AGEING AND HIV INFECTION.
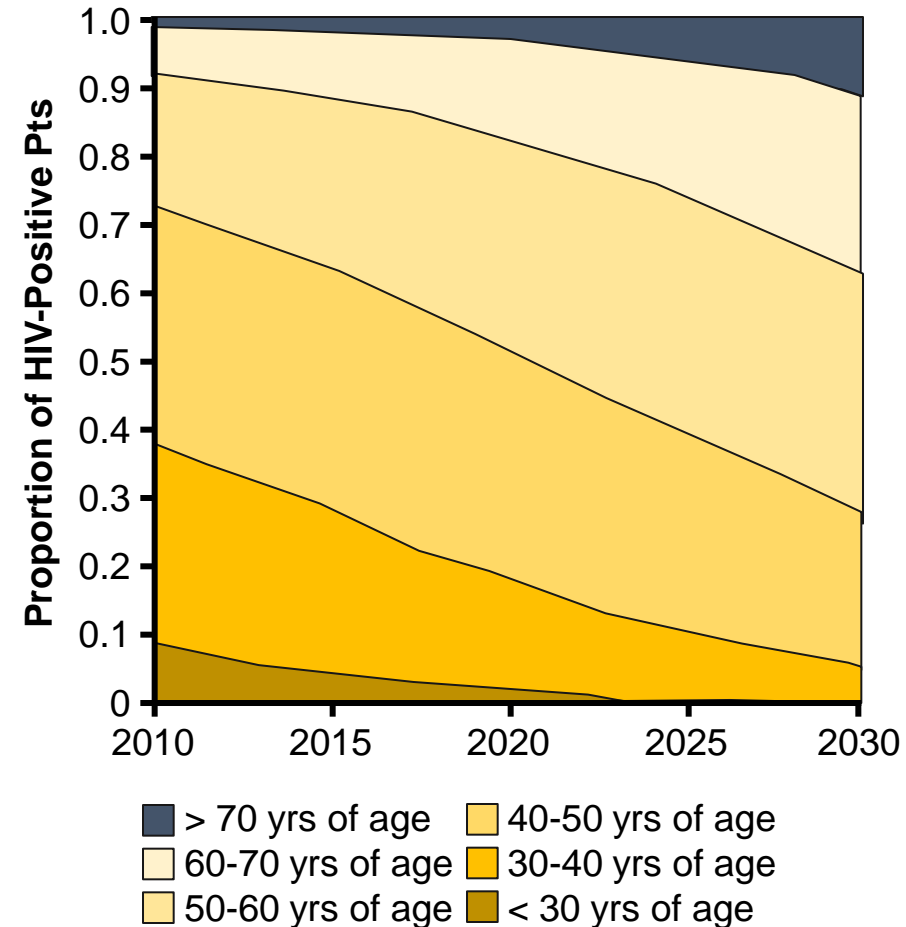**Dr DC Spencer   Right to Care Helen Joseph Hospital**
Johannesburg South Africa   April 2016

ATHENA: Older Patients Becoming More Prevalent in the HIV-Positive Population

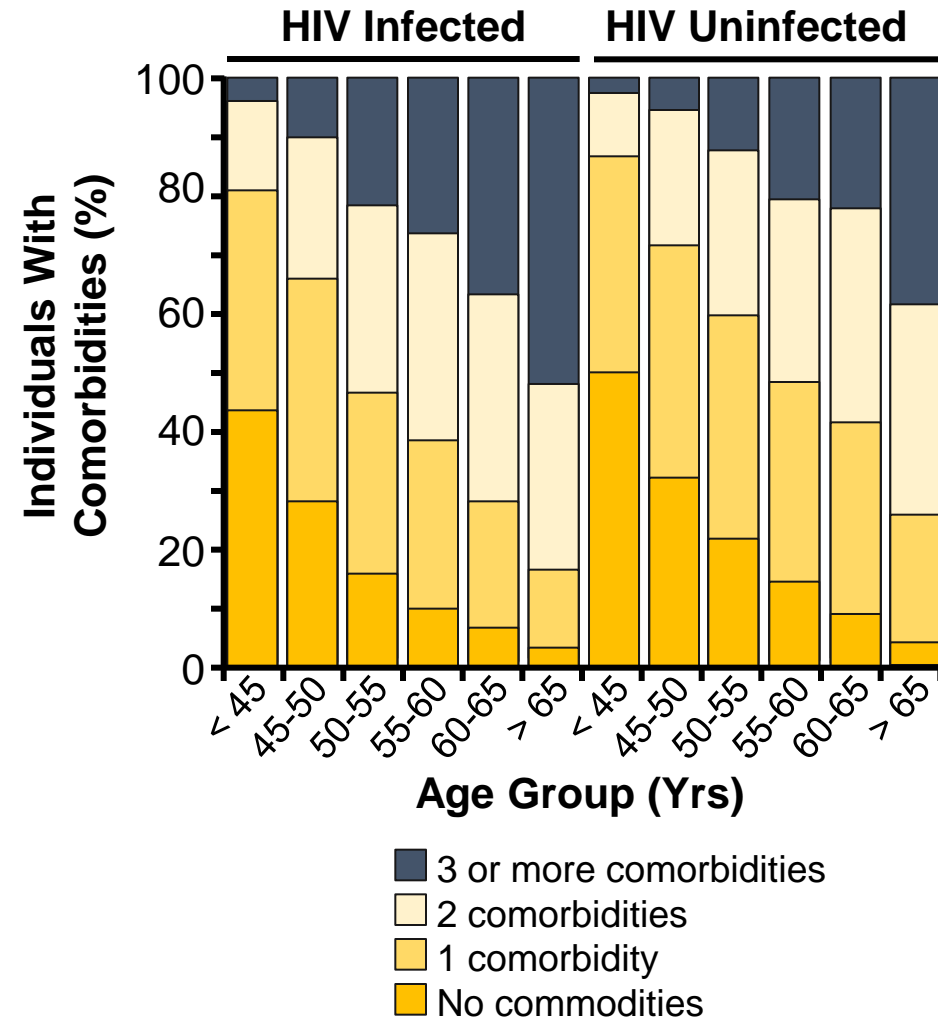- **ATHENA:** Observational cohort of 10,278 HIV-positive pts in the Netherlands

- **Modeling study projections:**

  - Proportion of HIV-positive pts ≥ 50 yrs of age to increase from 28% in 2010 to 73% in 2030

  - Median age of HIV-positive pts on combination ART to increase from 43.9 yrs in 2010 to 56.6 yrs in 2030

Proportion of HIV-Positive Pts (y-axis); years 2010–2030 (x-axis)

Legend:
- > 70 yrs of age
- 60-70 yrs of age
- 50-60 yrs of age
- 40-50 yrs of age
- 30-40 yrs of age
- < 30 yrs of age

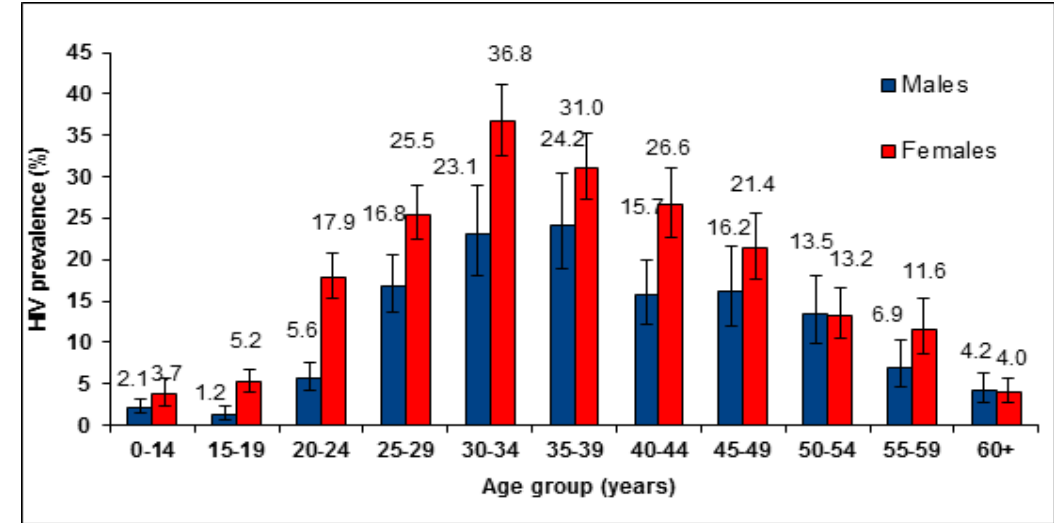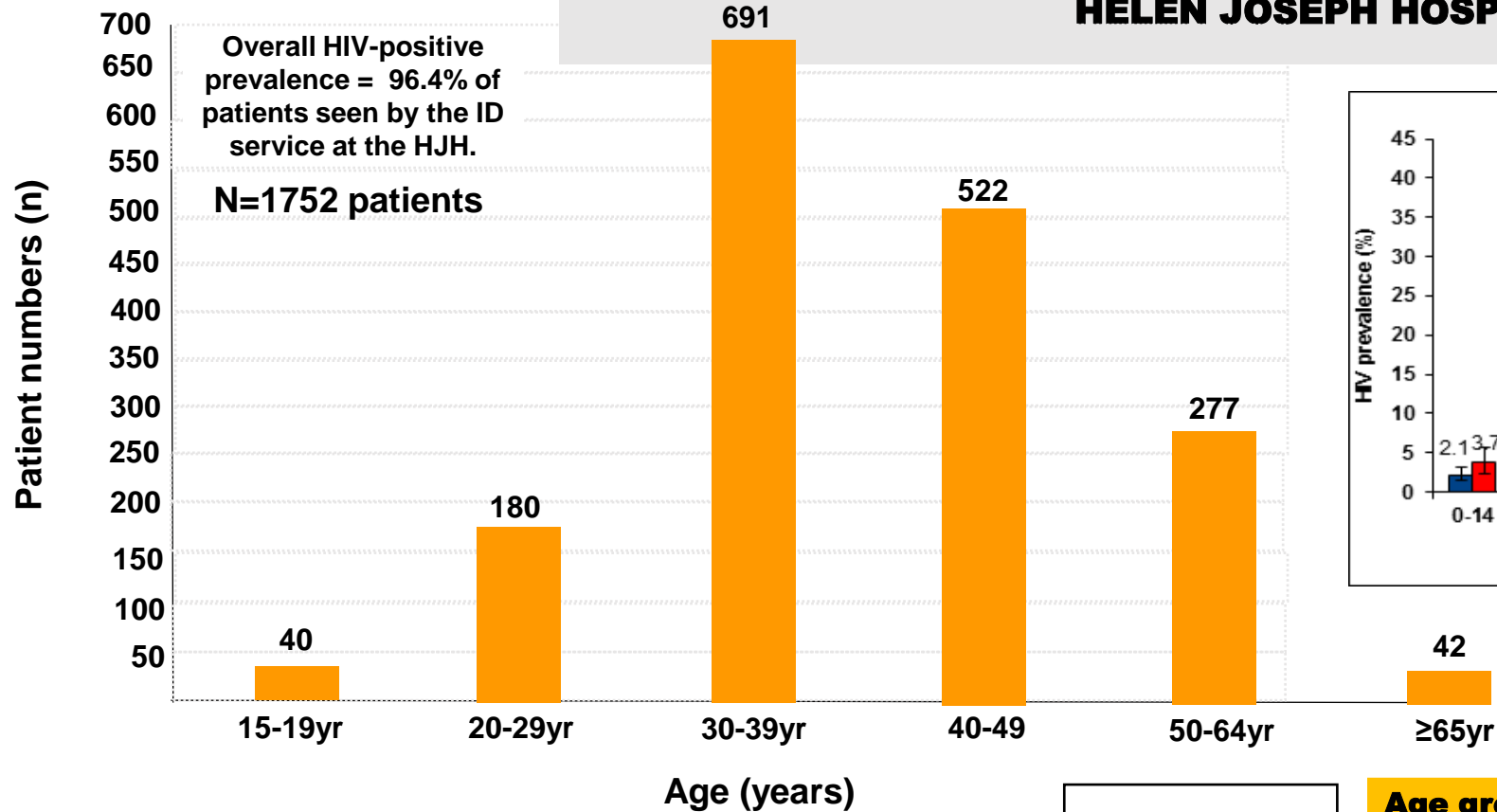Smit M, et al. Lancet Infect Dis. 2015;15:810-818.

ATHENA: Comorbidities Increase With Age and With HIV Infection

Modeling study suggests that in 2030:

- **84% of HIV+ pts will have ≥ 1 NCD**
  - Increased from 29% in 2010
  - Pts with comorbidities higher in every age group in HIV+ pts vs uninfected

- **28% of HIV+ pts will have ≥ 3 NCDs**

- **54% of HIV+ pts will be prescribed meds other than ART**
  - Increased from 13% in 2010

- **20% will take ≥ 3 meds besides ART**
  - Mostly driven by increase in CVD

Smit M, et al. Lancet Infect Dis. 2015;15:810-818.

Individuals With Comorbidities (%) vs Age Group (Yrs); HIV Infected and HIV Uninfected

Legend:
- 3 or more comorbidities
- 2 comorbidities
- 1 comorbidity
- No commodities

HIV-POSITIVE SUBJECTS REFERRED TO THE INFECTIOUS DISEASES UNIT, HELEN JOSEPH HOSPITAL, 2013-2015

Patient numbers (n) vs **Age (years)** bar chart:
- 15-19yr: 40
- 20-29yr: 180
- 30-39yr: 691
- 40-49: 522
- 50-64yr: 277
- ≥65yr: 42

Overall HIV-positive prevalence = 96.4% of patients seen by the ID service at the HJH.

N=1752 patients

Inset chart — HIV prevalence (%) by Age group (years), Males and Females:

Age group	Males	Females
0-14	2.1	3.7
15-19	1.2	5.2
20-24	5.6	17.9
25-29	16.8	25.5
30-34	23.1	36.8
35-39	24.2	31.0
40-44	15.7	26.6
45-49	16.2	21.4
50-54	13.5	13.2
55-59	6.9	11.6
60+	4.2	4.0

Whiteside A., Health Economics and HIV and AIDS Research Division (HEARD), University of KwaZulu-Natal. 2013
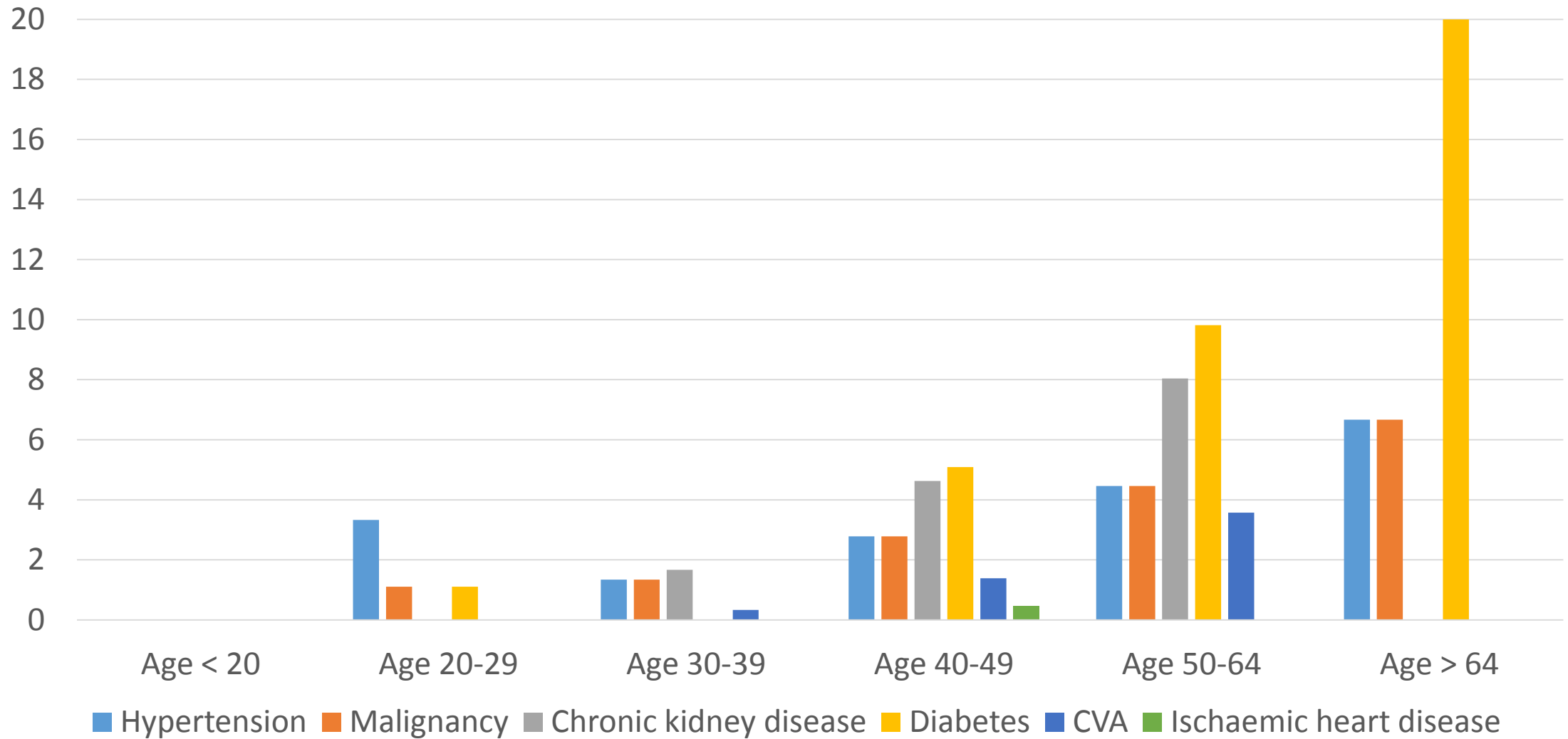
Nel J, Ive P, Spencer DC. Infectious Diseases Database ID Department. Helen Joseph Hospital, Johannesburg, SA. April 2016

Mortality in HIV+ve patients seen by the ID unit of the Helen Joseph Hospital

| Age group	Number of Deaths (n)	Deaths (%)
15-19yr	2/40	5%
20-29yr	13/180	7%
30-39yr	73/691	10.5%
40-49yr	66/522	12.6%
50-64yr	29/277	10.5
≥65yr	5/42	11.9

Comorbidities (%) in HIV-infected patients seen in the Infectious Diseases Programme, Helen Joseph Hospital, 2015

Non-infectious Comorbid Conditions as a Percentage of the Total HIV Cohort (%)

Legend: Hypertension, Malignancy, Chronic kidney disease, Diabetes, CVA, Ischaemic heart disease

X-axis: Age < 20, Age 20-29, Age 30-39, Age 40-49, Age 50-64, Age > 64

Kaiser Permanente: Life Expectancy in HIV-Infected vs Uninfected Persons

- **Analysis of life expectancy in 24,768 HIV-infected and 257,600 HIV-uninfected adult pts in Kaiser Permanente California 1996-2011; 2 groups matched for age, sex, medical center, yr**
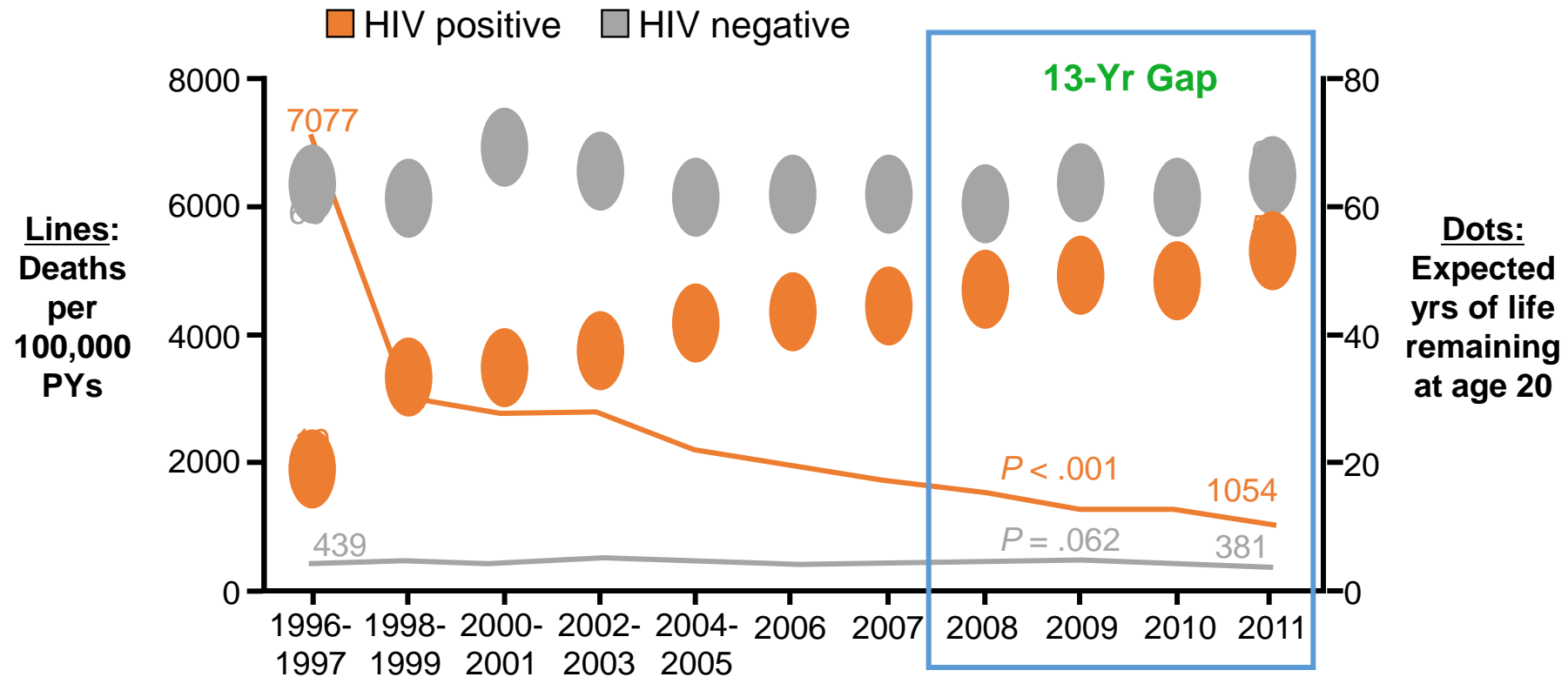
KP: Factors Contributing to Reduced Life Expectancy With HIV (2008-11)

| Factor	Expected Yrs of Life Remaining at Age 20 Yrs		
	HIV Infected and Began ART With CD4+ ≥ 500 cells/mm^3	HIV Uninfected	Difference (95% CI)
Overall	54.5	62.3	7.9 (5.1-10.6)
▪ No HBV or HCV	55.4	62.6	7.2 (4.4-10.0)
▪ No drug or alcohol abuse	57.2	63.8	6.6 (3.9-9.3)
▪ No smoking	58.9	64.3	5.4 (2.2-8.7)
▪ None of the above	59.2	65.0	5.7 (2.4-9.0)

LONG-TERM MORTALITY IN HIV-INFECTED PERSONS 50 YEARS AND OLDER

Figure. Kaplan-Meier curve of survival from 50 years of age stratified by calendar period among HIV-infected persons and population controls.

RESULTS:
Estimated median survival time from age 50 years for HIV-infected individuals increased from 11.8 yr [95%CI: 10.2-14.5] during 1996-1999 to 22.8yr [95%CI:20.0-24.2] in 2006-2014.

Mortality Rate Ratios (MRRs) fell with increasing age from 3.8 [3.1-4.7] for those 50-55yr to 1.6 [1.0-2.6] for those 75-80 years of age.

n=2440 HIV+ve
n=14,588 controls

Probability of Survival

AGE (Years)
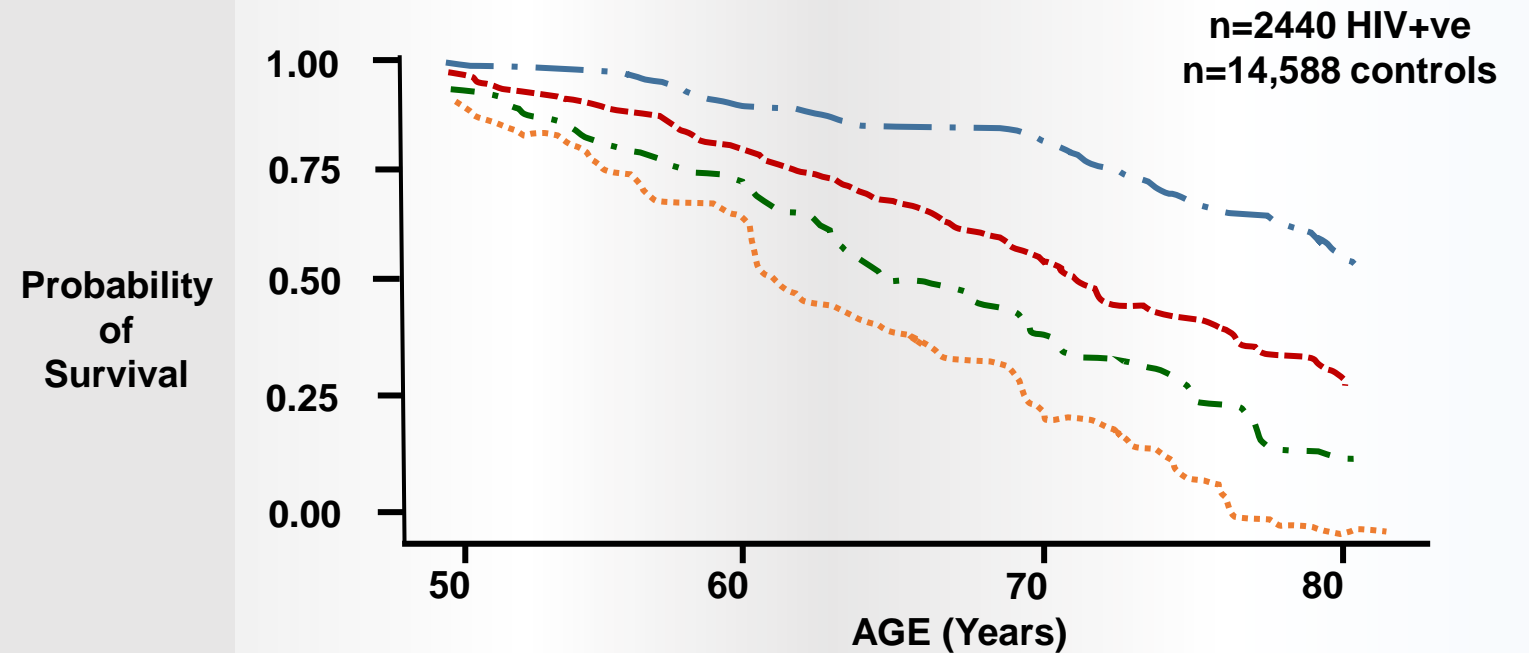
- ·········· HIV+ve observed 1996-1999
- ─·─·─ HIV+ve observed 2000-2005
- ─ ─ ─ HIV+ve observed 2006-2014
- ─··─··─ Population controls 1996-2014

Legarth RA, Ahlström MG, Kronborg G, et al. Long-term Mortality in HIV-Infected Individuals 50 Years or Older. *J Acquir Immune Defic Syndr* 2016; 71(2): 213-218

THE DANISH HIV COHORT STUDY (DHCS)

Progression to AIDS or Death Within 5 Years of ART Initiation Increases With Age

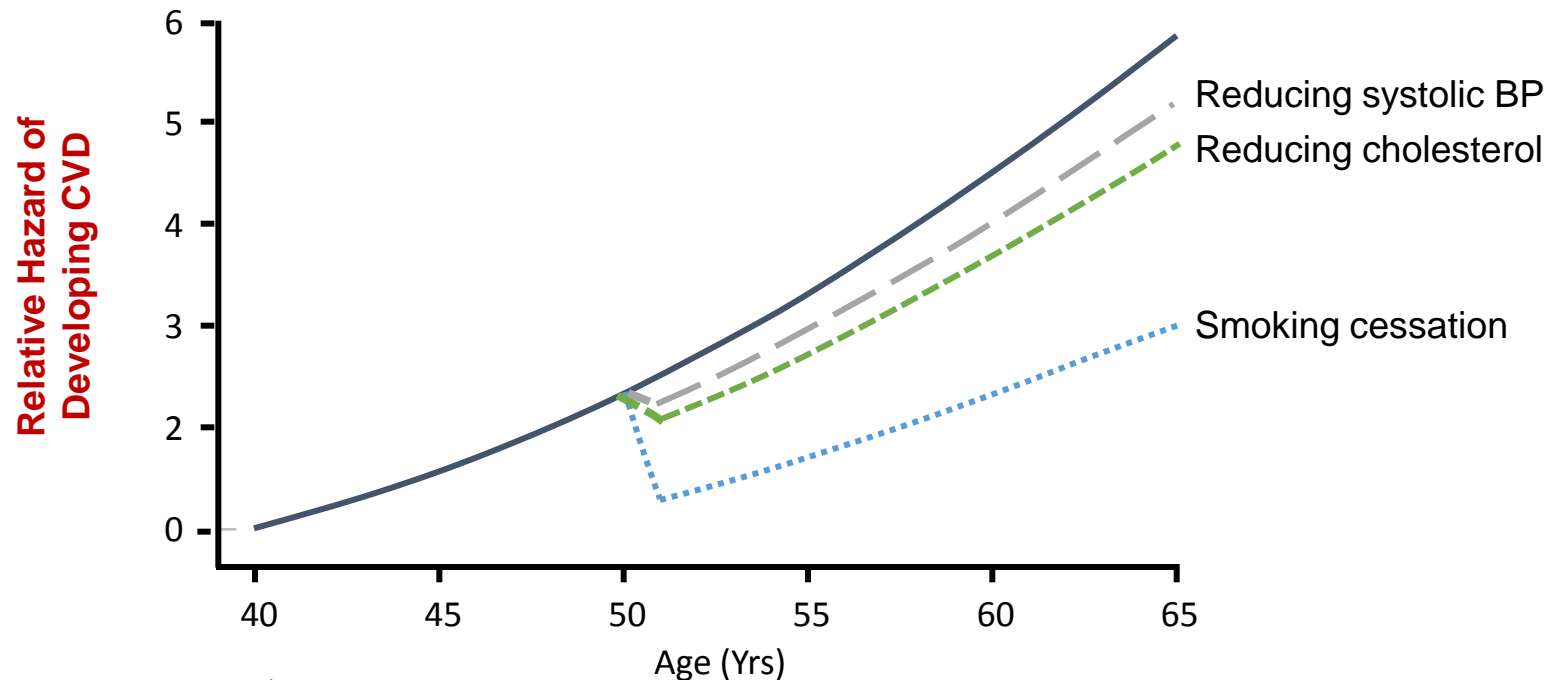- **Collaborative analysis of 12 HIV cohorts in US and Europe**
  - Assessed rates of progression to AIDS or death for pts with HIV-1 RNA ≥ 100,000 copies/mL, no previous AIDS-defining illness, and no history of injection-drug use

May M, et al. AIDS. 2007;21:1185-1197.
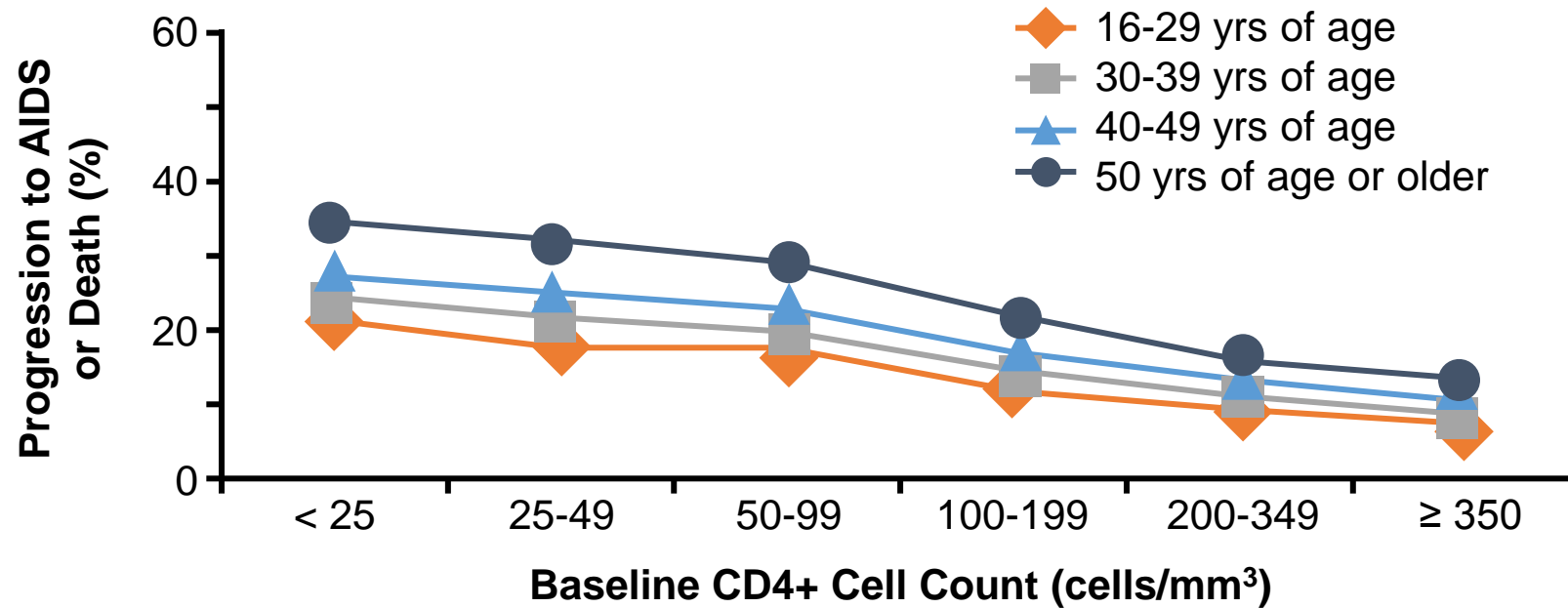
Reducing CVD Risk Factors Can Decrease Risk of CVD in Older HIV+ Patients

- Effective treatment of modifiable risk factors, such as smoking, cholesterol, and BP can significantly reduce an individual's CVD risk

Model for Change in Relative Risk of CVD From Smoking Cessation, Reducing Cholesterol,* or Reducing Systolic BP† in a Cohort of 24,323 HIV-Positive Pts Without Prior CVD (D:A:D Study)

*Reduced by 1 mmol/L. †Reduced by 10 mm Hg.

Petoumenos K, et al. HIV Med. 2014;15:595-603.

PREMATURE AGEING IN HIV PERSONS

More than ONE comorbid condition

- HIV+ve Patients
- HIV-ve controls

(Estimated probability vs AGE)

Factors significantly associated with poly-pathology in HIV patients were

Age: per year increase, OR 1.11, 95%CI, 1.10-1.12

Male sex: OR 1.77, 95% CI, 1.44-2.17, P<.001

Nadir CD4 count <200, OR 4.46, 95%CI, 3.73-5.34, P<.001

Exposure to ART, per mth of exposure, OR, 1.01, 95% CI, 1.001-1.019, P=.001

Effect on age

(Age difference vs Estimated probability)

Expected age difference between patients (HIV+ve) and control subjects (HIV-ve) at which poly-pathology would be observed across a spectrum of odds ratios for Pp.

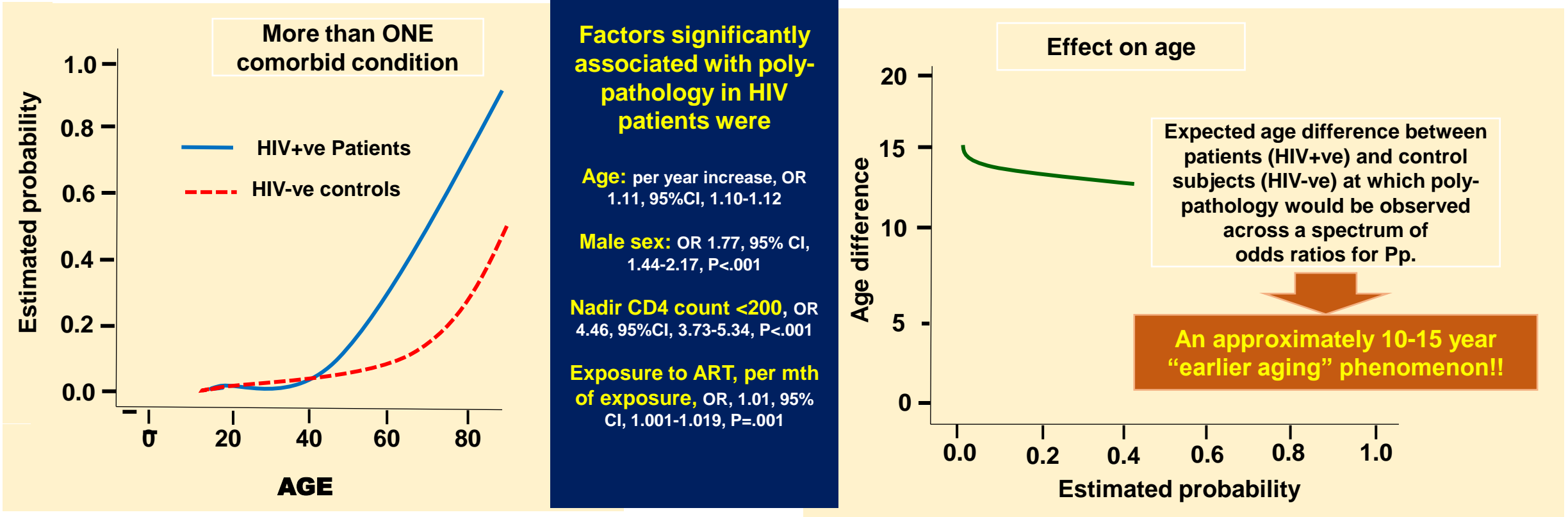**An approximately 10-15 year "earlier aging" phenomenon!!**

Figure. The risk (probability) of poly-pathology (Pp) by age
– as a continuous variable – for HIV+ve patients and uninfected controls in the cohort.

Case-control study n=2854 patients, n=8562 control subjects
Modena University, Italy. 2002-2009. Age = 46yr (Mean)
Conclusion: Specific age-related non-infectious comorbidities and poly-pathologies were more common among HIV+ve group.

Guaraldi G, Orlando G, Zona S, et al. Premature Age-Related Comorbidities Among HIV-Infected Persons Compared With the General Population. *Clin Infect Dis* 2011; 53(11): 1120-6

HIV+ve subjects

HIV-ve controls

Guaraldi G, Orlando G, Zona S, et al. Premature Age-Related Comorbidities Among HIV-Infected Persons Compared With the General Population. *Clin Infect Dis* 2011; 53(11): 1120-6
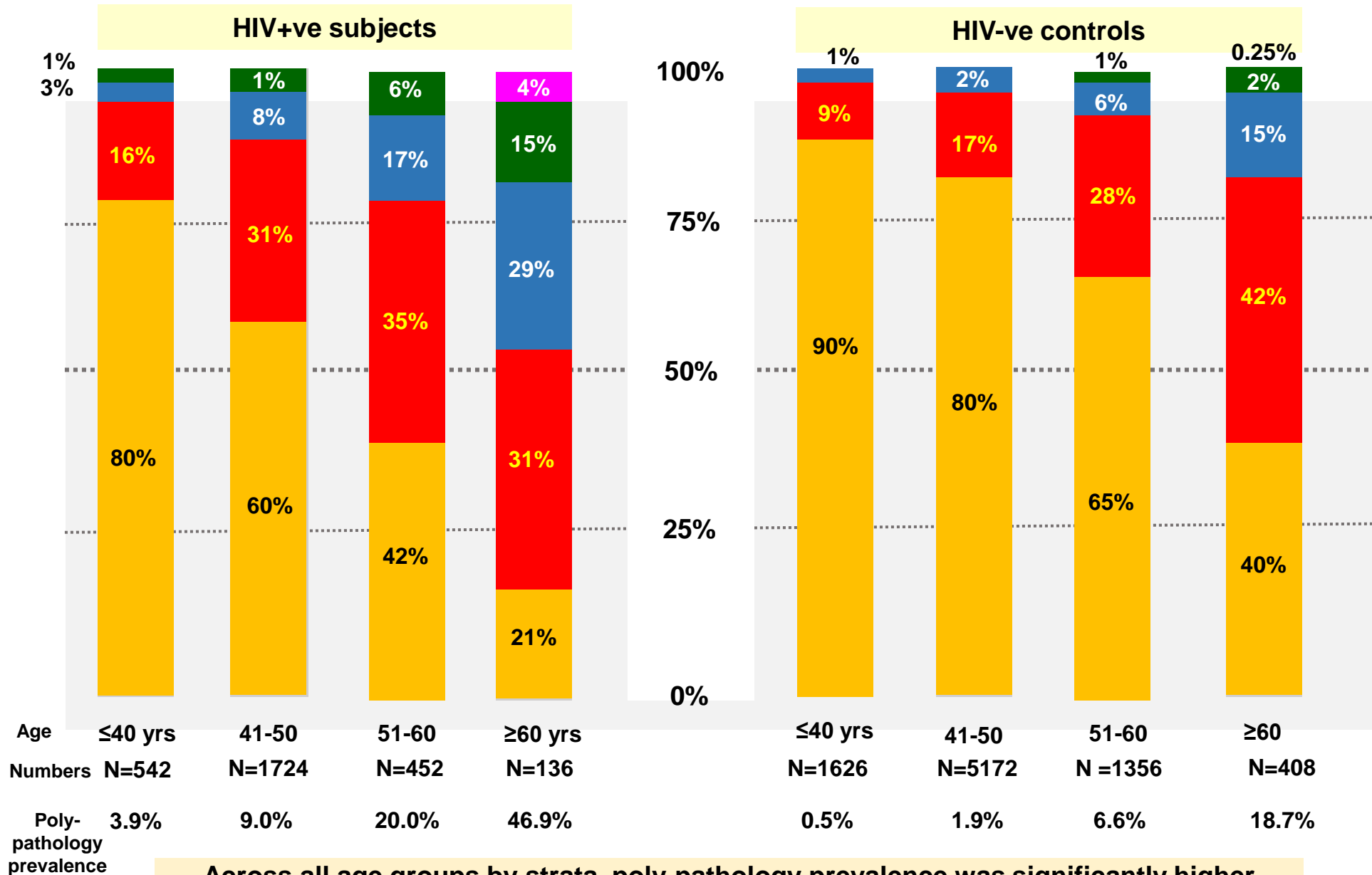
Legend

- No age-related comorbidity
- One comorbidity
- Two comorbidities
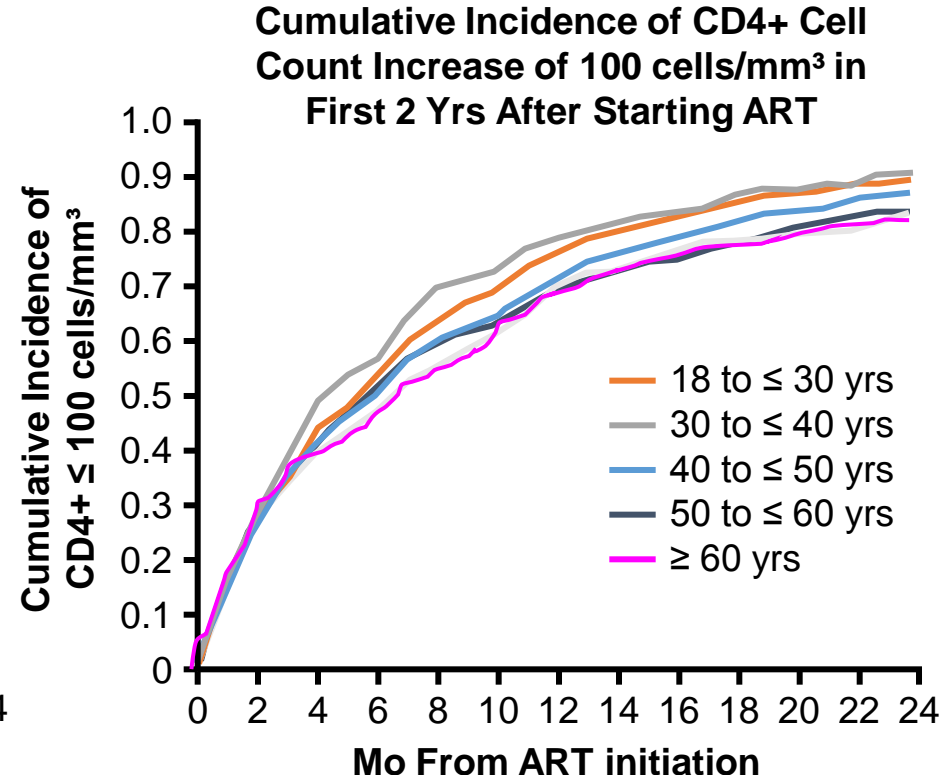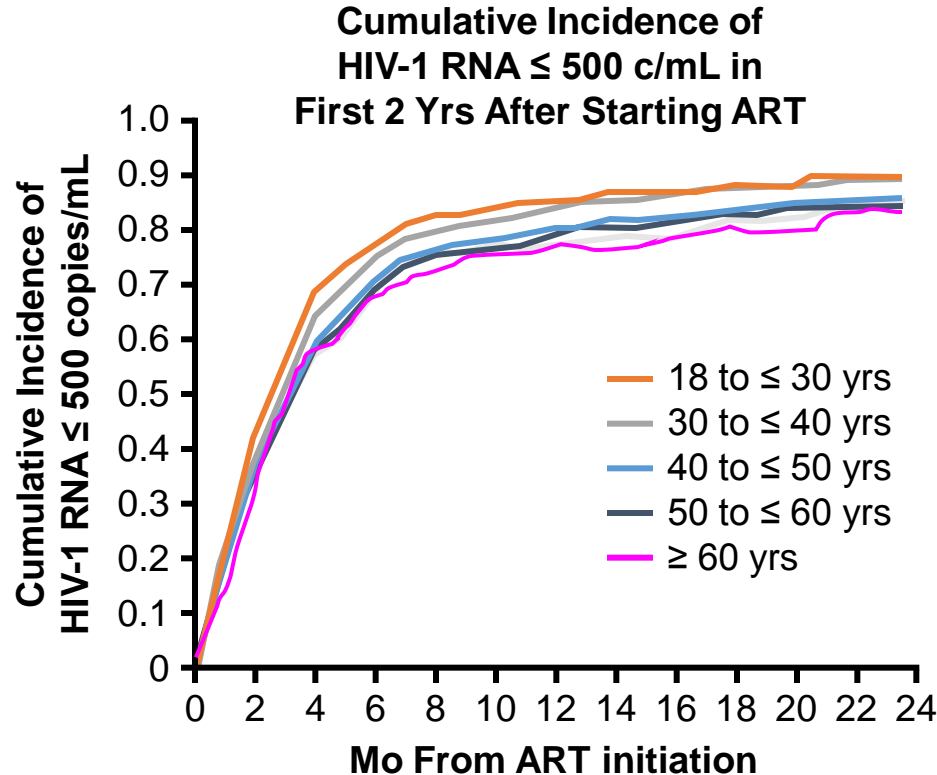- Three comorbidities
- Four comorbidities

Comorbidities assessed in this Study

- Cardiovascular
- Hypertension
- Renal disease
- Bone fractures
- Diabetes Mellitus Type II

	HIV+ve subjects				HIV-ve controls			
Age	≤40 yrs	41-50	51-60	≥60 yrs	≤40 yrs	41-50	51-60	≥60
Numbers	N=542	N=1724	N=452	N=136	N=1626	N=5172	N =1356	N=408
Poly-pathology prevalence	3.9%	9.0%	20.0%	46.9%	0.5%	1.9%	6.6%	18.7%

Across all age groups by strata, poly-pathology prevalence was significantly higher among patients (HIV+ve), compared with uninfected controls, *P*<.001.

NA-ACCORD: Immunologic but Not Virologic Response Decreased in Older Pts

- Analysis of pts who received initial ART with a boosted PI or NNRTI-based regimen in 19 cohort studies (NA-ACCORD; N = 12,196)
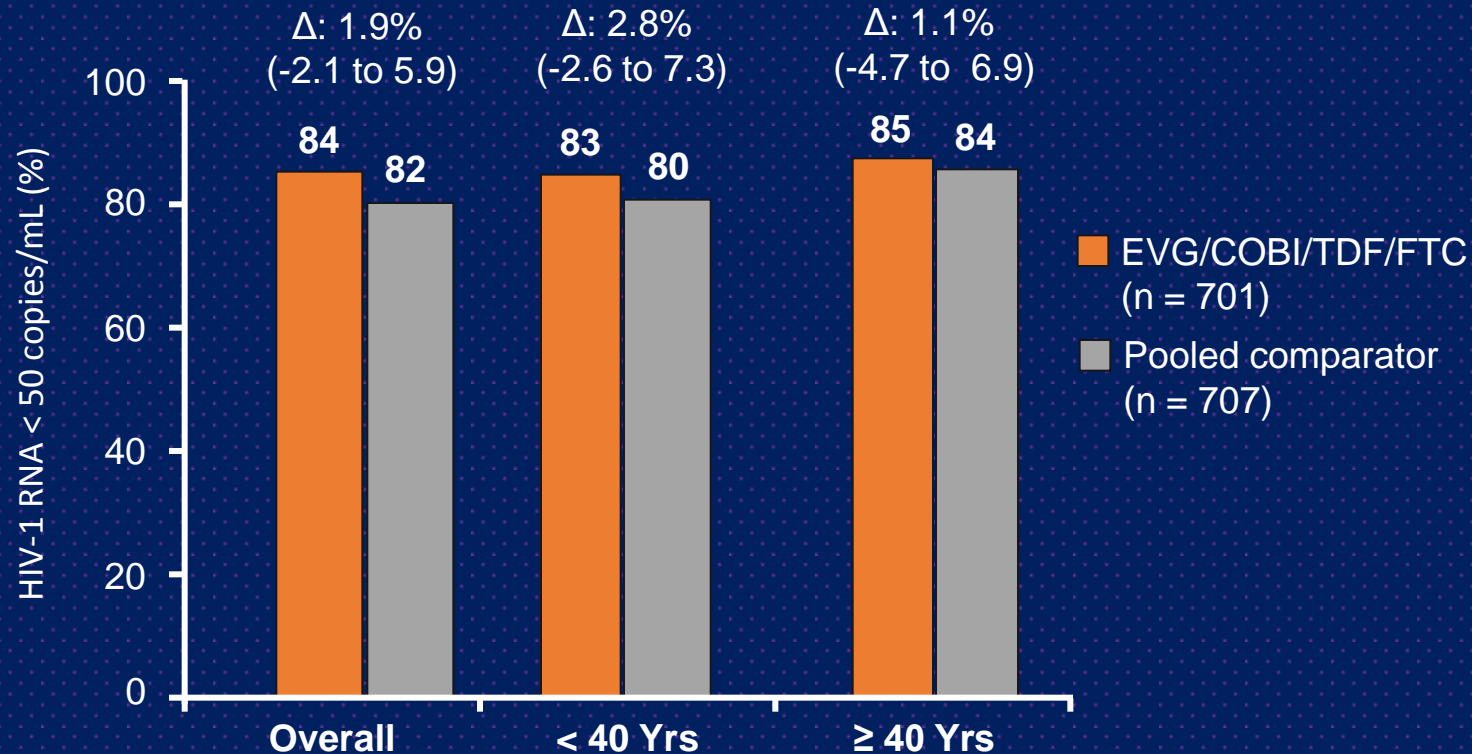
Viral load

Cumulative Incidence of HIV-1 RNA ≤ 500 c/mL in First 2 Yrs After Starting ART

Cumulative Incidence of HIV-1 RNA ≤ 500 copies/mL

Mo From ART initiation

- 18 to ≤ 30 yrs
- 30 to ≤ 40 yrs
- 40 to ≤ 50 yrs
- 50 to ≤ 60 yrs
- ≥ 60 yrs

Cumulative Incidence of CD4+ Cell Count Increase of 100 cells/mm³ in First 2 Yrs After Starting ART

Cumulative Incidence of CD4+ ≤ 100 cells/mm³

Mo From ART initiation

- 18 to ≤ 30 yrs
- 30 to ≤ 40 yrs
- 40 to ≤ 50 yrs
- 50 to ≤ 60 yrs
- ≥ 60 yrs

CD4 response

Althoff KN, et al. AIDS. 2010;24:2469-2479.

EVG/COBI/TDF/FTC: Pooled 96-Wk Efficacy by Age

- **Analysis of 96-wk subgroup efficacy data from 2 randomized, double blind, active-controlled phase III studies**

RANDOMIZED CONTROLLED CLINICAL STUDIES

Age does not appear to influence the response to ART

Δ: 1.9%
(-2.1 to 5.9)

Δ: 2.8%
(-2.6 to 7.3)

Δ: 1.1%
(-4.7 to 6.9)

HIV-1 RNA < 50 copies/mL (%)

84 82 — Overall
83 80 — < 40 Yrs
85 84 — ≥ 40 Yrs

- EVG/COBI/TDF/FTC (n = 701)
- Pooled comparator (n = 707)
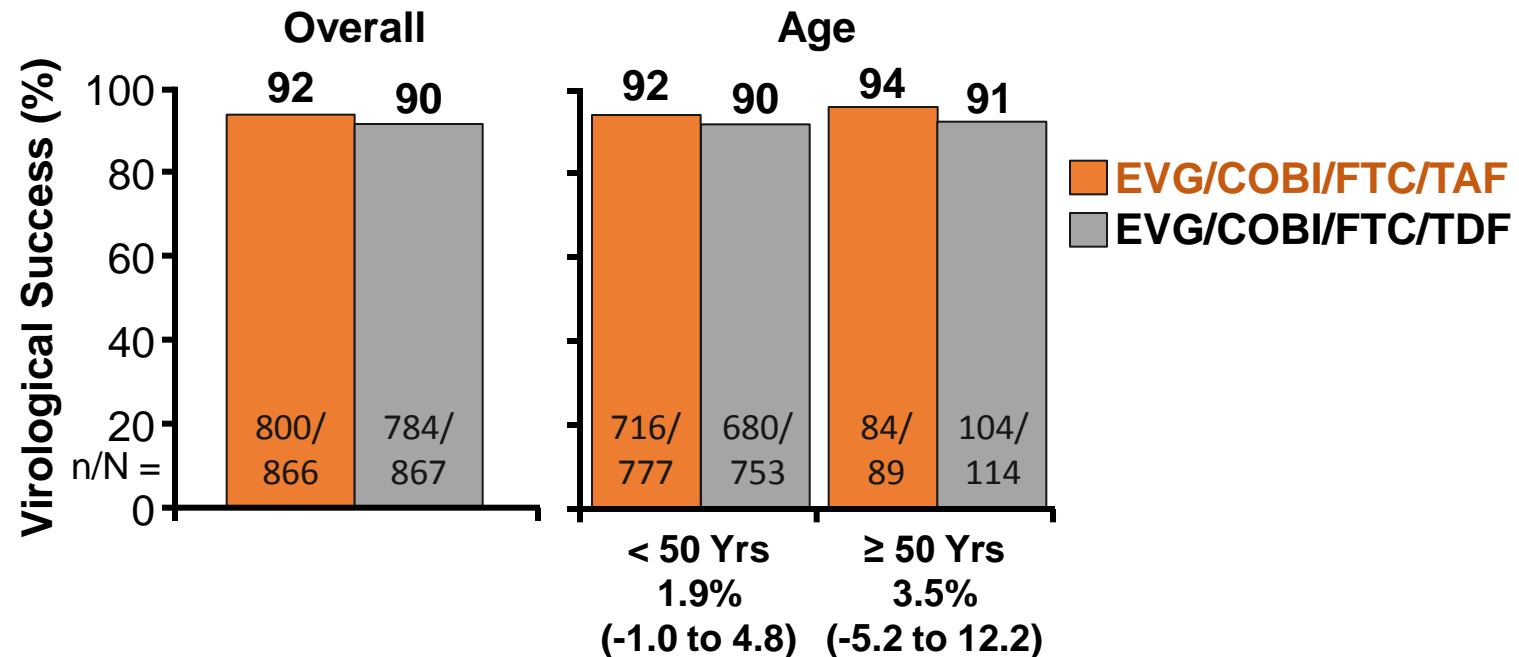
Cooper D, et al. IAS 2013. Abstract TUPE281.

TAF vs TDF + EVG/COBI/FTC: Efficacy in Older Pts

- GS-US-292-0104/0111:

- Phase III trials in which treatment-naive pts, HIV-infected pts with estimated creatinine clearance of ≥ 50 mL/min were randomized to TAF (n = 866) or TDF (n = 867) coformulated with EVG/COBI/FTC
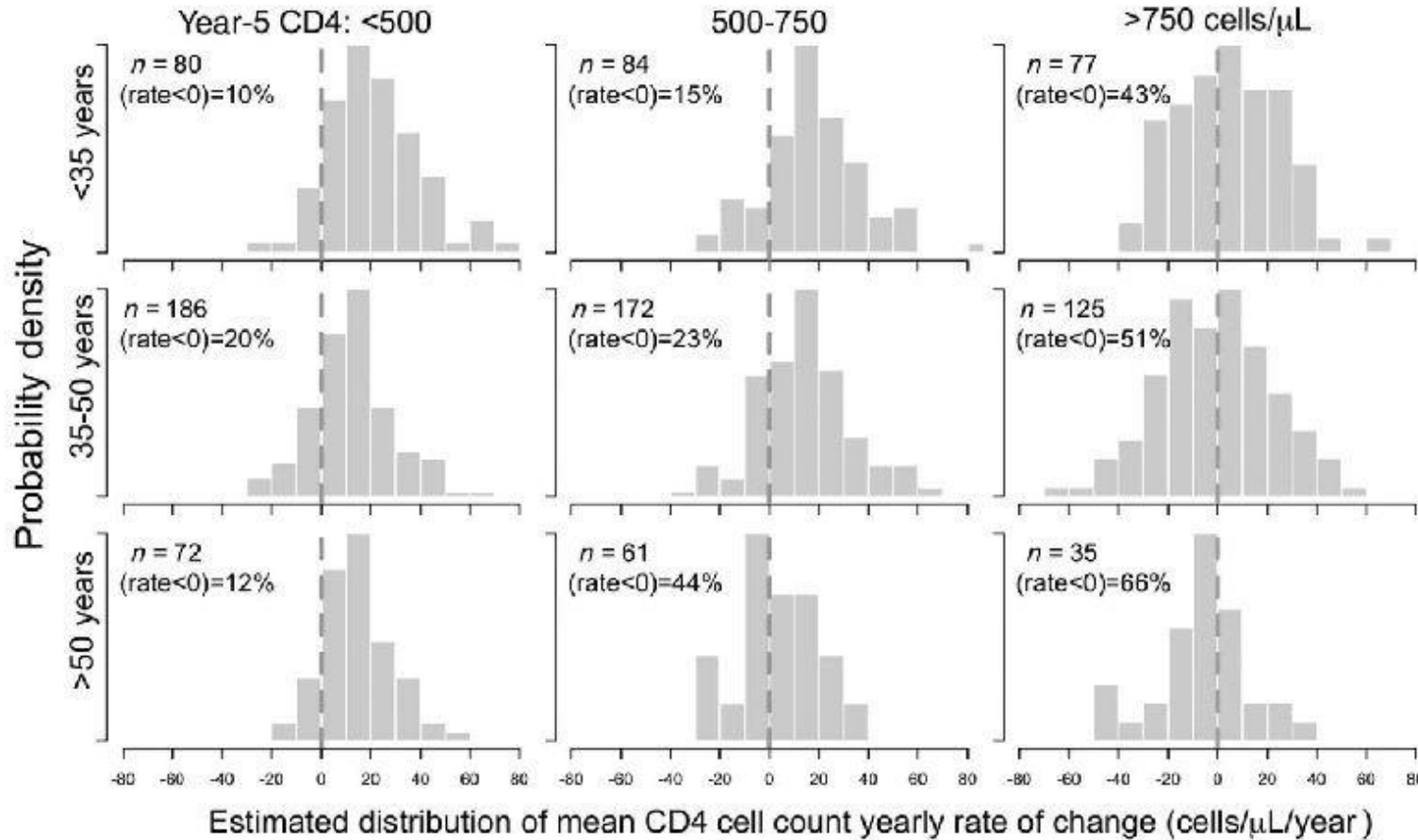
RANDOMIZED CONTROLLED CLINICAL STUDIES

Age does not appear to influence the response to ART

Overall / Age

Virological Success (%)

	Overall			Age	
Value	92	90	92	90	94	91
n/N =	800/866	784/867	716/777	680/753	84/89	104/114

EVG/COBI/FTC/TAF
EVG/COBI/FTC/TDF

< 50 Yrs
1.9%
(-1.0 to 4.8)

≥ 50 Yrs
3.5%
(-5.2 to 12.2)

*HIV-1 RNA < 50 copies/mL as defined by FDA Snapshot algorithm.

Sax P, et al. Lancet. 2015;385:2606-2615.

Year-5 CD4: <500   500-750   >750 cells/μL

Probability density

<35 years
n = 80 (rate<0)=10%
n = 84 (rate<0)=15%
n = 77 (rate<0)=43%

35-50 years
n = 186 (rate<0)=20%
n = 172 (rate<0)=23%
n = 125 (rate<0)=51%

>50 years
n = 72 (rate<0)=12%
n = 61 (rate<0)=44%
n = 35 (rate<0)=66%

Estimated distribution of mean CD4 cell count yearly rate of change (cells/μL/year)

Medscape   Source: HIV Med © 2013 Blackwell Publishing

AUSTRALIAN HIV OBSERVATIONAL DATABASE

Estimated the mean CD4 cell count changes following the completion of 5 years of cART.

N=892 patients

Of the CD4 cell count rates of change estimated, none was indicative of long term declines in CD4 cell counts

Of the yearly rates of change estimated for each level of the year-5 count and age interaction, none was found to be indicative of decreasing mean CD4 cell count change, even for the older patients who were aged up to 60 to 70 years. Nonetheless it is clear that some patients ARE experiencing declines in mean CD4 count over time viz. Stratum >750 CD4 and age >50yr.

The authors of the MACs study (below) indicate that equivalent patients differing only by age after 5-12 years of ART had significantly different long-term immunological outcomes.

Specifically older patients would need to initiate cART with a baseline CD4 count higher than younger patients to achieve the same levels of immunological reconstitution at 5-12 years on cART. This suggests that older HIV+ve patients experience smaller rates of change in their CD4 counts per year.
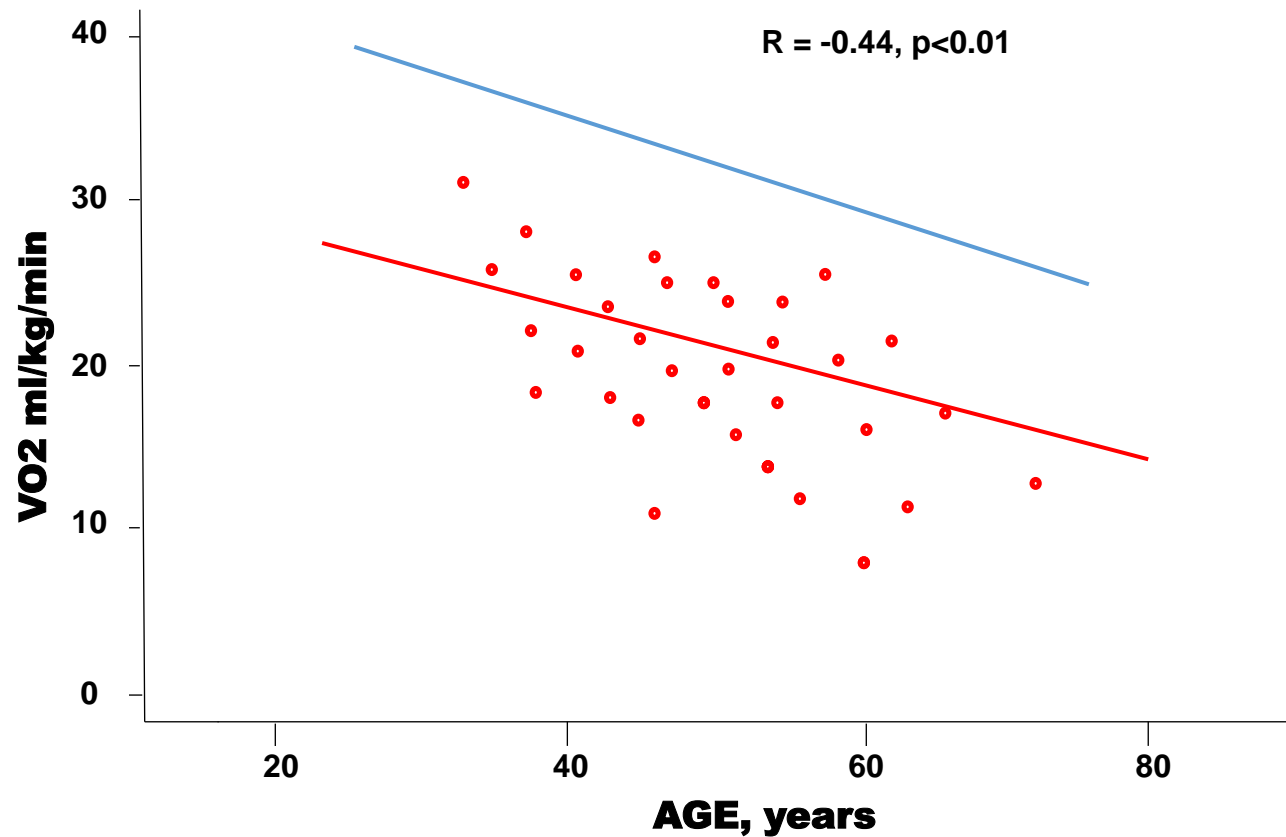
Li X, Margolick JB, Jamieson BD, et al. CD4 cell counts and plasma HIV-1 RNA levels beyond 5 years of highly active antiretroviral therapy.
J Acquir Immune Defic Syndr 2011; 57: 421-428

Figure. Reductions in aerobic capacity (VO2) in HIV-infected patients aged 30-80 years. Data on healthy subjects are shown in blue and data on HIV-infected patients are shown in red.
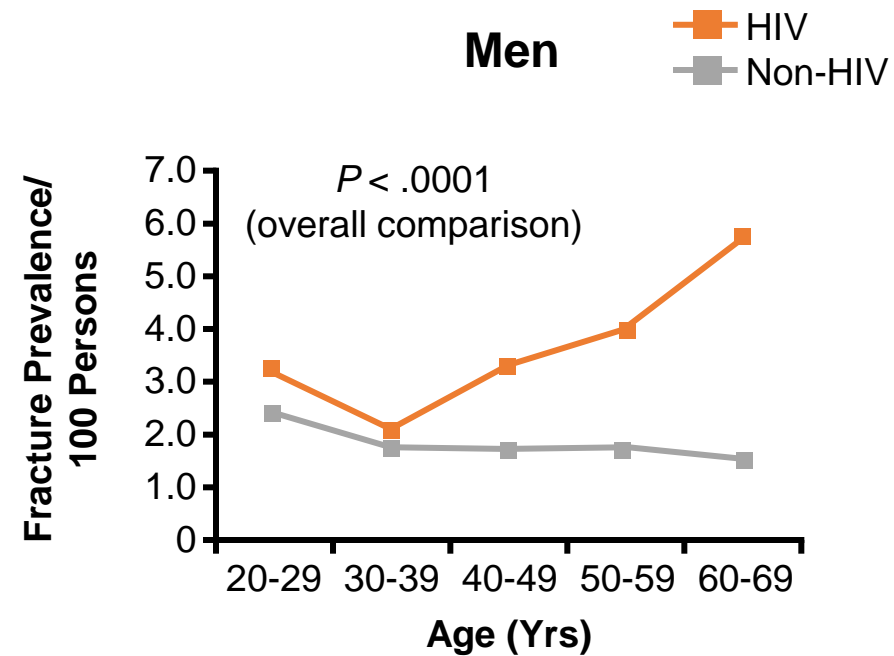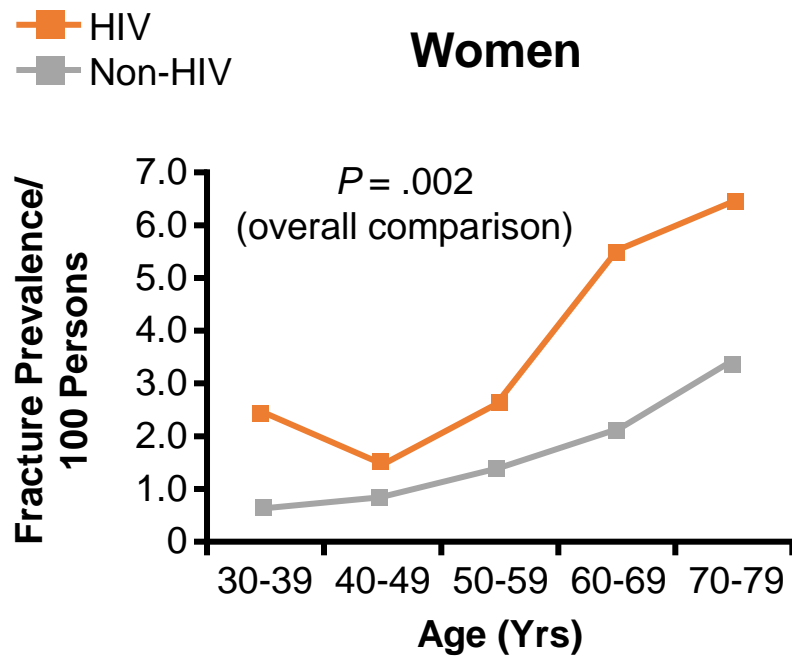
Despite receiving antiretroviral therapy middle-aged HIV infected men show **reductions** in exercise capacity, functional performance, physical activity and grip strength.

Oursler KK, Sorkin JD, Smith BA, Katzel LI. Reduced aerobic capacity and physical functioning in older HIV-infected men. *AIDS Res Hum Retroviruses* 2006; 22: 1113-21
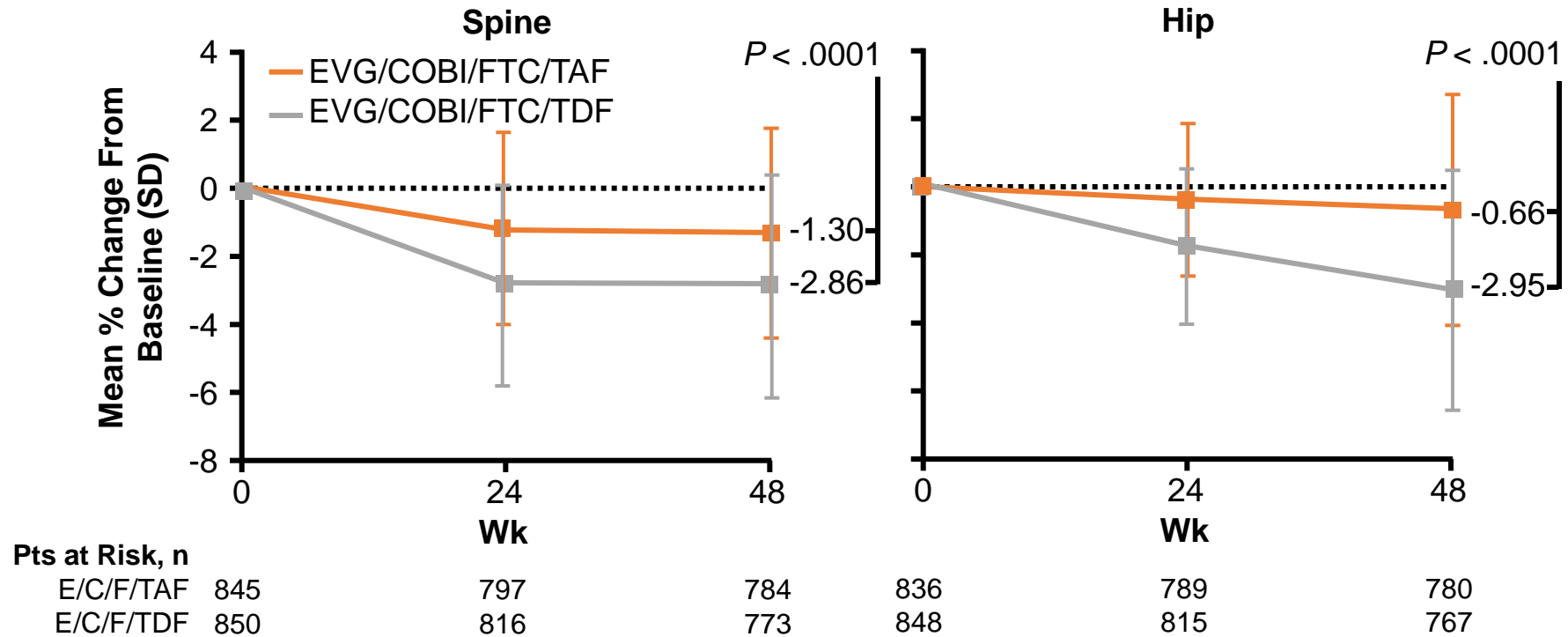
FRAILTY AND THE AGEING HIV POPULATION

Fracture Prevalence Is Increased in Older HIV-Positive Pts

- 8525 HIV-infected pts compared with 2,208,792 uninfected pts in Partners HealthCare System

Triant V, et al. *J Clin Endocrinol Metab*. 2008;93:3499-3504.

TAF vs TDF + EVG/COBI/FTC:
Changes in BMD (GS-US-292-0104/0111)

Spine

EVG/COBI/FTC/TAF
EVG/COBI/FTC/TDF

P < .0001

-1.30
-2.86

Mean % Change From Baseline (SD)

Hip

P < .0001

-0.66
-2.95

Wk

| Pts at Risk, n						
E/C/F/TAF	845	797	784	836	789	780
E/C/F/TDF	850	816	773	848	815	767

- **TAF treatment was associated with smaller BMD loss than TDF treatment**

Sax P, et al. Lancet. 2015;385:2606-2615.

START Sub-study: BMD Changes With Immediate vs Deferred ART Over 3 Yrs

- Sub-study included 193 pts in early ART arm and 204 pts in deferred ART arm with f/u

- Greater BMD loss in hip and spine with immediate vs deferred ART

  - Estimated mean difference for hip: -1.5% (95% CI: -2.3% to -0.8%; *P* < .001)

  - Estimated mean difference for spine: -1.6% (95% CI: -2.2% to -1.0%; *P* < .001)

- Osteoporosis incidence similar between arms (*P* = .27)

Hoy JF, et al. EACS 2015. Abstract ADRLH-62. Reproduced with permission.
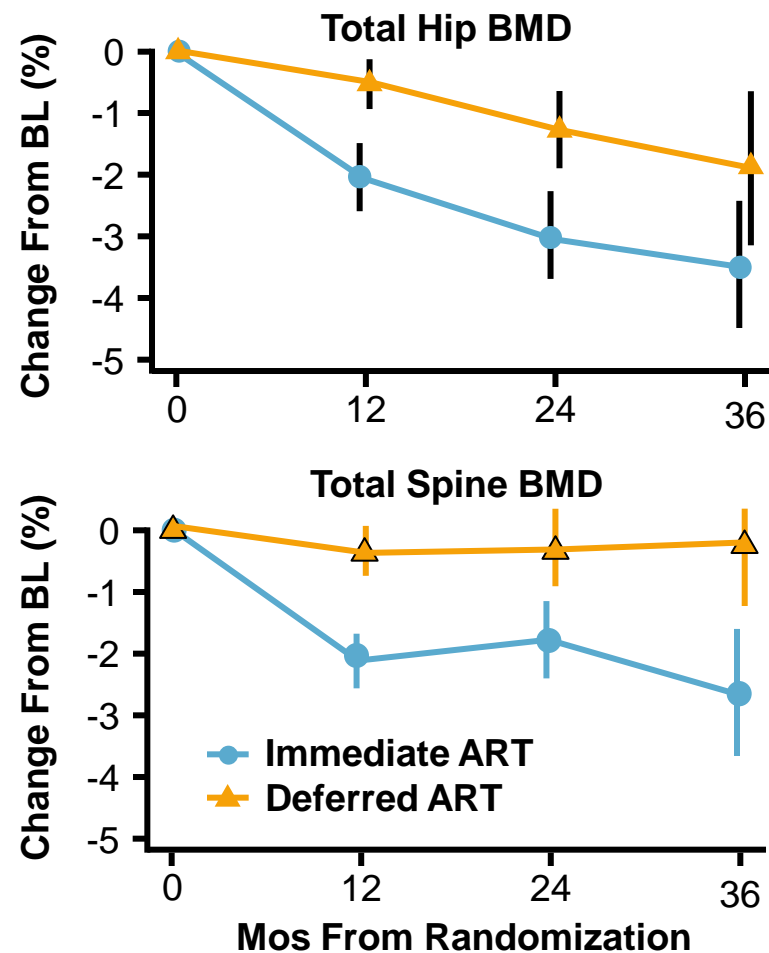
NRTI-Sparing or NRTI-Limiting Regimens

Regimen	Results
DRV/RTV + RAL (ACTG 5262)[1]	Poor performance at high VL
DRV/RTV + RAL (NEAT)[2]	**Less effective at high VL, low CD4**
DRV/RTV + 3TC (switch study)[3]	Small study; encouraging efficacy
DRV/RTV + MVC (MODERN)[4]	
ATV/RTV + RAL (HARNESS – switch)[5]	Less effective than standard ART
LPV/RTV + RAL (PROGRESS)[6]	**Small study; few pts with high VL**
LPV/RTV + EFV (ACTG 5142)[7]	Poorly tolerated but effective
LPV/RTV + 3TC (GARDEL)[8]	**As effective as standard ART**
LPV/RTV + 3TC or FTC (OLE – switch)[9]	As effective as standard ART
ATV/RTV + 3TC (SALT – switch)[10]	**As effective as standard ART**

1. Taiwo B, et al. AIDS. 2011;25:2113-2122. 2. Raffi, et al. CROI 2014. Abstract 84LB. 3. Casado JL, et al. J Antimicrob Chemother. 2015;70:630-632 4. Stellbrink HJ, et al. IAS 2014. Abstract MOAB0101. 5. Van Lunzen J, et al. IAC 2014. Abstract A-641-0126-11307. 6. Reynes J, et al. AIDS Res Hum Retroviruses. 2013;29:256-265. 7. Daar ES, et al. Ann Intern Med. 2011;154:445-456. 8. Cahn P, et al. Lancet Infect Dis. 2014;14:572-580. 9. Gatell J, et al. AIDS 2014. Abstract LBPE17. 10. Perez-Molina JA, et al. IAC 2014. Abstract LBPE18.

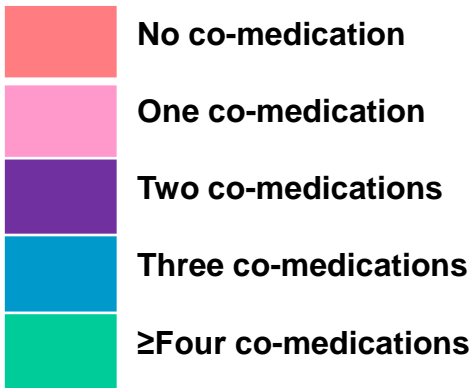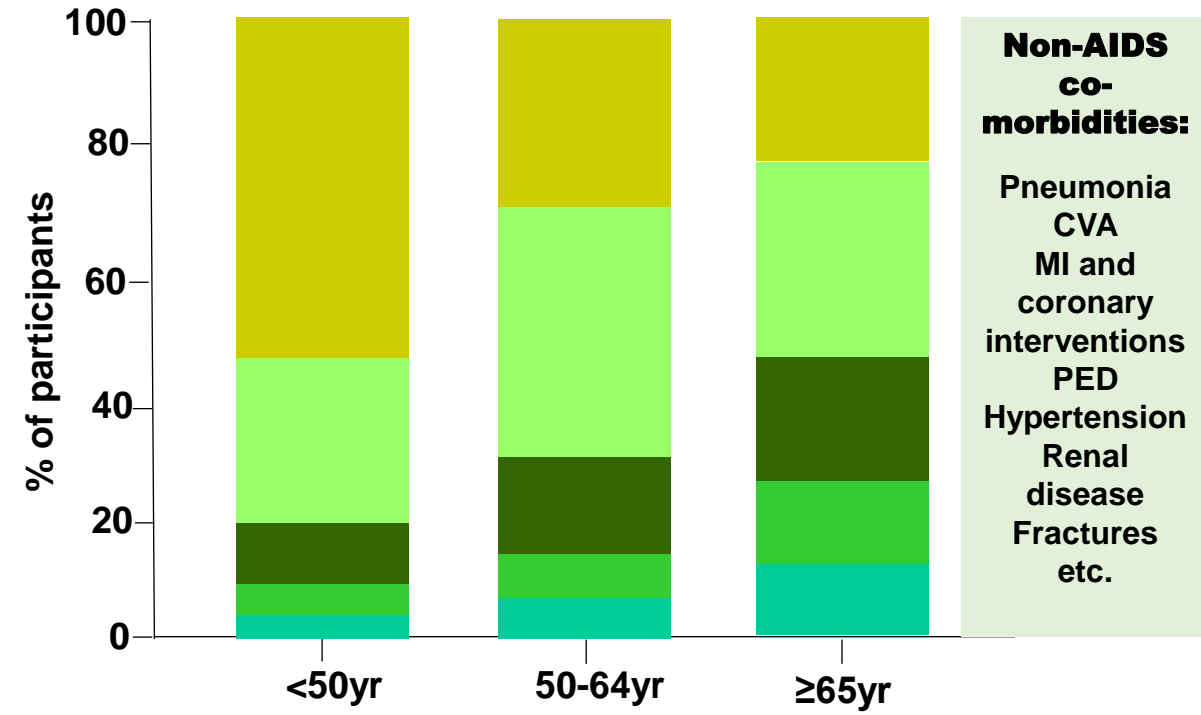# ART Considerations for Pts With Bone Complications

- **DHHS considerations:**

  - Consider avoiding TDF: associated with greater decrease in BMD along with renal tubulopathy, urine phosphate wasting, and osteomalacea

  - Consider ABC/3TC

- **Significantly greater BMD loss with PI-based regimens vs RAL-based regimens**

- **DTG + ABC/3TC associated with less bone turnover than EFV/TDF/FTC**

Practical Challenges With ART
Use in Older Patients

- **Comorbidities**

- **Poly-pharmacy**
  - DDI, dosing, adherence challenges

- **Renal or hepatic impairment**
  - Alterations in pharmacokinetics, potential for drug toxicity

- **Challenges with single-tablet regimens**
  - Inability to alter single component dosing (ie, ABC or TDF) as needed

Non-HIV medications:

Antihypertensives
Lipid-lowering agents
Anti-diabetic agents
Insulin
Anti-platelet agents
Anti-depressants

Non-AIDS co-morbidities:

Pneumonia
CVA
MI and coronary interventions
PED
Hypertension
Renal disease
Fractures
etc.

No co-medication
One co-medication
Two co-medications
Three co-medications
≥Four co-medications

No co-morbid condition
One co-morbid condition
Two co-morbid conditions
Three co-morbid conditions
≥Four co-morbid conditions
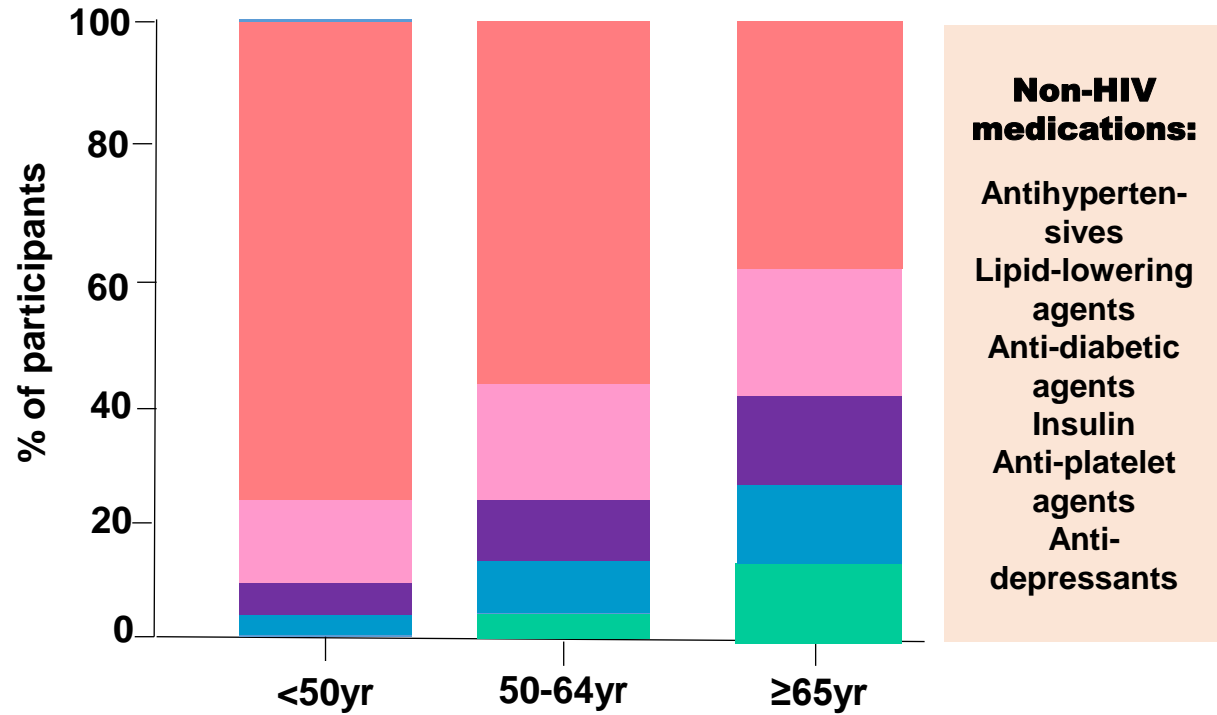
Older patients were more frequently taking ART, had more frequently suppressed viral loads, and were more frequently taking non-ART co-medication.
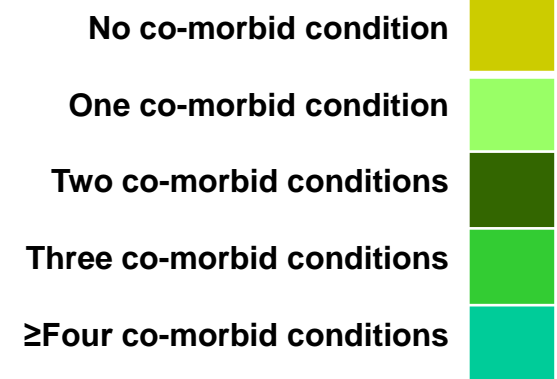
Additional Drug–Drug Interactions With ART

	ATV/R TV	DRV/RTV	EFV	RPV	DTG	EVG/COBI	RAL	ABC	FTC	3TC	TDF
Antacids	■	■	■	■	■	■	■	■	■	■	■
PPIs	■	■	■	■	■	■	■	■	■	■	■
Alfuzosin	■	■	■	■	■	■	■	■	■	■	■
Budesonide	■	■	■	■	■	■	■	■	■	■	■
Fluticasone	■	■	■	■	■	■	■	■	■	■	■
Slidenafil	■	■	■	■	■	■	■	■	■	■	■
St John's wort	■	■	■	■	■	■	■	■	■	■	■
Escitalopram	■	■	■	■	■	■	■	■	■	■	■
Aspirin	■	■	■	■	■	■	■	■	■	■	■
Ibuprofen	■	■	■	■	■	■	■	■	■	■	■
Codeine	■	■	■	■	■	■	■	■	■	■	■
Methadone	■	■	■	■	■	■	■	■	■	■	■
Morphine	■	■	■	■	■	■	■	■	■	■	■
Oxycodone	■	■	■	■	■	■	■	■	■	■	■
Tramadol	■	■	■	■	■	■	■	■	■	■	■
Diazepam	■	■	■	■	■	■	■	■	■	■	■
Midazolam	■	■	■	■	■	■	■	■	■	■	■
Pimozide	■	■	■	■	■	■	■	■	■	■	■
Phenytoin	■	■	■	■	■	■	■	■	■	■	■
Rifampicin	■	■	■	■	■	■	■	■	■	■	■

Legend:
- **Orange** — No clinically significant interaction expected
- **Grey** — These drugs should not be co-administered
- **Light blue** — Potential interaction that may require a dosage adjustment
- **Dark blue** — Potential interaction predicted to be of weak intensity

EACS Guidelines. V7.1. November 2014.

Drug–Drug Interactions With ART and Diabetes and Lipid-Lowering Therapy

Antiretroviral	Contraindicated	Titrate Dose	No Dose Adjustment
RPV[1]			Atorvastatin Pitavastatin
EVG/COBI/FTC/	Lovastatin Simvastatin	Atorvastatin Rosuvastatin	
DTG[1,2]		Metformin	
ATV/RTV[1]	Lovastatin Simvastatin	Atorvastatin Rosuvastatin	Pitavastatin
DRV/RTV[1]	Lovastatin Simvastatin	Atorvastatin Pravastatin Rosuvastatin	Pitavastatin
EFV[1]		Atorvastatin Simvastatin Pravastatin Rosuvastatin	Pitavastatin
RAL[1]			
ATV/COBI or DRV/COBI	Lovastatin Simvastatin		

1. DHHS Guidelines. April 2015. 2. Dolutegravir [package insert].

IMPACT OF AGING ON DRUG TOXICITY IN HIV-INFECTED PATIENTS

❑ Higher rates of **adverse medication effects**

❑ Ageing associated with **decreased hepatic cytochrome P450 activity** and **decreased renal tubular secretion and glomerular filtration**

❑ Age-related **body composition and physiological** changes affect drug PD and PK

❑ The elderly frequently use prescription and Over-the-Counter medications i.e. are exposed to **predictable and un-predictable drug-drug interactions**

❑ Concurrent **comorbidities are frequent**:
- Metabolic, Renal and Cardiac
- Tuberculosis, Fungal disease, infectious disease in the HIV-infected in Africa associated with poorer outcomes

Eron J, Kuritzkes DR, Squires KE. Impact of Aging on Drug Toxicity in HIV-Infected Patients. Accessed 12/15/2015 at http://www.inpractice.com.