRTI

Regimen	Key Drug–Drug Interactions
ATV/RTV + FTC/(TDF or TAF) **DRV/RTV** + FTC/(TDF or TAF)	▪ Avoid **lovastatin, simvastatin** (lipid-lowering agents), **salmeterol** (asthma/COPD medication) ▪ Use caution with other lipid-lowering agents (eg, **atorvastatin, rosuvastatin, pravastatin**) ▪ Use caution with/avoid **specific antiarrhythmics** (eg, **dronedarone**) ▪ Avoid **PPIs** (eg, **omeprazole**) with ATV ▪ Use caution with/avoid **inhaled, injected,** or **systemic steroids**
RPV/FTC/TDF **RPV**/FTC/TAF DTG/**RPV**	▪ Avoid **PPIs** (eg, **omeprazole, pantoprazole**), **dexamethasone**
EFV/FTC/TDF	▪ No notable comedications to avoid for EFV; consider alternative corticosteroid to dexamethasone

References in slidenotes.

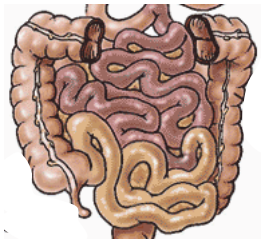
Key DDI: INSTI

Regimen	Key Drug–Drug Interactions
All INSTI	▪ Use caution with/avoid simultaneous polyvalent cation-containing **antacids***
BIC/FTC/TAF	▪ Contraindicated with dofetilide or rifampin
DTG/3TC/ABC **DTG** + FTC/(TDF or TAF) **DTG**/RPV	▪ Dose adjust **metformin** (diabetes medication) ▪ Contraindicated with dofetilide
EVG/COBI/FTC/TDF **EVG**/COBI/FTC/TAF	▪ Avoid **lovastatin, simvastatin** (lipid-lowering agents), **salmeterol** (asthma/COPD medication) ▪ Avoid/use caution with **inhaled, injected,** or **systemic steroids**
RAL + FTC/(TDF or TAF)	▪ None notable except antacid issue described for all INSTIs above

*BIC or DTG can be coadministered with Ca- or Fe-containing supplements if given with food

Why we should be concerned about age and PK

Absorption

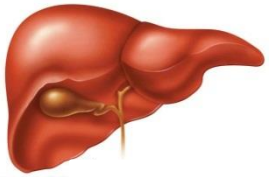


Age-related changes may be associated with increased gastric pH and decreased small bowel surface area, and may lead to a ***higher inter individual variability in drug exposure***. [1]

Distribution

Increase in body fat associated with older age increases Vd of highly lipophilic drugs (i.e. diazepam, HIV PIs) and may increase their elimination t1/2. If this is combined with a reduction in plasma CL, ***greater drug accumulation and increased risk of toxicity*** are possible. [1]

Metabolism



With increasing age, reduced liver volume and blood flow have shown ***decreased drug clearance***. [1] Increased p-gp expression/function may explain altered drug effects and DDI in older patients. [1]

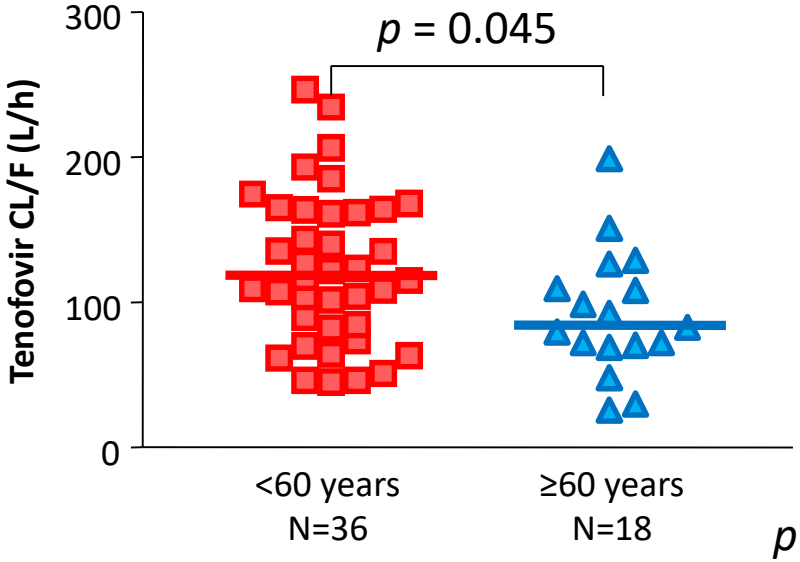
Renal elimination

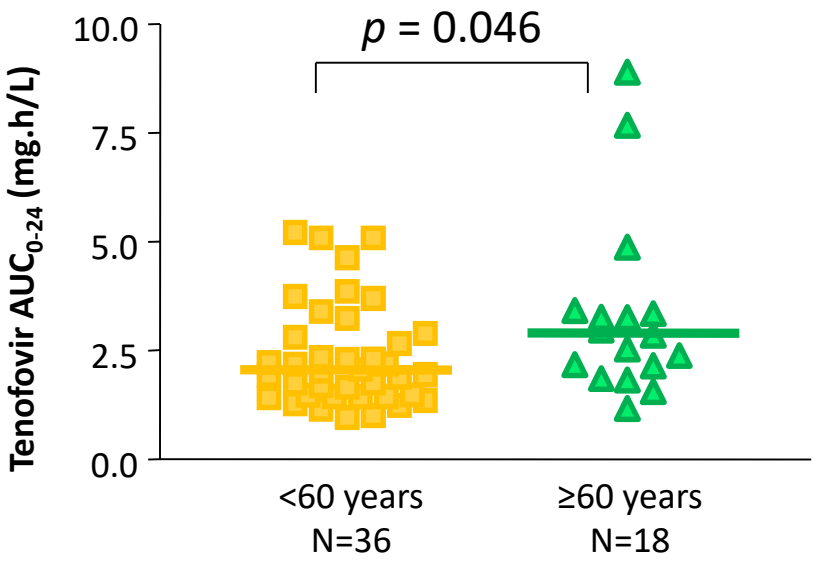
GFR may decrease as much as 50% with increasing age, which can directly affect the renal elimination of drugs and their metabolites. Clinical consequences (i.e. development of ***toxicity***) depend on the extent that renal elimination contributes to drug systemic elimination and on its therapeutic index. [1]

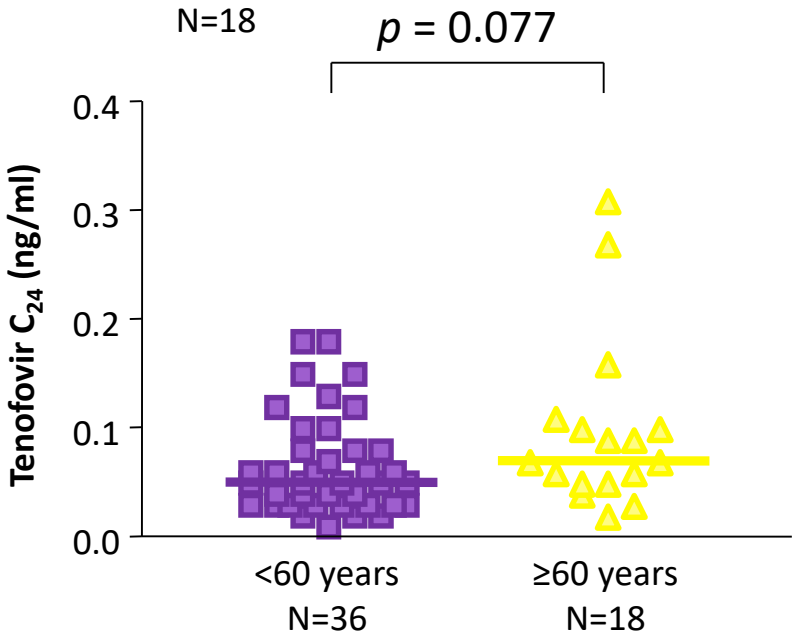
Vd=volume of distribution; CL=cardiolipin; AAG= alpha-1-acid glycoprotein; GFR=glomerular filtration rate

Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th Edition. 2007

Tenofovir (TFV) PK in PLWH > 40 years of age



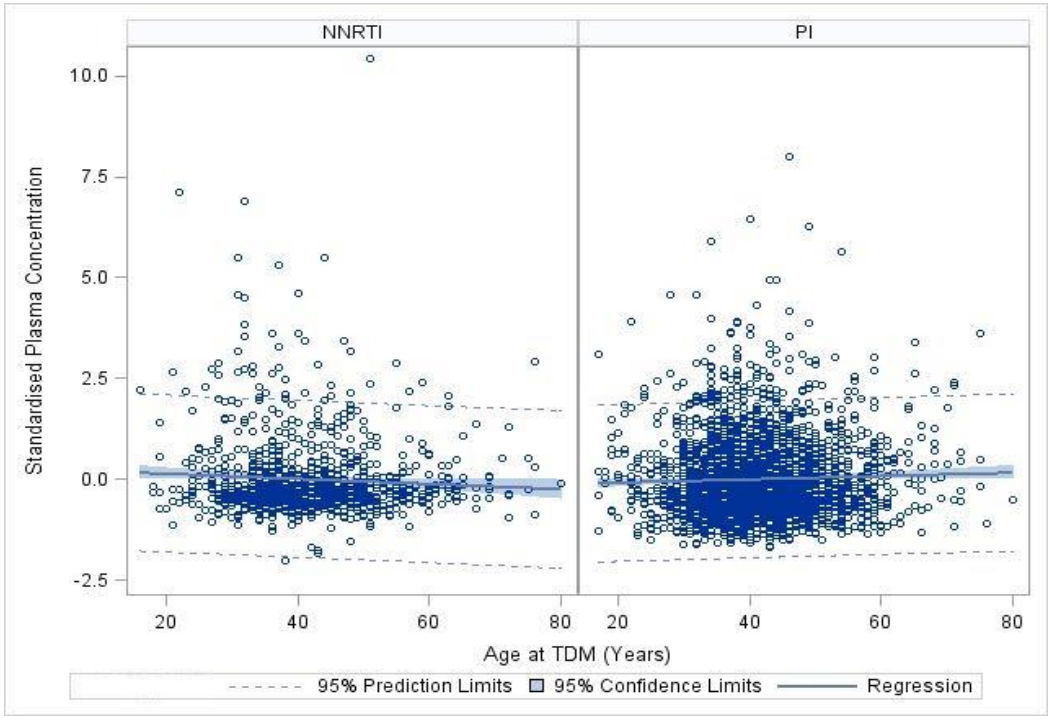




Cevik et al. EACS 2011

The effects of age on antiretroviral plasma drug concentration in HIV-infected subjects undergoing routine therapeutic drug monitoring

- Data from 3589 TDM samples were available for 2447 subjects (404 were > 50 years)
- As age increased, NNRTI concentrations remained constant but PI concentrations increased.



Winston et al. CID 2013

CROI 2017 seattle
WASHINGTON STATE CONVENTION CENTER
February 13–16, 2017

Steady-state Pharmacokinetics of Dolutegravir In People Living With HIV Over the Age of 60 Years

Emilie Elliot[1], Xinzhu Wang[2], Nicole Pagani[1], Alison Jenkin[1], Jaime Vera-Rojas[3], Isaac Day-Weber[2], Graeme Moyle[4], Myra McClure[2], Marta Boffito[1]
[1]St. Stephen's AIDS Trust–Chelsea and Westminster Hosp, London, UK, [2]Imperial Coll, London, UK, [3]Brighton and Sussex Med Sch, Brighton, UK, [4]Chelsea and Westminster Hosp, London, UK

London St Stephen's AIDS TRUST

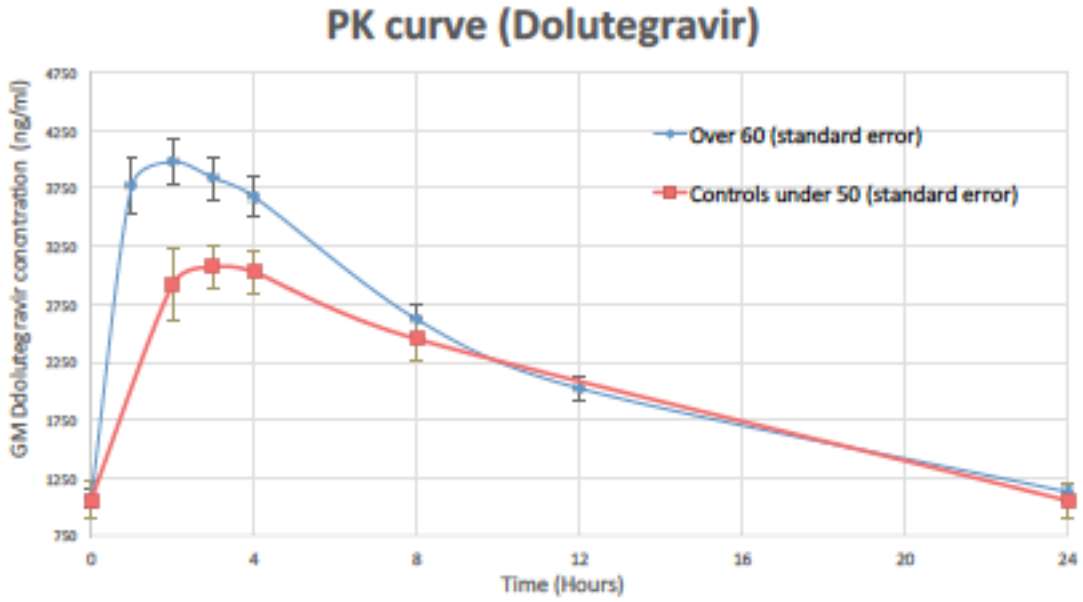


Figure 1 : Dolutegravir (DTG) concentrations 1,2,3,4,8,12 and 24hrs post-dose expressed as geometric mean concentrations and standard error in the observed (blue line) and control (red line) groups.

Polypharmacy

- Has been variously defined
- In research studies a commonly applied definition has been the concomitant use of five or more drugs

≥ 5

- Has been linked to heightened risk of occurrence of drug-related problems (toxicities and DDIs) and a detrimental health outcome

Polypharmacy and potential drug-drug interactions in older and younger people living with HIV: The POPPY Study

POPPY
Pharmacokinetic and clinical observations in people over 50

M. O Halloran[1], C. Boyle[1], B. Kehoe[1], E. Bagkeris[2], P. Mallon[3], D. Babalis[4], J. Vera[5], A. Winston[4], C. Sabin[2], M. Boffito[4], for the POPPY Study

1Mater Misericordiae University Hospital, Pharmacy Department, Dublin, Ireland, 2University College London, London, United Kingdom, 3University College Dublin, Dublin, Ireland, 4Imperial College London, London, United Kingdom, 5Brighton and Sussex University Hospitals NHS Trust, Brighton, United Kingdom

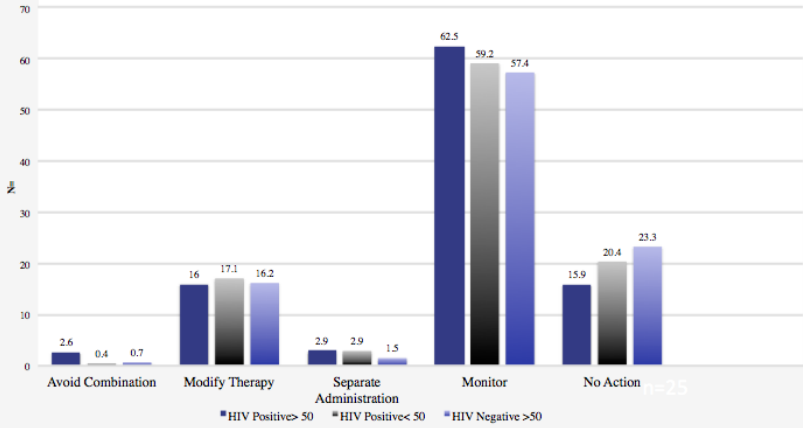
RESULTS

- Polypharmacy was more frequent in older PLWH than the other two groups (p=0.001).
- The prevalence of at least one PDDI was highest in the group of older PLWH (p=0.001).
- Within the HIV positive groups, 17 PDDI (1.5%) between ARV/non-ARV drugs were classified as contraindicated, 14 in the older group, three in the younger group. In older PLWH, PPI (35.7%) and inhaled corticosteroids (28.6%) were most frequently implicated in contraindicated PDDI. Inhaled corticosteroids were involved in all contraindicated PDDI in younger PLWH.
- From the PDDI classified as major by the Lexicomp® database between non-ARV/non-ARV drugs, 77.1% were in the older HIV positive group, 15.9% in the younger HIV positive group and 7% in the older HIV negative control group. In both older and younger PLWH, opioids (29.1% & 50.9% respectively) and anti-depressants (27.5% & 40.4% respectively) were the most frequent drugs implicated in major PDDI. In HIV-negative controls, proton pump inhibitors (PPI) (47.4%) and statins (42.1%) were most frequently implicated in major PDDI.

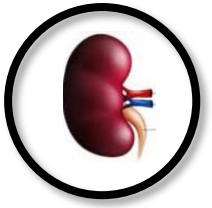
Table 1: *Characteristics of and prevalence of polypharmacy and PDDI among POPPY participants*

	PLWH aged >50 years	PLWH aged <50 years	HIV-negative controls aged >50 years	P-value
Age (years)				
Median (range)	56 (50-82)	43 (20-49)	58 (50-87)	0.001
% MSM	78.8%	71.9%	47.4%	0.001
% Hetrosexual	21.2%	28.1%	52.6%	0.001
% Male	87.7%	80.8%	64.1%	0.001
% Black African	13.6%	20.1%	10.2%	0.001
Total number of medications				
Median (range)	6 (0-27)	4 (0-17)	1 (0-39)	0.001
N (%) with PP	459 (65.3%)	180 (48.1%)	40 (13.2%)	0.001
PDDI between non-ARV and non-ARV drugs				
N (%) ≥ 1	252 (36.1%)	76 (20.3%)	49 (16.1%)	0.001
Median (range)	0 (0-48)	0 (0-21)	0 (0-14)	0.001
% on ARVs	98.7%	95.2%	-	
PDDI between ARV and non-ARV drugs				
N (%) ≥1	398 (57.3%)	121 (32.4%)	-	0.001
Median (range)	1 (0-11)	0 (0-5)	-	0.001

Figure 1*: Recommended Action based on non-ARV interactions*



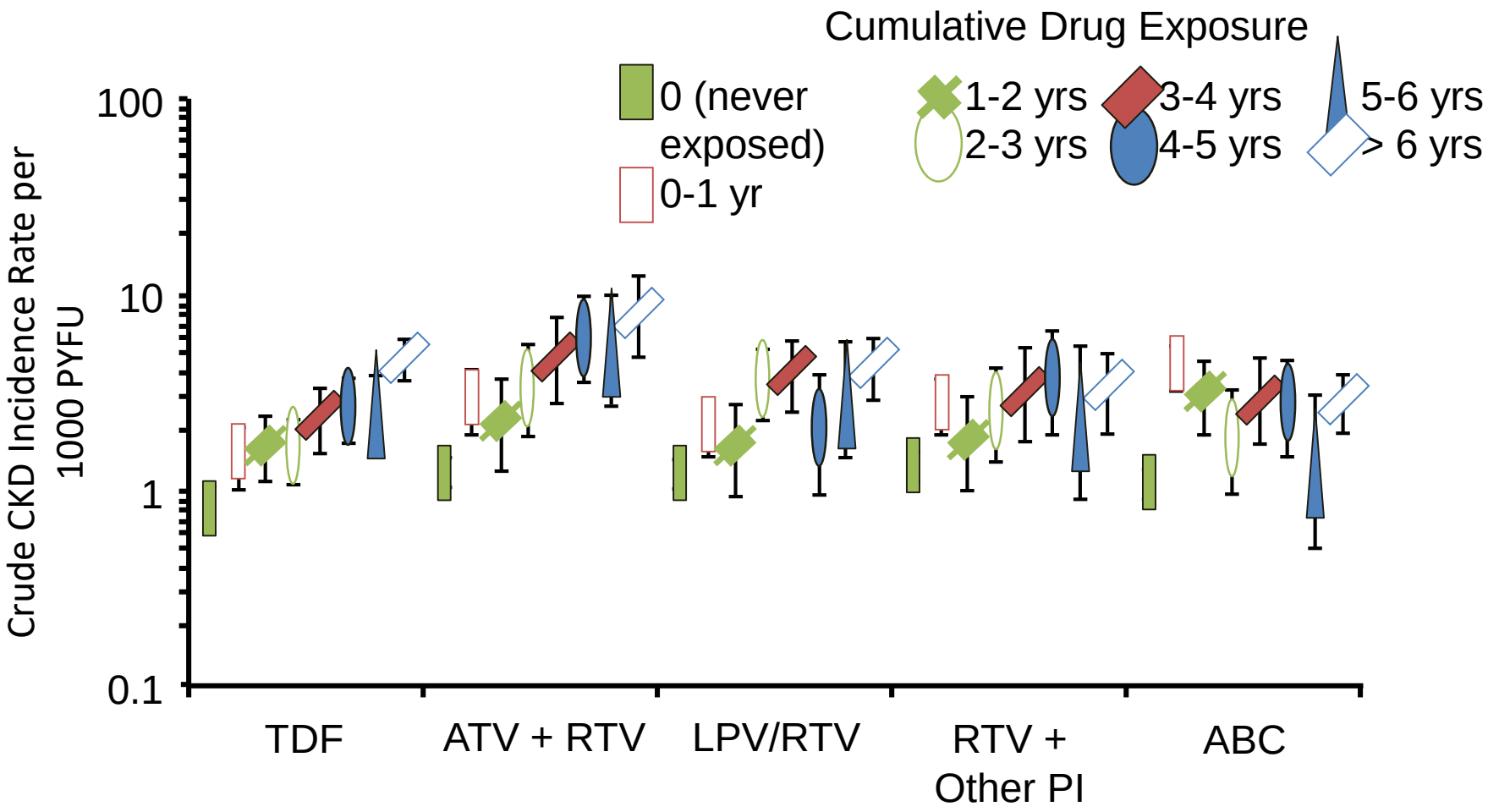
2- Renal function



- eGFR
- uPCR

Referral to HIV/renal clinic

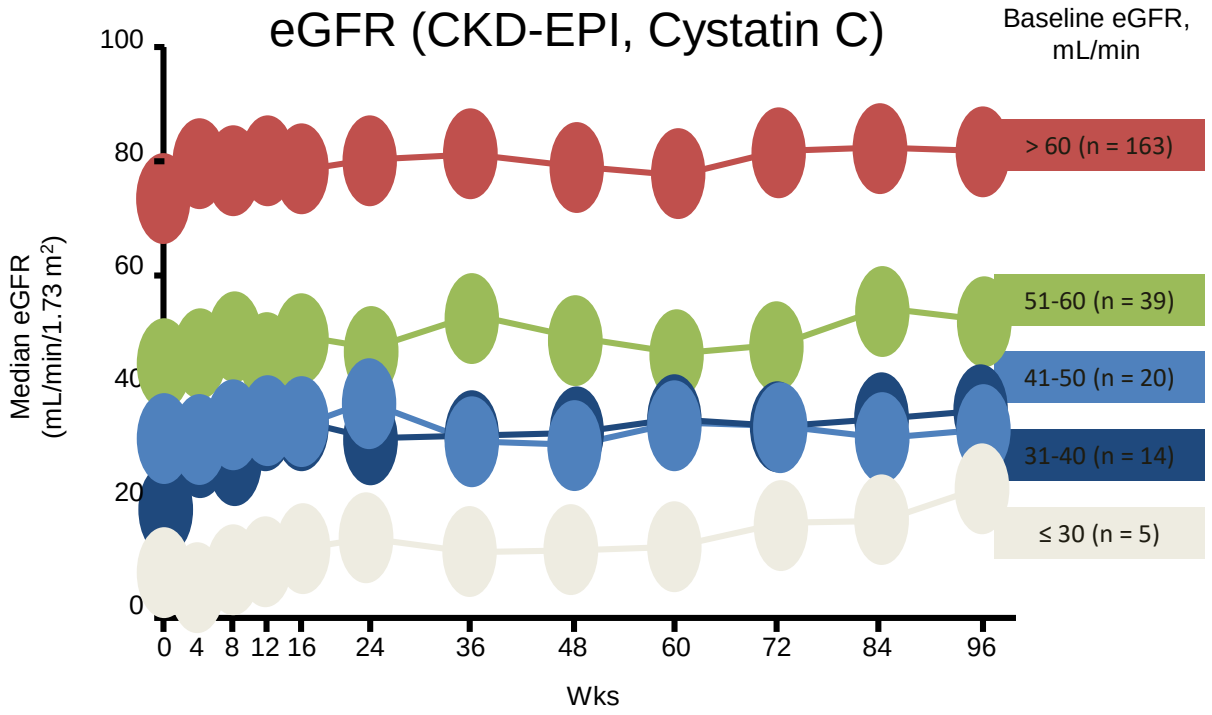
D:A:D: Cumulative exposure to ARVs associated with increased CKD risk



Mocroft et al. Lancet HIV 2016

TAF in patients with renal insufficiency

- Open-label trial of 242 virologically suppressed patients with stable $eGFR_{CG}$ 30-69 mL/min switched from TDF and non-TDF regimens to EVG/COBI/FTC/TAF[1]
  - eGFR remained stable through Wk 144 analysis[2]



1. Post et al. CROI 2016; 2. Podzamczer et al. IAS 2017

3 – Endocrine system

MEN

Check for hypogonadism

- low libido
- depression
- osteoporosis

WOMEN

Menopausal clinic

- depression
- osteoporosis
- ….

Transexual

- symptomatology
- drug interactions

Testosterone Total and FREE

Full hormonal profile

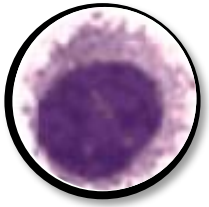
Hormonal History with appropriate referral

Impaired glucose intolerance and diabetes

- Fasting glucose
- HbA1c
- OGTT

Referral to HIV/metabolic clinic

4 - Cancer screening



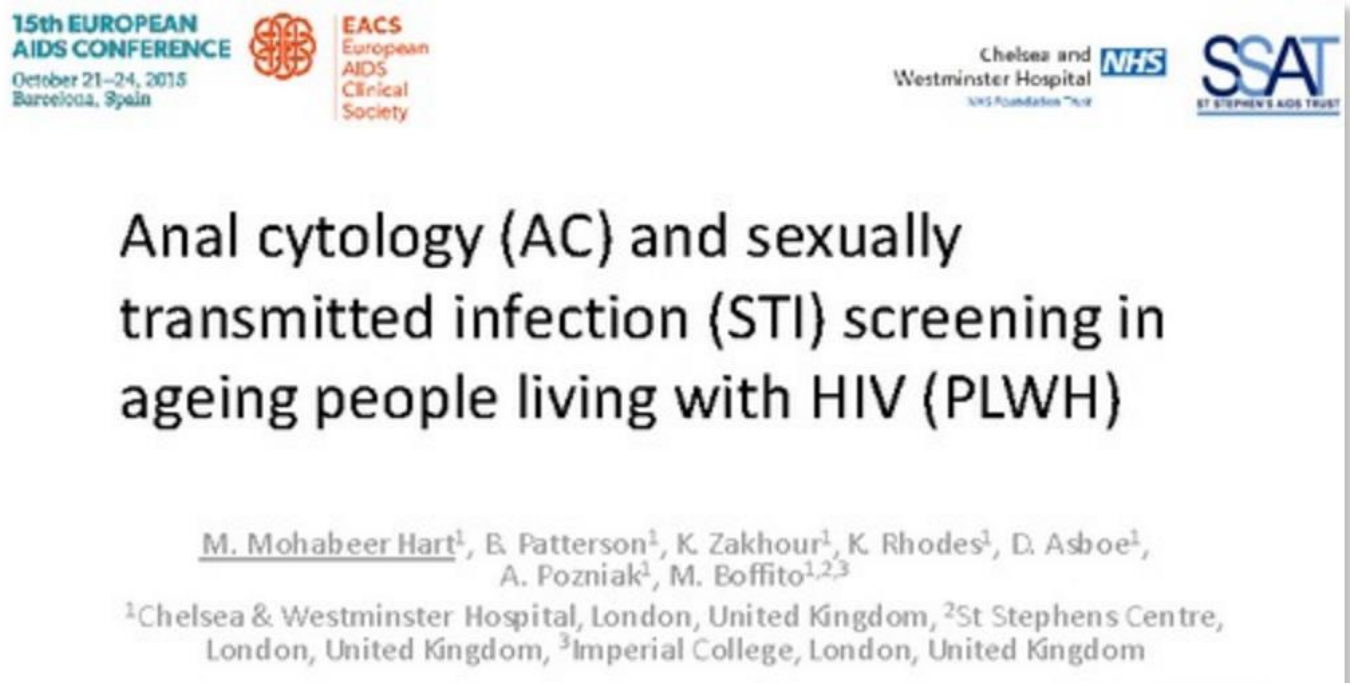
WOMEN

- Cervical smear*
- Ensure mammography is done or planned

MEN

- PSA
- Anal cytology
- Referral to anoscopy clinic if cytology is abnormal

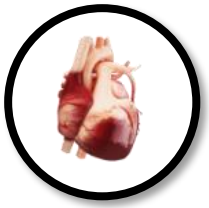
*cervical smear test is recommended every year regardless of patient's age



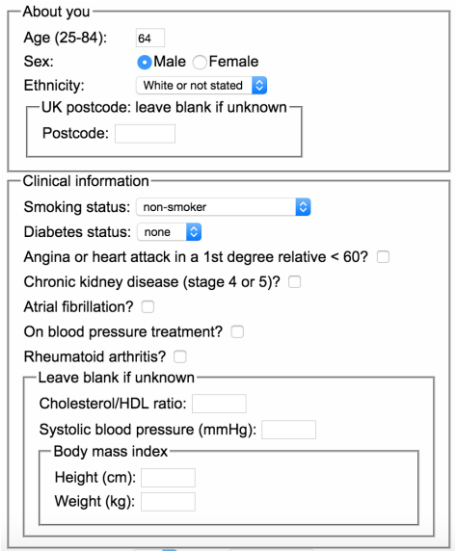
… anal cytology results reflected the fact that an ageing HIV-positive population is more at risk of having abnormalities; it is important that this group continues to be offered regular screens and educated about anal malignancy.

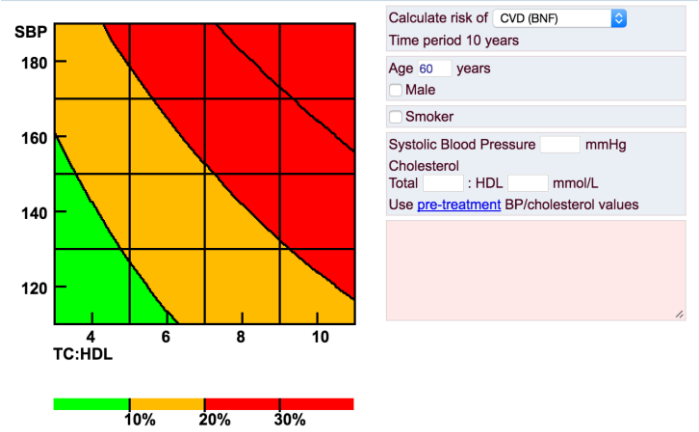
Mohabeer-Hart et al. EACS 2015

5 – CV risk assessment



Coronary artery calcification score





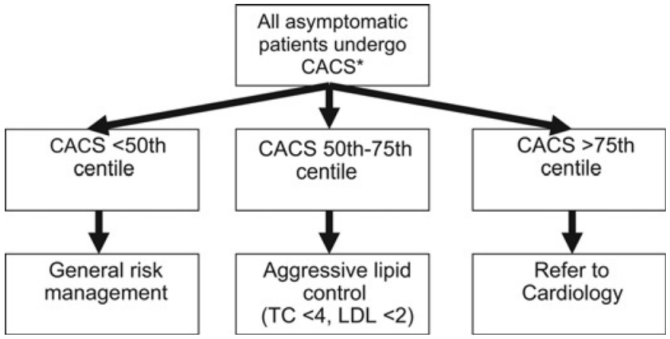
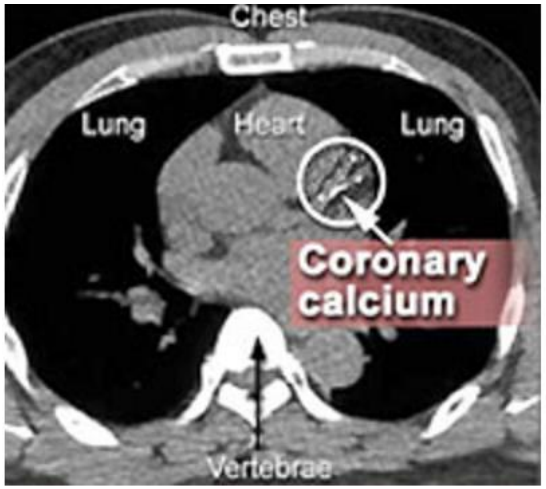


Figure 1 **Coronary artery calcium score (CACS) flowchart. TC = total cholesterol in mmol/L; LDL = low-density lipoprotein-cholesterol in mmol/L**



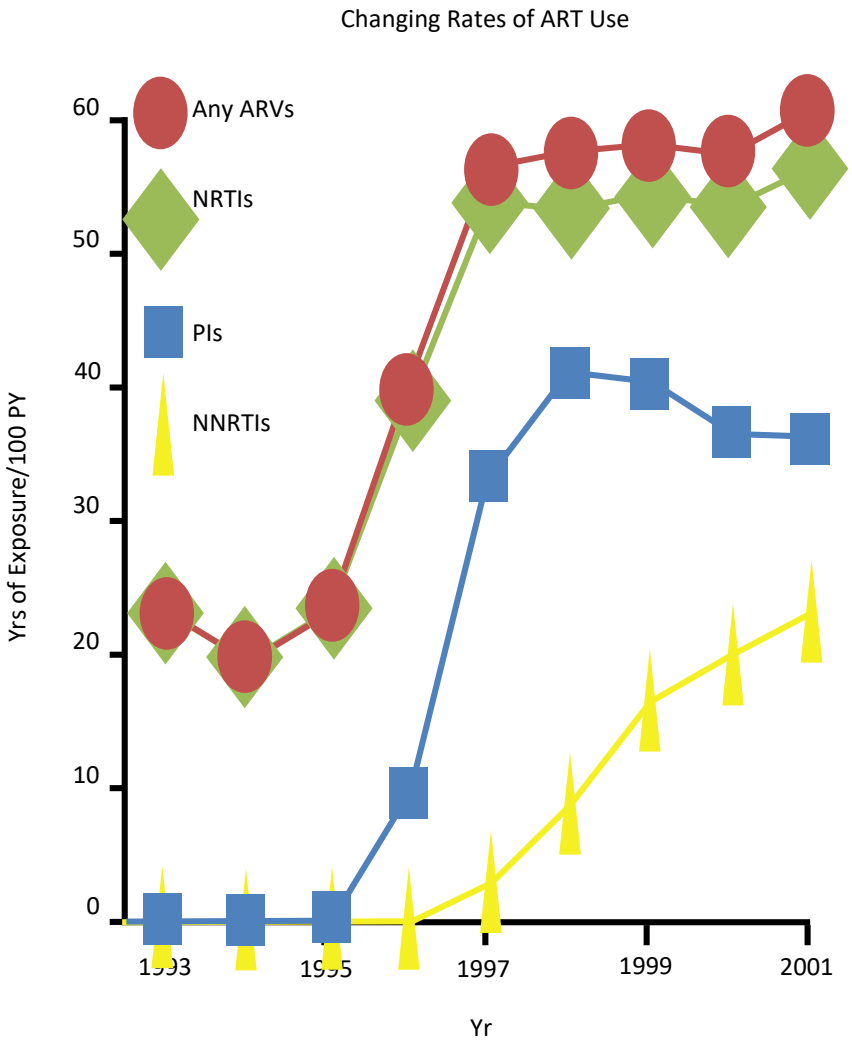
Referral to HIV/cardiology clinic

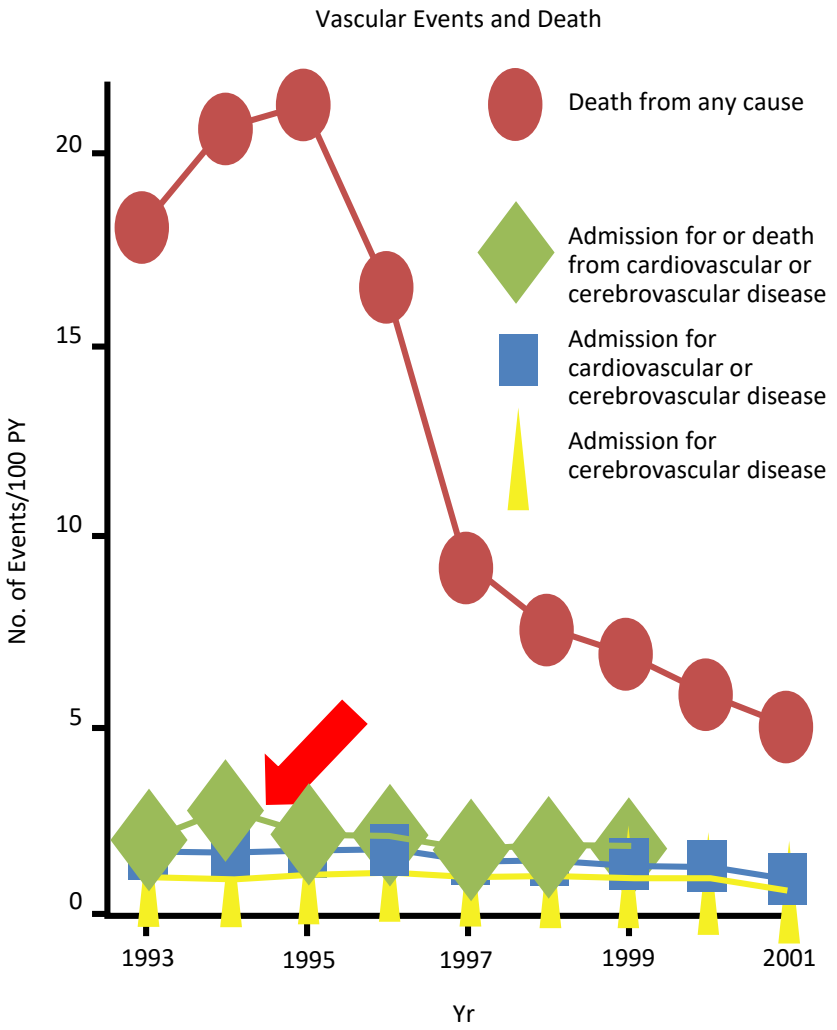
CVD mortality higher in HIV-infected patients, even with virologic suppression

- Analysis of CVD-related mortality in HIV-infected patients in New York City HIV Surveillance Registry 2001-2012 (N = 145,845)
  - 71.5% male; median age: 49 yrs
- From 2001-2012, CVD mortality increased in HIV-infected patients (from 6% to 15%) while decreasing in the general population
- Age-adjusted rate of CVD mortality markedly decreased for HIV-infected patients with virologic suppression
  - HIV-1 RNA ≥ 400 copies/mL: 8.02/1000 PY
  - HIV-1 RNA < 400 copies/mL: 3.99/1000 PY
  - General population: 3.22/1000 PY

Hanna et al. Clin Infect Dis. 2016

Starting ART decreases CVD event risk



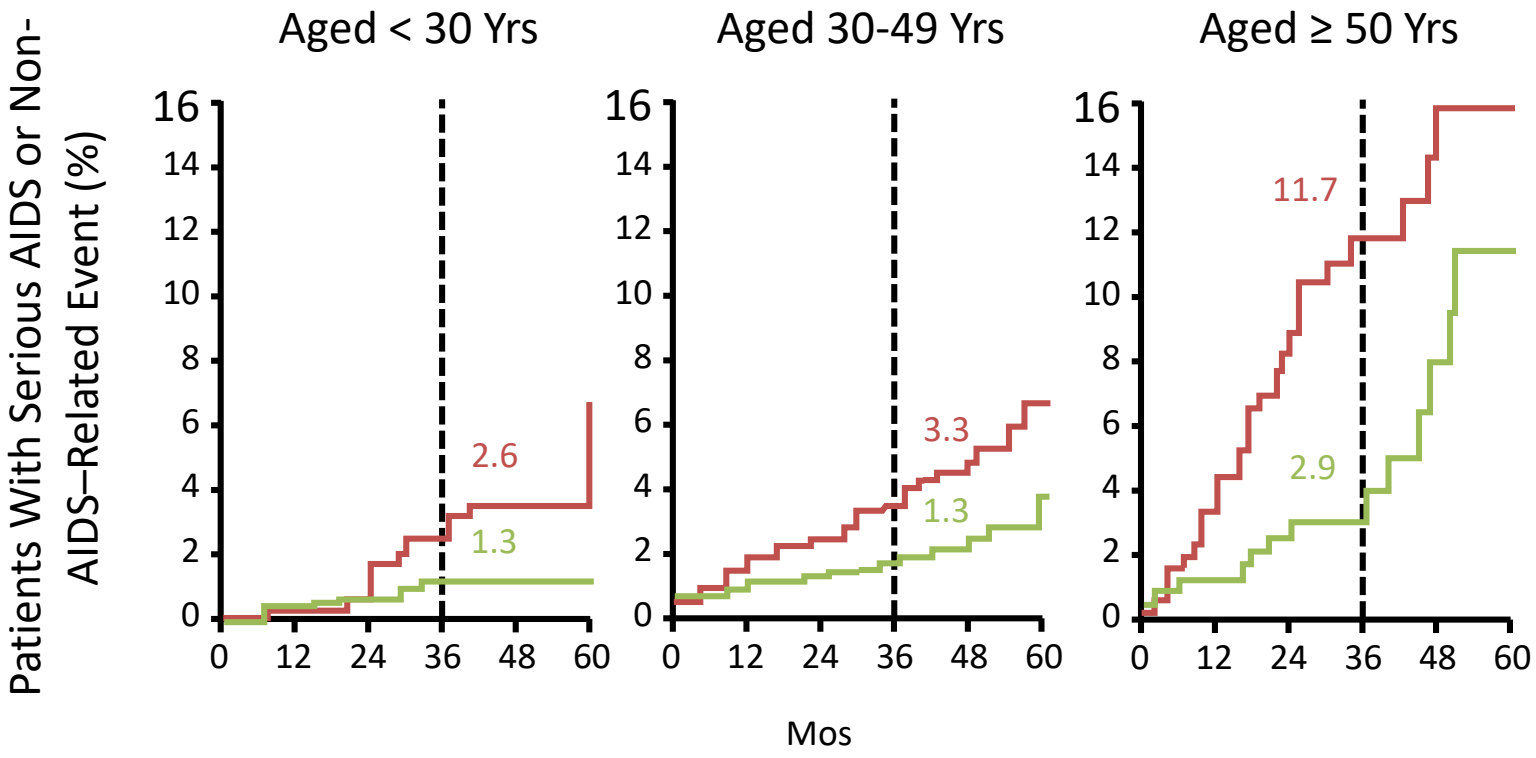


Bozzette et al. N Engl J Med. 2003

START: Immediate vs deferred ART by age

Immediate ART
Deferred ART

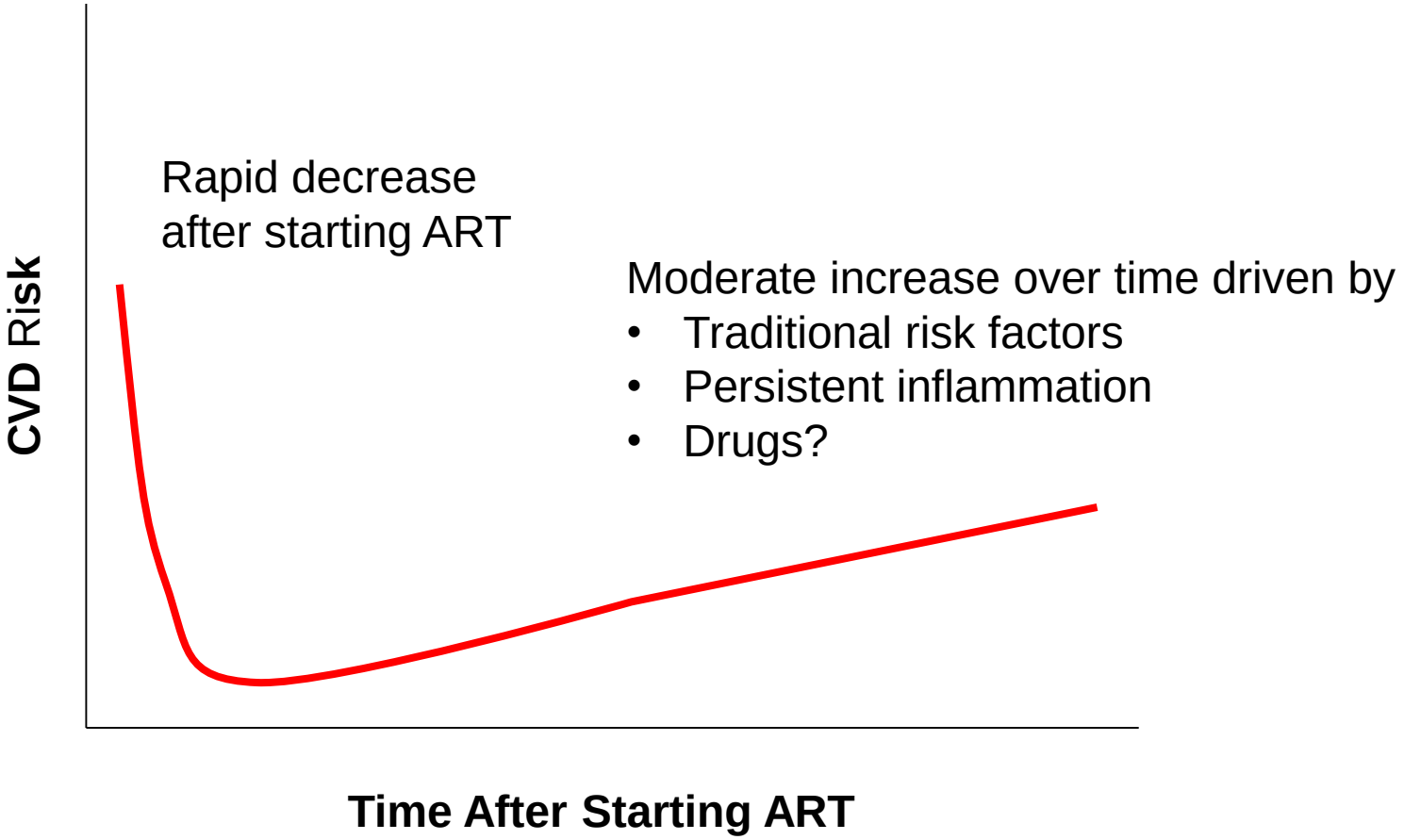
- Subgroup analysis of START, in which HIV-infected, ART-naive adults with CD4+ cell count > 500 cells/mm^3 randomized to immediate or deferred* ART (N = 4685)



*Until CD4+ cell count ≤ 350 cells/mm^3, AIDS-related event, or event requiring ART

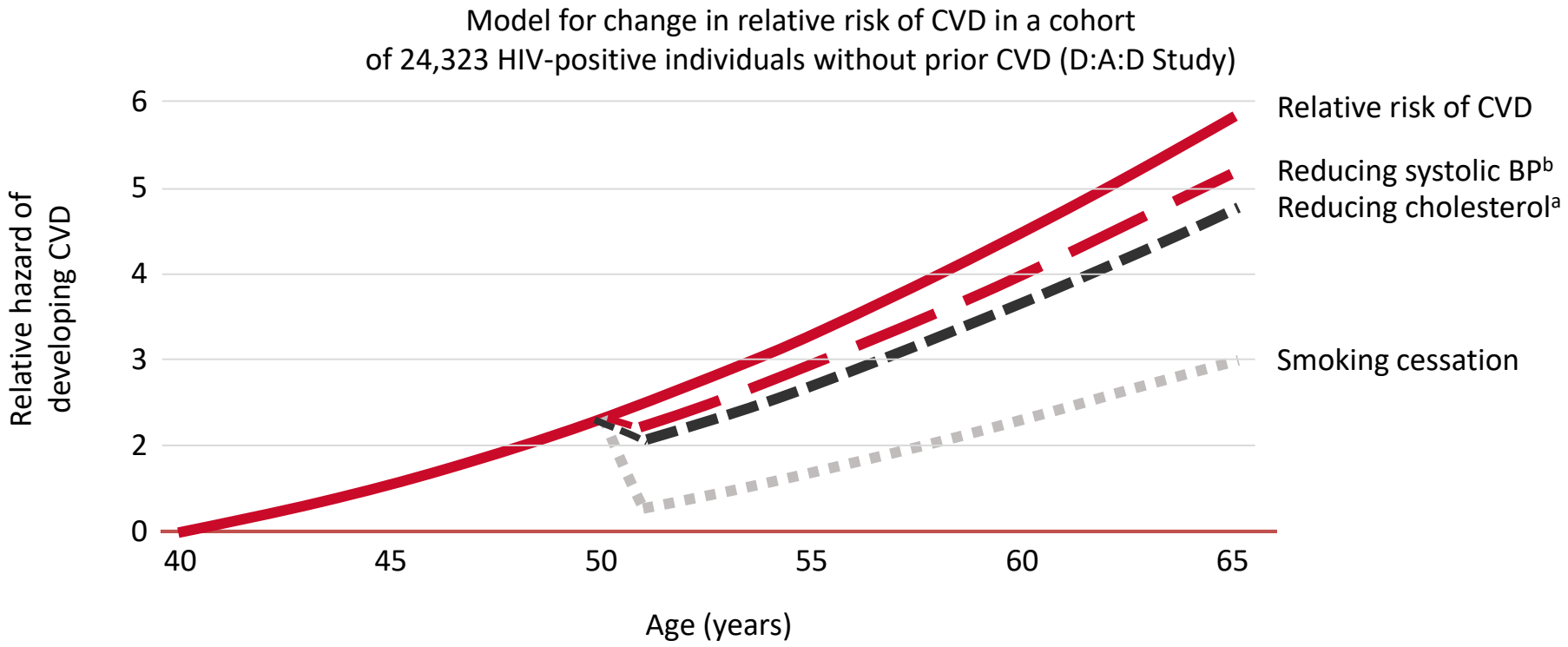
Molina et al. IAC 2016

The relationship between CVD risk in HIV and HIV treatment is U-Shaped



Reducing traditional CDV risk factors can decrease risk of CVD in older PLWHIV

Effective treatment of modifiable risk factors can significantly reduce an individual's CVD risk



[a]Reduced by 1 mmol/L;
[b]Reduced by 10 mmHg

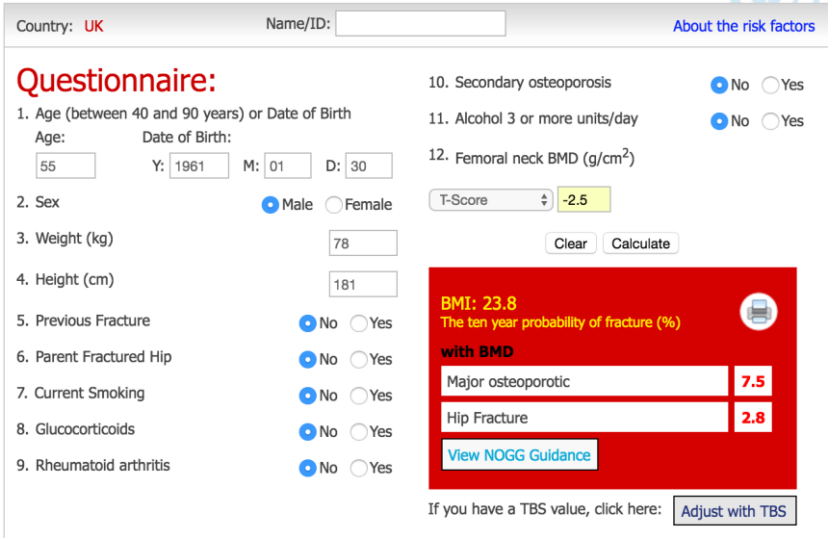
Petoumenos K et al. HIV Med2014

DHHS: Considerations for initial ART based on age-related comorbidity

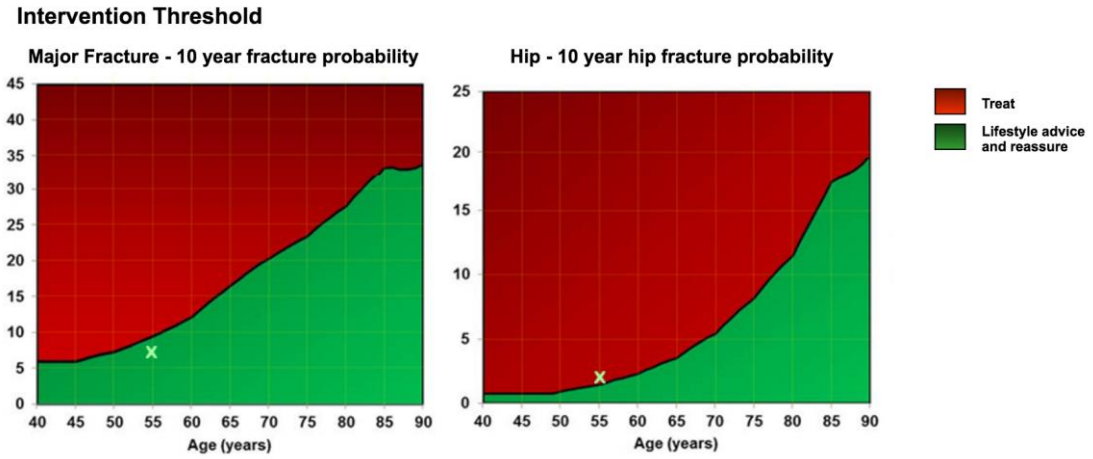
Scenario	Consider Avoiding	Options for Consideration*	
		Agent	Caveat
CKD (eGFR < 60 mL/min)	▪ TDF, especially in RTV-containing regimens	▪ FTC/TAF ▪ ABC/3TC ▪ DRV/RTV + RAL ▪ LPV/RTV + 3TC	▪ If eGFR > 30 mL/min ▪ If HLA-B*5701 negative; 3TC requires dose adjustment if CrCl < 50 mL/min ▪ If TAF or ABC cannot be used; if HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm^3 ▪ If TAF or ABC cannot be used; 3TC dose adjustment if CrCl < 50 mL/min
Osteoporosis	▪ TDF	▪ FTC/TAF ▪ ABC/3TC	▪ If HLA-B*5701 negative
CVD risk	▪ ABC	▪ DTG-, RAL-, or RPV-based regimens	▪ If choosing boosted PI, ATV may be preferable to DRV, but further study needed
Hyperlipidemia	▪ PI/RTV or PI/COBI ▪ EVG/COBI	▪ DTG-, RAL-, or RPV-based regimens ▪ TDF associated with lower lipid levels vs ABC or TAF	

*This section of the guidelines has not yet been updated to reflect February 2018 FDA approval of BIC/FTC/TAF.

6 – Bone mineral density



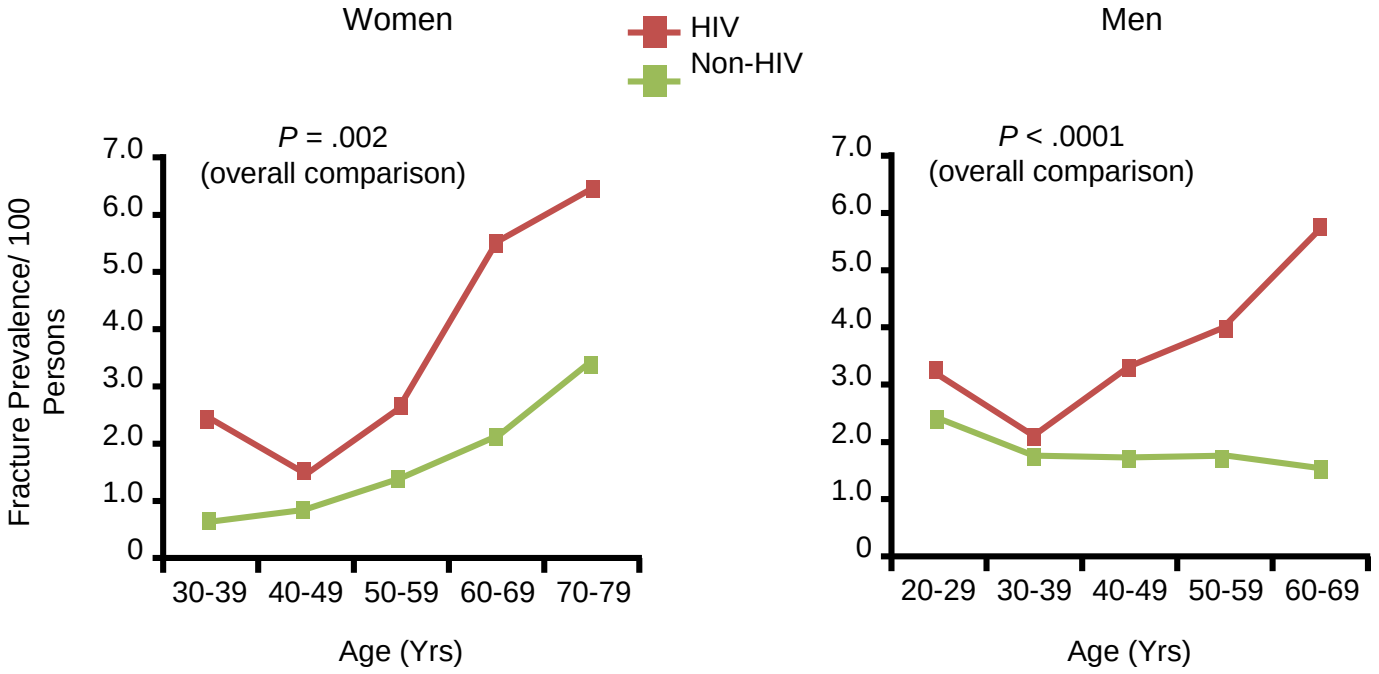
- DEXA scan
- Vitamin D
- FRAX score



Referral to HIV/metabolic clinic

Fracture prevalence increased in older HIV-infected patients

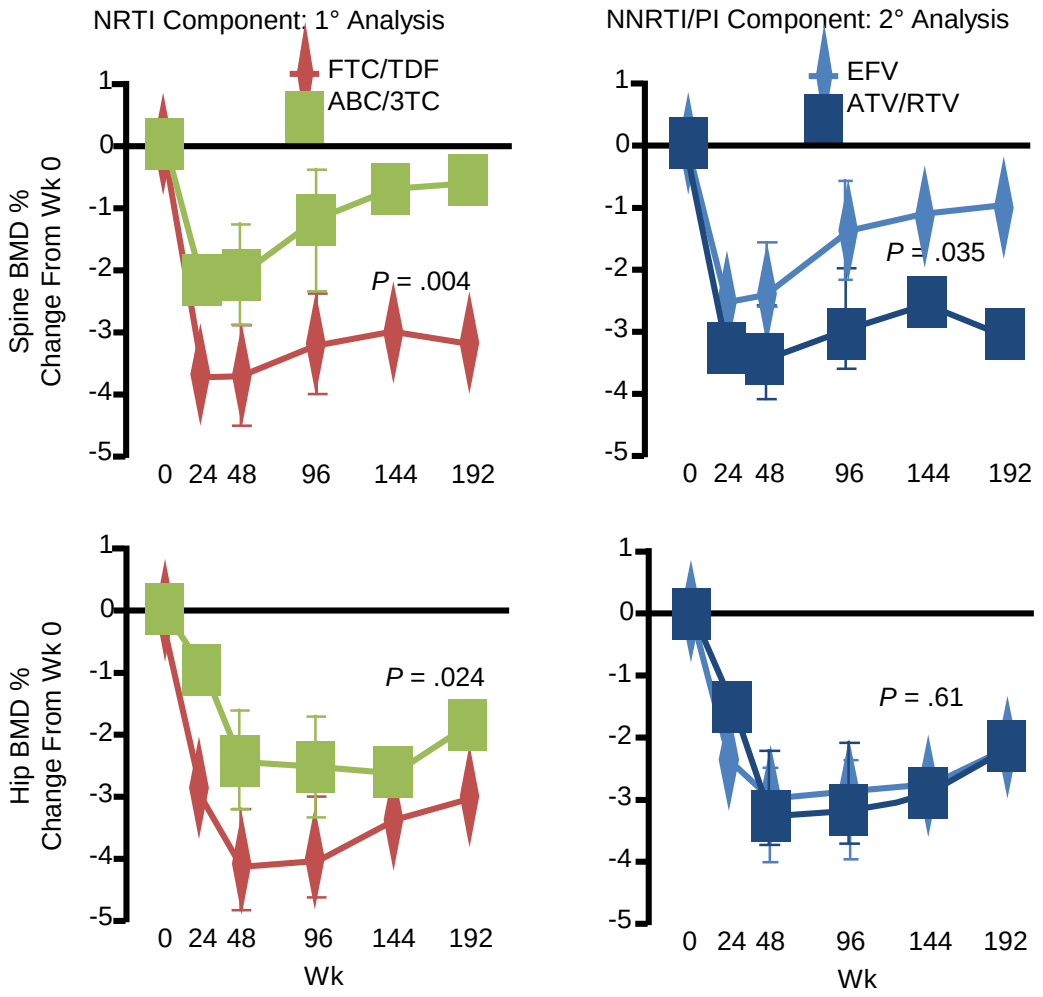
- Meta-analysis: HIV-positive patients had 6.4-fold increased risk of low BMD and 3.7-fold increased risk of osteoporosis[1]
- 8525 HIV-infected patients compared with 2,208,792 uninfected patients in Partners HealthCare System, 1996-2008[2]



1. Brown et al. AIDS; 2. Triant et al. J Clin Endocrinol Metab. 2008

Initiation of some ART associated with BMD decrease

- A5224s: Substudy of A5202 FTC/TDF vs ABC/3TC with either ATV/RTV vs EFV
- N = 269
  - 85% male, 47% white, median age: 38 yrs
- Significantly greater spine and hip BMD loss with FTC/TDF vs ABC/3TC
- Significantly greater BMD loss in spine but not hip with ATV/RTV vs EFV



McComsey et al. J Infect Dis. 2011

ART considerations for patients with bone complications

- DHHS considerations[1]
  - Consider avoiding TDF: associated with greater decrease in BMD along with renal tubulopathy, urine phosphate wasting, and osteomalacia
  - Consider ABC/3TC or FTC/TAF
- Significantly greater BMD loss with PI-based regimens vs RAL-based regimens (when used with FTC/TDF)[2]
- DTG/ABC/3TC associated with less bone turnover vs EFV/FTC/TDF[3]
- DTG/RPV: FDA approved in November 2017 as potential switch regimen for patients with virologic suppression on current ART, no drug resistance, and no history of VF[4]

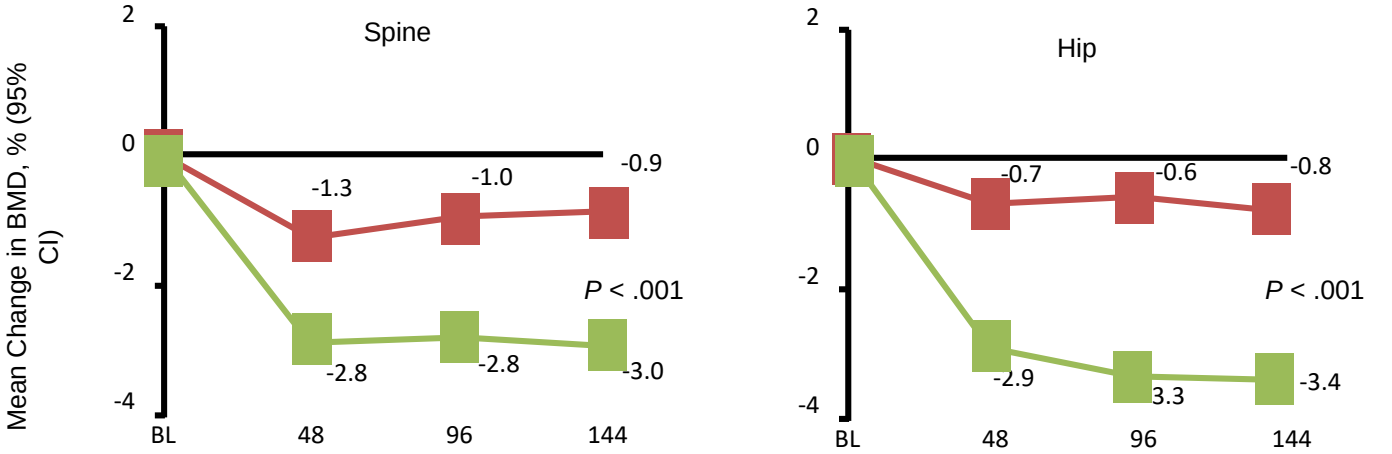
1. DHHS Guidelines. May 2018. 2. Brown et al. J Infect Dis. 2015 3. Tebas et al. AIDS. 2015; 4. DTG/RPV [package insert]. 2018.

What is the best management strategy for a patient with low BMD?

Initial ART in treatment-naive patients[1]

E/C/F/TAF (n = 845)

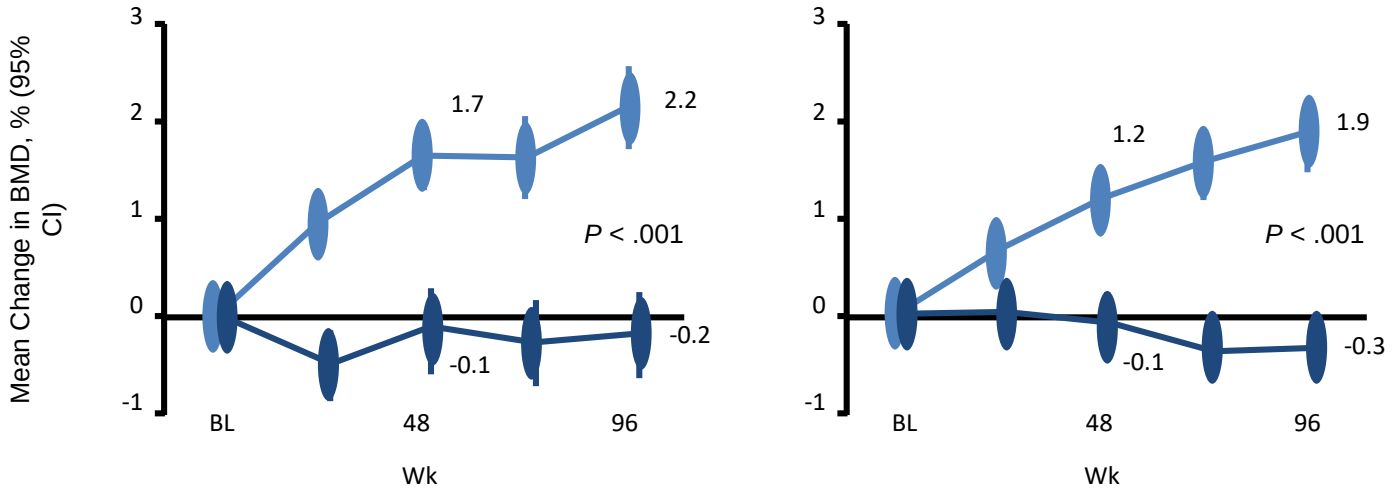
E/C/F/TDF (n = 850)



Switch ART in virologically suppressed patients[2]

Switch to TAF (n = 333)

Continue TDF (n = 330)



1. Arribas et al. J Acquir Immune Defic Syndr. 2017; 2. Raffi et al. J Acquir Immune Defic Syndr. 2017

Switching from TDF to TAF ± bisphosphonate therapy in patients with low BMD

- Data pooled from 2 prospective phase III studies of switching virologically suppressed patients from TDF-based ART to EVG/COBI/FTC/TAF (Study 109 or 112)
- Current analysis included 214 patients with low BMD by DXA at baseline of switch trials; compared BMD outcomes by use/nonuse of bisphosphonates
  - Low BMD defined as T-score ≤ -2 at lumbar spine, femoral neck, or total hip

Mean Δ at Wk 144 (95% CI)	Hip BMD			Spine BMD		
	BP	No BP	*P* Value	BP	No BP	*P* Value
Unadjusted	4.2 (2.8-5.6)	3 (2.2-3.9)	.29	5.9 (4.2-7.7)	2.8 (1.8-3.9)	.002
Adjusted, linear	4.3 (2.2-6.4)	4.2 (2.8-5.5)	.89	5.6 (2.7-8.4)	3.0 (1.2-4.9)	.08
Adjusted, IPTW	4.4 (2.9-5.6)	4.2 (2.8-5.6)	.79	5.7 (3.8-7.6)	3.5 (1.7-5.4)	.02

Brown et al. CROI 2018

Recommendations for evaluation of bone disease in HIV

HIV-Infected Population	Assessment	Monitoring
Men 40-49 yrs of age Premenopausal women ≥ 40 yrs of age Men ≥ 50 yrs of age Postmenopausal women Patients with fragility fracture history, receiving chronic glucocorticoids, or at high risk of falls	▪ Assess risk of fragility fracture using FRAX ▪ Assess BMD using DXA	▪ For patients with FRAX score ≤ 10%, monitor FRAX in 2-3 yrs ▪ For patients with FRAX score > 10%, perform DXA ▪ For patients with advanced osteopenia, monitor DXA in 1-2 yrs ▪ For patients with mild or moderate osteopenia, monitor DXA in 5 yrs ▪ For patients started on bisphosphonates (significantly reduced BMD or fracture history), repeat DXA in 2 yrs

Brown et al. Clin Infect Dis. 2015

7 – Cognitive assessment

- HIV Associated Neurocognitive Disorder (HAND)
- SOCIAL SITUATION: combination of all social factors that come into play at any one time

Are you concerned about your memory/concentration/cognition?

Has anybody around you expressed concern about your memory/concentration/cognition?

PHQ – 9

GAD - 7

Referral to HIV/neurology clinic

EMQ

Disabil Rehabil. 2008;30(2):114-21.

The Everyday Memory Questionnaire-revised: development of a 13-item scale.

Royle J[1], Lincoln NB.

Author information

Abstract

PURPOSE: The Everyday Memory Questionnaire (EMQ) was developed as a subjective measure of memory failure in everyday life. Previous studies have investigated the factor structure of the EMQ in both healthy participants and people with multiple sclerosis (MS). The aim of the present study was to confirm the factor structure of the EMQ, to determine the internal consistency and criterion validity of the scale and to develop a shortened version.

METHOD: A retrospective design, including participants from a study on MS patients and their carers and a study on stroke patients. Psychometric properties of the EMQ-28 were explored, and the measure was further revised from comparative analyses between the clinical and non-clinical groups.

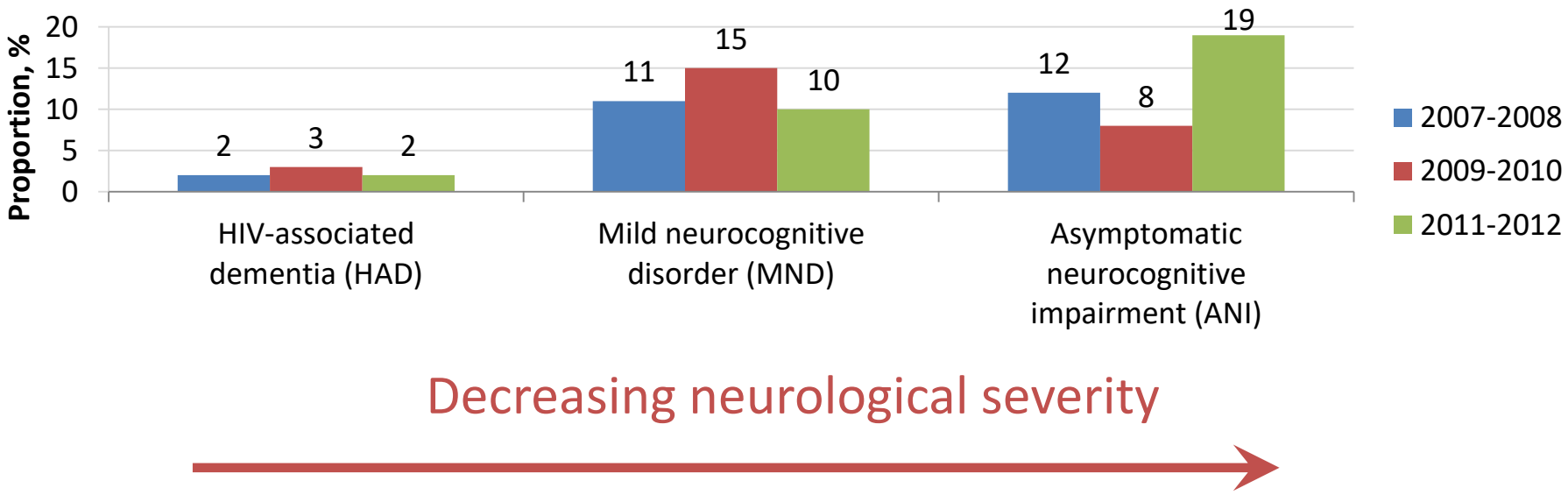
RESULTS: Reliability and factor analysis of the EMQ-28 identified two main factors, general memory and attentional function, showing some concordance with previous research. Further analysis reduced the questionnaire to a 13-item measure (EMQ-R), with two main factors (Retrieval and Attentional tracking), strong internal reliability, and good discriminatory properties between clinical and control groups.

CONCLUSIONS: The 28-item questionnaire consistently differentiated between two broad systems of memory and attention, with some differentiation of visual and verbal, or language systems. Results showed some consistency with previous findings. The revised, 13-item questionnaire is a valid and reliable tool that has good face validity for use with neurological patients. Further exploration of the revised EMQ is recommended to provide information regarding its psychometric and clinical properties.

HAND in PLWH

- HAND results from neural damage caused by HIV replication and immune activation[1]
- HAND is fairly prevalent, even in patients with low VLs and high CD4+ T-cell counts[2]

Frequency of HAND in MACS[3], n=364



Decreasing neurological severity

HAND, HIV-associated neurocognitive disorders; MACS, Multicenter AIDS Cohort Study

1. Letendre Top Antivir Med 2011; 2. McArthur et al. Ann Neurol 2010; 3. Sacktor et al. Neurology 2016

CROI 2017 seattle
WASHINGTON STATE CONVENTION CENTER
February 13–16, 2017

Abstract Number:
352LB

LONGITUDINAL ANALYSIS SHOWS NO EVIDENCE FOR ACCELERATED BRAIN AGEING IN TREATED HIV

Author(s):
James H. Cole[1], Matthan W. Caan[2], Jonathan Underwood[1], Rosan van Zoest[3], Davide De Francesco[4], Alan Winston[1], Caroline Sabin[5], David J. Sharp[1], Peter Reiss[6]

A major concern for people living with HIV is the reportedly high prevalence of cognitive impairment, which may reflect an exacerbation of the effects of ageing on the brain. Using longitudinal neuroimaging and neuropsychological data from participants in the EU-funded COBRA collaboration, we determined whether successfully treated HIV infection is associated with accelerated age-related changes to brain structure and function.

HIV+ve people with plasma HIV RNA <50 copies/ml on antiretroviral therapy for >1 year and demographically comparable HIV-ve controls were recruited at centres in Amsterdam and London. Participants were assessed at baseline and two years using multi-modal magnetic resonance imaging (T1-weighted, diffusion, resting-state fMRI, arterial spin labelling, spectroscopy), processed to generate global and regional summary metrics of brain structure and function. Neuropsychological assessments (reported as domain T-scores adjusted for age, sex, education) tested the cognitive domains of attention, executive function, language, memory, motor function and processing speed. Between-group comparisons of baseline values and change over time were assessed using linear and mixed-effects regression respectively, with models accounting for age, time between assessments and (for neuroimaging only) intracranial volume and scanner type.

At baseline, the 134 HIV+ve people (mean age 57.4 [SD=7.4] years, 6.7% female) had smaller grey matter volume, abnormal white matter microstructure and poorer cognitive function compared to 79 HIV-ve controls (58.8 [7.8] years, 7.6% female). Age-related declines in neuroimaging measures were observed in both groups, e.g., HIV+ve people lost 0.82% of brain volume per year, while HIV-ve controls lost 0.77%. Importantly, there were no group differences in the rates of brain volume loss or change in any neuroimaging measure ($p>0.1$, Table). Measure of cognitive function showed limited change. In fact global cognition T-score increased in both groups (HIV+ve 0.79, HIV-ve 0.45). There were no group differences in rates of change in cognition ($p>0.1$), with the exception of attention T-score, where the groups became more similar.

While HIV+ve persons had abnormal measures of brain structure and function at baseline, we found no difference in the dynamics of these measures over time between HIV+ve and HIV-ve persons. Our findings suggest that there is no evidence for accelerated brain ageing in successfully treated HIV+ve people.

AIDS. 2018 Jun 14. doi: 10.1097/QAD.0000000000001910. [Epub ahead of print]

Clinical research cerebral MRI findings in HIV positive subjects and appropriate controls.

Chhabra S[1], Underwood J[1,2], Cole JH[3], Caan M[4], Waldman A[5], Reiss P[6], Sabin CA[7], Sharp DJ[3], Winston A[1,2]; CoBRA collaboration.

Author information

Abstract

Abnormalities in cerebral magnetic resonance imaging (MRI) are frequently reported in persons-living-with HIV (PLWH). We compared clinical cerebral MRI reports in 59 PLWH and 29 lifestyle matched controls. Although clinical abnormalities were highly prevalent (47.7%), and included white-matter lesions (46.6%), microvascular disease (22.7%) and cerebral volume loss (11.4%), no differences were apparent between PLWH and controls with abnormalities being associated with age and hypertension rather than HIV-serostatus.

8- Frailty

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

DALHOUSIE UNIVERSITY *Inspiring Minds*

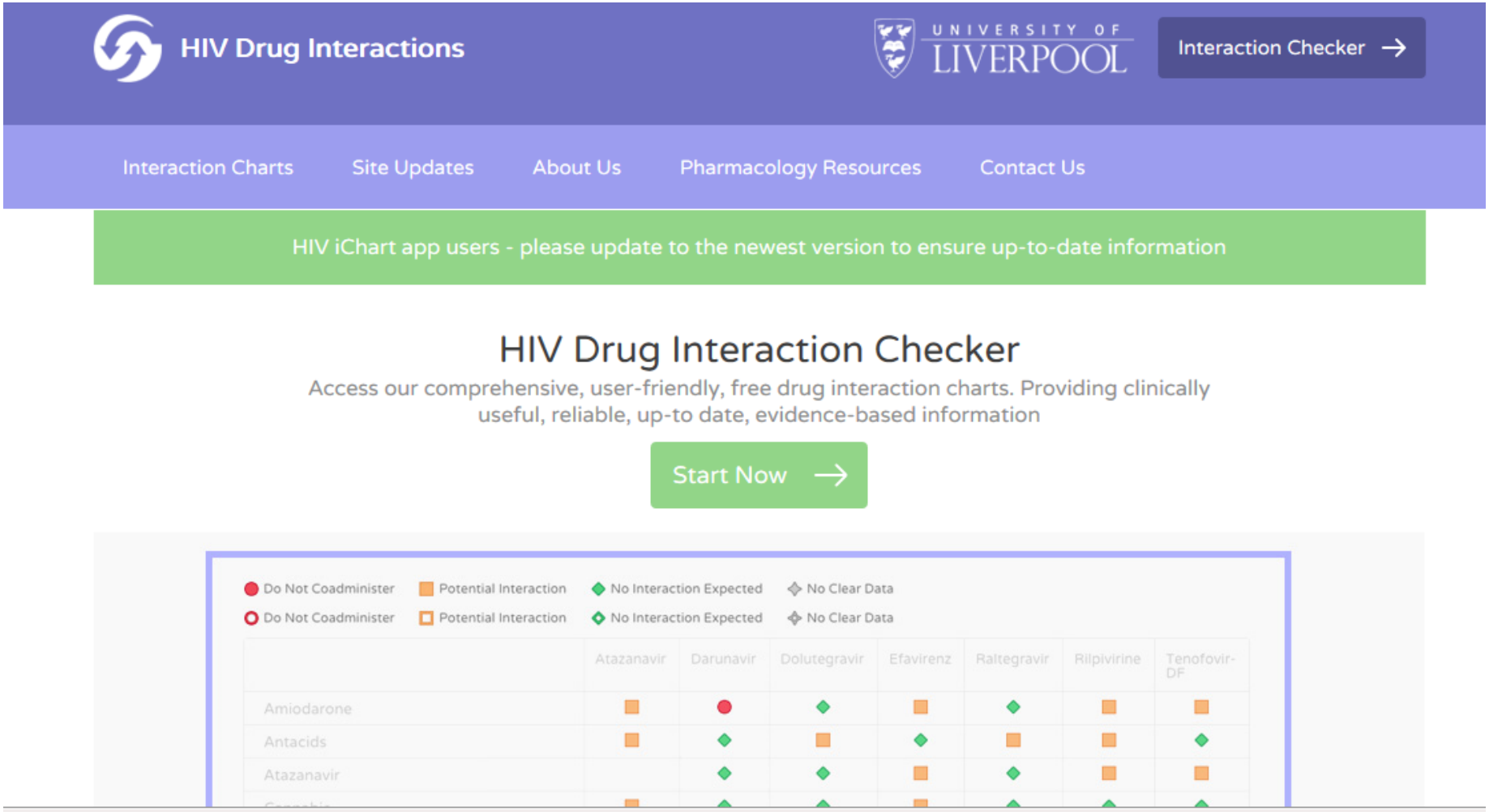
Referral to HIV/CoE clinic

Before starting cART in older patients

- ART recommended for all patients regardless of CD4+ cell count; **especially important for older patients**
  - Greater risk of serious non-AIDS complications
  - Potentially a blunted immunologic response to ART
- **Adverse drug events** from ART and concomitant drugs may occur more **frequently** in older patients with HIV
  - Bone, kidney, metabolic, cardiovascular, and liver health should be monitored closely
- **Polypharmacy** is common in older patients with HIV
  - Greater risk of **drug–drug interactions**
- HIV experts should collaborate with **primary care** providers and other specialists to optimize medical care of older HIV-infected patients with complex comorbidities

DHHS Guidelines. May 2018.

Drug interaction resources HIV



Questions?

Back up

Telomere Shortness Links to Common Diseases

- Cardiovascular disease
- Infection
- Cancer
- Diabetes
- Alzheimer’s disease
- Depression
- PTSD
- Autoimmune diseases
- COPD
- Pulmonary fibrosis
- Liver cirrhosis

- *Telomere length decreases with age and is associated to age related disease and decreased life span.*

Non-genetic Influences On Telomeres

SHORTENS TELOMERES

Chronic stress
Depression
Low education
Prenatal stress
Childhood trauma
Intimate partner violence
Neighborhood disorder
Poor diets
Smoking

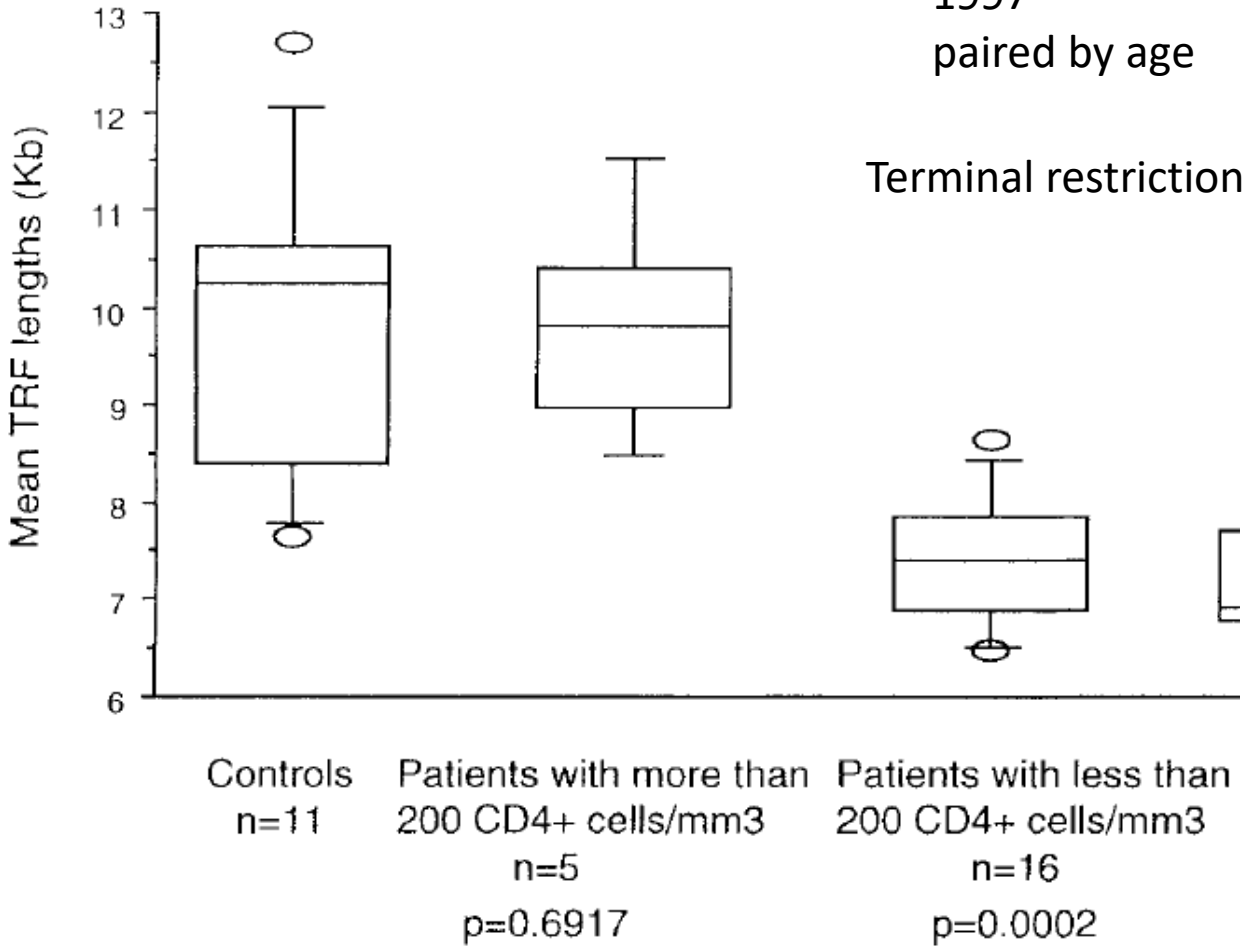
MAINTAINS TELOMERES

Exercise
Sleep
Stress-reduction
Omega-3

HIV infected persons have shorter telomeres than HIV uninfected

1997
paired by age

Terminal restriction fragment



Source: Pommier JP Virology 1997; 231:148–154.