VIH et maladie coronaire
Que doit-on savoir?

GRCI 28ème édition

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Sommaire

- Epidémiologie
- FDR CV spécifiques
- Spécificités?
- Prise en charge

Epidémiologie

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Complications cardiovasculaires	AVANT ART (1980-1995)	APRES ART (1995-2015)	Exposition chronique et à long terme ART après 2020
Myocardite/Cardiomyopathie dilatée→ Insuffisance cardiaque	8-20 %	Disparition Persistance PVD	Impact du vieillissement? De la stéatose/fibrose cardiaque (IC diastolique)
Pericardite	10 %	Disparition PVD	Pas de risque potentiel
Endocardite	6.3-34 %	?	Pas de risque potentiel
Hypertension pulmonaire (HTP)	0.5%	0.5%	?
Hypertension systémique (HTA)	?	20-30%	Impact du vieillissement?
Maladie coronaire	NR	2-5%	Impact du vieillissement?
Atteinte vasculaire périphérique	NR	5%	Impact du tabac, drogues illicites, Hépatite C
Trouble du rythme auriculaire **Allongement du QT (mort subite)**	NR NR	1% ?	Impact du vieillissement? Impact des nouvelles molécules?
Accident vasculaire cérébral	NR	?	Impact du vieillissement?
Maladie thrombo-embolique veineuse	NR	?	Impact des nouvelles molécules?

Mortalité chez PVVIH en 2010
The ANRS EN20 Mortalité 2010 Survey in France

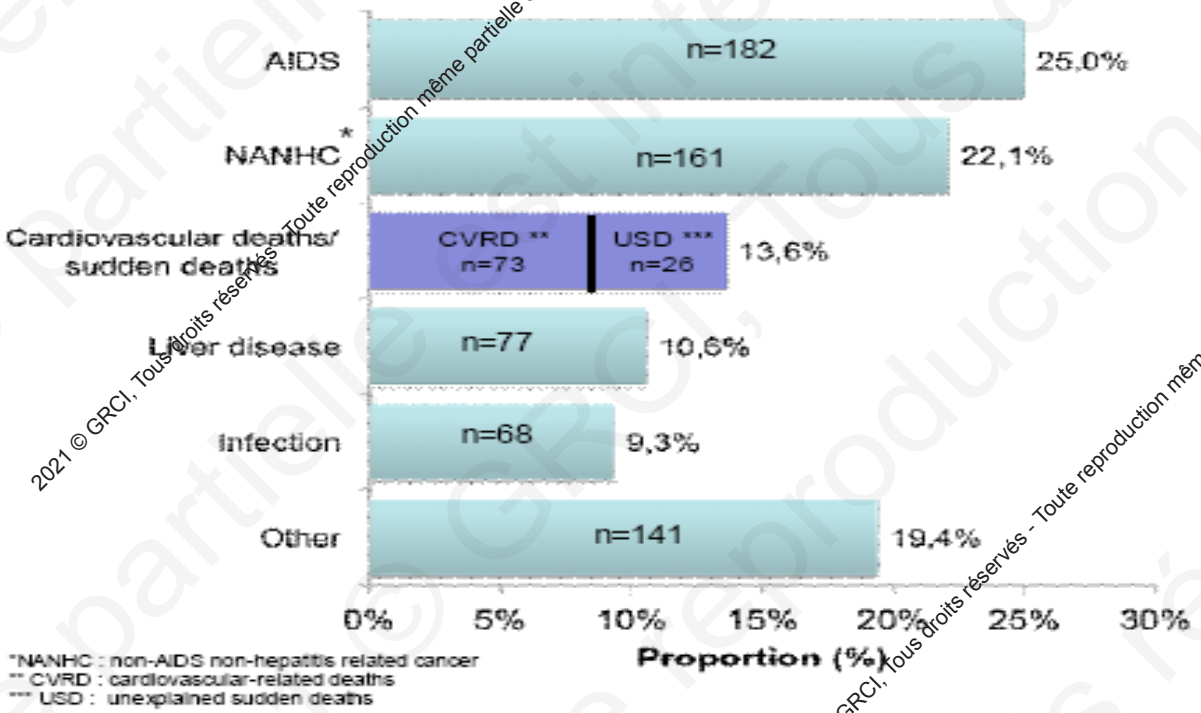

Figure 1 : Distribution of causes of 728 deaths among HIV-infected adults dying in 2010 in France

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

Est-ce que le risque d’IDM dans la population VIH+ est supérieure à celui de la population VIH-?

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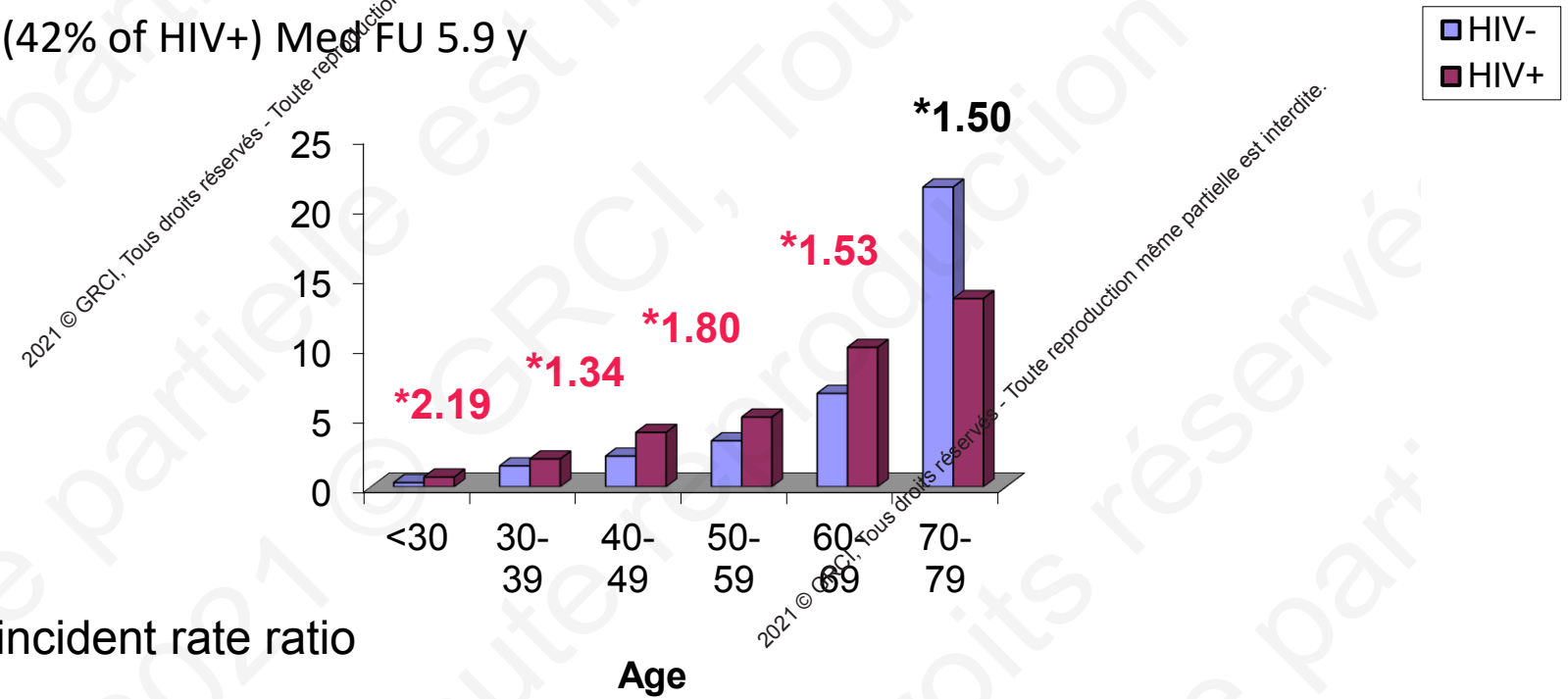
HIV veterans had a 50% increased risk of MI as compared to the HIV- veterans, USA

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

871 MI (42% of HIV+) Med FU 5.9 y

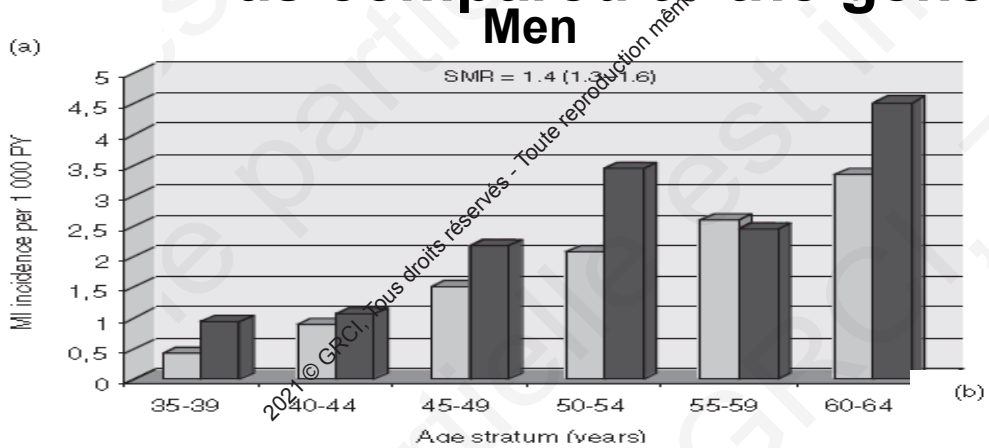


* incident rate ratio

Freiberg MS et al. JAMA Intern Med 2013

What about France?

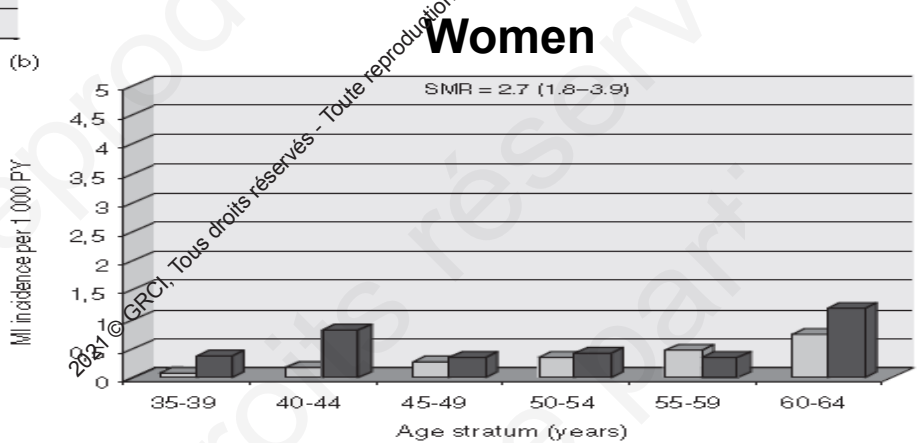
RR of MI is also increased by 50% in HIV+ population as compared to the general population (FHDH)



HIV- men
HIV+ men

SMR Men 1.4

Global SMR 1.5



HIV- women
HIV+ women

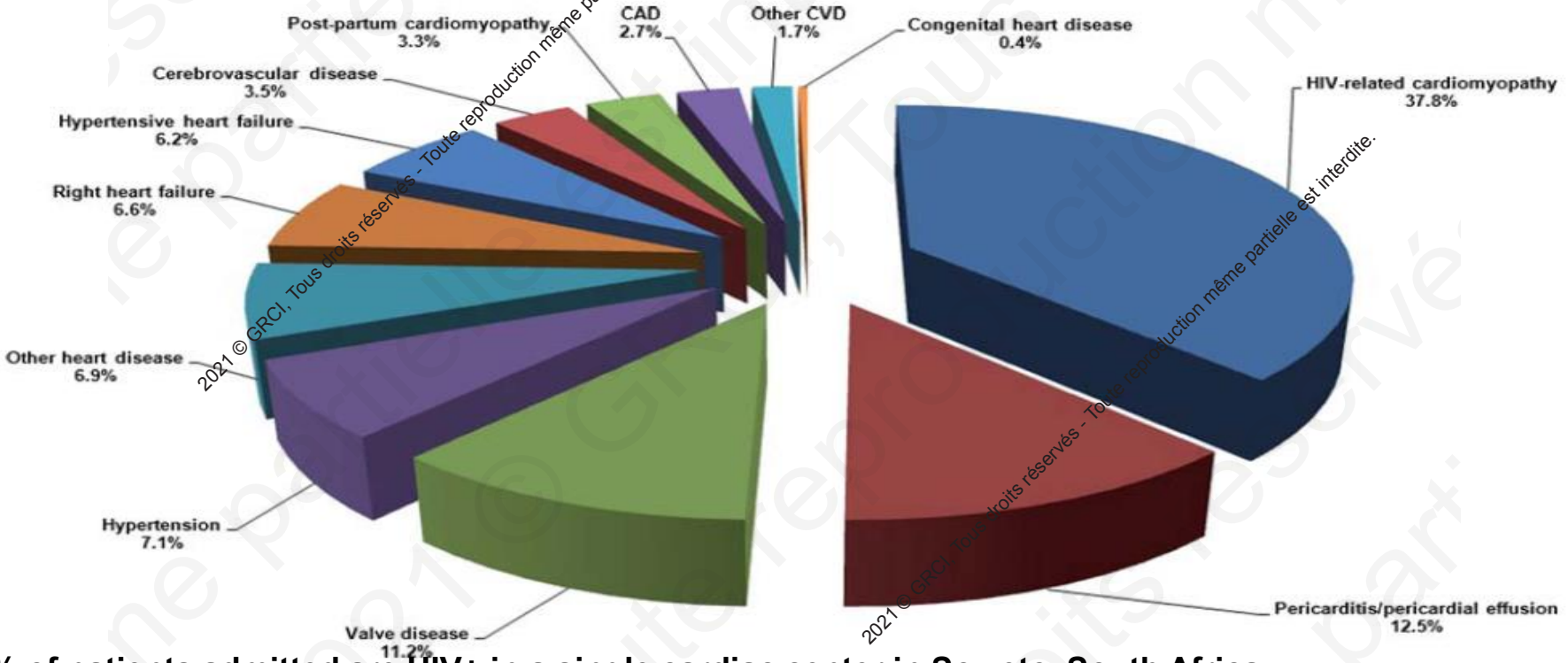
SMR women 2.7

Lang S. et al. AIDS 2010;24:1228-30.

In Sub-Saharan Africa, HIV-related cardiomyopathy is the first cause of cardiac manifestation

De novo admissions

62% female, mean age 38y



10% of patients admitted are HIV+ in a single cardiac center in Soweto, South Africa.

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

Y-a-t-il des FDR spécifiques?

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Traditional CV risk factors are associated with MI

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

VETERANS Study

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
Viral load ≥ 500 c/ml	1.75	1.40-2.18
CD4 cell count < 200	1.88	1.46-2.40

871 MI (42% HIV+), Median FU 5.9 years

Freiberg MS et al. JAMA Intern Med 2013

Increased of MI with some PI and NRTI

	DAD 2007[1]	DAD 2008[2]	DAD2009[3]	FHDH2009[4]
PI (as a family)	16% per year (relative to NNRTI) (10% per year, after adjustment for dyslipidemia, hypertension, and DM)	-	-	16% per year (relative to SQV)
LPV/r		-	13% per year	37% per year
IDV	-	-	12% per year	Not significant
APV/fAPV	-	-	Not significant	52% per year
ABC	-	90% recent exposure *	60% recent exposure * 7% per year	No effect if IVDU and cocaine are excluded
ddI	-	49% recent exposure *	41% recent exposure *	Not significant

1. DAD NEJM 2007; 2. DAD Lancet 2008; 3. DAD CROI 2009; 4. FHDH Archives of Int Med 2010

Spécifités cliniques et angiographiques au cours SCA?

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Comparaison FDRCV HIV+ vs HIV- avec SCA

Studies without an age matched control group

Studies, period, type of study, country	N HIV+ vs HIV-	Age, yrs *Male,%*	Tobacco, %	Cocaine, %	HTN, %	DM, %	Dyslip, %
Hsue 1993-2003 Database, USA	68 vs 68	50 vs 61 ***90 vs 62 ****	**46 vs 28***	NA	36 vs 41	9 vs 28	**17 vs 28 ***
Perelló 2006-2009 Retropective, Spain	44 vs 583	47 vs 72 ***92 vs 67 ****	**59 vs 20***	**11 vs 0.3***	**18 vs 6%***	16 vs 28	36 vs 49
Pearce 1997-2006 Database, USA	5,984 vs 2,501,904	48 vs 54 ***85 vs 72****	25 vs 30	NA	**46 vs 51***	**20 vs 28***	**25 vs 42 ***
Knudsen,2000-2009 Prospective, Den	48 vs 48	49 vs 59 *94 vs 94*	78 vs 75	ND	33 vs 24	0	37 vs 32

Young HIV+ have higher rate of smoking, illicit drugs use
Lower rate of HTN, DM and dyslipidemia

Comparaison FDRCV HIV+ vs HIV- avec SCA

Studies with an age matched control group

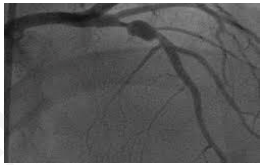
Studies, period, type of study, country	N HIV+ vs HIV-	Age, yrs Male,%	Tobacco, %	Cocaine, %	HTN, %	DM, %	Dyslip, %
Matetzky 1998-2000 **Prospective, USA**	24 vs 48	47 vs 48 88 vs 88	58 vs 48	0	**29 vs 44***	**12 vs 19***	58 vs 56
Boccara 2003-2006 **Prospective, Fr**	103 vs 195	48 vs 50 93 vs 94	59 vs 64	**5 vs 2***	19 vs 24	**9 vs 12***	45 vs 46
Lorgis 2005-2009 **Retrospective, Fr**	608 vs 1216	50 ± 10 vs match age and sex HIV-	30 vs 30	NA	**17 vs 22***	9 vs 11	31 vs 29
Ren, 2000-2007 **Database, USA**	97 vs 97	53 vs 54 100	26 vs 24	3 vs 2	**46 vs 67***	**10 vs 26***	60 vs 65
Badr, 2003-2011 **Database, USA**	112 vs 112	58 vs 58 64 vs 64	30 vs 27	ND	85 vs 84	25 vs 25	79 vs 81

Young HIV+ have higher rate of cocaine use, lower rate of HTN and DM

Données angiographiques HIV+ vs HIV- avec SCA

STEMI 50-60%, NSTEMI 30%, UA 20%

Studies, Patients (n)	Extent of CHD, %	No. diseased vessels	Culprit Vessel, %	Revascularization, %
Hsue **68 HIV+ vs 68 HIV-**	NR	HIV+ 1.3±1.0 **HIV- 1.9±1.2†**	NR	52% PCI 11% CABG
Pearce **5,984 HIV+ vs 2,501,904 HIV-**	NR	NR	NR	**PCI, thrombolytics and CABG > in HIV-**
Knudsen **48 HIV+ vs 48 HIV-**	**71% vs 63% 1T** **10% vs 27% 2T** **3% vs 19% 3T**	Type B2/C 38% vs. 94%	ND	81% vs 84%
Matetzky **24 HIV+ vs 48 HIV-**	76% ≥ 2VD 14% NSS	NR	NR	71% ATL 13% CABG
Ren **97 HIV+ vs 97 HIV-**	NR	2 vs. 2	LAD 42%	100% PCI
Boccara **103 HIV+ vs 195 HIV-**	56% 1T 28% 2T 13% 3T	1.5±0.8 1.5±0.7 Type B2 /C 77%	LAD 51% LCA 14% RCA 23%	76% PCI 4% CABG 20% Med
Lorgis **608 HIV+ vs 1216 HIV-**	ND	ND	ND	**66% vs 62% PCI**
Badr **112 HIV+ vs 112 HIV-**	ND	1.76 ± 0.85 vs 1.67 ± 0.83 Type C 33% vs 37%	LAD 40% RCA 32% LCx 24% LM 0.6%	100% PCI Similar Success 99%



Baseline coronary angiographic features

Characteristics	HIV-, N=107	HIV+, N=60	p
Radia/femoral access	66%/30%	57%/38%	0.31
No coronary lesion	1.9%	1.7%	0.86
1 vessel disease/2VD/3VD or LM	48%/33%/13%	43%/33%18%	
Number of coronary stenosis ≥ 50%	**1.7 ± 1.1**	**2.0 ± 1.3**	**0.04**
Number coronary stenosis < 50%	1.0 ± 1.1	1.0 ± 1.0	0.60
Coronary spam	2%	3%	0.87
Coronary aneurysm (≥ 1)	**5%**	**15%**	**0.02**
Chronic total occlusion	8.4%	8.3%	0.96
Initial Syntax score	11.5 ± 7.8	12.4 ± 9.0	0.42
Modified Initial Syntax score	11.0 ± 7.8	11.7 ± 8.6	0.56
Residual Syntax score	**2.7 ± 4.9**	**4.7 ± 7.0**	**0.04**
Modified residual Syntax score	2.4 ± 4.7	4.0 ± 6.6	0.09

Mean ± SD

Robert R. et al. en cours soumission

Resténose et thrombose de stent

Study Patients (n) HIV status	Follow-up, months	Clinical restenosis rate HIV+ vs HIV-, %	Stent thrombosis rate, %
Hsue 1993-2003 **68 HIV+ vs 68 HIV-**	NR	**52% vs 14%*** stent (76%) : In stent group : 50% vs 18% NS	ND
Matetzky 1998-2000 **24 HIV+ vs 48 HIV-**	14.7 ± 8	**43% HIV+**	ND
Ren 2000-2007 **97 HIV+ vs 97 HIV-**	36	18% vs 13% 11% DES vs 2% DES	4% vs 3 %
Boccara 2003-2006 **103 HIV+ vs 195 HIV-**	12	9% vs 7% HR 1.4; 95% CI [0.5 – 3.08]	1% vs 0.5%
Lorgis 2005-2009 **608 HIV+ vs 1216 HIV-**	12	ND but need for **PCI 3.2% vs 1.6%, p = 0.078**	ND
Badr 2003-2011 **112 HIV+ vs 112 HIV-**	24	Similar TLR<10% No difference at 6, 12, 24 months	3.3% vs 1.1%

Prognostic post-SCA

Studies, Period, N	Follow-up, months	MACE HIV+ vs HIV-	Cardiac death HIV+ vs HIV-	Recurrent ACS HIV+ vs HIV-
Matetzky 1998-2000 24 HIV+ vs 48 HIV-	14.7 ± 8	ND	0% vs 2%	**45% vs 11%***
Ren 2000-2007 97 HIV+ vs 97 HIV-	36	33% vs 30%	3% vs 2%	9.4% vs 2.4%
Boccara 2003-2009 103 HIV+ vs 195 HIV-	12	10 % vs. 9% **Heart failure 4% vs 0%**	0% vs 1%	**9% vs 3% HR 6.5 [1.7 – 23.9]**
Lorgis 2005-2009 608 HIV+ vs 1216 HIV-	12	ND **Heart failure 3.3% vs 1.4%**	1.4% vs 1.7%	6.7% vs 6% (recurrent MI)
Badr 2003-2011 112 HIV+ vs 112 HIV-	24	31% vs 21%	5.4% vs 5.4%	3.3% vs 1.1%

PACS-HIV study

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]

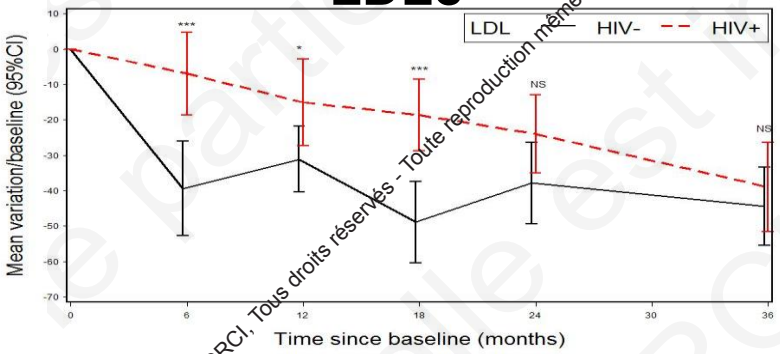
ACS: acute coronary syndrome, PCI : percutaneous coronary intevention

Boccara F. et al. Eur Heart J 2011;32:41-50.
Boccara F. Et al. JAHA 2020;9:e017578.

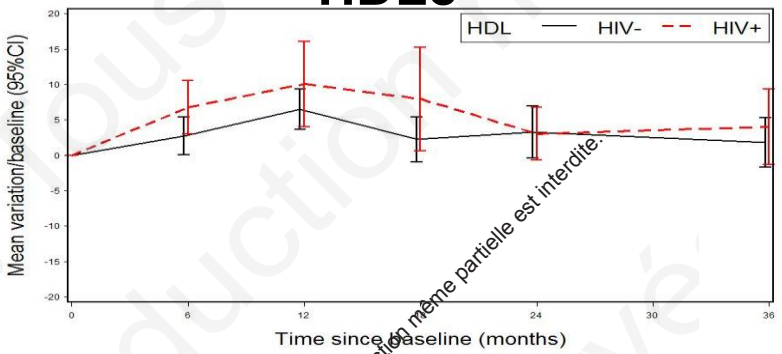
LIPIDS-PACS substudy

Lipid parameters variation over 36 months

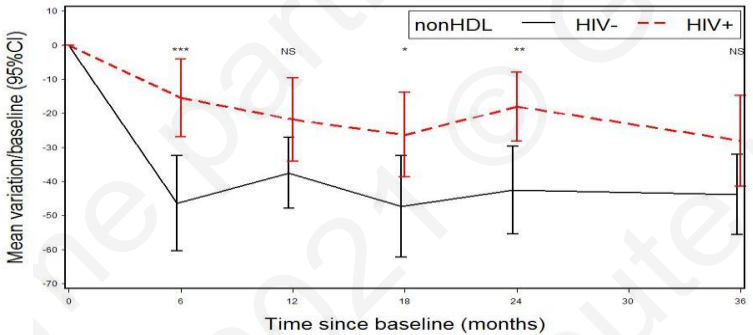
LDLc



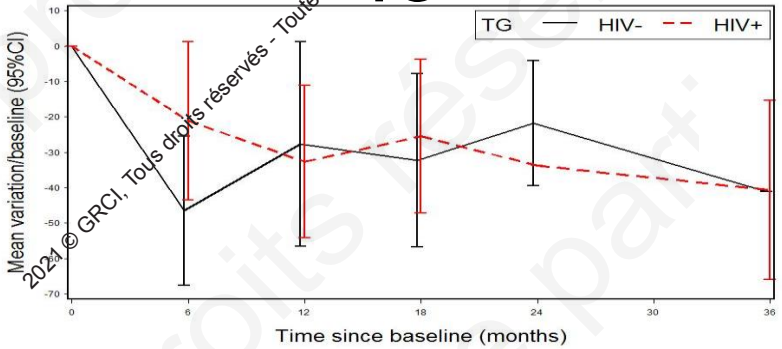
HDLc



Non-HDLc



TG



Boccara F. et al. AHJ. 2017;183:91-101

Hyper réactivité plaquettaire (P2Y12) post SCA chez les VIH+

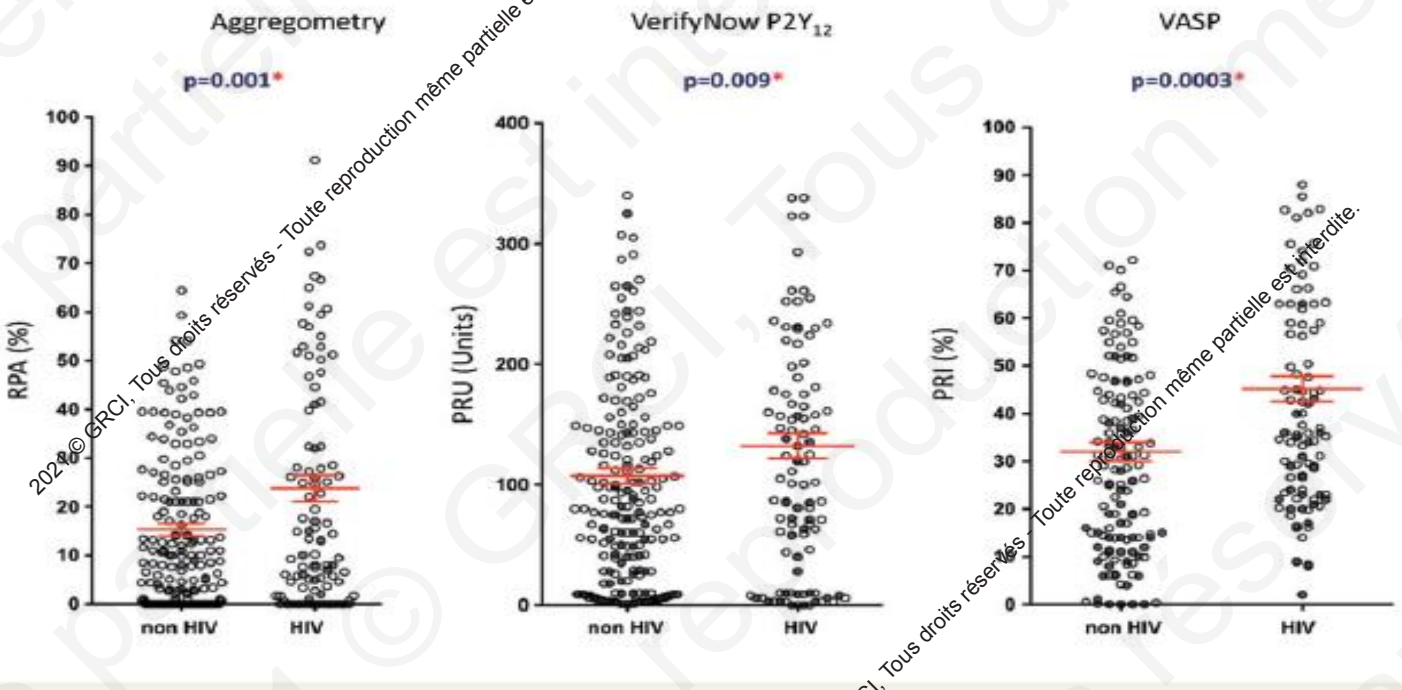


Figure 2 Response to $P2Y_{12}$ inhibitors in HIV (HIV+) and non-HIV patients. Evaluated by residual platelet aggregation (RPA), Platelet Reaction Units (PRU) and VASP Platelet Reactivity Index (PRI). White circles indicate patients under clopidogrel and grey circles patients under prasugrel or ticagrelor.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

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

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 (0.8[illegible]-1.23)	0.9
≤500/mm^3	1.13 (0.39-3.30)	0.8	1.49 (0.[illegible]4-5.11)	0.5
≤350/mm^3	1.86 (0.48-7.17)	0.4	3.4[illegible] (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.

Quelle prise en charge?

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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

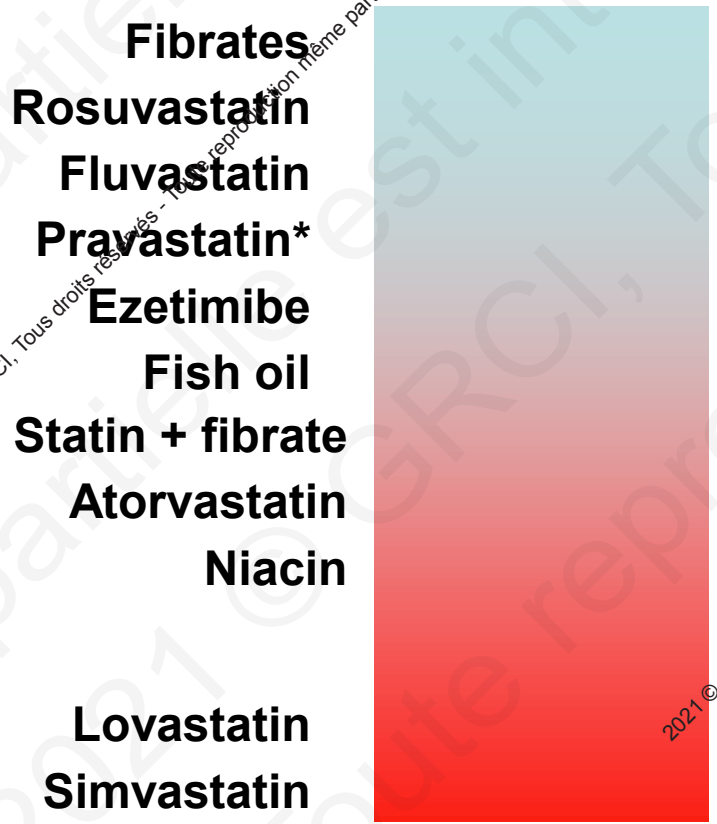
Table 32 Recommendations for lipid-lowering drugs in HIV patients

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.

Lipid-Lowering Agents and PIs: Drug-Drug Interactions



*AUC ↑↑↑ with DRV.

QUE FAIRE EN PRATIQUE avec la DAPT?

Quel est le traitement antiVIH?	Quelle DAPT? Aspirine +?
Antiprotéases (ritonavir [Norvir®], darunavir [Prezista®], lopinavir [Kaletra®], atazanavir (Reyataz®]) **cobicistat** [Tybost®, Stribild®, Genvoya®] **Autres: Efavirenz** [Sustiva®, Atripla®], **Etravirine** [Intelence®] **Nevirapine** [Viramune®]	**Prasugrel**
Rilpivirine [Edurant®, Eviplera®] **Emtricitabine** [Emtriva®, Eviplera®, Trivada®] **Doravirine** **Anti-intégrases** **Raltegravir** [Isentress®], **Dolutegravir** [Tivicay®, Tirumeq®], **Elvitegravir** [Stribild®, Genvoya®], Bictégravir [Biktarvy®], Cabotegravir Tenofovir [Stribild®, Truvada®, Atripla®….. **Maraviroc** [Celsentri®]	**Clopidogrel** **Ticagelor** **Prasugrel**

Le plus simple Liverpool HIV drug interactions
https://www.hiv-druginteractions.org/checker#

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

Conclusions

- **Athérosclérose coronaire est maintenant la 1ère cause de maladie CV chez les patients VIH+ traités (3ème cause de décès)**

→ ***Risque IDM VIH+> VIH-***

- **Physiopathologie complexe avec des FDR CV (tabac, cocaïne) et des FDR spécifiques: lipodystrophie, inflammation chronique, VIH lui-même, activation immune, ART.**

- **Aspects angiographiques peu différent MC du sujet jeune non VIH (anévrismes plus fréquent, plus difuse?)**

- **Prise en charge MC identique avec focus sur DDI (statines, AAP)**

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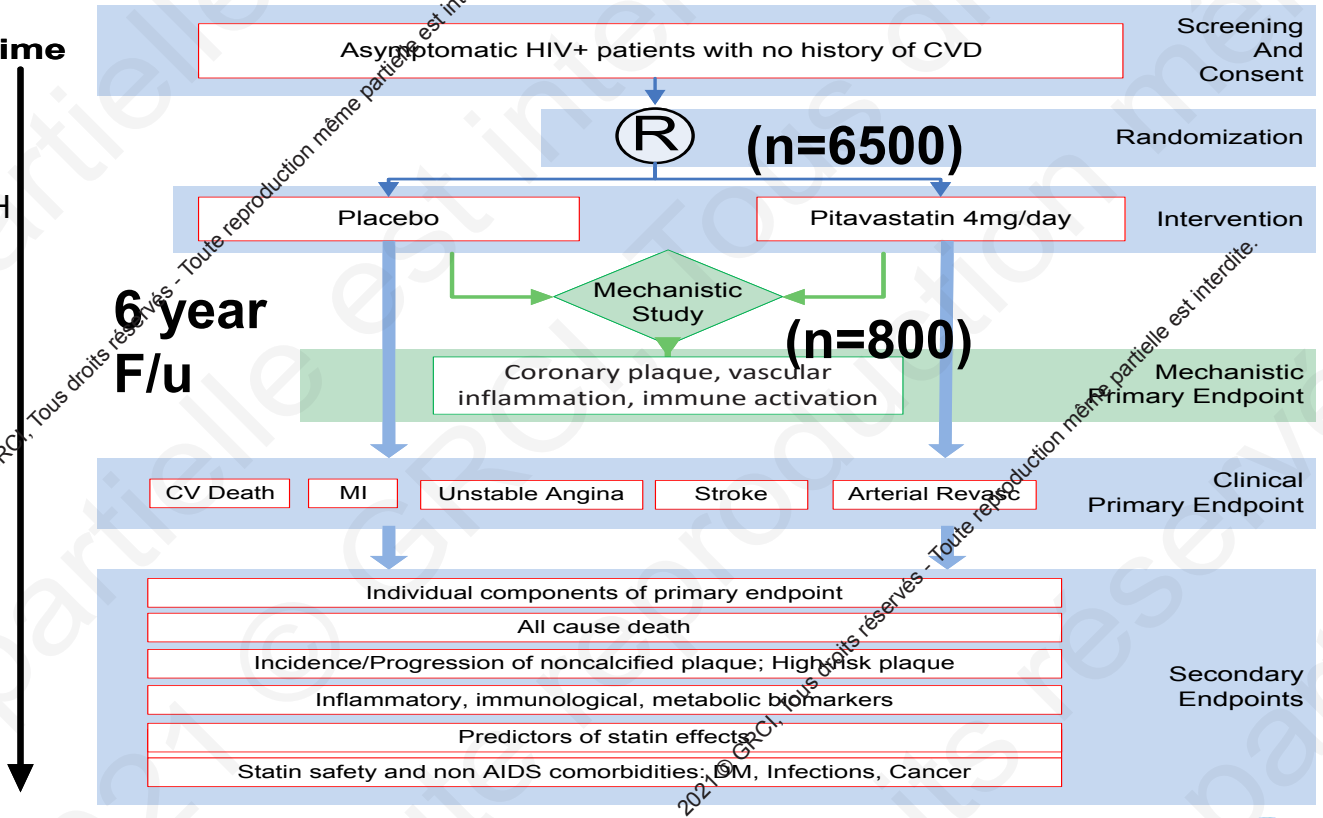
Randomized Trial to Prevent Vascular Events in HIV REPRIEVE (A5332)

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