Infezione da HIV: comorbidità

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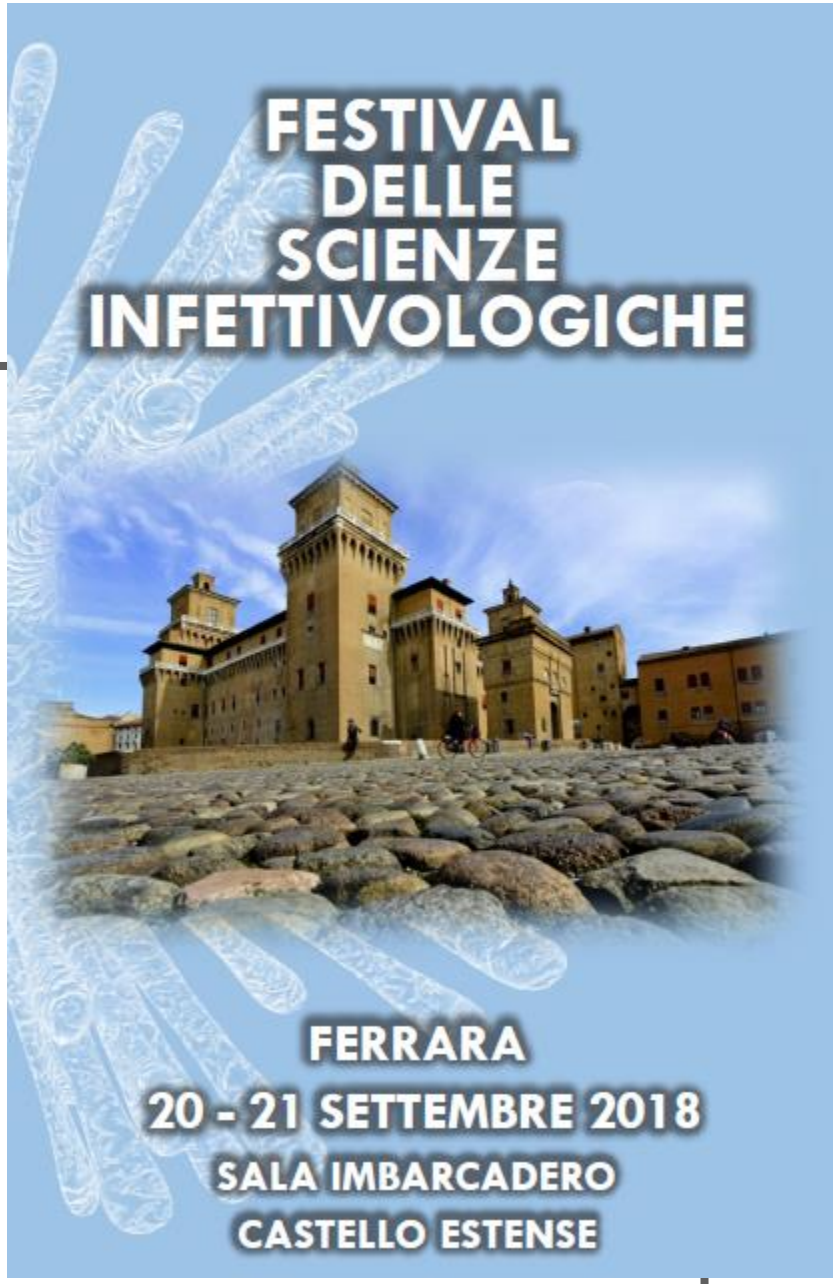


IL SOTTOSCRITTO LEONARDO CALZA

IN QUALITÀ DI RELATORE DELL'EVENTO IN CORSO, AI SENSI DELL'ART. 3.3 SUL CONFLITTO DI INTERESSI, PAG. 17 DEL REG. APPLICATIVO DELL'ACCORDO STATO-REGIONI DEL 5/11/09, PER CONTO DEL PROVIDER **DICHIARA CHE NEGLI ULTIMI DUE ANNI HA AVUTO I SEGUENTI RAPPORTI ANCHE DI FINANZIAMENTO CON SOGGETTI PORTATORI DI INTERESSI COMMERCIALI IN CAMPO SANITARIO:**

-JANSSEN
-ABBVIE
-MSD

Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies

- 18 European and North American HIV-1 cohorts
- 88,504 HIV+ patients

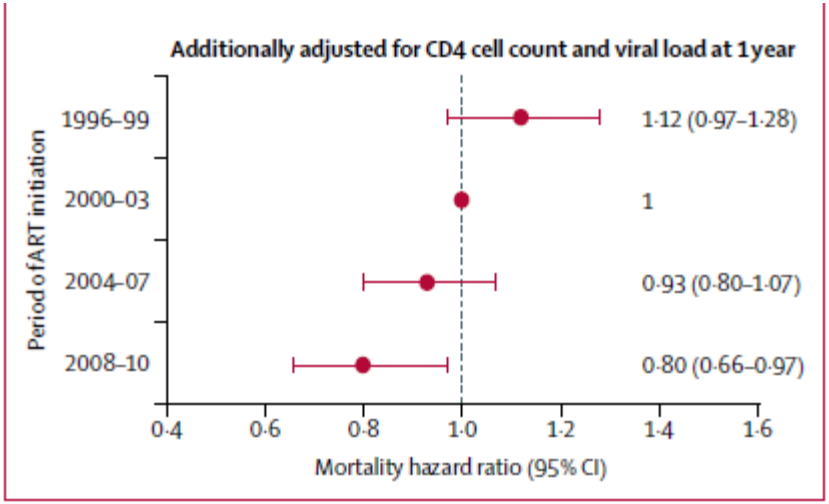


***Figure 2*: All-cause mortality hazard ratios for the second and third years after starting antiretroviral therapy (ART), by period of initiation**
*Adjusted for age, sex, AIDS, risk group, CD4 cell count, and HIV-1 RNA at the time of starting ART.

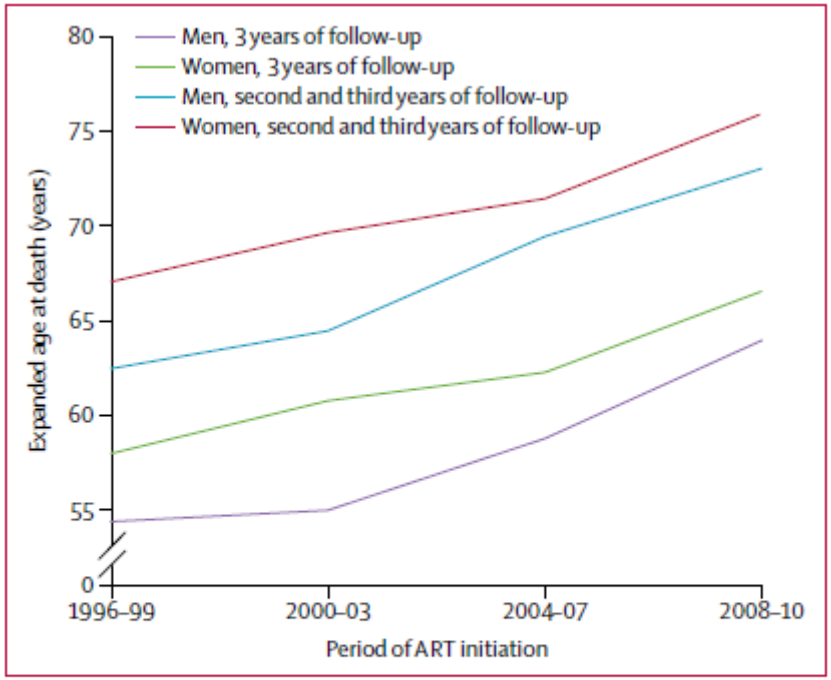
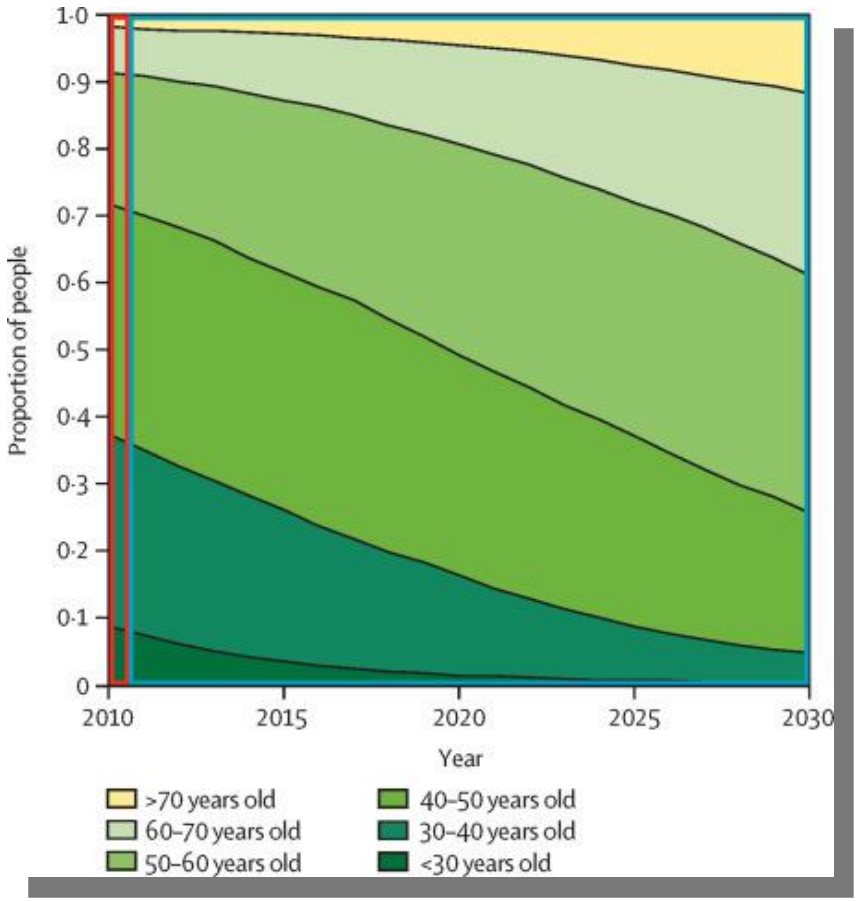


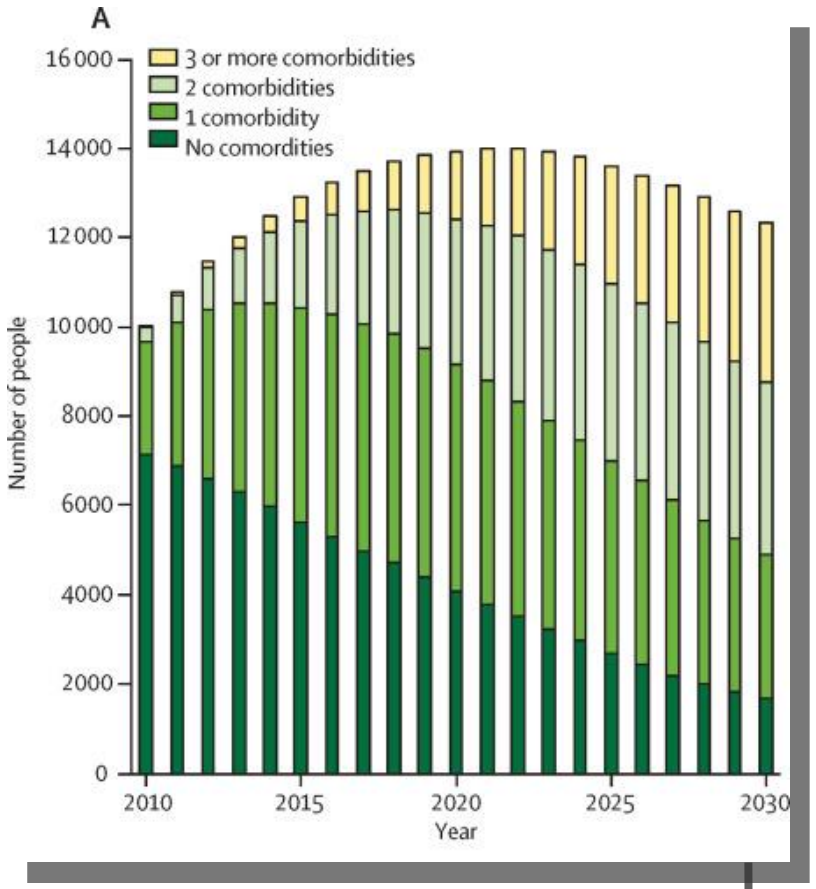
***Figure 3*: Expected age at death of men and women living with HIV starting antiretroviral therapy (ART) aged 20 years, by period of initiation**
Estimates of life expectancy were based on mortality during the first 3 years of follow-up and the second and third years of follow-up. Data are for all regions.

(Lancet HIV 2017, 4: e349-e356)

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



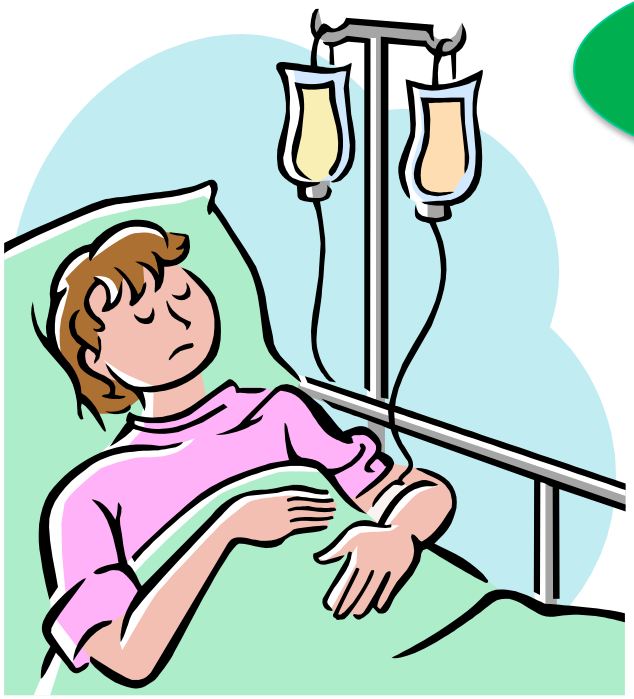


(Lancet Infect Dis 2015)

HIV-related comorbidities

Cardiovascular disease

Neurocognitive disorders



Liver disease

Dysmetabolisms

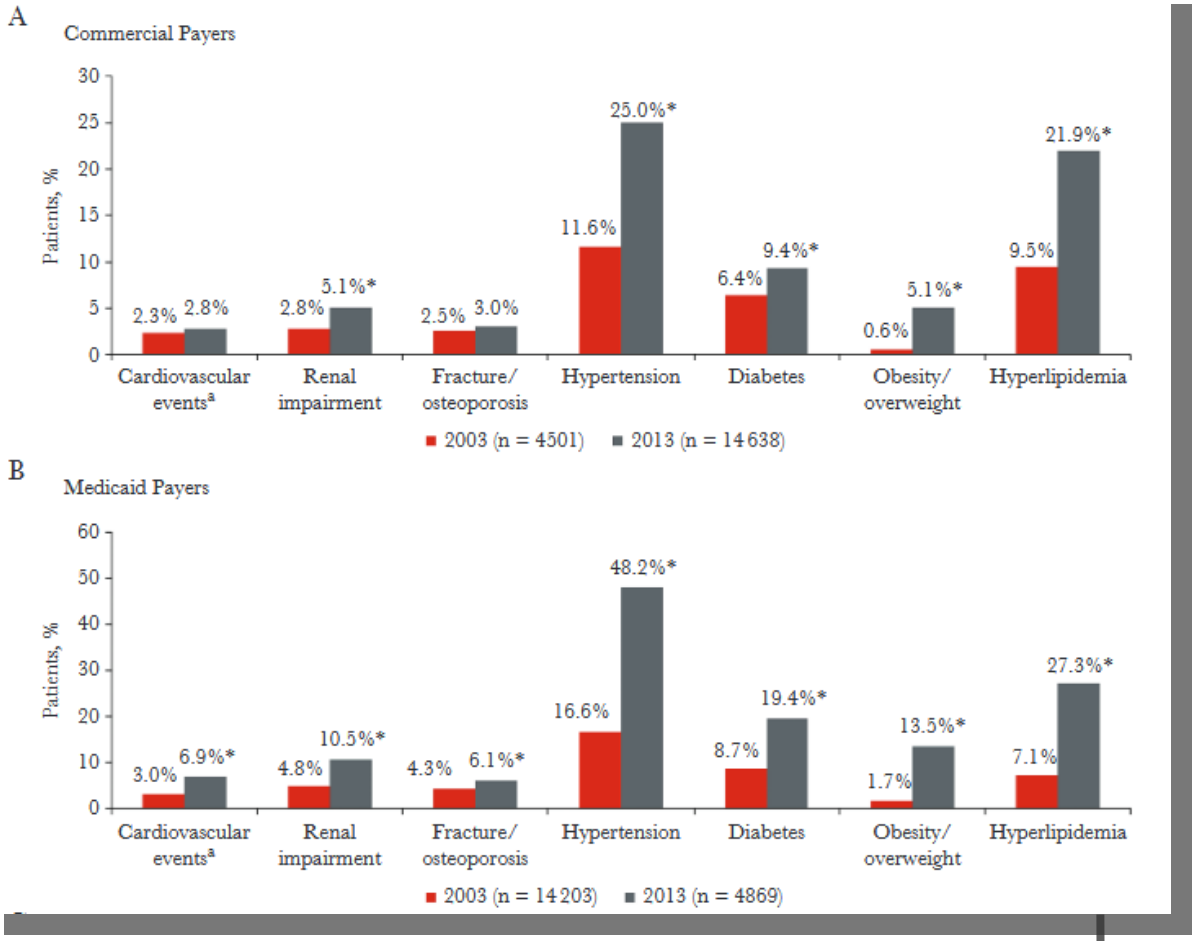
Renal disease

Malignancies

Bone disease

Comorbidities Among US Patients With Prevalent HIV Infection—A Trend Analysis

- MarketScan Database
- 36,298 HIV+ patients
- Observation period: 2003-2013

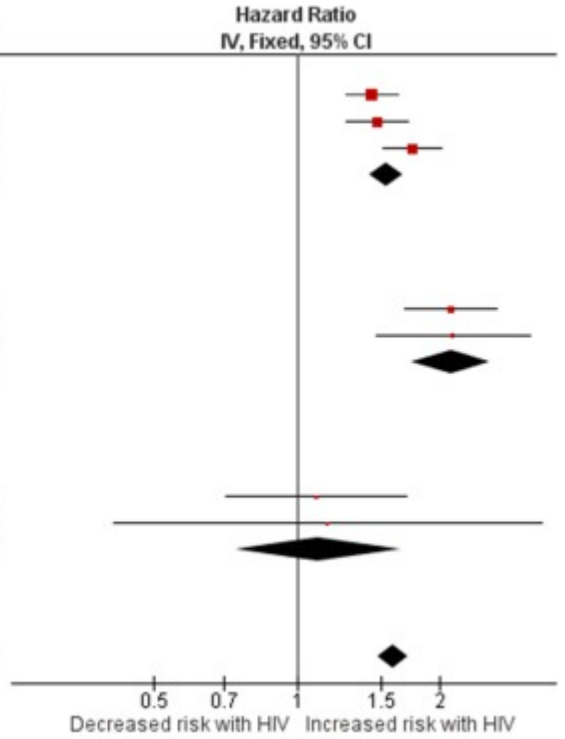


(Gallant J et al., J Infect Dis 2017)

Risk of myocardial infarction in HIV+ patients vs HIV- controls

(44 Cohort Studies; 334,417 HIV+ patients)

Study or Subgroup	log[Hazard Ratio]	SE	HIV+ Total	HIV- Total	Weight	Hazard Ratio IV, Fixed, 95% CI
1.2.1 United States						
Silverberg et al. 2014	0.365	0.065	22081	230069	33.0%	1.44 [1.27, 1.64]
Freiberg et al. 2013	0.392	0.077	27350	55109	23.5%	1.48 [1.27, 1.72]
Triant et al. 2007	0.56	0.074	3851	1044589	25.4%	1.75 [1.51, 2.02]
Subtotal (95% CI)			**53282**	**1329767**	**81.9%**	**1.54 [1.42, 1.67]**
Heterogeneity: $Chi^2 = 4.32$, df = 2 (P = 0.12); $I^2 = 54\%$						
Test for overall effect: Z = 10.51 (P < 0.00001)						
1.2.2 Europe/ Canada						
Durand et al. 2011	0.747	0.113	7053	27681	10.9%	2.11 [1.69, 2.63]
Rasmussen et a. 2015	0.756	0.19	3233	12932	3.9%	2.13 [1.47, 3.09]
Subtotal (95% CI)			**10286**	**40613**	**14.8%**	**2.12 [1.75, 2.56]**
Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0\%$						
Test for overall effect: Z = 7.72 (P < 0.00001)						
1.2.3 Recurrent events						
Lorgis et al. 2013	0.095	0.223	435	945	2.8%	1.10 [0.71, 1.70]
Carballo et al. 2015	0.15	0.53	133	5328	0.5%	1.16 [0.41, 3.28]
Subtotal (95% CI)			**568**	**6273**	**3.3%**	**1.11 [0.74, 1.66]**
Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0\%$						
Test for overall effect: Z = 0.50 (P = 0.62)						
Total (95% CI)			**64136**	**1376653**	**100.0%**	**1.60 [1.49, 1.72]**
Heterogeneity: $Chi^2 = 16.58$, df = 6 (P = 0.01); $I^2 = 64\%$						
Test for overall effect: Z = 12.57 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 12.25$, df = 2 (P = 0.002), $I^2 = 83.7\%$						

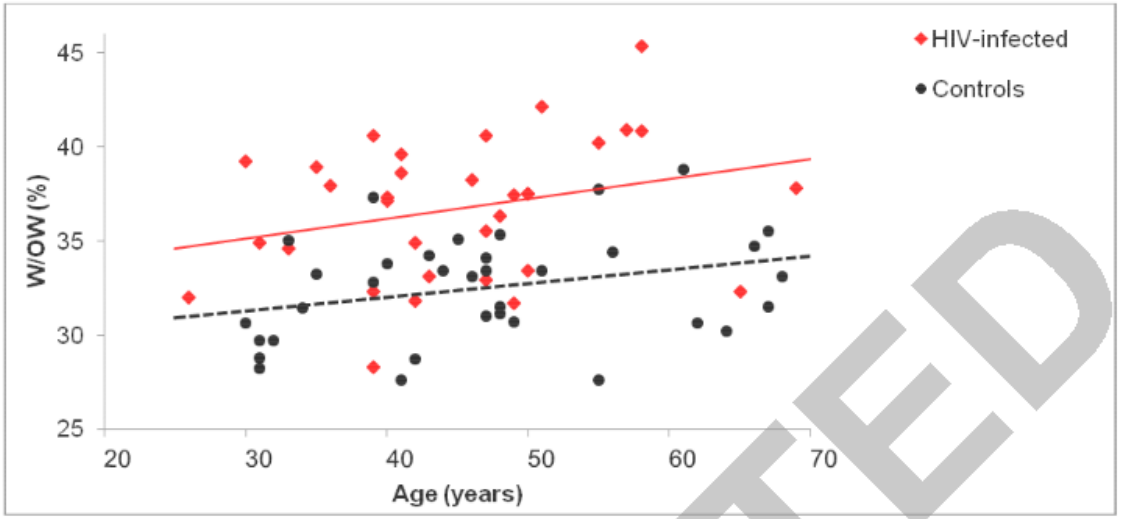


(Gutierrez J et al., PLoS One 2017)

Atherosclerosis is evident in treated HIV-infected subjects with low cardiovascular risk by carotid cardiovascular magnetic resonance

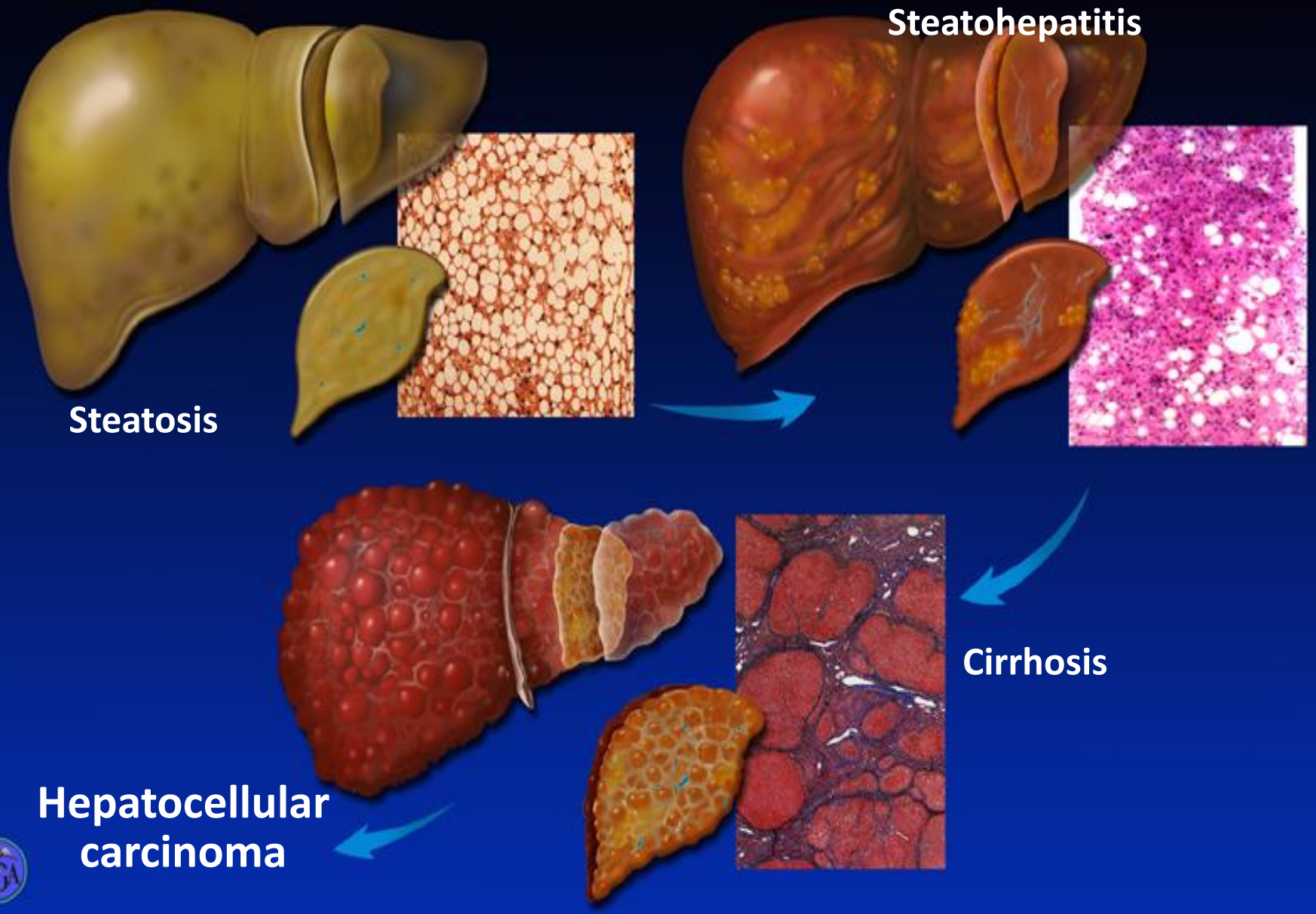
	HIV-infected subjects (n=33)	Control subjects (n=35)	*p*
Total Lumen Volume (mm^3)	2966.6 (2763.5, 3169.7)	3277.5 (2988.4, 3566.7)	0.079
Total Wall Volume (mm^3)	1712.1 (1599.4, 1824.8)	1574.8 (1431.3, 1718.3)	0.13
Total Vessel Volume (mm^3)	4678.7 (4391.7, 4965.8)	4852.3 (4433.3, 5271.4)	0.49
W/OW Ratio (%)	36.7 (35.4, 38.0)	32.5 (31.5, 33.5)	**< 0.0001**
Distensibility (%)	22.9 (20.6, 25.1)	24.2 (22.4, 26.1)	0.35

- Case-control study
- 33 HIV+ patients on cART with HIV RNA <50 cp/mL vs 35 HIV- controls
- Low CVD risk
- Wall/outer-wall ratio (W/OW) index evaluated by cardiovascular magnetic resonance



(Rose KA et al., J AIDS 2015)

Non Alcoholic Fatty Liver Disease (NAFLD)
Spectrum of Hepatic Pathology



Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH) in HIV

Table 1 Cross-sectional studies assessing NAFLD or NASH in HIV patients from 2013 to 2016

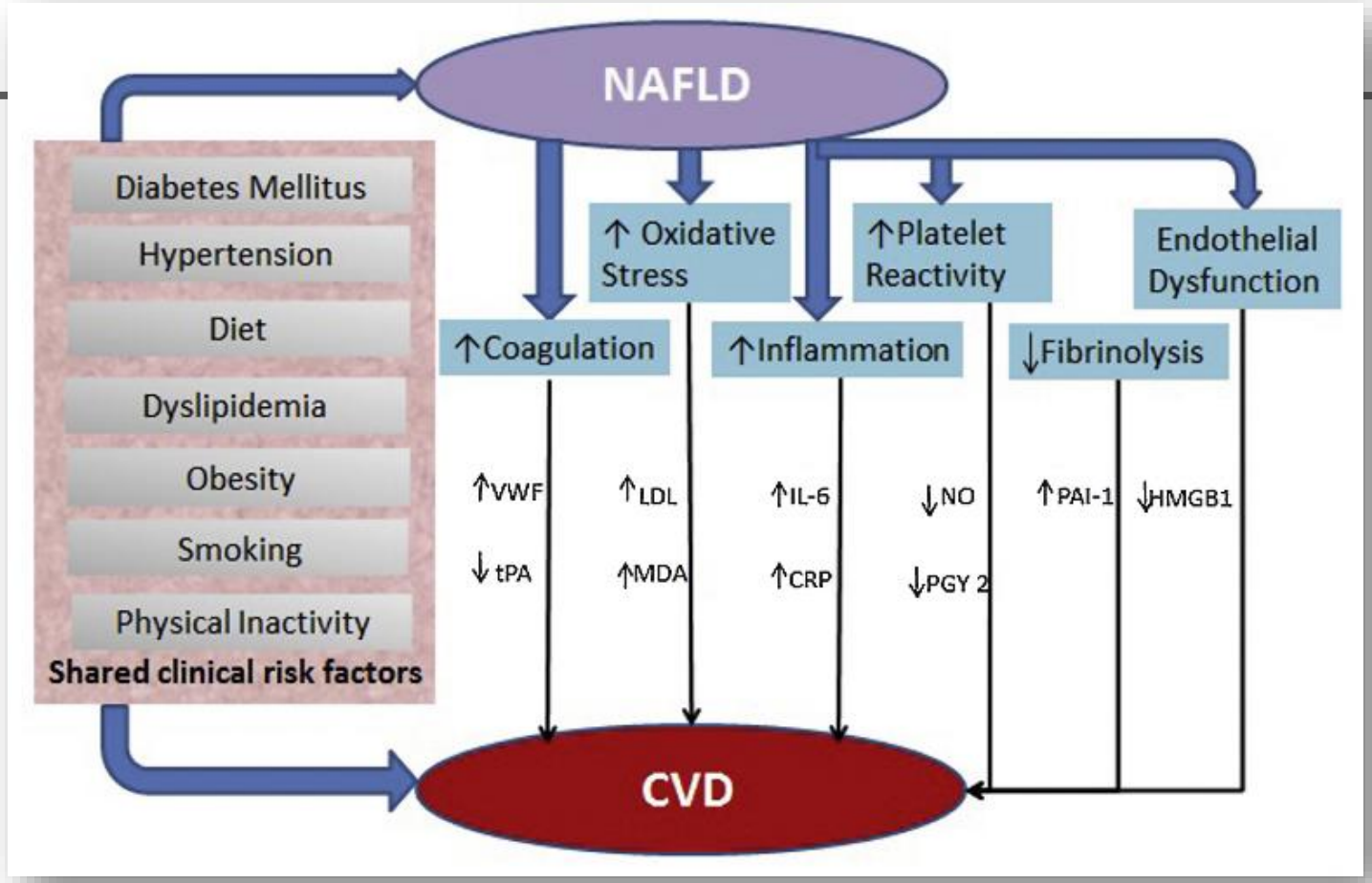
Author (year)	Number of subjects (HIV)/ (HIV+HCV)	Number of patients on HIV therapy	Median CD4-count cells/μl (IQR) or Mean ± SD	Median HIV-RNA (range) or % undetectable	Main inclusion criteria and study design	Prevalence of NAFLD or fatty liver disease	Histological diagnosis of NASH	Association with PNPL3 or other genetic markers
Vuille-Lessard et al. (2016) [12]	300/0	90%	570 ±	70%	Prospective study in unselected HIV-infected adults without significant alcohol intake or viral hepatitis coinfection. NAFLD was defined as CAP at least 238 dB/m. Significant liver fibrosis and cirrhosis were defined as transient elastography measurement at least 7.1 and 13 kPa, respectively.	48%[c]	n.a.	n.a.
Morse et al. (2015) [3••]	62/0	100%	548 (105–1631)	<40 (<40–726)	Biopsy study in patients with elevated aminotransferase levels ≥6 months	73%[a]	55%	yes
Macias et al. (2015) [4]	413/276	96%	519 (330–746)	78.6%	CAP higher than 238 dB/m was selected to define the presence of FLD. Elevated alanine aminotransferase levels and presence of FLD was considered as a surrogate marker of steatohepatitis.	41.5%[c]	n.a.	Yes (LPPR4 rs 12743824 and SAMM50 rs738491)
Price et al. (2014) [5]	465/0	92%	n.a.	90%	Fatty liver was defined as a liver-to-spleen attenuation ratio < 1 on noncontrast computed tomography in the MACS cohort who consumed less than 3 alcoholic drinks daily	13%[b]	n.a.	yes
Sterling et al. (2013) [11]	14/0	100%	614 ± 357	100%	Biopsy study in patients without viral hepatitis, alcohol abuse or diabetes with more than one elevated liver enzyme ≥6 months	65%[a]	26%	n.a.

[a] defined as steatosis involving > 5% of hepatocytes

[b] CT- defined fatty liver disease

[c] defined as CAP > 238 dB/m

Nonalcoholic fatty liver disease and the risk of clinical cardiovascular events: A systematic review and meta-analysis



(Mahfood Haddad T et al., Diabetes Metab Syndr 2016)

Bone Mineral Density Changes in HIV+ Patients

HIV-infected patients:

- Reduced BMD:
  - Prevalence 67%
  - Risk 6.4x
- Osteoporosis:
  - Prevalence 15%
  - Risk 3.7x

Publication	% reduced BMD	
	HIV+	HIV–
Amiel *et al* 2004	82.5	35.8
Brown *et al* 2004	63	32
Bruera *et al* 2003	64.8	13
Dolan *et al* 2004	63	35
Huang *et al* 2002	66.6	11
Knobel *et al* 2001	87.5	30
Loiseau-Peres *et al* 2002	68	34
Madeddu *et al* 2004	59.3	7.8
Tebas *et al* 2000	40	29
Teichman *et al* 2003	76	4
Yin *et al* 2005	77.4	56

(Brown TT et al., AIDS 2006)

EuroSIDA Study: Risk for Chronic Kidney Disease

Analysis of patients with ≥3 creatinine measurements + body weight (2004)

- 6,842 patients with 21,482 person-years of follow-up

Definition of CKD (eGFR by Cockcroft-Gault)

- If baseline eGFR ≥60 mL/min/1.73 m^2, fall to <60
- If baseline eGFR <60 mL/min/1.73 m^2, fall by 25%

225 (3.3%) progressed to CKD

Cumulative Exposure to ARVs and Risk of CKD

	Univariable			Multivariable		
	IRR/year	95% CI	P-value	IRR/year	95% CI	P-value
Tenofovir	1.32	1.21-1.41	<0.0001	1.16	1.06-1.25	<0.0001
Indinavir	1.18	1.13-1.24	<0.0001	1.12	1.06-1.18	<0.0001
Atazanavir	1.48	1.35-1.62	<0.0001	1.21	1.09-1.34	0.0003
Lopinavir/r	1.15	1.07-1.23	<0.0001	1.08	1.01-1.16	0.030

- Risk factors for CKD on TDF: age, HTN, HCV, lower eGFR, lower CD4+ count

(Mocroft A et al., AIDS 2010)

Low-grade proteinuria is highly prevalent in HIV-positive patients on antiretroviral treatment

(Cross-sectional study: 945 HIV+ patients, Germany)

-Low-grade proteinuria (LGP):
UPC>70 mg/g
- Prevalence of LGP: 55%
  glomerular: 20%
  tubular: 41%

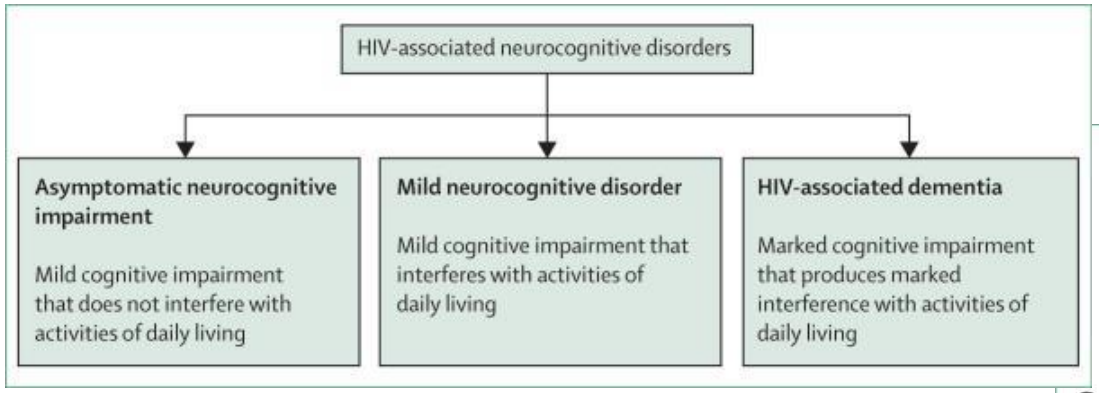
Table 2. Multivariate analysis.

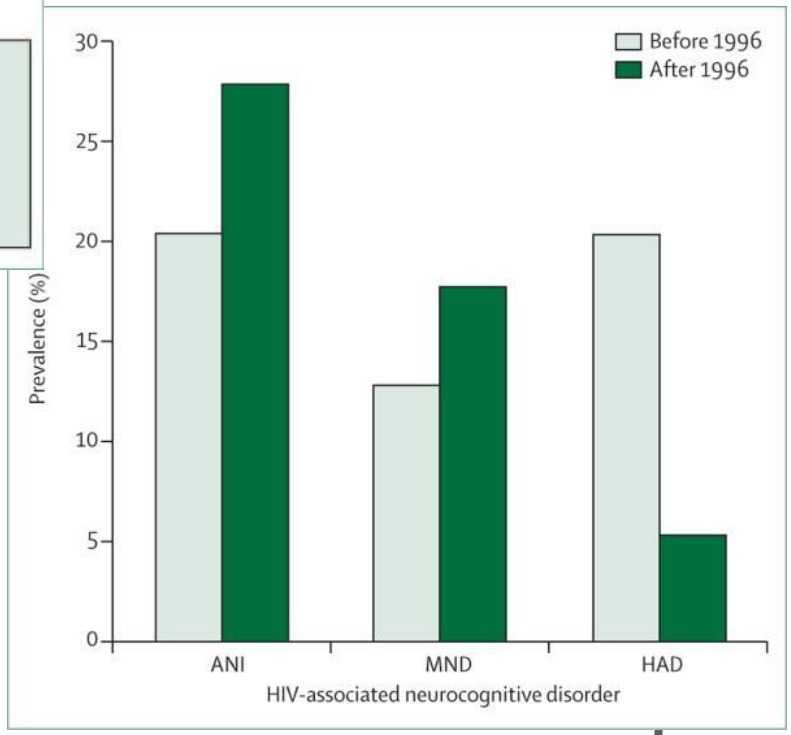
	Low-grade proteinuria		Tubular proteinuria		Glomerular proteinuria	
Risk factor	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Model A						
Age (per 10 years)	1.4 (1.3–1.6)	<0.001	1.6 (1.4–1.8)	<0.001	1.3 (1.1–1.5)	<0.001
Diabetes (yes versus no)	3.0 (1.4–7.1)	0.006	–	–	3.1 (1.6–5.8)	<0.001
Hypertension (yes versus no)	–	–	–	–	2.1 (1.5–3.1)	<0.001
Current NRTI with TDF (versus no NRTI)	–	–	2.5 (1.6–3.7)	<0.001	–	–
Current NRTI without TDF (versus no NRTI)			0.96 (0.6–1.6)	0.87		
Model B						
Age (per 10 years)	1.5 (1.3–1.7)	<0.001	1.6 (1.4–1.8)	<0.001	1.3 (1.1–1.5)	<0.001
Diabetes (yes versus no)	3.1 (1.5–7.3)	0.006	–	–	3.1 (1.6–5.8)	<0.001
Hypertension (yes versus no)	–	–	–	–	2.1 (1.5–3.1)	<0.001
Any exposure to NRTI, with TDF (versus no NRTI)	1.3 (0.8–2.0)	0.33[a]	2.4 (1.4–4.2)	0.002	–	–
Any exposure to NRTI, no TDF (versus no NRTI)	0.7 (0.4–1.3)	0.26[a]	0.7 (0.4–1.2)	0.19	–	–

Risk factors for low-grade proteinuria, and tubular and glomerular proteinuria after multivariable logistic regression. Multivariable logistic regression using forward selection based on the variables age, time since HIV infection, any exposure to cART, current (Model A)/any (Model B) exposure to NRTI (with/without TDF) and other substance classes; history of diabetes, hypertension, or cardiovascular events. cART, combined antiretroviral therapy; CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; TDF, tenofovir.
[a]*P*-value from joint Wald test 0.005.

(Gravemann S et al., AIDS 2014)

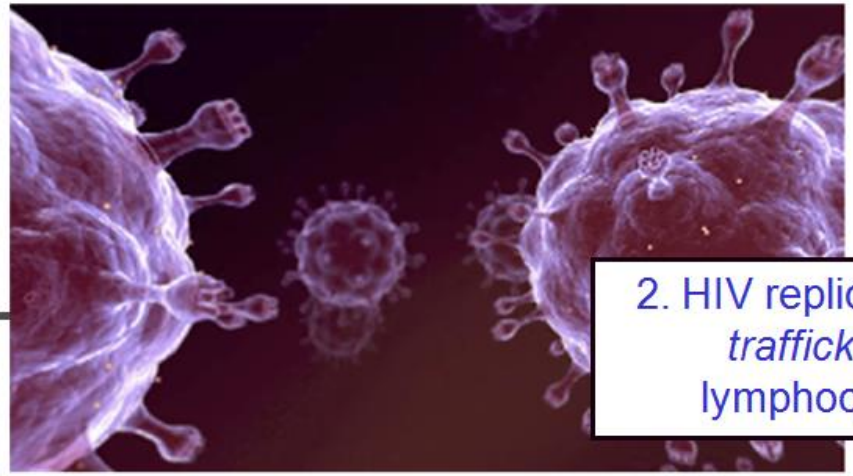
HIV-Associated Neurocognitive Disorders (HAND)





(Nightingale S et al., Lancet Neurol 2014)

HIV brain infection and neurocognitive dysfunction



1. Systemic HIV Replication

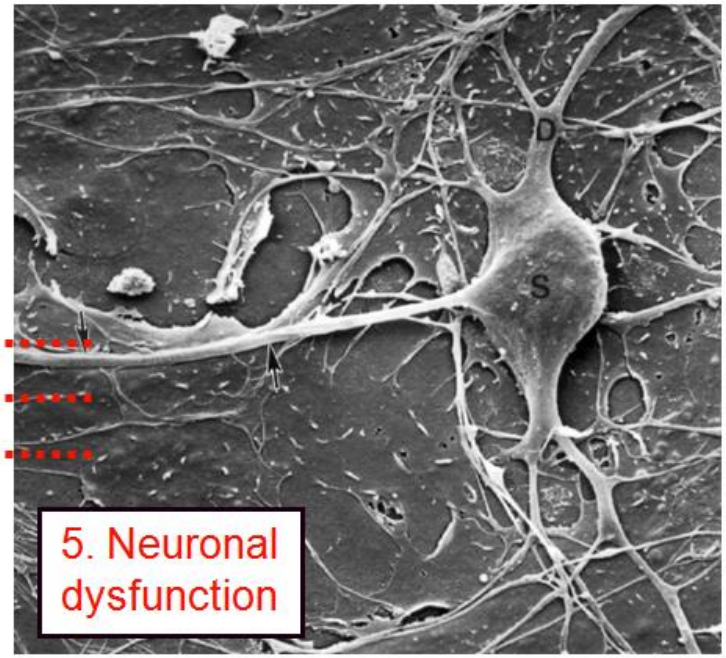
2. HIV replication in *trafficking* lymphocytes

BBB

3. HIV replication in CNS macrophages

4. Macrophage activation

Soluble factors



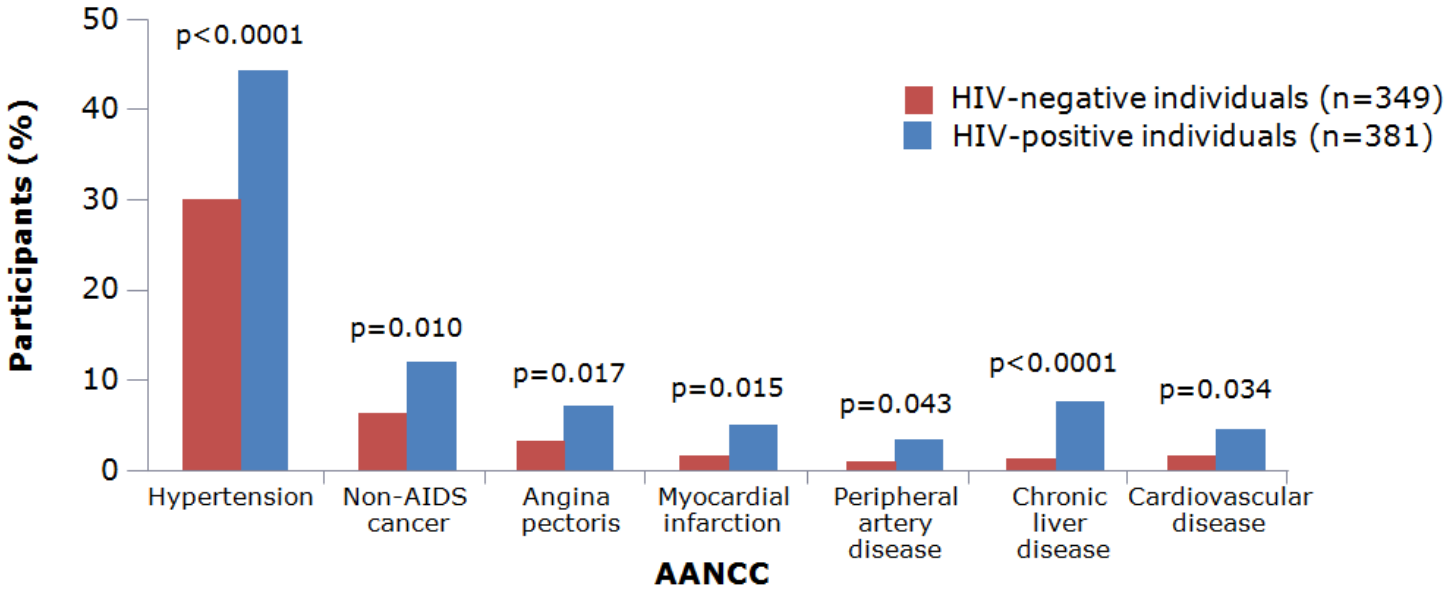
5. Neuronal dysfunction

Ageing…

AGE$_h$IV
Prevalence of comorbidities in HIV-positive individuals

Cross-sectional analysis of prospective comparative cohort of 381 HIV-1-positive individuals and 349 HIV-negative controls in the Netherlands

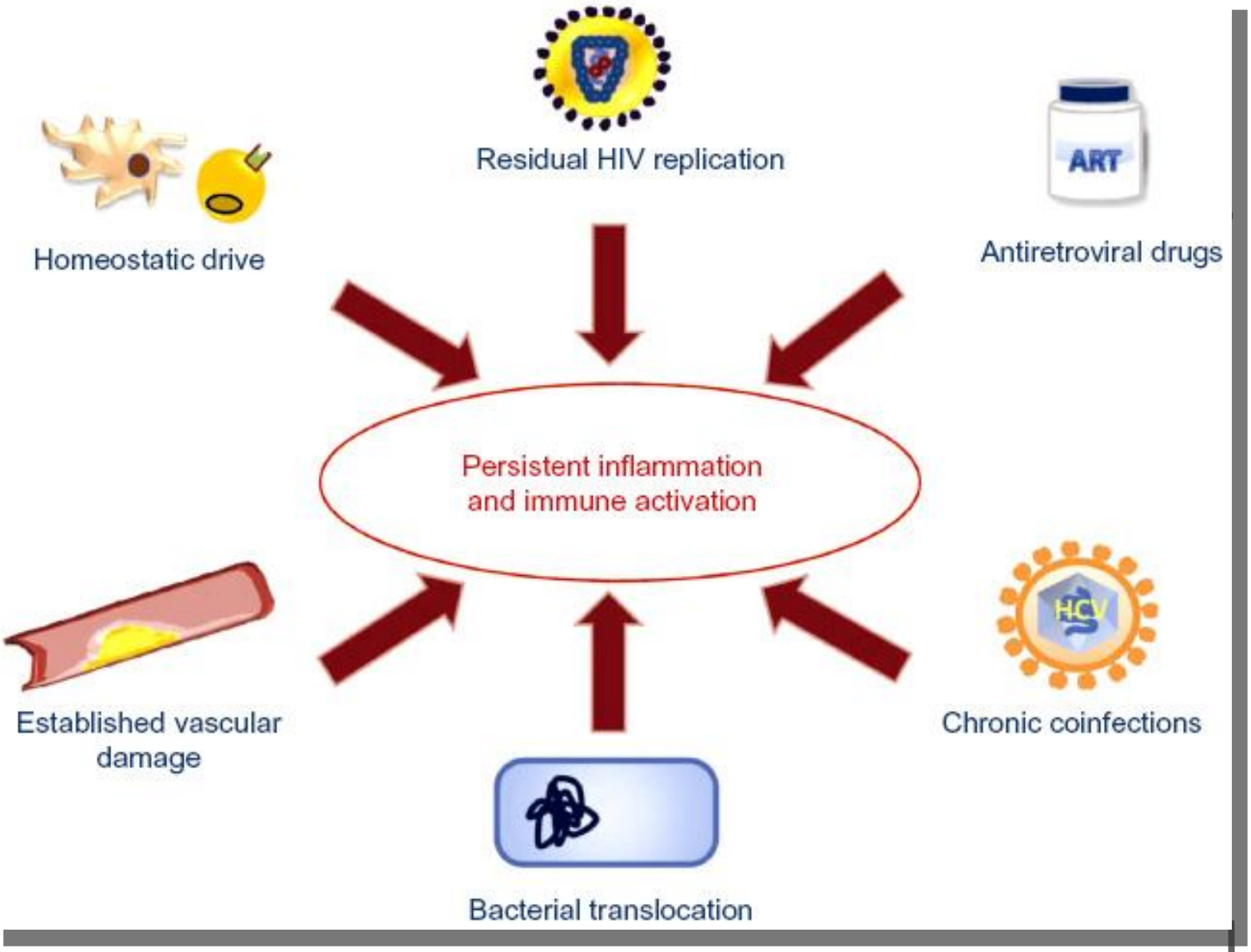
Prevalence of age-associated non-communicable comorbidity (AANCC) distribution in HIV-positive and HIV-negative individuals



- **AANCCs were significantly more prevalent amongst HIV-positive individuals compared to HIV-negative controls of similar age**

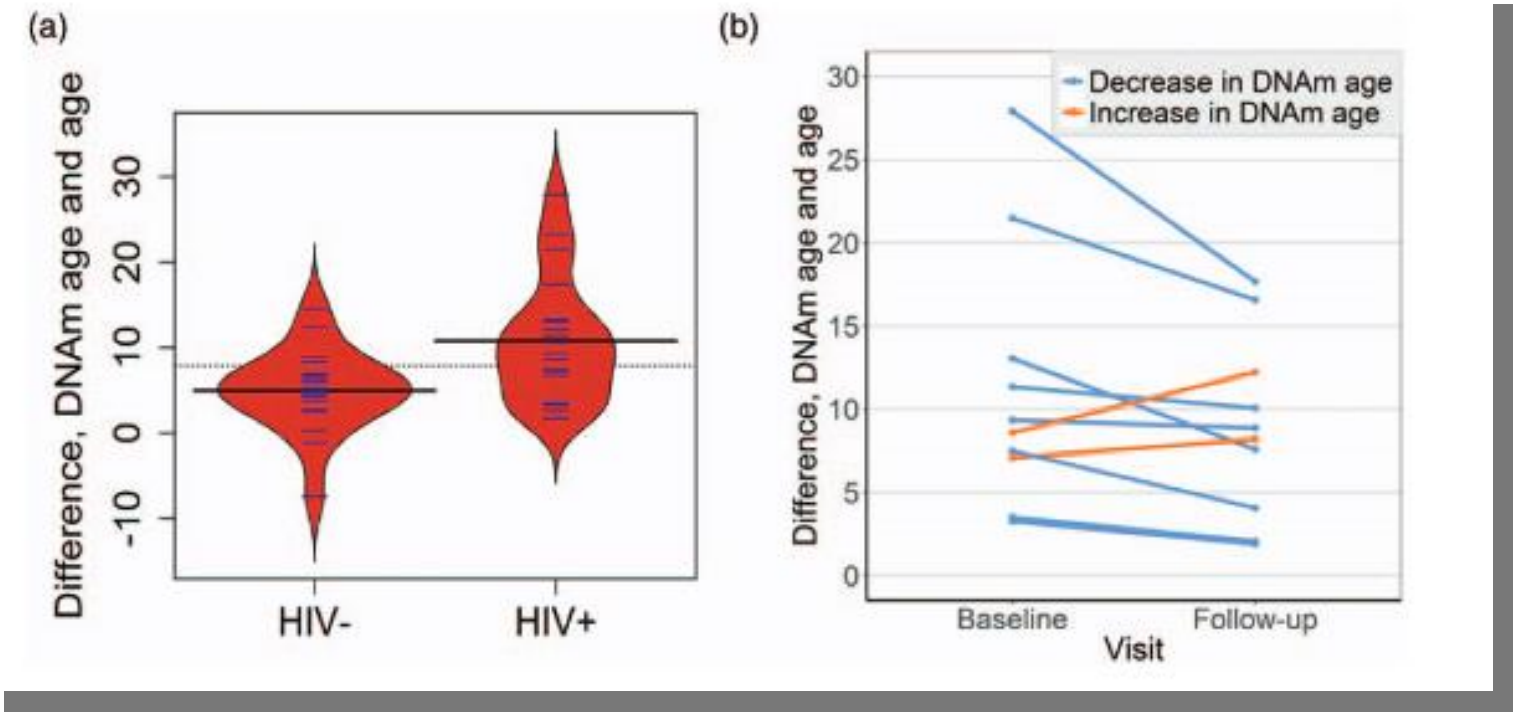
Schouten et al. IAC 2012. Washington, DC. #THAB0205

Not just ageing…



Identification of HIV infection-related DNA methylation sites and advanced epigenetic aging in HIV-positive, treatment-naive U.S. veterans

(19 ART-naive HIV+ patients vs 19 HIV- patients matched by age and race; median age 51 years)

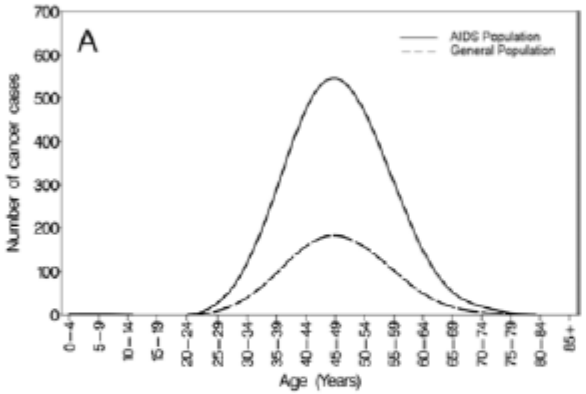


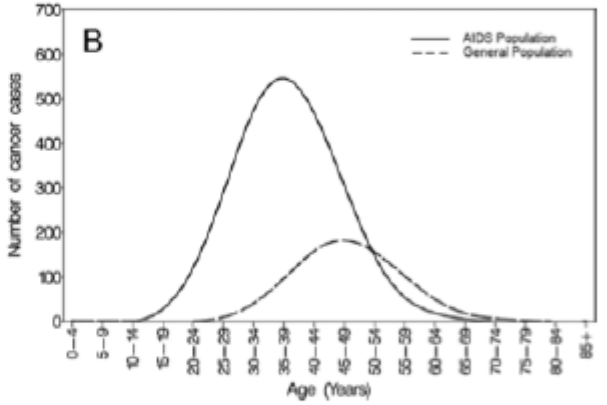
(Nelson KN et al., AIDS 2017)

Review Article

Is HIV a Model of Accelerated or Accentuated Aging?

Sophia Pathai,[1,*] Hendren Bajillan,[2,*] Alan L. Landay,[3,4] and Kevin P. High[5]



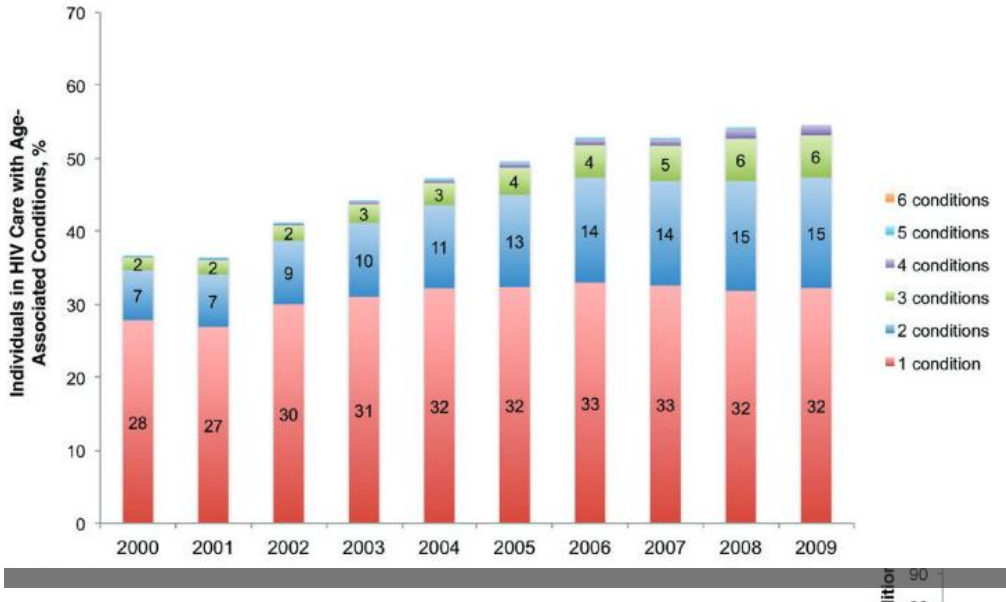


Accentuated Aging: cancer (and **geriatric syndroms**) occurs at the same ages but more often among HIV-infected participants than among HIV-uninfected comparators.
This configure a **Premature aging process.**

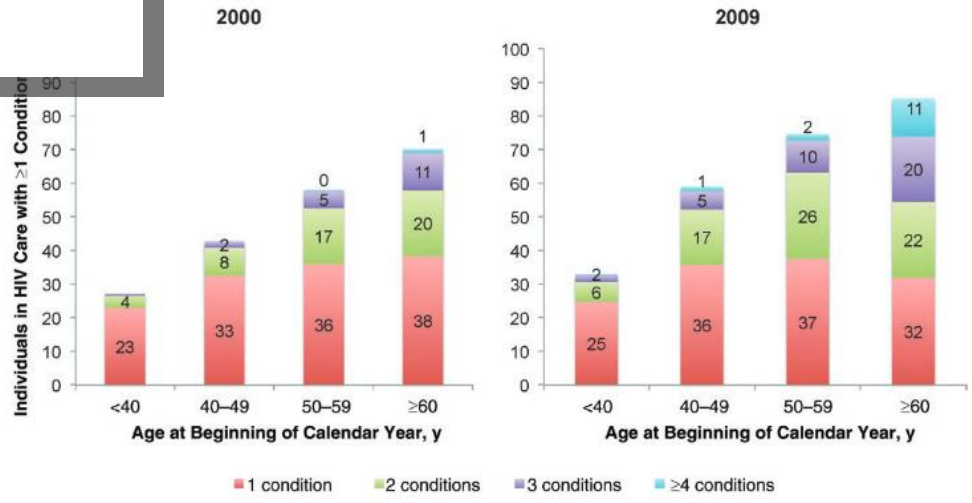
Accelerated Aging and accentuated aging: cancer (and **geriatric syndroms**) occurs earlier among HIV-infected participants compared with HIV-uninfected comparators and there are more cancer events.

(J Gerontol 2014; 69: 833-842)

Multimorbidity Among Persons Living with Human Immunodeficiency Virus in the United States



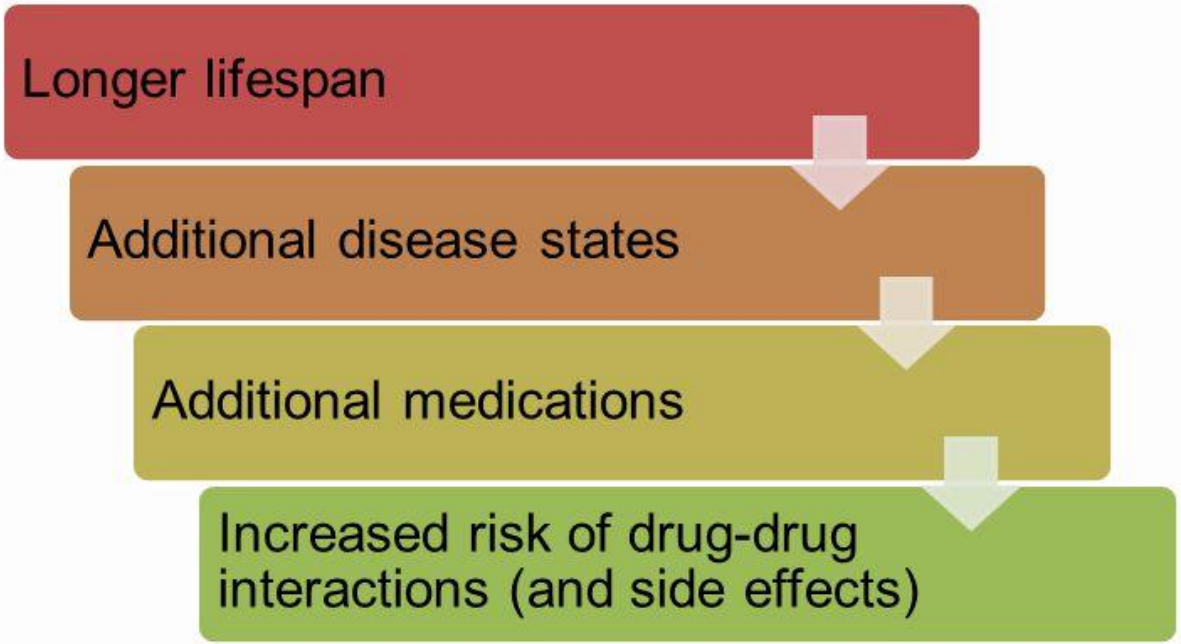
- NA-ACCORD Cohort
- 22,969 adult HIV+ outpatients
- 2000-2009



(Wong C et al., Clin Infect Dis 2017)

Polypharmacy & Aging HIV-Infected Patients

Antiretroviral therapy (ART) transformed HIV into complex chronic disease with multimorbidity



Ageing with HIV: do comorbidities and polymedication drive treatment optimization?*

- French database retrospective analysis
- 11 large HIV centers
- 23,683 HIV+ patients

Table 3 Proportion of patients with coprescription in addition to antiretroviral therapy (ART), and comparisons between the younger patients, recently diagnosed ageing patients, diagnosed after 2000 ('recent'), and experienced ageing patients, with a long HIV history ('exp.')

	Total	≤50 years old	Ageing, recent	Ageing, exp.	P*
NSAIs (%)	9.9	9.6	9.7	10.7	0.027
Corticosteroids (%)	3.5	3.2	4.6	3.7	0.001
Vitamin K antagonists (%)	4.1	3.7	4.8	4.6	0.001
Tuberculosis treatments (%)	2.0	2.2	2.9	1.4	<0.0001
Cardiovascular drugs (%)	30.2	22.9	39.3	39.7	<0.0001
Cancer chemotherapy (%)	1.2	1.1	1.2	1.1	0.79
Fibrates (%)	7.1	5.6	7.1	10.1	<0.0001
Statins (%)	25.2	18.8	32.1	34.1	<0.0001
Post-transplant agents (%)	0.9	0.9	0.9	0.9	0.93
Proton pump inhibitors (%)	21.0	18.5	24.1	24.4	<0.0001
Psychiatric medications† (%)	39.5	36.5	40.4	44.6	<0.0001
Erectile dysfunction treatments (%)	3.8	3.0	5.2	4.7	<0.0001
Number of comedications (%)					
0	39.9	47.2	33.4	29.2	<0.0001
1	20.6	20.2	20.5	21.7	
2	14.0	11.8	16.1	17.3	
3	9.6	7.2	11.3	13.4	
4	6.9	5.7	8.1	8.7	
≥5	8.8	7.9	10.6	9.7	

NSAI, nonsteroidal anti-inflammatory.
*Comparisons between the three patient groups.
†Including hypnotics.

(Cuzin L et al. HIV Med 2017)

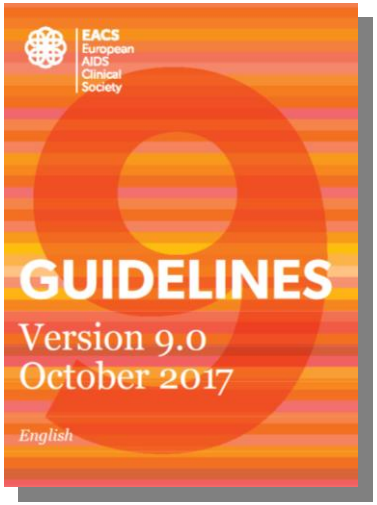
Nonantiretroviral polypharmacy and adverse health outcomes among HIV-infected and uninfected individuals

- U.S. Veterans Affairs Healthcare System
- 9473 HIV+ and 39812 HIV- patients
- 2010-2015

Table 4. Unadjusted and adjusted hazard ratio of nonantiretroviral medication count (continuous measure), hospitalization and mortality by HIV status.

	Unadjusted Non-ARV medication count			Fully adjusted Non-ARV medication count		
Outcome	Hazard ratio	95% CI		Hazard ratio	95% CI	
Hospitalization[a]						
Combined	1.10	1.09	1.10	1.08	1.08	1.08
HIV+	1.10	1.09	1.10	1.08	1.07	1.09
Uninfected	1.12	1.09	1.15	1.08	1.07	1.08
Mortality[b]						
Combined		na[b]			na[b]	
HIV+	1.11	1.10	1.11	1.05	1.03	1.06
Uninfected	1.27	1.20	1.34	1.07	1.06	1.07

(Justice AC et al., AIDS 2018)

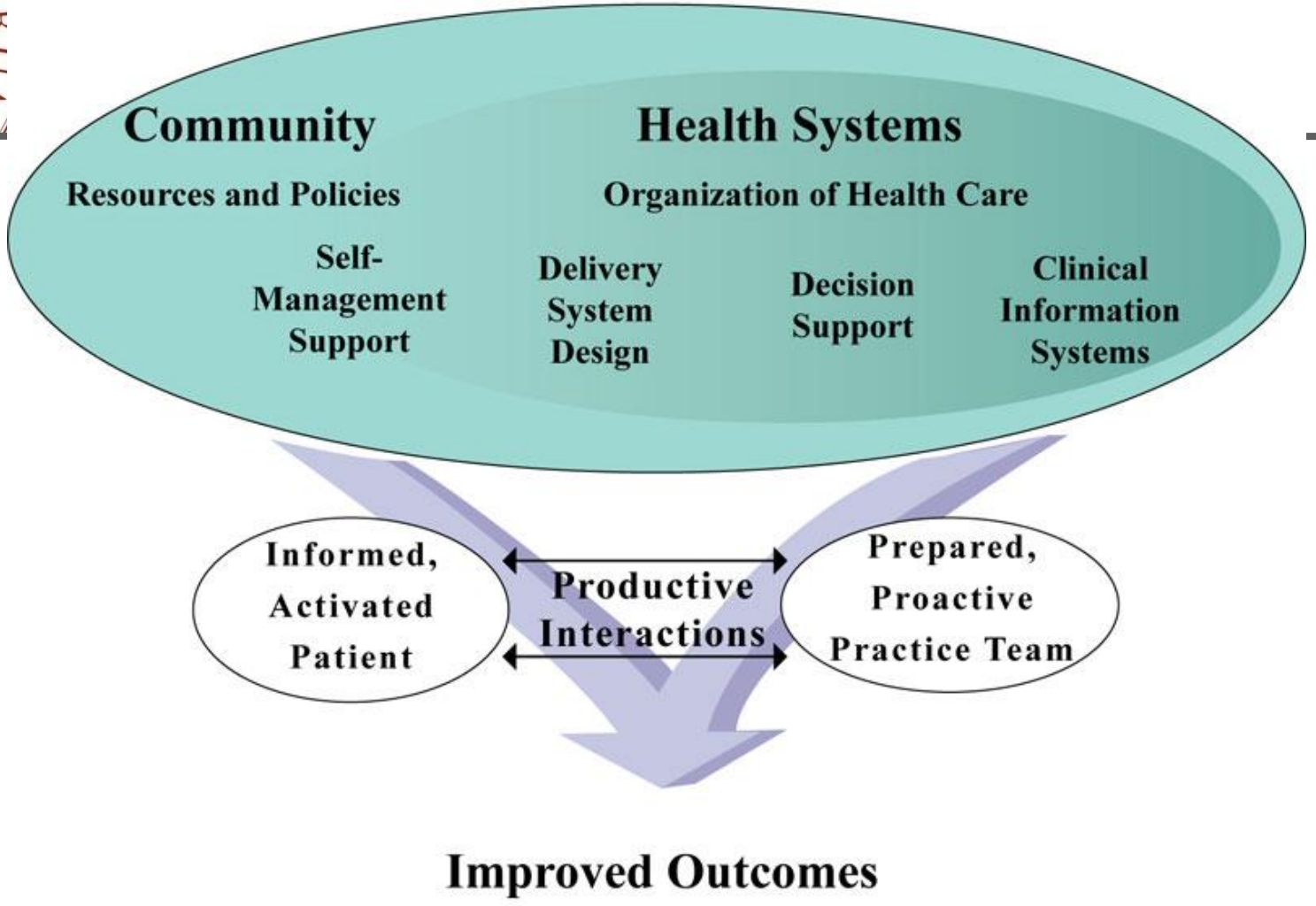


	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment
CO-MORBIDITIES					
Haematology	FBC	+	+	3-12 months	
	Haemoglobinopathies	+			Screen at risk persons
	G6PD	+			Screen at risk persons
Body Composition	Body-mass index	+	+	Annual	
Cardiovascular Disease	Risk assessment (Framingham score[iii])	+	+	2 years	Should be performed in all men > 40 years and women > 50 years without CVD
	ECG	+	+/-	As indicated	Consider baseline ECG prior to starting ARVs associated with potential conduction problems
Hypertension	Blood pressure	+	+	Annual	
Lipids	TC, HDL-c, LDL-c, TG[iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)
Glucose	Serum glucose	+	+	Annual	Consider oral glucose tolerance test / HbA1c if fasting glucose levels of 5.7-6.9 mmol/L (100-125 mg/dL)
Pulmonary Disease	Respiratory symptoms and risk factors[xii]	+	+	Annual	If severe shortness of breath is reported with preserved spirometry, echocardiography may be performed to rule out heart failure and/or pulmonary hypertension
	Spirometry			As indicated	Spirometry should be performed in all symptomatic persons[xii]
Liver Disease	Risk assessment[v]	+	+	Annual	
	ALT/AST, ALP, Bilirubin	+	+	3-12 months	More frequent monitoring prior to starting and on treatment with hepatotoxic drugs
	Staging of liver fibrosis			12 months	In HCV and/or HBV co-infected persons (e.g. FibroScan, serum fibrosis markers)
	Hepatic ultrasound			6 months	Persons with liver cirrhosis and persons with HBV co-infection at high risk of HCC[xiii]
Renal Disease	Risk assessment[vi]	+	+	Annual	More frequent monitoring if eGFR < 90mL/min, CKD risk factors present[vi] and/or prior to starting and on treatment with nephrotoxic drugs[ix]
	eGFR (CKD-EPI)[vii]	+	+	3-12 months	
	Urine dipstick analysis[viii]	+	+	Annual	Every 6 months if eGFR < 60 mL/min or rapid decline in eGFR [xiv], if proteinuria ≥ 1+ and/or eGFR < 60 mL/min perform UP/C or UA/C[viii]
Bone Disease	Bone profile: calcium, PO_4, ALP	+	+	6-12 months	
	Risk assessment[x] (FRAX®[xi] in persons > 40 years)	+	+	2 years	Consider DXA in specific persons (see page 47 for details)
Vitamin D	25(OH) vitamin D	+		As indicated	Screen at risk persons
Neurocognitive Impairment	Screening questionnaire	+	+	As indicated	Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 72 for further assessment.
Depression	Questionnaire	+	+	As indicated	Screen at risk persons
Cancer	Mammography			1-3 years	Women 50-70 years
	Cervical PAP			1-3 years	HIV-positive women > 21 years or within 1 year after sexual debut
	Rectal exam and anoscopy			1-3 years	MSM and persons with HPV-associated dysplasia. Evidence of benefit not known
	Ultrasound and alpha-foetoprotein			6 months	Controversial; persons with cirrhosis and persons with HBV co-infection at high risk of HCC[xiii]
	Others				Controversial

2. Nuove necessità di cura e di assistenza

INTERVENTI PROPOSTI	INDICATORI DI RISULTATO
• Porre in atto una rilevazione/indagine prospettica del fenomeno "nuova malattia da HIV", finalizzata alla raccolta di dati di popolazione italiana aggiornati, che possano anche guidare rispetto all'insorgenza delle nuove necessità assistenziali.	• Valutare la % delle singole comorbosità nella popolazione con HIV versus la % degli interventi di successo/insuccesso in merito allo stato di benessere della persona.
• Favorire protocolli diagnostico-terapeutici omogenei sul territorio nazionale, dedicati alla prevenzione delle comorbosità e/o alla loro cura/gestione. In questo contesto, porre in atto strategie assistenziali polispecialistiche, che consentano, con la regia dell'infettivologo curante, di porre in essere percorsi assistenziali integrati e coordinati, anche attraverso la ricognizione di modelli già esistenti.	• Rilevare la % di soddisfazione del personale sanitario e dei pazienti in merito al modello assistenziale proposto, attraverso *survey* opportunamente dedicati e miranti ad evidenziare eventuali criticità, al fine di potere porre correttivi.
• Favorire percorsi di integrazione con l'assistenza extra-ospedaliera (riabilitativa, domiciliare e/o in casa alloggio/diurno), al fine di garantire la continuità di cura delle persone con disabilità/fragilità (compresa la	• Monitorare, a seguito di interventi specifici, la % di riduzione della dispersione dei pazienti dal *continuum of care*, con particolare focus su popolazione anziana, con fragilità/disabilità e con tensione alla

The Chronic Care Model



(Wagner EH, JAMA 2002)

Successful ageing

- Early initiation of safer cART
- Prevention and management of comorbidities
- Avoidance of disease and related disability
- Retention of high physical and cognitive functional capacity
- Active engagement with life