Which NRTI Backbone?

Dr Laura Waters

HIV/GU Medicine

Brighton & Sussex University NHS Trust

Introduction

- 2 NRTI + 3rd agent recommended for initial therapy
- Lots of studies into NRTI sparing but, to date, nothing competes in large enough studies
- PI monotherapy studied widely but works best as maintenance not induction

Guidelines: European
v6 October 2011

Guidelines: US

Guidelines: US

Guidelines: WHO 2010 revision

Guidelines: British 2008

Summary of NRTI recommendations

	WHO	EACS	DHHS[1]	IAS-USA
Preferred	AZT/3TC or TDF/FTC	ABC/3TC or TDF/FTC **Caution ABC if VL>100k or high CVD risk**	TDF/FTC	TDF/FTC
Alternative		AZT/3TC or ddI + 3/FTC*	ABC/3TC	ABC/3TC
Acceptable or other	Consider ABC or ddI if can't take TDF or AZT	*only if others unavailable or intolerance	AZT/3TC	AZT/3TC Reserved if ABC or TDF can't be used

1 – DHHS recommend REGIMENS; only TDF/FTC features in recommended regimens. Some TDF/FTC based regimens are alternatives; some ABC/3TC and TDF/FTC regimens are acceptable

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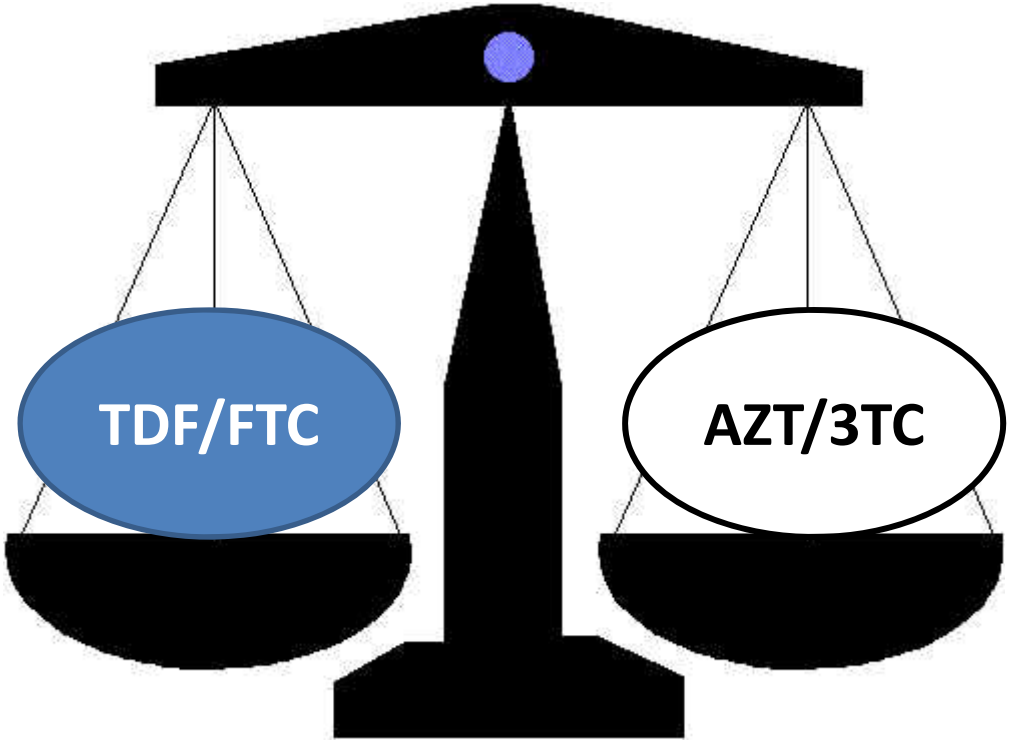
TDF/FTC vs AZT/3TC



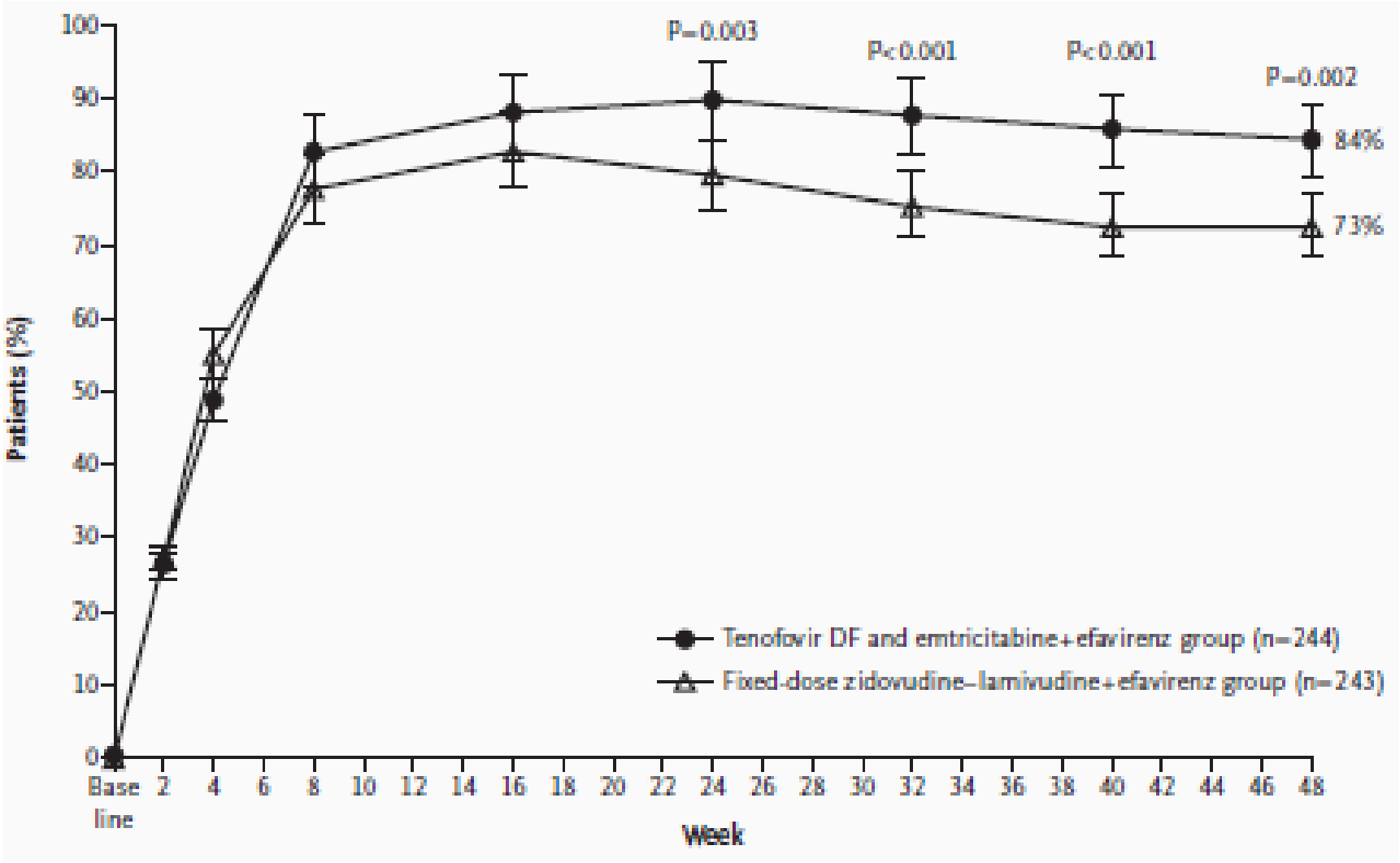
What drive the choice?

- Efficacy
- Toxicity & tolerability

Efficacy

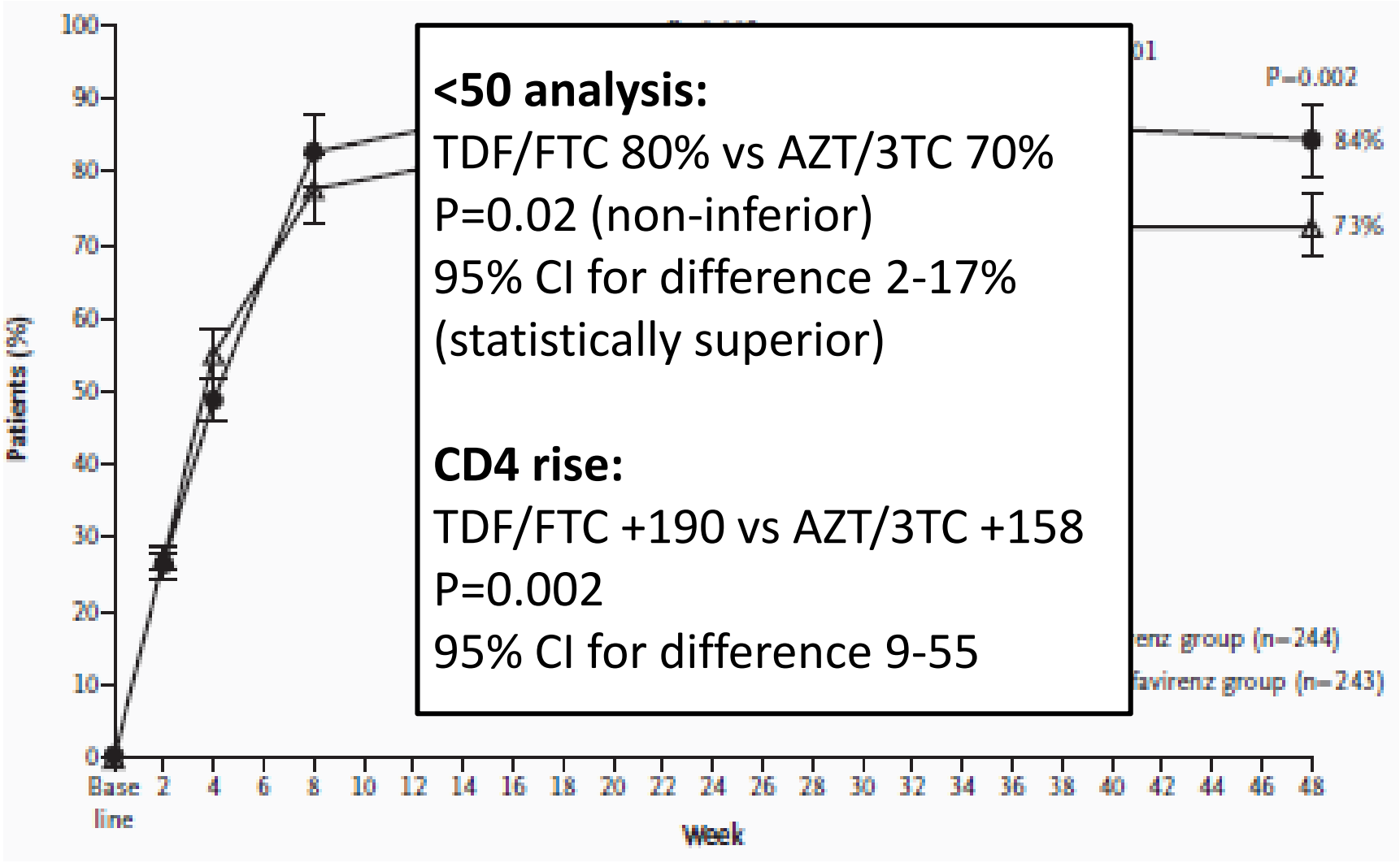
- Gilead 934
  - Open label TDF/FTC (separate components till week 96 then FDC) vs AZT/3TC, both with EFV
- 517 randomised 1:1

Primary end-point



Gallant *et al.* NEJM 2006.

Primary end-point



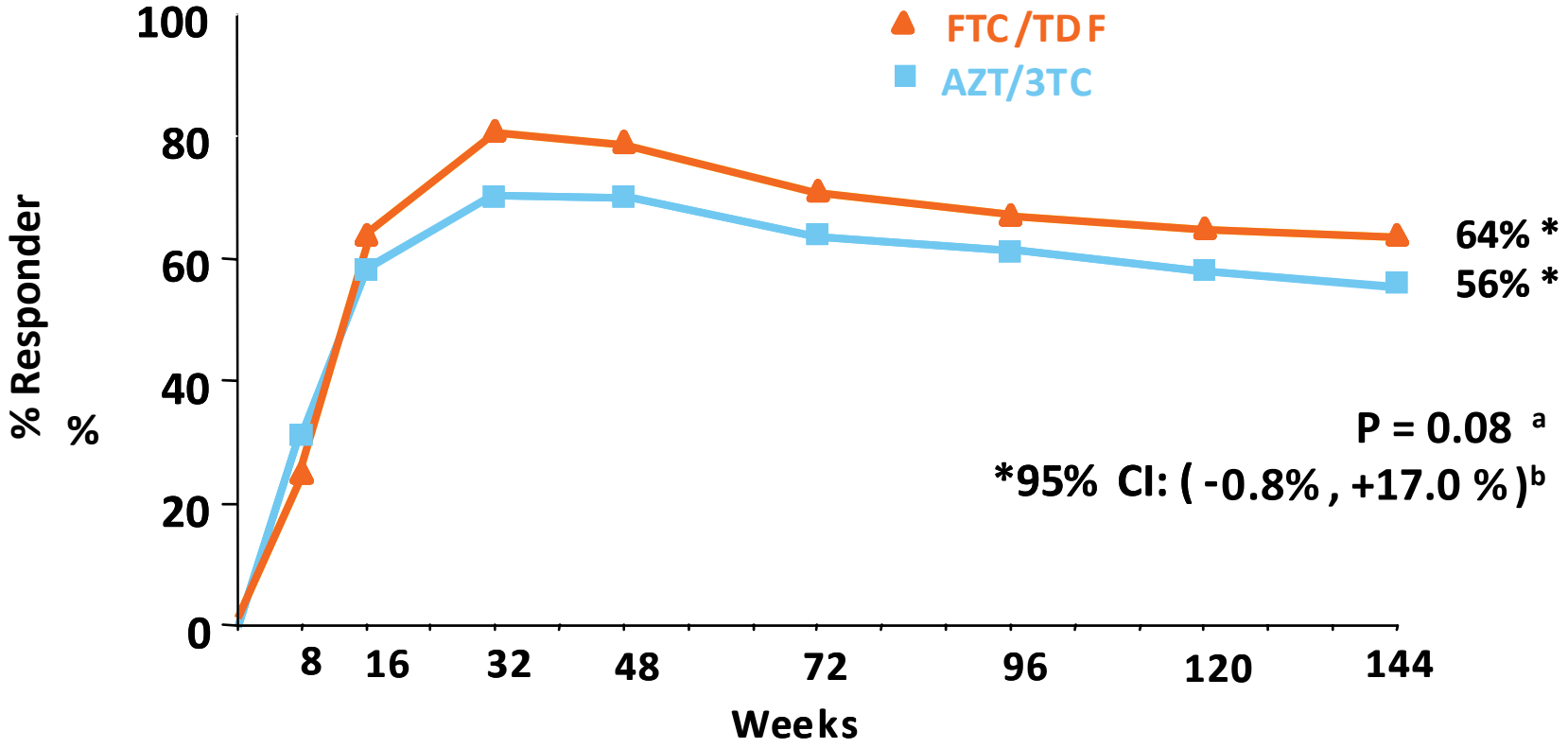
<50 analysis:
TDF/FTC 80% vs AZT/3TC 70%
P=0.02 (non-inferior)
95% CI for difference 2-17%
(statistically superior)

CD4 rise:
TDF/FTC +190 vs AZT/3TC +158
P=0.002
95% CI for difference 9-55

Gallant *et al.* NEJM 2006.

% with HIV RNA < 50 (TLOVR) (n = 458*)

*Lower number due to lack of consent for w96 and w144



a. Cochran-Mantel-Haenszel test stratified by baseline CD4

b. 95% CI for the difference between treatments stratum weighted on baseline CD4

Aribas *et al.* JAIDS 2008.

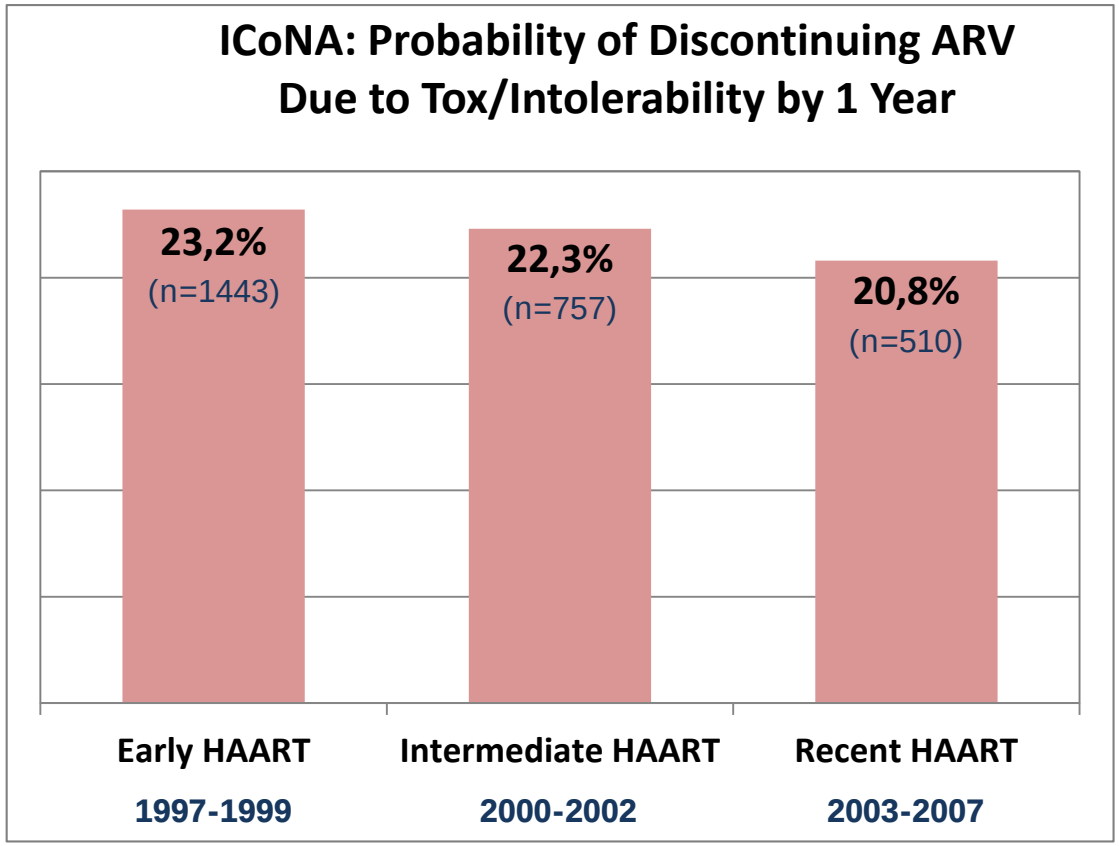
What drives the difference?

- Efficacy
  - VF rate similar at week 48 (1.6% TDF, 3.7% AZT)
  - Cumulative VF over 144 weeks greater on AZT:
    - 6% vs 2%; p=0.038
- Toxicity
  - More toxicity discontinuations on AZT W48/W144
    - Week 48
      - 9.1% vs 3.9% (p=0.02)
      - 5.5% vs 0 for anaemia (p<0.001)
    - Week 144
      - 11% vs 5% (p=0.01)

Toxicity

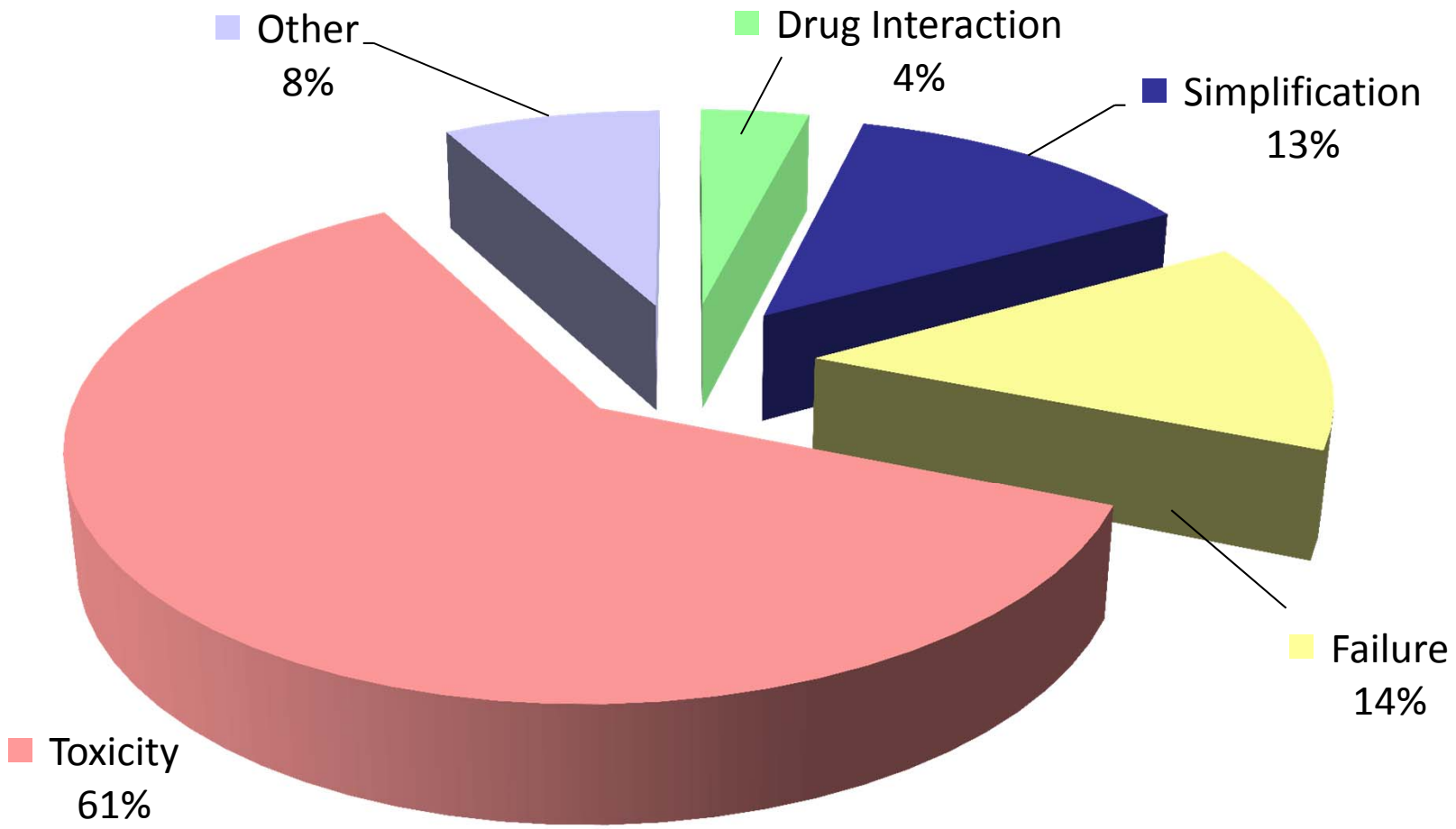
Toxicity was a significant reason for switching ART

ICoNA Study - 3,291 treatment-naive patients



Source: Cicconi P, *HIV Med*. 2010

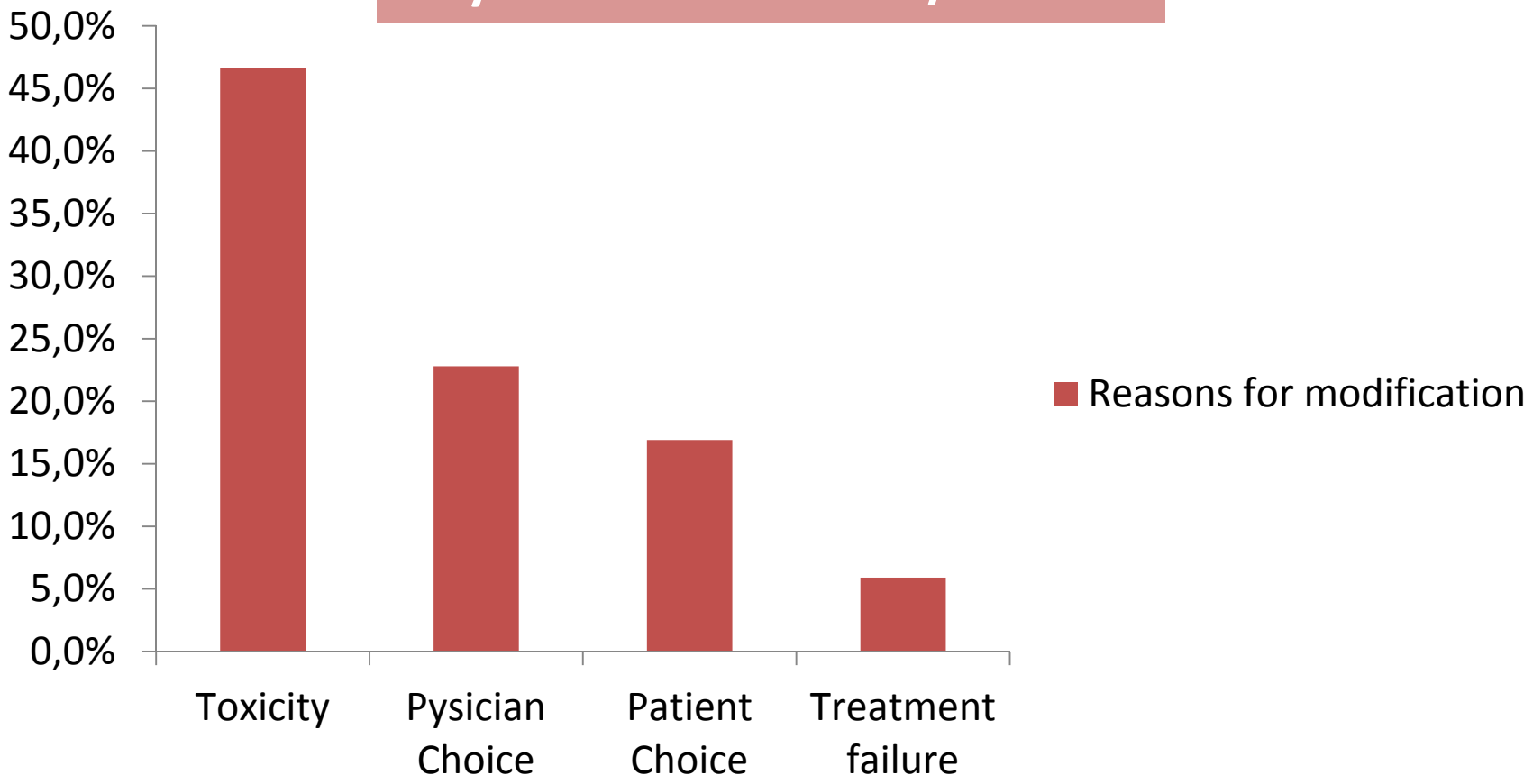
And remains so….



Davidson I, et al. Antiviral Res. 2010 May;86(2):227-9.

Swiss HIV Cohort: 2005–2008

Treatment modification during 1st year of CART = 41.5/100PY



Elzi L et al Arch Intern Med. 2010;170:57-65.

Swiss Cohort: Reasons for toxicity switch

- GI 28.9%
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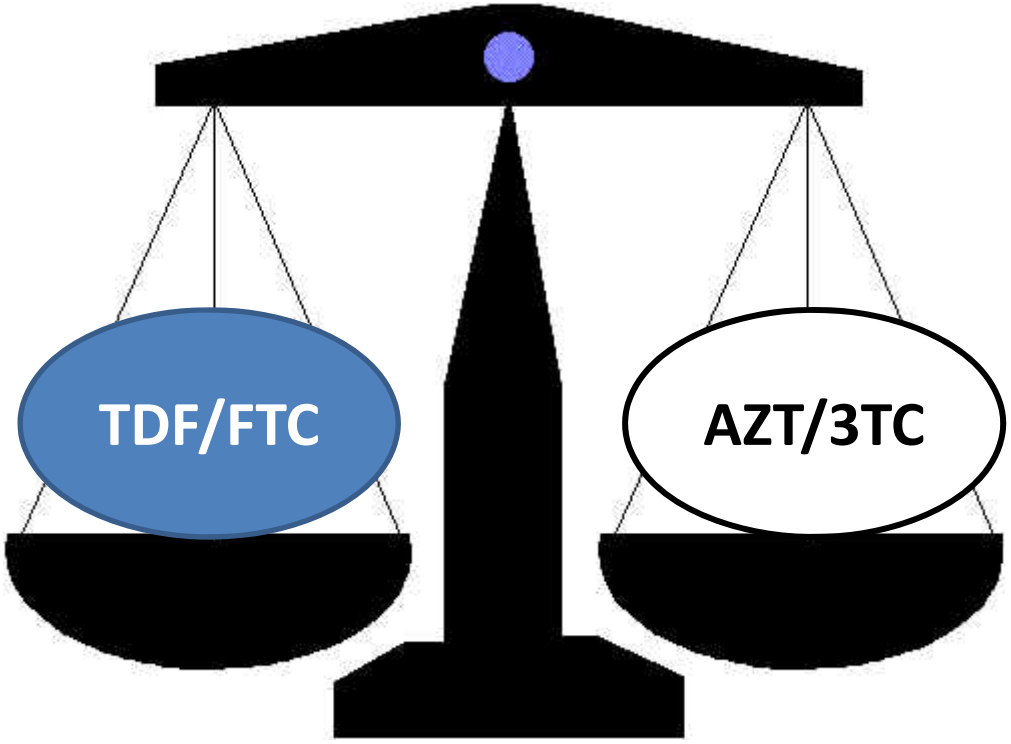
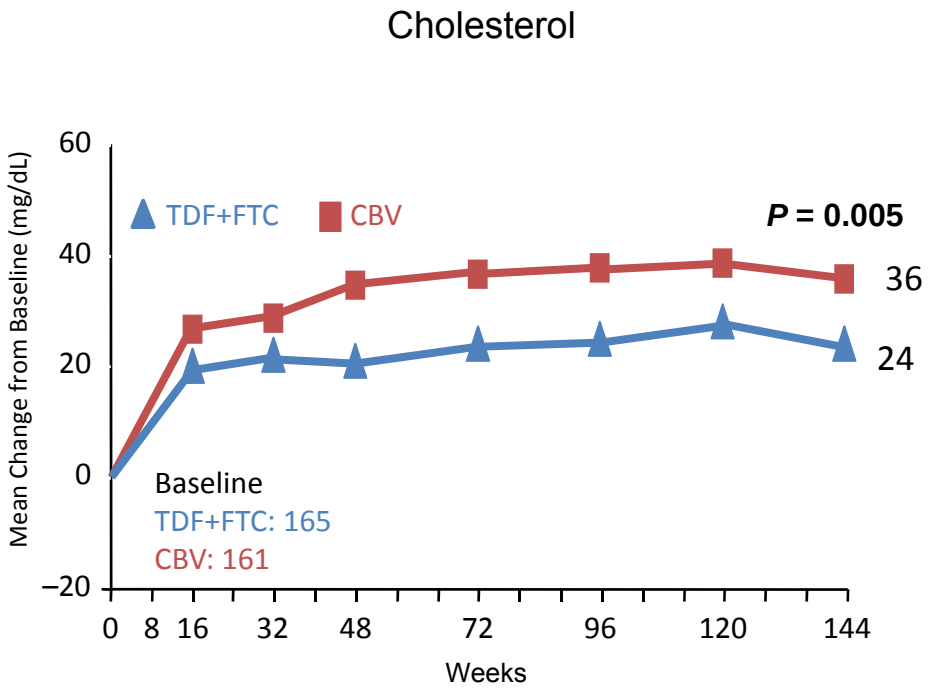
TDF/FTC vs AZT/3TC

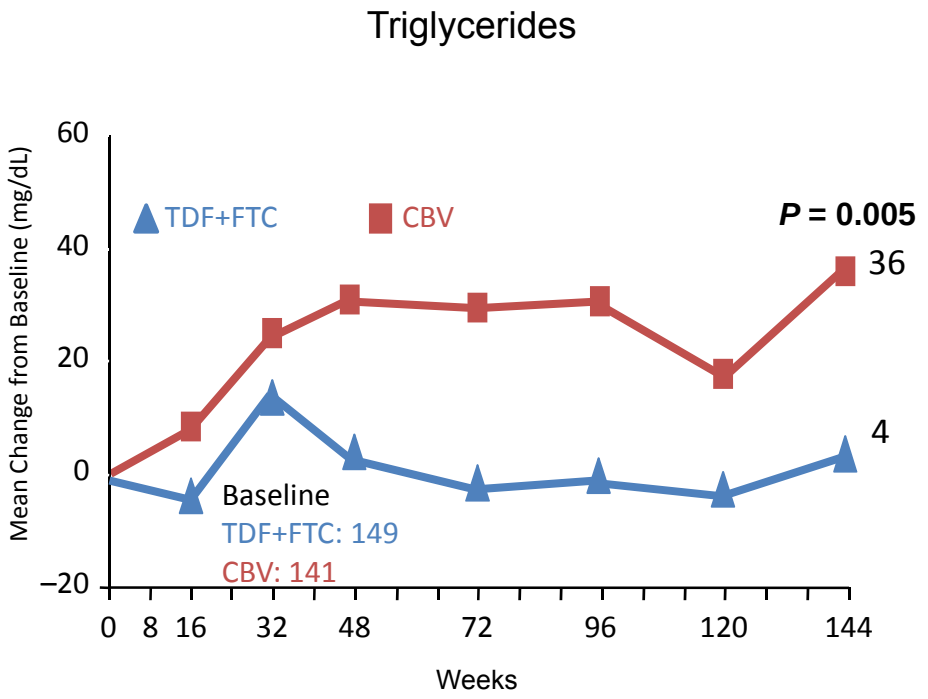


Toxicity basics

Toxicity	AZT/3TC	TDF/FTC
Short-term	Nausea Headache	Nausea Headache (FTC) Renal
Long-term	Anaemia Lipoatrophy Other mitochondrial	Renal Bone

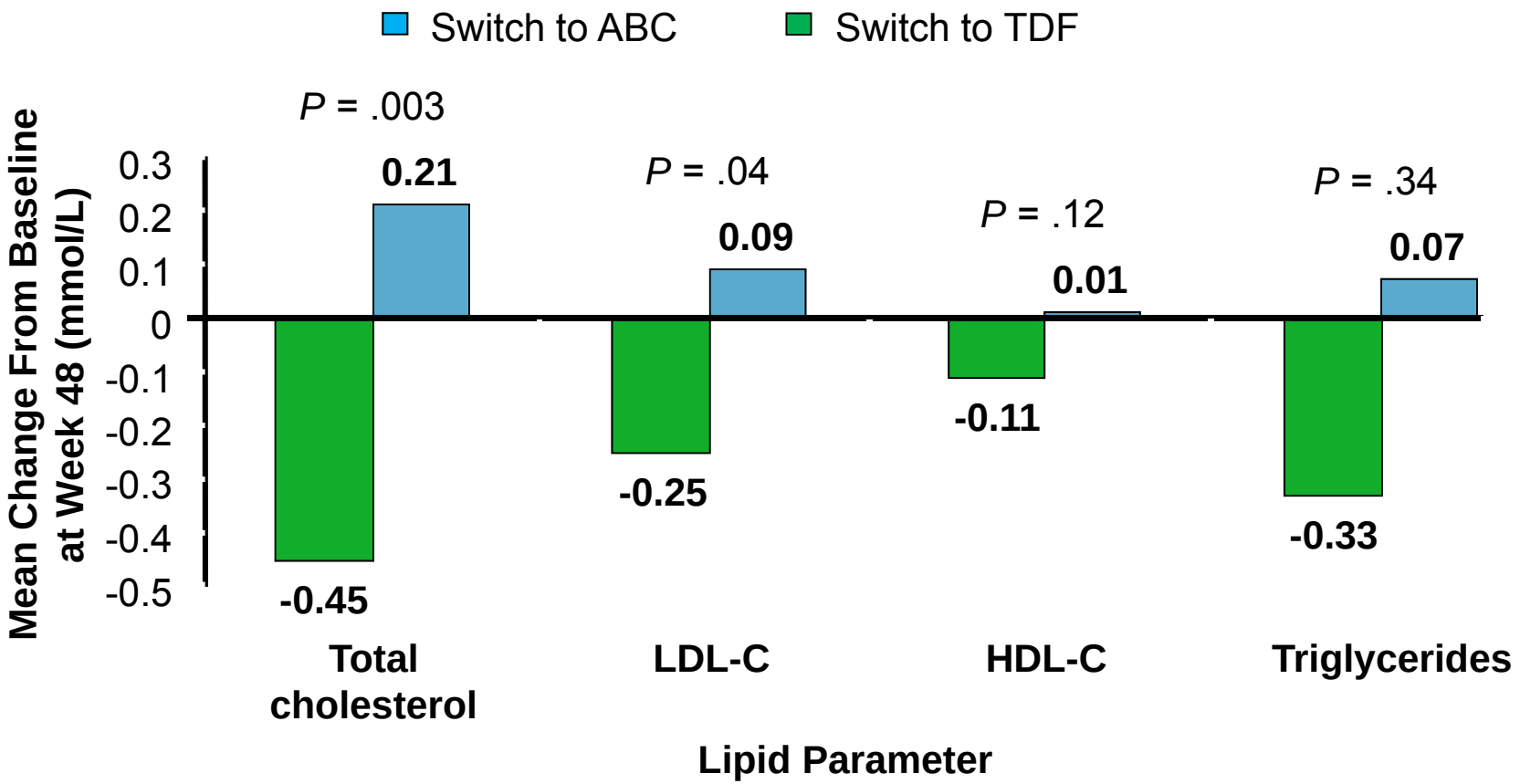
Study 934: 144W
Mean Change in Fasting TC & TG





Data on file, Gilead Sciences.

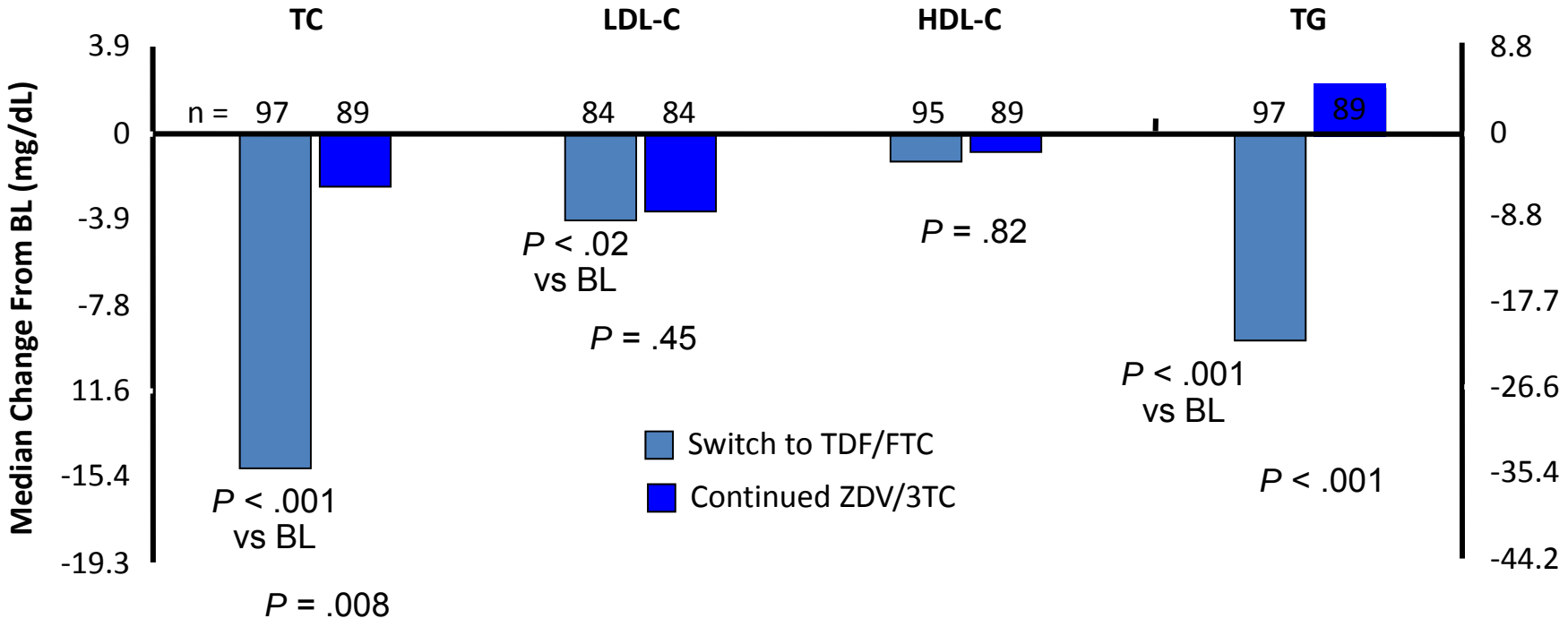
Metabolic Effects of Switch From d4T or ZDV to ABC or TDF: RAVE Study



Moyle GJ, et al. AIDS. 2006;20:2043-2050.

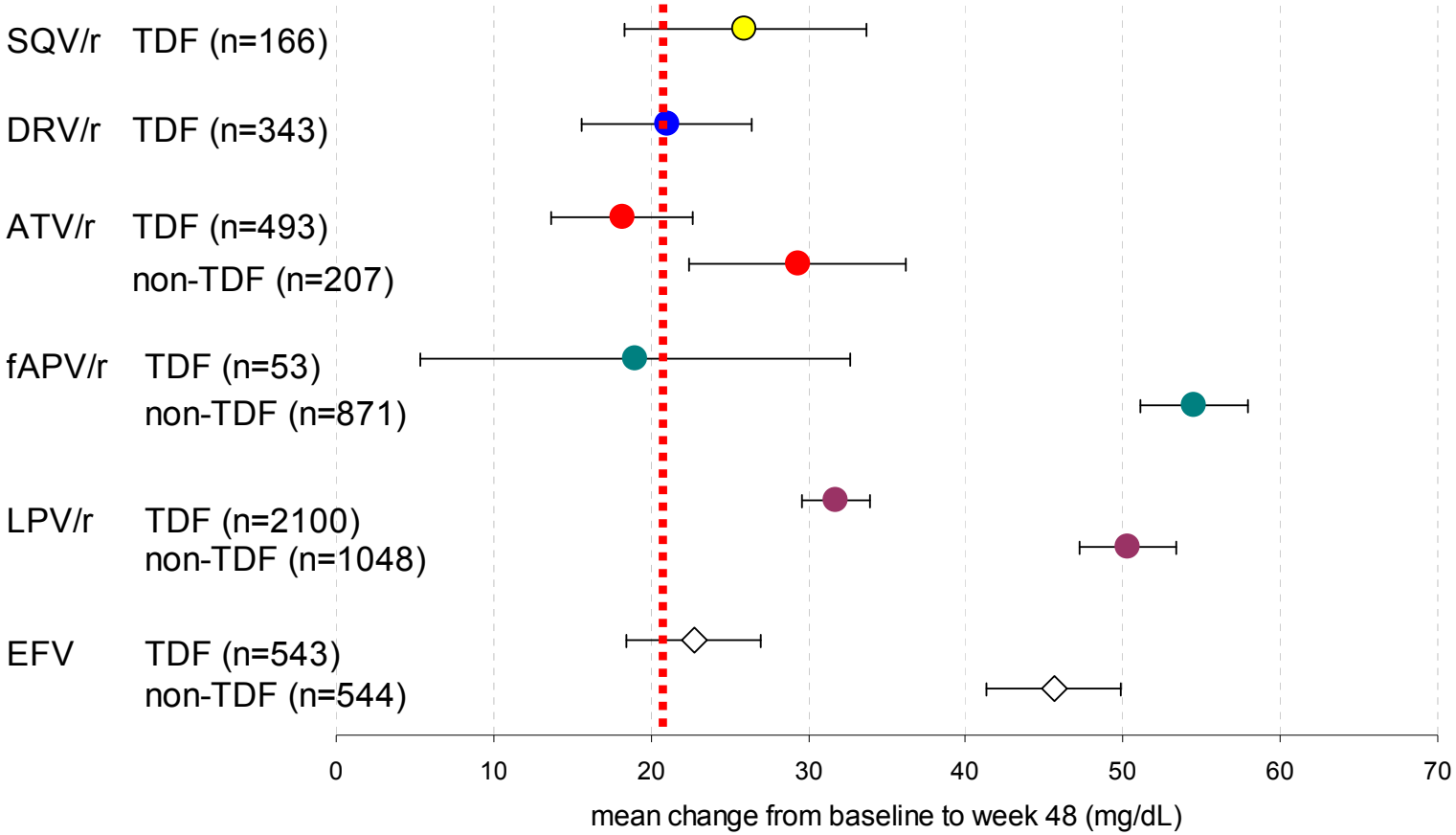
SWEET: Randomized Switch From ZDV/3TC to TDF/FTC

Patients with HIV-1 RNA < 50 copies/mL on most recent 2 consecutive tests and < 400 copies/mL for ≥ 3 months, and on stable EFV + ZDV/3TC for ≥ 3 months (n = 117 in each am)



Moyle G, et al. IAS 2007. Abstract WEPEB028.

Meta-analysis: Total cholesterol



Use of ABC, d4T or ZDV (non-TDF) raised total cholesterol vs TDF with any third line agent

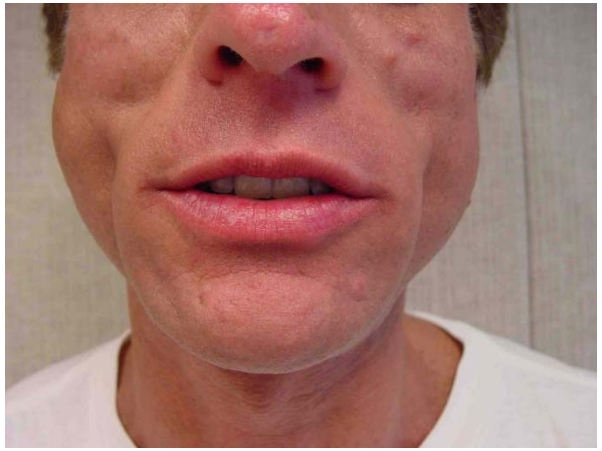
Hill & Sawyer. HIV Clin Trials. In press.

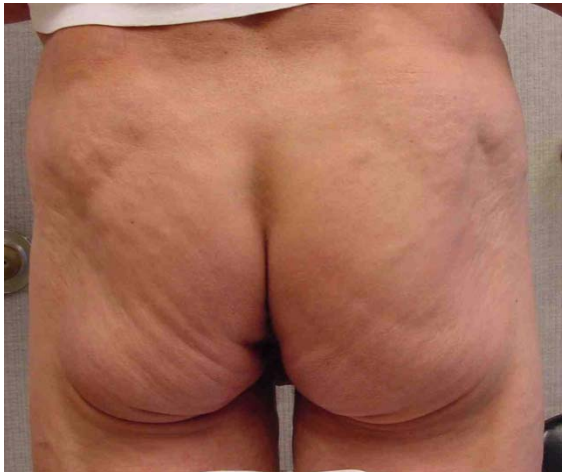
Mitochondrial toxicity

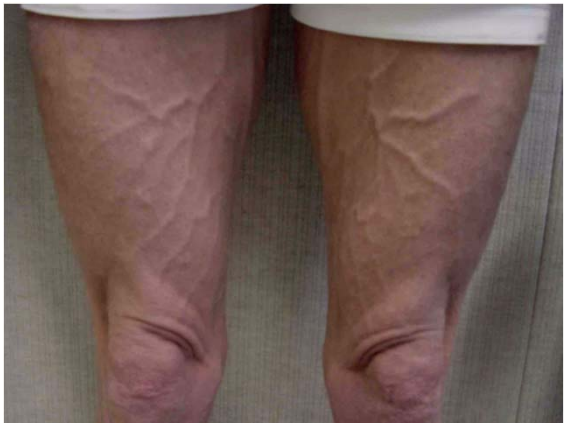
- NRTIs inhibit mitochondrial DNA (mtDNA) polymerase γ
- Most common in ddI and thymidine analogs (d4T>AZT)
- Least likely with TDF, ABC, 3TC, FTC
- Potentially associated with toxicities:
  - Lactic acidosis
  - Pancreatitis
  - Peripheral neuropathy
  - Lipoatrophy
  - Myopathy

Walker UA. HIV Ther. 2003;8(2):32-5.

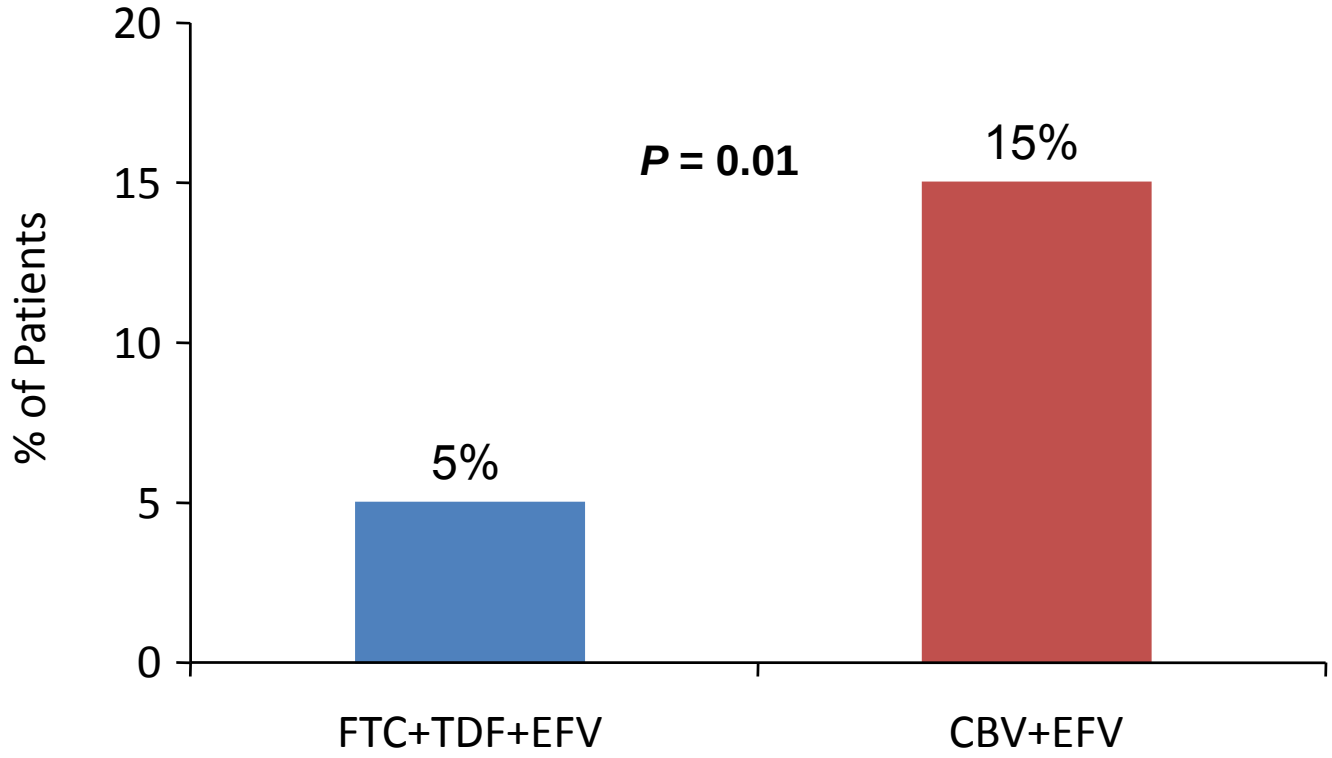
Lipoatrophy







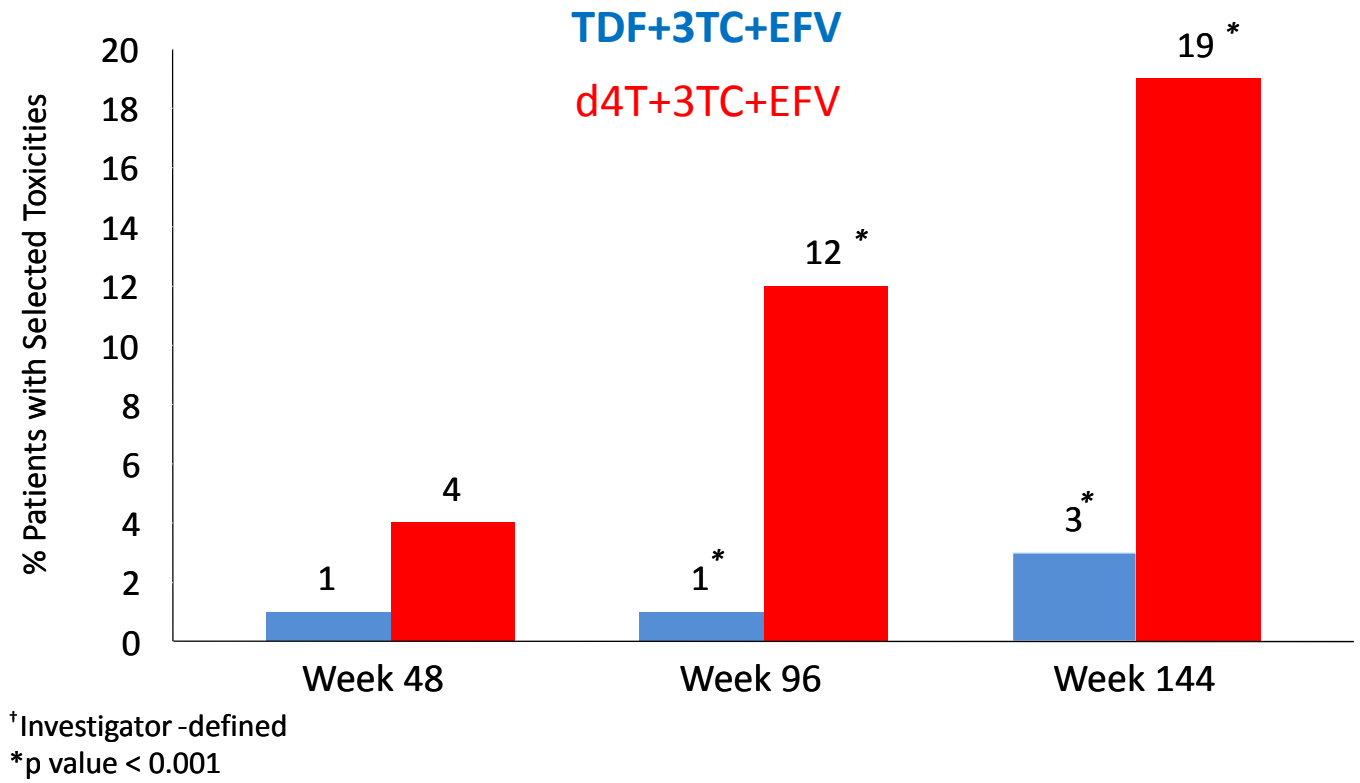
Study 934: % with Lipoatrophy (>20% Loss of Limb Fat W96 to W144)



Number with DXA at weeks 96 and 144	
n =	142
	122

Data on file, Gilead Sciences.

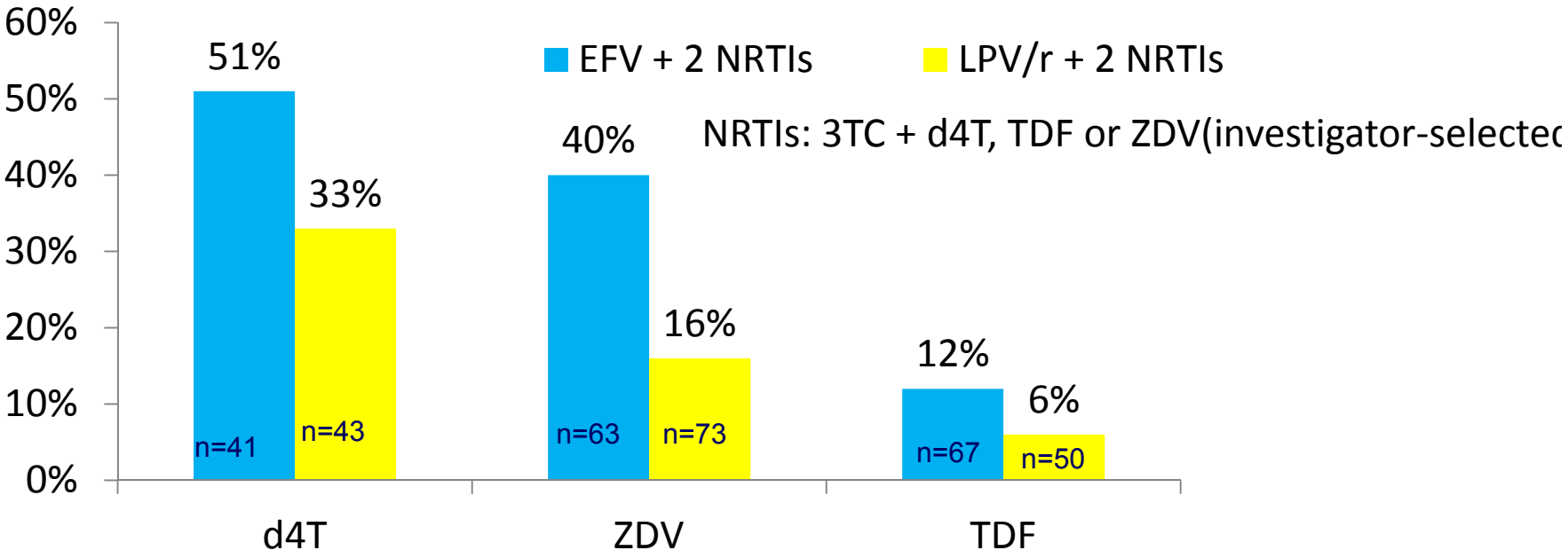
Study 903 – Week 144
Patients (%) with Lipodystrophy†



†Investigator -defined
*p value < 0.001

Gallant et al. JAMA 2004

ACTG 5142: Lipoatrophy at Week 96 Within NRTI Subgroups



Logistic Regression Week 96 Lipoatrophy

Model includes randomized arm and NRTI, for NRTI-containing regimens only

Factor	OR (95% CI)	*P* Value
EFV vs LPV/r	2.7 (1.5–4.6)	<0.001
d4T vs ZDV	1.9 (1.1–3.5)	0.029
TDF vs ZDV	0.24 (0.12–0.5)	<0.001

Haubrich R et al. *AIDS* 2009, (23) 1109-1128

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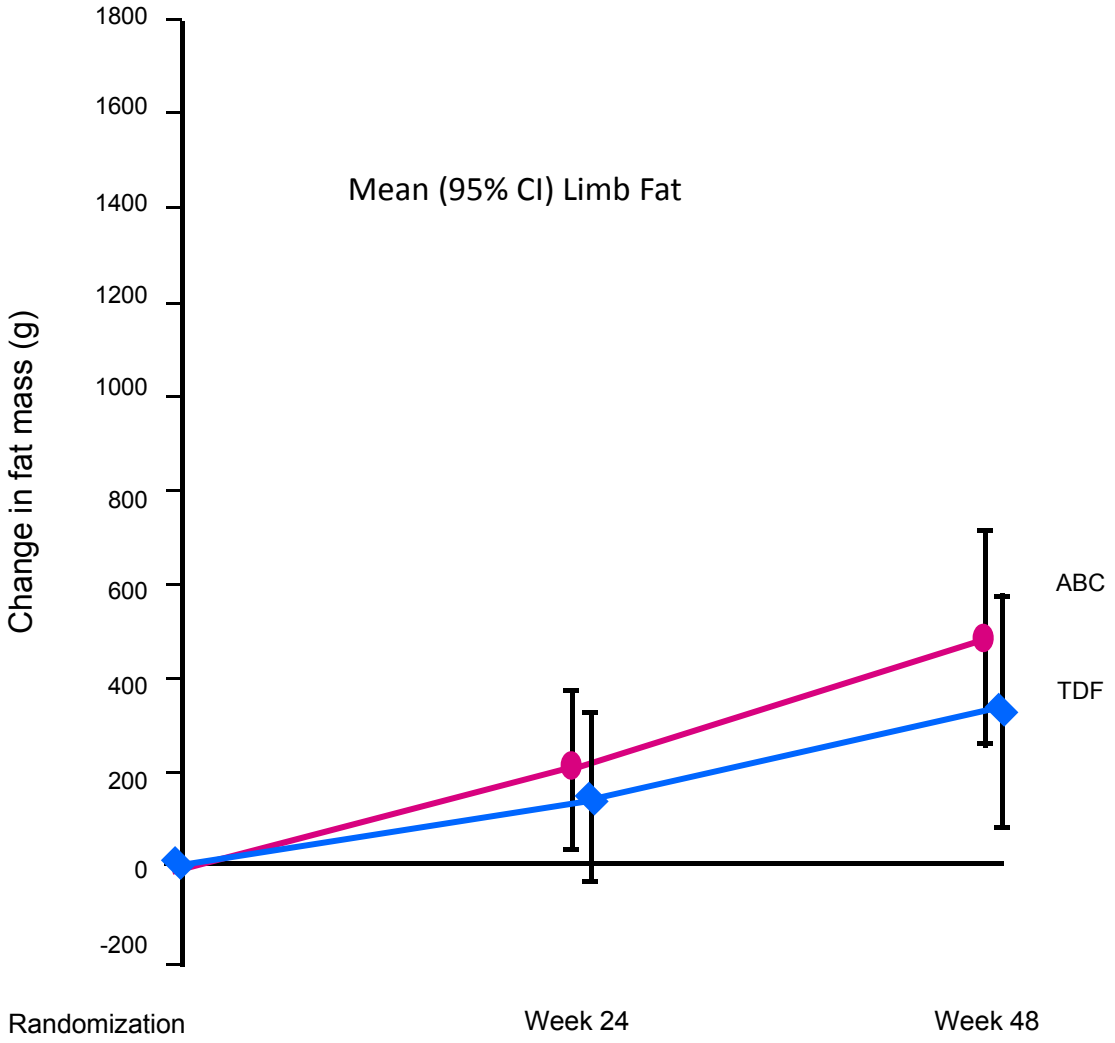
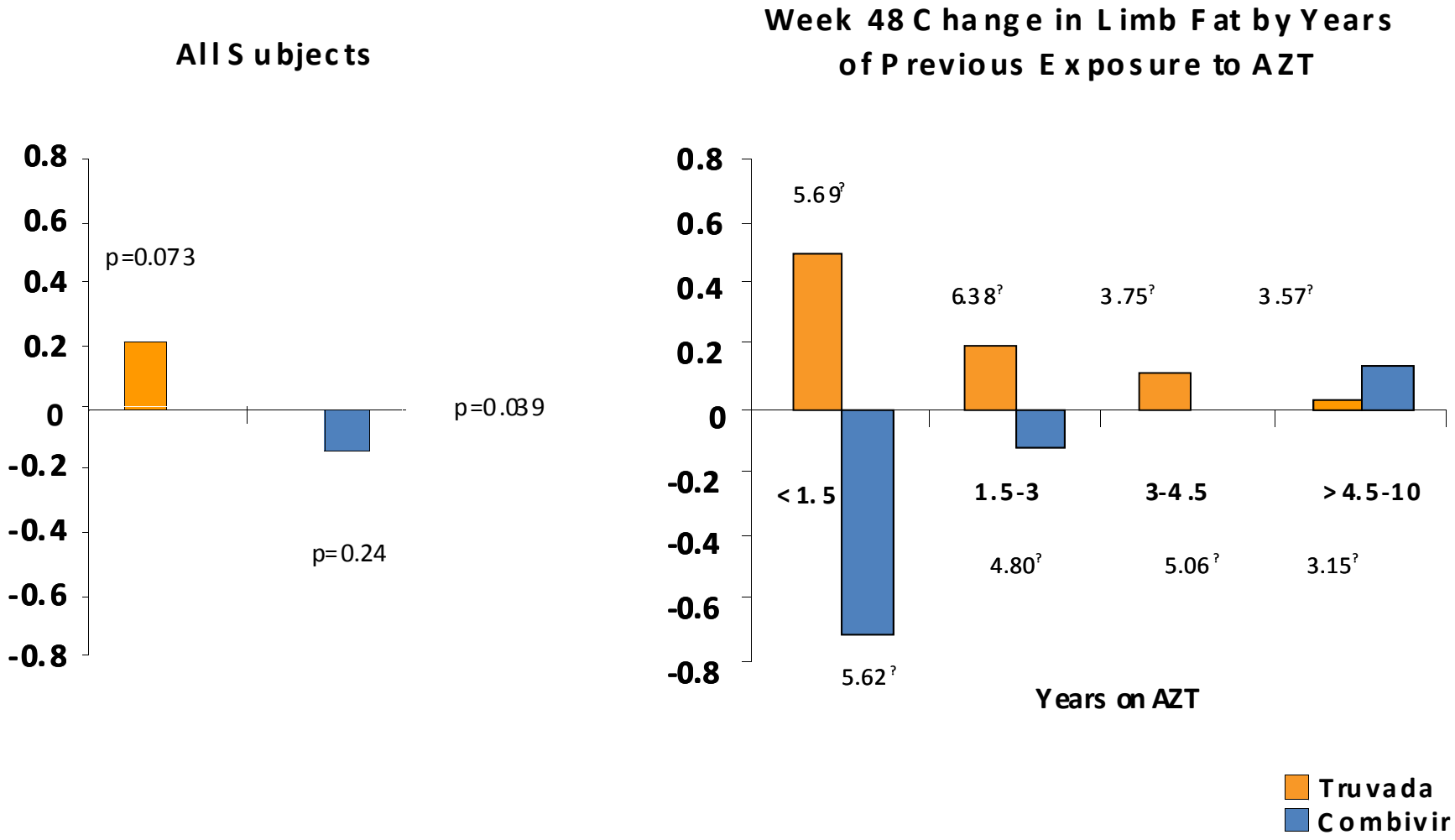
RAVE: d4T or AZT to ABC or TDF

- Methods
  - Randomized, open-label, N=105 HIV+ patients with moderate to severe lipoatrophy
  - Switched from thymidine to ABC or TDF
  - DEXA and CT scans at W0/24/48
- Result
  - Gradual, incomplete reversal
- Limitation
  - Study not powered to detect a difference between the ABC & TDF arms



Moyle G et al. *AIDS.* 2006;16:2043-2050.

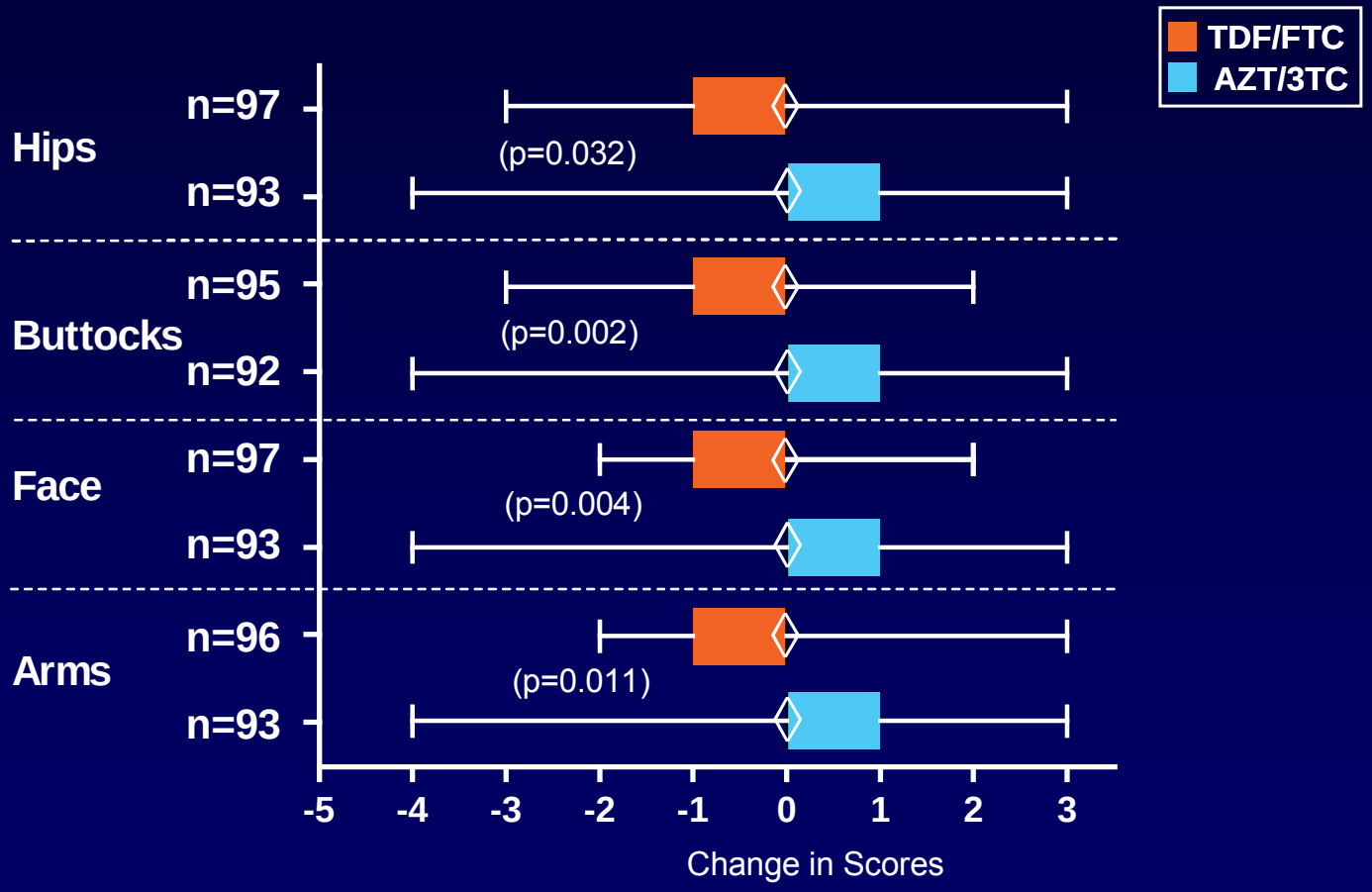
SWEET: Previous AZT & Change in Limb Fat at Week 48*



* DEXA sub-study treated analysis set and sub-set of Whole Body Fat composition

† Median Baseline Limb Fat with Week 48 data

SWEET - Concerns about the Shape of Hips, Buttocks, Face and Arms. Change from Baseline to Week 48



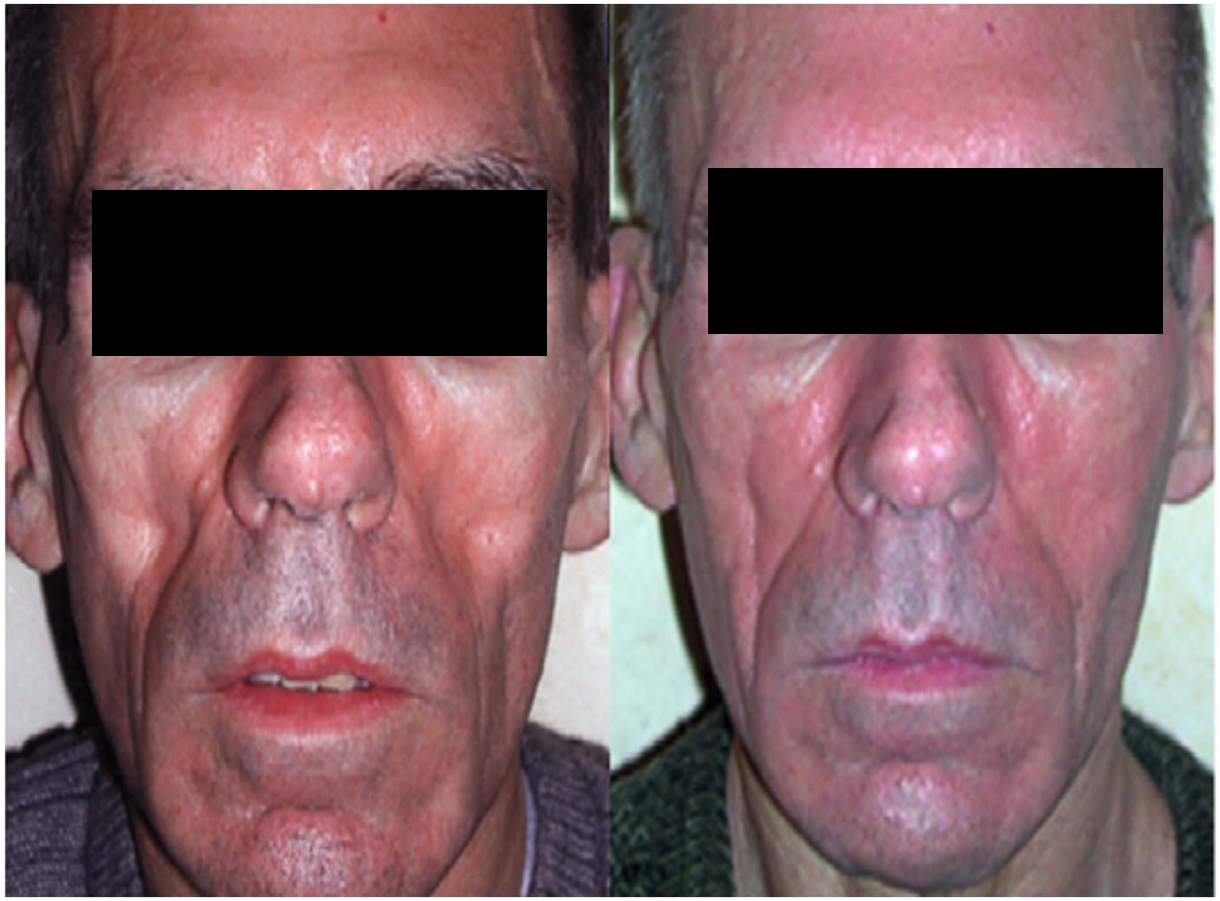
Horne R et al. SWEET Study. EACS 2007

Switch: Swiss Cohort

- Virologic suppression <50 at 12 months
  - 87.9% in individuals who switched
  - 89.2% in those who did not modify treatment
  - *P* = 0.90

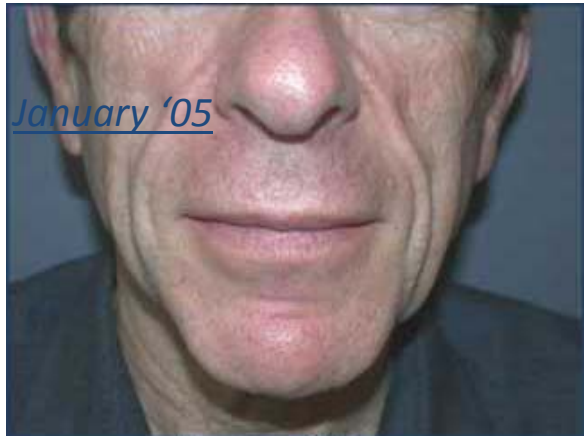
Elzi L et al Arch Intern Med. 2010;170:57-65.

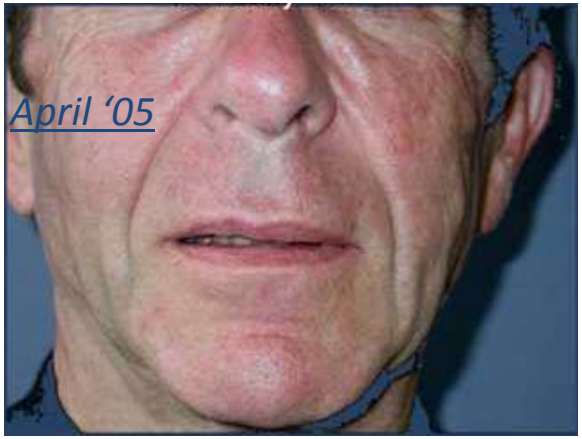
Cosmetic treatments

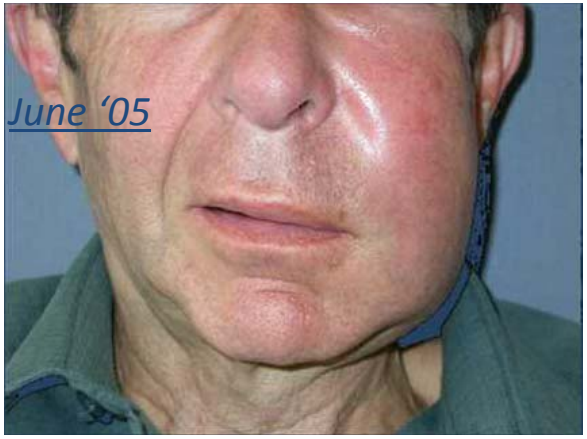


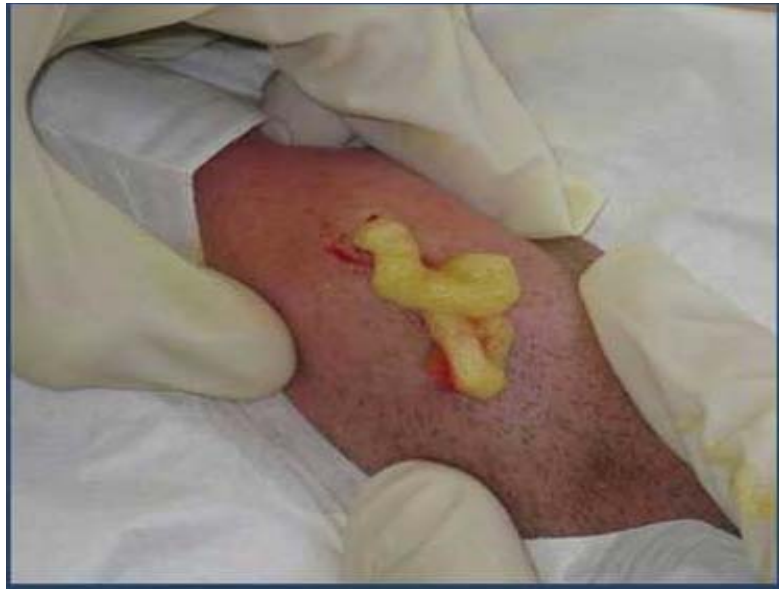
1. About Sculptra: http://www.sculptra.com/US/aboutsculptra/WhatItDoes.jsp. 2. Burgess CM et al. J Am Acad Dermatol 2005;52:233-239.

Complications of Plastic Surgery









Jones D et al. Dermatol Surg. 2007, in press.

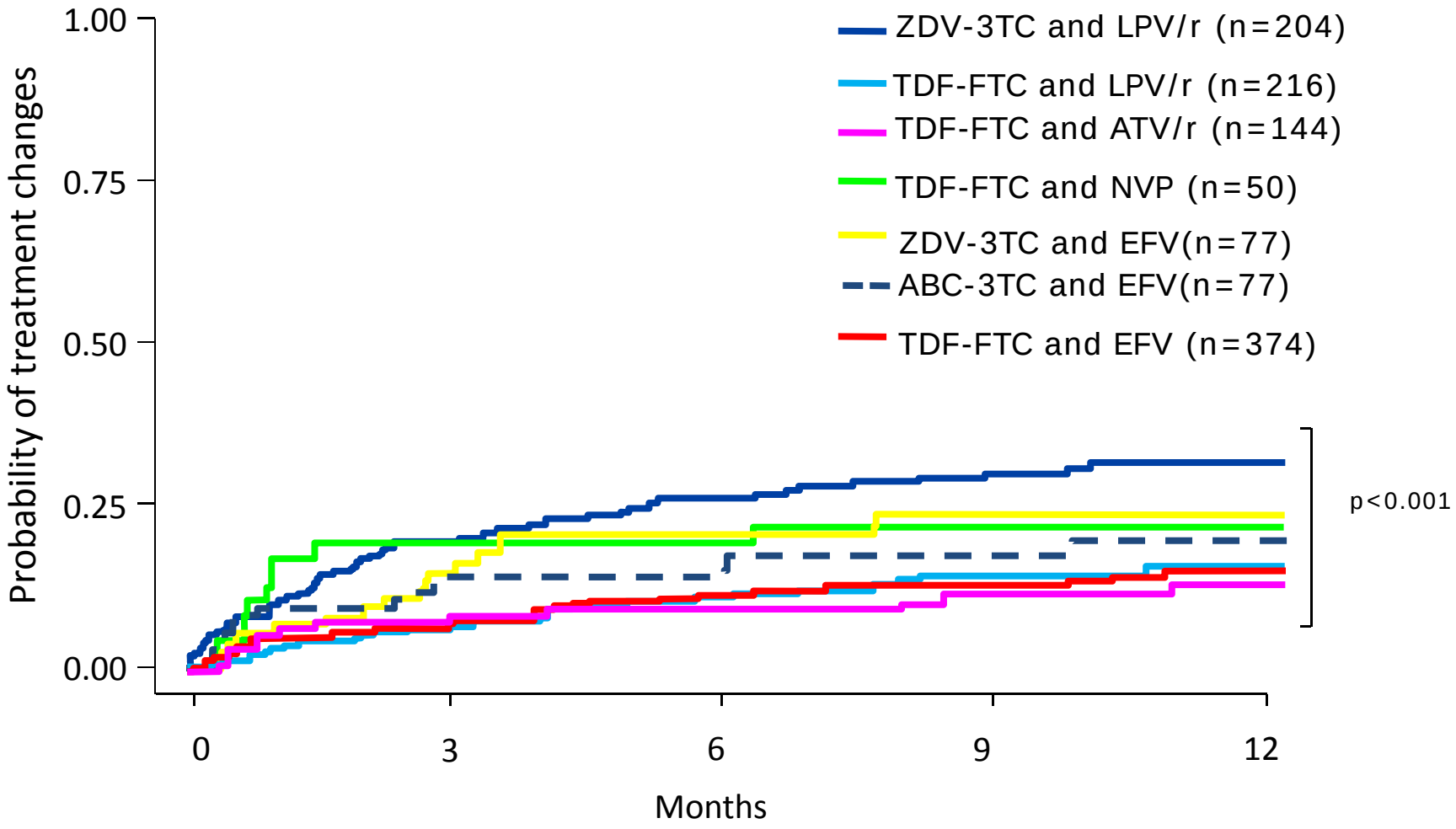
Swiss Cohort: Reasons for toxicity switch

- GI 28.9%
- HSR 18.3%
- CNS 17.3%
- Hepatic 11.5%

AZT/3TC significantly associated (p=0.006)

Elzi L et al Arch Intern Med. 2010;170:57-65.

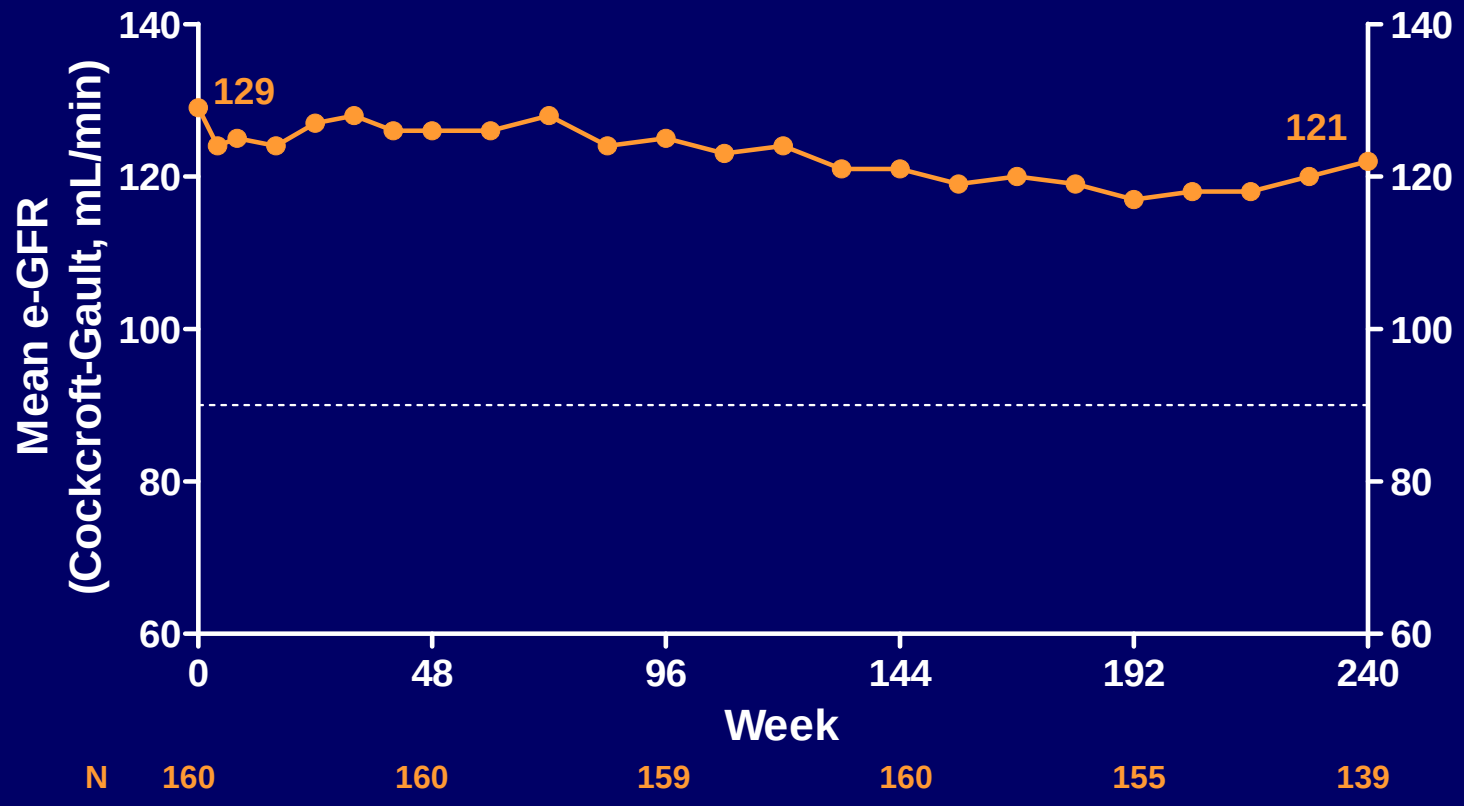
Toxicity modification 1st year



Adapted from Elzi L, et al. Arch Intern Med 2010;170:57–65

GS 934: 5-Year Renal Function

Mean eGFR Change from Baseline



No patient discontinued study drugs due to renal adverse event

Lazzarin A, et al. HIV-10 2010; Glasgow, UK. Poster #P6

The Swiss HIV Cohort Study

TDF & PI use are associated with an increased prevalence of proximal renal tubular dysfunction

Rates of PRT & pathological FE-p differed significantly between treatment groups (p=0.006 for PRT; p<0.001 for FE-p)

Logistical regression for proximal tubulopathy (PRT) & a pathological fractional excretion of phosphate (path FE-p) according Tx				
Treatment	OR (95% CI) for PRT	p	OR (95% CI) for FE-p	p
TDF - / PI -	1	-	1	-
TDF + / PI -	2.9 (0.9 – 6.7)	0.06	2.4 (1.6 – 3.6)	<0.001
TDF - / PI +	2.0 (0.6 – 7.3)	0.3	1.3 (0.8 – 2.2)	0.3
TDF + / PI +	7.1 (2.5 – 19.8)	<0.001	3.4 (2.3 – 5.1)	<0.001

Fux C et al., CROI 2009, Poster 743;

What to measure?

- Creatinine and eGFR
- Tubular markers
  - Serum phosphate
  - FE of phosphate
  - Urine protein
  - Urine glucose
  - Urine phosphate
  - Uric acid
  - Other proteins…

BMD Loss With ART Initiation
A Consistent Finding; TDF > others

Author, y	N	Duration (wks)	ART-type	Study outcomes
Gallant, 2004[1]	602	144	TDF vs. d4T	Spine : TDF: -2.2%; d4T: -1.0% Hip : TDF: -2.8%; d4T: -2.4%
Tebas, 2007[2]	157	96	NFV vs. EFV	2.5% decrease in total BMD; NFV=EFV
Bonnet, 2007[3]	74	36	PI vs. non-PI	0.8% decrease in lumbar BMD.
Brown, 2009[4]	106	96	ZDV/3TC + LPV/RTV vs. EFV	2.5% loss in total BMD; LPV/r=EFV
Duvivier, 2009[5]	71	48	PI vs. Non-PI	Spine: -4.1% , Hip: -2.8%
van Vonderen, 2009[6]	50	104	ZDV/3TC/LPV/RTV vs. NVP/LPV/RTV	Fem Neck: -6.3% v -2.3% Spine: -5.1% v -2.6%
Shellbrink, 2009[7]	385	48	TDF vs. ABC with EFV	Hip: ABC: -1.9%; TDF: -3.6% Spine: ABC: -1.6%; TDF: -2.4%

Gallant JE, et al. JAMA. 2004;292:191-201; 2 Tebas P, et al. CROI 2007. Abstract 837.
3.Bonnet E, et al. Antivir Ther. 2007. 12:L17..4.Brown TT, et al. J Acquir Immune Defic Syndr. 2009;51:554-561.
5. Duvivier C, et al. AIDS. 2009;23:817-824; 6. van Vonderen MG, et al. AIDS. 2009 ;23:1367-1376; 7. Shellbrink H, et al. EACS 2009. Abstract PS10/1.

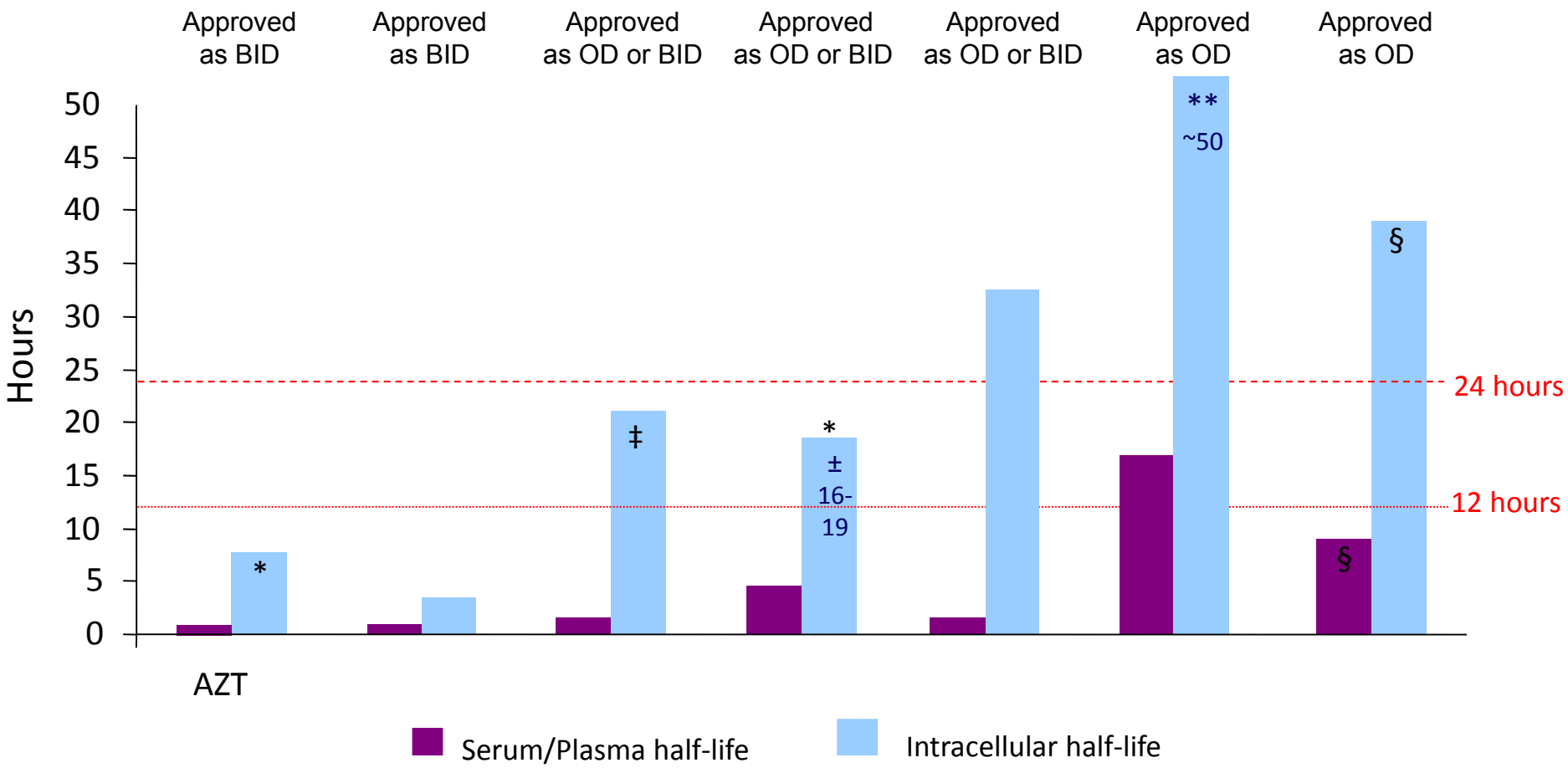
Fracture Risk: HOPS Cohort (IAS 2011)

- Traditional risk factors important
- Whole study period (1998-2009) – no impact of individual ART
- If analyse cART era only
  - TDF and LPV/r associated with increased fracture risk in different models
  - TDF: HR 1.08/1.12* (p=0.026/0.011*)
  - LPV/r: HR 1.13/1.09* (p=0.005/0.051*)

*after adjustment for exposure to other ARVs

PK & Resistance

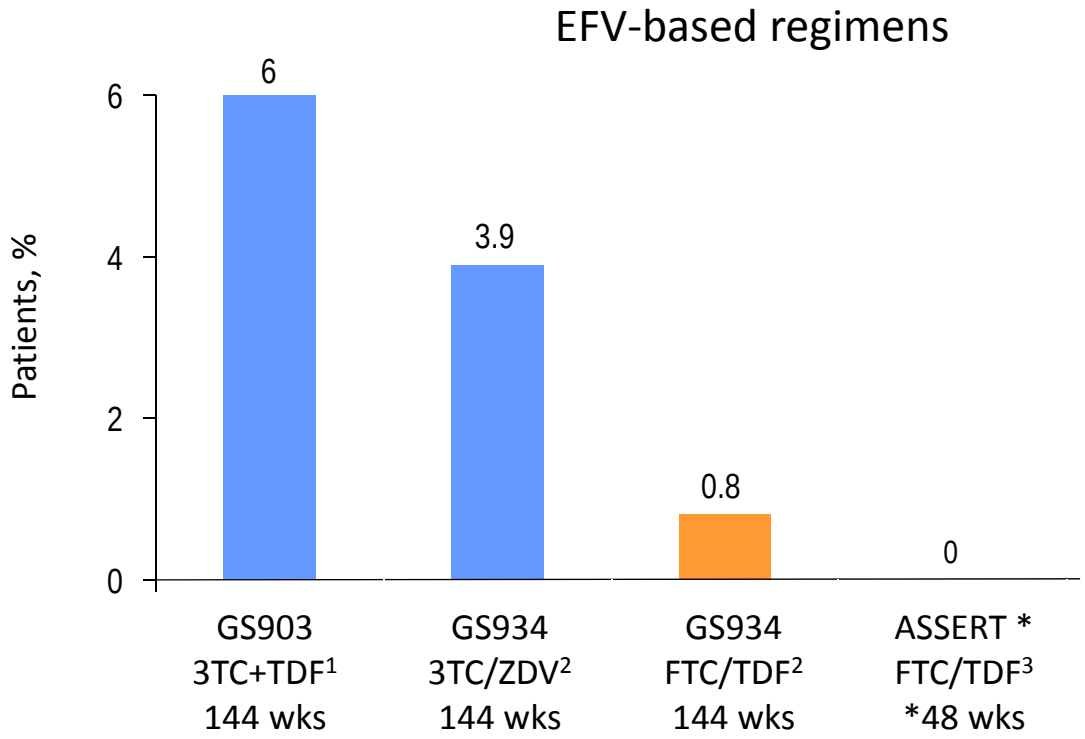
Cross Study Comparison Pharmacokinetics of NRTIs†



†Data from: Centers for Disease Control and Prevention. *MMWR Recomm Rep.* 2002;51(RR-7):1-64, unless otherwise noted.
*Anderson et al. AIDS 2003; 17(15):2159-2168. ‡Kivexa SmPC. ± Emtriva SmPC. **Viread SmPC. §Wang et al. IAC 2002 #4546.

Cross Study Comparison

Rates of M184V/I in Recent Trials



The components of Atripla (EFV/FTC/TDF) had lower rates of M184V/I compared to other EFV-based regimens

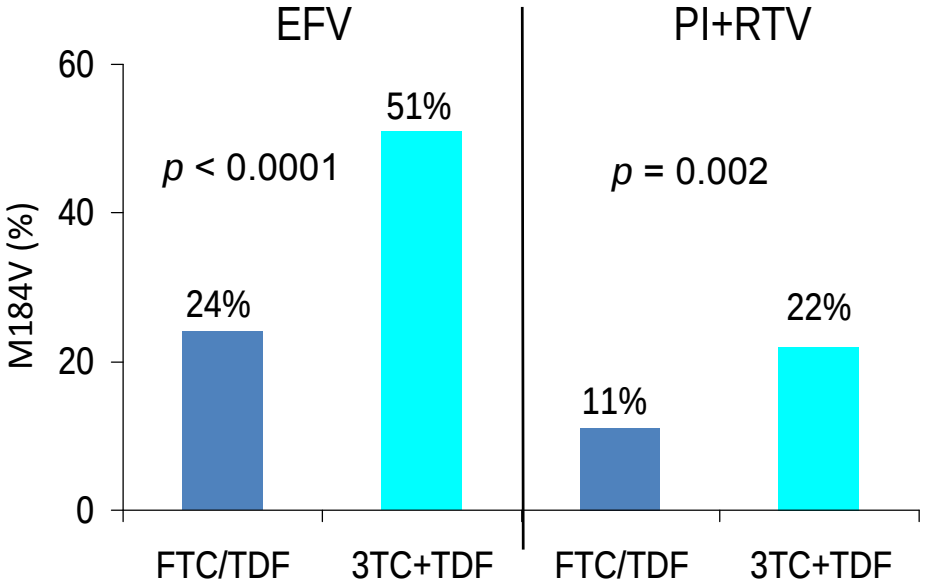
1. Margot NA, et al. HIV Medicine 2006;7:442-450
2. Arribas JR, et al. IAS 2007. Sydney, Australia. Poster #WEPEB029
3. Post FA, et al. J Acquir Immune Defic Syndr 2010 (May 12, 2010 e-pub)

French Clinic Cohort Database

Different Resistance Profiles: FTC vs. 3TC in TDF-containing Regimens

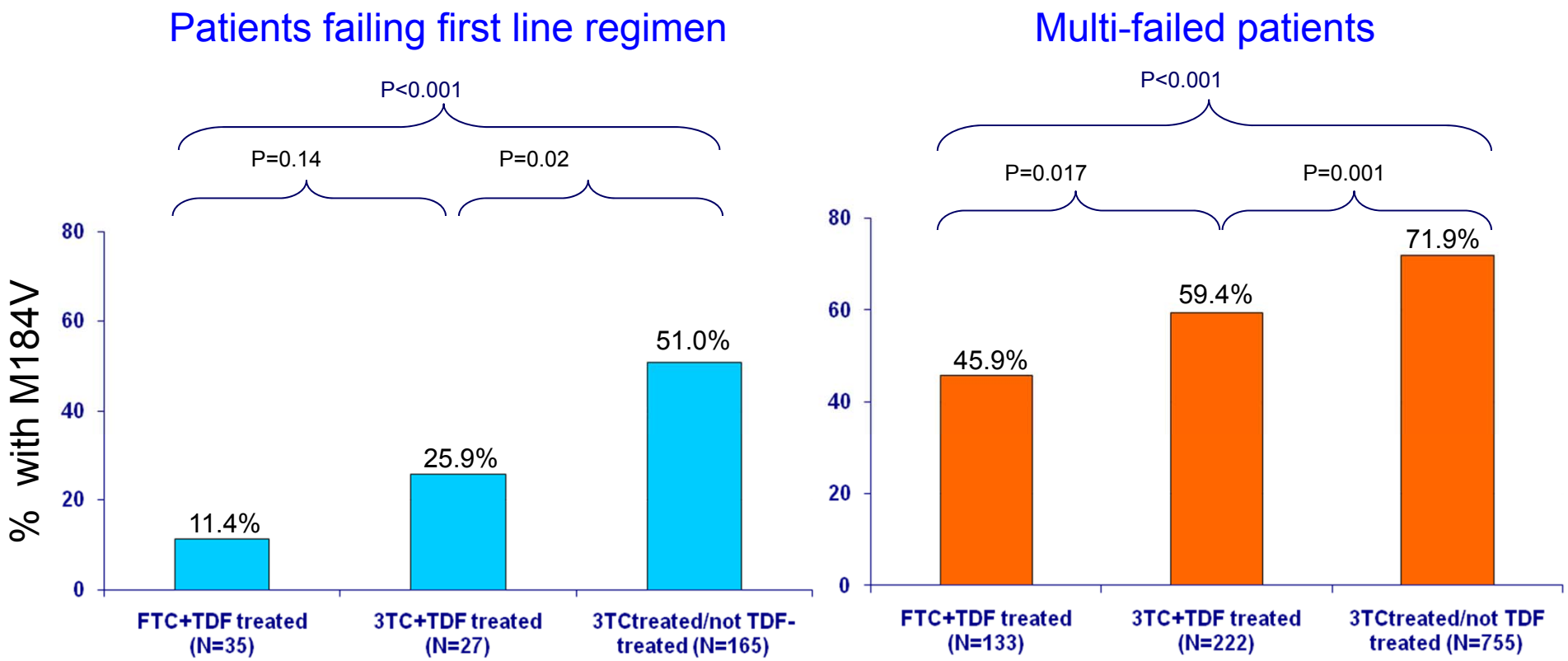
Genotypic resistance analysis after first virologic failure of
880 pts on FTC/TDF (n=535) or 3TC+TDF (n=345) with EFV or PI+RTV

- Statistically lower prevalence of M184V/I associated with FTC use
- No significant differences observed in the prevalence of NNRTI resistance or PI mutations for FTC vs. 3TC
- Possible explanations
  - Higher FTC potency
  - Longer plasma & intracellular half-life with FTC
  - Greater FTC use in fixed dose combinations



Marcelin AG, et al. CROI 2011. Boston. #617

Frequency of M184V



Statistically significant differences were assessed by Fisher exact test.

Overall prevalence of M184V: 38.7% in FTC+TDF-treated patients

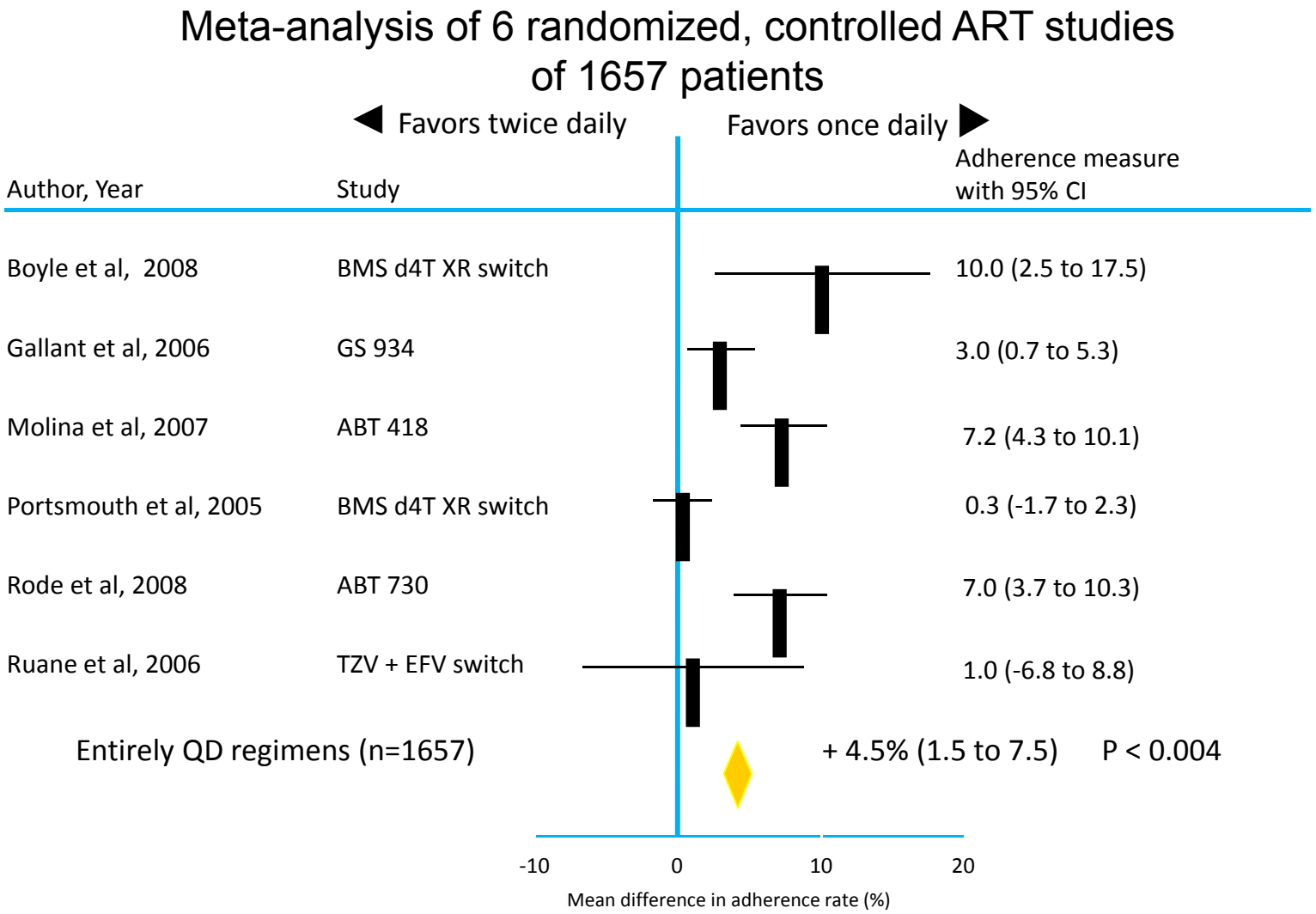
55.8% in 3TC+TDF-treated patients

68.0% in 3TC

Forgiveness & Adherence

Parienti Meta-analysis

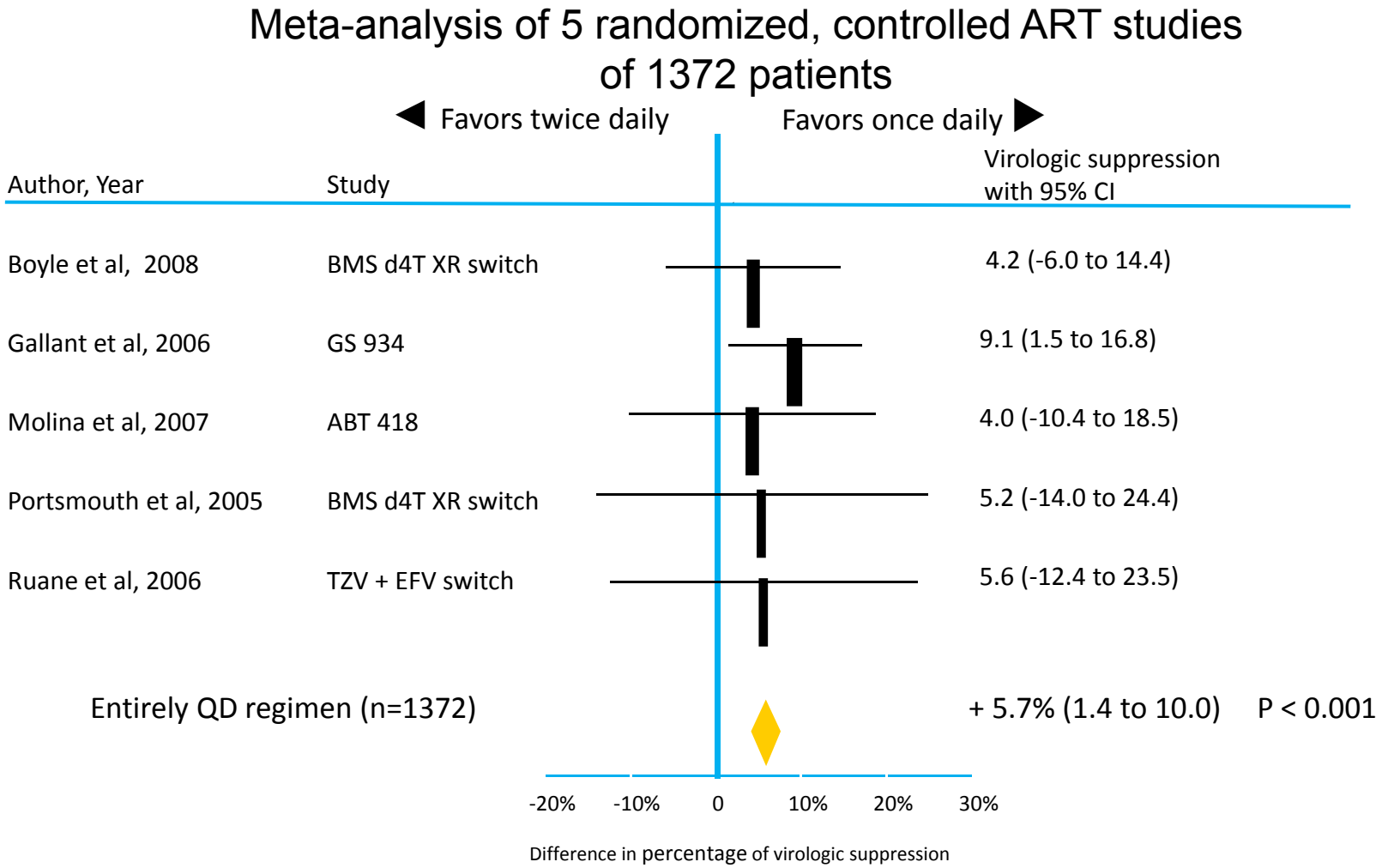
Better Adherence with QD ART



Adapted from Parienti JJ, et al. CID 2009;48:484-8

Parienti Meta-analysis

Better Viral Suppression with QD ART



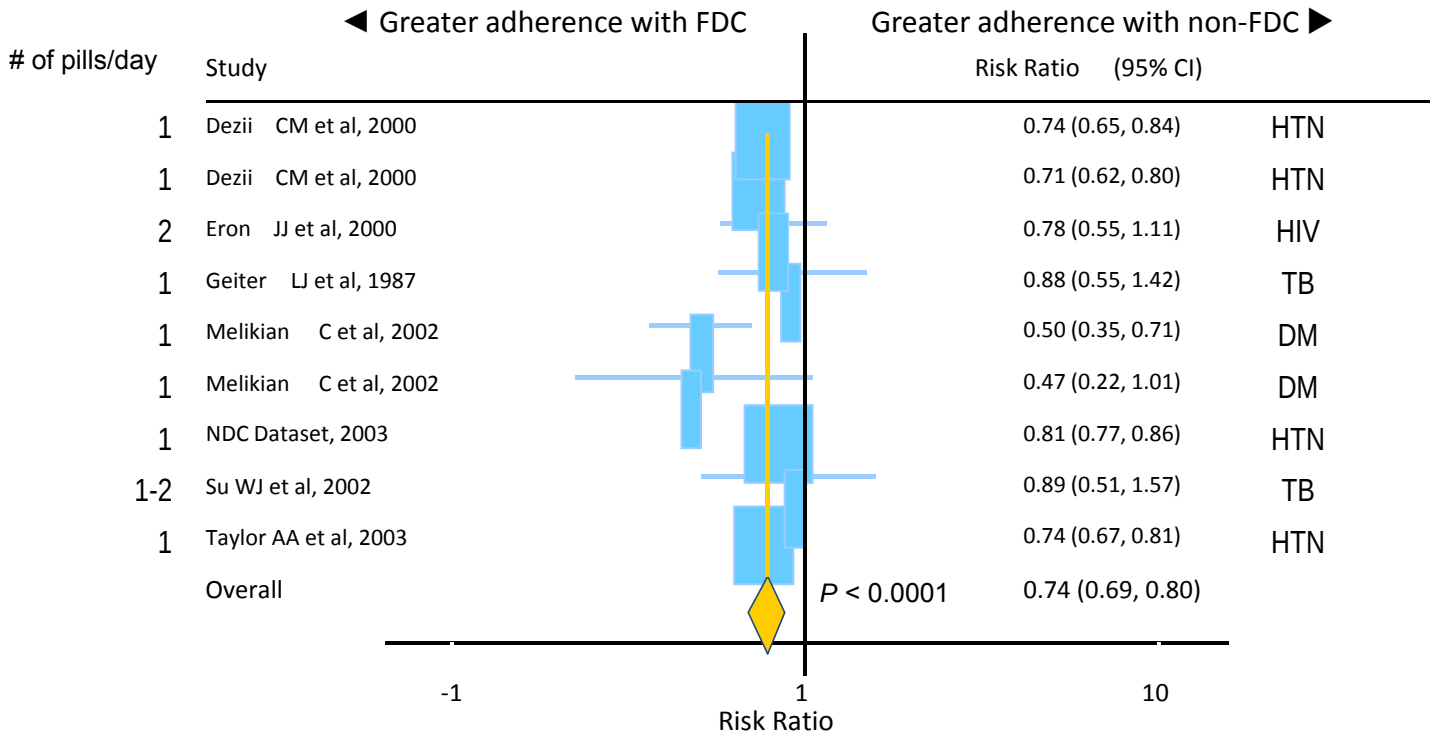
Adapted from Parienti JJ, et al. CID 2009;48:484-8

Bangalore Meta-analysis

Less Risk of Non-adherence with FDCs

Meta-analysis of 9 clinical trials in 4 therapeutic areas (TB, HTN, HIV, DM)
11,925 FDC patients and 8317 non-FDC patients

Effect of FDCs versus non-FDC on risk of non-adherence



FDC regimens reduce risk of non-adherence by ~25% compare to non-FDC

Bangalore S, et al. Am J Med 2007;120:713-9

GS 934: Atripla and Components

Adherence Analysis of 3 QD Regimens

	Year 1 and 2 (n=238)	Year 3 (n=162)	Year 4 and 5 (n=157)
Study Drugs	TDF + FTC + EFV	FTC / TDF + EFV	FTC / TDF / EFV
Daily Pill Burden	3	2	1
Mean Adherence	95.6%	97.0%	97.9%

Analysis of adherence rates during the full 240 weeks of follow-up revealed adherence rates were statistically better when patients had smaller daily regimen pill burdens

Daily Pill Burden Comparison	P-Value
1 vs. 3	0.0005
2 vs. 3	0.0262
1 vs. 2	0.2304

FTC/TDF/EFV Single Tablet Regimen
was associated with the highest adherence

DeJesus E, et al. ICAAC 2009. Poster #H-1572

Cost-effectiveness

- Spanish analysis (cited in WHO guidelines) [1]
  - Truvada/EFV cost-saving vs Combivir/EFV over 24 months (including AE, laboratory monitoring etc)
- US analysis (first one on PubMed today!) [2]
  - Estimated lifetime costs of TDF/FTC, ABC/3TC and AZT/3TC
  - TDF/FTC predicted to be more effective and cost-saving compared with ABC/3TC and AZT/3TC in treatment-naïve adults with HIV-1 in the US

[1] Sanchez de la Rosa R *et al*. Clin Ther. 2008 Feb;30(2):372-81. [2] Brogan AJ *et al*. Value Health. 2011 Jul-Aug;14(5):657-64.

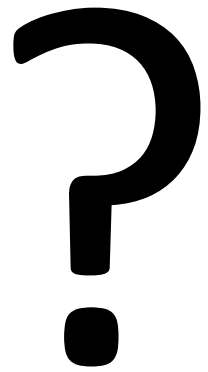
Role of AZT

- Huge use globally
- Some guidelines prefer for pregnancy:
  - DHHS
  - EACS
- CNS disease?
- Resistance

Summary

- AZT/3TC works
- TDF/FTC works
- For many reasons, if you have a choice, TDF/FTC is preferred

Thank you



lwaters@nhs.net