Comment évaluer le risque vasculaire chez les patients vivant avec le VIH en Afrique ?

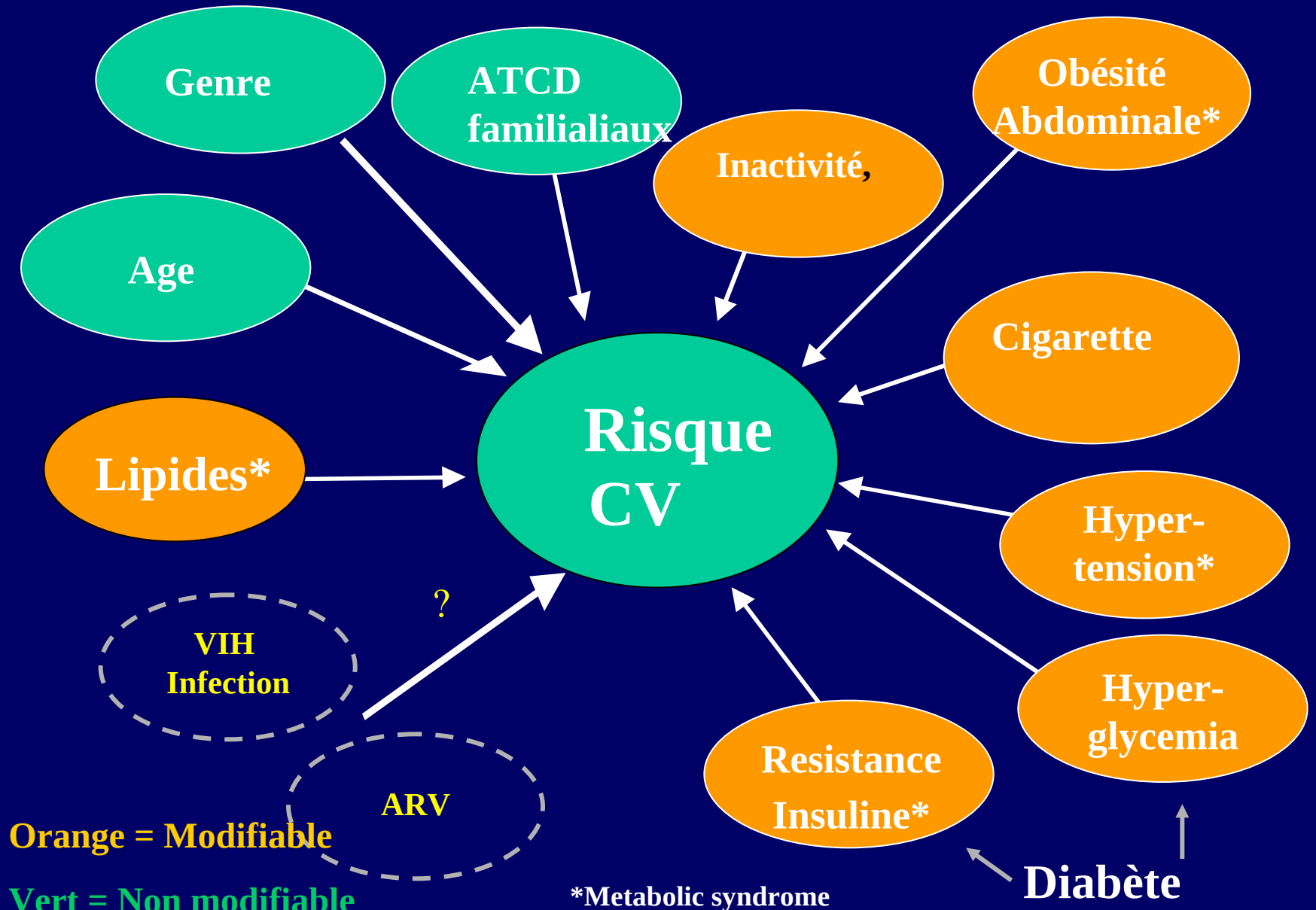
Papa Salif Sow, Service des Maladies Infectieuses CHU de Fann, Dakar Sénégal

11ème JNI Montpellier 9-11 Juin 2010

Introduction

- **Fréquence plus accrue de maladie cardiovasculaire chez les patients VIH+**
- **Maladies cardiovasculaires chez les VIH+**
  - **Facteurs risque traditionnels CV**
  - **Effets de la thérapie antirétrovirale**
  - **Infection par le VIH**

Facteurs de risque CV chez les patients VIH+



Plan de l'exposé

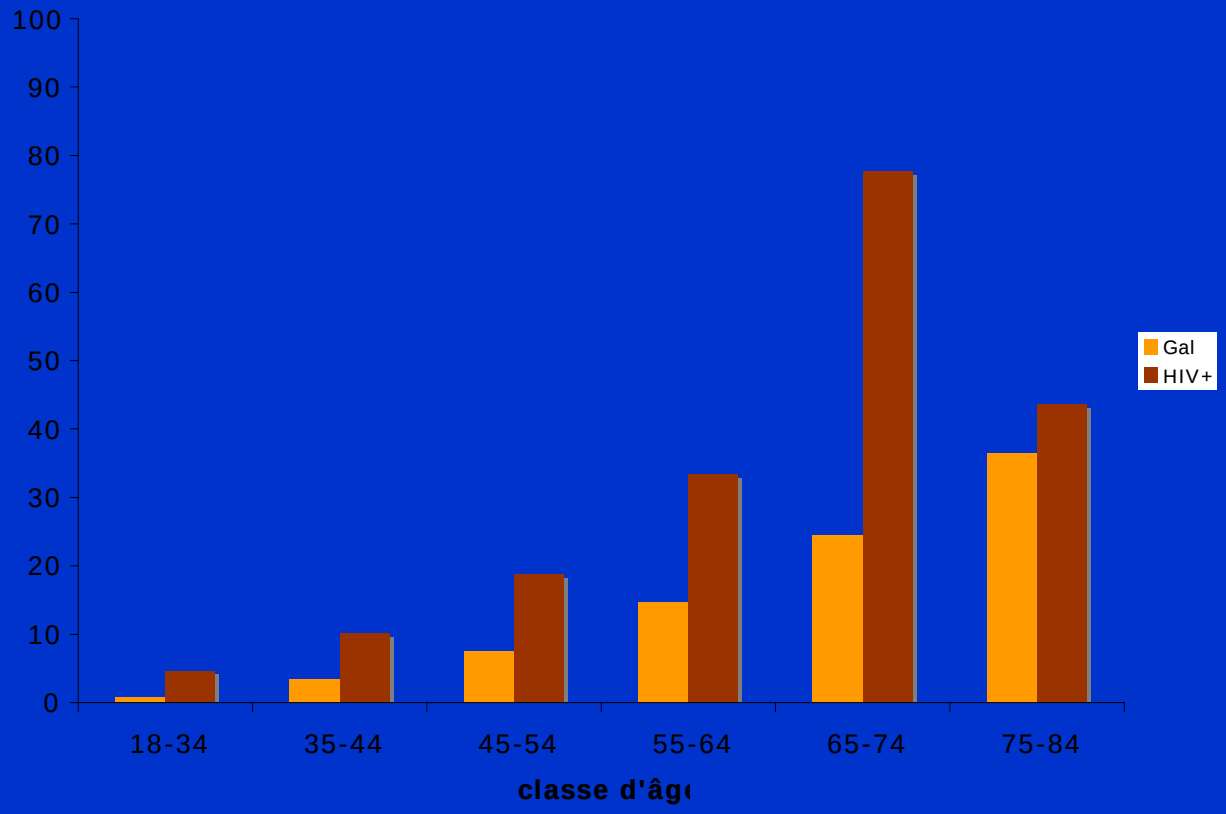
- **Facteurs de risque traditionnels de MCV**
- **Infection par le VIH et MCV**
- **Thérapie antirétrovirale et MCV**
- **Perspective Africaine VIH et MCV**
- **Conclusion**

Comparaison à la population générale dans un pays où le risque de base est élevé : USA

Total
SMR 1.8 (1.5-2.0)

Hommes
SMR 1.4 (1.2-1.7)

Femmes
SMR 3.0 (2.3-3.8)



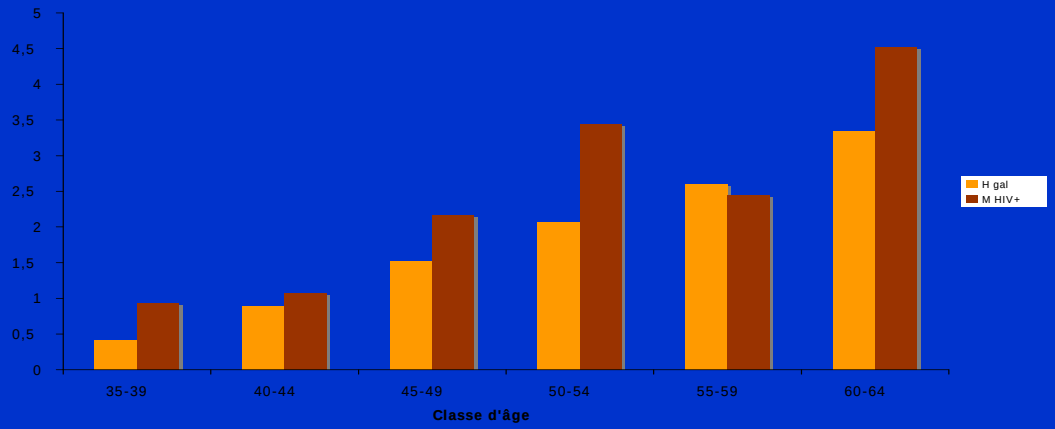
Triant et al, JCEM 2007

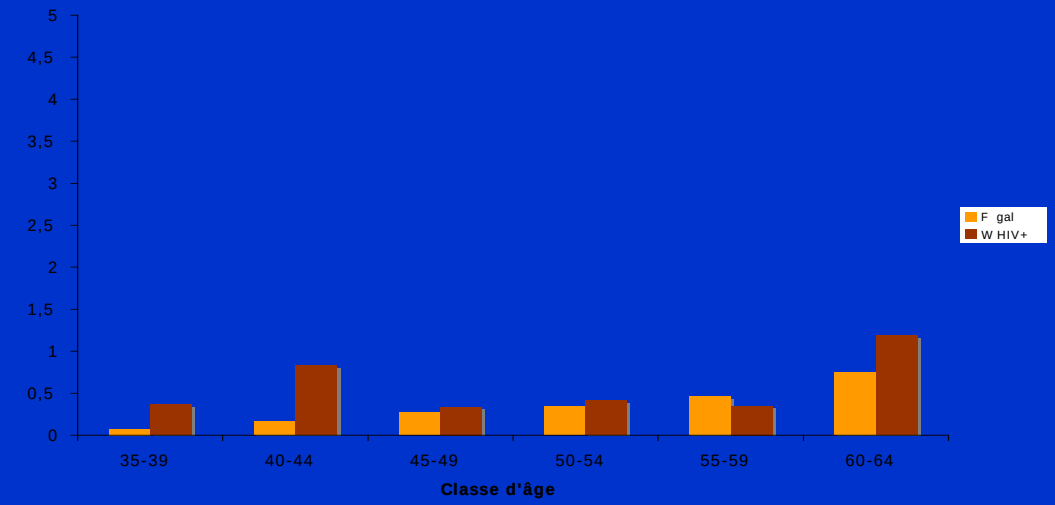
Comparaison à la population générale dans un pays où le risque de base est élevé : France

Total
SMR 1.5 (1.3-1.7)

Hommes
SMR 1.4 (1.3-1.6)

Femmes
SMR 2.7 (1.8-3.9)





Lang et al, AIDS 2010, sous presse

Epidemiological Evidence for Cardiovascular Disease in HIV-Infected Patients and Relationship to Highly Active Antiretroviral Therapy

Judith S. Currier, MD, Co-Chair; Jens E. Lundgren, MD, PhD, Co-Chair; Andrew Carr, MD; Daniel Klein, MD; Caroline A. Sabin, PhD; Paul E. Sax, MD; Jeffrey T. Schouten, MD; Marek Smieja, MD, PhD; for Working Group 2

Circulation July 8, 2008

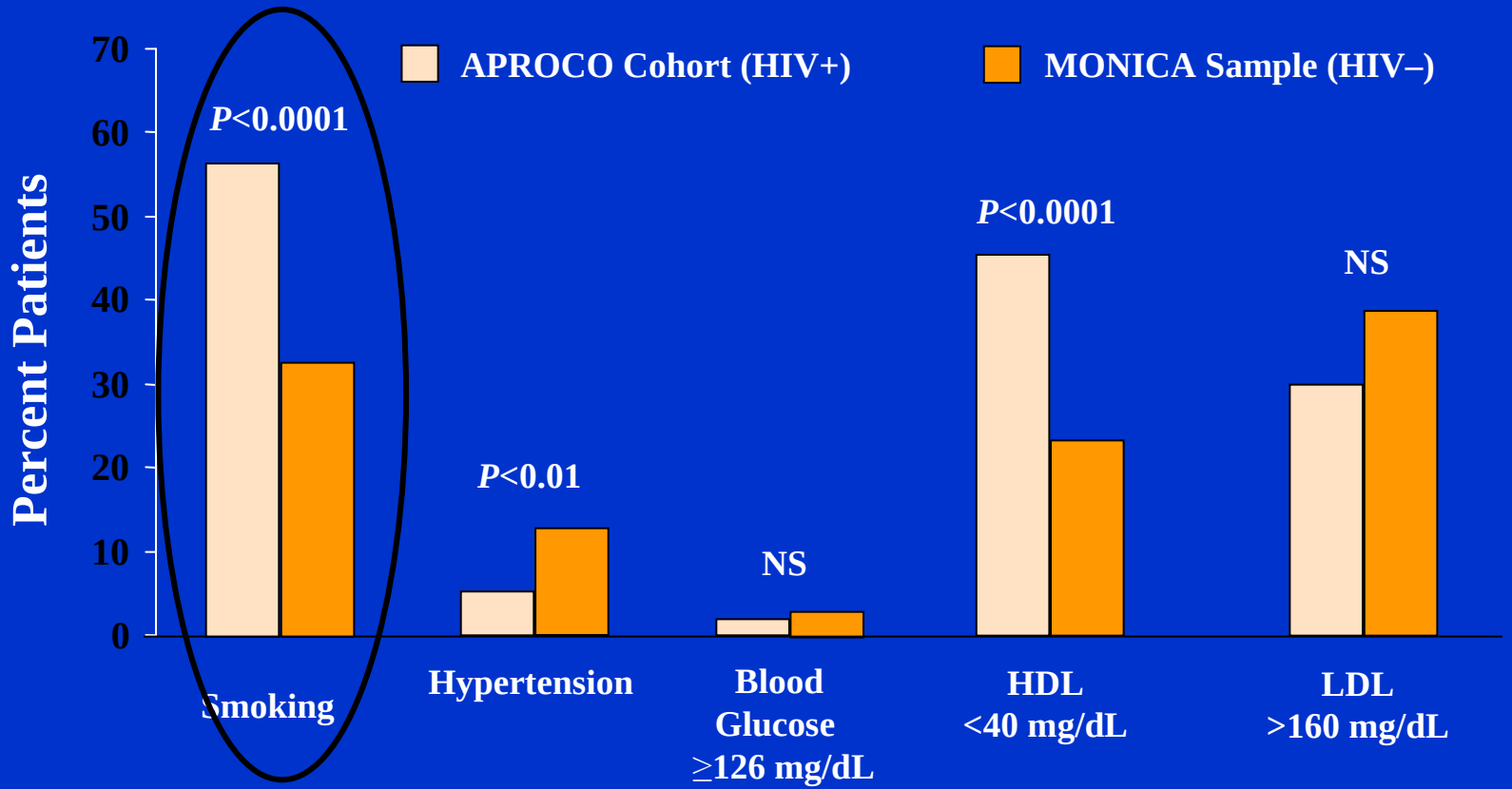
Table 2. Do Traditional Cardiovascular Risk Factors Predict the Risk of CHD/CVD in HIV-Infected Persons Similarly to HIV-Uninfected Persons?

Cardiovascular Risk Factor	Unit	% Increase in Risk per Unit for Each Study		
		HIV-Positive[5,9]		
		Ilioeje et al[9]	Friis-Møller et al[5]	HIV-Negative (No. of Studies)*
Age	Per 1 year older	9%	6%	6% to 9% (7)
Sex	Male vs female	NS	110%	110% to 160% (2)
Diabetes mellitus	Yes vs no	260%	90%	140% to 252% (3)
Smoking	Yes vs no	140%	290%	70% to 290% (3)
Hypertension	Yes vs no	30%	80%	80% to 90% (3)
Total cholesterol	Per 1-mmol/L increase†	. . .	26%	25% to 33% (3)
HDL cholesterol	Per 1-mmol/L increase†	. . .	−28%	−52% (1)

*Mensah et al (2005),[18] Yusuf (2004),[19] Rosengren et al (1997),[21] Thomsen (2002),[20] Cooper et al (2005),[22] Wu et al (2006),[23] and Wilson et al (1998).[24]

†1 mmol/L=39 mg/dL.

Incidence of Smoking Is Increased Among HIV-Infected vs General Population



- N=223 HIV+ men and women on PI-based regimens vs 527 HIV– male subjects:
  - HIV+ patients have lower HDL and higher TG
  - Predicted risk of CHD > in HIV+ men (RR=1.2) and women (RR = 1.6), *P*<0.0001

Savès M et al. *Clin Infect Dis.* 2003;37:292–298.

Plan de l'exposé

- **Facteurs de risque traditionnels de MCV**
- **Infection par le VIH et MCV**
- **Thérapie antirétrovirale et MCV**
- **Perspective Africaine VIH et MCV**
- **Conclusion**

Infection par le VIH et risque Cardio-vasculaire

- **Replication virale active**
- **Inflammation chronique**
  - **CRP**
  - **IL-6**
  - **ICAM-1**
- **Activation facteurs thrombotiques**
  - **Fibronogène**
  - **D-dimers**

Mécanismes de l'atteinte cardio-vasculaire

* lésions endothélium vasculaire;
* Agrégation plaquettaire;
* Thrombose vasculaire;
* Dépôt athéromateux par dyslipidémie, hypertrigly;
* Activation des adhésines vasculaires: Vascular Cellular Adhesines Molecule (VCAM)
* Toxicité mitochondriale vasculaire (coronaires) et cellules musculaires myocardiques

High-Density Lipoprotein Particles and Markers of Inflammation and Thrombotic Activity in Patients with Untreated HIV Infection

Jason Baker,[1,3] Woubeshet Ayenew,[1,3] Harrison Quick,[2] Katherine Huppler Hullsiek,[2] Russell Tracy,[4] Keith Henry,[1,3] Daniel Duprez,[1] and James D. Neaton[2]

Departments of [1]Medicine and [2]Biostatistics, University of Minnesota, and [3]Hennepin County Medical Center, Minneapolis, Minnesota; and [4]Department of Biochemistry, University of Vermont, Burlington

JID 2010:201 (15 January) • 285

Table 2. Lipid Measures and Biomarkers

Variable	Median value (IQR)			
	HIV-infected group (n = 32)	HIV-uninfected group (n = 29)	Percentage difference (95% CI)[a]	P
Traditional lipid panel				
Total cholesterol, mg/dL	168 (148–186)	191 (161–221)	−8 (−19 to 3)	.15
HDLc, mg/dL	34.5 (30.0–44.5)	47.0 (42.0–56.0)	−26 (−37 to −13)	<.01
LDLc, mg/dL	108 (81–114)	108 (93–145)	−5 (−21 to 15)	.61
Triglycerides, mg/dL	126 (90–178)	112 (77–143)	23 (−5 to 59)	.11
HDL				
HDL size, nm	8.50 (8.38–9.03)	8.90 (8.60–9.10)	−2 (−5 to 1)	.12
Total HDL particles, nmol/L	23.9 (20.2–27.8)	30.4 (25.5–33.1)	−21 (−30 to −11)	<.01
Large HDL particles, nmol/L	3.80 (2.50–6.78)	6.40 (4.20–8.80)	−50 (−67 to −23)	<.01
Medium HDL particles, nmol/L	1.05 (0.27–2.97)	0.90 (0.30–3.30)	−6 (−61 to 127)	.9
Small HDL particles, nmol/L	18.4 (13.9–21.0)	21.5 (17.1–24.4)	−20 (−33 to −5)	.01
Inflammatory, endothelial, and thrombotic markers				
hsCRP, μg/mL	1.94 (0.82–5.84)	1.46 (0.68–5.04)	27 (37–156)	.49
IL-6, pg/mL	1.79 (1.32–5.35)	1.26 (0.72–2.14)	71 (11–162)	.01
E-selectin, ng/mL	40.8 (26.6–56.6)	46.4 (35.8–56.4)	−7 (−28 to 19)	.54
sICAM-1, ng/mL	312 (251–488)	225 (168–279)	65 (25–117)	<.01
Fibrinogen, mg/dL	409 (334–479)	413 (340–447)	2 (−9 to 14)	.76
D-dimer, μg/mL	0.39 (0.19–0.67)	0.19 (0.13–0.38)	71 (10–165)	.02

NOTE. HDL, high-density lipoprotein; HDLc, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; IQR, interquartile range; LDLc, low-density lipoprotein cholesterol; sICAM-1, soluble intercellular adhesion molecule-1.

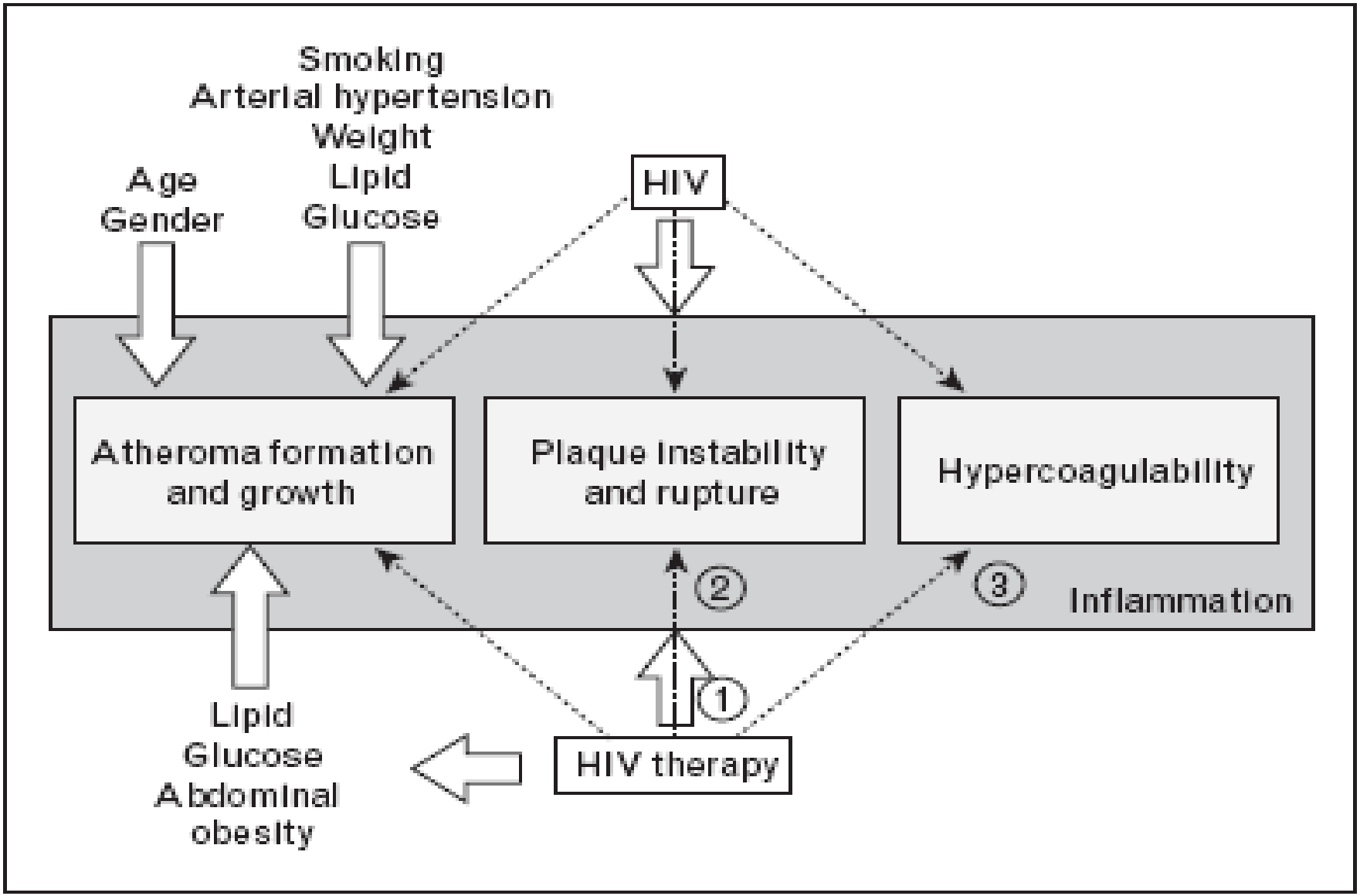
[a] Comparisons between HIV-infected group and HIV-uninfected group (percentage difference) reflect differences in mean values after natural log transformation.

Table 3. Correlation of Lipid Measures with Human Immunodeficiency Virus (HIV) RNA and Biomarkers among HIV-Infected Participants

	Spearman rank correlation coefficient (*P*)				
Lipid measurements	HIV RNA, $\log_{10}$ copies/mL	hsCRP, μg/mL	IL-6, pg/mL	sICAM-1, ng/mL	D-dimer, μg/mL
Total cholesterol, mg/dL	−0.34 (.06)	0.08 (.66)	−0.02 (.93)	−0.37 (.04)	−0.46 (.01)
Triglycerides, mg/dL	0.09 (.64)	−0.10 (.58)	−0.29 (.11)	0.20 (.27)	−0.27 (.14)
HDLc, mg/dL	−0.21 (.26)	−0.01 (.98)	−0.01 (.97)	−0.45 (.01)	−0.10 (.59)
Total HDL particles, nmol/L	−0.24 (.19)	−0.04 (.85)	−0.32 (.08)	−0.52 (<.01)	−0.38 (.03)
Large HDL particles, nmol/L	−0.15 (.43)	−0.07 (.70)	0.16 (.38)	−0.16 (.37)	−0.25 (.18)
Small HDL particles, nmol/L	−0.22 (.23)	0.11 (.56)	−0.41 (.02)	−0.50 (<.01)	−0.57 (<.01)

NOTE. HDL, high-density lipoprotein; HDLc, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; LDLc, low-density lipoprotein cholesterol; sICAM-1, soluble intercellular adhesion molecule-1.

Figure 1 Disease-associated and therapy-associated factors contributing to cardiovascular disease in HIV-infected patients



Plan de l'exposé

- **Facteurs de risque traditionnels de MCV**
- **Infection par le VIH et MCV**
- **Thérapie antirétrovirale et MCV**
- **Perspective Africaine VIH et MCV**
- **Conclusion**

Etudes sur le risque CV chez les patients VIH+ traités par les ARV

Study	N	Study	Event	ARV	Effect	Traditional Risk Factors
VA[1]	36,766	R	1,207 CHD	ART or PI	No	Not evaluated
HOPS[8]	1807	P	84 CV events	Specific ARVs	No	Age >40 y, diabetes, HTN
SMART[9]	5472	p	63 CHD	Intermittent ART	No – stopping therapy led to complication	Age
Kaiser[3]	4408	R	86 MI	PIs	Risk of HIV+ vs HIV- No risk on PI	Not evaluated
Medi-Cal[4]	28,513	R	NA	ART	Risk with ART in 18–33-year-olds	Not evaluated
DAD[2]	23,490	P	345 MI	cART and PI	Yes	Smoking, age, gender, HTN, DM
French[5]	34,976	R	49 MI	PI	Yes	Age
Johns Hopkins[6]	2671	Case control	43 CHD	HIV+ vs HIV-	Yes	Age, HTN, DM
Frankfurt[7]	4993	R	29 MI	ART	Yes	Age >40 y

1. Bozzette SA. *N Engl J Med*. 2003;348:702-710.
2. Friis-Møller N. 13th CROI 2006. Denver. #144.
3. Klein D. 13th CROI 2006. Denver. #737.
4. Currier JS. *JAIDS*. 2003;33:506-512.
5. Mary-Krause M. *AIDS*. 2003;21:2479-2486.
6. Moore RD. 10th CROI 2003. Boston. #132.
7. Rickerts V. *Eur J Med Res*. 2000;5:329-333.
8. Lichtenstein K. 13th CROI 2006. Denver. #735.
9. El-Sadr W et al. 13th CROI 2006. Denver. #106LB.

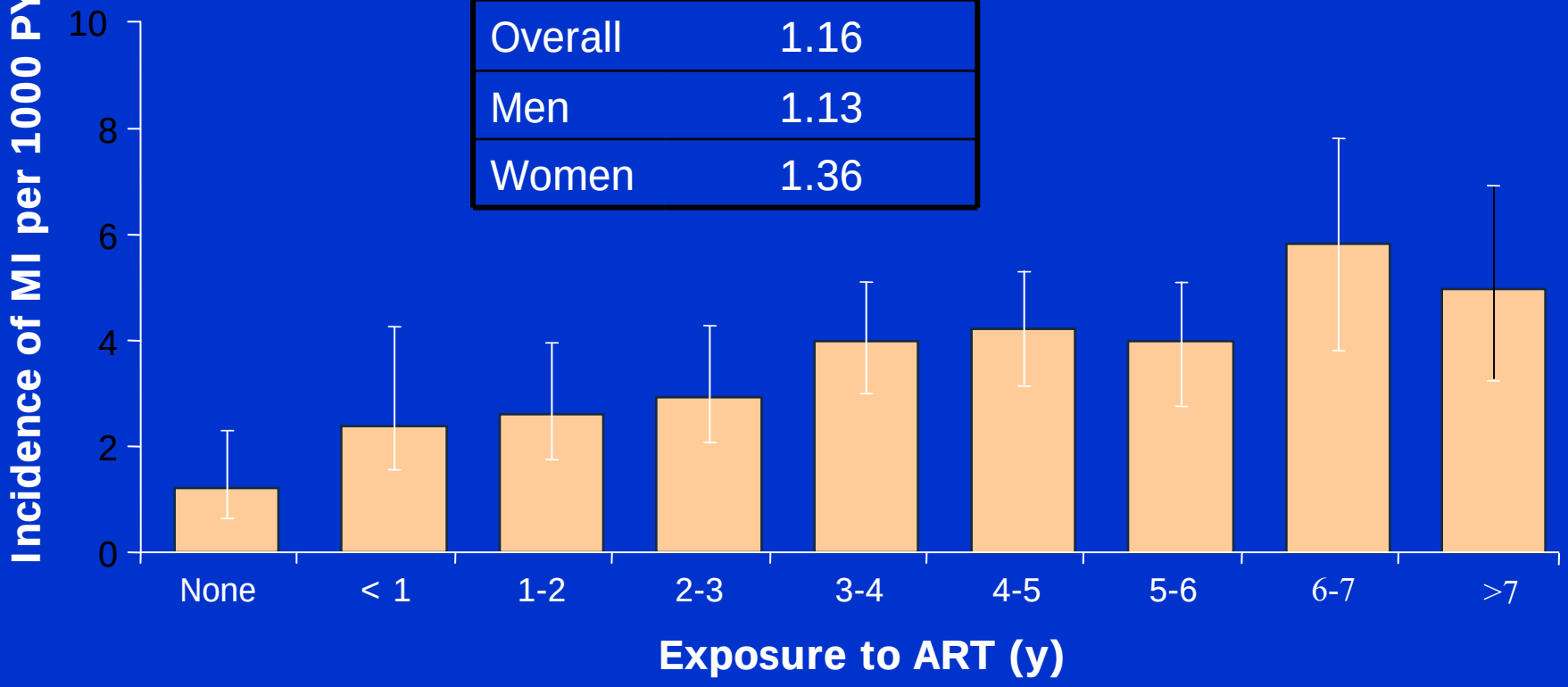
Table 3. Does ART (or Its Components) Increase Risk of CV Disease?

Study/First Author	No. of Persons/ No. of Events	Type of Event	Main Findings Related to ART	Adjustment for CV RF?*	NRTI Effect?†	NNRTI Effect?†	PI Effect?†
Randomized, controlled trial							
Coplan, 2003[26]	10 986/19	MI	PI vs no PI: 69% (NS)	NA	NA	NA	Yes
Phillips, 2008[27]	2752 (VS)/31	CVD	PI exp: 13% increase per y ($P=0.06$)	Yes	NA	No	Yes
Prospective observational studies							
Holmberg, 2002[28]	5672/21	CVD	PI vs no PI: increase 6.5-fold (NS)	Yes	NA	NA	Yes
Iloeje, 2005[9]	7542/127	CVD	PI vs no PI: increase 71% ($P<0.05$)	Yes	NA	NA	Yes
DAD I, 2007[5]	23 437/345	MI	PI exp: 16% increase per year ($P<0.001$)	Yes	NA	No	Yes
DAD II, 2007[5]	10 002/40	MI	ART: 24% increase per year ($P<0.05$)	Yes	NA	NA	NA
Retrospective observational studies							
Mary-Krause, 2003[7]	34 976/66	MI	>18 mts exp to PI: increased risk	Partial	NA	NA	Yes
Rickerts, 2000[29]	4993/29	MI	ART exp: increased risk	Partial	NA	NA	NA
Administrative databases							
Klein, 2007[30]	5000/162	CAD adm (/1000 PY)	Increase 7.1 (PI) vs 4.9 (no PI) ($P=0.02$)	Partial	NA	NA	Yes
Bozzette, 2003[8]	36 766/1207	CAD adm	No change	Partial	NA	No	No
Currier, 2003[3]	28 513/1360	CAD adm	Increase, but only in young persons	Partial	NA	NA	NA

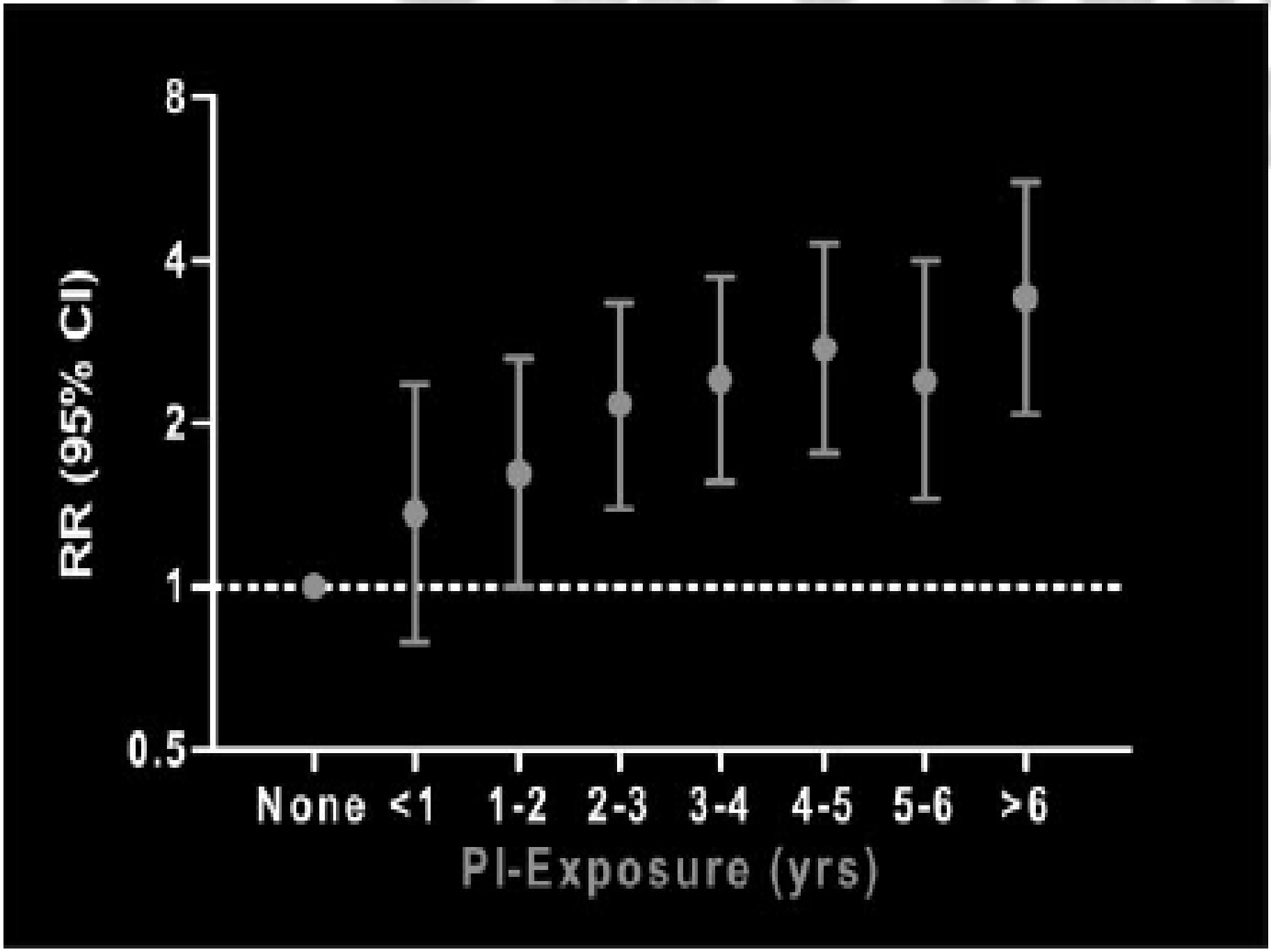
D:A:D Study: Incidence IM

Augmentation Incidence CV est associée avec la durée de la thérapie ARV

RR per Year of ART	
Overall	1.16
Men	1.13
Women	1.36



Friis-Moller N et al. *N Engl J Med.* 2007;356:1723-1735.


RR (95% CI)
8
4
2
1
0.5
None
<1
1-2
2-3
3-4
4-5
5-6
>6
PI-Exposure (yrs)

Diabetes Risk Factors

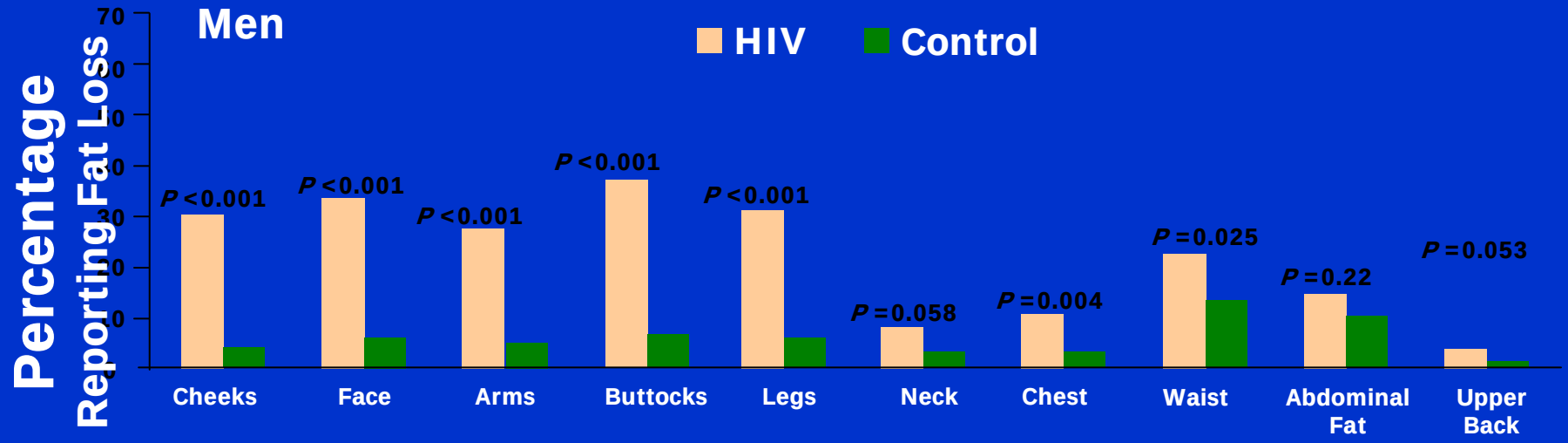
Classic Type 2 Diabetes Risk Factors

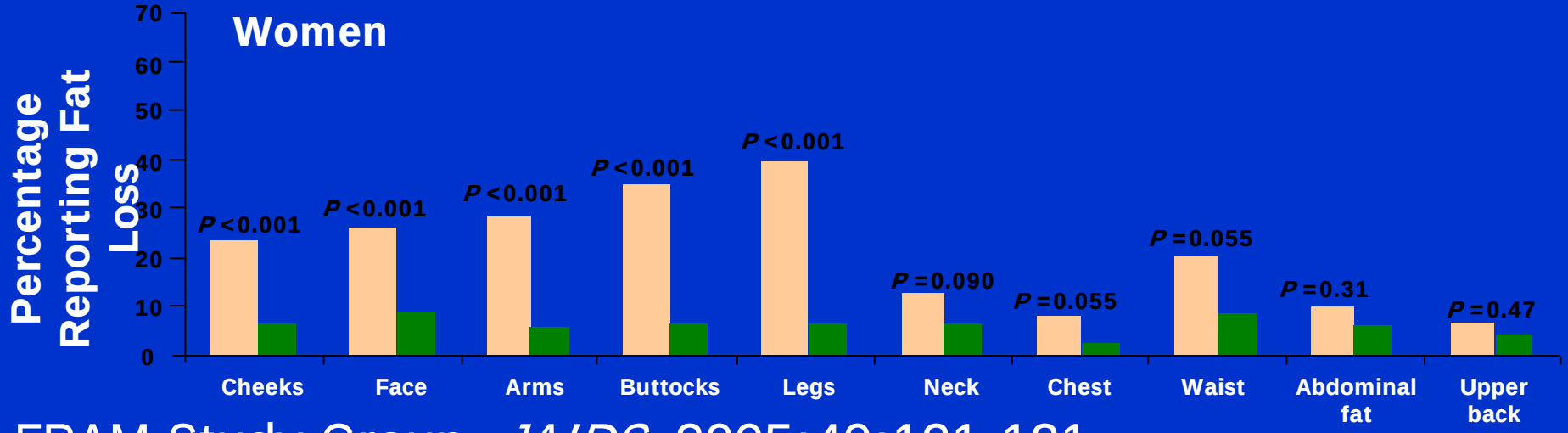
- Obesity (abdominal)
- Physical inactivity
- Genetic
  - Family history
  - Race/ethnicity
- Older age
- Dyslipidemia

Potential HIV-Associated Risk Factors

- Peripheral lipoatrophy
- Reduced adiponectin
- Increased liver/muscle fat
- Inflammatory cytokines
- Low testosterone
- Oxidant stress
- HCV infection
- Protease inhibitors

Lipoatrophy Prevalence Distribution in HIV+ vs HIV– Controls



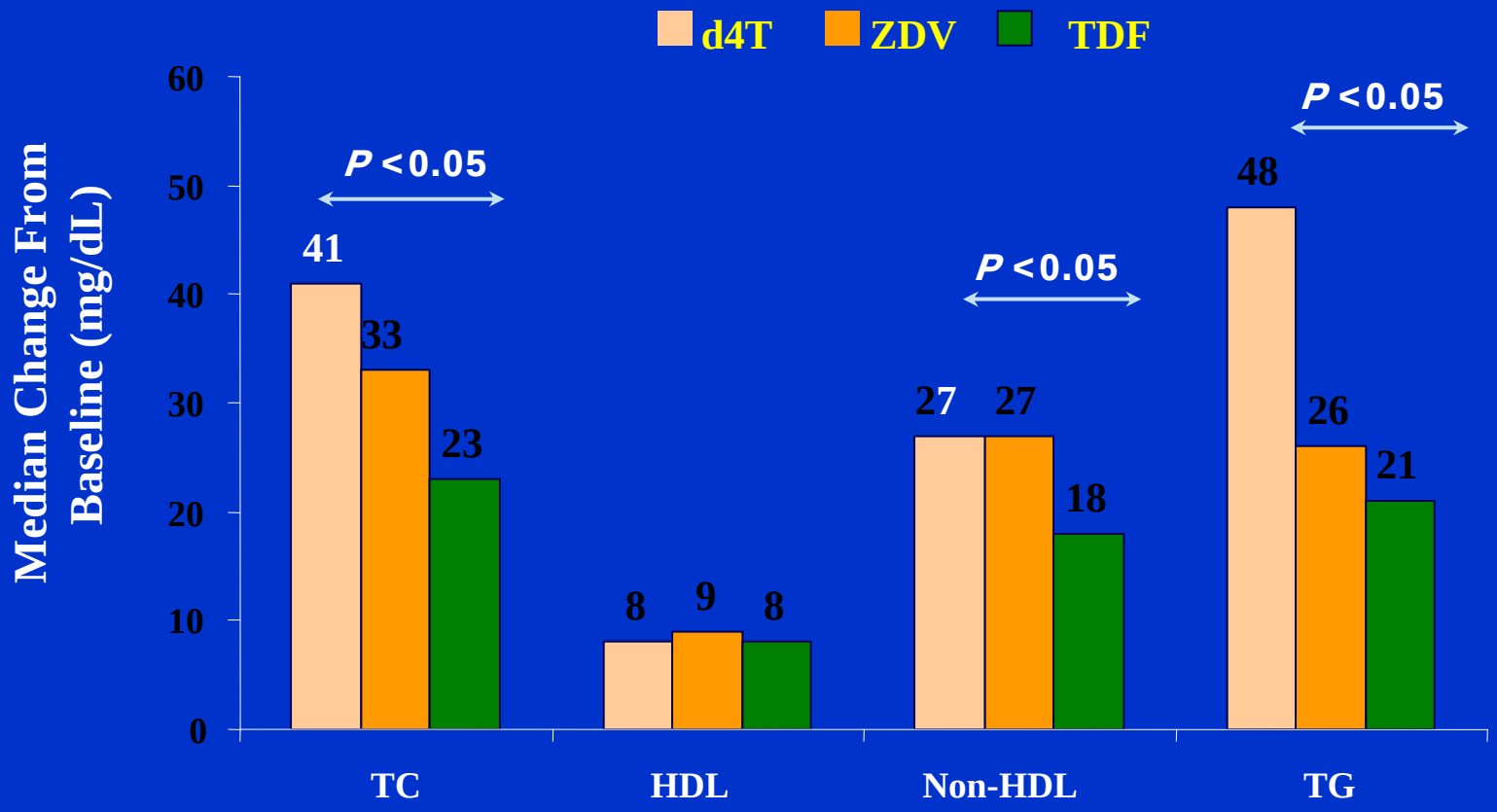


FRAM Study Group. *JAIDS.* 2005;40:121-131.

FRAM Study Group. *JAIDS.* 2006;42:562-571.

A5142: LPV/r + EFV vs LPV/r + 2 NRTIs vs EFV + 2 NRTIs

Median Changes in Lipids by NRTI From Baseline – Week 96

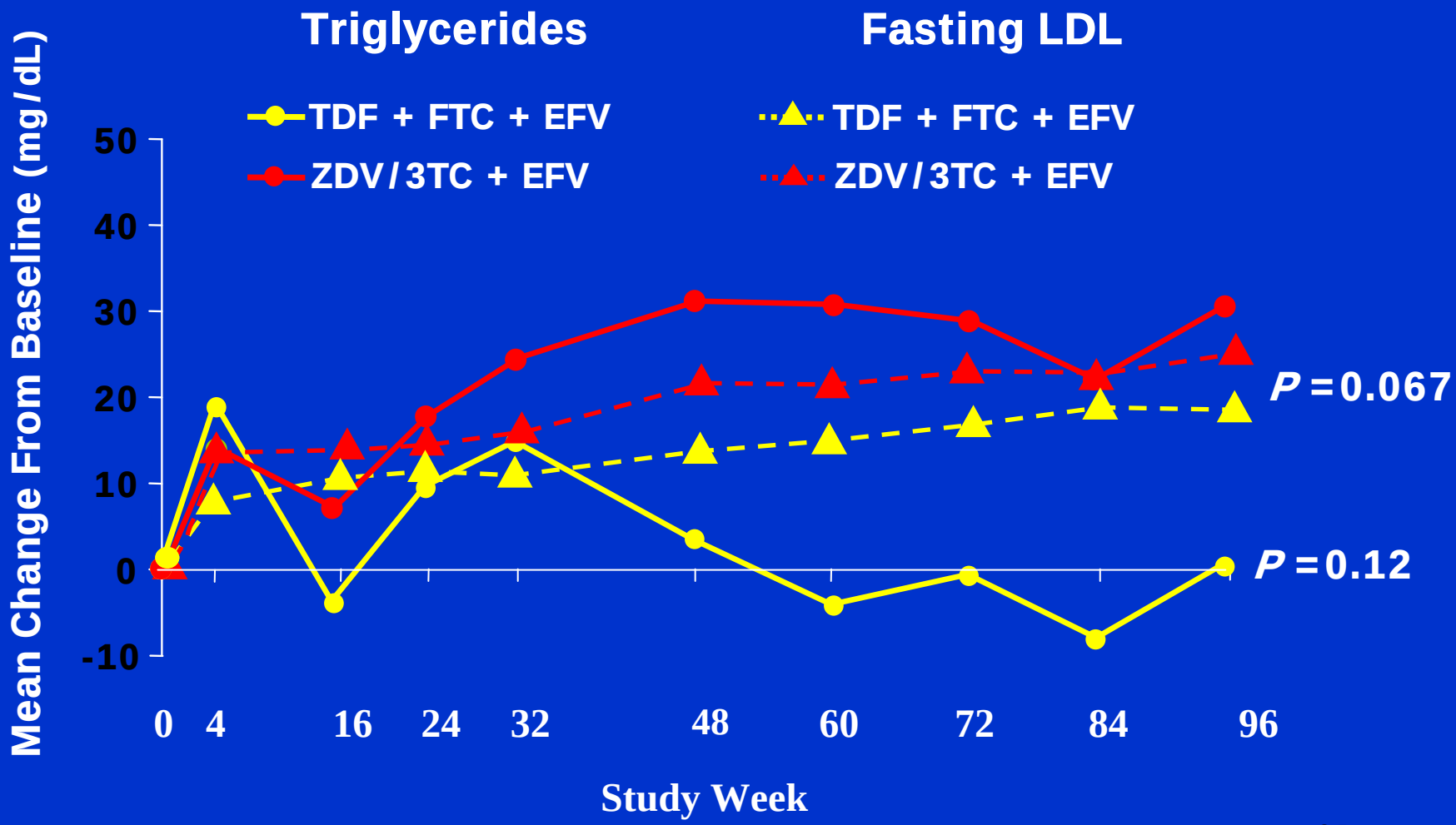


By week 96, 10% and 12% of EFV and LPV subjects used a lipid-lowering agent.

Haubrich R et al. 14th CROI 2007. Los Angeles, CA. Abstract 38.

Study 934: ZDV/3TC vs TDF + FTC

Mean Change Lipid Profile



Pozniak AL et al. *JAIDS.* 2006;43:535-540.

ABC et risque cardiovasculaire

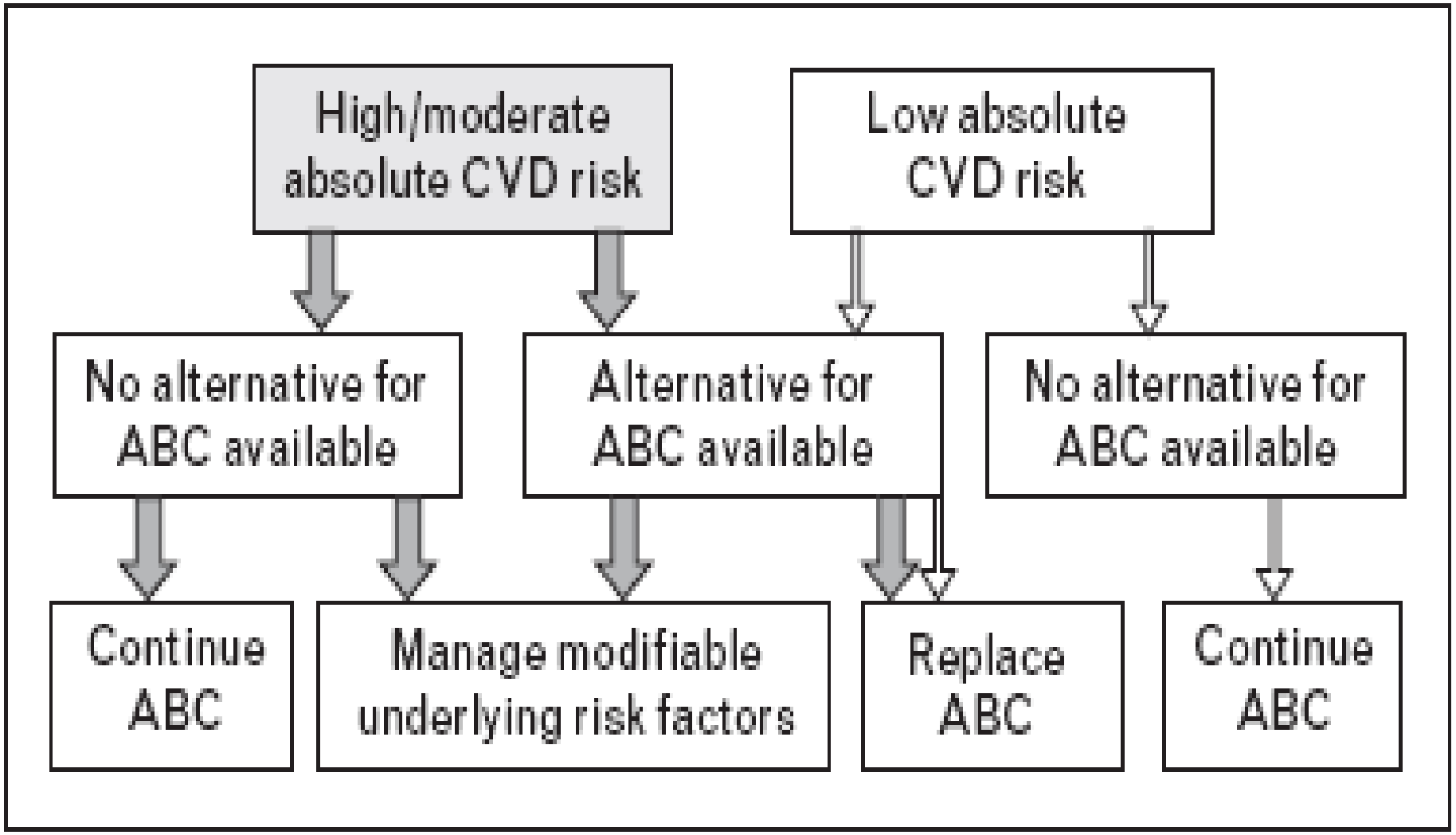
Major characteristics	D.A.D. Study [1a,1b] ☹	SMART Study [2a,2b] ☹	STEAL Study [3] ☹	ANRS CO4 Study [4] ☹	GSK Studies [5a, 5b] 😐	ACTG 5001 (ALLRT Study)[6] 😐
Study outline	International Prospective observational cohort study designed and powered to look at cardiovascular risk of cART. Includes all patients in 7 cohorts.	Randomized prospective study looking at continuous vs CD4-guided treatment. Largest randomized Database able to look at DAD findings.	Randomized open label non-inferiority trial. Simplification with fixed-dose tenofovir/ emtricitabine or abacavir/lamivudine in adults with suppressed HIV Replication.	Case control of an observational study to evaluate the risk of MI with several ARVs.	Retrospective meta analysis from GSK Studies (pooled data from 52 ABC clinical trails). Healthier 'trial' population. Expect low CVD risk (as exclusion criteria). Comparator group to ABC is predominantly PI-based regimens already associated with CVD.	Long term follow up of randomized data from 5 prospective ACTG studies; extended follow-up was available for 2164 patients trough the ALLRT long-term protocol.
Patient" numbers and f/u	33,347 pts for >7 Years (.~ 178,000 PYF).	Average f/u >18 months. N=2753 from continuous treatment arm.	357 patients were randomized from January to August 2006. 96 weeks analysis. 1.7% were lost to follow-up with no between-group difference. No patient developed AIDS or renal failure.	1173 patients (MI cases=289; controls=884).	Less than one year follow-Up of 14174 patients (7,641 PYFU ABC vs 4267 PYFU non ABC).	3205 patients (10,187 PYF) Follow-up was censored at the first of off-study, death, initiation of non-randomized ABC or 6 months after the last visit or discontinuation of randomized ART (not including within class substitutions not involving ABC).
Key findings	Increased risk of MI with recent or current ABC use ~ double risk . Reverses within 6 months of stopping ABC. Most significant for pts with high baseline cardiovascular risk (Framingham).	Confirm DAD signal. ABC use reported higher incidence of MI in Adjusted analysis compared to other RTIs. Similar results when comparator was TDF.	In this population, TDF-FTC and ABC-3TC had similar virological efficacy. However, ABC-3TC was associated with more SNAEs (particularly cardiovascular disease) and lipid endpoints, and TDF-FTC caused more BMD loss.	The results showed an association between recent use of ABC (< 1 year) and an increased risk of MI (approximately 2 fold increase) but not for other NRTI. Cumulative use of ABC not associated with MI.	No signal that ABC has higher risk compared to PI-based combinations.	Significant associations between either MI or severe CVD and recent ABC exposure were not detected in unadjusted (RR = 1.02 and 0.8, respectively) and adjusted analyses.
Comment	Real signal, Unknown mechanism. Adjusted for al known CVD risk factors. IDV and LPVr with increased risk of MI. No association with TDF, SQV and NNRTI use.	"Channeling" effect possible. Lower power in some endpoints. Increase of IL-6 & hsCRP by other causes than ABC use. Some overlap in patient study population (DAD) ~10% but same results when excluded from analysis.	Groups were well balanced, except smoking was more prevalent with ABC-3TC (40%) than with TDF-FTC (29%).	In addition, cumulative exposure to LPVr and FPVr was also associated with MI risk. No association with SQV. ATV not assessed. A trend was also observed with AZT and d4T cumulative exposure.	Retrospective. Low number of events in each arm. Not powered to detect a safety or toxicity signal. Comparator group already likely to be associated with higher cardiovascular risk as PI-based regimens.	Significant increases in the risk of events were detected for some classic CVD risk factors, i.e. older age and hypertension.

Abacavir and cardiovascular risk

Georg M.N. Behrens[a] and Peter Reiss[b]

Current Opinion in Infectious Diseases 2010, 23:9–14

Figure 2 Proposed algorithms for the use of abacavir in HIV-infected patients



Plan de l'exposé

- **Facteurs de risque traditionnels de MCV**
- **Infection par le VIH et MCV**
- **Thérapie antirétrovirale et MCV**
- **Perspective Africaine VIH et MCV**
- **Conclusion**

Identifier les patients risque cardio-vasculaire

* Age: homme ≥ 50 ans, femme ≥ 60 ans ou plus ou ménopausée;
* Antécédents familiaux de maladie coronaire précoce;
* Infarctus myocarde ou mort subite chez parent du premier degré;
* Tabagisme actuel ou arrêté depuis moins de 3 ans;
* BMI (poids et taille) Obésité
* HTA permanente traitée ou non;
- Diabète sucré;
- Cholestérol total - Triglycérides
* HDL-cholestérol
- Examen clinique complet à chaque visite médicale

Barriers to management of cardiovascular risk in a low-resource setting using hypertension as an entry point

Shanthi Mendis, Dele Abegunde, Olulola Oladapo, Francesca Celletti and Porfirio Nordet

Journal of Hypertension 2004, 22:59–64

Table 1 **Investigations available for assessment and management of cardiovascular risk in hypertensive patients: proportion of facilities that offer the listed service**

Investigation	Percentage (*n*/*N*)
Urine analysis	37.2 (16/43)
Plasma creatinine or blood urea	16.3 (7/43)
Blood glucose	20.9 (9/43)
Serum electrolytes	16.3 (7/43)
Total cholesterol	9.3 (4/43)
Serum lipoproteins	9.3 (4/43)
Electrocardiogram	7.0 (3/43)
Abdominal ultrasound	11.6 (5/43)
Echocardiogram	0.0 (0/43)

n = Number of facilities with service, *N* = total number of facilities.

Monitoring Antiretroviral Therapy in Resource-Limited Settings: Balancing Clinical Care, Technology, and Human Resources

Mina C. Hosseinipour · Mauro Schechter

Published online: 25 May 2010
Curr HIV/AIDS Rep

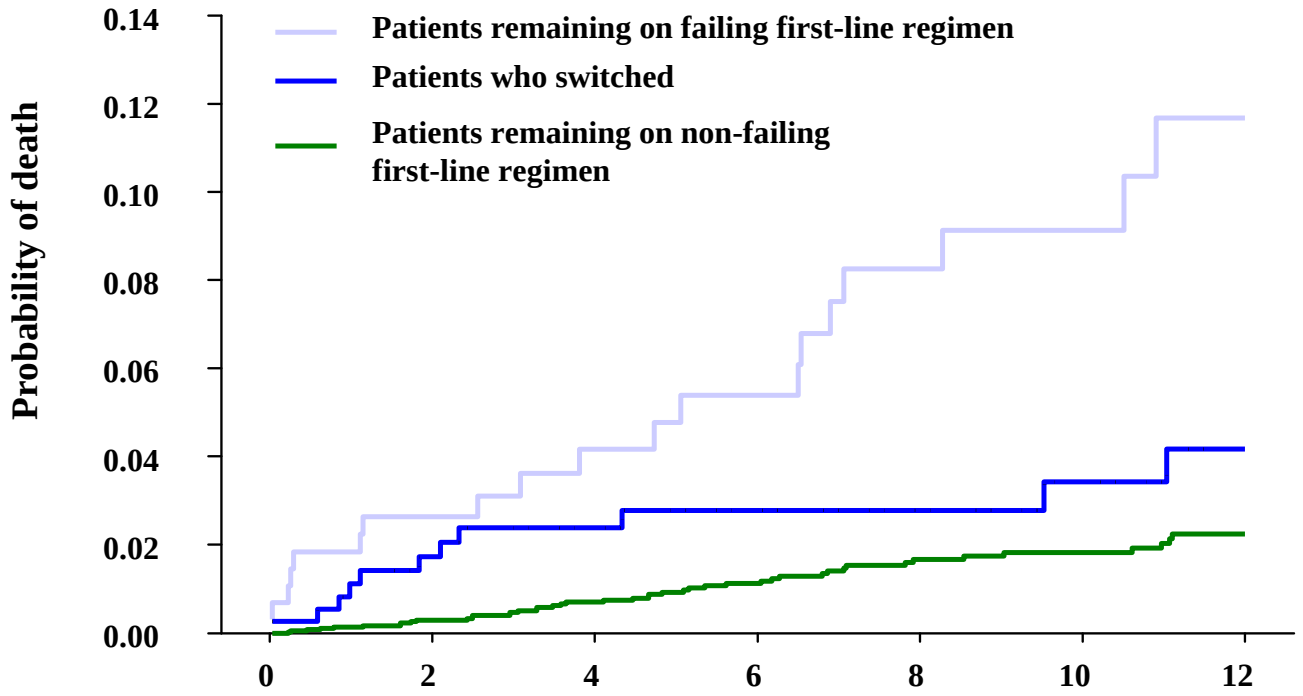
Table 2 Summary of resistance patterns seen at the time of first-line failure in resource-limited settings

	South Africa [27]	Thailand [28]	Cameroon 12month [30]	Cameroon 24month [30]	Malawi [26••]	India [29]	South Africa [31]
N sequenced	115	98	34	38	94	138	226
Clade	C	AE	AG, D		C	C	C
Monitoring strategy	Virologic	Virologic	Clinical and immunologic				Virologic
Median CD4 at failure	161	159	NR	NR	68	144	165
Log HIV RNA at failure	4.29	4.1	3.13	4.39	4.72	NR	4.34
Duration of ART, *months*	10.8	20	12	24	36.5	50	NR
Wild type	16.5%	5%	68%	21%	5%	5%	17%
M184V or I	64%	89%	29%	71%	81%	79%	72%
Any NNRTI	78%	92%	29%	73%	93%	65%	77%
Any TAMs	32%	37%	6%	18%	56%	60%	31%
≥3 TAMs	13%	13%	3%	8%	25%	NR	18%
K65R or K70E	2.6%	6%	0%	0%	23%	5%	4%
Q151M	0.9%	8%	0%	0%	19%	11%	<1%

ART antiretroviral therapy; *NNRTI* nonnucleoside reverse transcriptase inhibitor; *NR* not recorded; *TAMs* thymidine analog mutations

Mortality after failure of antiretroviral therapy in sub-Saharan Africa

Olivia Keiser[1], Hannock Tweya[2], Paula Braitstein[3–6], François Dabis[7], Patrick MacPhail[8], Andrew Boulle[9], Denis Nash[10], Robin Wood[11], Ruedi Lüthi[12], Martin W. G. Brinkhof[1], Mauro Schechter[13] and Matthias Egger on behalf of the ART-LINC of IeDEA Study Group[1,14,*]



Meilleur contrôle de la charge Virale Plasmatique

- **Traiter plus précocement**
- **Choisir schémas ARV moins toxiques**
- **Monitoring de la charge virale : POC**
  - **Simple et facile à utiliser en décentraliser**
  - **Pas d'infrastructures lourdes**
  - **Température ambiante**
  - **Pas de chaine de froid**
  - **Peu cher (< 2 Euros)** Harries Lancet ID: 2010 Jan;10(1):60-65.

Quelle CAT proposer ?

- **Autres examens d'investigation**
  - **Marqueurs biologiques ?**
  - **Marqueurs morphologiques ?**
  - **Marqueurs fonctionnels ?**
- **Importance équipe pluridisciplinaire : cardiologue, diabétologue, néphrologue, infectiologue, microbiologiste, nutritionniste….**
- **Conseils pour prévention du risque CV : sport, alimentation, arrêt tabac, hypolipémiant, traiter HTA, schéma ARV**

Faciliter l'accés aux tests VIH et aux traitements ARV

Remerciements

- **Collaborateurs de l'Initiative Sénégalaise**
- **Serge Paul Eholié**
- **Alexandra Calmy**
- **Dominique Costagliola**
- **Eric Delaporte et collaborateurs IRD**
- **Pierre-Marie Girard collaborateurs IMEA**
- **ANRS**