Gestion des complications cardiovasculaires au cours du traitement antirétroviral

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NSFA
La Santé au Cœur de nos Artères

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Liens d'intérets

Bourses de Recherche : Amgen

Consultant : Amgen, Sanofi Regeneron, Gilead, ViiV Healthcare

Honoraires : AstraZeneca, Bayer, MSD France, Novartis, Novo Nordisk

Sommaire

Epidémiologie des complications CV

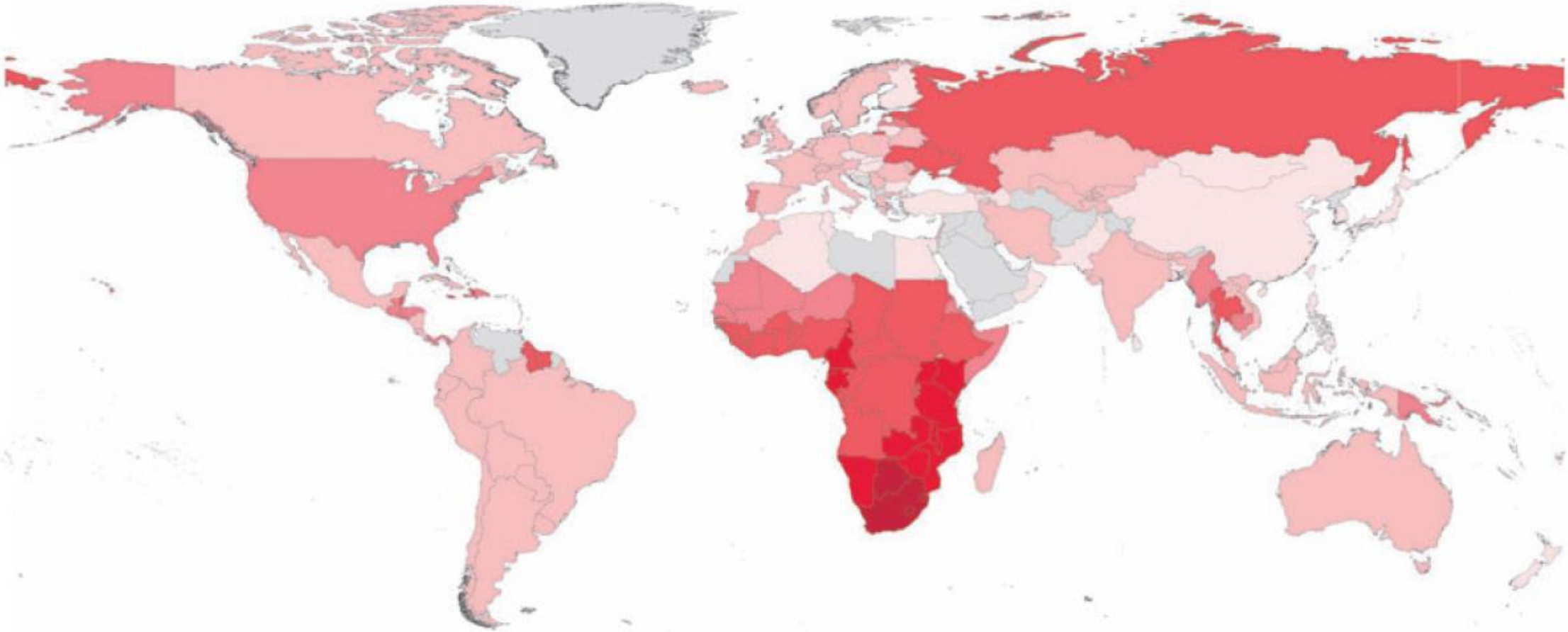
Epidémiologie en Afrique

Facteurs de risque

Pris en charge des complications CV

2010: A global view of HIV infection

33.3 million people [31.4–35.3 million] living with HIV, 2009



Thienemann et al. European Heart Journal 2013;34, 3538–3546.

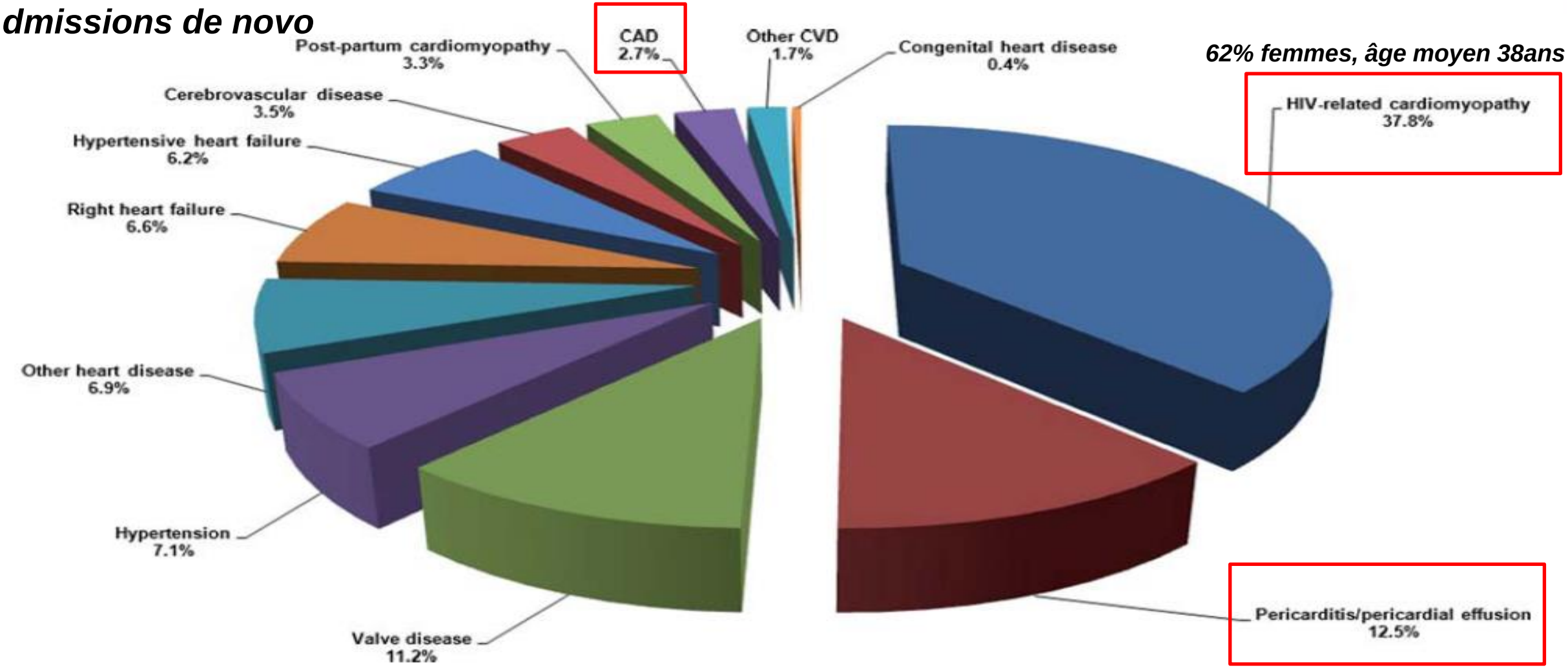
Complications CV	Avant ART (1980-1995)	Après ART (1995-2015)	Après 2020
Myocarditis/Cardiomyopathy Herat failure	8-20 %	Not found Still in developing countries	Impact of ageing? Cardia fibrosis and steatosis (Diastolic dysfn)
Pericarditis	10 %	Not found developing countries	No potential risk
Endocarditis	6.3-34 %	?	No potential risk
Pulmonary hypertension	0.5%	0.5%	?
Arterial hypertension	?	20-30%	Impact of ageing
Coronary artery disease	NR	2-5%	Impact of ageing
Peripheral vascular disease	NR	5%	Impact of tobacco, illicit drugs, HVC
SupraV tachycardia	NR	1%	Impact of ageing
QT (sudden death)	NR	?	Impact of new ART
Stroke	NR	?	Impact of ageing
Thromboembolic veinous disease	NR	?	Impact of new ART

Société Française de Cardiologie

In South Africa, heart failure-related dilated cardiomyopathies are the first CV complications

Admissions de novo

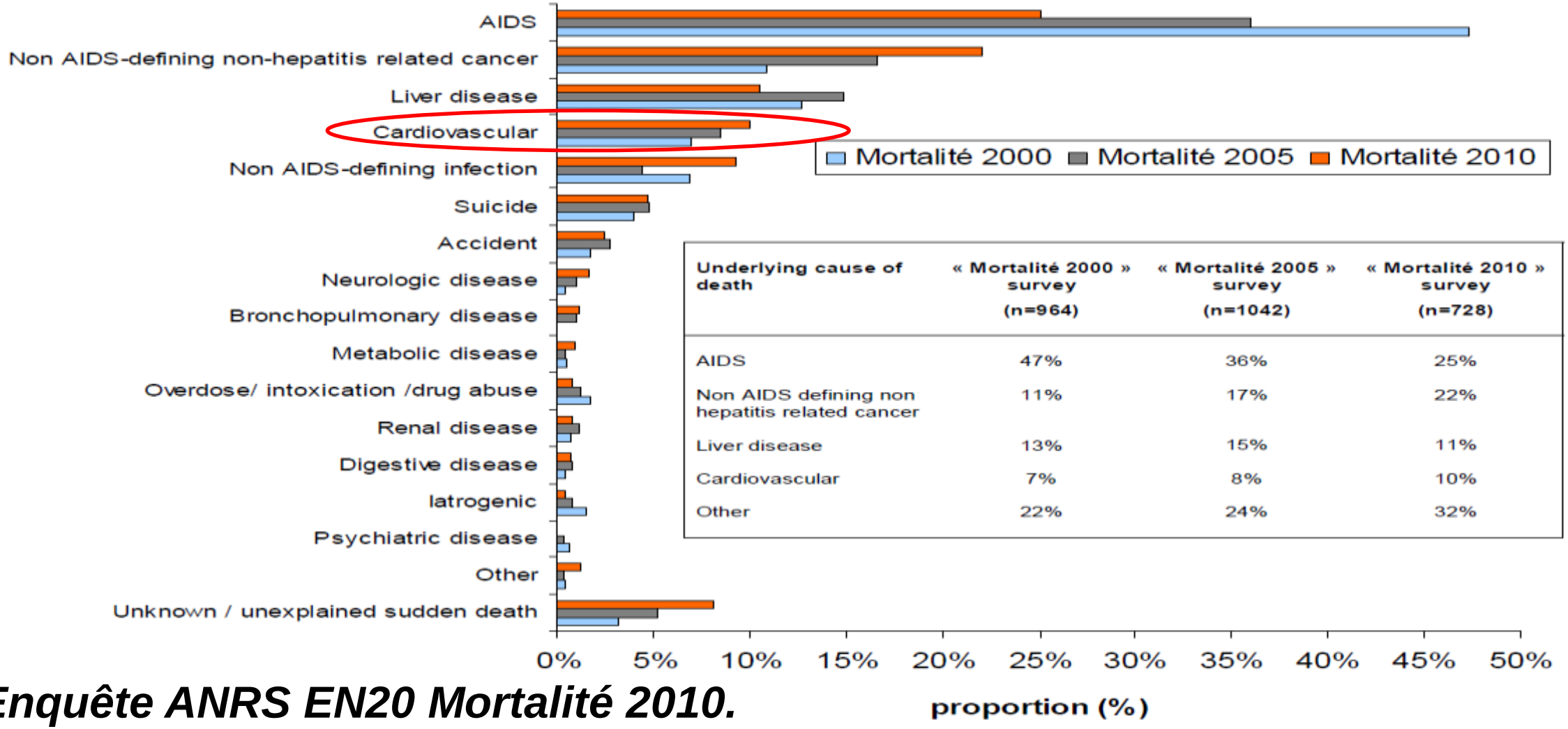
62% femmes, âge moyen 38ans



10% of patients admitted to ICU are HIV+ (Soweto, South Africa)

Sliwa K et al. Eur Heart J. 2012;33:866-74.

Causes de décès entre 2000 et 2010 en France



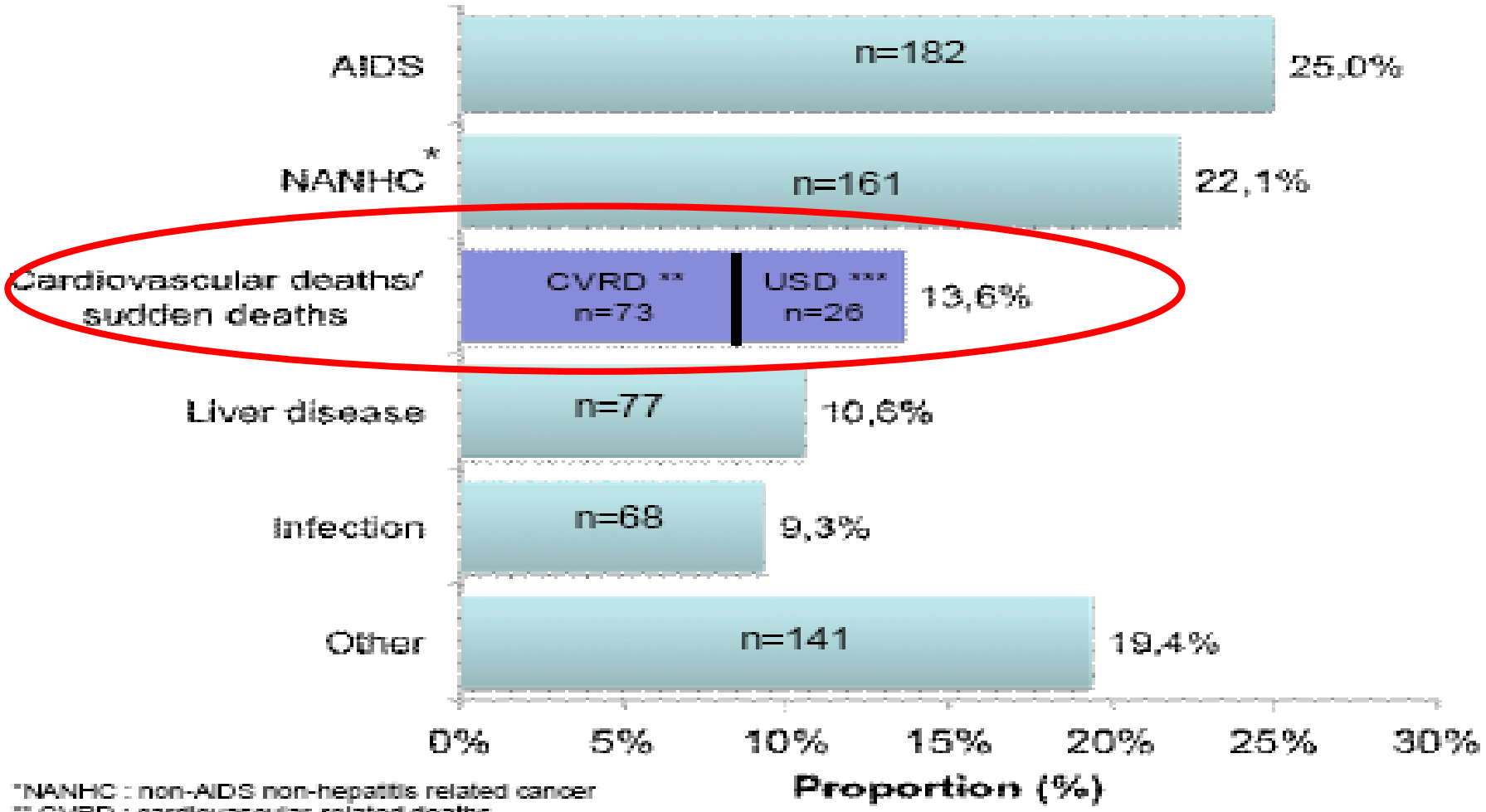
Underlying cause of death	« Mortalité 2000 » survey (n=964)	« Mortalité 2005 » survey (n=1042)	« Mortalité 2010 » survey (n=728)
AIDS	47%	36%	25%
Non AIDS defining non hepatitis related cancer	11%	17%	22%
Liver disease	13%	15%	11%
Cardiovascular	7%	8%	10%
Other	22%	24%	32%

Enquête ANRS EN20 Mortalité 2010.

Figure 1: Evolution of the distribution of the underlying cause of death in HIV-infected adults, 2000 (n=964), 2005 (n=1042) and 2010 (n=728)

Morlat P. et al. AIDS. 2014;28:1181-91.

Causes de décès en France



*NANHC : non-AIDS non-hepatitis related cancer
** CVRD : cardiovascular-related deaths
*** USD : unexplained sudden deaths

Figure 1 : Distribution of causes of 728 deaths among HIV-infected adults dying in 2010 in France

Morlat P. et al. AIDS. 2014;28:1181-91.

Causes de décès en France

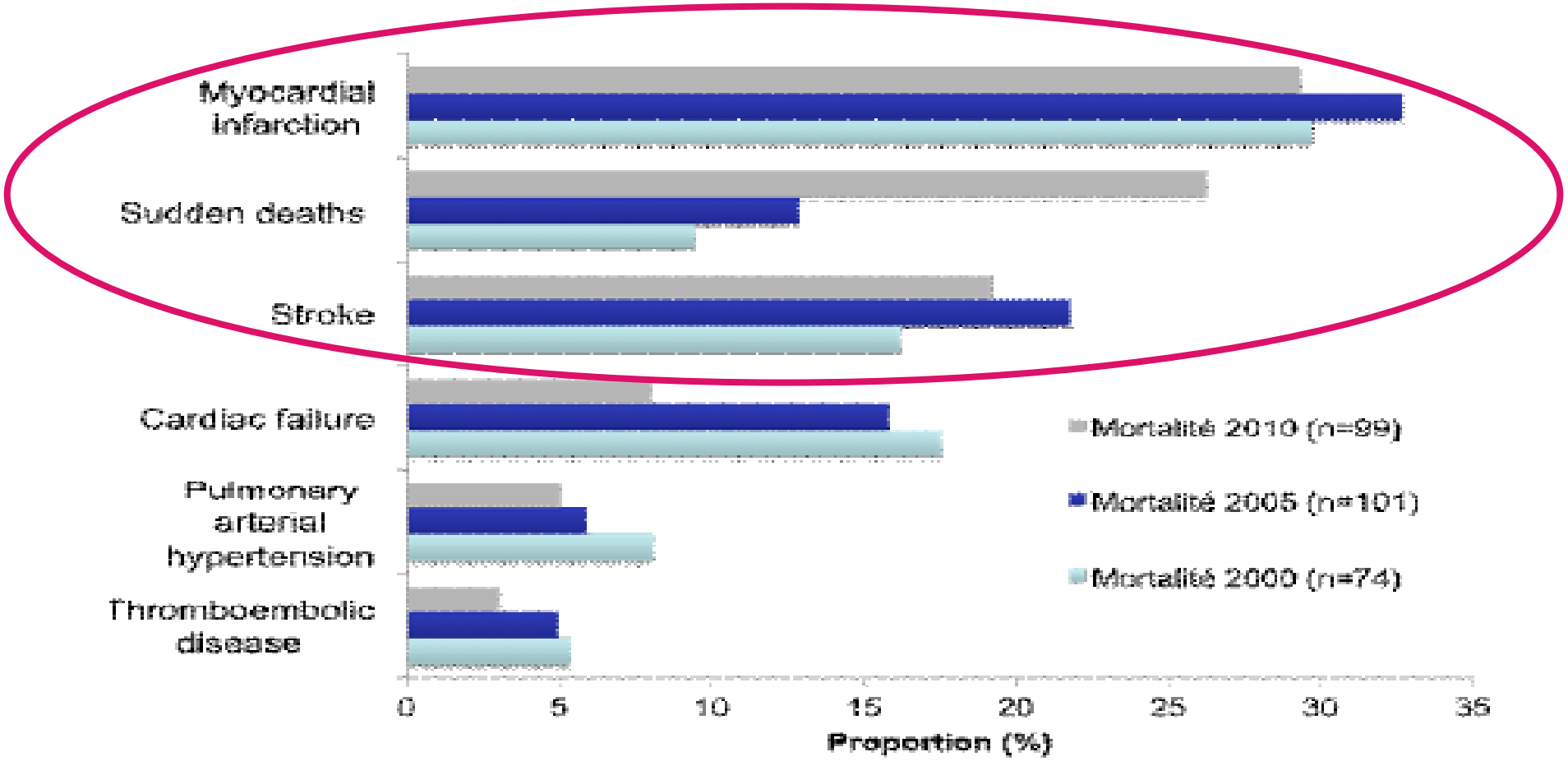
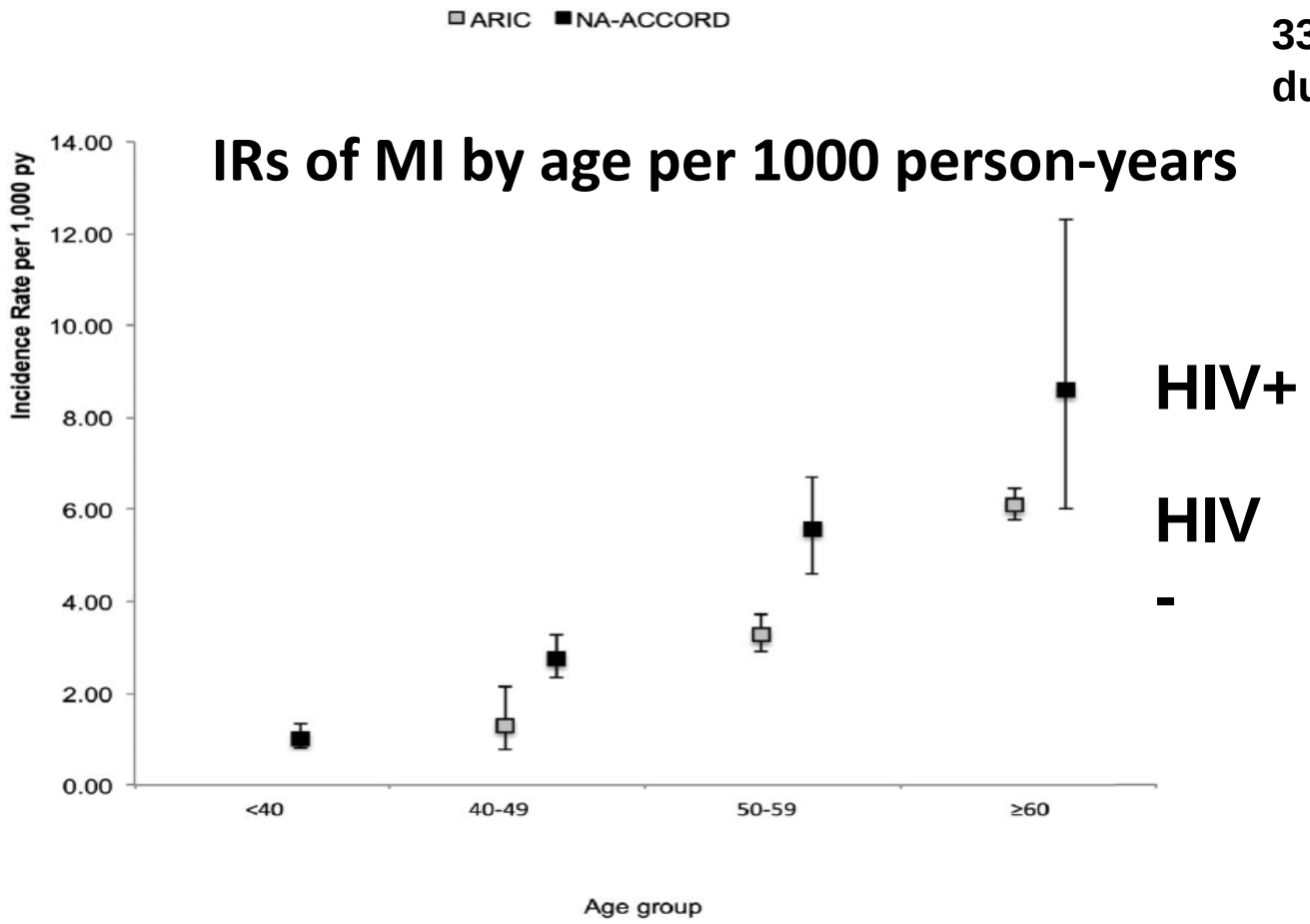


Figure 2 : Evolution of the distribution of the major underlying causes of cardiovascular-related deaths among HIV-infected adults in 2000 (n=74), 2005 (n=101) and 2010 (n=99) in France.

Morlat P. et al. AIDS. 2014;28:1181-91.

Risque IDM de type 1 supérieur chez les VIH+ vs VIH-

29,169 HIV+ in NAACCORD, 335 had an incident T1MI during 131,534 Pys of FU



In multivariable, traditional CVD risk factors: age, hypertension, diabetes, statin treated dyslipidemia, and eGFR < 30 mL/min were independent predictors of incident T1MI.

Time-updated detectable HIV RNA was significantly associated with increased risk of T1MI [1.36 (1.06 to 1.75)].

Drozd DR et al. JAIDS 2017;75:568-576.

IDM type 2 est plus fréquent que IDM type 1 chez les VIH+

NAACCORD, USA

- **571 patients (49 years; 430 men and 141 women) with definite or probable MIs**

→ 288 MIs (50.4%) were type 2 and 283 (49.6%) were type 1.

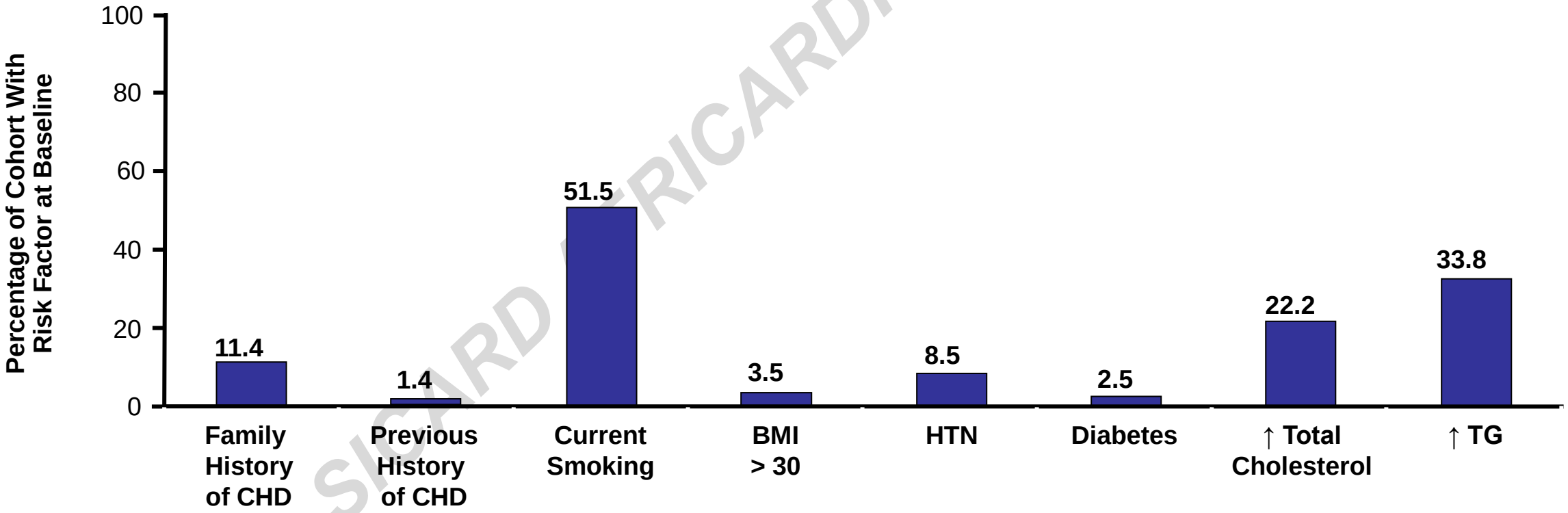
- **Sepsis or bacteremia (100 [34.7%]) and recent use of cocaine or other illicit drugs 39 [13.5%]) were the most common causes of type 2 MIs.**

- **A higher proportion of patients with type 2 MIs were younger than 40 years (47 of 288 [16.3%] vs 32 of 362 [8.8%]) and had lower current CD4 cell counts (median, 230 vs 383 cells/µL), lipid levels (mean [SD] total cholesterol level, 167 [63] vs 190 [54]mg/dL, and mean (SD) Framingham risk scores (8% [7%] vs 10% [8%]) than those with type 1 MIs**

Crane HM et al. JAMA Cardiol 2017;2:260-267.

Prévalence accrue de FDR CV dits traditionnels

- Large cohort of HIV-infected patients on HAART followed longitudinally (N = 23,468)
- 18,962 (80.8%) with previous ART exposure; 4506 (19.2%) antiretroviral naive



Friis-Møller N, et al. AIDS. 2003;17:1179-1193.

L'insuffisance rénale et la présence d'albuminurie sont aussi associées au risque d'IDM

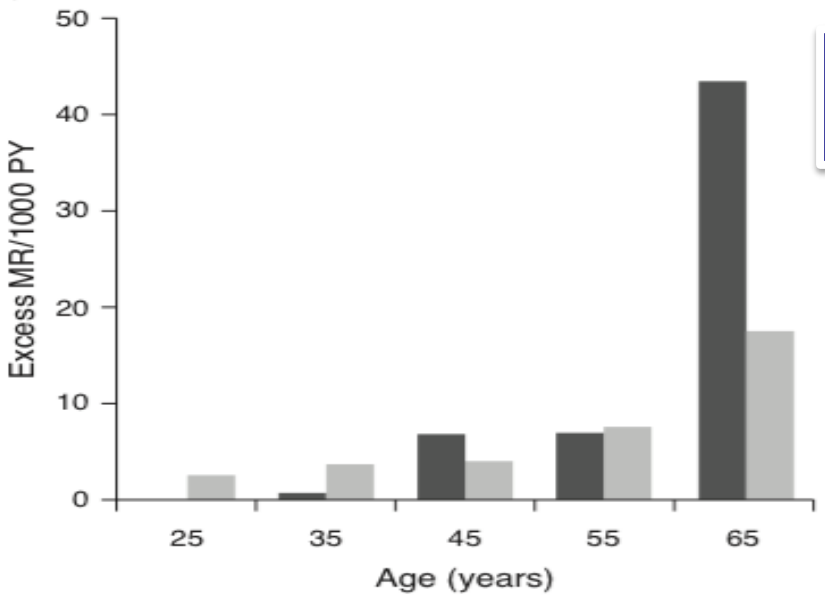
Veterans Affairs cohort : 17 264 HIV+

Risk of cardiovacular events according to renal failure and albuminuria

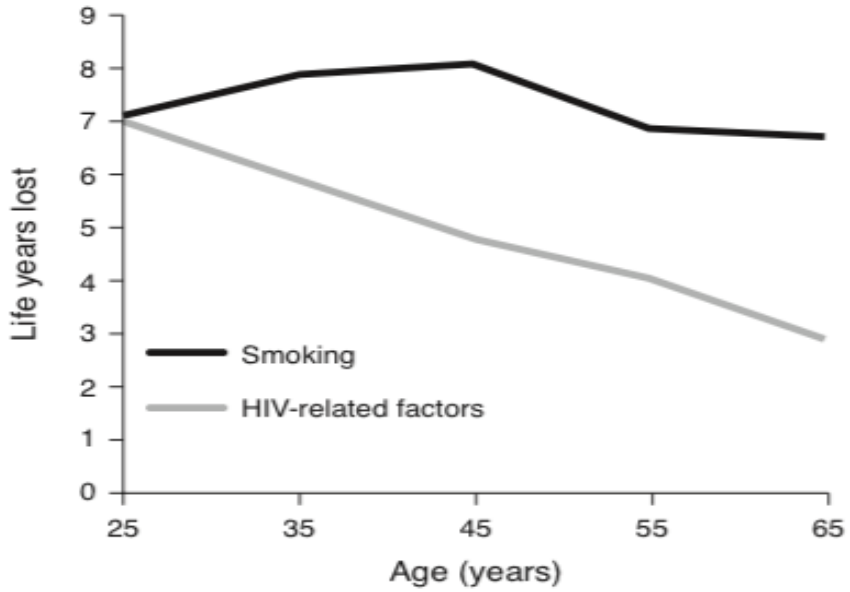
	Normal	Albuminuria ≥30 mg/mL	eGFR <60 mL/min per 1.73 m²	Both Conditions
Atherosclerotic cardiovascular event*				
No. of events	410	235	49	139
Demographic adjusted	1.0	1.52 (1.30–1.79)	1.99 (1.47–2.70)	3.88 (3.18–4.73)
Multivariable adjusted	1.0	1.35 (1.15–1.59)	1.61 (1.19–2.18)	2.62 (2.13–3.20)
Heart failure				
No. of events	100	128	25	124
Demographic adjusted	1.0	3.00 (2.30–3.92)	5.18 (3.30–8.12)	13.93 (10.61–8.31)
Multivariable adjusted	1.0	2.54 (1.94–3.33)	3.86 (2.45–6.06)	8.63 (6.50–11.47)
Individual outcomes				
Coronary disease				
No. of events	257	128	34	84
Demographic adjusted	1.0	1.36 (1.10–1.69)	2.16 (1.50–3.12)	3.86 (2.99–4.97)
Multivariable adjusted	1.0	1.23 (1.00–1.53)	1.71 (1.19–2.47)	2.66 (2.05–3.45)
Cerebrovascular disease				
No. of events	112	66	9	32
Demographic adjusted	1.0	1.43 (1.05–1.94)	1.40 (0.70–2.78)	2.84 (1.90–4.24)
Multivariable adjusted	1.0	1.21 (0.89–1.66)	1.16 (0.58–2.32)	1.88 (1.24–2.83)
Peripheral arterial disease				
No. of events	45	42	7	24
Demographic adjusted	1.0	2.36 (1.54–3.61)	2.88 (1.27–6.49)	6.03 (3.62–10.03)
Multivariable adjusted	1.0	2.07 (1.35–3.18)	2.43 (1.07–5.53)	4.05 (2.39–6.88)

Choi A et al. Circulation. 2010;121:651-658

Le tabagisme fait perdre plus d'années de vie que le VIH en Europe et Etats-Unis



17,995 HIV+
79,760 PY-FU



Age specific excess mortality rates in association with smoking and HIV-related

Numbers of life years lost in association with smoking and HIV-related factors

- ✓ Well treated HIV-infected individuals may lose more life years through smoking than through HIV
- ✓ Excess mortality associated with smoking increases markedly with age.
- ✓ Increases in smoking-related mortality can be expected as the treated HIV-infected population ages

Helleberg M et al. AIDS 2015, 29:221–229

Les facteurs de risque traditionnels sont prépondérants chez les VIH+

VETERANS Study

82 459 patients :33% HIV+, 97% M, 48% Afro-Am, FRS 6%

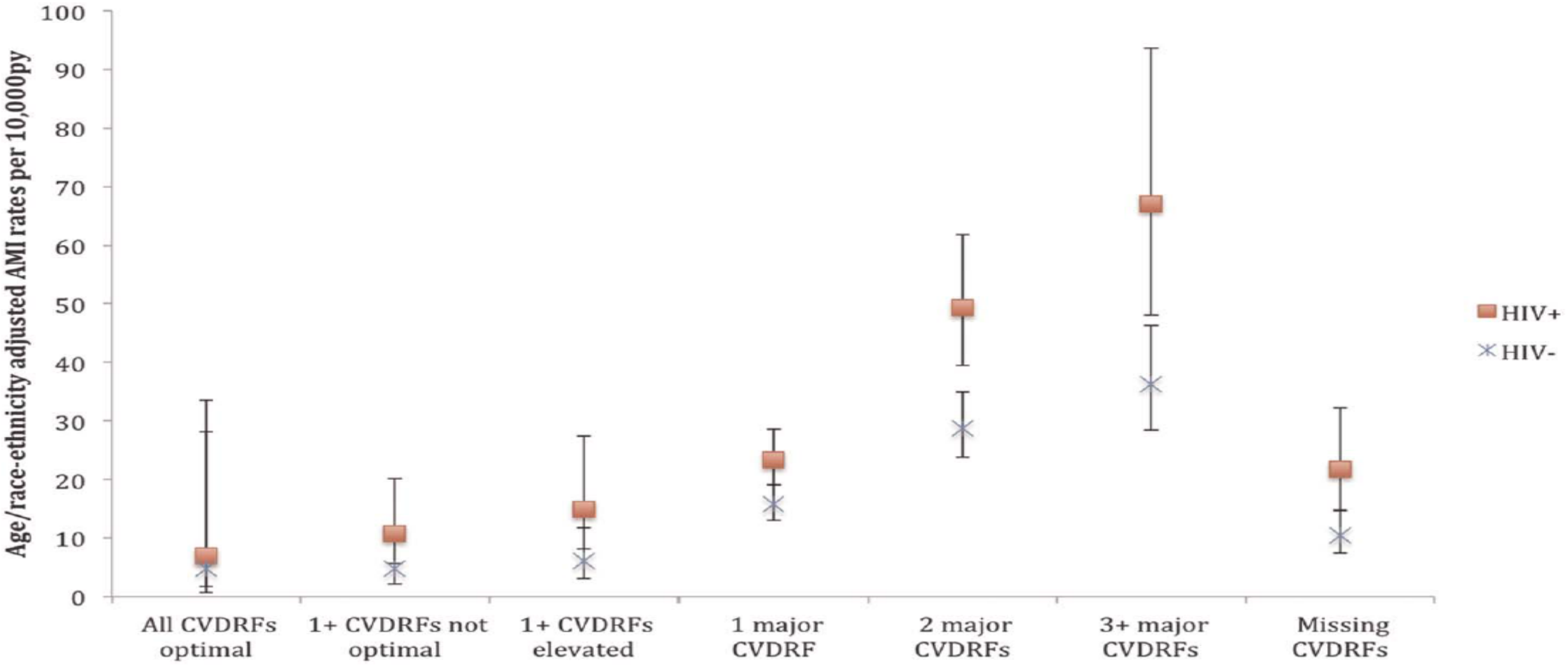
871 MI (42% HIV+)
Median FU 5.9y

Characteristics	Relative risk	95% CI
Age	1.78	1.65-1.92
Controled HTN	1.36	1.08-1.70
Uncontroled HTN	1.64	1.41-1.71
Diabetes mellitus	1.74	1.49-2.02
LDLc ≥ 160mg/dL	1.88	1.50-2.35
HDLc < 40mg/dL	1.05	0.83-1.35
Triglycerides > 150mg/dL	1.16	1.00-1.34
Current smoking	1.78	1.47-2.16
HVC infection	1.19	1.01-1.40
eGFR 30-60ml/mn/1.73m²	1.57	1.23-1.99
HIV infection	1.48	1.27-1.72

Freiberg MS et al. JAMA Intern Med 2013

Les FRDCV et les comorbidités sont plus fréquentes chez le VIH+

VACS Veteran aging cohrot study



Age-/race-/ethnicity adjusted rates of acute myocardial infarction (AMI) by cardiovascular disease risk factor profile (CVDRF) stratified by HIV status.

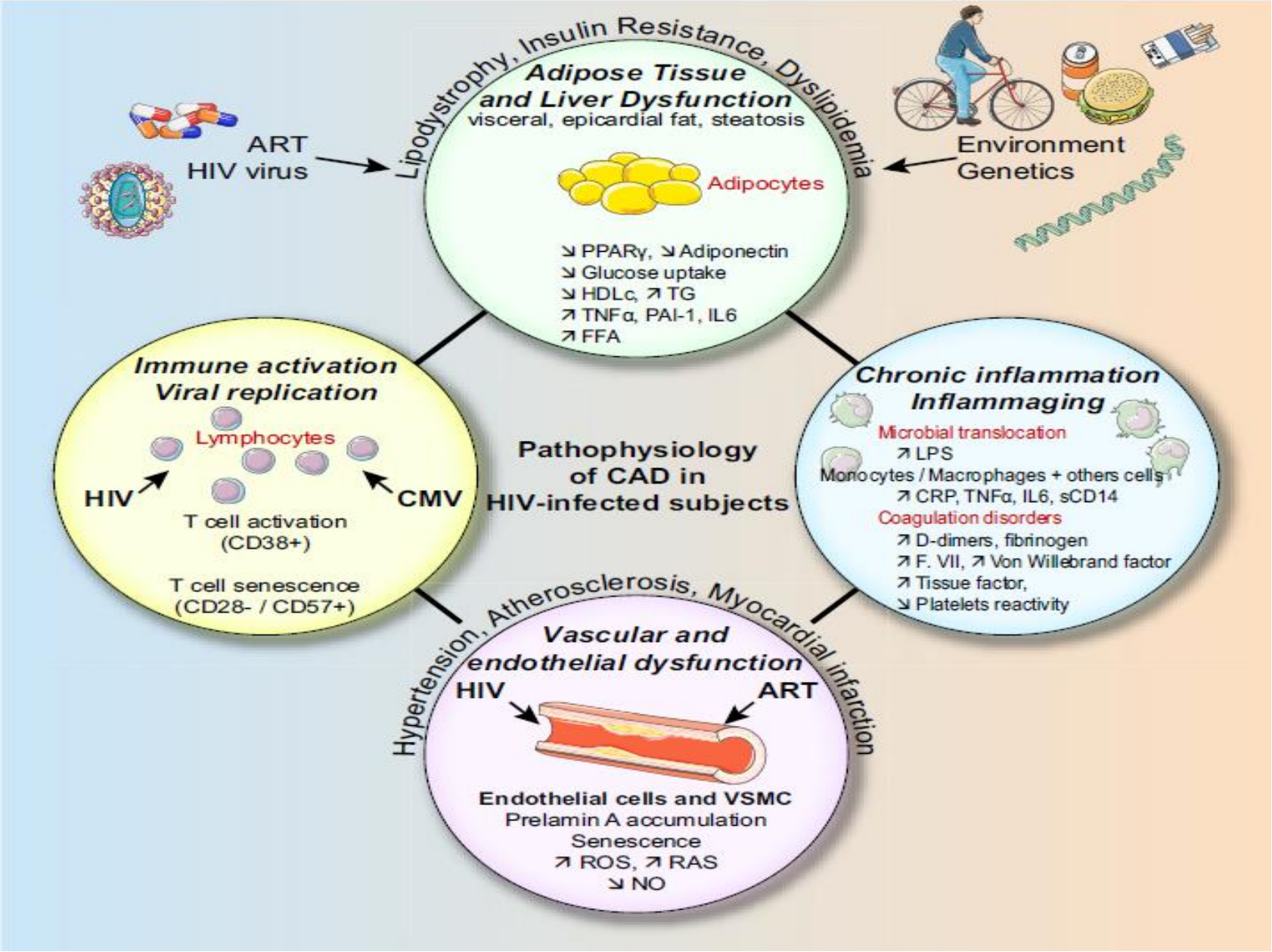
Paisible AL et al. J Acquir Immune Defic Syndr. 2015;68:209-16.

L'immunité est aussi associée au risque d'IDM

HIV parameters	Relative risk	95% CI
HIV infection	1.48	1.27-1.72
Viral load ≥ 500 c/ml	1.75	1.40-2.18
CD4 cell count < 200	1.88	1.46-2.40

Freiberg MS et al. JAMA Intern Med 2013

Mécanismes physiopathologiques du développement de l'athérosclérose



Boccara F. et al. J Am Coll Cardiol. 2013;61:511-23.

Quelle prise en charge du RCV ?

ESC/EAS Guidelines for the management of dyslipidaemias

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

European Heart Journal (2011) **32**, 1769–1818

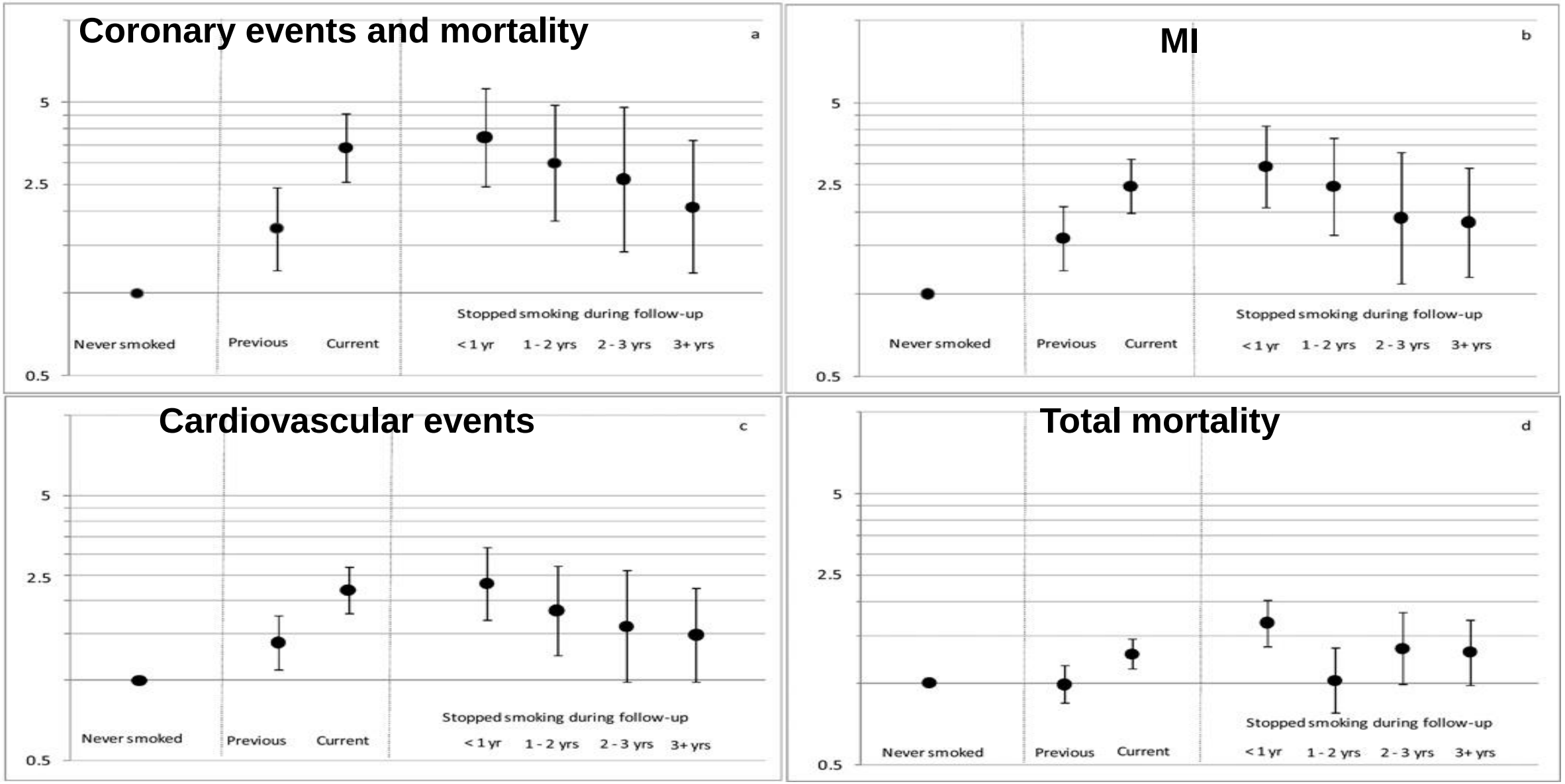
Table 32 Recommendations for lipid-lowering drugs in HIV patients

Recommendations	Class[a]	Level[b]
Lipid-lowering therapy, mostly statins, should be considered in HIV patients with dyslipidaemia to achieve the LDL-C goal as defined for high risk subjects.	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein-cholesterol.

ESC/EAS. Eur Heart J. 2011;32:1769-818.

The risk of MI decreased with the cease of smoking in HIV+ DAD study



Petoumenos K. et al. HIV Med 2011;12:412-21.

PACS-HIV study. Secondary prevention

ACS STEMI, NSTEMI, UA

Matched age (± 5yrs), gender, type of ACS

HIV+
N = 103

MACE

HIV-
N = 195

	HIV+ n = 103	HIV- n = 195	Hazard ratio HR [95% CI]
1 year FU			
Recurrent ACS	9	6	HR 4.6 [1.4-15.0]
Urgent PCI	7	3	HR 3.0 [1.4-15.0]
3 year FU			
Recurrent ACS	12	11	HR 3.4 [1.3-8.8]*

ACS: acute coronary syndrome, PCI : percutaneous coronary intevention

*** Data not published**

Boccara F. et al. Eur Heart J 2011;32:41-50.

PACS-HIV study

Multivariate analysis of factors associated with increased risk of recurrent ACS at 3 years FU

Multivariate analysis	Hazard Ratio	95% CI	P value
HIV+ versus HIV-	5.35	1.04-27.42	0.04
Total cholesterol, mg/dL*	6.80	0.98-47.42	0.05
LDLc, mg/dL*	13.39	1.18-151.67	0.04

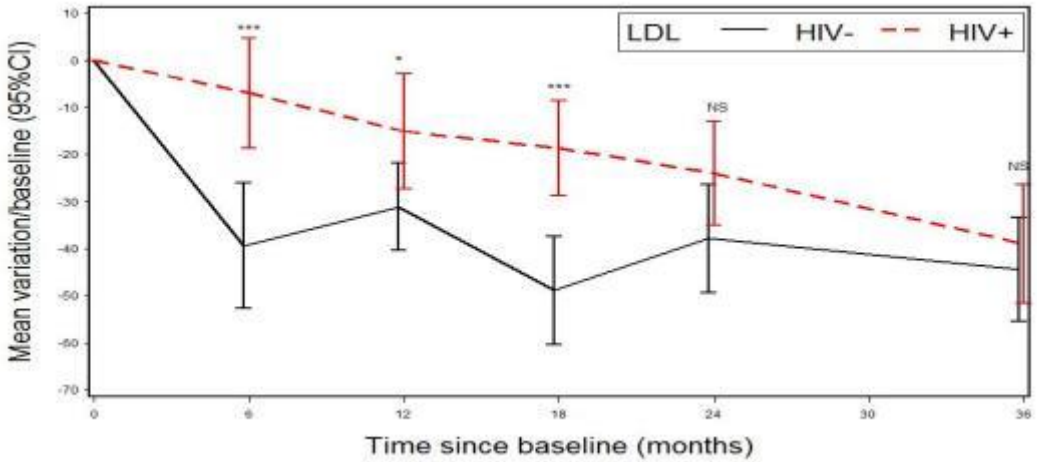
*time-dependent covariates

ESC 2014

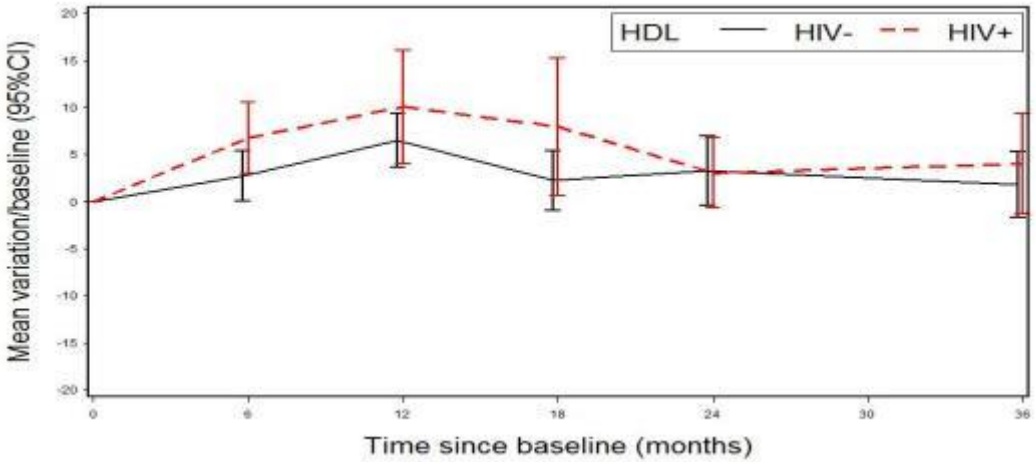
LIPIDS-PACS substudy (1)

Lipid parameters variation over 36 months

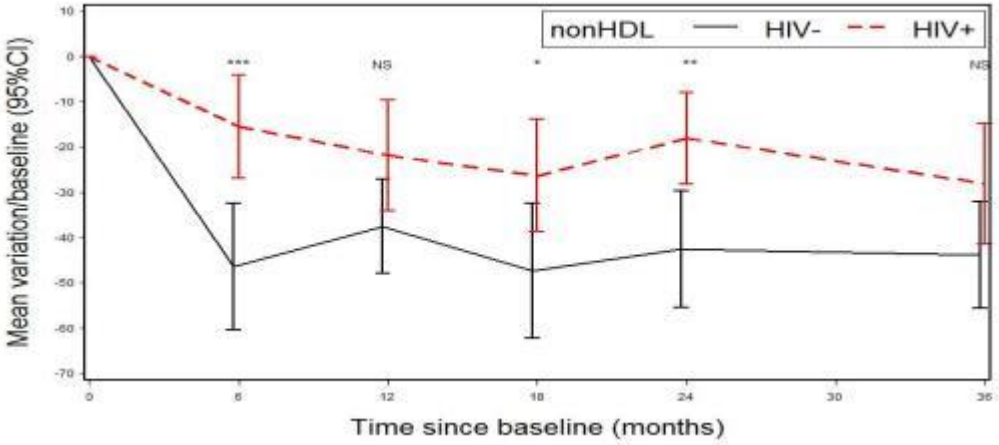
LDLc



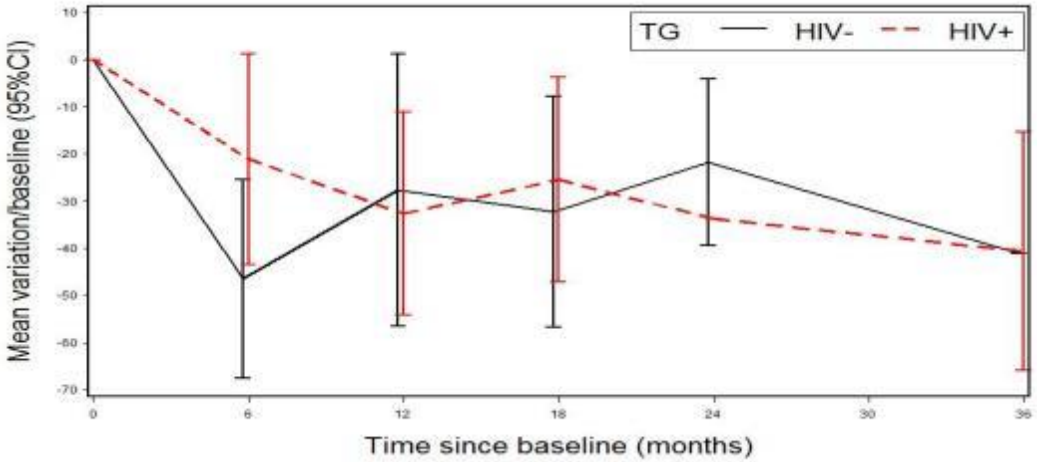
HDLc



Non-HDLc



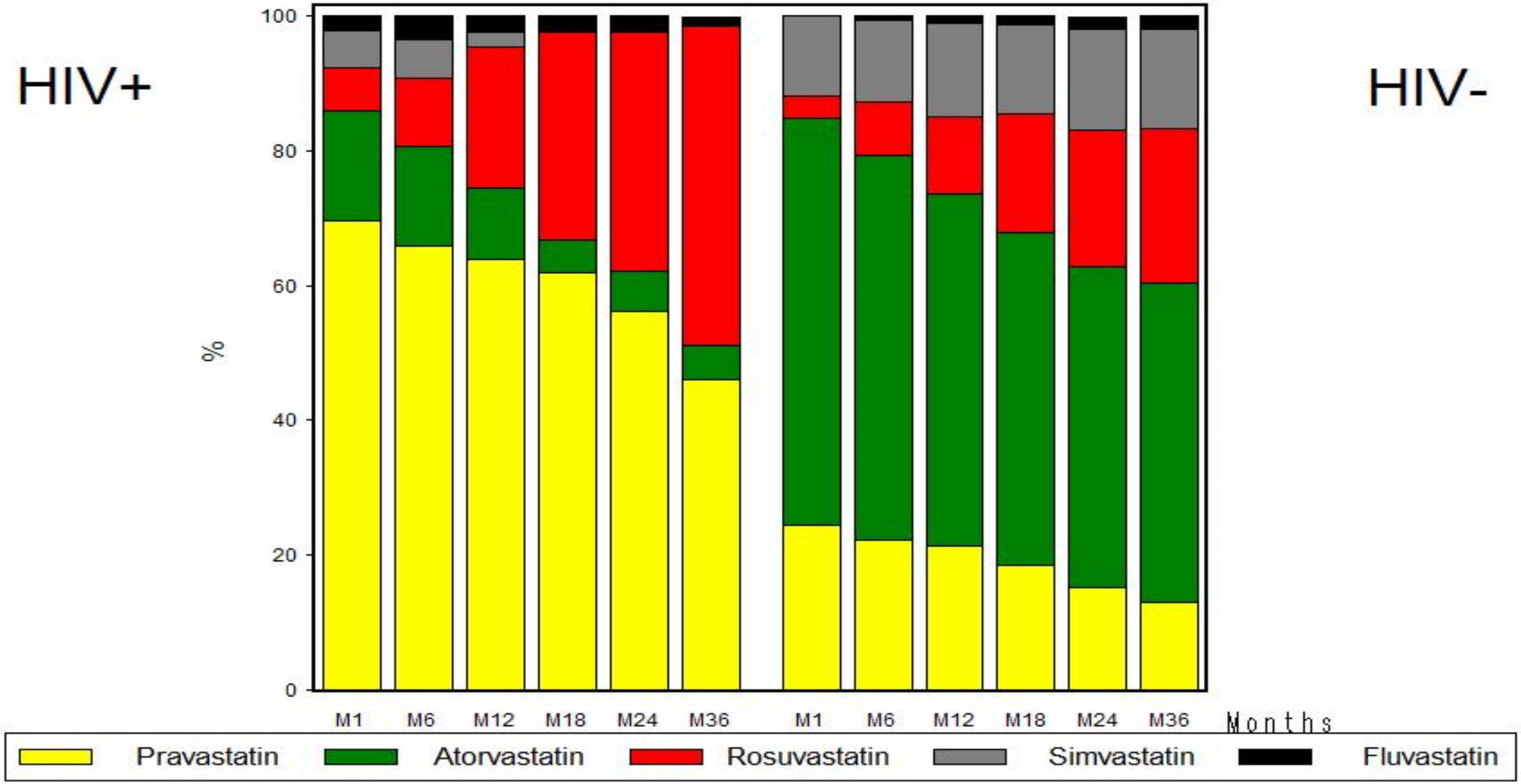
TG



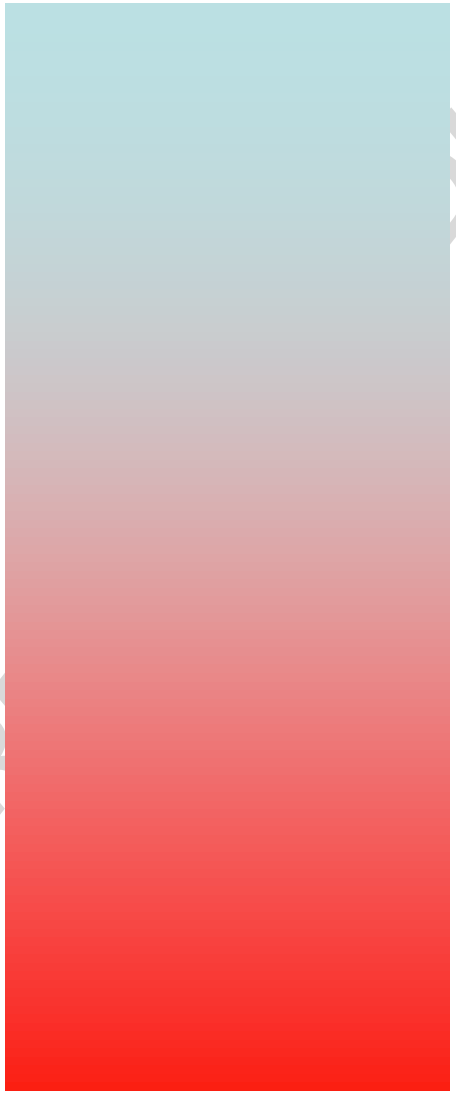
Boccara F. et al. Am Heart J. 2017;183:91-101.

LIPIDS-PACS substudy (2)

Distribution of statins prescribed along the 3 year FU



Intéractions statines et inhibiteurs de protéases/ Cobicistat



Fibrates
Rosuvastatin
Fluvastatin
Pravastatin*
Ezetimibe
Fish oil

Faible interaction

Statin + fibrate
Atorvastatin
Niacin

Précaution d'emploi

Lovastatin
Simvastatin

Contre-indiqué

*AUC ↑↑↑ with DRV.

Prévalence HTA- Facteurs associés

Etude norvégienne. VIH+ n=542 (27% F), Mesure PA à 3 visites.
Groupe contrôle VIH- (n= 24 968)

Prévalence = 36.5%

	BMI < 25 (kg/m²)				BMI ≥ 25 (kg/m²)			
Sex	HIV positive	Controls	OR (95% CI)	*P*	HIV positive	Controls	OR (95% CI)	*P*
Men	*n* = 120	*n* = 4335			*n* = 69	*n* = 7517		
Hypertension, *n* (%)	35 (29.2)	1033 (23.8)	1.32 (0.87–2.0)	NS	26 (37.7)	3091 (41.1)	0.87 (0.52–1.45)	NS
SBP (mmHg)	131.1 ± 13.9	130.2 ± 12.8		NS	136.8 ± 13.4	135.8 ± 13.9		NS
DBP (mmHg)	81.1 ± 10.3	77.4 ± 9.3		<0.0001	85.8 ± 8.9	81.9 ± 10.4		0.002
Women	*n* = 35	*n* = 7090			*n* = 12	*n* = 6026		
Hypertension, *n* (%)	4 (11.4)	838 (11.8)	0.96 (0.29–2.86)	NS	1 (8.3)	1542 (25.6)	0.26 (0.01–1.96)	NS
SBP (mmHg)	120.5 ± 13.5	121.1 ± 13.8		NS	123.9 ± 8.1	128.4 ± 16.1		NS
DBP (mmHg)	77.4 ± 8.3	73.9 ± 9.4		0.028	80.0 ± 6.9	78.2 ± 10.6		NS

Characteristic or laboratory value	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (years)	1.1 (1.07–1.12)*	1.08 (1.06–1.11)*
Sex	0.24 (0.15–0.41)*	0.33 (0.18–0.61)‡
Race		
White	Reference	Reference
Black	0.37 (0.15–0.9)†	1.01 (0.42–2.40)a
Asian	0.51 (0.32–0.82)†	0.97 (0.23–4.04)a
Smoking	0.73 (0.50–1.05)a	1.65 (0.94–2.89)a
BMI (kg/m²)	1.15 (1.09–1.21)*	1.17 (1.08–1.26)*
Cholesterol (mmol/l)	1.47 (1.25–1.74)*	1.28 (1.01–1.62)†
Diabetes mellitus	2.96 (1.1–8.67)†	1.64 (0.24–11.1)a
Duration since HIV test (years)	1.05 (1.02–1.09)‡	1.01 (0.96–1.06)a
cART duration (years)	1.17 (1.08–1.28)*	1.13 (1.02–1.24)†
GFR (ml/min)	0.99 (0.98–0.99)†	1.01 (1.0–1.02)a
Microalbuminuria	3.11 (1.72–5.62)*	3.55 (1.53–8.26)†
Hepatitis C positive	1.96 (0.96–4.03)a	1.27 (0.48–3.39)a

Analyse mulivariée

Age, sexe, IMC,
Cholesterol,
durée ART, Microalbu

Baekken M. et al. JHypert 2008;26:2126-2133.

HTA et lipodystrophie

Etude USA. 347 VIH+ suivi 6 mois. PA brassard. Def HTA PA > 140/90

Table 2 Odds ratios for factors associated with hypertension including any body morphology and body morphology severity

Variable	Hypertension* Unadjusted models OR (95% CI, *P*)	Adjusted model 1† OR (95% CI, *P*)	Adjusted model 2‡ OR (95% CI, *P*)
Body morphology			
No abnormality	1 (ref)	1 (ref)	
Any lipoatrophy	2.7 (1.3–5.5, 0.006)	2.2 (1.0–4.5, 0.04)	
Any lipohypertrophy	3.0 (1.5–5.9, 0.001)	2.5 (1.2–5.1, 0.01)	
No abnormality	1 (ref)		1 (ref)
Mild lipoatrophy	2.4 (1.2–5.0, 0.02)		2.0 (0.9–4.2, 0.08)
Mild lipohypertrophy	2.7 (1.3–5.4, 0.005)		2.3 (1.1–4.7, 0.03)
Moderate lipoatrophy	5.8 (1.7–19.8, 0.004)		4.3 (1.2–15.6, 0.03)
Moderate lipohypertrophy	5.6 (2.1–15.1, 0.001)		4.3 (1.5–12.4, 0.006)
Age (years)			
<30	1 (ref)	1 (ref)	1 (ref)
30–39	5.9 (0.8–46.7, 0.09)	4.2 (0.5–34.1, 0.2)	4.4 (0.5–35.9, 0.2)
40–49	13.4 (1.8–102.3, 0.01)	9.7 (1.2–77.2, 0.03)	9.4 (1.2–75.2, 0.04)
>50	23.2 (3.0–180.9, 0.003)	15.5 (1.9–126.3, 0.01)	14.9 (1.8–123.2, 0.01)
Current CD4 T-cell count§	1.1 (1.0–1.2, 0.01)	1.1 (1.0–1.3, 0.02)	1.1 (1.0–1.2, 0.02)

Analyse mulivariée
Lipodystrophie : atrophie et hypertrophie

Crane HM et al. HIV Med 2009

Attention aux intéractions médicamenteuses et tolérance

- **Inhibiteur calciques contre-indiqués**
  - Diltiazem (AUC +27%), Amlodipine (AUC + 90%) avec RTV et IDV

- **Bêtabloquants à éviter**
  - Aténolol augmenté par Atazanavir
  - Métoprolol augmenté par RTV

- **Diurétiques à éviter si Indinavir** (risque lithiase)

Glesby MJ, et al. Clin Pharmacol Ther. 2005;78:143-53.

Traitement de 1ère intention

- **Monothérapie : IEC ou AA2**
  - → Efficace, bonne tolérance
  - → Réduit l'apparition du diabète de 10%- 80%
  - → Action sur le tissu adipeux??
  - → Diminution du tissu adipeux viscérale?
  - → Amélioration de l'insulinosensibilité?

Abuissa H, et al. J Am Coll Cardiol. 2005:46:821-6.

Hyperéactivité plaquettaire (P2Y12) post SCA chez les VIH+

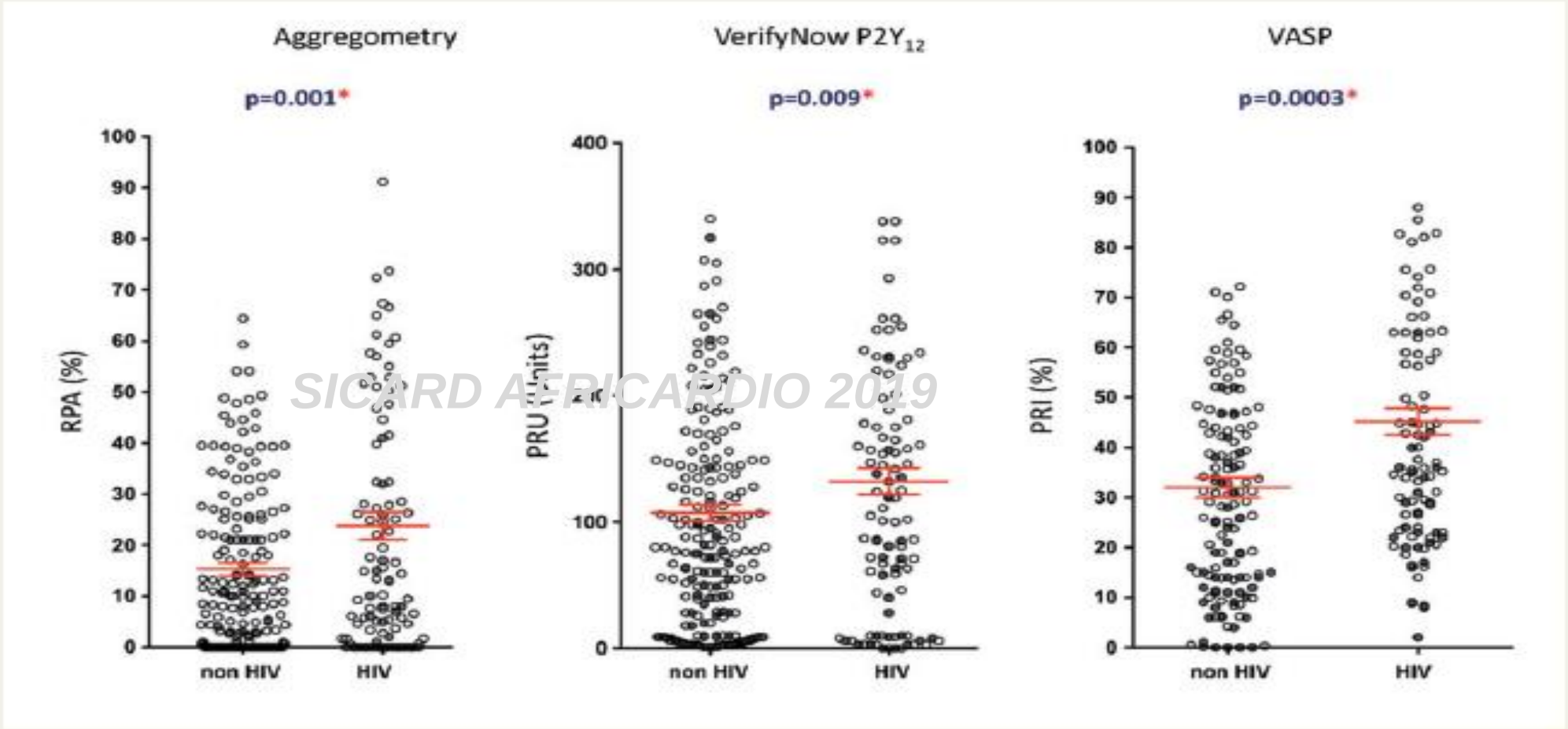


Figure 2 Response to $P2Y_{12}$ inhibitors in HIV (HIV+) and non-HIV patients. Evaluated by residual platelet aggregation (RPA), Platelet Reaction Units (PRU) and VASP Platelet Reactivity Index (PRI). White circles indicate patients under clopidogrel and grey circles patients under prasugrel or ticagrelor. * indicates a *P* value <0.05.

Hauguel-Moreau M, Boccara F, et al. Eur Heart J. 2017;38:1676-1686.

Hyperéacitvité plaquettaire (ASA) post SCA chez les VIH+

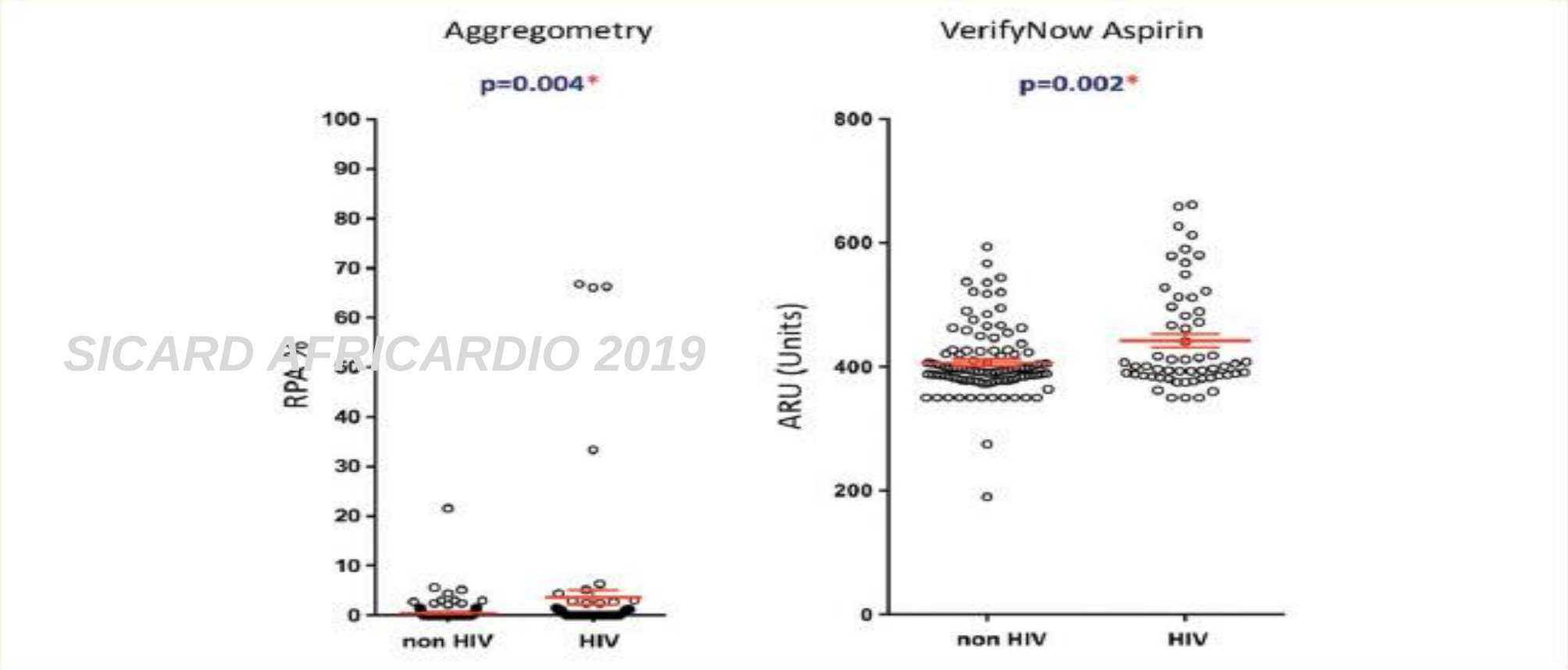


Figure 3 Response to Aspirin in HIV (HIV+) and non-HIV patients. Evaluated by residual platelet aggregation (RPA) and Aspirin Reaction Units (ARU). * indicates a *P* value <0.05.

Hauguel-Moreau M, Boccara F, et al. Eur Heart J. 2017;38:1676-1686.

Les drogues illicites et IP sont associés à une hyperéactivité plaquettaire chez le VIH

Table 5 HIV-related factors (among HIV patients) associated with HPR under $P2Y_{12}$ inhibitors

HIV Related factors	Unadjusted (n = 80)		Adjusted[a] (n = 75)	
	OR (95% CI)	P value	OR (95% CI)	P value
Illicit drug use	3.86 (1.08-13.81)	0.04*	4.98 (1.07-23.16)	0.04*
HIV RNA viral load				
per $\log_{10}$ copies/mL	1.26 (0.54-2.93)	0.6	1.29 (0.47-3.59)	0.6
<50 copies/mL	0.75 (0.17-3.22)	0.7	0.58 (0.09-3.75)	0.6
CD4+ T-cell count				
per 100/mm^3	1.04 (0.89-1.21)	0.6	1.02 (0.84-1.23)	0.9
≤500/mm^3	1.13 (0.39-3.30)	0.8	1.49 (0.44-5.11)	0.5
≤350/mm^3	1.86 (0.48-7.17)	0.4	3.41 (0.60-19.36)	0.17
CD8+ cell count per 100/mm^3	1.13 (1.02-1.25)	0.02*	1.08 (0.95-1.21)	0.2
CD4+:CD8+ ratio	0.30 (0.06-1.41)	0.13	0.54 (0.10-3.09)	0.5
Current exposure to HIV drugs				
Nucleoside reverse transcriptase inhibitors	0.65 (0.21-2.01)	0.5	0.64 (0.14-3.05)	0.6
Abacavir	1.00 (0.35-2.89)	0.9	0.93 (0.25-3.46)	0.9
Non-nucleoside reverse transcriptase inhibitors	0.41 (0.14-1.18)	0.10	0.44 (0.12-1.59)	0.2
Protease inhibitors	4.57 (1.37-15.29)	0.01*	4.42 (1.08-18.10)	0.04*

HPR was defined as RPA > 46.2%. Odds ratios (OR) and their 95% confidence intervals (CI) were directly estimated from a logistic regression model while accounting for within-triad correlation using a cluster sandwich variance estimator.

[a]Adjusted a priori for age, sex, ethnicity/race, body mass index, current smoking status, diabetes, family history of cardiovascular disease, and impaired renal function.

*indicates a P value < 0.05.

Hauguel-Moreau M, Boccara F, et al. Eur Heart J. 2017;38:1676-1686.

QUE FAIRE EN PRATIQUE?
QUELLE DAPT EN CAS DE SCA chez le VIH+?

Quel est le traitement antiVIH?	Quelle DAPT? Aspirine +?
IP (ritonavir [Norvir®], darunavir [Prezista®], lopinavir [Kaletra®], atazanavir (Reyataz®]) **cobicistat** [Tybost®, Stribild®, Genvoya®]	Prasugrel
Efavirenz [Sustiva®, Atripla®], **Etravirine** [Intelence®]	Ticagelor Prasugrel
Nevirapine [Viramune®] **Rilpivirine** [Edurant®, Eviplera®, Odefsey®,Juluca®]	Clopidogrel Ticagelor Prasugrel
Raltegravir [Isentress®] **Dolutegravir** [Tivicay®, Tirumeq®] **Bictegravir** [Biktarvy®]	Clopidogrel Ticagelor Prasugrel
Maraviroc [Celsentri®]	Clopidogrel Ticagelor Prasugrel

Antiaggrégants plaquettaires/NACO

Interactions Between Antithrombotic Drugs and Antiretroviral Therapy

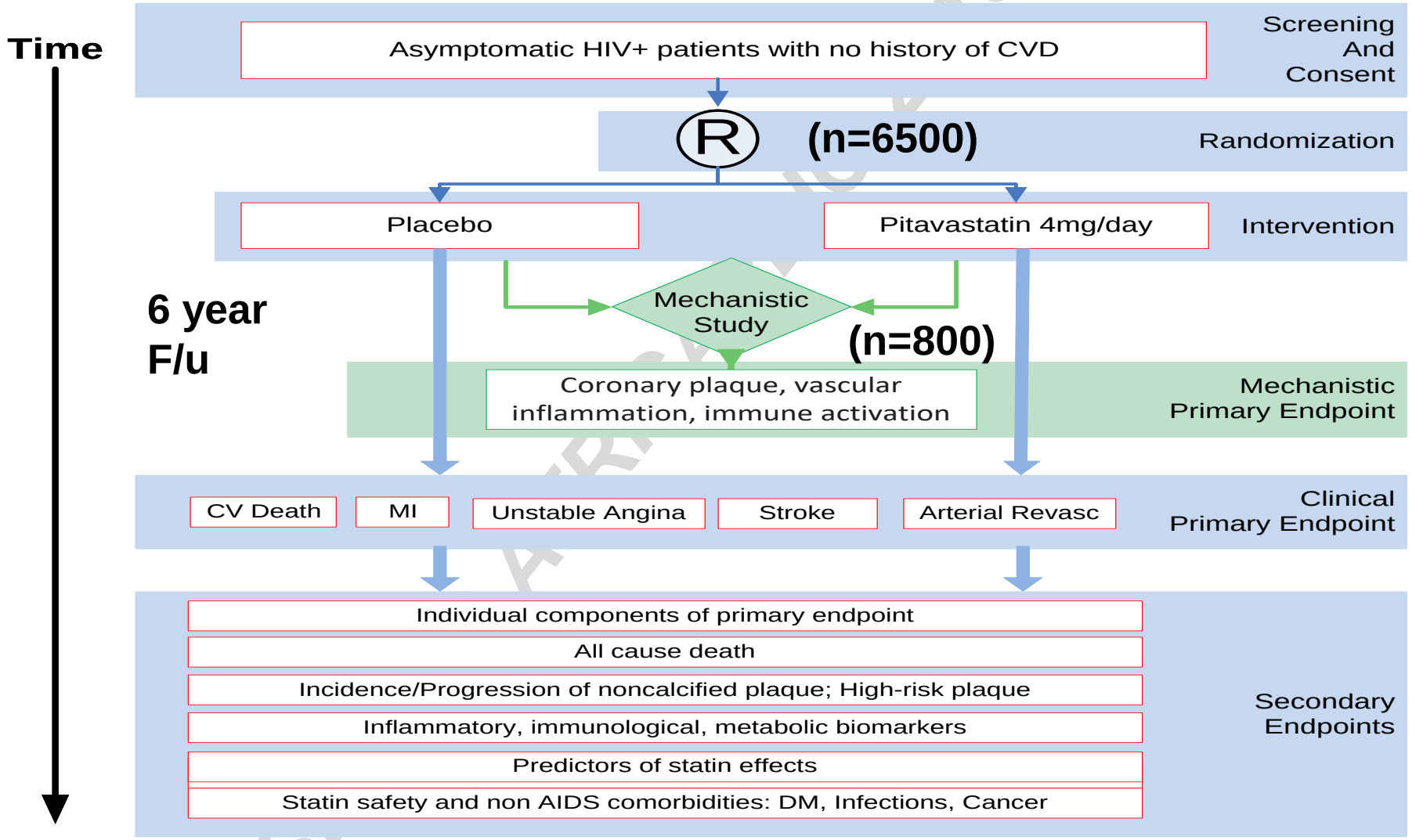
Antithrombotic drugs	Antiretroviral therapy
Clopidogrel	Weak interaction with PIs and cobicistat (decrease clopidogrel efficacy) and interaction with efavirenz and etravirine. No interaction with oher NNRTis, anti-integrase or maraviroc
Ticagrelor	Contraindicated with PIs (risk of bleeding)
Prasugrel	Possible use with PIs
New oral anticoagulants	Contraindicated with PIs except for dabigatran (slight decrease of AUC in healthy volunteers)
Warfarin	Precaution with PIs (decrease plasma levels of warfarin)

AUC, area under the curve; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

Boccara F. Rev Esp Cardiol 2016

Randomized Trial to Prevent Vascular Events in HIV REPRIEVE (A5332). Recruitment terminated April 2019

Principal Investigators:
Steven Grinspoon, MD
Pamela S Douglas, MD
Udo Hoffmann, MD, MPH
Heather Ribaudo, PhD



Funded by NHLBI and NIAID. Supported by KOWA Pharmaceuticals.

ACTG AIDS CLINICAL TRIALS GROUP

CONCLUSIONS

- La gestion des complications CV chez le VIH doit être une prise en charge pluridisciplinaire (cardiologues/infectiologues/endorrinologues)
- Priorité à l'efficacité et tolérance du traitement antiVIH le moins cardio ou lipidotoxique
- Priorité à l'aide au sevrage tabagique et drogues illicites
- Corrections des FDR CV traditionnels modifiables (HTA, dyslipidémie, diabète)
- Etudes sur la réactivité plaquettaire en prévention primaire et secondiare sont nécessaires
- La prévention CV de la population VIH sous traitement antirétrovirale est devenue une priorité (vieillissement de la population, accumulation de FDR CV et action directe du VIH et ART)

Société Française de Cardiologie

Merci pour votre attention

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