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HIV complications and morbidity

University Hospital Basel

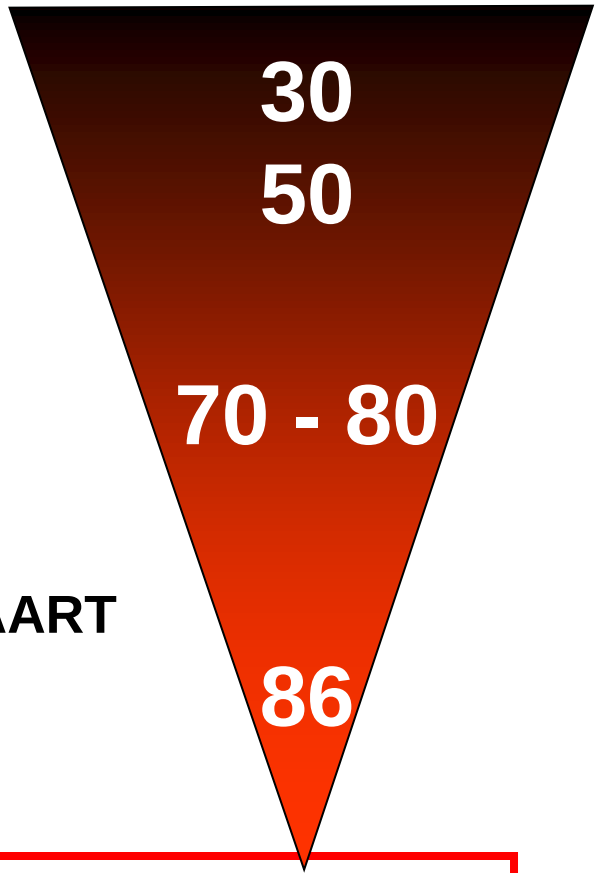
SWISS HIV COHORT STUDY

Content

- Introduction
- Selected specific adverse events
- ART and body shape changes
- ART, HIV and metabolism
  - Cardiovascular risk general remarks
  - ART and Lipids
  - ART, Insulin resistance and diabetes
  - HIV and cardiovascular risk
  - Therapeutic approaches, Guidelines
- Immune reconstitution inflammatary syndrome

cART dramatically improves life expectancy

	Type of study		≈ Decrease Mortality %
1996	Delta	RCT	AZT vs dual ART
1996	ACTG 175	RCT	AZT vs dual ART
1997	ACTG 320	RCT	Dual vs HAART
1997	SHCS	OS	No HAART vs HAART
1998	HOPS	OS	No HAART vs HAART
2003	EUROSIDA	OS	96/97 HAART vs 98-02 HAART
2005	SHCS	OS	No HAART vs HAART
2007	Danish Coh. OS		HIV versus non HIV



2008 20 year old: another 43 years years life prolongation with cART
≈ Normal life expectancy (?), The ART-Cohort Collaboration, The Lancet 2008

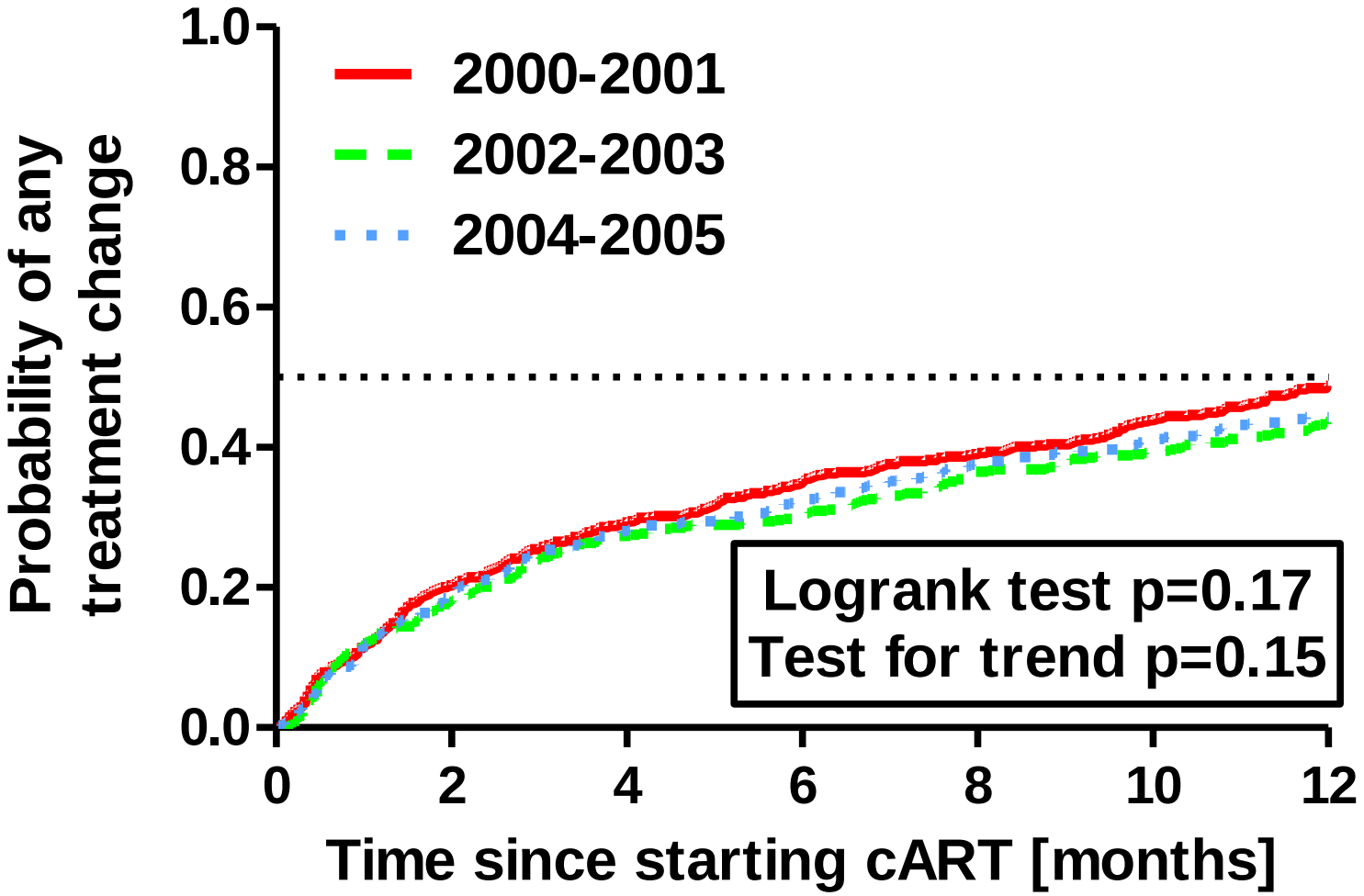
Hammer et al NEJM 1996; NEJM 1997; Gulick et al, NEJM 1998, Lancet 1996; Lancet 1997, Egger & Battegay et al, The SHCS, BMJ 1997; Palella et al, NEJM 1998; Jaggy et al, Lancet 2003; Mocroft et al, EuroSIDA, Lancet 2003; Sterne et al, The SHCS, Lancet, 2005, Lohse N et al, Ann Med, 2007

HIV Complications

1. **HIV**
   - diarrhea, dementia, wasting
2. **Defined HIV related complication**
   - opportunistic diseases
3. **Drug - related complication**
   - ART
   - OI treatment
   - Interaction
4. **IRIS**
5. **Concurrent unrelated complication**
   - Catheter related infection
   - Urinary tract infection
6. **Unrelated diseases**
   - Tumors
   - Cardiovascular

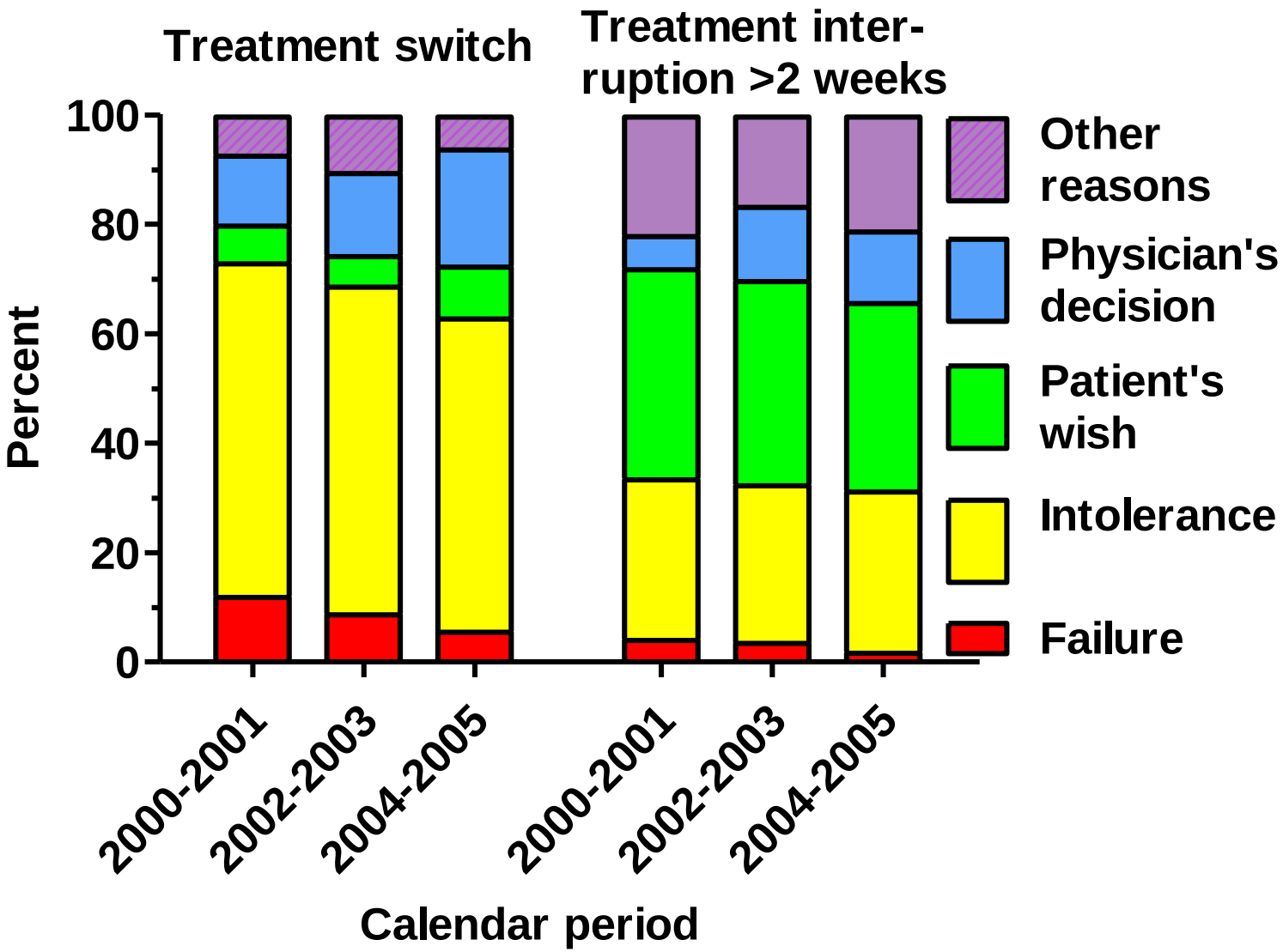
Battegay et al, Antiviral Ther 2007

cART switch Swiss HIV Cohort Study 2000-2005



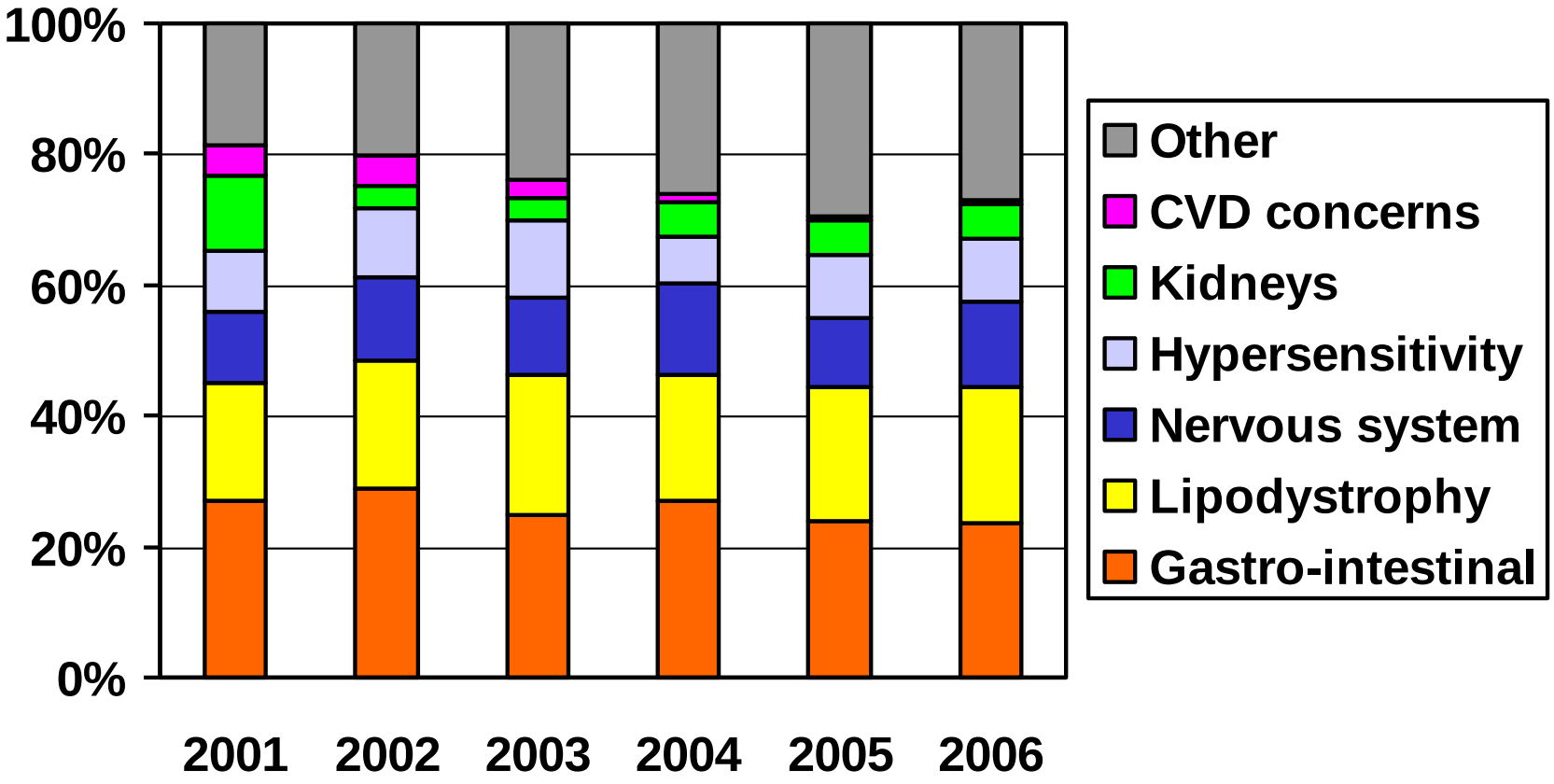
Vo et al., JID, Juni 2008

Reasons for switch



Vo et al., JID, Juni 2008

Trends for specific side effects



Vo et al., JID, Juni 2008

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Recommended Components of Initial Antiretroviral Therapy and Considerations for Choosing a Regimen

JAMA

Table 3. Recommended Components of Initial Antiretroviral Therapy and Considerations for Choosing a Regimen

Component	Considerations for Choice	Major Toxic Effects and Cautions
Nucleoside reverse transcriptase inhibitors[a]		
Tenofovir/emtricitabine[b, c]	Well tolerated Efficacy superior to zidovudine/lamivudine[4,62] and similar to stavudine/lamivudine[63] Available as a once-daily fixed dose	Baseline renal function should be evaluated before initiating tenofovir Reduce dose or avoid in patients with renal dysfunction
Abacavir/lamivudine[d]	Noninferior to tenofovir/emtricitabine in 1 trial[10] May have less activity in patients with viral load ≥100 000 HIV RNA copies/mL[83] Available as a once-daily fixed dose	Hypersensitivity syndrome in 5% to 8% of persons (risk associated with HLA-B*5701 genotype) Risk reduced with HLA-B*5701 screening[84,85] May be associated with increased risk of myocardial infarction[74,75]
Nonnucleoside reverse transcriptase inhibitors[e]		
Efavirenz	Standard-of-care comparator in many trials Available as a once-daily fixed dose with tenofovir/emtricitabine	Central nervous system toxicity may be limiting Potentially teratogenic in first trimester of pregnancy Associated with lipoatrophy when given with thymidine reverse transcriptase inhibitors[60]

Hammer, S. M. et al. IAS Guidelines JAMA 2008;300:555-570.

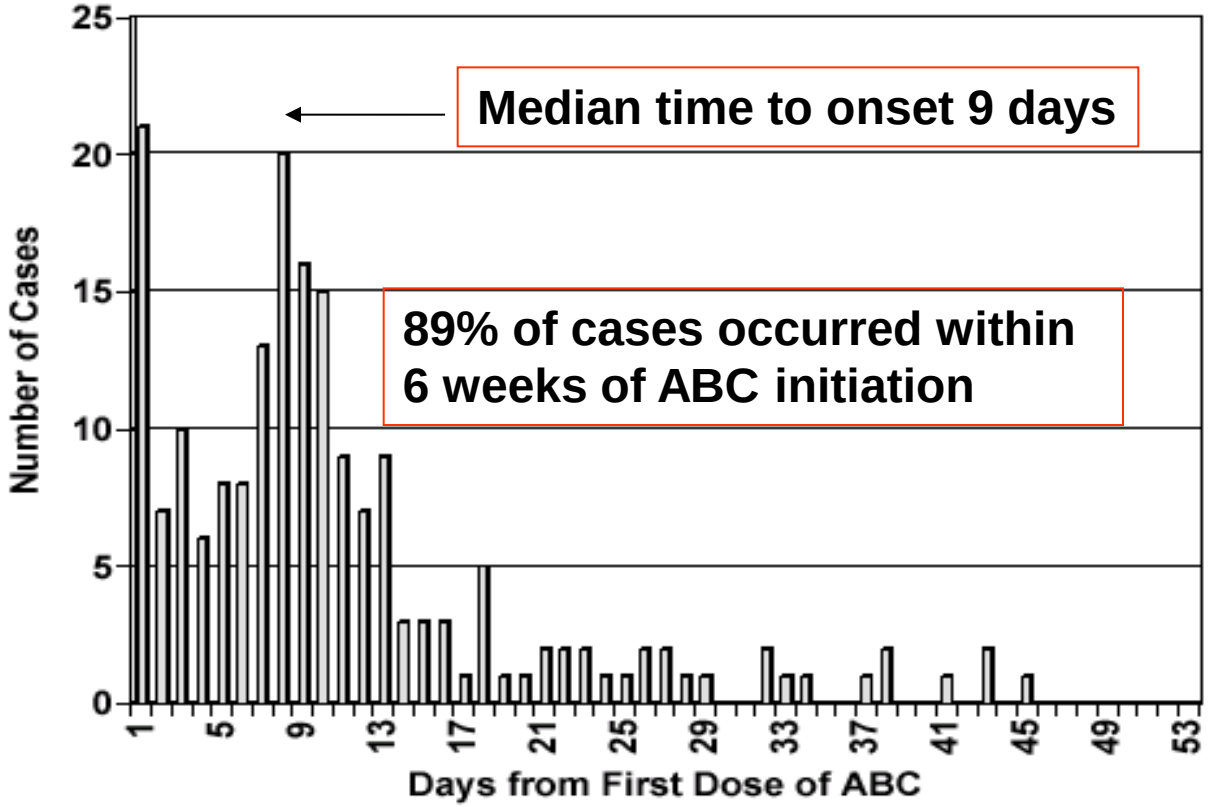
Recommended Components of Initial Antiretroviral Therapy and Considerations for Choosing a Regimen

JAMA

Ritonavir-boosted protease inhibitors[f]		
Lopinavir	Substantial clinical trial data and phase 4 experience supporting efficacy Heat-stable tablet 1 or 2 doses per day for treatment-naive patients	Gastrointestinal adverse effects Hyperlipidemia, especially hypertriglyceridemia
Atazanavir	Noninferior to ritonavir-boosted lopinavir Less hyperlipidemia and diarrhea[66] Once-daily dosing	Hyperbilirubinemia (UGT1A1-28 alleles and T3435C polymorphism in *MDR1* gene) Occasionally associated with nephrolithiasis Acid-reducing agents decrease atazanavir concentrations; proton pump inhibitors should be used cautiously
Fosamprenavir	Noninferior to ritonavir-boosted lopinavir[13] Once-daily or twice-daily dosing possible; more robust data with twice-daily dose	Similar adverse effect profile to ritonavir-boosted lopinavir Rash
Darunavir	Noninferior to ritonavir-boosted lopinavir and superior in those with viral load ≥100 000 HIV RNA copies/mL Less nausea, lower triglyceride levels[68] 800 mg + 100 mg ritonavir once daily	Rash
Saquinavir	Noninferior to ritonavir-boosted lopinavir, with lower triglyceride levels.[67] Twice-daily dosing	High pill burden

Hammer, S. M. et al. IAS Guidelines JAMA 2008;300:555-570.

Time to Onset of Abacavir HSR in Clinical Trials (n=206)



Serious and sometimes fatal hypersensitivity

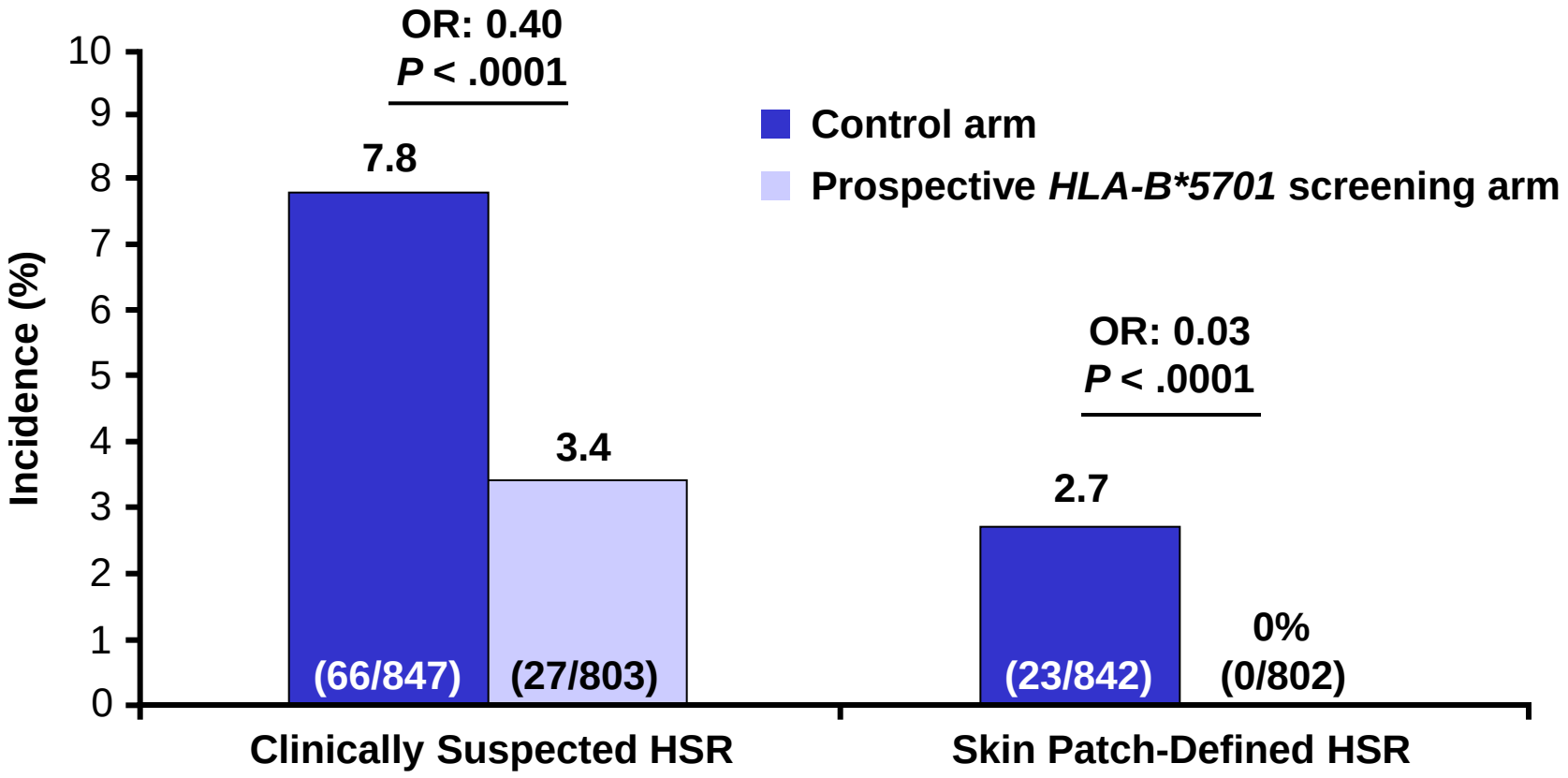
Symptoms worsen during continued therapy with abacavir and usually resolve upon discontinuation

Hypersensitivity to Abacavir

multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups:

- fever
- rash
- gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)
- constitutional (including generalized malaise, fatigue, or achiness)
- respiratory (including dyspnea, cough, or pharyngitis).

PREDICT-1: Clinically Suspected or Skin Patch–Defined HSR with abacavir treatment



Mallal S, et al. NEJM 2008

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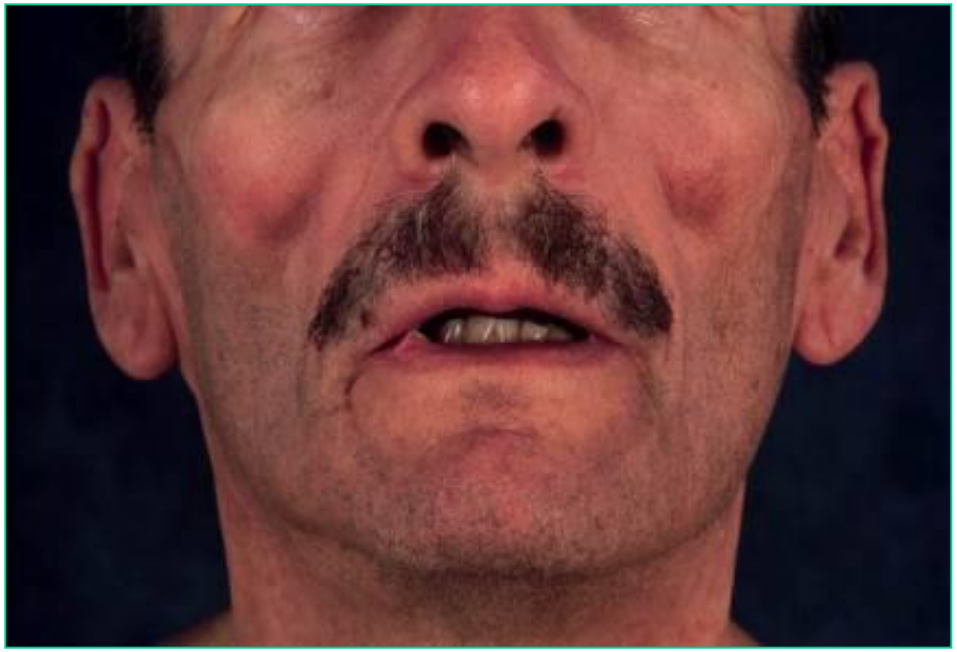
Lipoatrophy vs Wasting Syndrome

- Lipoatrophy: loss of subcutaneous fat in face, buttocks, abdomen, and limbs
- Lean tissue: (muscle) not lost
- Wasting syndrome: both fat, lean tissue, and weight diminish



Grinspoon S, Carr A. N Engl J Med. 2005;352:48; James J et al. Dermatol Surg. 2002;11:979–986.

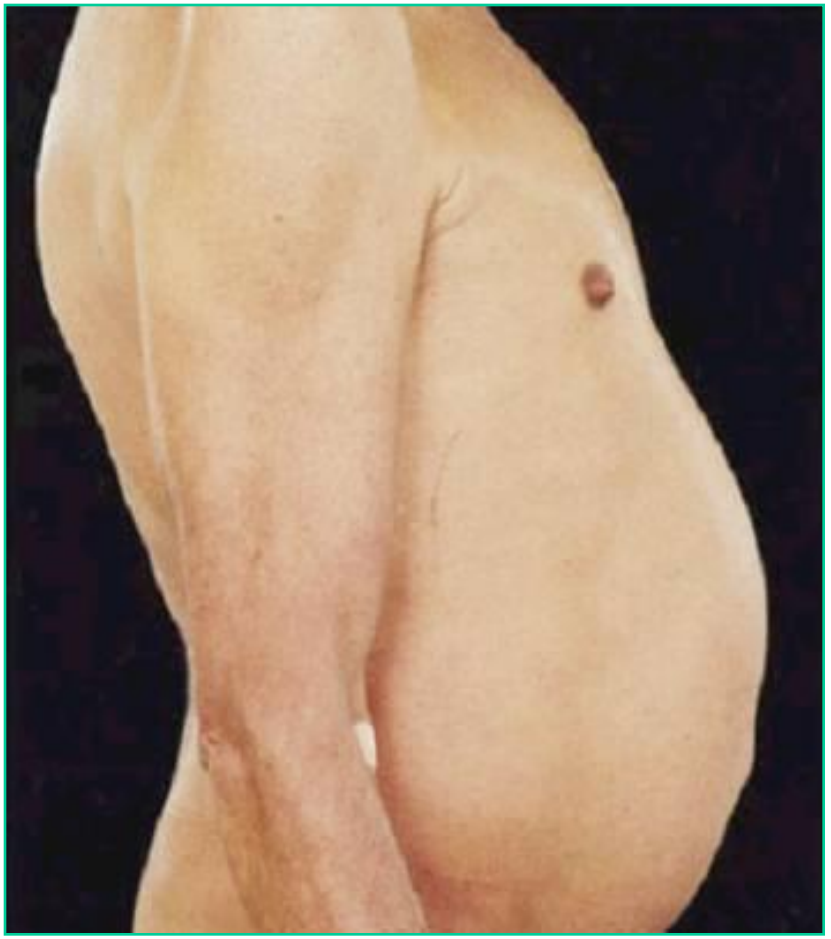
Lipoatrophy: Risk Factors

- Almost certainly interrelated
  - Antiretroviral therapy
    - Thymidine analogue exposure (d4T >ZDV)
    - Combinations of ART (eg, EFV + NRTIs, NFV + NRTIs)
  - Host factors
    - Age
  - HIV disease factors
    - Duration of illness
    - Severity of illness: AIDS, low $CD4^+$ cell count

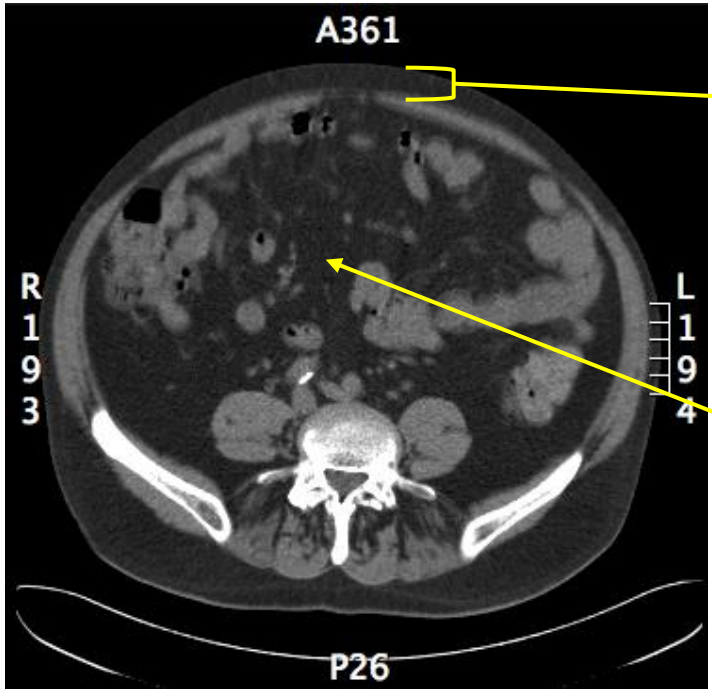
Grinspoon S, Carr A. N Engl J Med. 2005;352:48; James J et al. Dermatol Surg. 2002;11:979–986.

Lipohypertrophy

- increase in fat depots — typically visceral, dorsocervical, and breast tissue fat
- Subcutaneous fat (pinch an inch fat) does not increase
- Difficult to distinguish from general “lipohypertrophy” associated with modern living

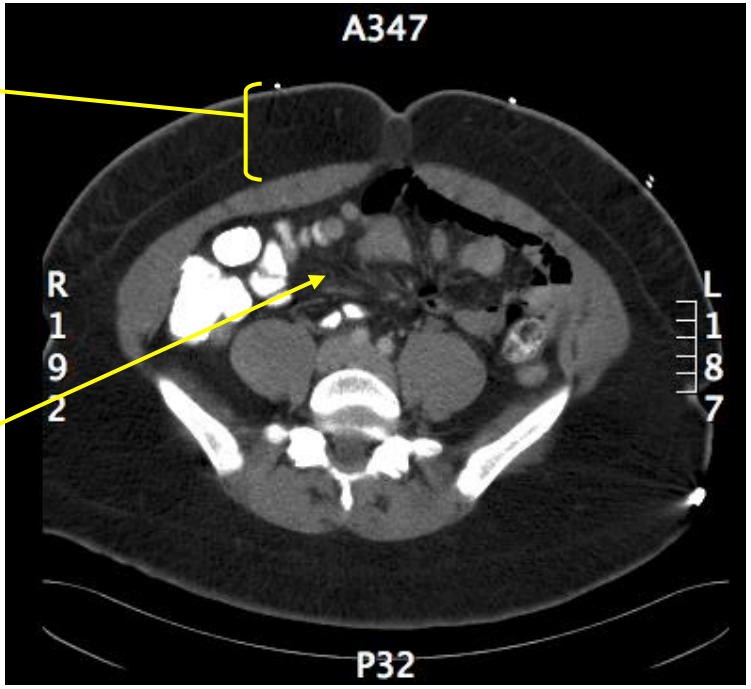


CT Scans of Two HIV+ Patients



Subcutaneous Fat (pinch an inch fat)

Visceral Fat (dark shaded areas)

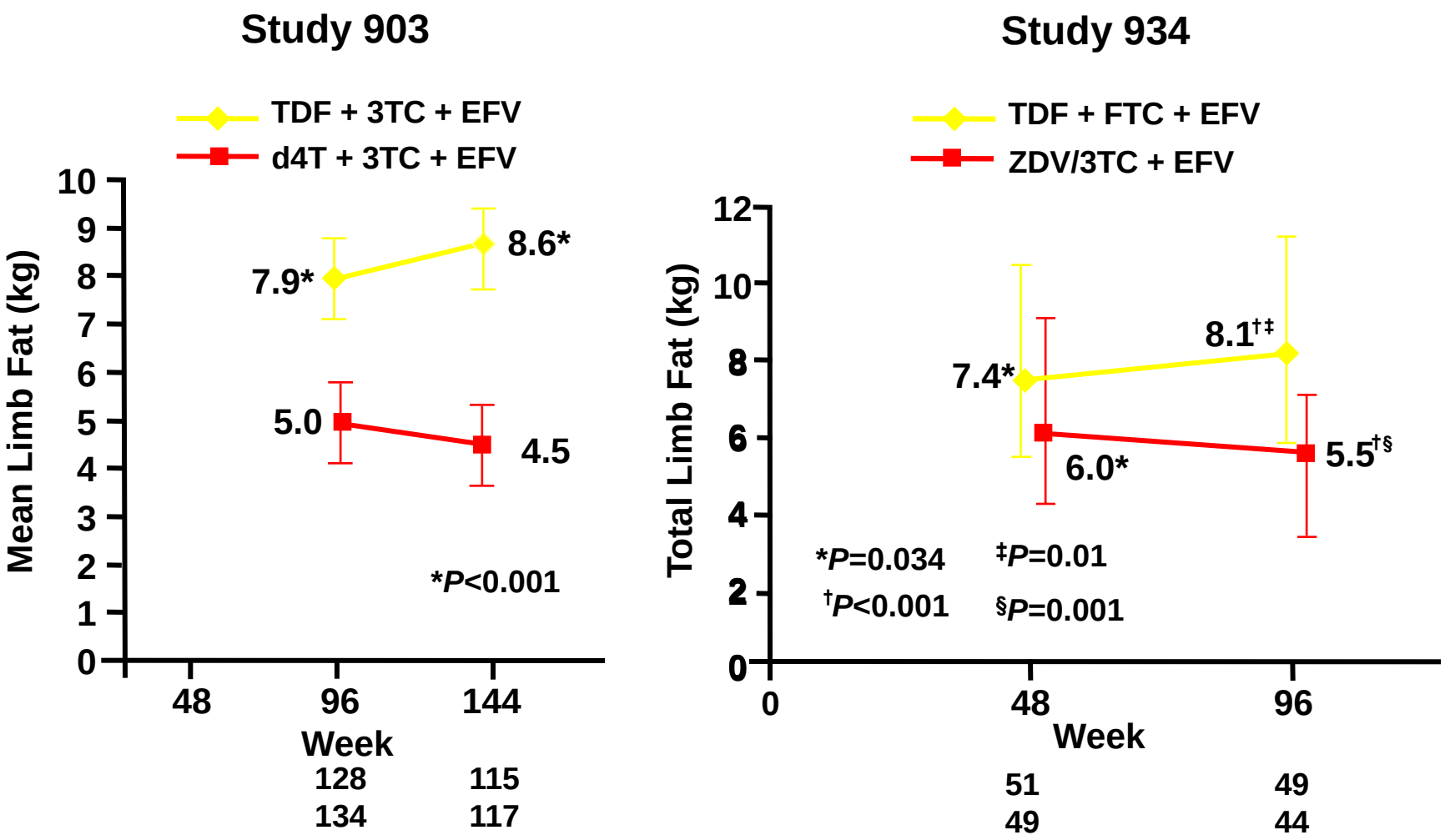


HIV+ patient with visceral adiposity. Subcutaneous fat is scant and fat in the abdomen is thick.

HIV+ patient with obesity. Subcutaneous fat is thick and fat in the abdomen is scant.

Images courtesy of D.A. Wohl.

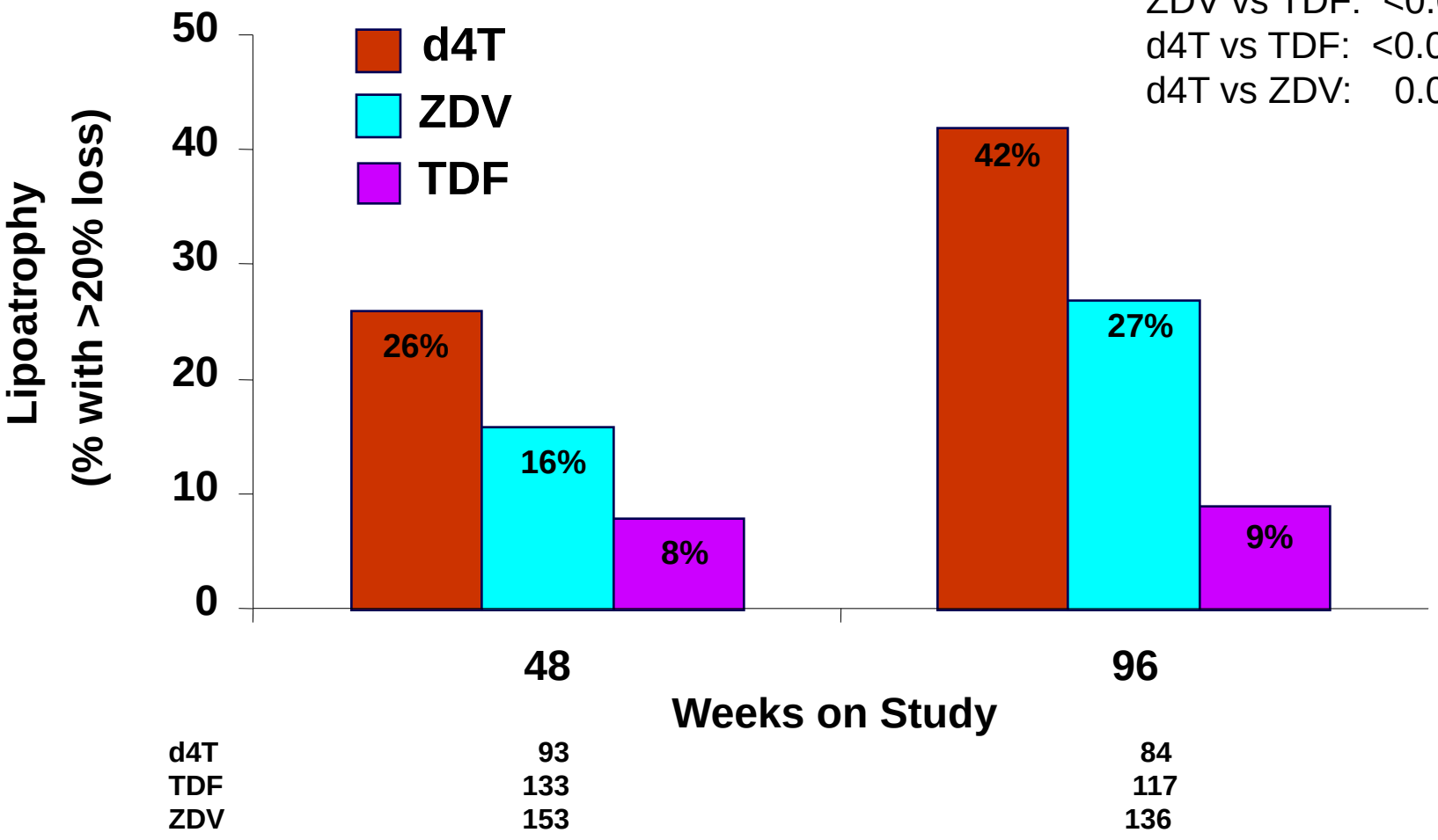
Effect of NRTIs on Limb Fat



Gallant JE et al. JAMA. 2004;292:191-201; Pozniak AL et al. JAIDS. 2006;43:535-540.

Lipoatrophy at Weeks 48 and 96 (NRTI Arms Only)

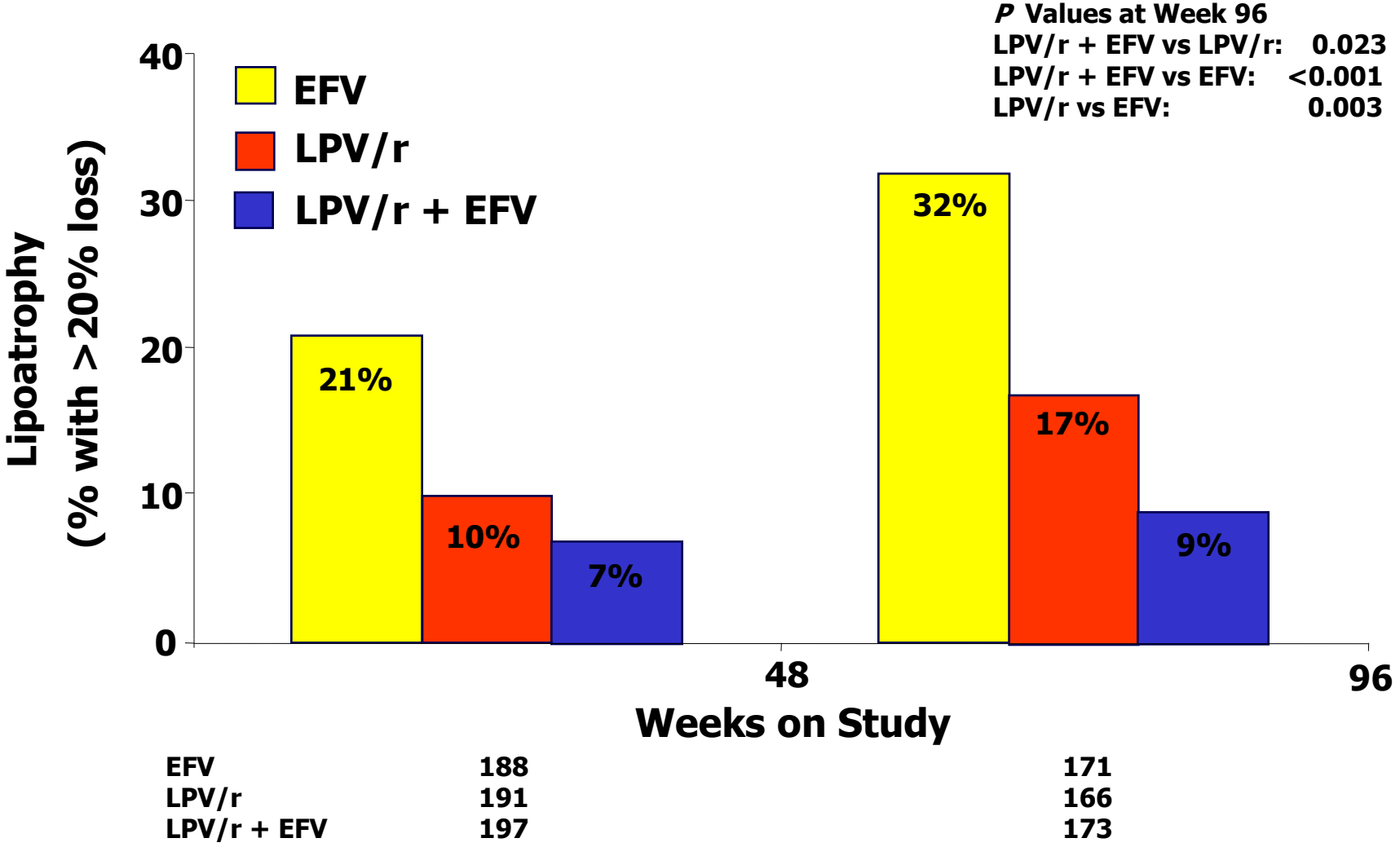
P Values at Week 96
ZDV vs TDF: <0.001
d4T vs TDF: <0.001
d4T vs ZDV: 0.038



d4T	93	84
TDF	133	117
ZDV	153	136

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

Lipoatrophy (>20% loss of extremity fat) at Weeks 48 and 96



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

Psychosocial Impact of body shape changes

- Self-evaluated quality of relationships with friends, family, sexual partner is inversely associated with self-perception of peripheral fat loss in HIV/AIDS outpatients (N=457)[1]

- A survey of HIV/AIDS patients with body fat changes (N=33)[2]
  - Social withdrawal
  - Adversely affected sexual relationships
  - Forced disclosure of HIV status due to facial lipoatrophy
  - Depression
  - Poor body image
  - ART noncompliance
  - Economic impact of surgical interventions
  - more challenging than living with HIV

Santos CP et al. AIDS. 2005;19(suppl 4):S14-S21.
Collins E et al. AIDS Reader. 2000;10:546-551.

Conclusions

- Body shape changes are multifactorial
- Lipoatrophy and lipohypertrophy do not commonly occur together
- Newer NRTI have low- or non-existing potential for body shape changes (abacavir, tenofovir)
- Body shape changes are partly reversible
- Abdominal fat increases are common to all ART regimens studied so far
- The psychosocial impact is strong

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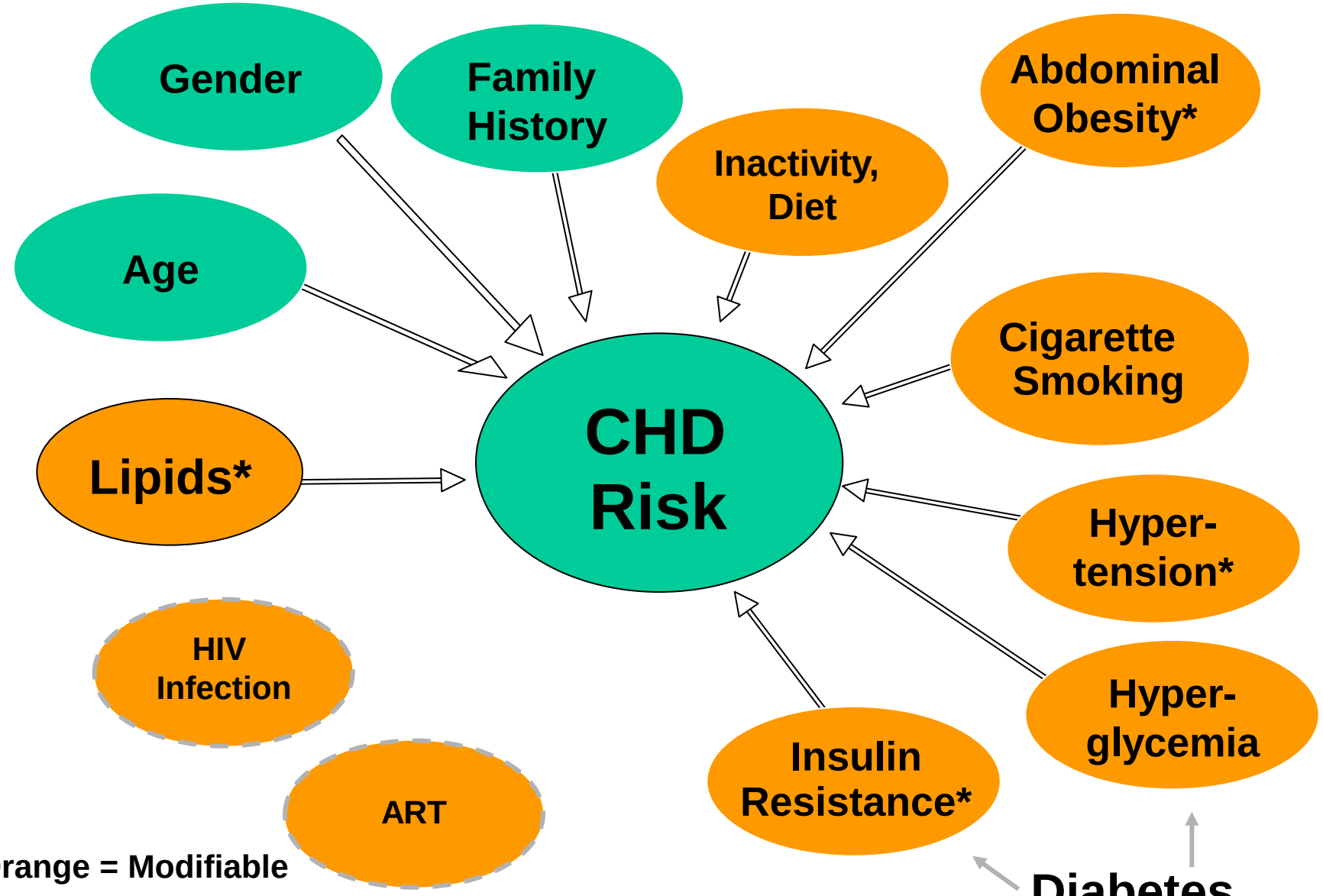
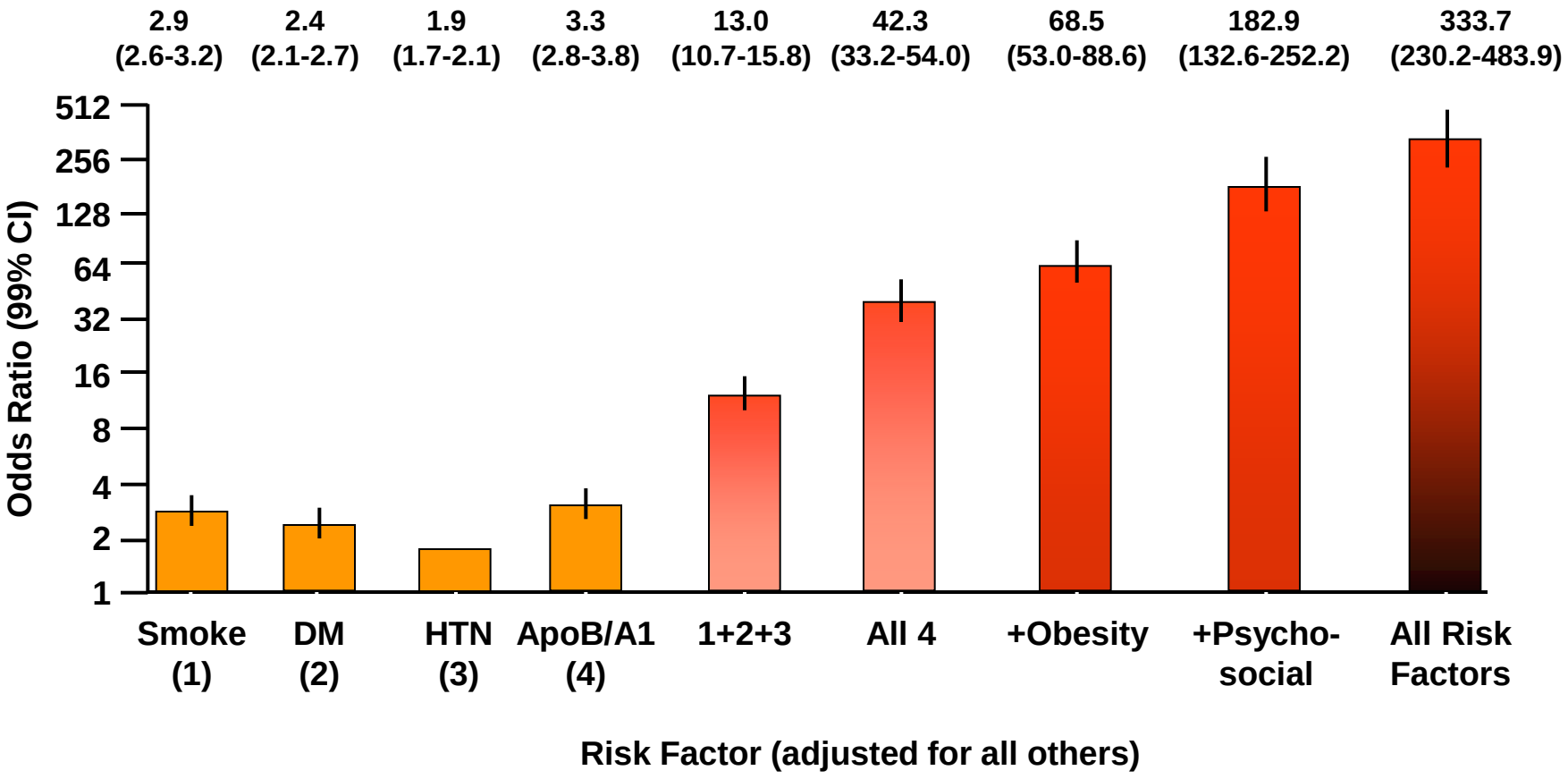
CHD risk ractors in HIV - infected population



Multiple Risk Factors: INTERHEART

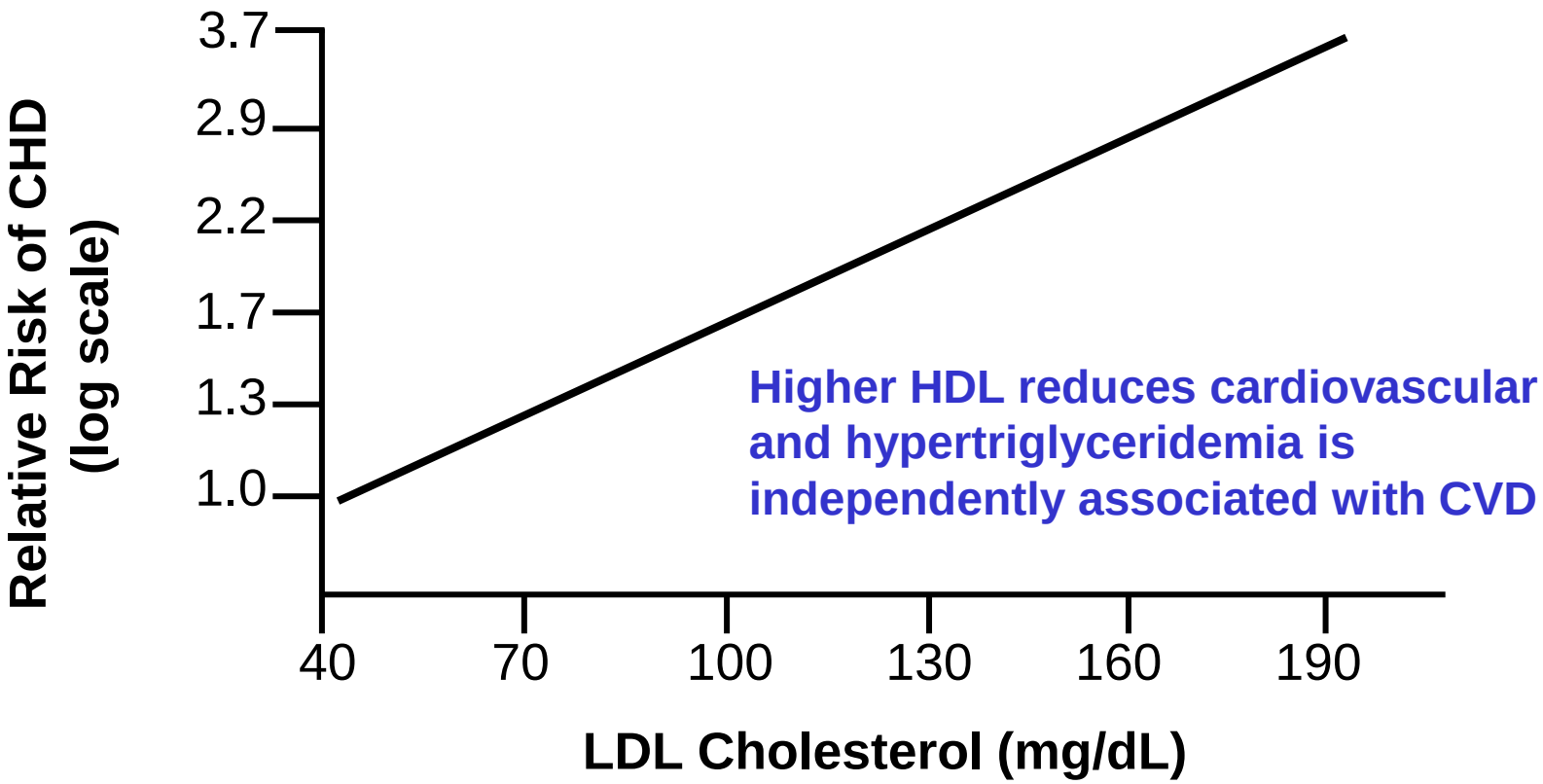
Multiple Traditional Risk Factors Confer Synergistic Increase in Risk of MI in General Population



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

Lipids and CVD Risk

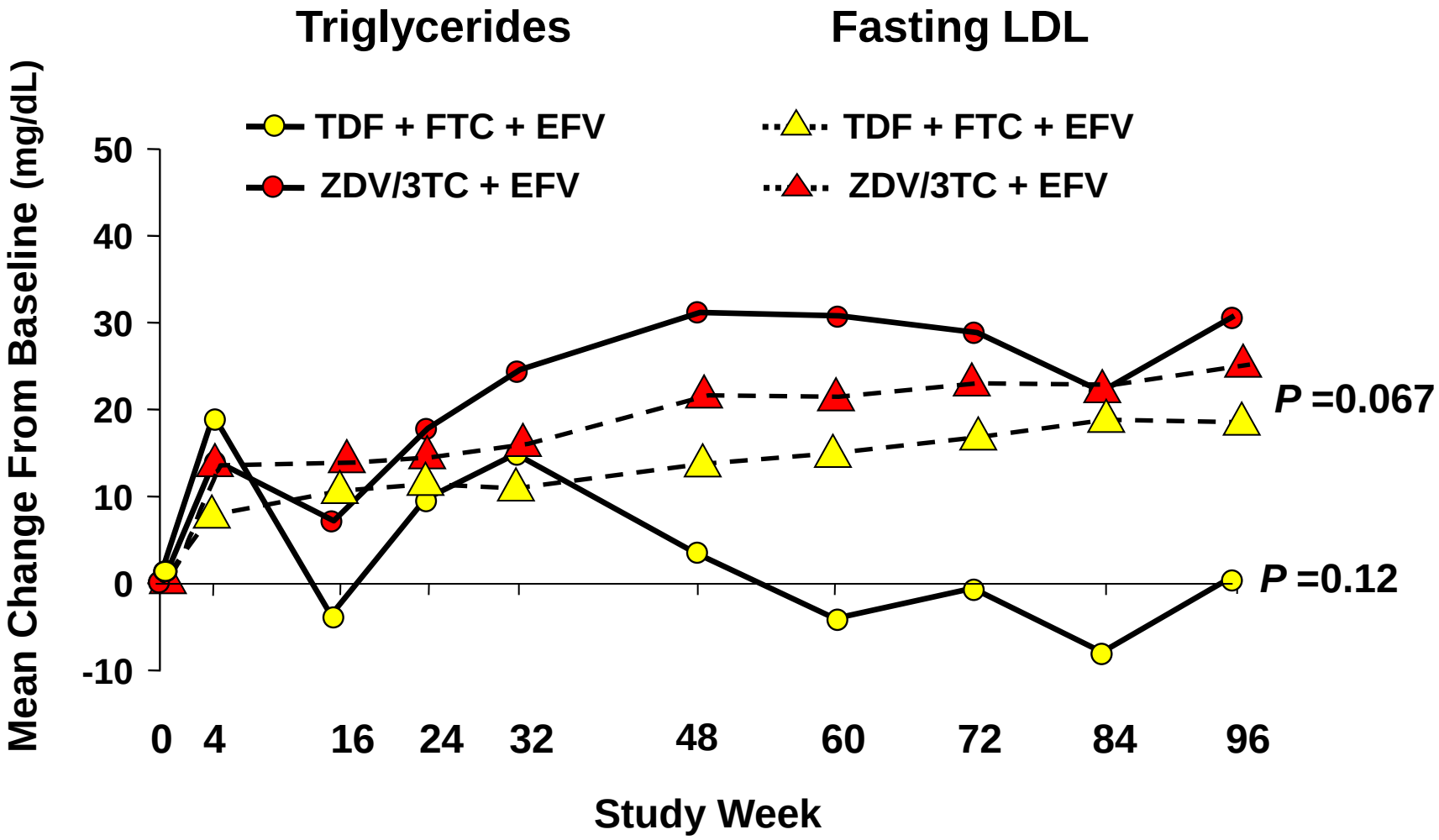
- Increasing plasma LDL increases relative risk of CHD
- A 30 mg/dL ↑ in LDL is associated with ~30% ↑ CHD risk



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

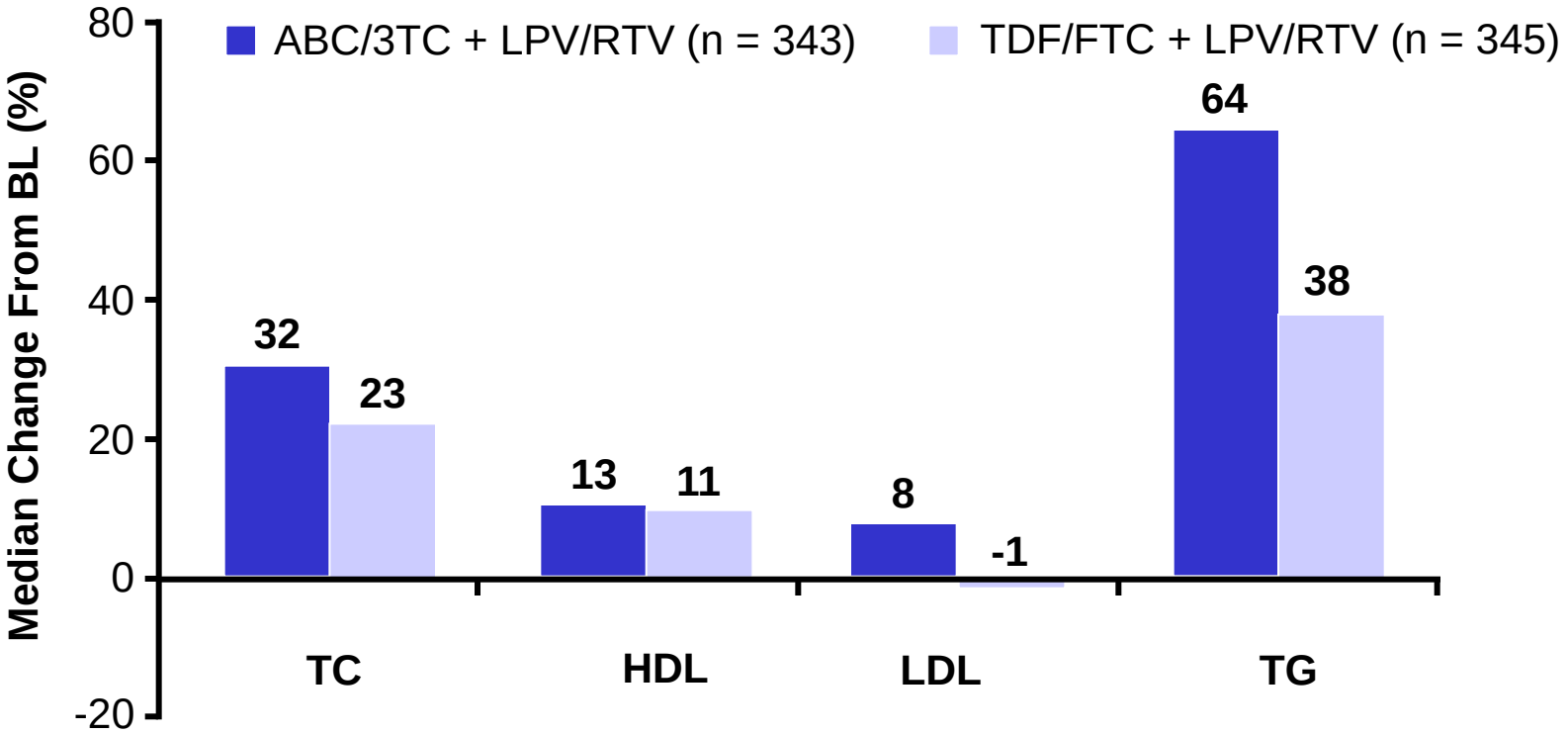
Study 934: ZDV/3TC vs TDF + FTC

Mean Change Lipid Profile



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

HEAT: Lipid Effects of ABC/3TC vs TDF/FTC at Week 48

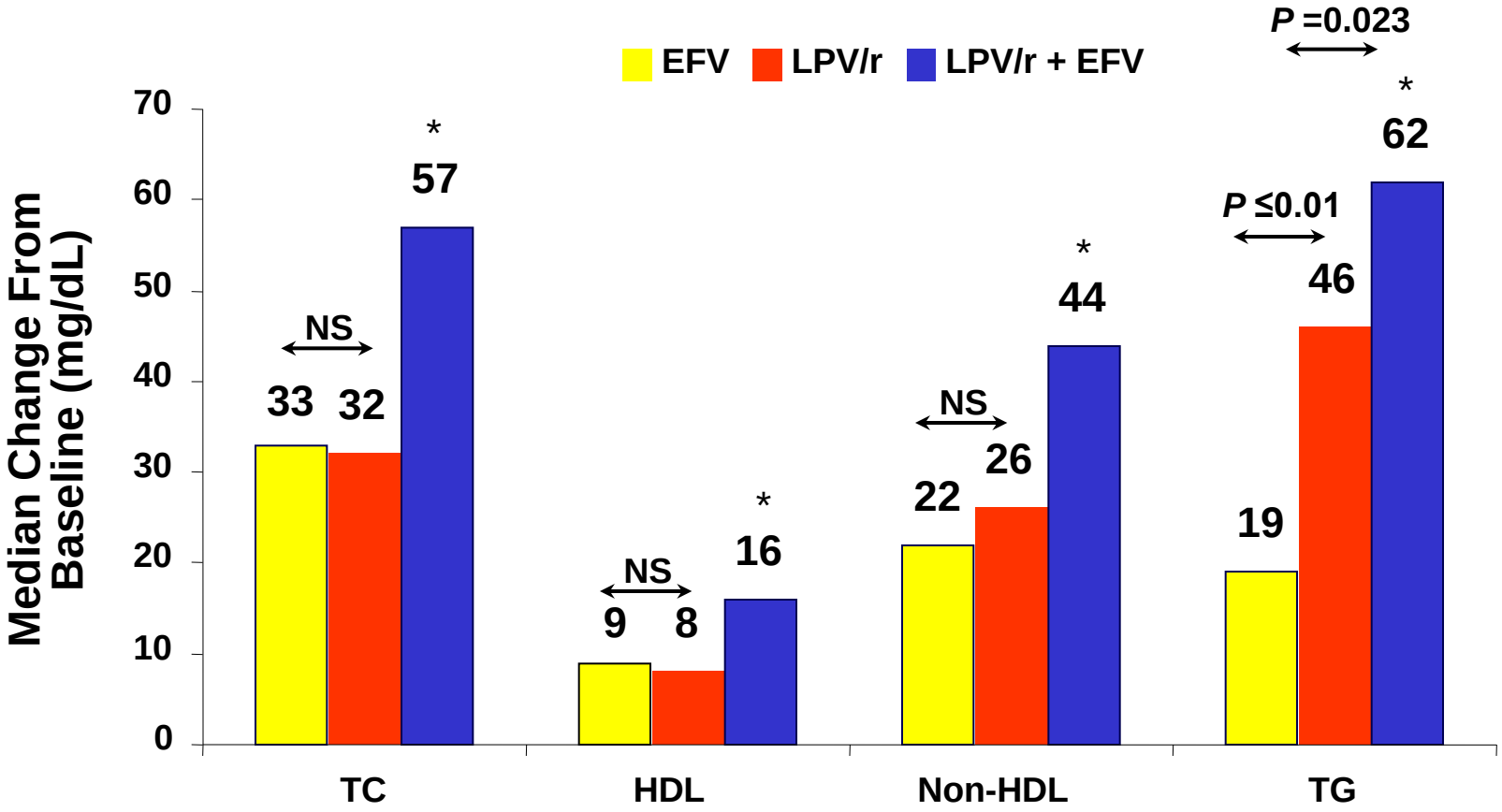


- Lipid effects comparable between arms

Smith K, et al. CROI 2008. Abstract 774.

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

Median Changes in Lipids From Baseline – Week 96

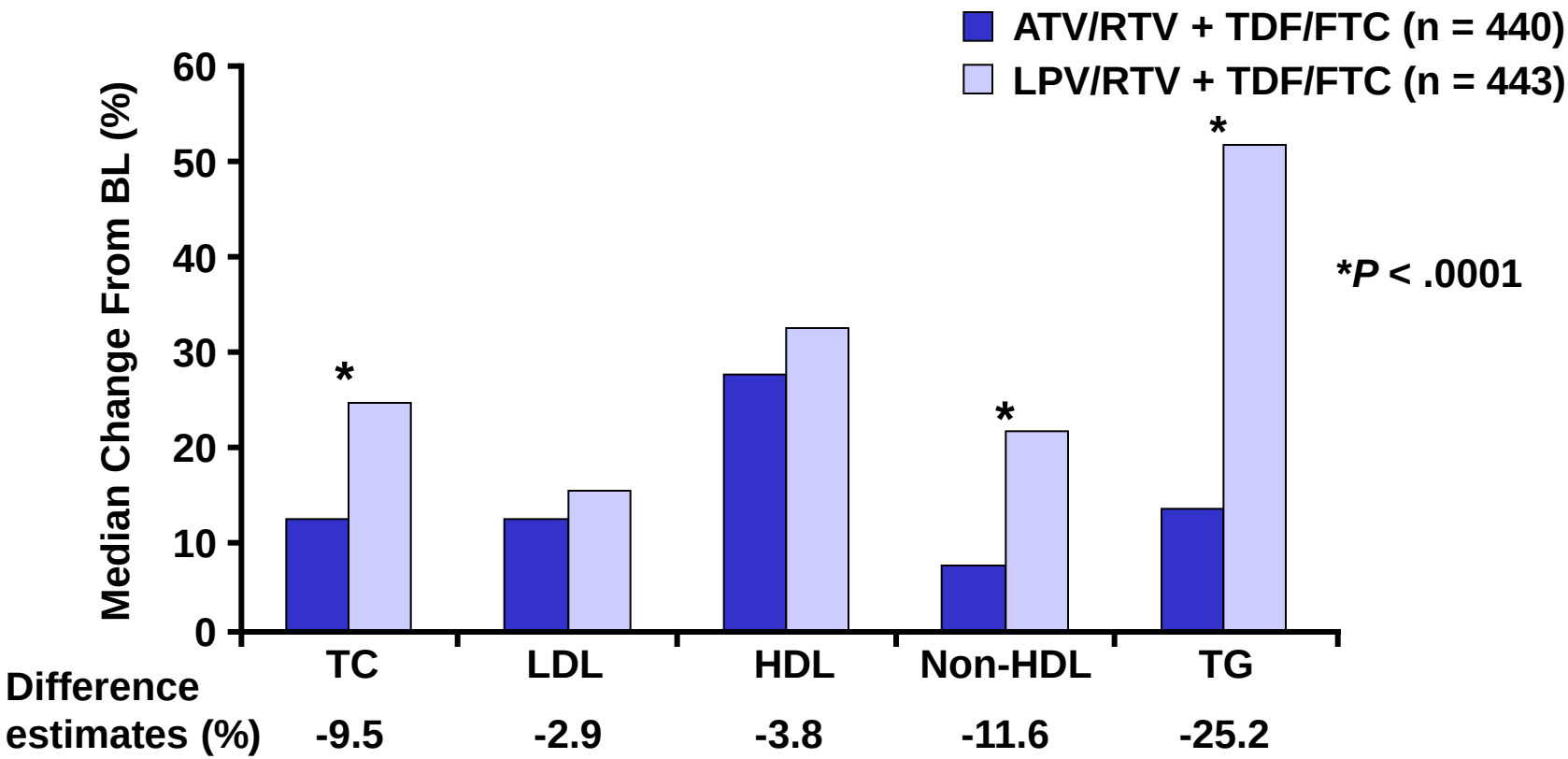


*Statistically significant difference with other 2 arms, *P* ≤0.01.

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.

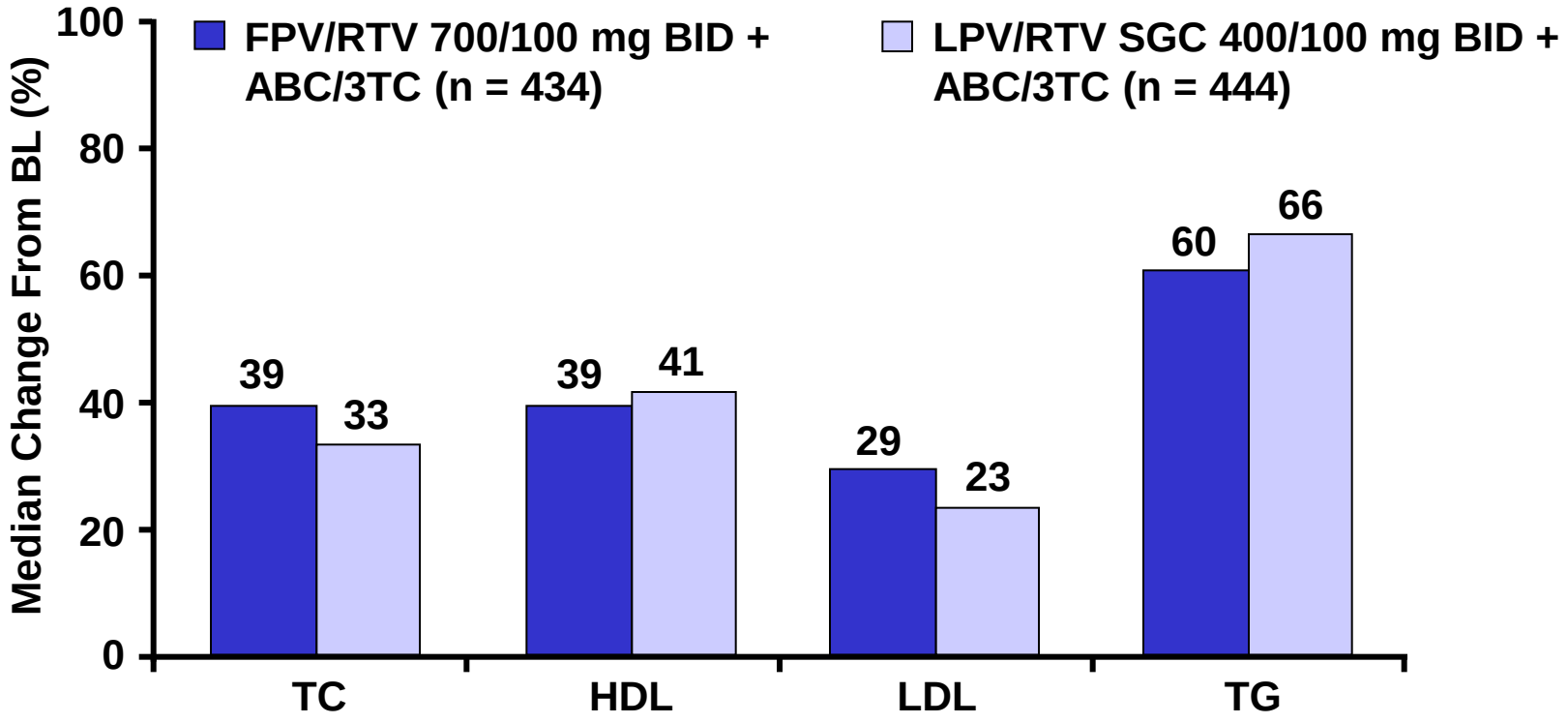
CASTLE: Lipid Effects of ATV/RTV vs LPV/RTV at Week 48



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

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

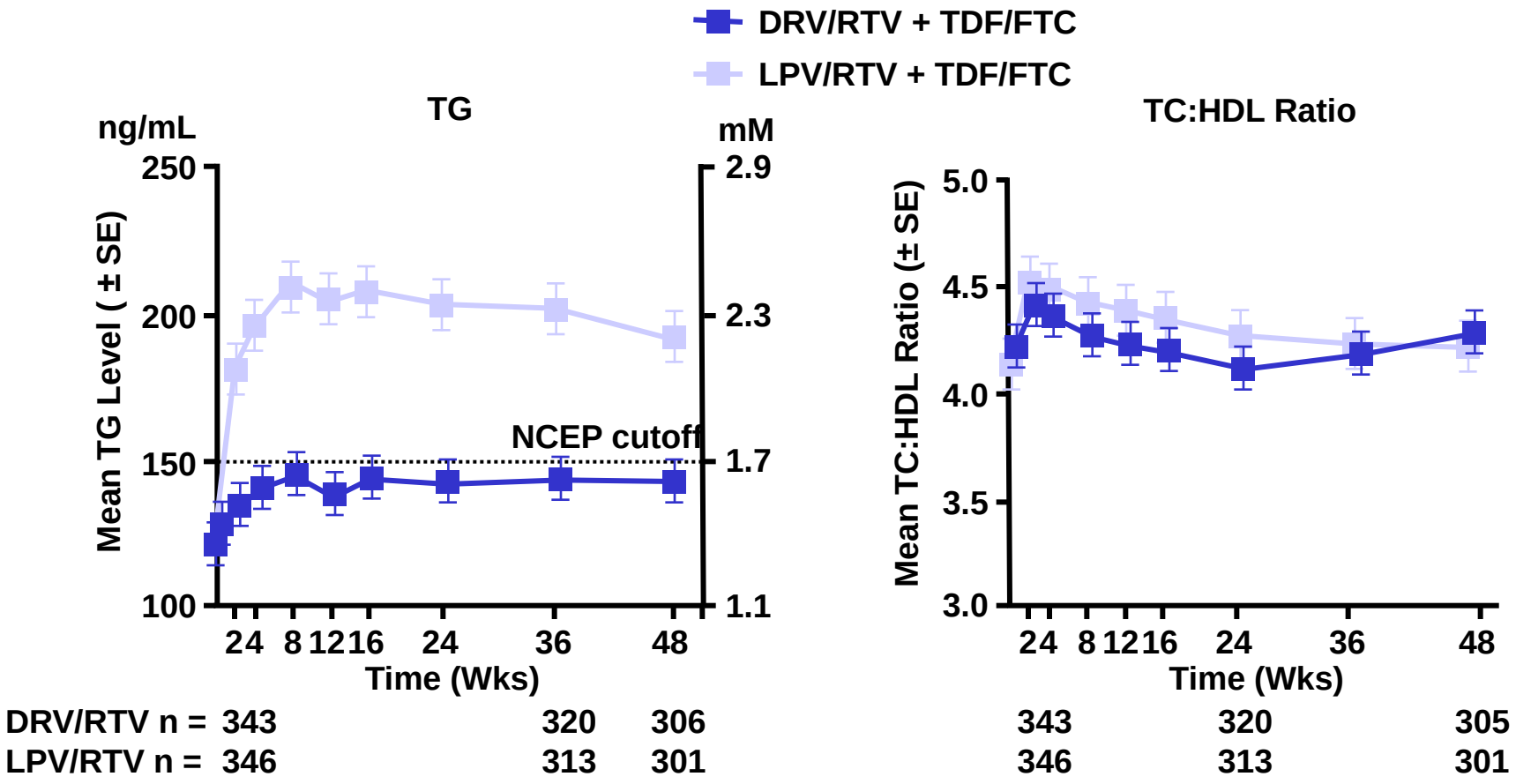
KLEAN: Lipid Effects of FPV/RTV vs LPV/RTV at Week 48



- **Lipid effects comparable between arms**

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

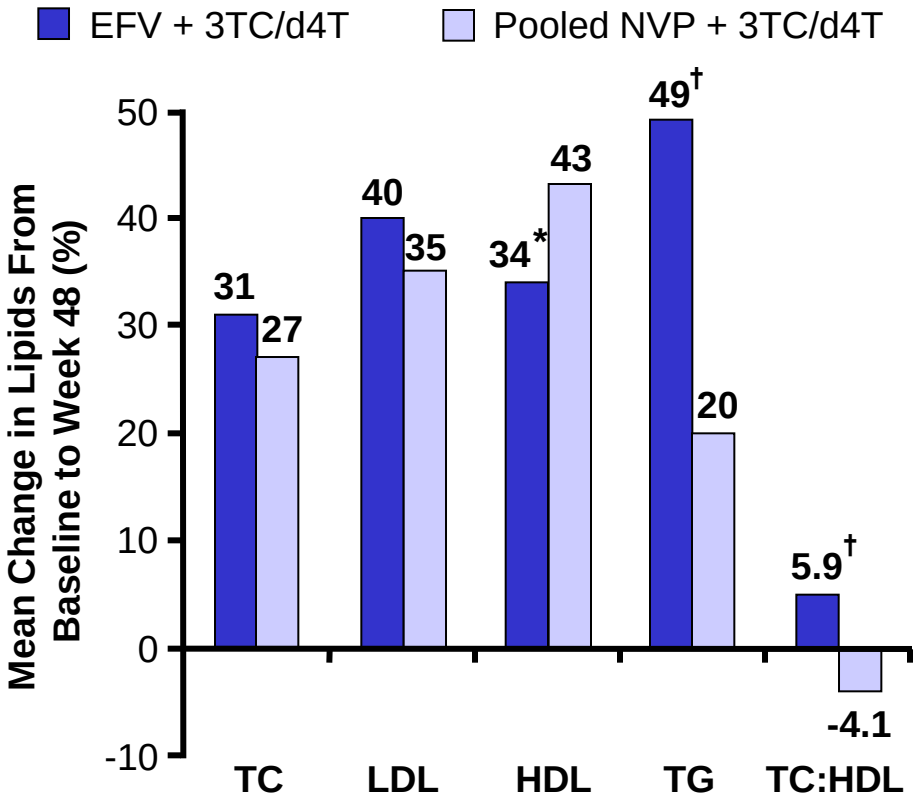
ARTEMIS: Mean Fasting Lipid Levels Over Time for DRV/RTV vs LPV/RTV



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

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



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

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

Insulin Resistance

Failure of target organs to respond normally to the action of insulin

↓ Ability of insulin to store exogenous glucose (muscle/fat)

↓ Ability of insulin to suppress endogenous glucose production (liver)

Impact of Various PIs on Glucose and Glucose Disposal Rate

PI	2-Hour OGTT
IDV	↑↑↑
LPV/r	↑↑
ATV/r	↑↑
d4T	↑↑↑
3TC	↑

1. Noor MA et al. *AIDS*. 2001;15:F11-F18; 2. Dubé MP et al. *JAIDS*. 2001;27:130-134; 3. Behrens G et al. *AIDS*. 1999;13:F63-F70; 4. Martinez E et al. *AIDS*. 1999;13:805-810; 5. Walli RK et al. *Eur J Med Res*. 2001;6:413-421; 6. Noor MA et al. *AIDS*. 2002;16:F1-F8; 7. Dubé MP et al. *Clin Infect Dis*. 2002;35:475-481; 8. Sension M et al. *Antivir Ther*. 2002;7:L26; 9. Noor MA et al. *AIDS*. 2004;18:2137-2144; 10. Lee GA et al. *Clin Infect Dis.* 2006;43:658-660.

Metabolic Syndrome in HIV-Infected vs HIV-Uninfected Patients

- Conflicting data on whether metabolic syndrome more prevalent in HIV-infected patients and whether associated with antiretroviral therapy
- May also reflect background regional variations in risk

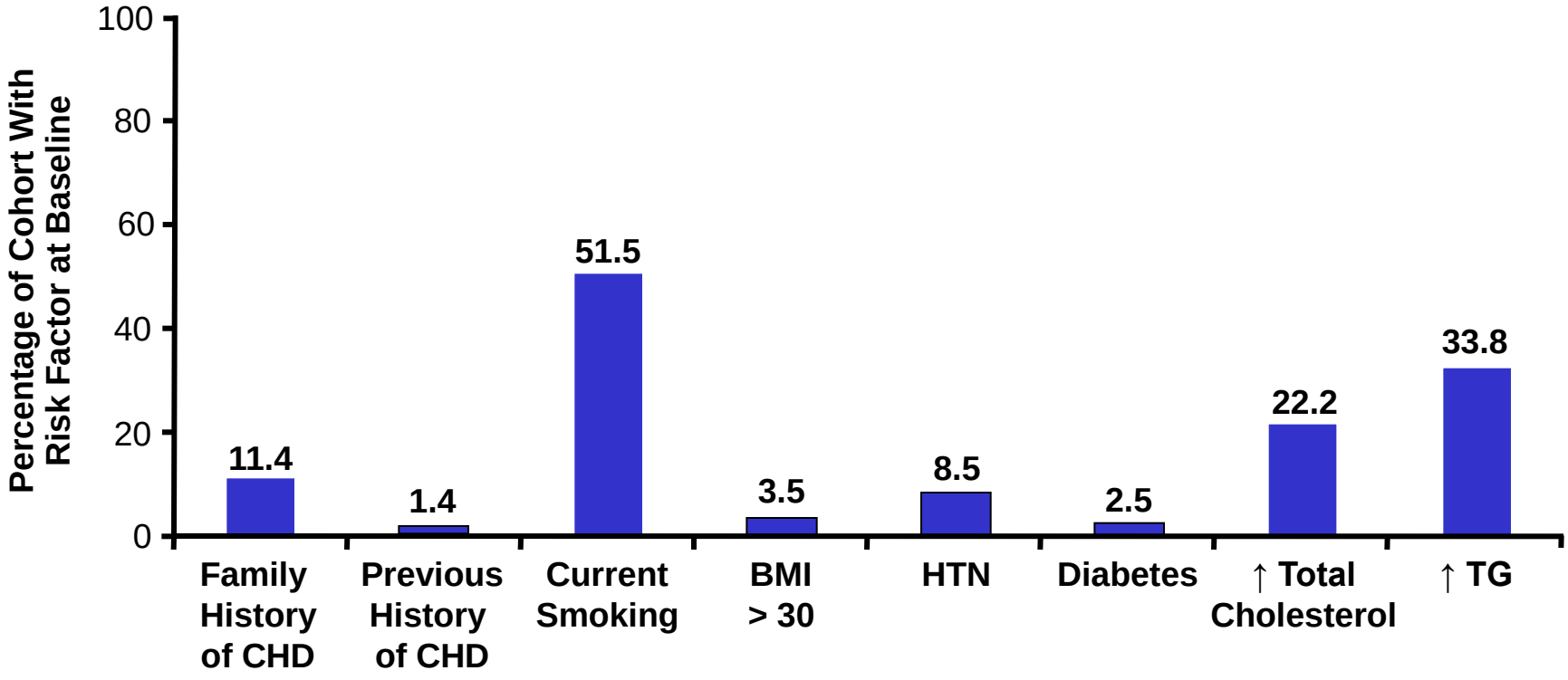
Study, %	Prevalence of Metabolic Syndrome		*P* Value
	HIV-Infected Patients	HIV-Uninfected Controls	
US; 471 men and women[1]	26	27	.77
US; 2394 women[2]	33	22	< .001
Spain; 710 men and women[3]	17	N/A	--

NCEP ATP III, ≥ 3 of the following: **Abdominal obesity** (waist circumference > 102 cm for men; >88 cm for women), **TG** ≥ 150 mg/dL (≥ 1.70 mmol/L), **HDL** < 40 mg/dL (< 1.04 mmol/L) for men, < 50 mg/dL (< 1.30 mmol/L) for women, **Blood pressure** ≥ 130/≥ 85 mm Hg, **Fasting glucose** ≥ 110 mg/dL (≥ 5.55 mmol/L)

1. Mondy K, et al. Clin Infect Dis. 2007;44:726-734. 2. Sobieszczyk ME, et al. IAS 2006. Abstract WEPE0147. 3. Jerico C, et al. Diabetes Care. 2005;28:132-137.

Prevalence of Traditional Cardiac Risk Factors at Baseline in the D:A:D Study

- 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

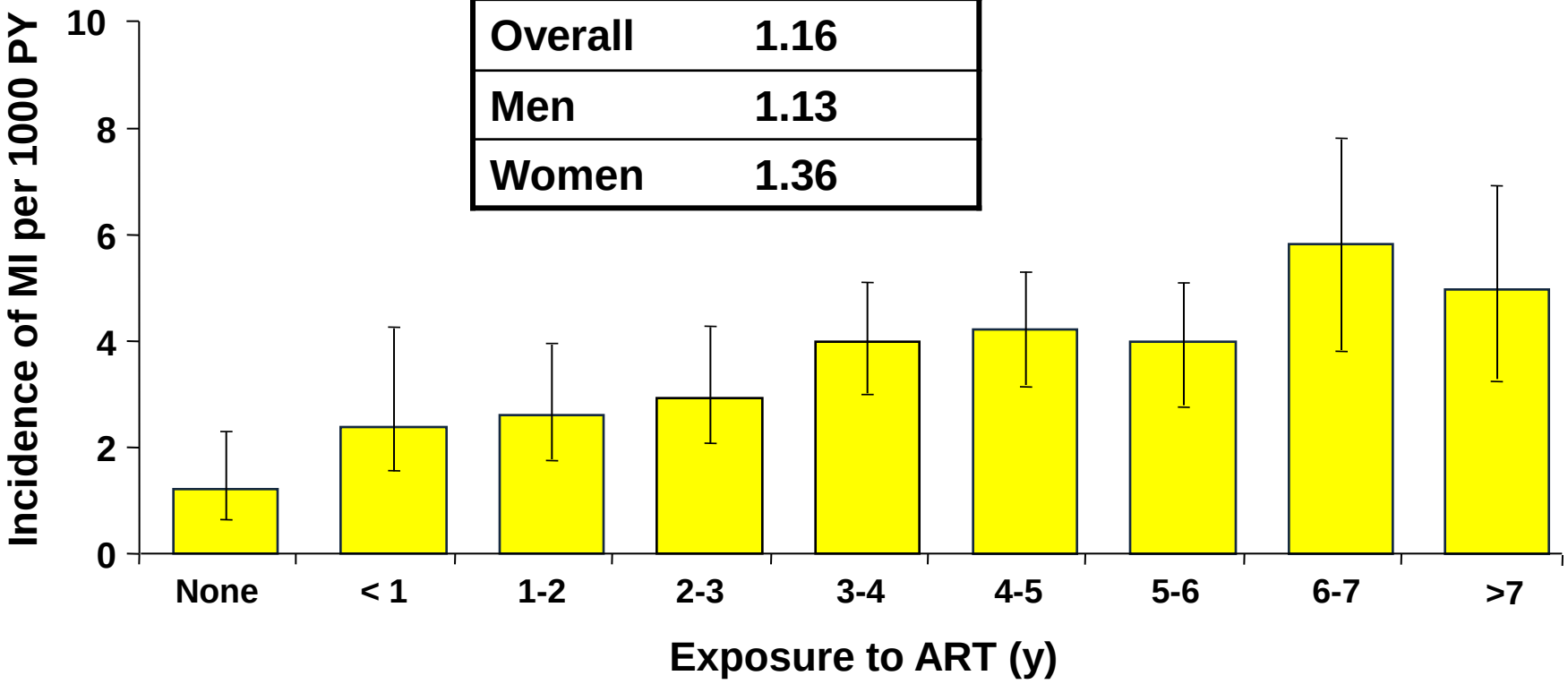


Friis-Møller N, et al. AIDS. 2003;17:1179-1193.

D:A:D Study: Incidence of MI

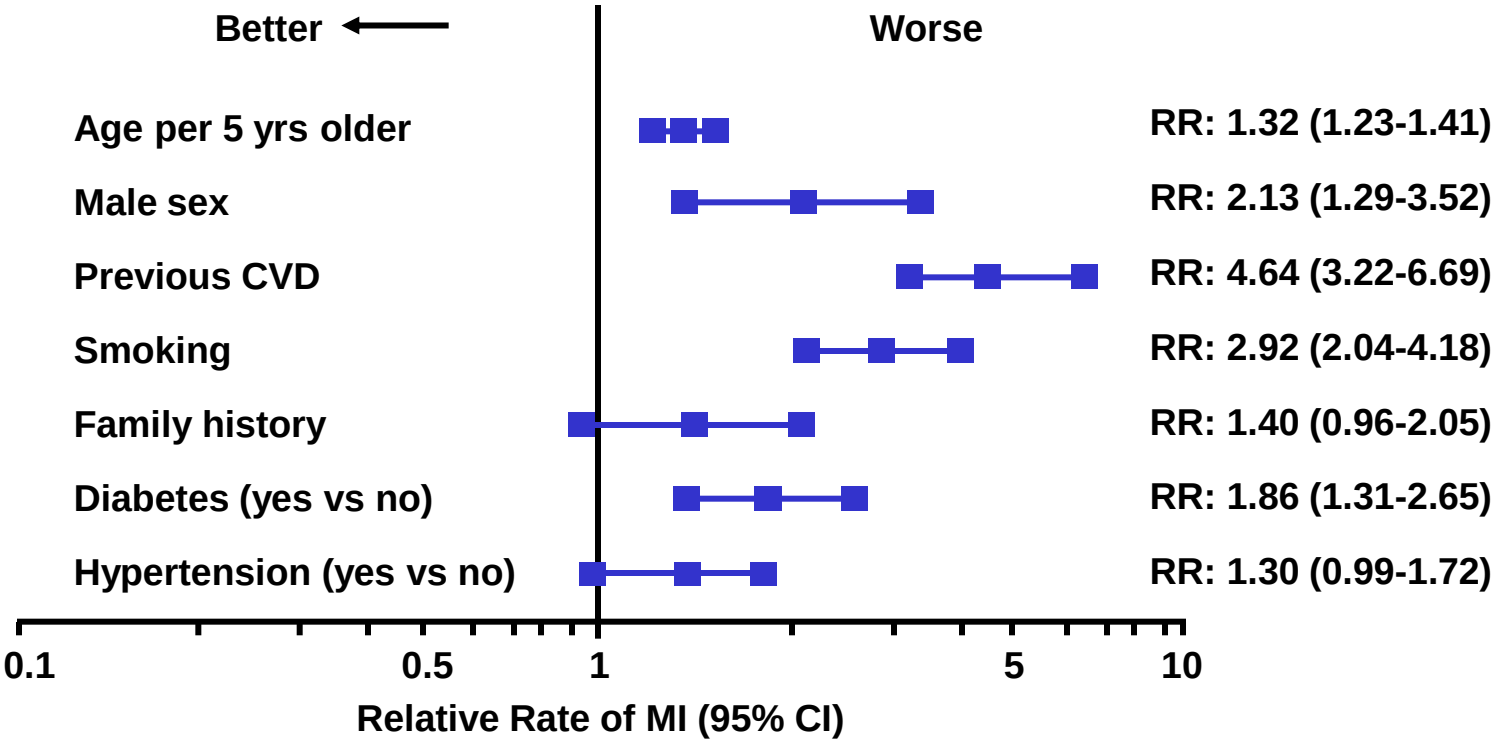
A Small Increase in Incident CVD Is Associated With Duration of Combination Antiretroviral Therapy

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.

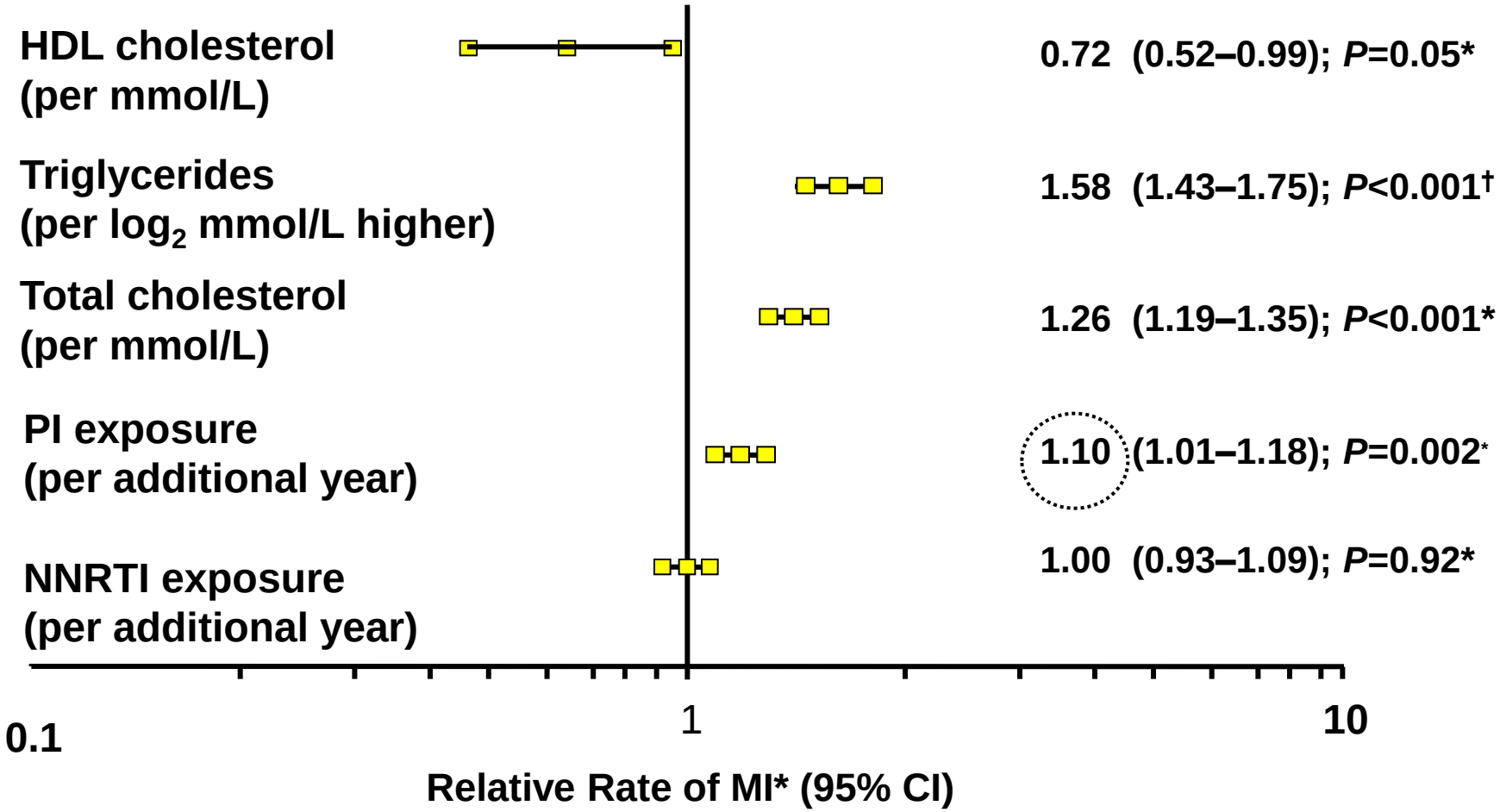
D:A:D: Traditional Risk Factors for CHD in an HIV-Infected Population



Multivariable Poisson model adjusted for age, sex, BMI, HIV risk, cohort, calendar year, race, family history of CVD, smoking, previous CVD event, TC, HDL, hypertension, diabetes.

Friis-Møller, et al. N Engl J Med. 2007;356:1723-1735.

Contribution of Dyslipidemia to MI Risk



†Unadjusted model.

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

D:A:D – study results and abacavir

- 1st Feb 2007, 33,347 patients, 157,912 person-years.
- 517 MI (event rate 3.3 [95% CI 3.0-3.6] per 1,000 person-years)
- Abacavir and ddI associated with increased relative risk of MI of 1.9# and 1.49 respectively
- Associated with recent abacavir and ddI use (<6mths), not cumulative exposure. Reversible on cessation of drug therapy
- Association remained after adjustment for HIV-RNA levels, CD4 count, dyslipidaemia, blood pressure, diabetes, fat loss/gain or latest glucose, Most pronounced in patients with a high underlying cardiovascular risk
- Insufficient data to assess TDF and FTC

D:A:D Study Group, The Lancet, 26 April, 2008

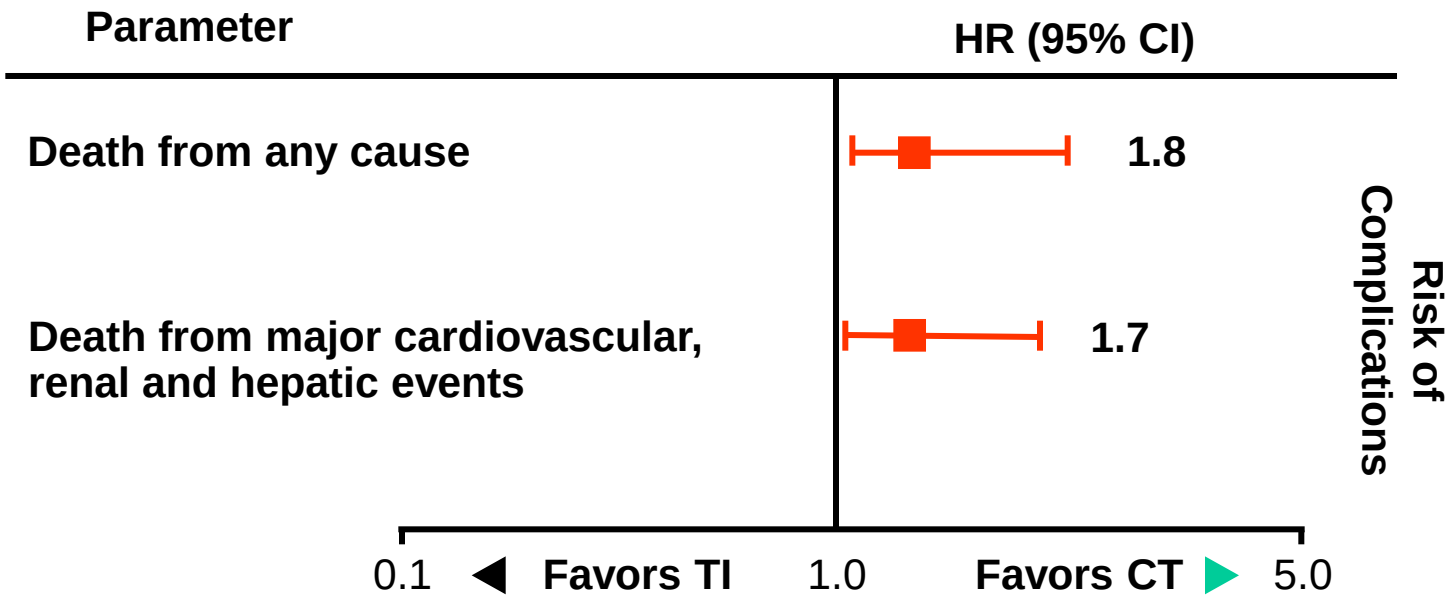
D:A:D – study results and abacavir

- Analysis of 54 clinical trials involving 9,639 subjects exposed to ABC (7845 pyrs) and 5,044 subjects treated with non-ABC-containing regimens (4653 pyrs)
- Incidence of myocardial ischaemic events and MI similar regardless of therapy.
- no increased risk of coronary or myocardial events in any of the ABC-treated groups.
- Analysis of spontaneous reports submitted to GSK and the FDA found no signal of an increased risk of MI associated with use of ABC.
- 1 million patient years of abacavir experience

Cutrell A et al, The Lancet, 26 April, 2008

SMART: Treatment Interruption Associated With Increased CV Risk

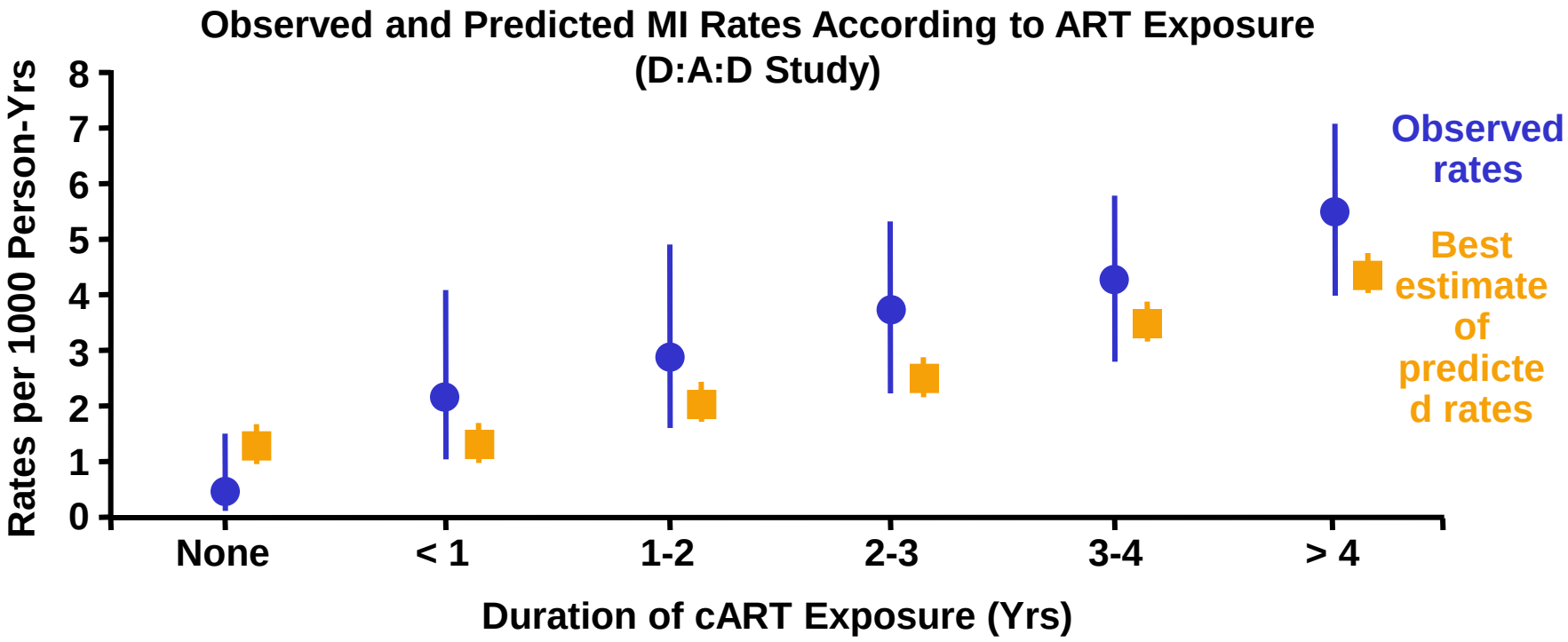
- **2 HIV treatment strategies assessed for overall clinical benefit: CT or CD4-guided TI**
- **TI associated with significantly greater disease progression or death, compared with CT: RR: 2.5 (95% CI: 1.8-3.6; *P* < .001)**



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

Framingham Underpredicts MI Risk in HIV

Age, Sex, TC, HDL, Smoking, SBP, Medication for HBP



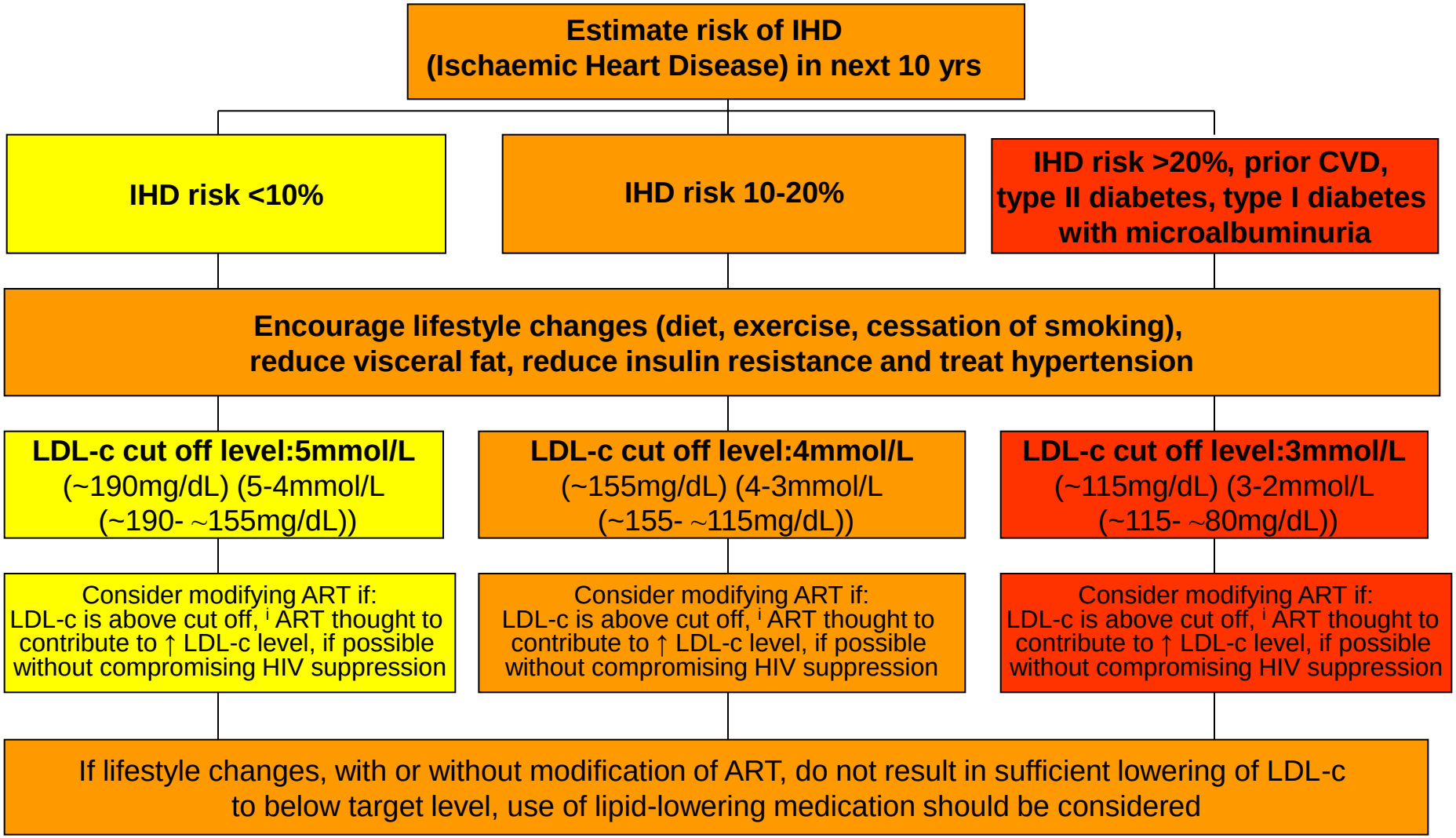
Does not include HIV-specific factors; Immune status, Increased inflammatory markers, Insulin resistance

Law MG, et al. HIV Med. 2006;7:218-230.
Friis-Moller N, et al. CROI 2007. Abstract 808.

Conclusions

- Strong correlation between LDL-C and CVD risk
- HDL-C independent predictor of CVD
- cART associated with increased risk of CVD, but uncontrolled HIV infection also risk for CV events
- Other traditional risks for CVD prevalent, including those that can be modified (smoking)
- NRTIs, NNRTIs, and PIs have varying effects on lipids, insulin resistance, and fat distribution changes
- Boosted PIs associated with increased prevalence of dyslipidemia, although evidence suggests that RTV contributes substantially to lipid effects

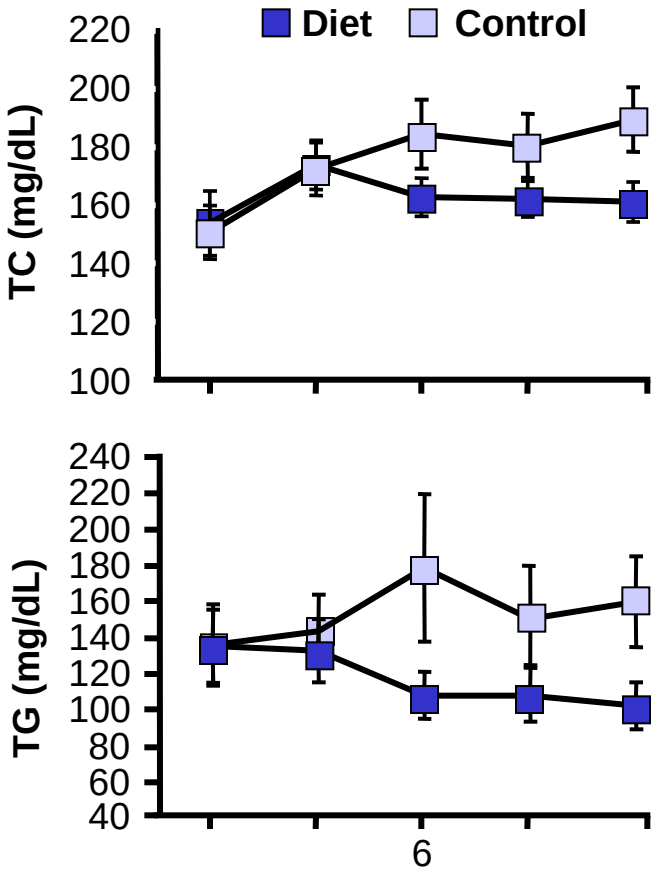
Prevention of cardiovascular disease
EACS guidelines 2007



Accessed from http://www.eacs.eu/guide/index.htm

Dietary Prevention of Dyslipidemia

- Randomized trial of NCEP diet in adults initiating ART (N = 90)
  - **95% on ZDV/3TC**
  - **75% on EFV**
- 15- to 30-minute session with a dietician every 3 months
- Other outcomes
  - **Reduced fat, calorie intake**
  - **Reduced BMI**
  - **Increased dietary fiber intake**



Lazzaretti F, et al. IAS 2007. Abstract WEAB303.

Smoking Cessation: Nonpharmacologic Therapy

- Interventions
  - Identify reasons for quitting
  - Discuss options
  - Set a quit date, chosen by the patient
  - Set up a support system
  - Identify rationalizations
  - Identify alternatives for cravings
  - Provide reliable sources of information
  - Refer to local smoking cessation programs

Effective Smoking Cessation Strategies

- DHHS guidelines: pharmacotherapy for all patients attempting to quit smoking except those with medical contraindications
  - Approved pharmacotherapies: sustained-release bupropion, varenicline, nicotine gum, inhaler, nasal spray, and patch

- More intensive intervention strategies significantly more effective than less intensive ones
  - Counseling sessions lasting > 3 minutes and > 10 minutes were 1.3-fold and 2.3-fold, respectively, more likely to result in abstinence vs < 3 minutes
  - 8 sessions were 2.3-fold more likely to result in abstinence vs 0-1 sessions
  - Treatment by various clinician types, individualized counseling, and multiple intervention strategies associated with successful outcomes

Elzi L et al, Antiviral Therapy 2006, Fiore MC. Respir Care. 2000;45:1200-1262.

Interactions Between Antiretrovirals and Smoking Cessation Drugs

- Varenicline
  - No reported drug interactions with antiretroviral agents
  - minimal metabolism, 92% excreted unchanged in the urine

- Bupropion
  - Metabolized in liver by various CYP450 enzymes, predominantly CYP2B6
  - LPV/RTV and bupropion coadministration resulted in significantly decreased concentrations of bupropion and hydroxybupropion[1]
  - Administration of ritonavir alone—most potent CYP3A4 inhibitor—may slow buproprion metabolism[2]
  - Patients receiving boosted PIs should be monitored carefully for bupropion lack of efficacy and adverse effects

1. Hogeland GW, et al. Clin Pharmacol Ther. 2007;81:69-75.
2. Hesse LM, et al. Drug Metab Dispos. 2001;29:100-102

Lipid-Lowering Therapy Overview

Inhibit production of cholesterol

Statins

LDL ↓↓, TG ↓, HDL↑

Side effects: myopathy, ↑ liver enzymes

Ezetimibe

LDL ↓, TG ↓, HDL ↑

Side effects: ↑ liver enzymes, diarrhea

Nicotinic Acid

LDL ↑ ↔, TG ↓, HDL ↑↑

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

Augment lipoprotein lipase (↓VLDL)

Fibric Acids

LDL ↑, TG ↓↓, HDL ↑

Side effects: dyspepsia, gallstones, myopathy

Omega-3 Fatty Acids

LDL ↑↔, TG ↓↓, HDL ↑↔

Side effects: GI, taste

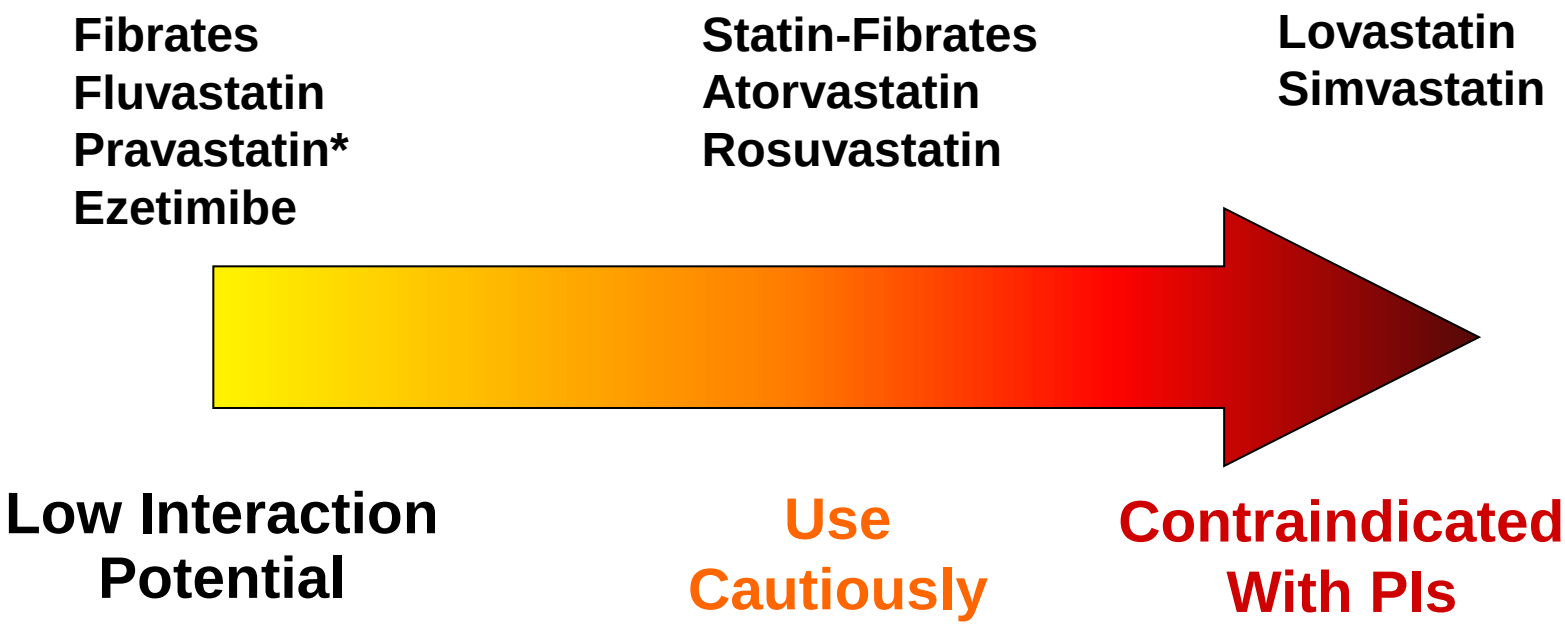
Bile Acid Sequestrants

LDL ↓, TG ↔↑, HDL ↑

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

Balancing ART and Lipid-Lowering Agents

Lipid Management With ART in HIV-Infected Patients
Potential Drug–Drug Interactions With PIs

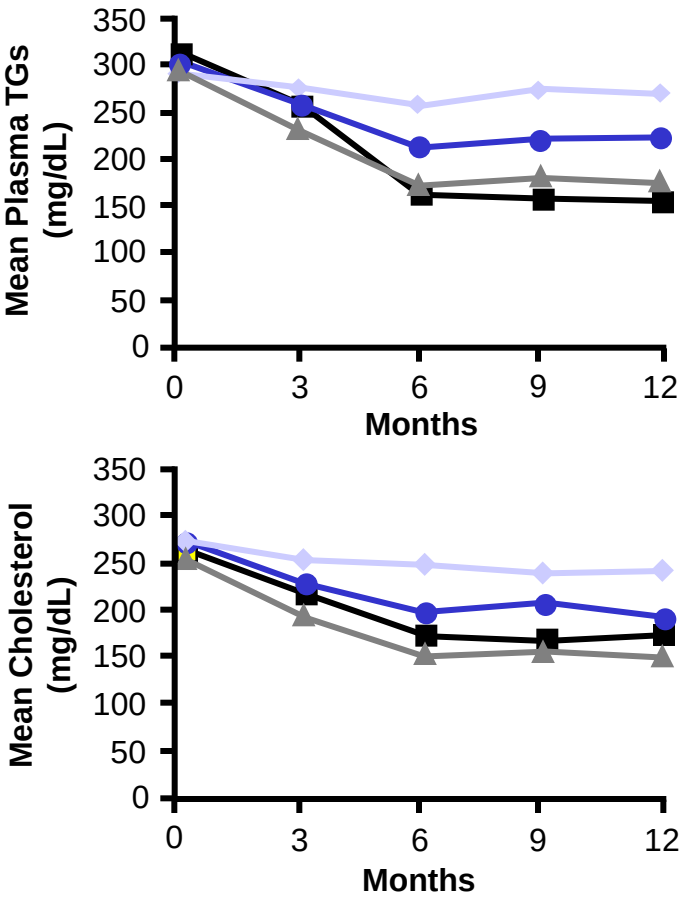


*Not recommended with darunavir/ritonavir.

Dubé M et al. Clin Infect Dis. 2003;37:613-627; Van Der Lee M et al. 13th CROI 2006. Denver, CO. Abstract 588; Prezista [package insert]. Raritan, NJ: Tibotec Therapeutics; 2006.

Lipid-Lowering Therapy vs Switching PI

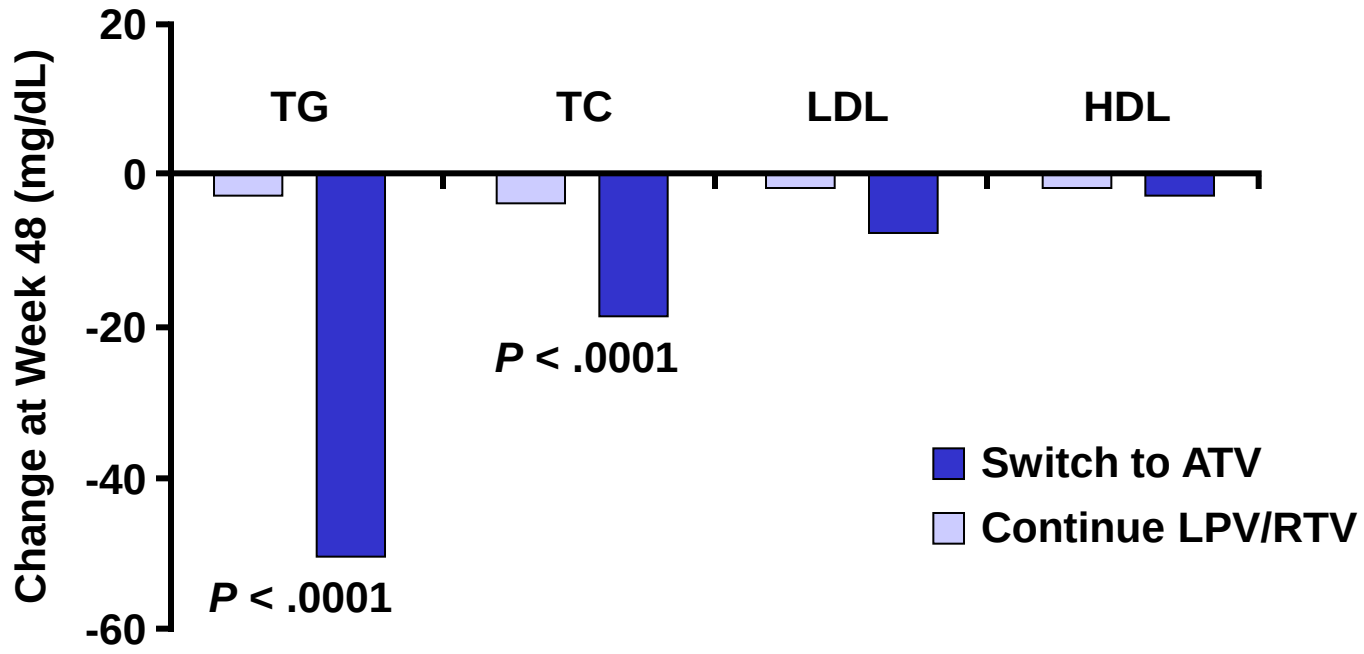
- 12-month, open-label study of 130 patients; 60% male; mean age: 39 years
- Stable on first HAART regimen randomized to
  - PI → EFV (n = 34)
  - **PI → NVP (n = 29)**
  - **Add bezafibrate (n = 31)**
  - Add pravastatin (n = 36)
- Pravastatin or bezafibrate significantly more effective in management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



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

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.

Strategies for Managing Hypertriglyceridemia

- Initial intervention: dietary modifications
- Consider antiretroviral switch options
- If TG > 500-1000 mg/mL (> 5.65-11.30 mmol/L) and antiretroviral switch not possible, consider fibrates
  - Gemfibrozil 600 mg BID or fenofibrate 200 mg QD associated with 20% to 50% decrease in TG in general population
- If hypertriglyceridemia remains uncontrolled
  - Fish oil (up to 6 g/day) or niacin (0.5 to 2g twice-dialy) can be added
    - Niacin associated with flushing and increased insulin resistance

NCEP ATP III final report. Circulation. 2002;106:3143-3421.

Content

- Introduction
- Selected specific adverse events
- ART and body shape changes
- ART, HIV and metabolism
  - Cardiovascular risk general remarks
  - ART and Lipids
  - ART, Insulin resistance and diabetes
  - HIV and cardiovascular risk
  - Therapeutic approaches, Guidelines
- Immune reconstitution inflammatary syndrome

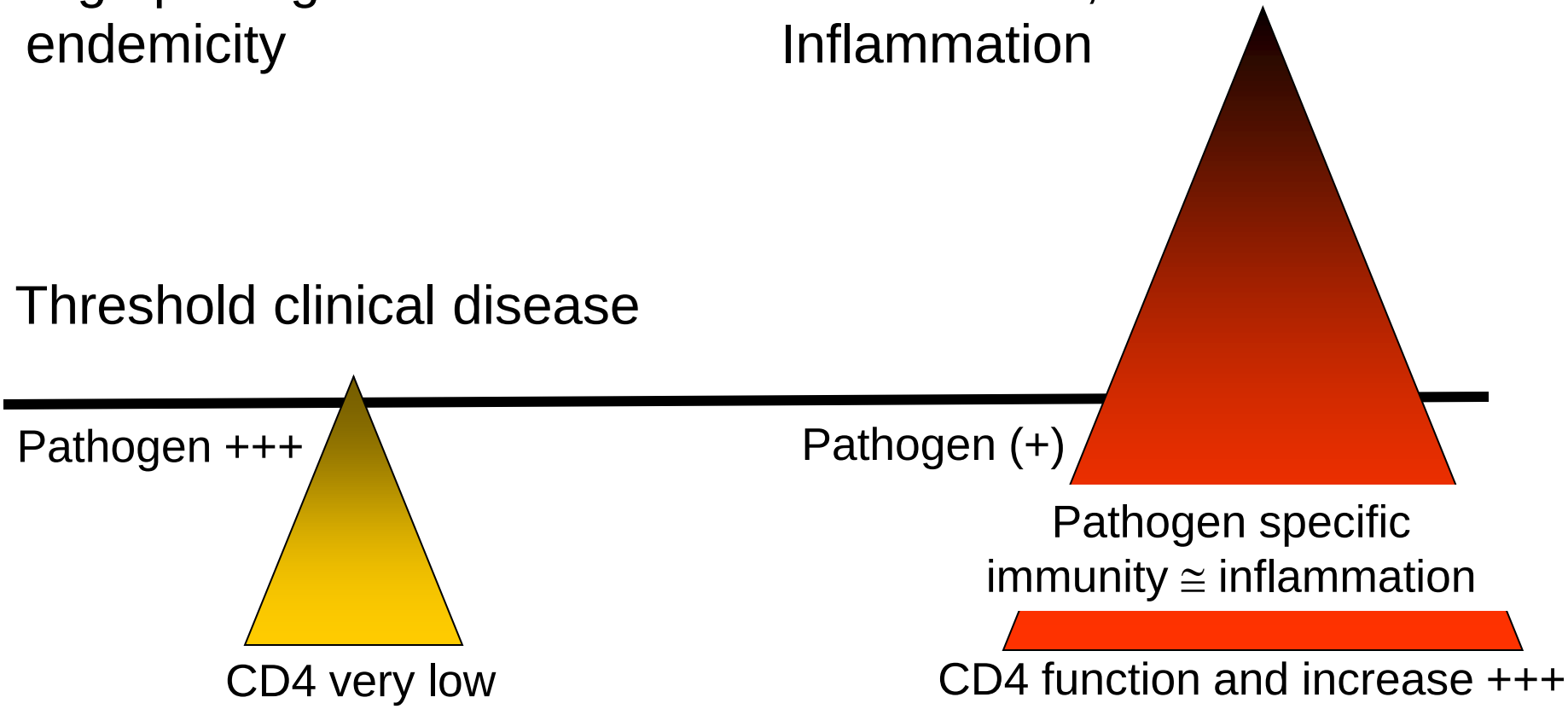
IRIS = Inflammatory Immune Reconstitution Syndrome Incidence 3-25%

Before ART

Advanced disease
High pathogen endemicity

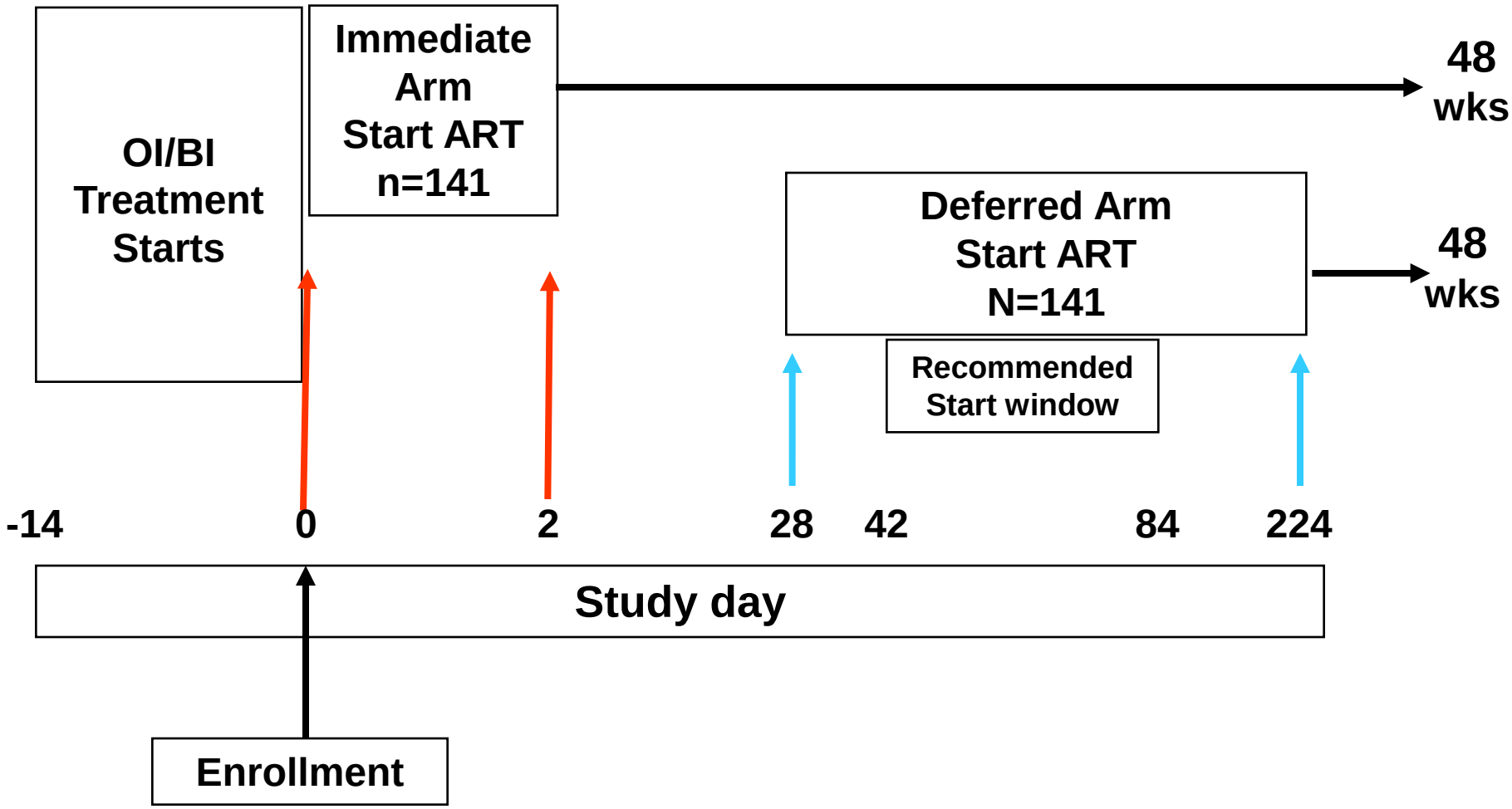
After ART initiation

ART early initiation
VL decrease, CD4 increase
Inflammation



Battegay et al, JAC, 2008, Hirsch et al, CID 2004, French et al, AIDS 2004; Shelbourne et al, Med 2002

Immediate vs. Deferred ART in the Setting of Acute AIDS-Related OIs: Final Results of a Randomized Strategy Trial ACTG A5164



A5164 Methods: Study Schema, n=282

Adapted from Andrew Zolopa. CROI 2008; abstract 142.

A5164: Safety outcomes over 48 weeks

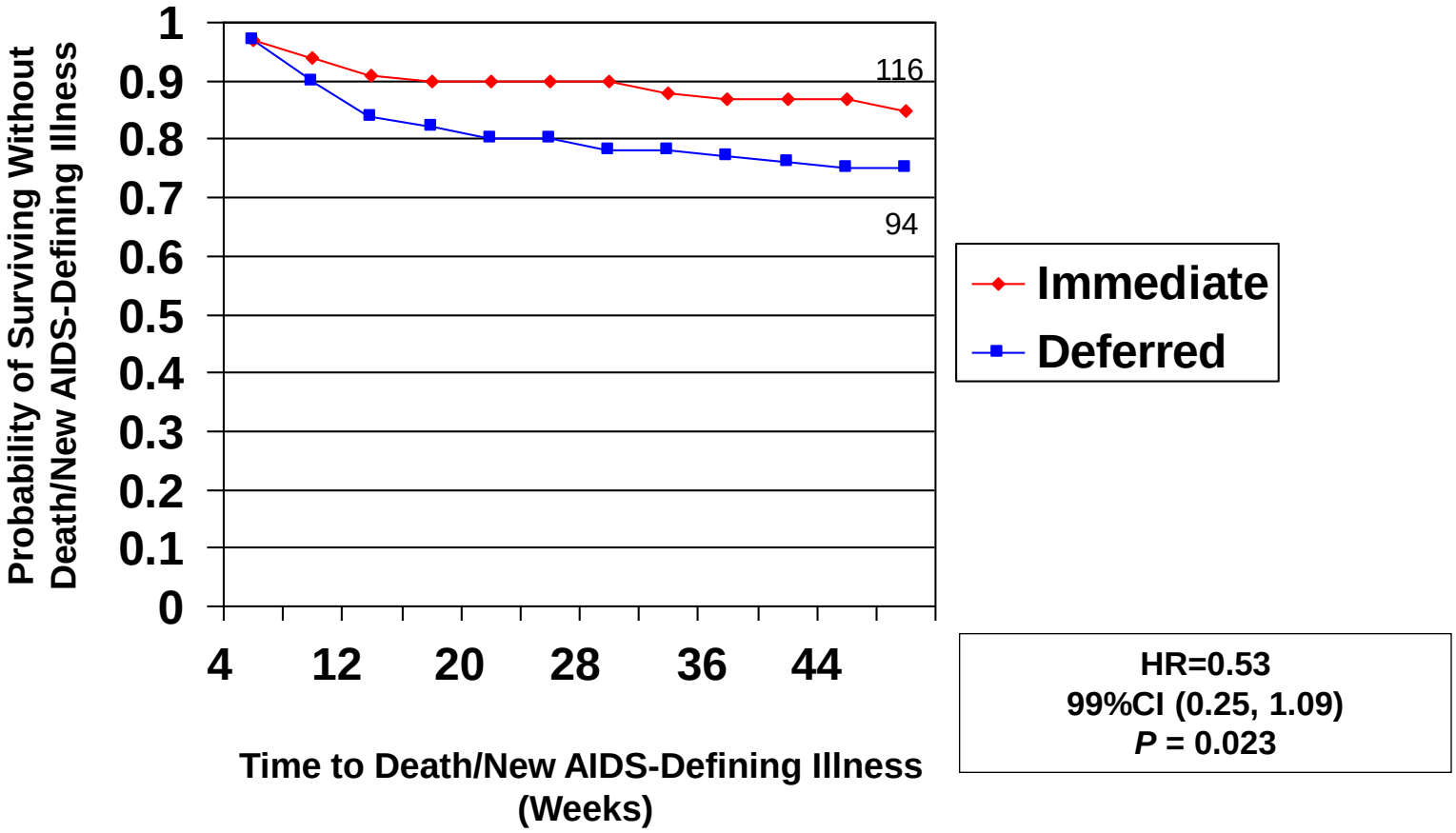
		Immediate	Deferred
CD4 (cells/mm^3)	Med (IQR)	31 (12 – 54)	28 (10 – 56)
Multiple OI/BI	< 30	32%	33%
PCP	n (%)	88 (62)	89 (63)

Outcome	*P*-Value	Immediate	Deferred
IRIS Reported		10	13
IRIS Confirmed		8 (5.7%)	12 (8.5%)

Outcome	*P*-Value	Immediate	Deferred
Lab Adverse Events Grades 2-3-4	0.77	31 – 39 – 20	36 – 45 – 21
Clinical Adverse Events Grades 2-3-4	0.87	14 – 40 – 7	34 – 29 – 6

Adapted from Andrew Zolopa. CROI 2008; abstract 142.

A5164: Time to AIDS progression or death



Better CD4 increase, non significantly different VL results
Less clinical progression

Adapted from Andrew Zolopa. CROI 2008; abstract 142.

NEW NIH DHHS Guidelines

„Some experts base the timing of initiation of antiretroviral therapy in treatment-naive patients with active TB disease on CD4 cell counts at the start of treatment, as shown below

- CD4 <100 — ART after 2 weeks
- CD4 =100–200 — ART after 8 weeks
- CD4 = 200–350 — ART after 8 weeks*
- CD4 >350 — ART after 8-24 weeks or after end of TB treatment*

* On case by case basis in clinician's judgment.

A rifamycin should be included for pts receiving ART (dose adjustment) (AII). Rifabutin is the preferred rifamycin in HIV-infected pts with active TB disease due to its lower risk of substantial interactions with ART (AII).

Compiled from Benson et al at http://aidsinfo.nih.gov/guidelines/ 2008