Cardiovascular Risk and dyslipidemia

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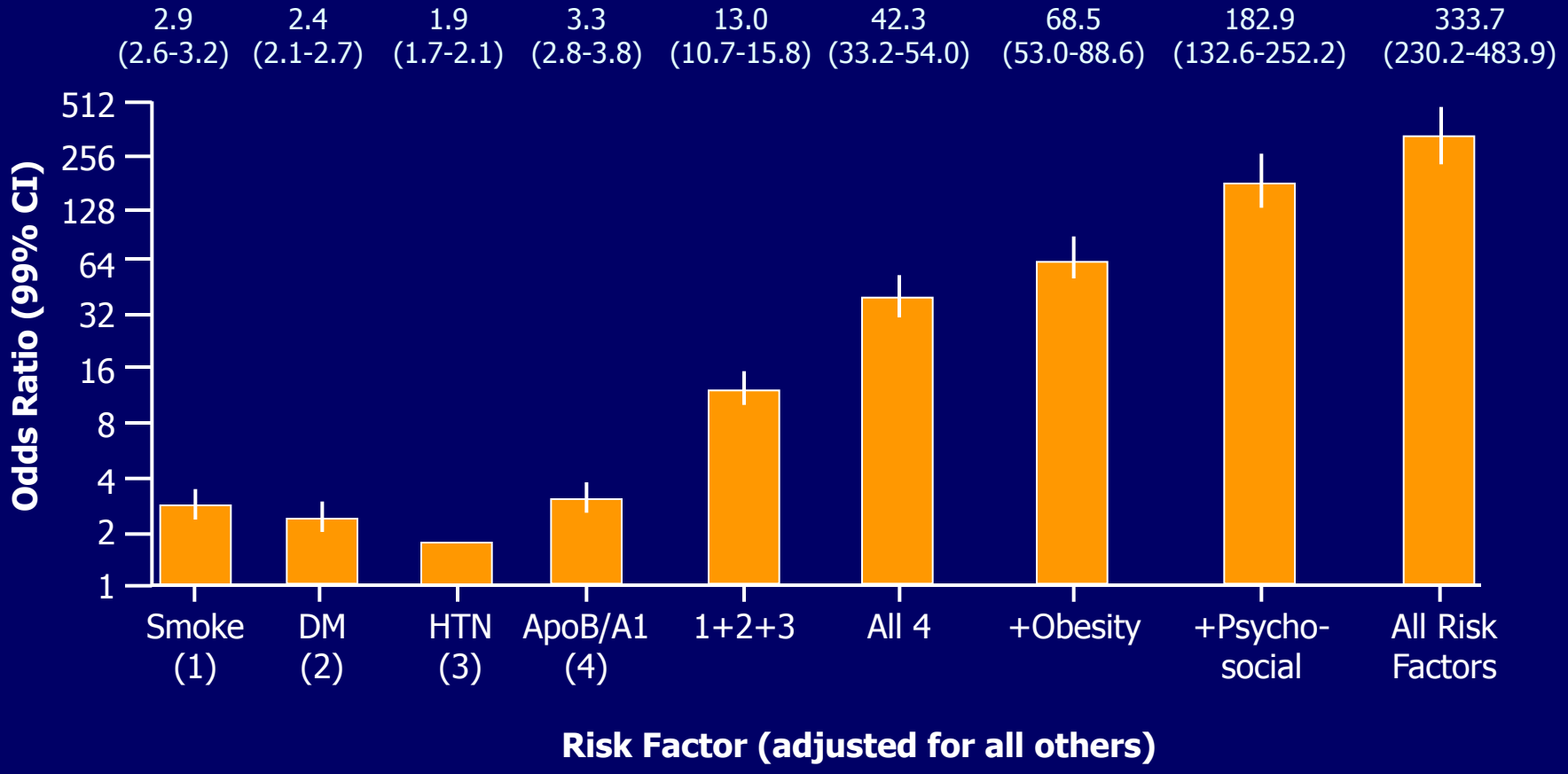
Cardiac Risk Factors

- What are cardiac risk factors?
  - Increased age
  - Sex (men are at higher risk)
  - Smoking
  - Elevated LDL cholesterol (LDL)
  - Low HDL cholesterol (HDL)
  - Hypertension
  - Presence of diabetes (or risk equivalent)
- How to define cardiac risk and need for intervention
  - Persons with 2 or more risk factors are at increased risk of coronary heart disease (CHD)
  - Risk assessment tools can be used to calculate percent of CHD risk

Wilson PW et al. *Circulation.* 1998;97:1837-1847.

Multiple Risk Factors: INTERHEART

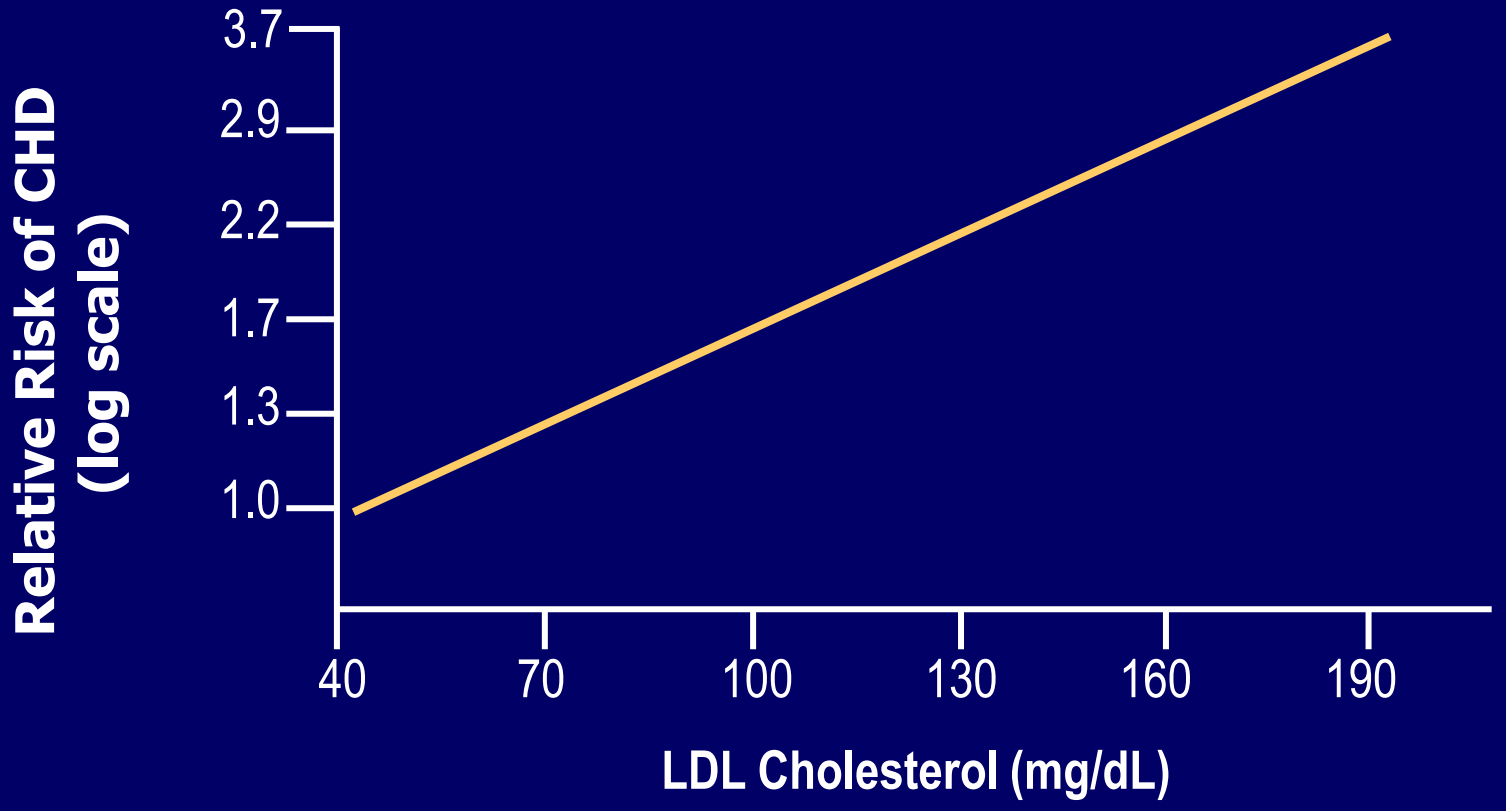
Multiple Traditional Risk Factors Confer Synergistic Increase in Risk of MI in General Population



Yusuf S et al. *Lancet.* 2004;364:937-952.

Lipids and CVD Risk

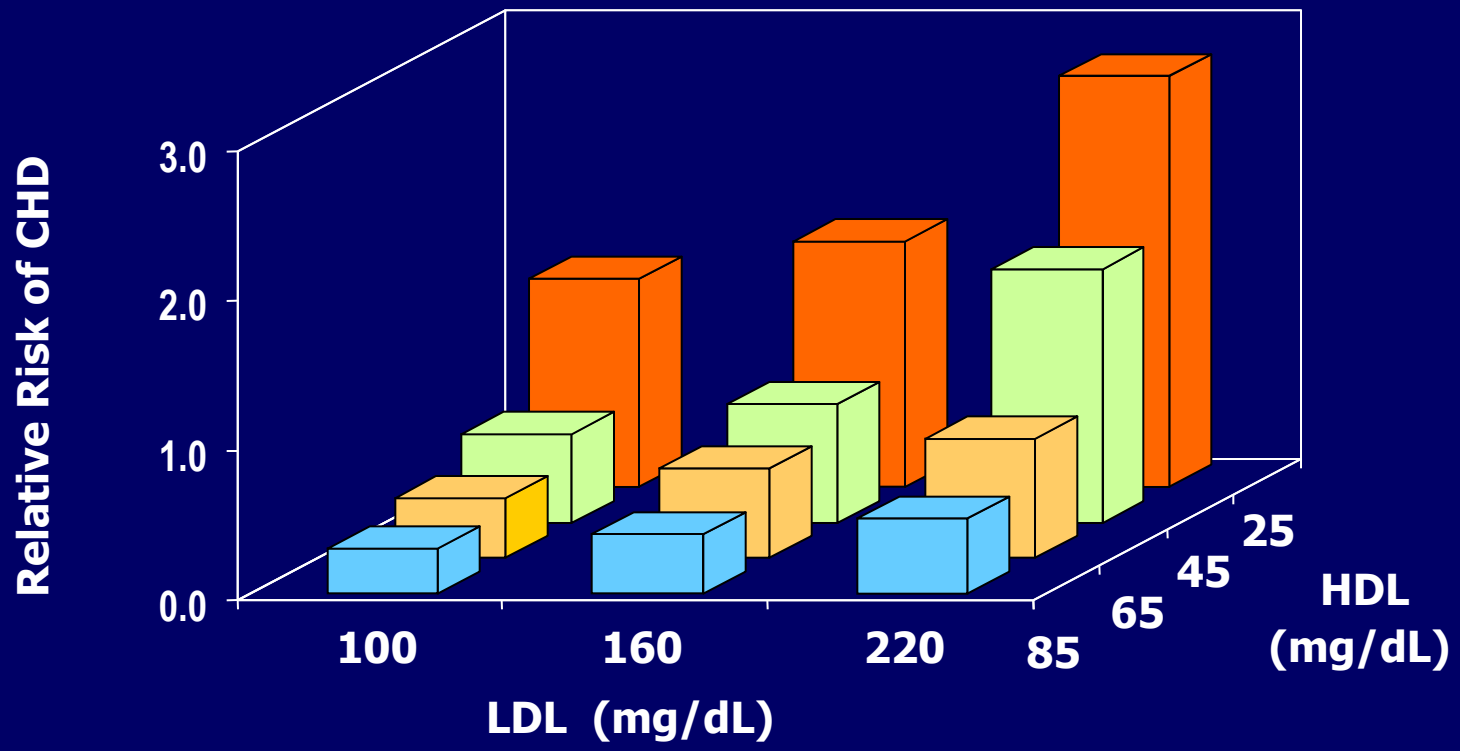
- Increasing plasma LDL increases relative risk of CHD
- A 30 mg/dL ↑ in LDL is associated with ~30% ↑ CHD risk



Grundy SM et al. *Circulation.* 2004;110:227-239.

Higher HDL Reduces Cardiovascular Risk at All LDL Levels

Framingham Heart Study – 10-Year Risk for CHD Event



- **1 mg/dL increase in HDL reduces CVD risk by 2% in men and 3% in women[1]**
- **Low HDL cutoffs: <40 mg/dL for men; <50 mg/dL for women[2]**

1. Gordon T et al. *Am J Med*. 1977;62:707-714; 2. Gordon DJ et al. *Circulation.* 1989;79:8-15.

which subsided quickly. No child developed autistic-spectrum disorder. Hyperornithaemic gyrate atrophy, an autosomal recessive disease, was diagnosed in one girl (patient 14) 8 years after vaccination. A boy developed *H influenzae* meningitis, and a girl meningococcal meningitis 1 day and 7 days after vaccination, respectively.

It is noteworthy that, besides gastrointestinal complaints, many children had similar symptoms and signs (fever, rash, seizure) as those in London.[2] Presumably, some patients with symptoms or signs not far from those listed in the table were not reported to us. We do not deem this shortcoming to be of a major concern because illness in all our 31 patients was mild, and probably sometimes caused by concomitant infection.[4]

Over a decade's effort to detect all severe adverse events associated with MMR vaccine could find no data supporting the hypothesis that it would cause pervasive developmental disorder or inflammatory bowel disease.

We thank Tapio Kurki, Olli P Heinonen, Kari Cantell, and Viena Karanko, and Irja Davidkin for their contribution. The study was partly funded by a grant by Merck Research Laboratories, West Point, PA, USA.

1 Lee JW, Melgaard B, Clements CJ, et al. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; 351: 905–09.
2 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.
3 Peltola H, Heinonen OP, Valle M, et al. The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two-dose vaccination program. *N Engl J Med* 1994; 331: 1397–402.
4 Tait DR, Ward KN, Brown DWG, Miller E. Measles and rubella misdiagnosed in infants as exanthem subitum (roseola infantum). *BMJ* 1996; 312: 101–02.

Helsinki University Central Hospital, Hospital for Children and Adolescents, FIN-00290 Helsinki, Finland (H P Peltola); **National Public Health Institute, Helsinki; and Department of Public Health, University of Helsinki,**

Severe premature coronary artery disease with protease inhibitors

Keith Henry, Holly Melroe, Jacquelyn Huebsch, Jessica Hermundson, Claudia Levine, Lyle Swensen, Jack Daley

Until recently, the prognosis for people with AIDS was so poor that concerns about other long-term health problems seemed irrelevant. The introduction of antiretroviral treatment with protease inhibitors has had a profound impact on mortality from AIDS.[1] After two young AIDS patients on protease inhibitors under our care developed coronary artery disease, we examined lipid abnormalities among HIV-1-infected people receiving protease inhibitors and designed an intervention based on the National Cholesterol Education Program (NCEP) guidelines.[2]

A 26-year-old HIV-1-infected man (CD4 T cell count <10 cells/μL) was admitted with angina. He had a history of cigarette smoking and occasional cocaine use (none recently). The plasma HIV-1-RNA level was more than 1 000 000 copies/mL, so 4 weeks before admission he was started on directly-observed ritonavir, saquinavir, lamivudine, and stavudine. Coronary angiography showed a large occlusive thrombus within the right coronary artery.

A 37-year old HIV-1-infected man presented with angina after shovelling snow. His lowest CD4 T-cell count was 14 cells/μL with a peak plasma HIV-1 RNA level of 685 000 copies/mL

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Peripheral lipodystrophy has been reported in patients receiving protease inhibitors.[3,4] In one study, metabolic abnormalities (higher triglyceride, cholesterol, insulin, and C-peptide levels, and insulin resistance scores) were described in 72 (64%) of 116 patients after a mean 10 months on treatment.[3] Clinicians need to be aware of the potential for accelerated atherosclerosis in patients treated with protease inhibitors. For now, we obtain a fasting lipid profile before and then 3–6 months after the start of protease inhibitor therapy and then use NCEP guidelines to treat abnormalities identified.

1 Cameron D
placebo-con
1998; 351:
2 National Ins
coronary art
education pa
3 Mann M, P
distribution in AIDS patients following protease inhibitor therapy. FDA summary. In: Programs and Abstracts of the 5th National Conference on Retroviruses and Opportunistic Infections; Chicago, Illinois, Feb 1–5, 1998 (abstr 412).
4 Miller K, Jones E, Yanovsky J, Shankar R, Feuerstein I, Falloon J. Visceral abd
351: 871–75
5 Carr A, Sam
A syndrome
HIV protease
National Co
Chicago, Ill

**HIV/AIDS P
Cardiol
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niversity**

Hormone-receptor status of breast cancer in Papua New Guinea

Aolhopo Pip, David Watters, Datti Murthy, Nick Wood, Peter Donnelly

The survival of women with breast cancer varies with racial background and geographical location. Whilst black women have a higher mortality than white women, the causes of racial difference in breast tumour biology are unknown.[1] The well-known association between oestrogen (ER) and progesterone (PR) receptor status and both response to tamoxifen treatment and prognosis has prompted several

Severe premature coronary artery disease with protease inhibitors

Keith Henry, Holly Melroe, Jacquelyn Huebsch, Jessica Hermundson, Claudia Levine, Lyle Swensen, Jack Daley

A review of 124 patients on protease inhibitors in our HIV clinic identified 41 (33%) with raised lipid concentrations

impact on mortality from AIDS.[1] After two young AIDS patients on protease inhibitors under our care developed coronary artery disease, we examined lipid abnormalities

LANCET 351;1328: 2 May, 1998

AIDS 1999, Vol 13 No 13

Increasing morbidity from myocardial infarction during HIV protease inhibitor treatment?

We have recently observed five cases of myocardial infarction (MI) within 6 months in one HIV outpatient

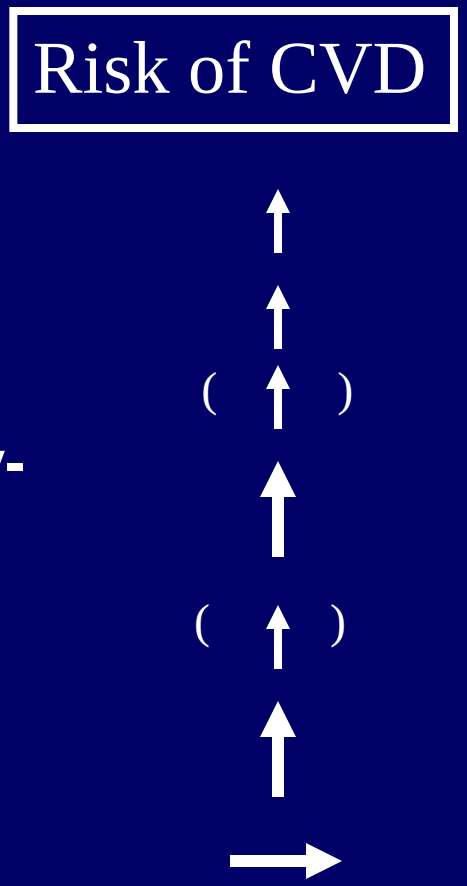
Table 1. Clinical characteristics of patients

Case no.	1	2	3	4	5
Age (years)	53	35	50	57	40
CDC cell stage	B3	B3	C3	A1	C3
CD4 cell count (per ml)	210	230	200	1070	150
Viral load (log 10)	3.6	<1.7	2.4	3.2	2.8
Antiretroviral treatment at time of event	Ritonavir, zidovudine, lamivudine	Ritonavir, zidovudine, lamivudine	Indinavir, stavudine, lamivudine	Nelfinavir, stavudine, lamivudine	Nelfinavir, stavudine, didanosine, nevirapine
Time on drugs (months)	10	3	17	4	11
Nicotine pack years	28.5	40	50	105	37.5
Hypertension	No	No	No	No	No
Genetic factors	No	Yes	No	Yes	Yes
Hyperglycemia	No	No	No	No	No
Total cholesterol (mg/dl)	396	301	263	270	294
Total cholesterol before PI treatment	209	147	255	173	161
LDL/HDL cholesterol ratio	10.7	12	9.2	ND	6.8
Triglycerides (mg/dl)	340	548	640	190	199
Triglycerides before PI treatment (mg/dl)	366	126	597	54	49
Fibrinogen (g/dl)	*3.9*	*2.4*	*6.0*	*2.4*	*2.7*
Adiposity (BMI >28 kg/m²)	*No*	*No*	*No*	*Yes*	*No*
Peripheral vascular disease	*Yes*	*No*	*No*	*No*	*No*
Coronary artery catheterization	RCA and LAD occlusion, 50% RCX-stenosis	RCA occlusion	Not done (refused by patient)	Diffuse coronary sclerosis, LAD occlusion	60% CX and RCA stenosis

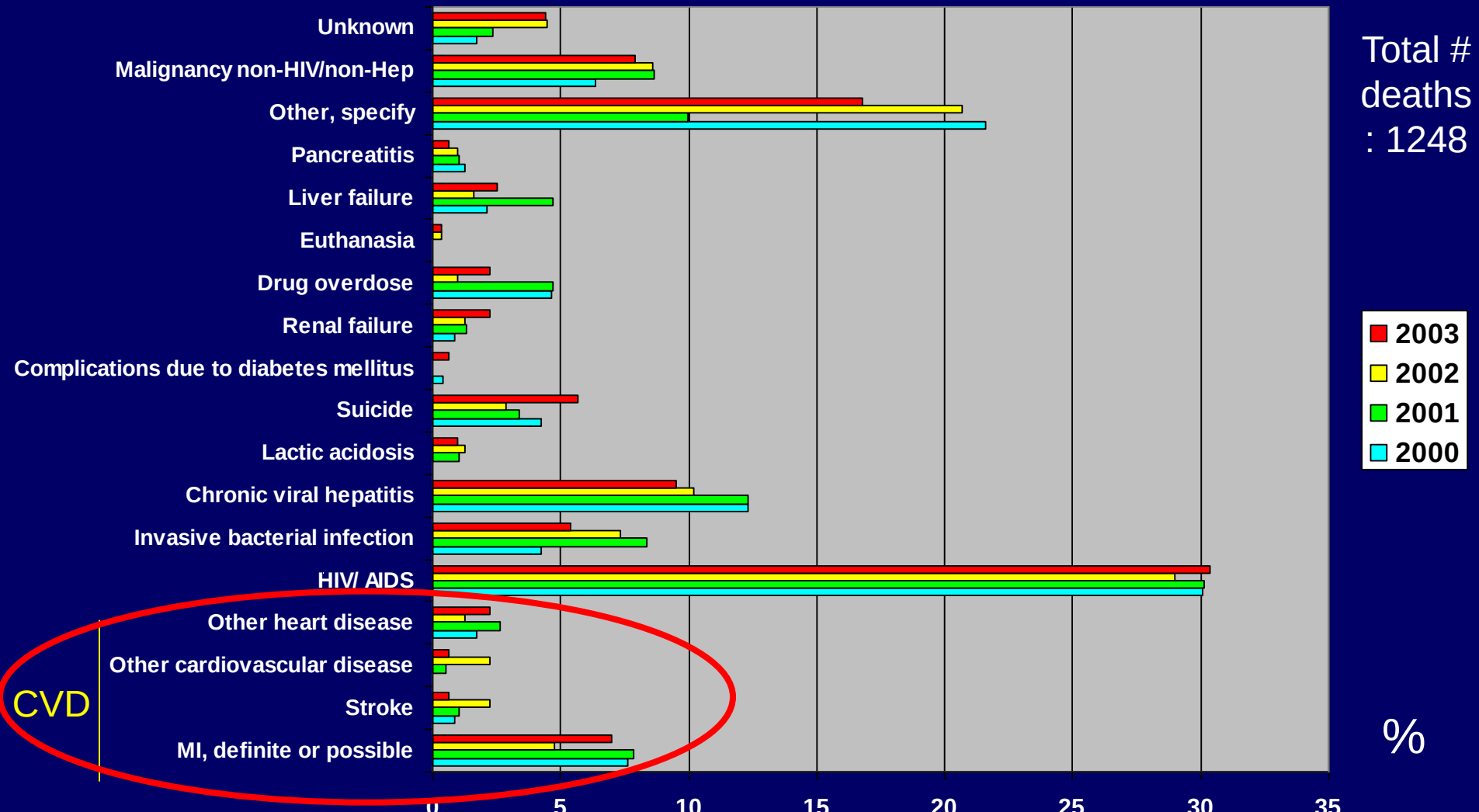
BMI, Body mass index; CDC, Centers for Disease Control and Prevention; LAD, left anterior descendent artery; LDL/HDL, low density lipoprotein/high density lipoprotein; ND, not determined; PI, protease inhibitor; RCA, right coronary artery; CX, circumflex coronary artery.

Studies of CVD risk associated with treatment in HIV

- Cohort studies of clinical outcome:
  - CDC/HOPS: Holmberg et al
  - John Hopkins
  - Medicaid: Currier et al
  - French HIV Hospital Database: Mary-Krause et al
  - Kaiser Permanente: Klein et al
  - Data collection of Adverse event of anti-HIV drugs (D:A:D)
  - VA database: Bozzette et al



Causes of death in D:A:D 2000-2004 percentage / year

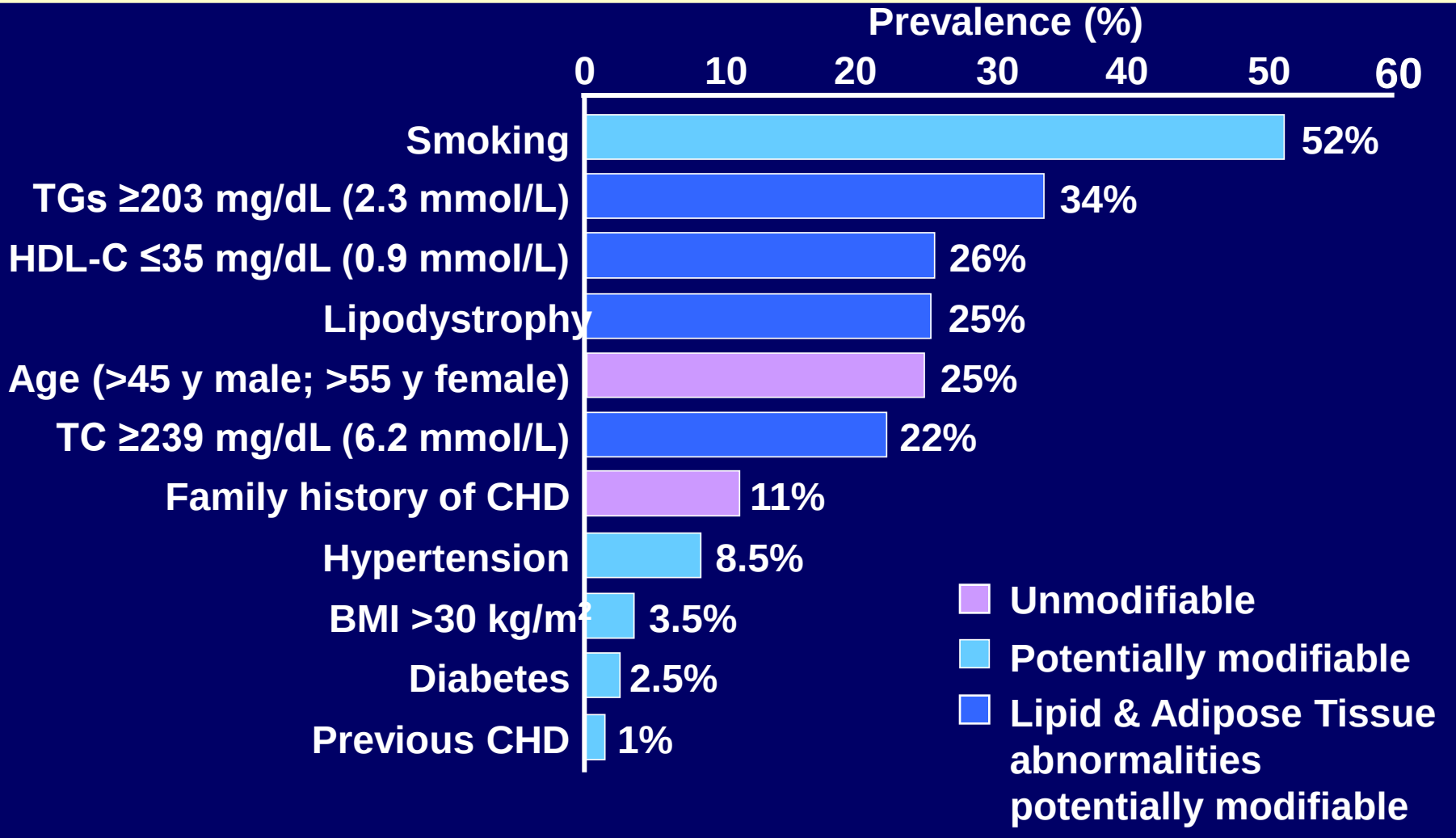


Weber et al, CROI, 2005

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study

- Prospective, multinational, observational study initiated in 1999
- Formed by collaboration of 11 previously established HIV cohorts
  - > 33,000 HIV-infected patients followed at 188 clinics in 20 countries in Europe, US, and Australia
- Purpose of the D:A:D study
  - To determine the prevalence of risk factors for CVD among HIV-infected persons
  - To investigate any association between risk factors, stage of HIV disease, and use of ART

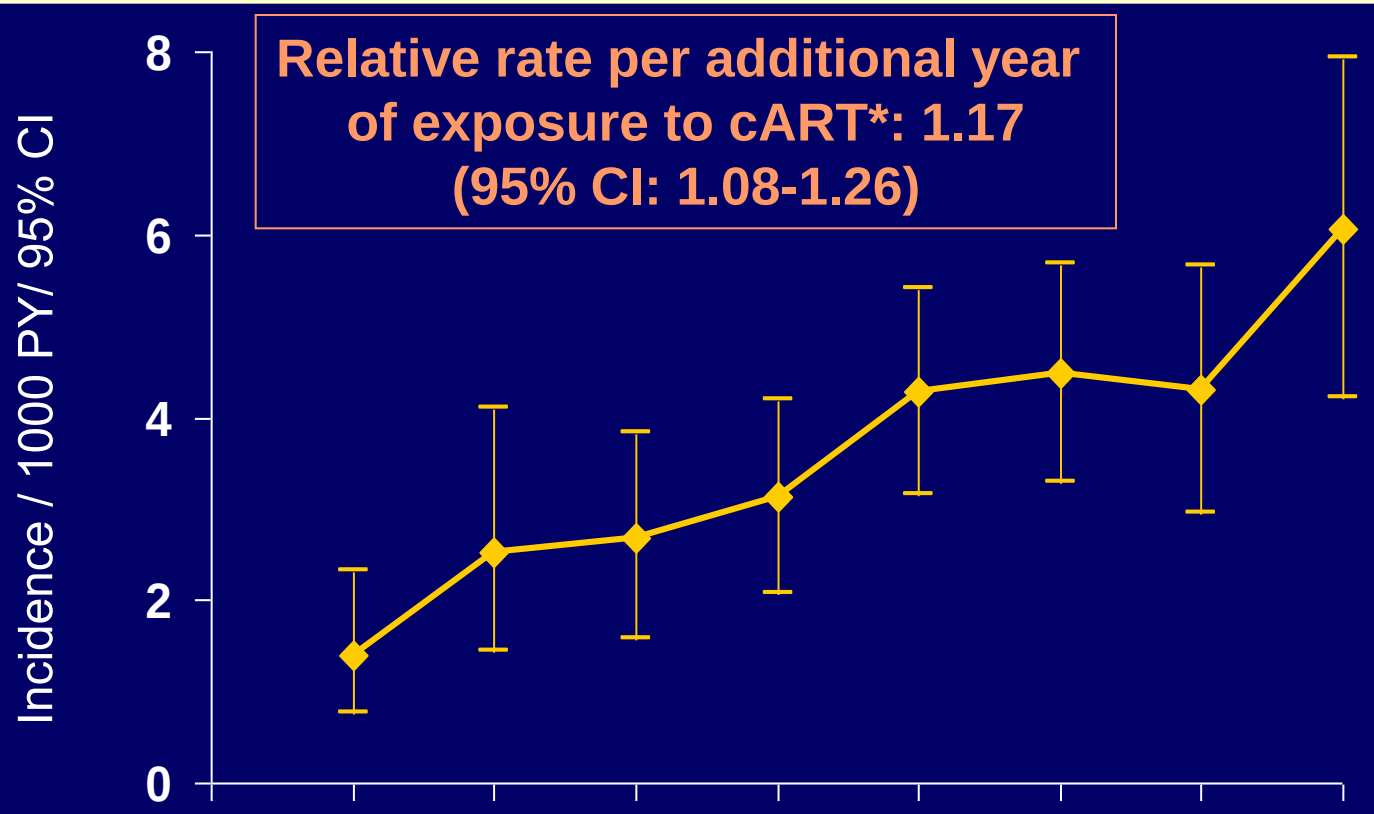
CV risk factors in an HIV-infected population: the DAD study



CHD: coronary heart disease; BMI: body mass index; DAD: Data Collection of Adverse Events

Friis-Moller N *et al*. *AIDS* 2003; **17**: 1179–1193

Incidence of myocardial infarction and duration of exposure to cART (D:A:D cohort)

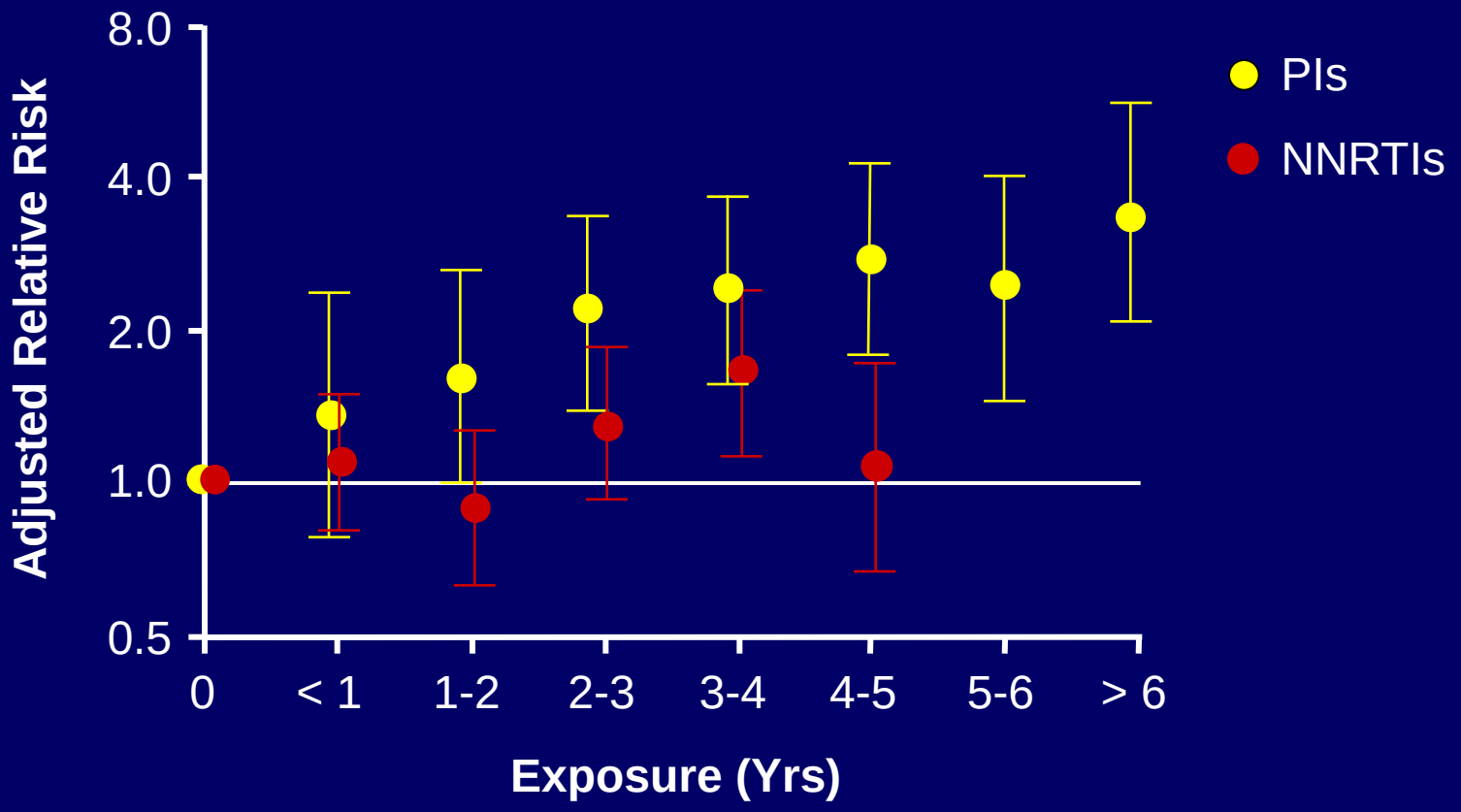


cART Exposure (yrs)	None	<1	1-2	2-3	3-4	4-5	5-6	>6	
# MI	14	16	22	34	56	55	39	41	277
PYFU	10,103	6,324	8,165	10,846	13,060	12,254	9,073	6,751	76,577

*: Adjusted for conventional risk factors not influenced by cART

El-Sadr *et al*, CROI 2005 (#N-186)

D:A:D Study
Risk of MI by Exposure to NNRTIs and PIs



Friis-Møller, et al. N Engl J Med. 2007;326:1723-1735.

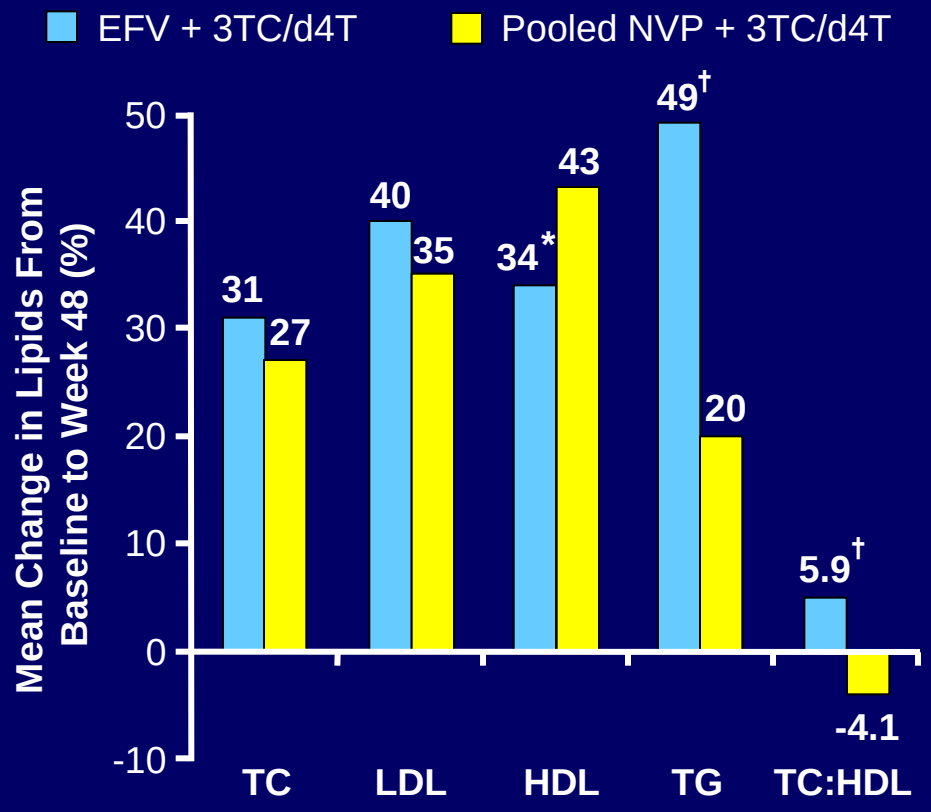
Antiretrovirals
Uses and Risks

Is there a hierarchy of treatment-associated risks for hyperlipidemia and cardiovascular disease

- **among NRTIs?**
- **among NNRTIs?**
- **among PIs?**

2NN: Lipid Effects of EFV vs NVP at Week 48

- **48-week, multicenter, open-label, randomized trial in treatment-naive patients (N = 1216)**
  - NVP 400 mg QD (n = 220)
  - NVP 200 mg BID (n = 387)
  - EFV 600 mg QD (n = 400)
  - NVP 400 mg + EFV 800 mg QD (n = 209)
  - All plus d4T + 3TC
- **Similar efficacy with NVP BID and EFV but NVP did not meet equivalence criteria**
- Greater lipid changes with EFV (combination NVP + EFV arm **excluded from lipid analysis)**



*$P < .05$ vs NVP.
†$P < .001$ vs NVP.

van Leth F, et al. PLoS Med. 2004;1:e19.

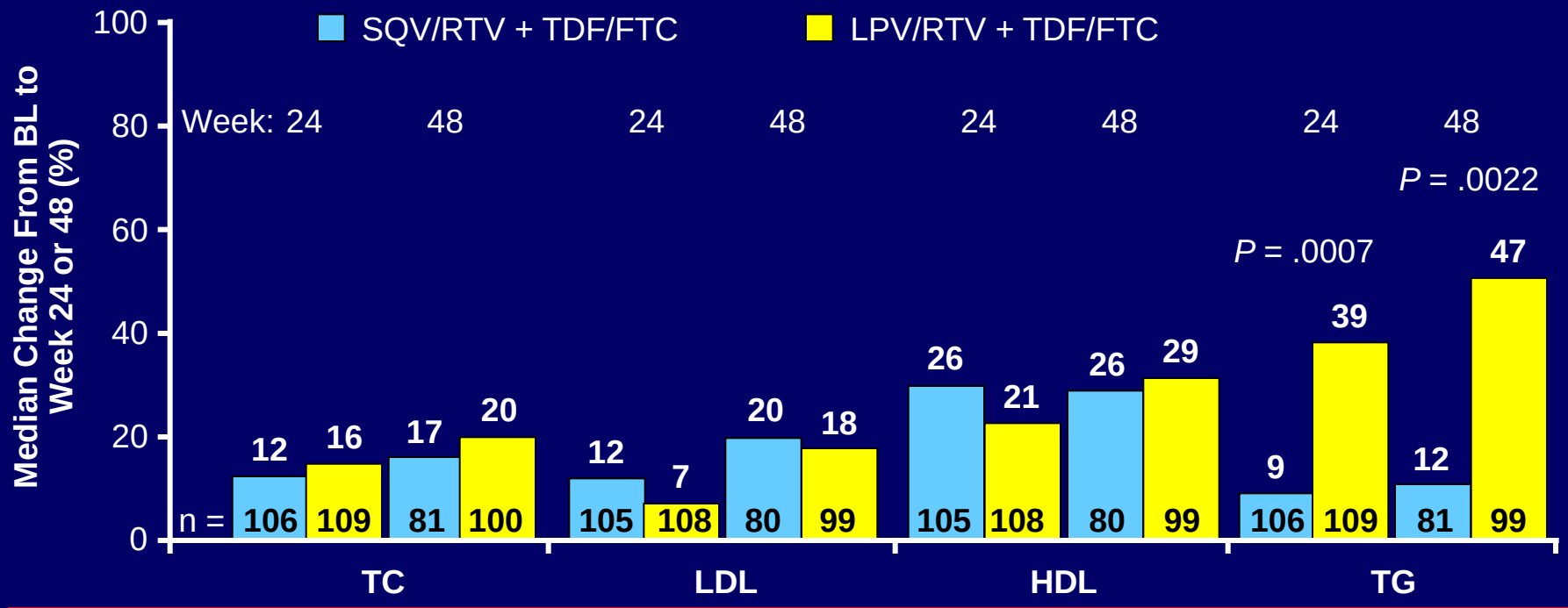
GS 934 and GS 903
Lipid Effects of Tenofovir vs Thymidine Analogues

- Prospective, randomized, double-blind studies in treatment-naive patients
- TDF associated with more benign lipid changes and less lipoatrophy

Mean Δ From BL to Week 144, mg/dL	GS 934[1]			GS 903[2]		
	TDF + FTC + EFV (n = 255)	ZDV/3TC + EFV (n = 254)	*P* Value	TDF + 3TC + EFV (n = 299)	d4T + 3TC + EFV (n = 303)	*P* Value
TC • mmol/L	24 0.62	36 0.94	.005	30 0.79	58 1.50	.001
LDL cholesterol • mmol/L	10 0.26	16 0.41	NS	14 0.36	26 0.67	.001
HDL cholesterol • mmol/L	13 0.34	12 0.31	NS	9 0.23	6 0.15	.003
TG • mmol/L	4 0.04	36 0.41	.047	1 0.01	134 1.51	.001

1. Arribas J, et al. J Acquir Immune Defic Syndr. 2008;47:74-78.
2. Gallant JE, et al. JAMA. 2004;292:191-201.

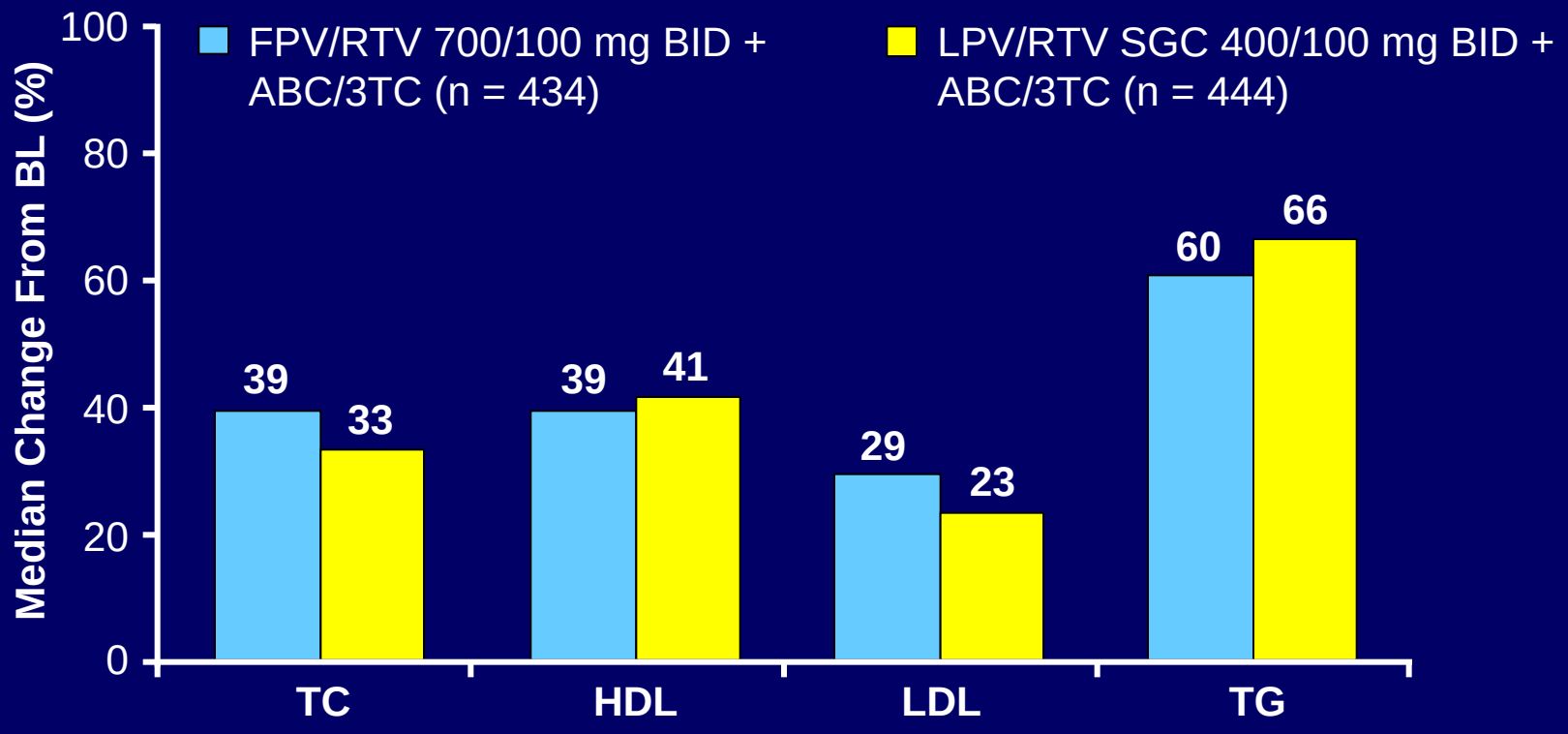
GEMINI Study
Lipids Effects of SQV/RTV vs LPV/RTV (On-Treatment Analysis)



- More patients in the LPV/RTV group exceeded the NCEP threshold (39%) for total cholesterol vs the SQV/RTV arm (31%)
- Significant difference in fasting TC:HDL ratio between arms at Week 24 lost at Week 48

Walmsley SL, et al. EACS 2007. Abstract PS1.4.

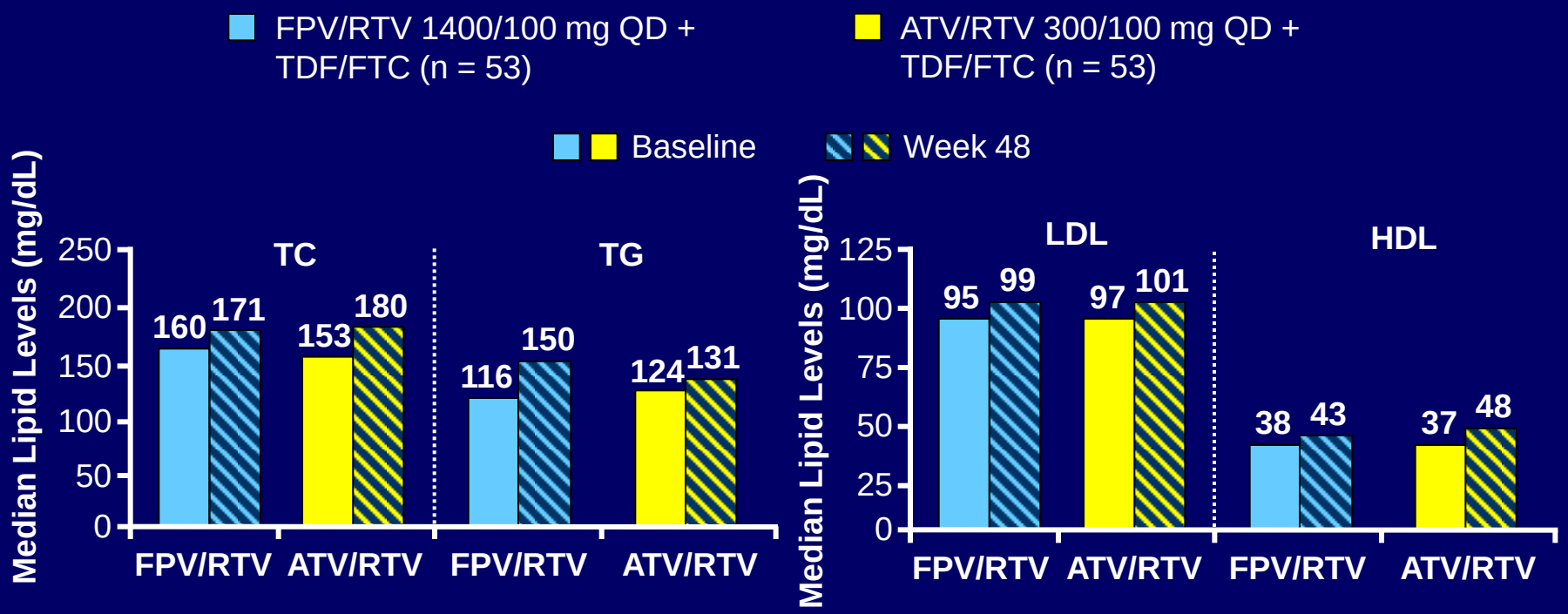
KLEAN Study
Lipid Effects of FPV/RTV vs LPV/RTV at Week 48



- **Lipid effects comparable between arms**

Eron JJ, et al. Lancet. 2006;368:476-482.

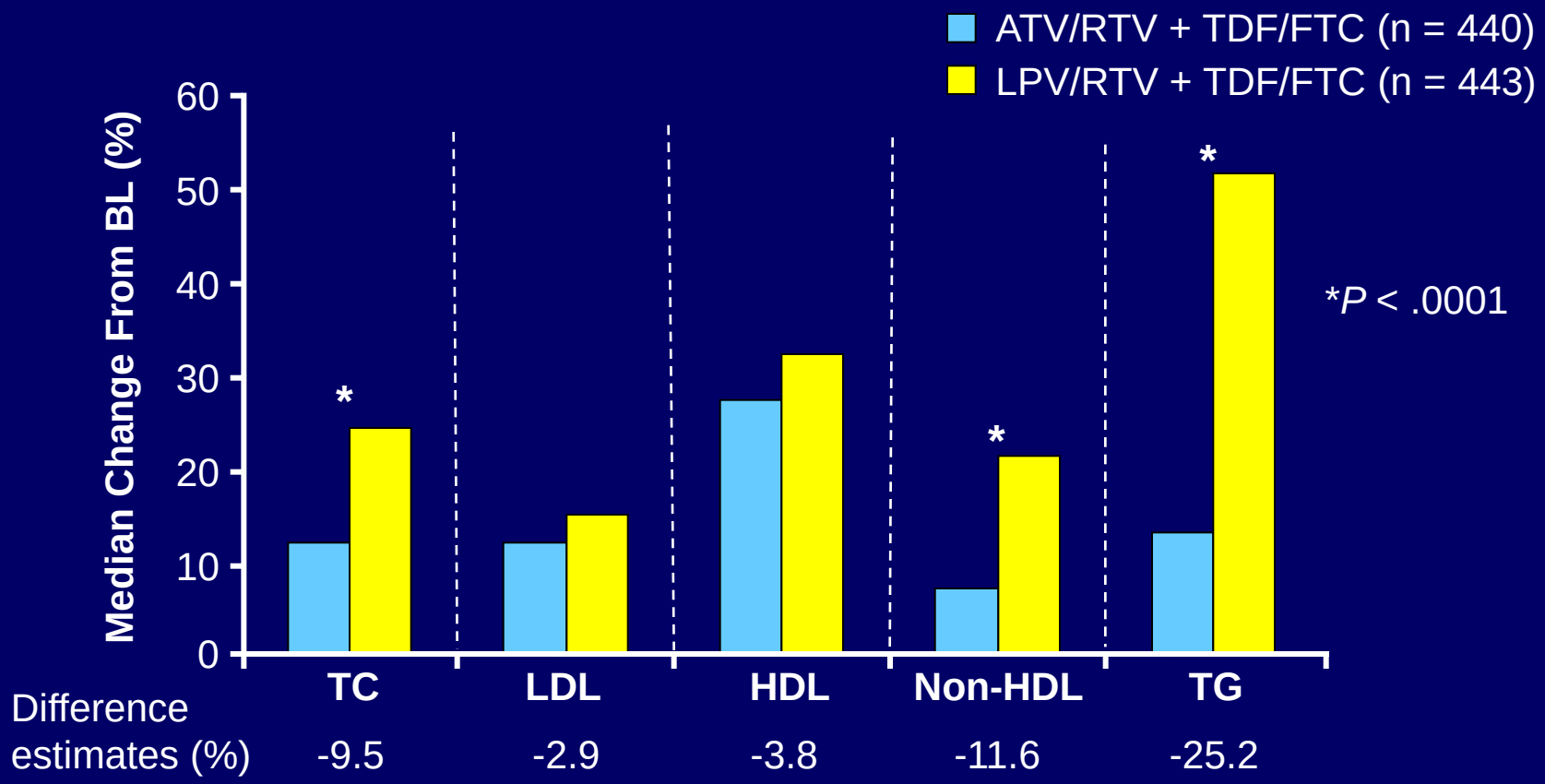
ALERT Study
Lipid Effects of FPV/RTV vs ATV/RTV at Week 48



- **Lipid effects comparable between arms**

Smith K, et al. IAS 2007. Abstract WEPEB023.

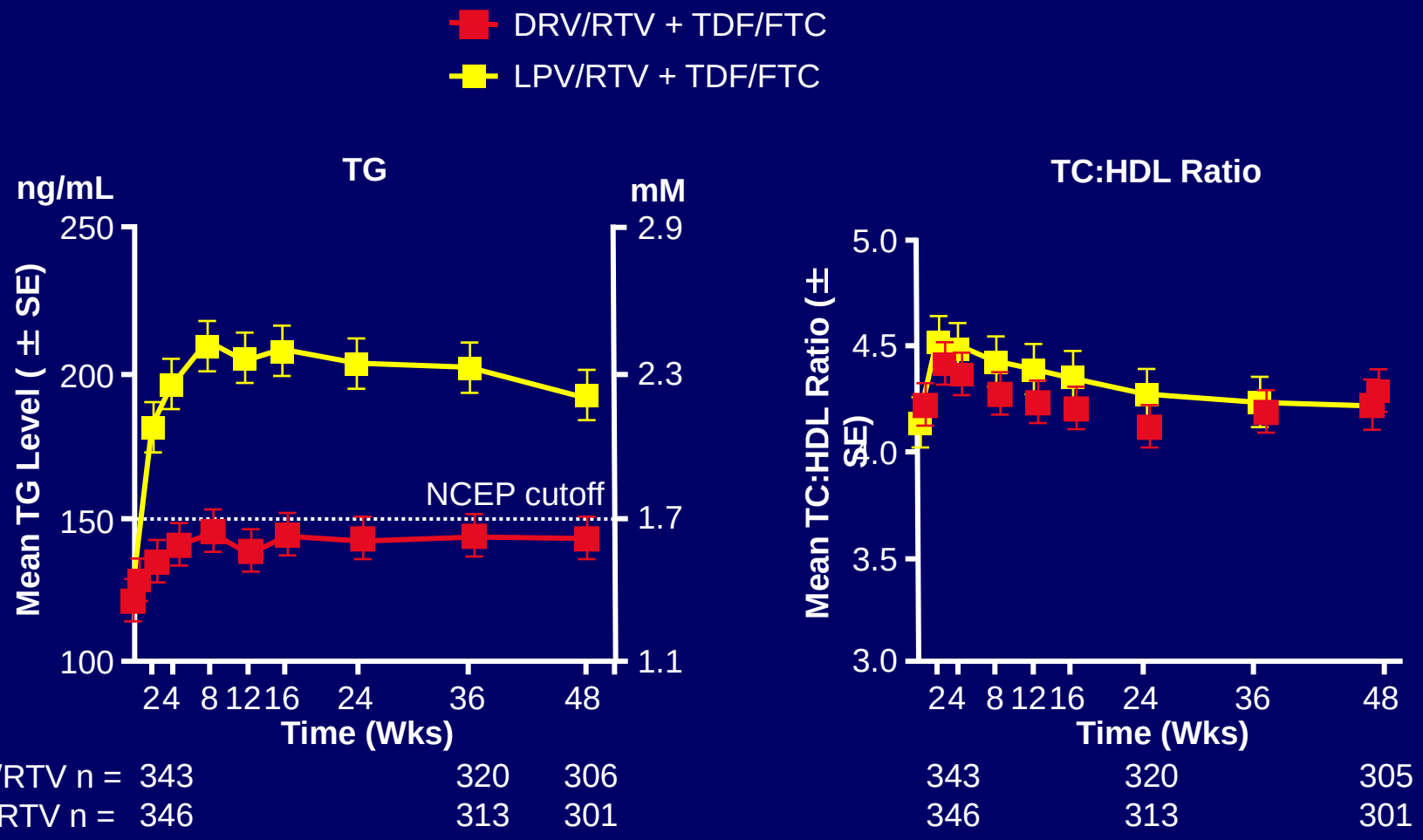
CASTLE Study
Lipid Effects of ATV/RTV vs LPV/RTV at Week 48



- 2% of ATV/RTV vs 7% of LPV/RTV subjects initiated lipid-lowering therapy during study

Molina JM, et al. CROI 2008. Abstract 37.

ARTEMIS Study
Mean Fasting Lipid Levels Over Time for DRV/RTV vs LPV/RTV



De Jesus E, et al. ICAAC 2007. Abstract 718b.

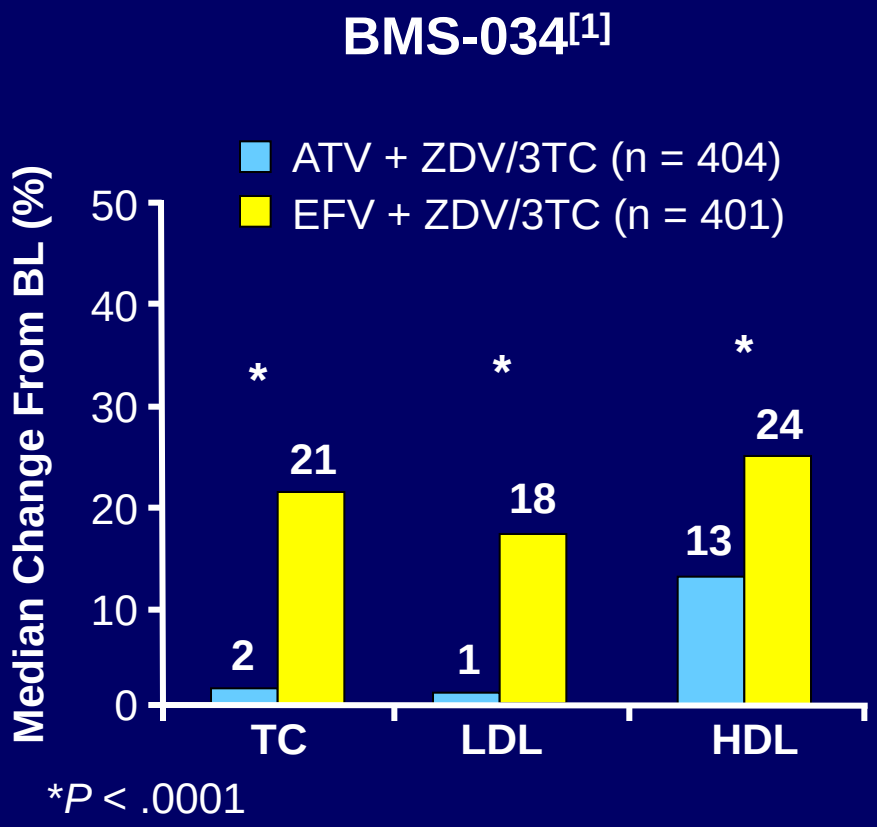
Boosted vs Unboosted PIs

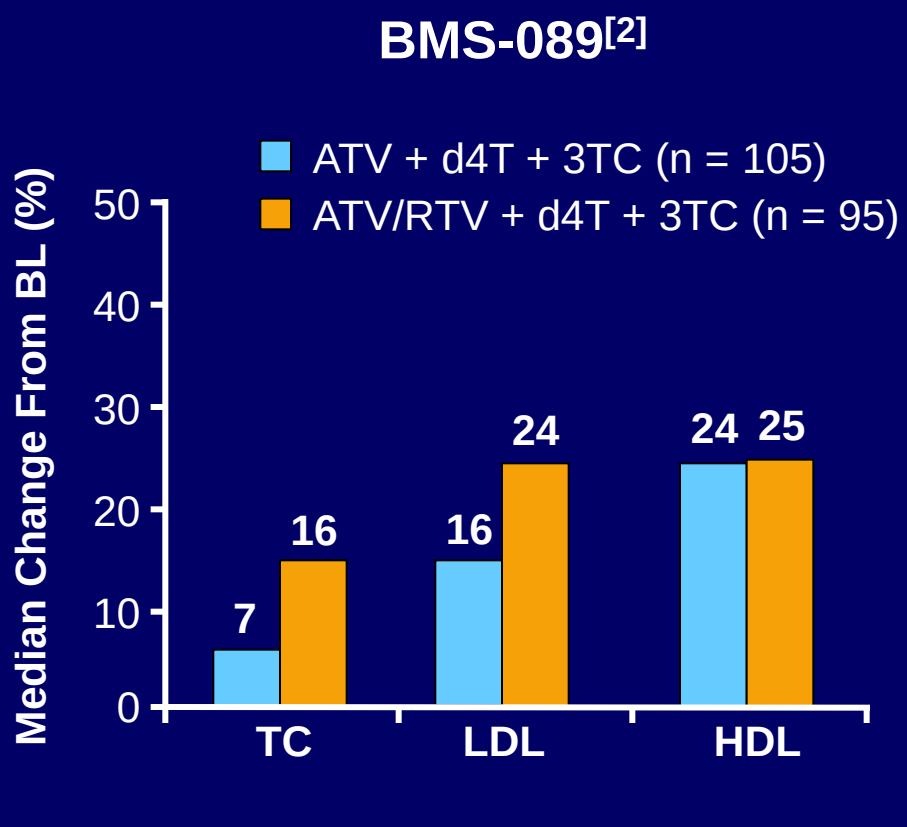
- Low-dose RTV boosting associated with
  - Increased efficacy, less frequent dosing, reduced resistance on failure
  - Increased incidence of AEs and metabolic events

PIs Administered Unboosted	PIs Boosted With RTV 100 mg/day	PIs Boosted With RTV ≥ 200 mg/day*
ATV	ATV/RTV	LPV/RTV
FPV	FPV/RTV (naive pts only)	FPV/RTV
NFV	DRV/RTV (naive pts only)	DRV/RTV
IDV		SQV/RTV
		TPV/RTV*
		IDV/RTV

*All RTV 200 mg/day except TPV requires RTV 400 mg/day,

BMS-034 & BMS-089
Lipid Effects of Boosted and Unboosted ATV at Wk 48





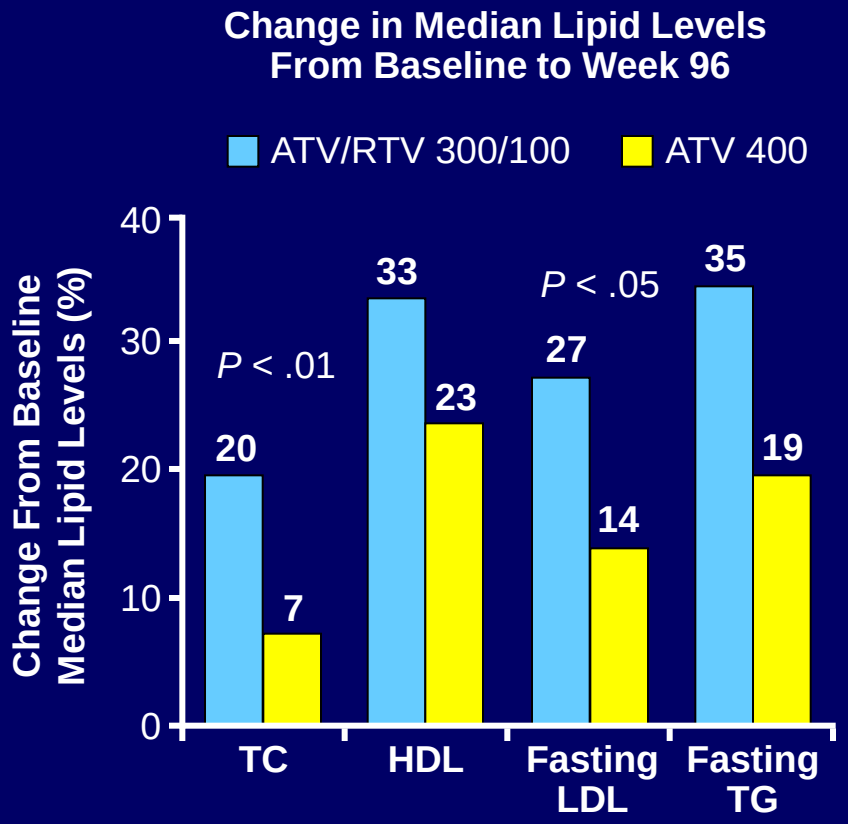
1. Squires K, et al. J Acquir Immune Defic Syndr. 2004;36:1011-1019.
2. Malan DR, et al. J Acquir Immune Defic Syndr. 2008;47:161-167.

BMS-089: Week 96 Results of Boosted vs Unboosted ATV in ART-Naive Pts

- AI424-089: randomized, open-label, multicenter trial
  - ATV 400 mg QD (n = 105)
  - ATV/RTV 300/100 mg (n = 95)
  - Both with d4T XR 100 mg QD + 3TC 300 mg QD

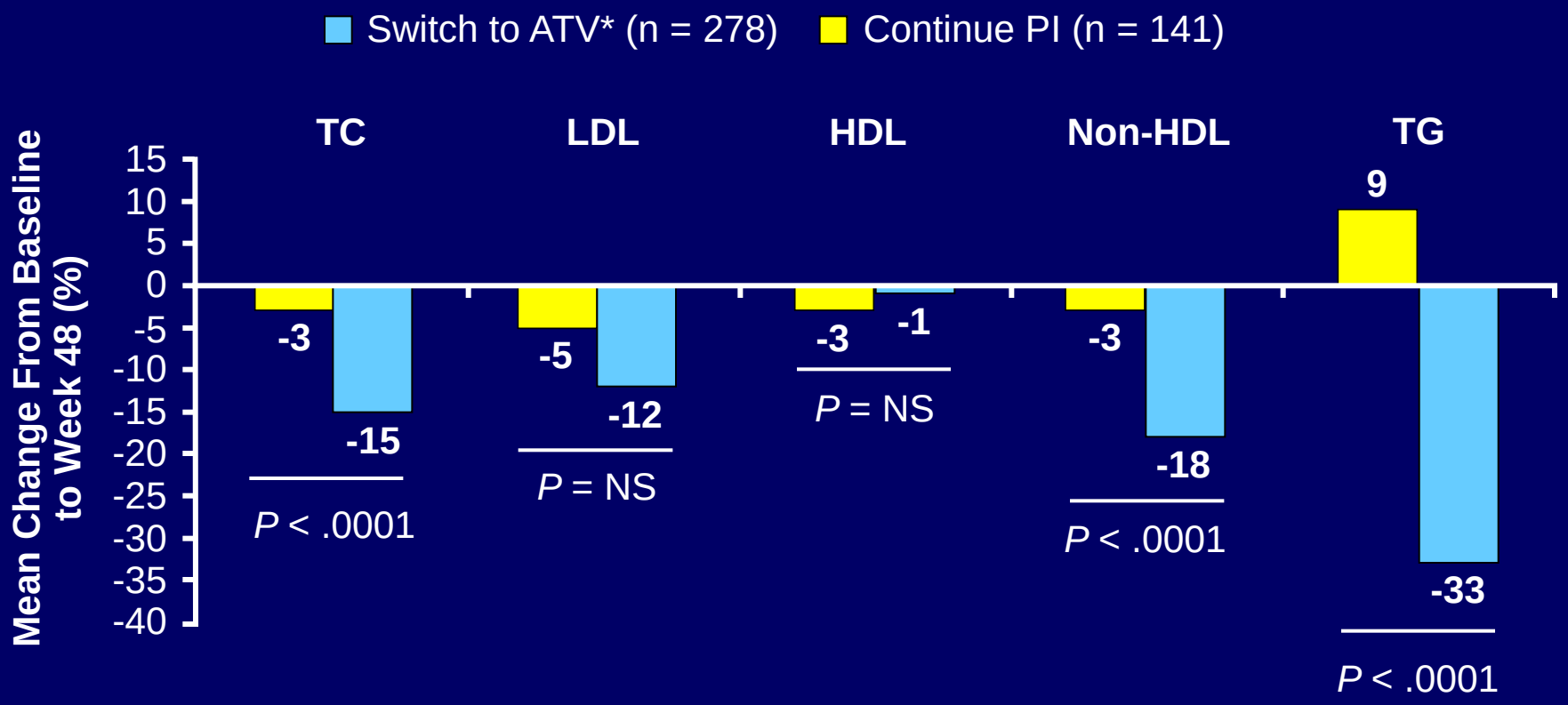
- Trend for more virologic failure in ATV arm at Week 96*
- Greater effects on lipids with ATV/RTV vs ATV
- Median lipid levels did not meet intervention levels at Week 96

*Not powered to determine if ATV noninferior to ATV/RTV.



Malan DR, et al. J Acquir Immune Defic Syndr. 2008;47:161-167.

SWAN: Change in Lipids After Switch From Comparator PI to ATV (Week 48)

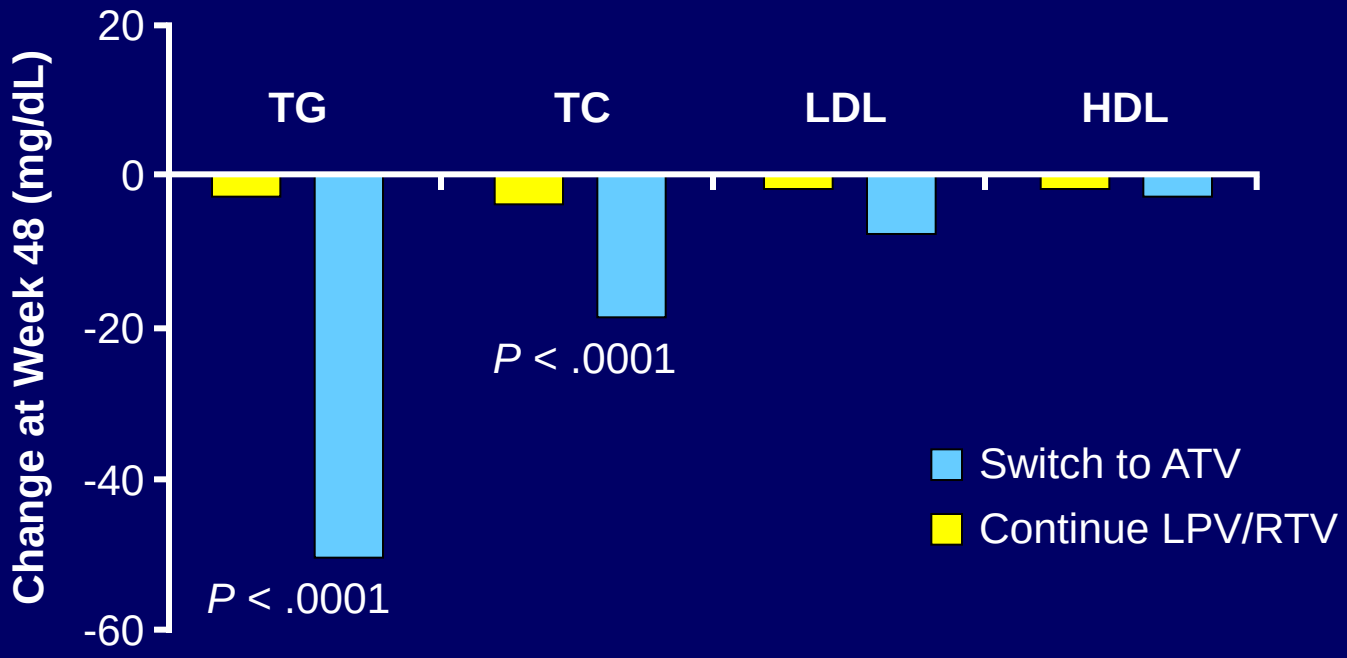


*Unboosted ATV, except ATV/RTV used in patients also receiving TDF.

Gatell JM, et al. EACS 2005. Abstract PS1/1.

ATAZIP: Switch From LPV/RTV to ATV/RTV

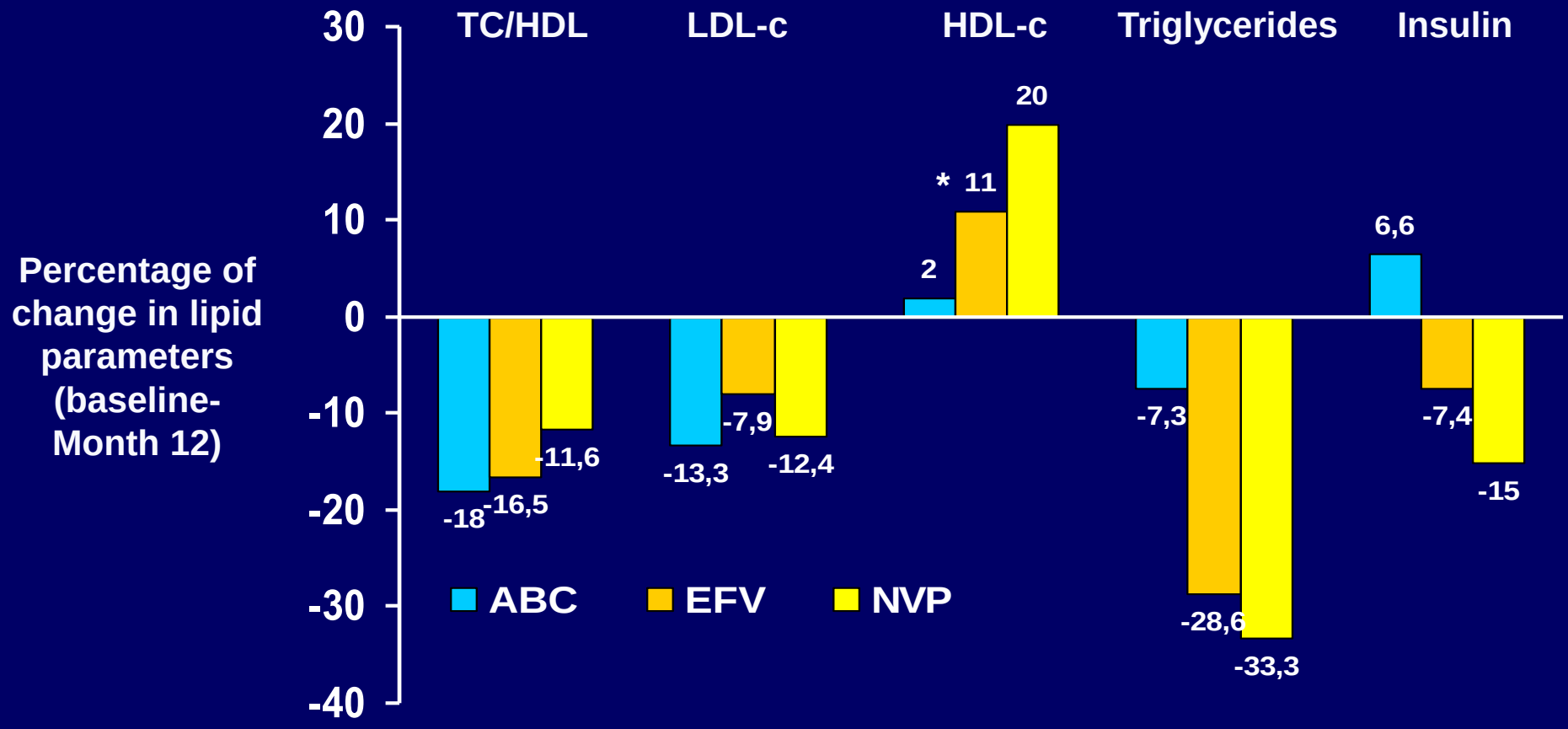
- **Randomized trial of patients on LPV/RTV > 6 months randomized to continue LPV/RTV 400/100 mg BID (n = 127) or switch to ATV/RTV 300/100 mg QD (n = 121)**



Mallolas J, et al. IAS 2007. Abstract WEPEB117LB.

NEFA study: Metabolic Changes in Patients Switching from PI to ABC, EFV or NVP

Changes in Lipid Profile and insulin by Treatment Group

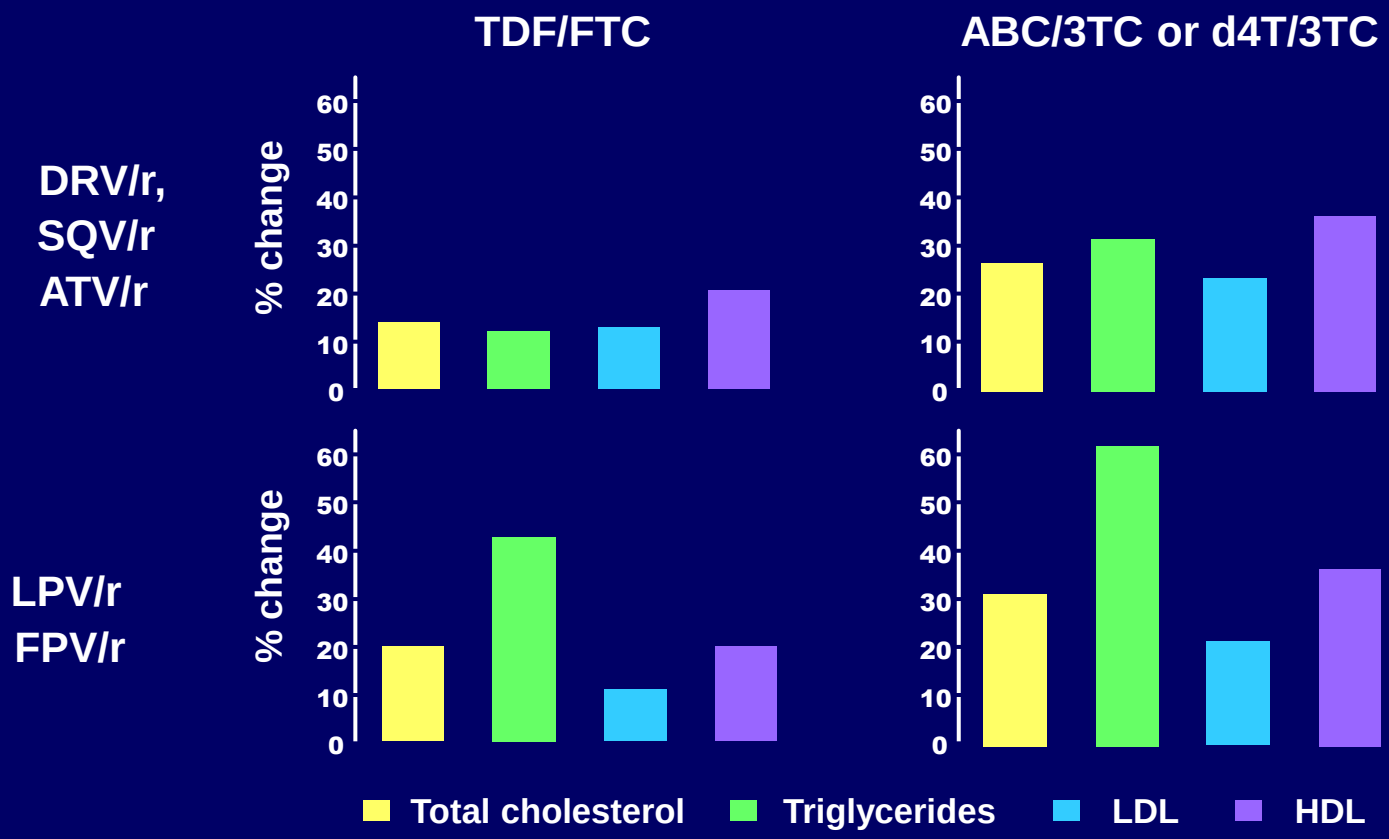


*p <0.005

Fisac C et al. Poster presented at: WAC Abstract ThPe7354

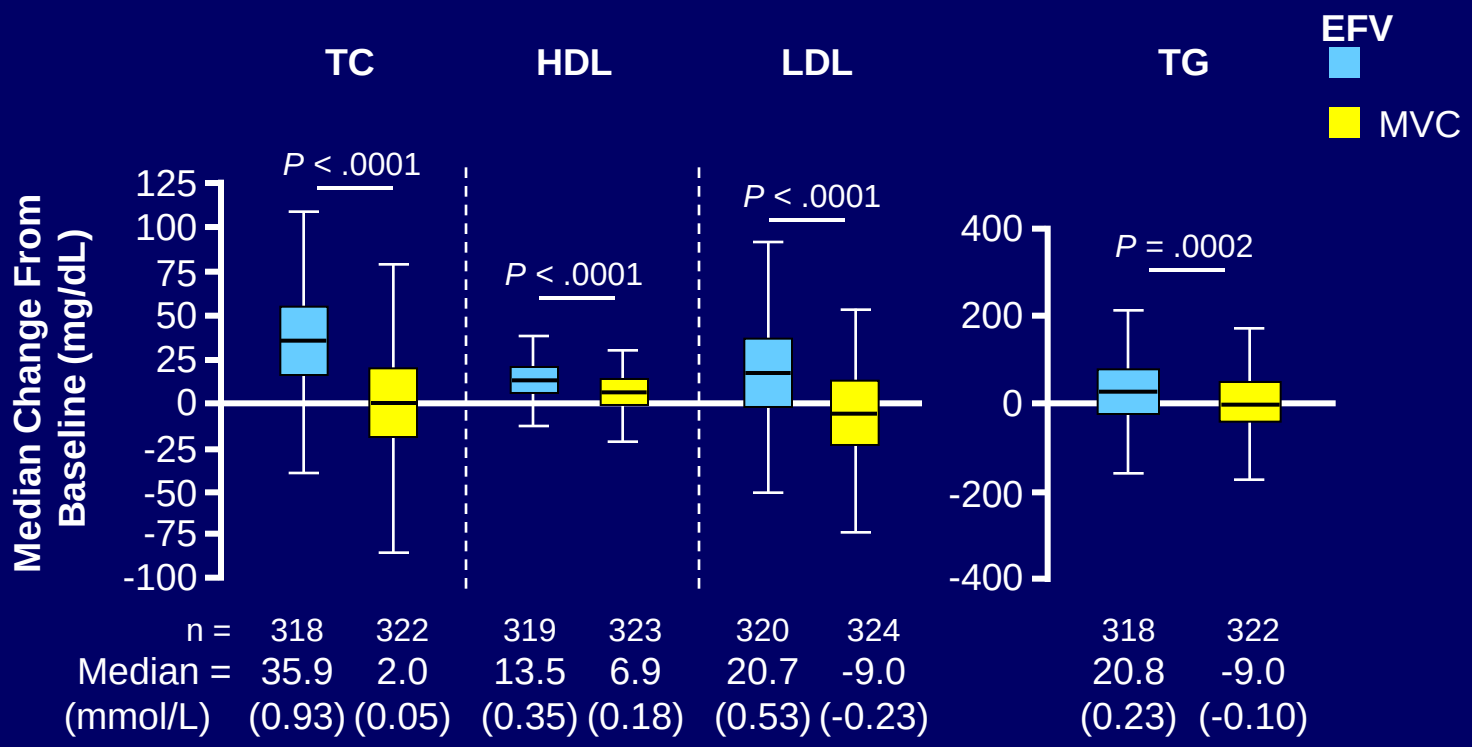
Meta-analysis of Impact of NRTI Backbone + PI/r on Lipids

Multivariate analysis of percentage change in lipids from baseline to week 48: Effects of NRTI versus PI used



Hill A, et al. 17th IAC; Mexico City, Aug 3-8, 2008; Abst. THPE0167.

MERIT Substudy: Fewer Lipid Effects With Maraviroc vs Efavirenz at Week 48 in naïve patients



- MVC + ZDV/3TC associated with greater decrease in TC-to-HDL ratio vs EFV + ZDV/3TC: -0.54 (-0.014) vs -0.43 (-0.011) (*P* = .005)

DeJesus E, et al. CROI 2008. Abstract 929.

MRK004: Serum Lipids at Week 96

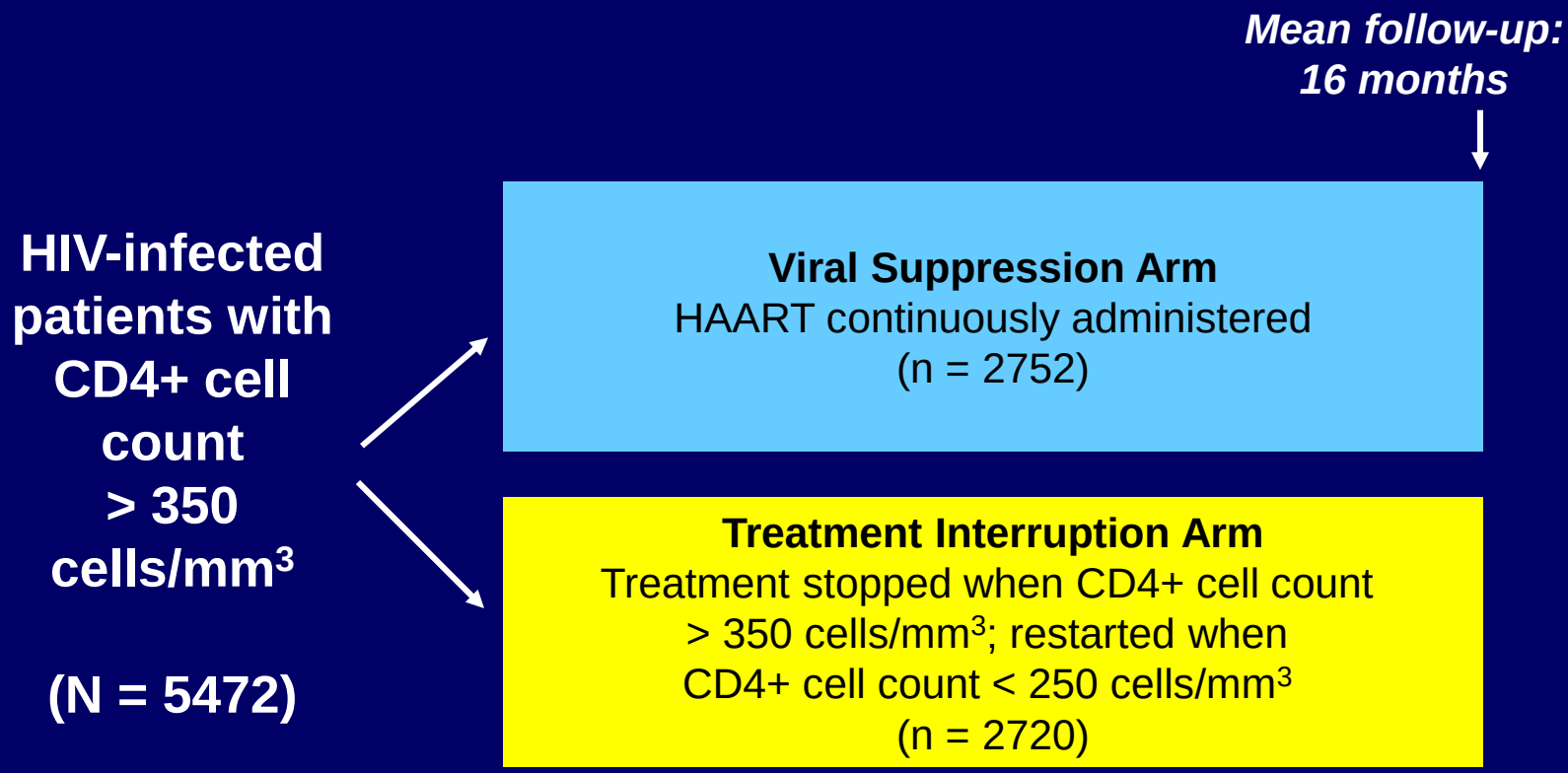
Mean change from baseline (mg/dL) at week 96

	RAL* + TDF/FTC (N=160)		EFV + TDF /FTC (N=38)		
	Baseline Mean	**Mean Change**	**Baseline Mean**	**Mean Change**	RAL vs EFV
Cholesterol	166.2	+1.1	168.9	+24.0	**P=0.002**
LDL-C	103.9	-5.8	108.5	+4.4	**P=0.045**
HDL-C	38.0	+7.4	37.9	+13.0	**P=0.017**
Triglycerides	134.7	-10.8	126.1	+13.4	**P=0.145**
Total: HDL ratio	4.6	-0.7	4.6	-0.7	**P=0.689**

*** All RAL dose groups combined**

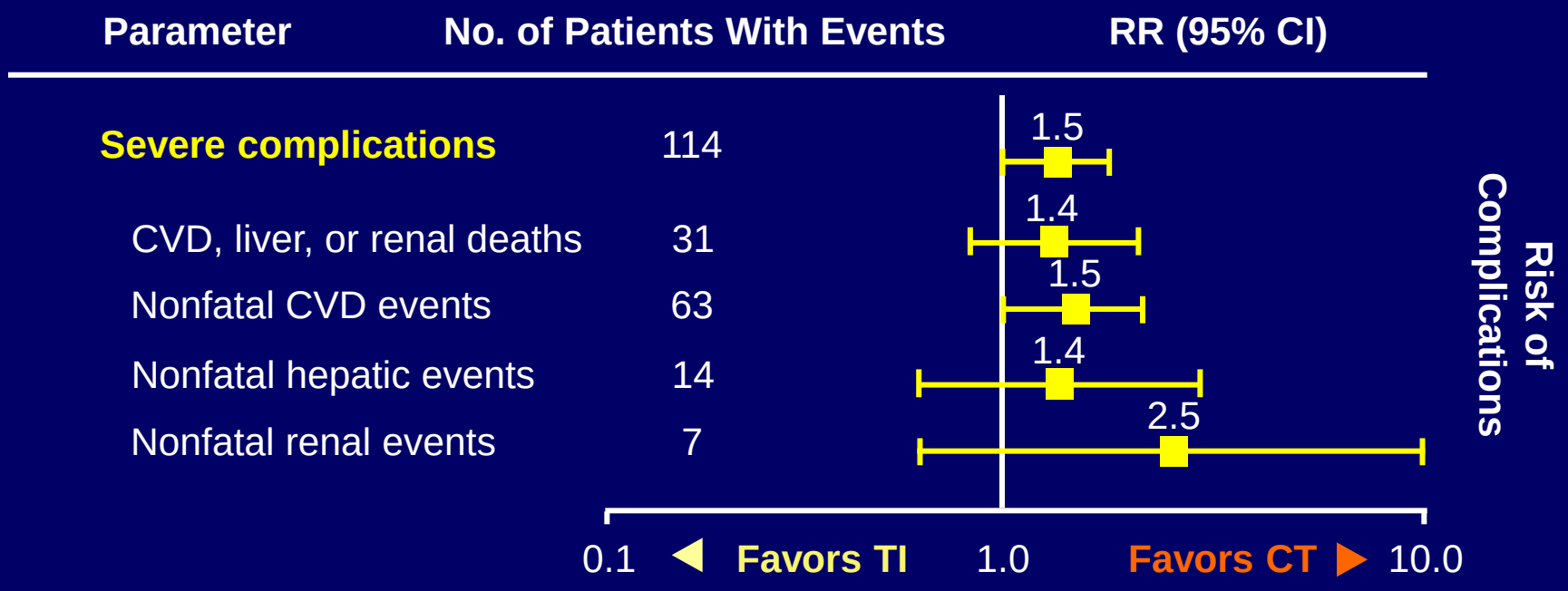
Markowitz M, et al. 17th IAC; Mexico City, Aug 3-8, 2008; Abst. TUAA0302.

SMART: Schematic of Study Design



SMART: HIV Progression With Continuous HAART vs Interruption

- **CD4-guided drug conservation strategy associated with significantly greater disease progression or death compared with continuous viral suppression: RR: 2.5 (95% CI: 1.8-3.6; *P* < .001)**

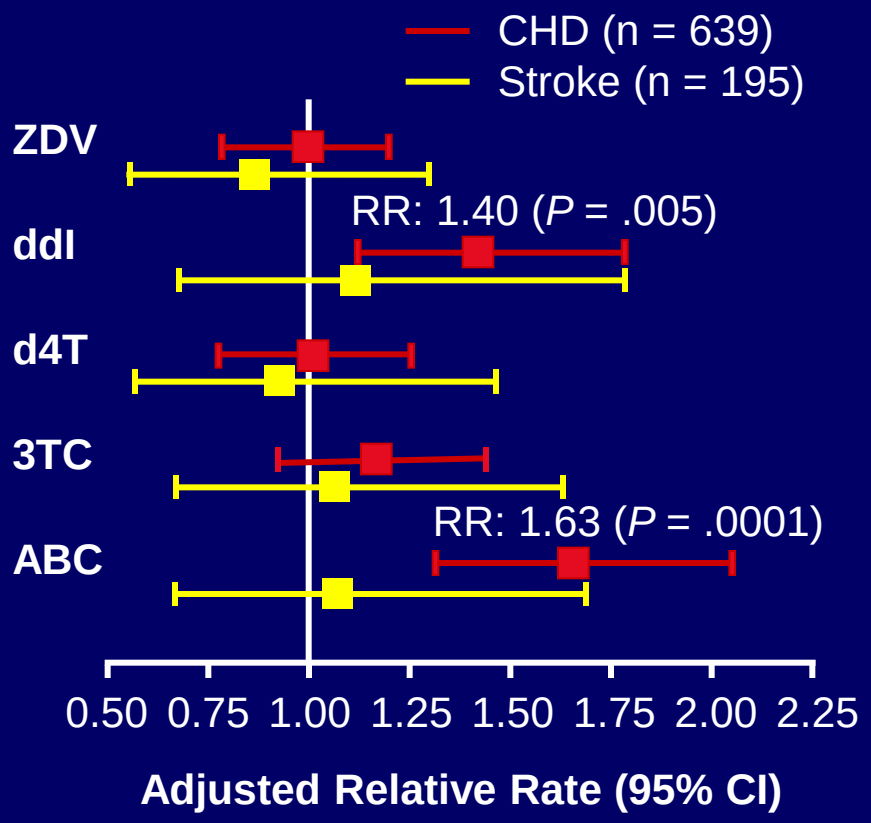


El-Sadr W, et al. N Engl J Med. 2006;355:2283-2296.

D:A:D Study

Recent Use of ABC, ddI Associated With Increased Risk of MI

- TAs not associated with increased risk of MI
- Current or recent (within 6 months) use of ABC or ddI associated with increased relative risk of MI
  - 90% increase of risk of MI with recent ABC
  - 49% increase of risk of MI with recent ddI
  - Risk most prominent in individuals with underlying CVD risk factors
- Increased risk no longer observed in patients who had discontinued ABC or ddI for > 6 months



D:A:D study group, Lancet 2008

Inflammatory markers and HIV replication:increased mortality risk.

- **SMART trial**
  - Interruption of ARV associated with a significant increase of IL- 6 and D-dimers
  - High levels of D-dimers and IL-6 associated with high risk of death (of any cause) (RR 26,5 & 11,8 respectively)
  - High levels of IL-6 and D-dimers could explain part of the increased risk of CVD and death in the DC arm.

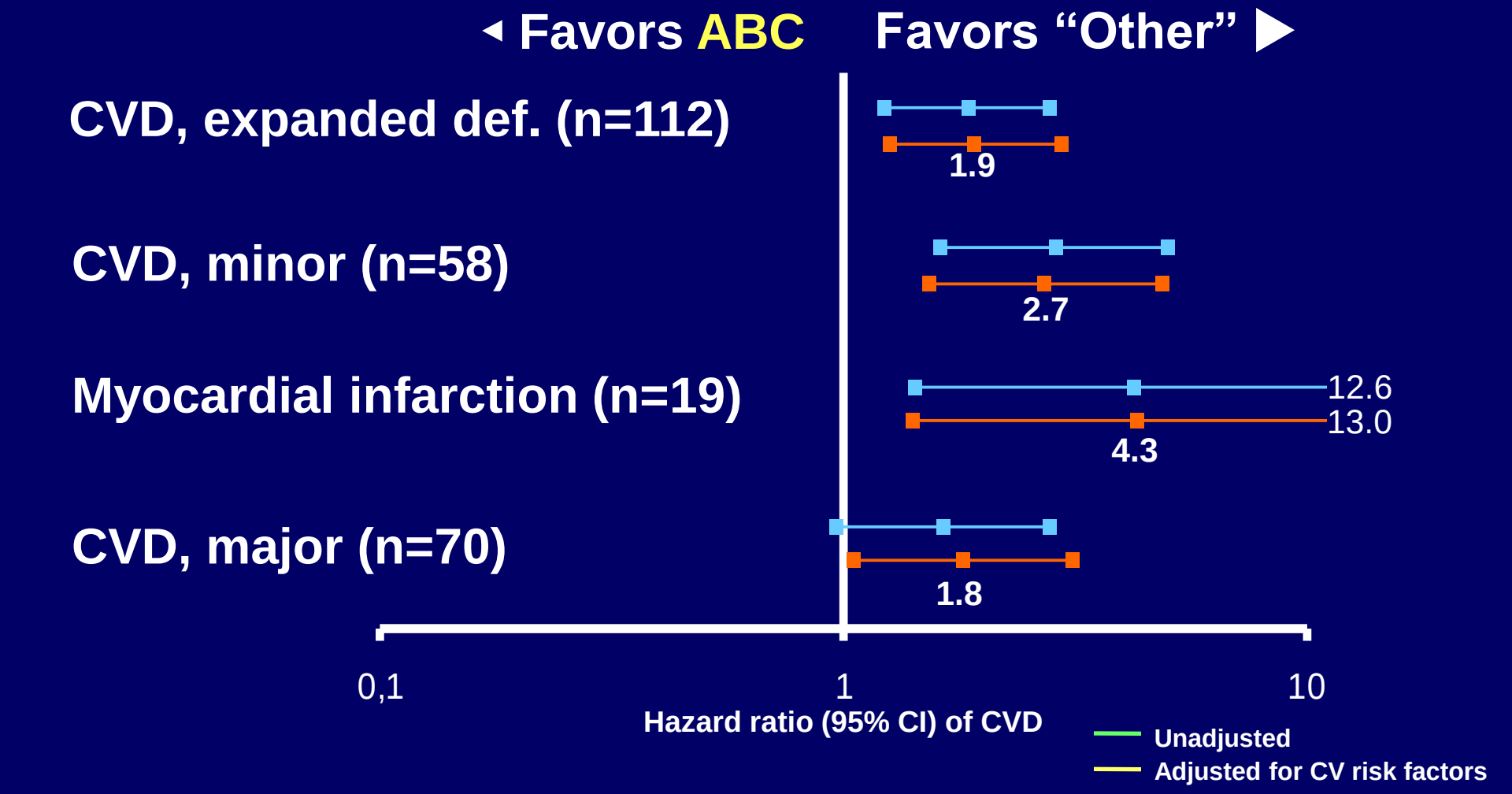
- **STACCATO trial**

  Viral replication rebound after tratment interruption associated with:

  - increase of markers of endothelial activation (s-VCAM-1 = *soluble vascular cell adhesion molecule*) and inflammation (MCP-1 = *monocyte chemotactic protein*).
  - these changes were partially reversible 12 weeks after treatment re-initiation.
  - decrease of IL-10 and adiponectin

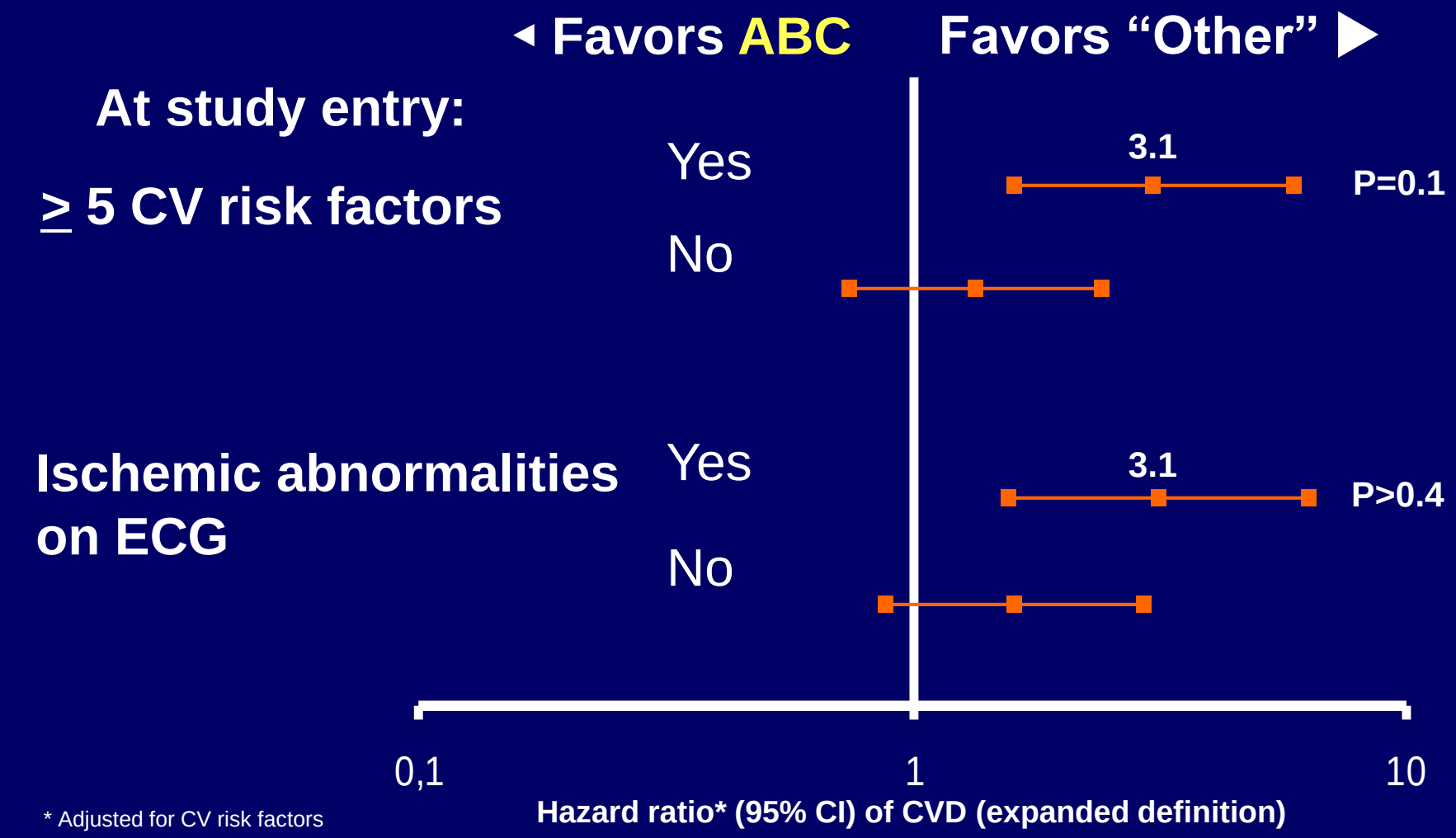
Kuller L, CROI 2008, Abs. 139 ; Calmy A CROI 2008, Abs. 140

Hazard Ratios for Four Groupings of CVD: "ABC (no ddI)" vs. "Other NRTIs"



Lundgren J, et al. 17th IAC; Mexico City, Aug 3-8, 2008; Abst. THAB0305.

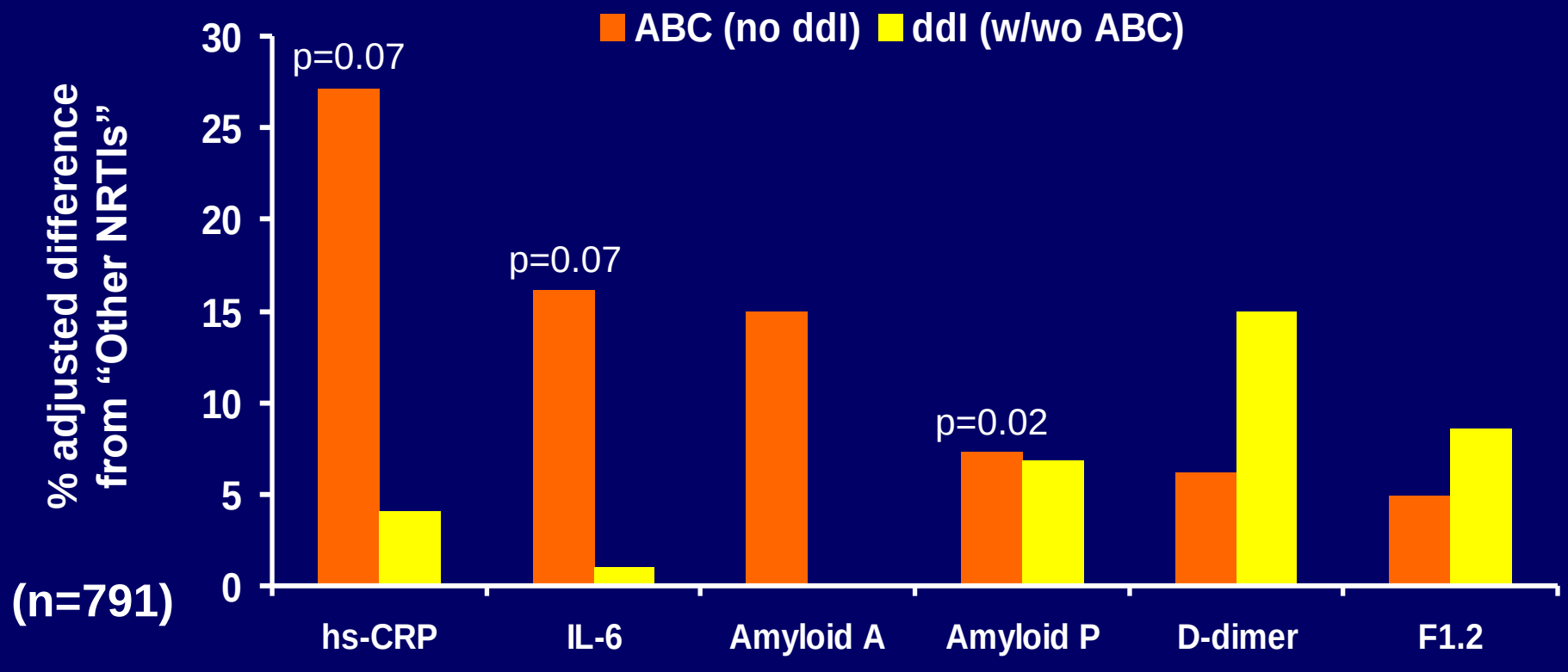
Hazards Ratios* for "ABC (no ddI)" vs. "Other NRTIs" by CV Risk Status at Study Entry



* Adjusted for CV risk factors

Lundgren J, et al. 17th IAC; Mexico City, Aug 3-8, 2008; Abst. THAB0305.

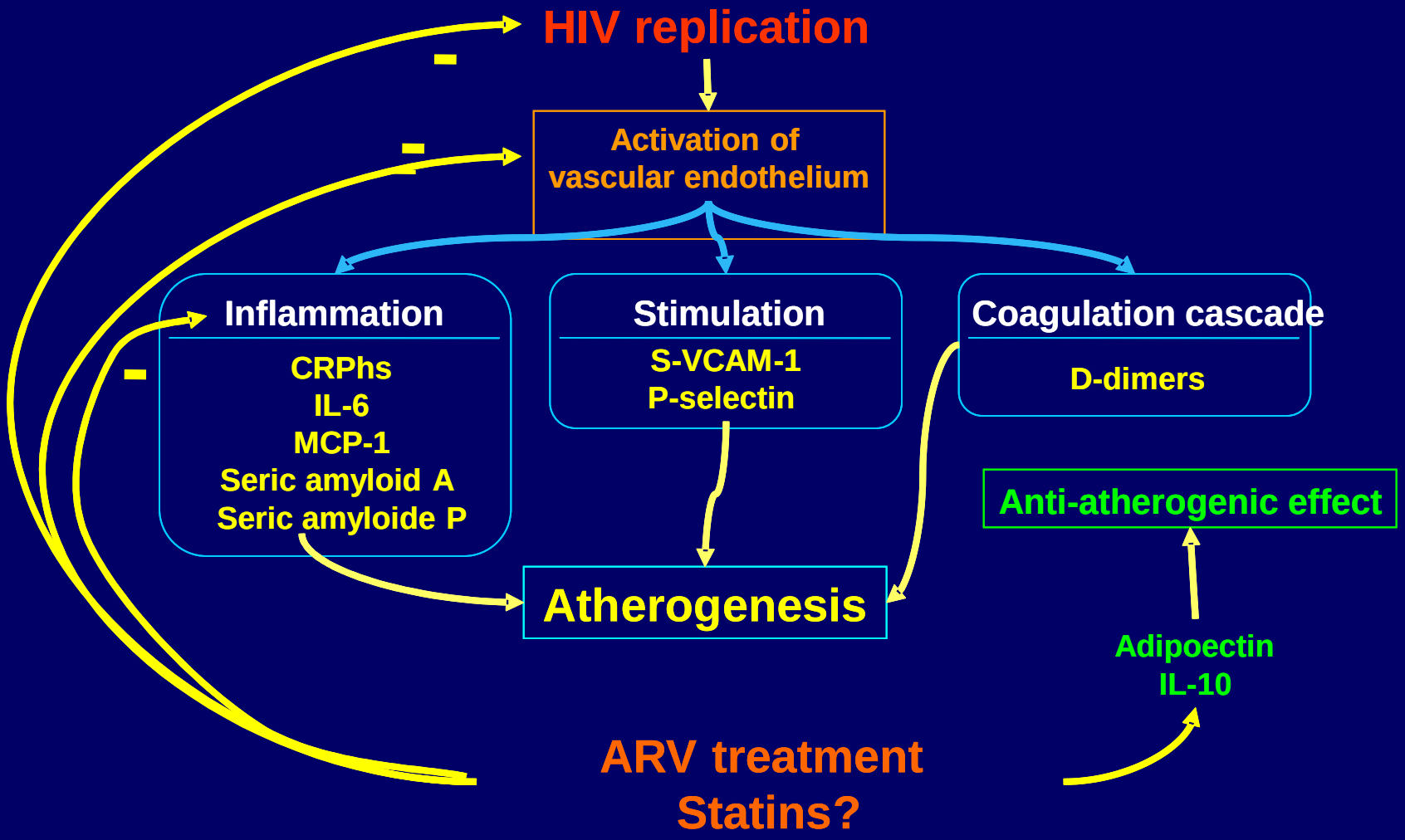
Biomarker Levels* at Study Entry: ”ABC (no ddI)” and ”ddI (+/- ABC)” vs. ”Other NRTIs”



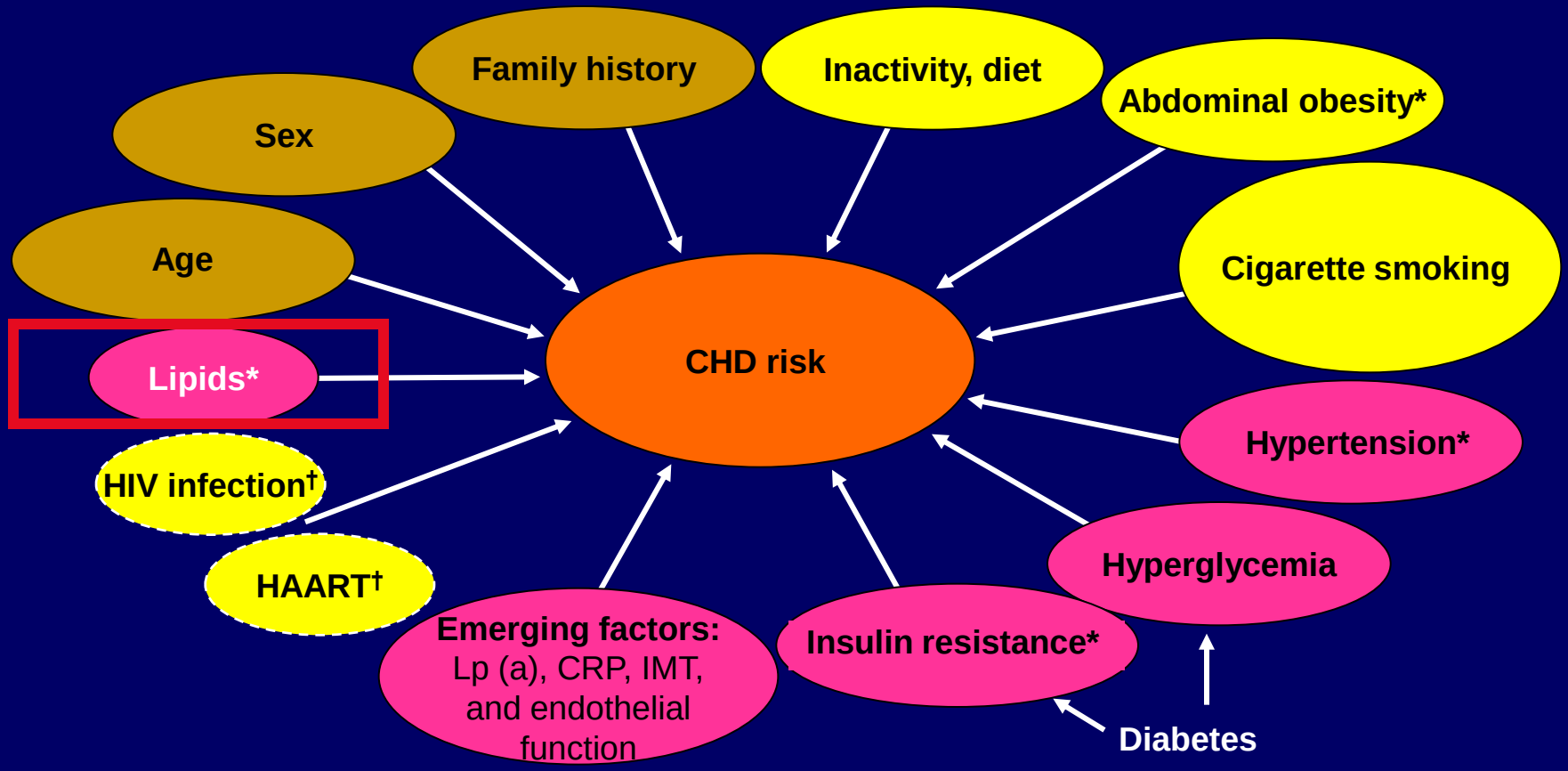
Median (IQR) levels in ”Others NRTIs”	hs-CRP	IL-6	Amyloid A	Amyloid P	D-dimer	F1.2
	2.3 (1.0-5.3) (µg/mL)	2.2 (1.4-3.7) (pg/mL)	3.6 (1.9-6.8) (mg/mL)	65 (51-86) (µg/L)	0.3 (0.2-0.5) (µg/mL)	0.4 (0.3-0.5) (nmol/L)

If not shown, p>0.1

Potential clinical implications of HIV as activator of atherogenic process?

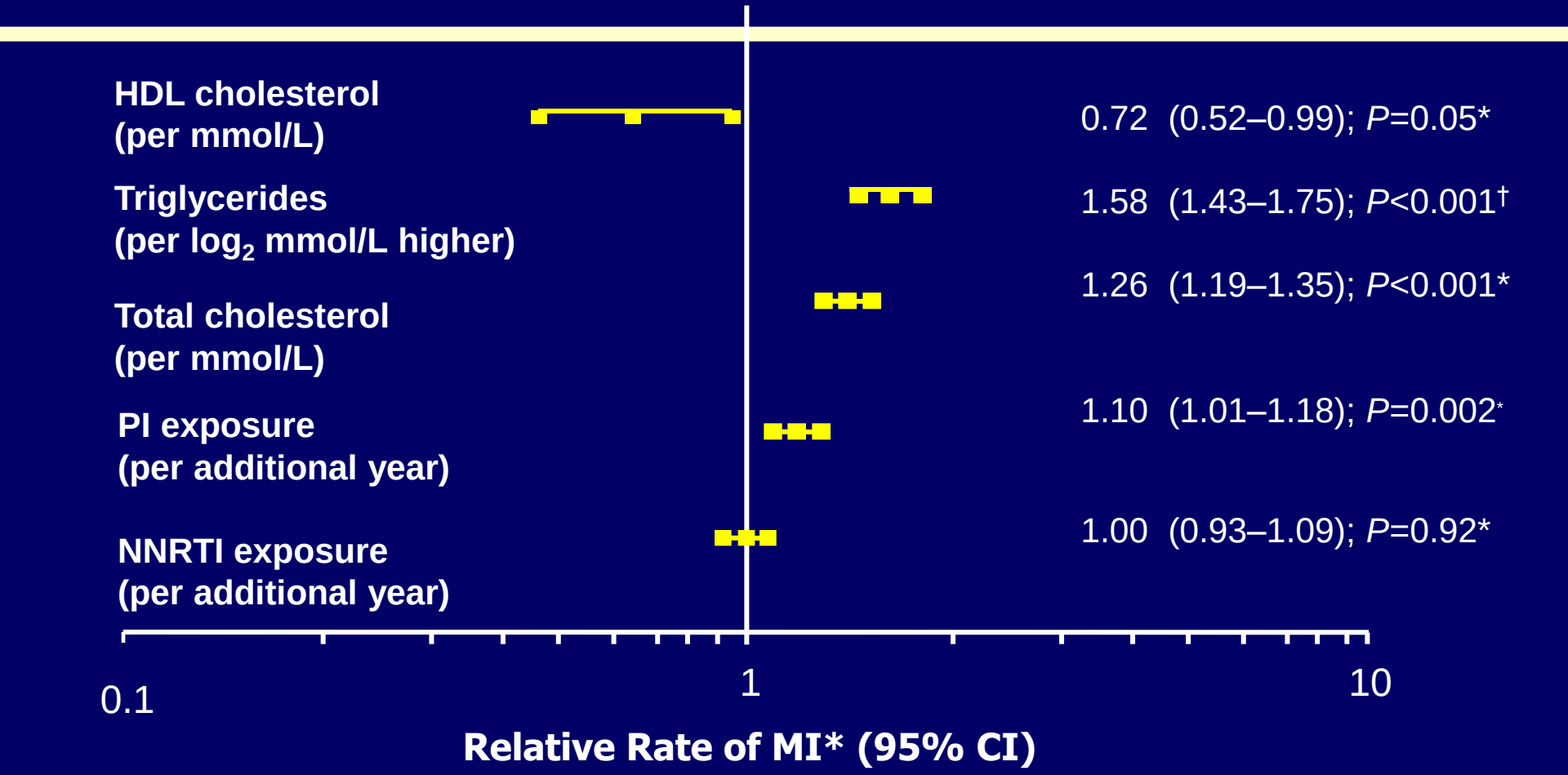


Integrate CVD prevention & management in the long term follow up of HIV patients taking into account all contributing factors



*Metabolic syndrome.
†Precise contribution unclear.

Contribution of Dyslipidemia to MI Risk



*Adjusted for conventional risk factors (sex, cohort, HIV transmission group, ethnicity, age, BMI, family history of CVD, smoking, previous CVD events, lipids, diabetes, and hypertension).

†Unadjusted model.

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

Lipid Goals For HIV-Infected Patients

- NCEP lipid goals intended for general population likely appropriate for HIV-infected patients
  - Lipid goals established to reduce cardiovascular risk
- Data from D:A:D cohort suggest Framingham risk equation overestimates risk of cardiovascular events in HIV-infected patients
- D:A:D equation more accurately predicted CHD outcomes in HIV-infected population
  - Incorporates PI exposure as well as conventional CHD risk parameters

Friis-Moller N, et al. CROI 2007. Abstract 808.

Lipid-Lowering Therapy Overview

Fibrates

LDL ↑, TG ↓↓, HDL ↑

Side effects: dyspepsia, gallstones, myopathy

Statins

LDL ↓↓, TG ↓, HDL↑

Side effects: myopathy, ↑ liver enzymes

Ezetimibe

LDL ↓, TG ↓, HDL ↑

Side effects: ↑ liver enzymes, diarrhea

Omega-3 Fatty Acids

LDL ↑↔, TG ↓ ↓, HDL ↑↔

Side effects: GI, taste

Nicotinic Acid

LDL ↑ ↔, TG ↓, HDL ↑↑

Side effects: flushing, hyperglycemia, hyperuricemia, upper GI distress, hepatotoxicity

Bile Acid Sequestrants

LDL ↓, TG ↔↑, HDL ↑

Side effects: GI distress/ constipation, ↓ absorption of other drugs

Utility of Lipid-lowering Agents for Dyslipidemia in HIV Infection?

- There is a role for fibrates, statins and niacin

BUT

- Target lipid levels infrequently achieved in clinical trials
- Interactions between statins and PIs can complicate use
- Increased cost
- Increased pill burden
- Potential for glucose intolerance with niacin

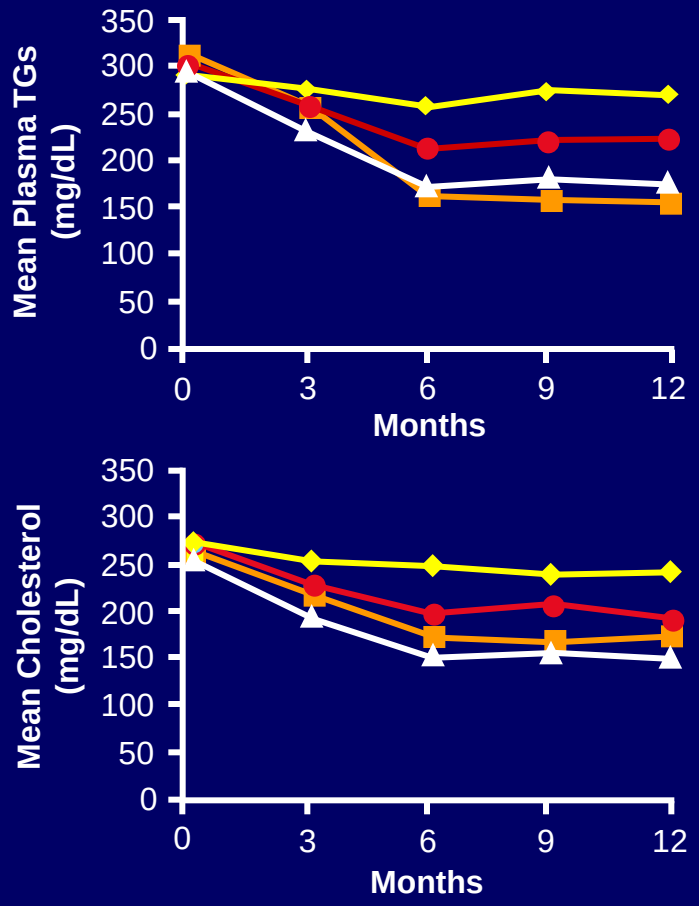
Lipids Management

What are the preferred management approaches for patients with HAART-associated hyperlipidemia?

Specifically, what factors should be considered in deciding whether to switch antiretroviral agents, use lipid-lowering therapy, or both?

Lipid-Lowering Therapy vs Switching PI

- 12-month, open-label study of 130 patients; 60% male; mean age: 39 years
- Stable on first HAART regimen randomized to
  - PI → EFV (n = 34)
  - PI → NVP (n = 29)
  - Add bezafibrate (n = 31)
  - Add pravastatin (n = 36)
- Pravastatin or bezafibrate significantly more effective in management of hyperlipidemia than switching ART to an NNRTI



Calza L, et al. AIDS. 2005;19:1051-1058.

Lipid Lowering Agents and ARVs: Drug Interactions

- SQV/RTV[1]
  - Atorvastatin ↑347% AUC
  - Simvastatin ↑3059% AUC
  - Pravastatin ↓50% AUC
- NFV[2,3]
  - Atorvastatin ↑74% AUC
  - Simvastatin ↑505% AUC
  - Pravastatin ↓47% AUC
- LPV/r[4]
  - Atorvastatin ↑588% AUC
  - Pravastatin ↑30% AUC
- fosAPV[5]
  - Atorvastatin ↑130% AUC
- EFV[6]
  - Atorvastatin ↓43% AUC
  - Simvastatin ↓58% AUC

Fibrates
Fluvastatin
Pravastatin

- Statin-Fibrates
  Atorvastatin

Lovastatin
Simvastatin

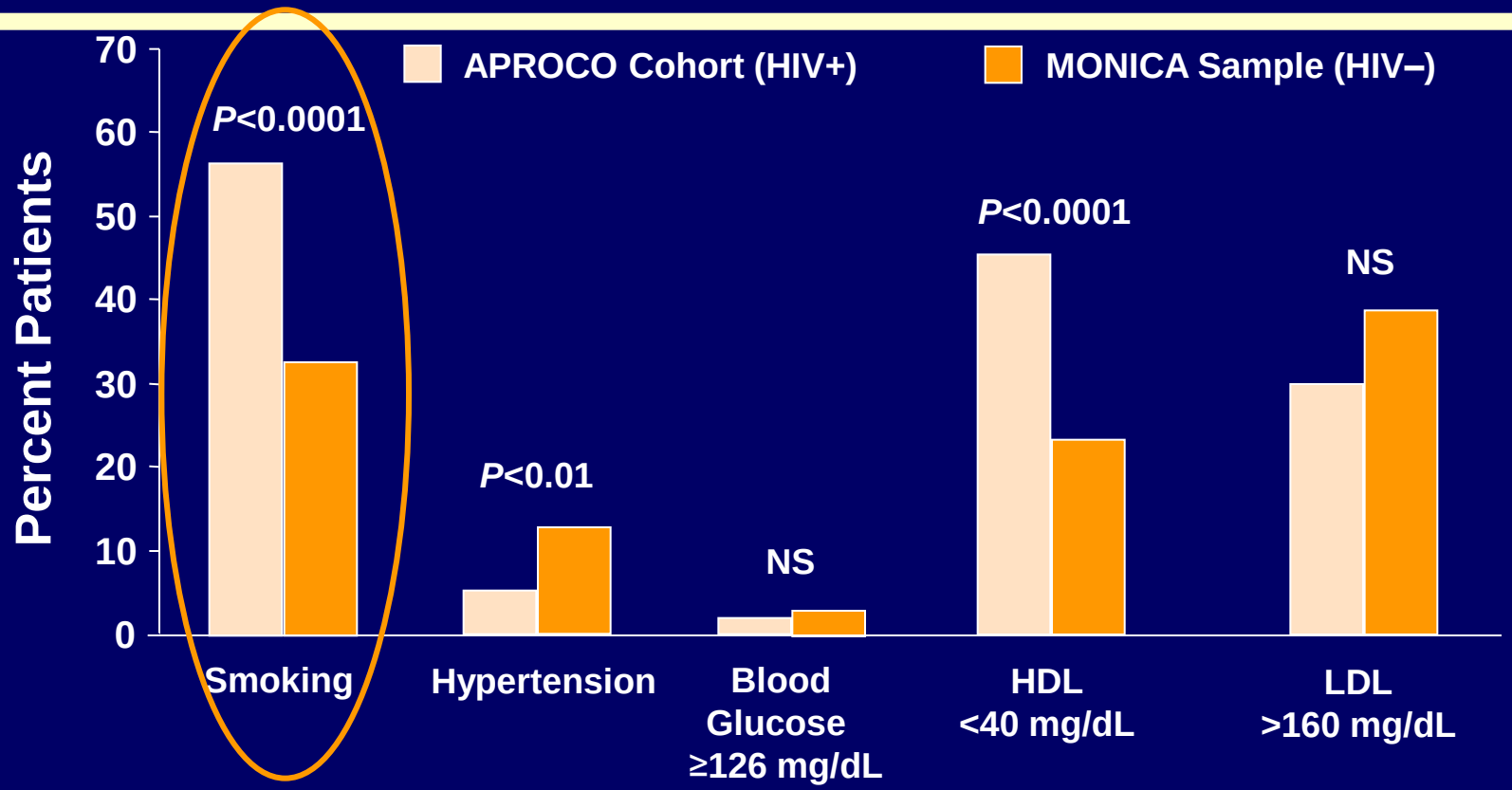
Low interaction potential

Use cautiously

Contraindicated with PIs

[1]Fitchenbaum CJ, et al. *AIDS.* 2002;16:569-577.
[2]Hsyu PH, et al. *AAC.* 2001;45:3445-3450.
[3]Gerber J *et al 2nd IAS* 2003, #870
[4]Carr RA, et al. 40th ICAAC, Toronto, 2000. Abstract 1644.
[5]Telzir Package Insert 2003.
[6]Gerber JG, et al. *11th CROI.* 2004. Abstr# 603.

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



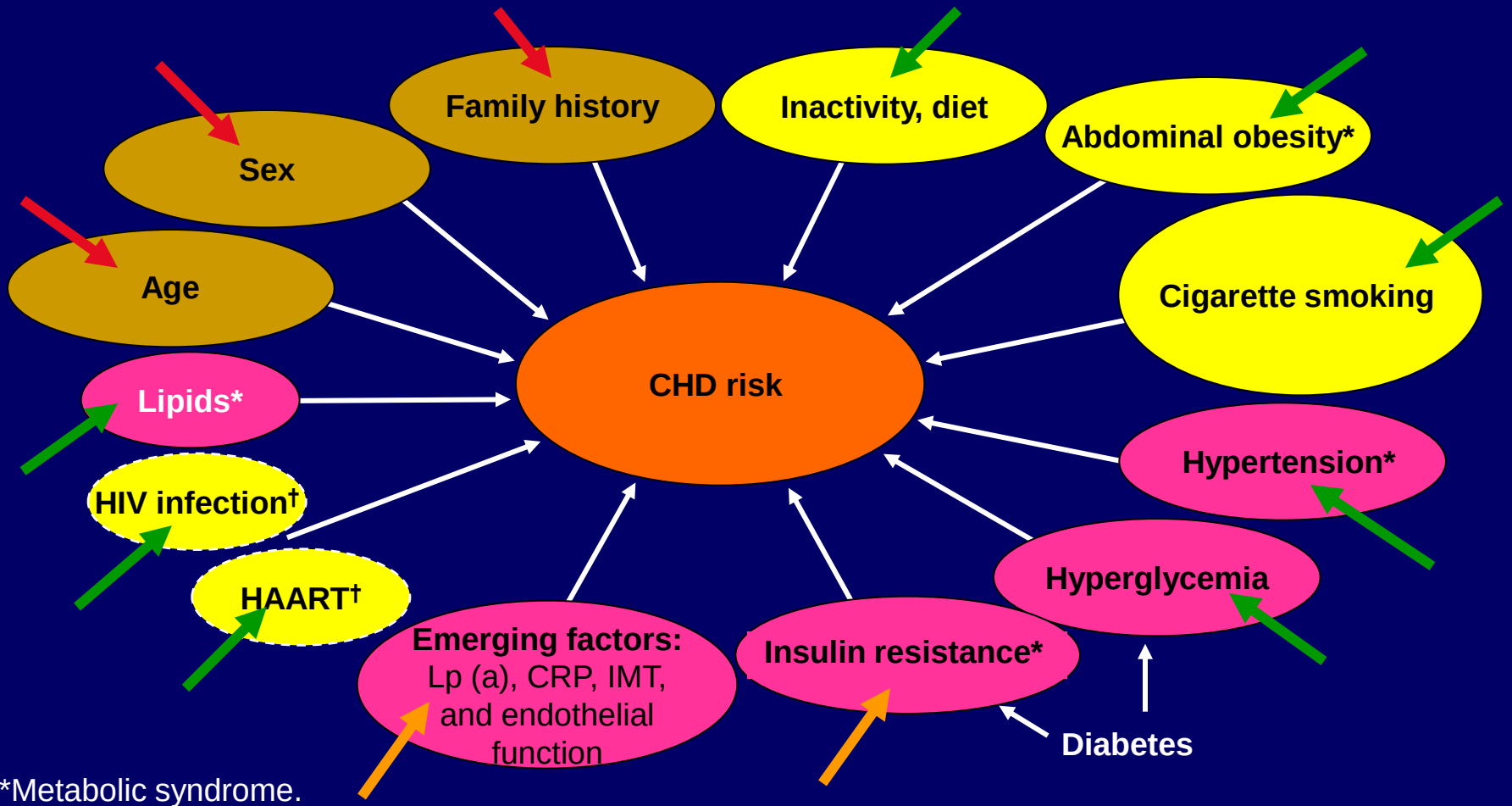
- N=223 HIV+ men and women on PI-based regimens vs 527 HIV– male subjects:
  - HIV+ patients have lower HDL and higher TG
  - Predicted risk of CHD > in HIV+ men (RR=1.2) and women (RR = 1.6), *P*<0.0001

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

Summary

- CVD risk is increasing in the aging HIV population
- CVD risk is associated with HAART and lipid elevation
- Prevalence of dyslipidemia is substantial especially with some PI-based regimens
- Consider smoking, diet and exercise interventions standard
- Watch for insulin resistance and the metabolic syndrome
- Use lipid lowering therapies along NCEP guidelines
- Switching ART to less dyslipidemic agents may avoid the need for additional interventions
- New agents appear to have few short term impact on lipid profile

Integrate CVD prevention & management in the long term follow up of HIV patients taking into account all contributing factors



*Metabolic syndrome.
†Precise contribution unclear.

European AIDS Clinical Society (EACS)

Guidelines on the Prevention and Management of Metabolic diseases in HIV

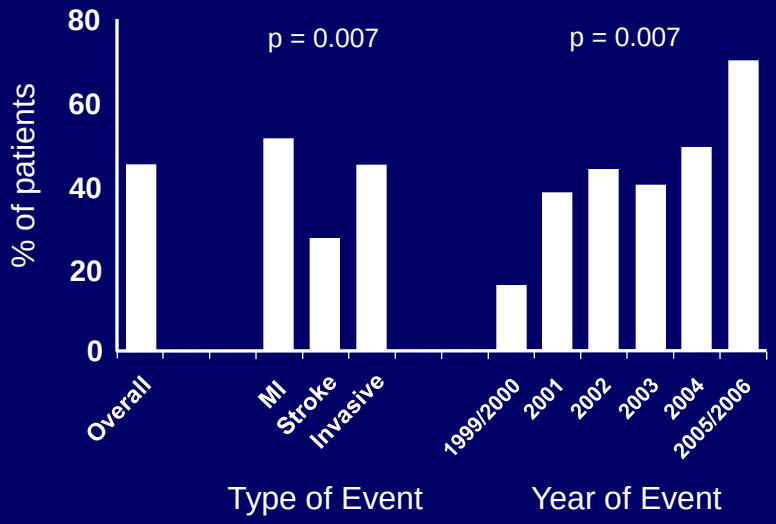
EACS
European AIDS Clinical Society

Background

- Metabolic diseases in HIV-infected persons
  - Associated with aging
    - prevalence will increase in years to come
  - Causes are multifactorial
    - Underlying risk (genetic and environmental influences)
    - Untreated HIV
    - ART – directly and indirectly
  - Management
    - HIV-specific issues
      - HIV infection and ART influences risk
        - » Pharmaceutical “push”
      - Polypharmacy (drug-drug interactions, pill burden, etc)
    - Guidelines used in general population
      - Compliance ? – next slide

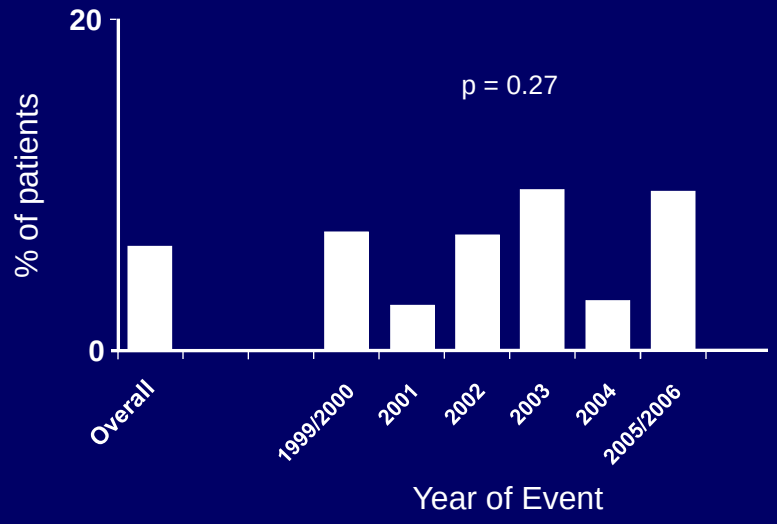
The use of lipid-lowering drugs in high-risk populations: D:A:D

Initiation of lipid-lowering drugs in six months following a first CV event if not already taking this



(n=384)

Initiation of lipid-lowering drugs in six months following a diagnosis of diabetes mellitus if not already taking this



(n=626)

Sabin C. *et al.*, *CROI*, 2007.

Scope

- When to seek consultation with metabolic specialists
- Diseases covered
  - Prevention of CV disease
  - Prevention and management of lipodystrophy
  - Treatment of type II diabetes
  - Prevention and management of hyperlactataemia
  - Management of hypertension
- Diseases not (yet) covered
  - Renal disease
  - Bone disease
  - Sexual dysfunction

Dynamic document

- No previous comprehensive HIV-specific metabolic disease management guidelines exist
- Direct evidence guiding prevention and management of metabolic diseases in HIV are limited
- Several extrapolations from guidelines in general population are made
  - Competing risks since untreated HIV is life-threatening
  - Conservative approach
- Version on web-site will be updated regularly based on:
  - Input from users – please
  - New information emerges