# TDF, TAF or nothing: the new era of generic antiretrovirals.

**Andrew Hill**
Pharmacology and Therapeutics, Liverpool University, UK

# How much could generic HIV drugs cost?

**UK prices per person-year: £ Sterling**

| Drug | List price (NHS) | -30% (Discount) | -80% (Generic) | Date |
|---|---|---|---|---|
| Tenofovir | £2880 | £2016 | **£403** | 2017 |
| FTC | £1956 | £1369 | **£274** | now (3TC) |
| Abacavir | £2136 | £1495 | **£300** | 2016 |
| 3TC | £1608 | £1126 | **£225** | now |
| Efavirenz | £2400 | £1680 | **£336** | now |
| Nevirapine | £2040 | £1428 | **£286** | now |
| Rilpivirine | £2400 | £1680 | - | 2023 |
| Darunavir/r | £3600 | £2520 | **£504** | 2017-9 |
| Atazanavir/r | £3636 | £2545 | **£509** | 2017 |
| Raltegravir | £5652 | £3956 | - | 2025 |

**Sources: BNF 2014, Clinton Foundation 2013, MSF 2014**

# Is there an efficacy benefit to new treatments to justify their much higher price than individual generic pills?

**Single pill**
**7000 – 9000 Euros/year***

TDF/FTC/EFV

TDF/FTC/RPV

TDF/FTC/ELV/c

ABC/3TC/DTG

TAF/FTC/ELV/c

**Three pills**
**<1000 Euros/year**

Generic ABC or TDF

Generic 3TC

Generic EFV or PI/r

***Prices include 30% discount from NHS list price (BNF)**
**Sources: BNF 2014, generic company prices**

# Patent Expiry dates: 2015-2029

**11 years (2015-2026) when many drugs are available as individual generics, but co-formulated versions are still on patent**

**2015:** ZDV, 3TC, NVP, EFV, RTV – already generic

**2016:** ABC, LPV/r

**2017:** TDF, ATV/r, DRV/r

---

**2019:** ABC/3TC (Kivexa)

**2021:** ETR

**2024:** TDF/FTC (Truvada)

**2025:** Raltegravir

---

**2026:** TDF/3TC/EFV (Atripla), TDF/FTC/RPV (Complera),

**2029:** ABC/3TC/DTG (Triumeq), TAF/FTC/ELV/c

Ref: Medecins Sans Frontieres 2014: Untangling the web of ARV price reductions

# 3TC patent: February 1990

Prime Minister
Margaret Thatcher

Number 1 Album
Phil Collins

# The original 20-year patent life of 3TC

**3TC basic patent-life:1990-2010**

1990 1995 2000 2005 2010 2015 2020 2025

# “Evergreen patenting” of 3TC

**3TC basic patent-life:1990-2010**
**1990-2010**

**ZDV/3TC**
**2013**

1990 1995 2000 2005 2010 2015 2020 2025






# “Evergreen patenting” of 3TC

**3TC basic patent-life:1990-2010**
**1990-2010**

**ZDV/3TC**
**2013**

**ABC/3TC**
**2019**

# “Evergreen patenting” of 3TC

**3TC basic patent-life:1990-2010**
**1990-2010**

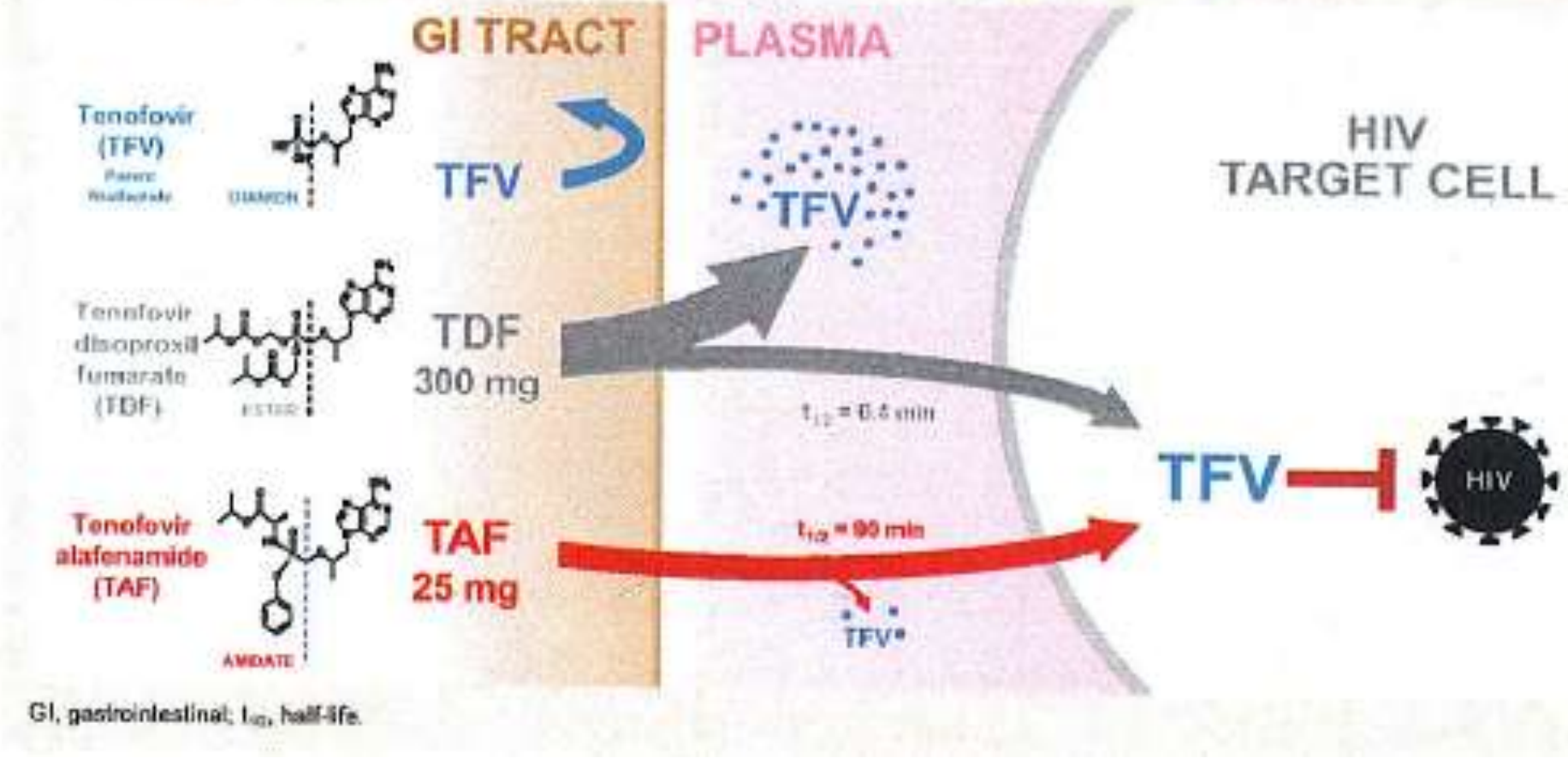
**ZDV/3TC**
**2013**

**ABC/3TC**
**2019**

**ABC/3TC/DTG**
**2029**

# Is TAF a true advance in the treatment of HIV, or just an “evergreen patent” on tenofovir?

# Mechanism of Action: TAF vs TDF[1-6]




GI, gastrointestinal; $t_{1/2}$, half-life.

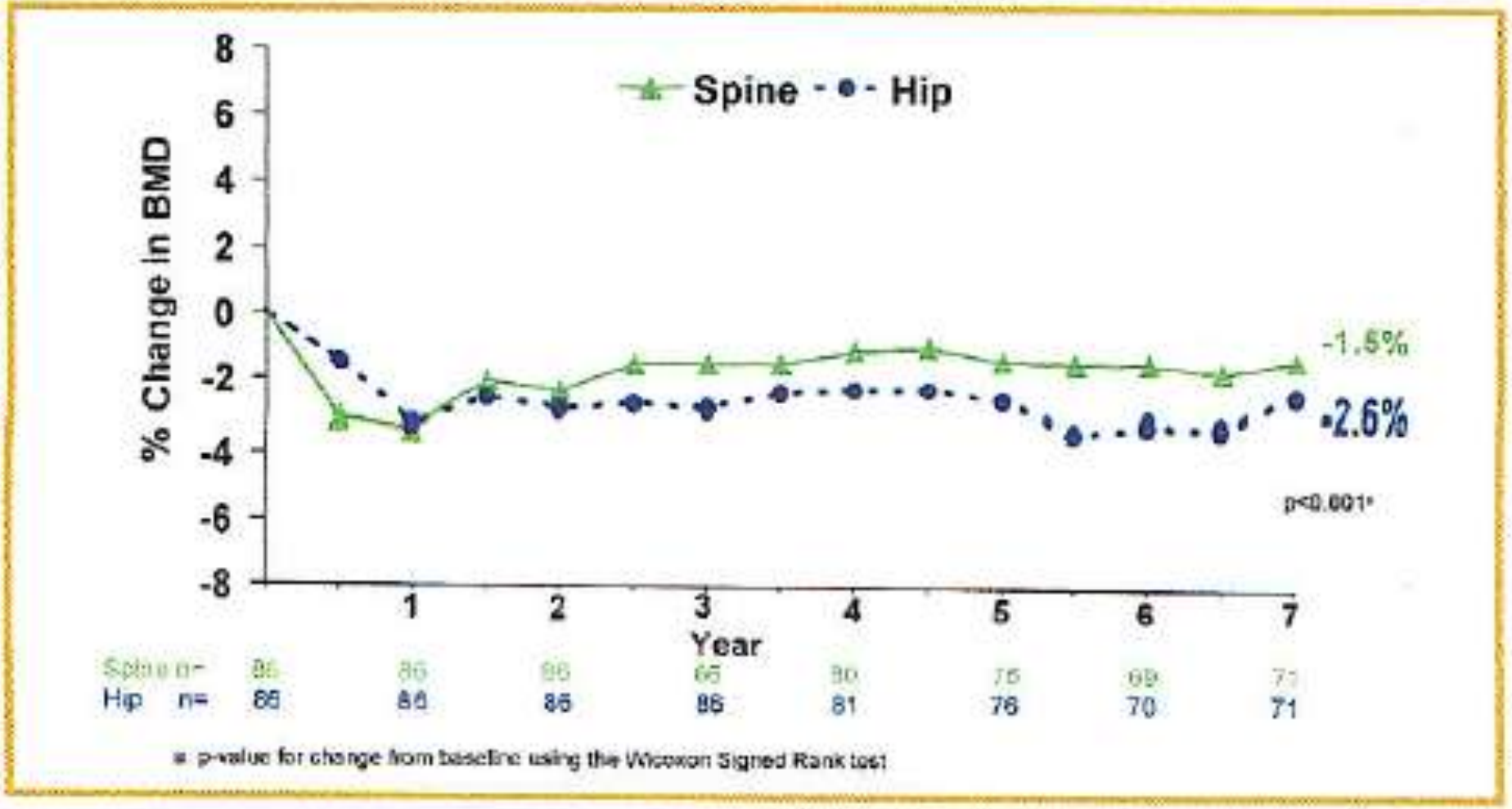
# The Safety and Efficacy of Tenofovir DF (TDF) in Combination with Lamivudine (3TC) and Efavirenz (EFV) in Antiretroviral-naïve Patients Through Seven Years

JVR Madruga[1], I Cassetti,[2] A Etzel,[3] J Suleiman,[4] Y Zhou,[5] AK Cheng,[5] and J Enejosa[5] for the 903E Study Team

[1]Centro de Referencia e Treinamento DST/AIDS, Sao Paulo, Brazil; [2]Fundacion Centro Estudios Infectologicos, Buenos Aires, Argentina; [3]Hospital Guilherme Álvaro, Santos, Brazil; [4]Brasilmed Assistência Médica e Pesquisas, São Paulo, Brazil; [5]Gilead Sciences, Inc., Foster City, CA, USA

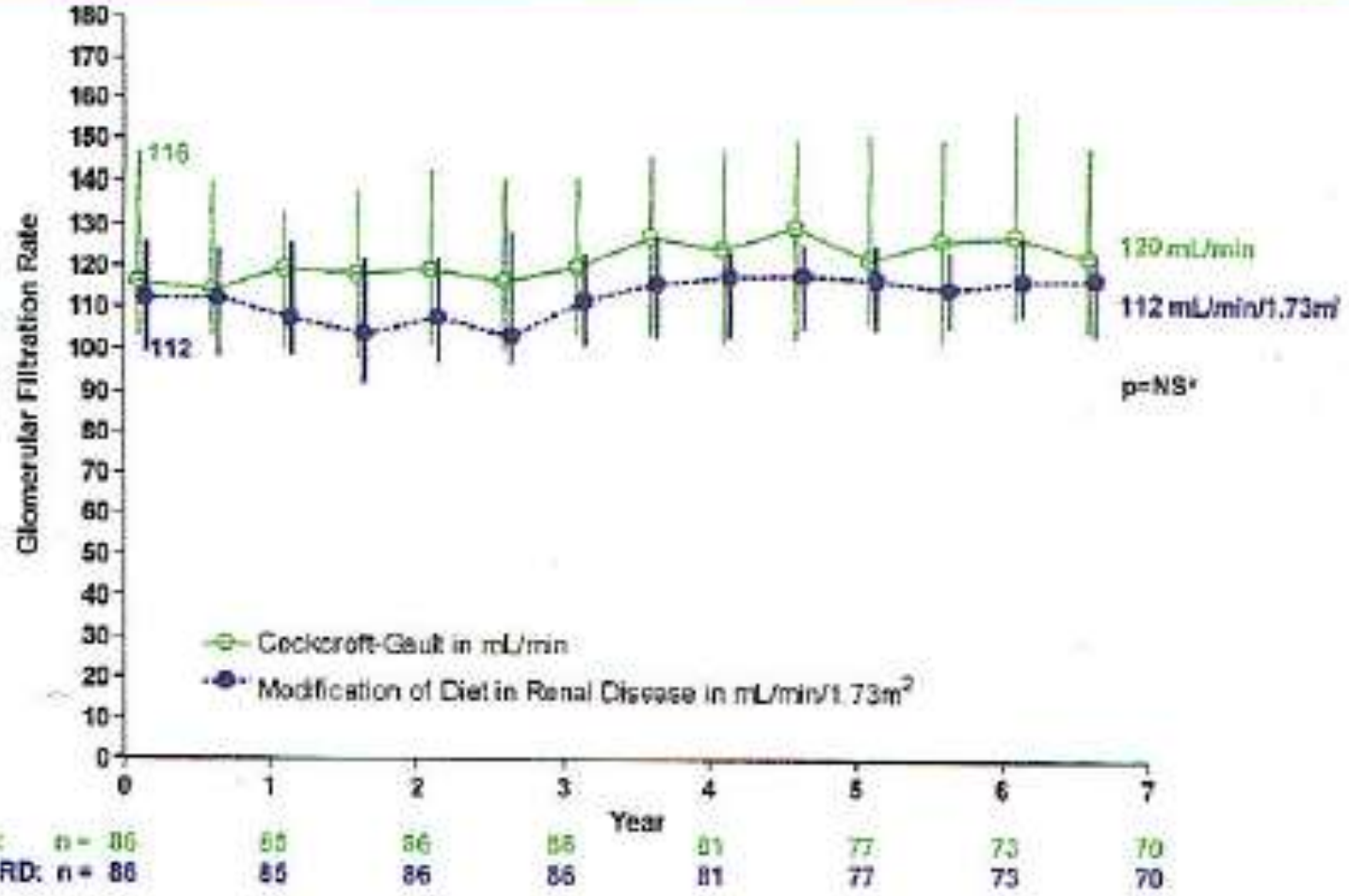

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: (650)574-3000
Fax: (650)578-9264

# Figure 6. Mean % Change from Baseline in Spine and Hip BMD Through 7 Years




* p-value for change from baseline using the Wilcoxon Signed Rank test

# Figure 5. Median Glomerular Filtration Rate (IQR) by Cockcroft-Gault (mL/min) and MDRD (mL/min/1.73m²) through 7 Years




a. p-value for change from baseline using the Wilcoxon Signed Rank test

Through 7 years of therapy in antiretroviral naïve patients, TDF+3TC+EFV demonstrated the following:

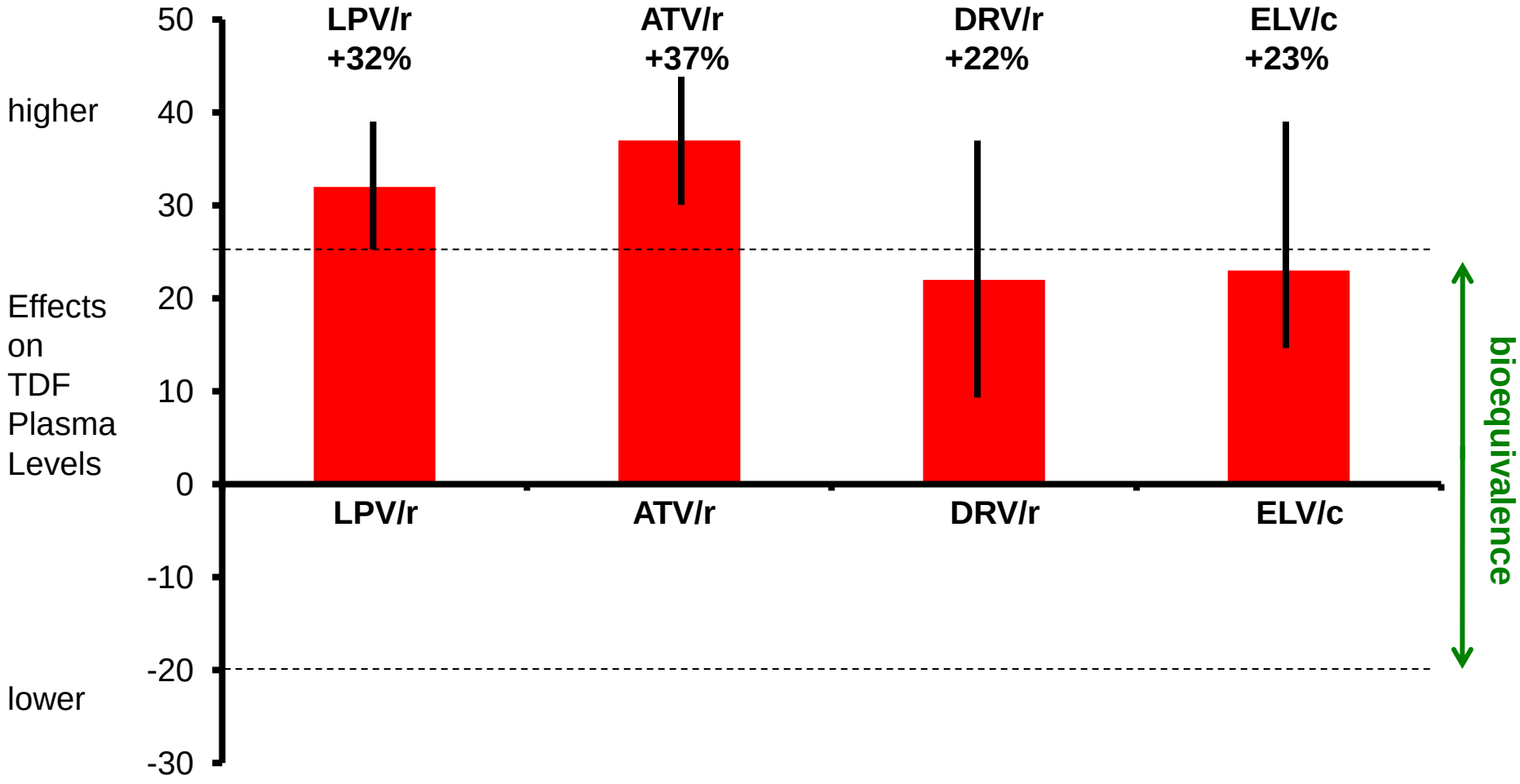
- Sustained, durable antiretroviral efficacy
- Continued CD4 cell count increases
- No discontinuations due to renal adverse events
- No evidence of clinically relevant bone effects
- Significant increases in limb fat from Years 2 through 7

**Tenofovir is boosted by ritonavir or cobicistat – this could worsen the safety profile, but the dose is not adjusted**

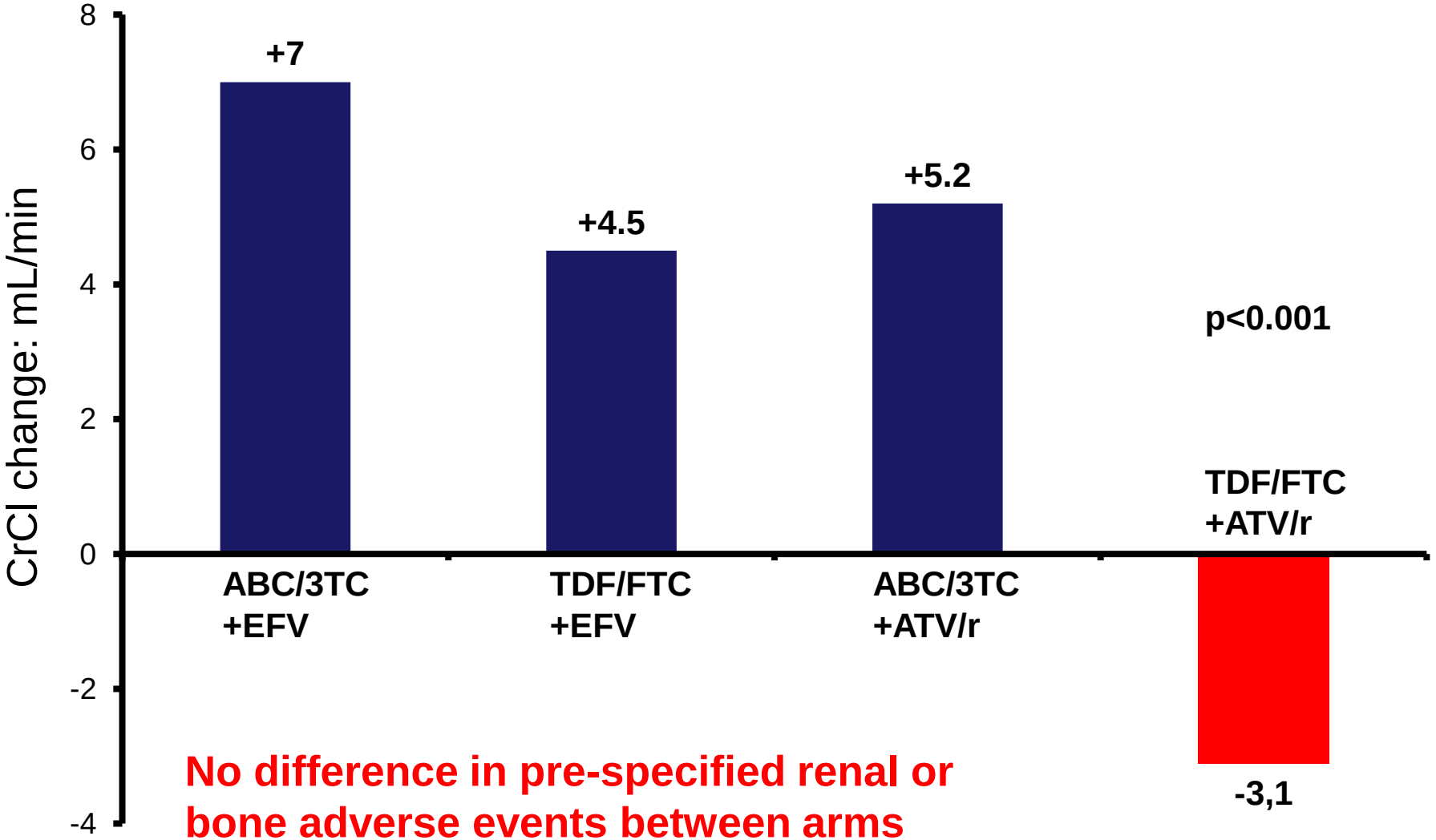
---

**By contrast, the dose of TAF is adjusted from 25mg to 10mg OD when given with ritonavir or cobicistat**

# Effects of PIs or Elvitegravir/c on Tenofovir AUC (95% C.I.)



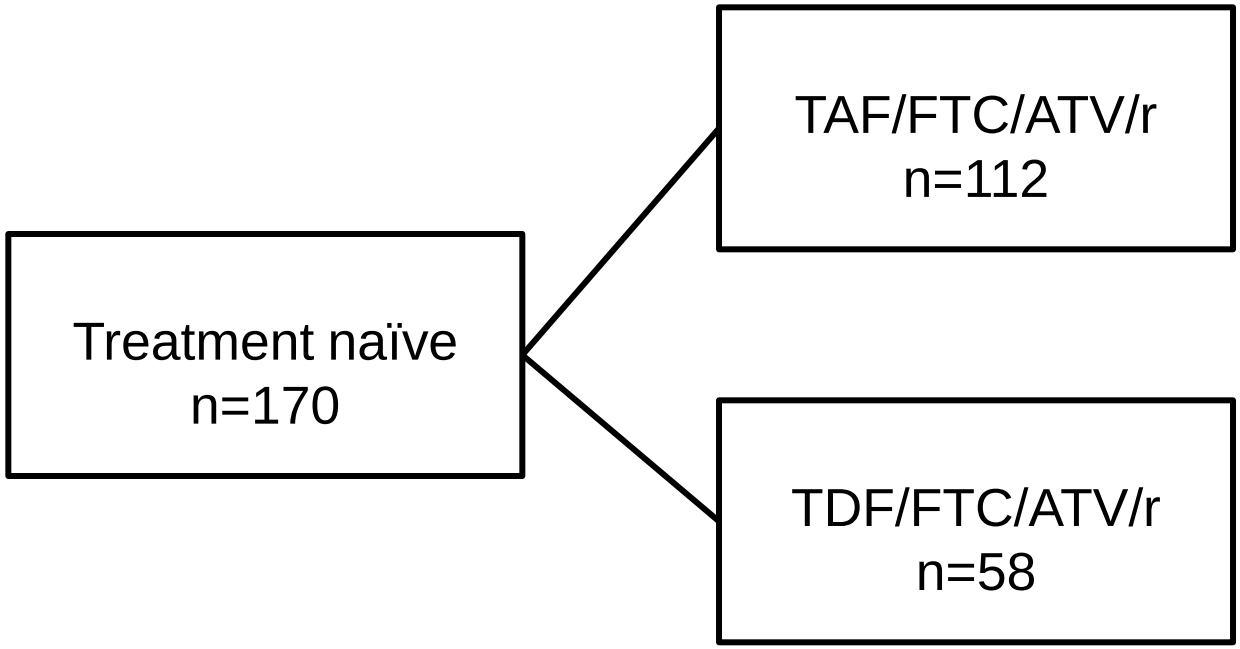
# ACTG 5202: change in creatinine clearance from baseline to Week 96




**No difference in pre-specified renal or bone adverse events between arms**

Sax et al. JID 2011, 204: 1191-1201

# TDF vs TAF – Phase 2 studies
# 105




Double-blinded, randomised
Primary endpoints: HIV RNA <50 copies/mL (FDA Snapshot)
Secondary endpoints: serum creatinine, bone density (hip/spine)

**Sax et al, JAIDS 2014, 67:52-58**

# Phase 2 ATV/r trial: TAF versus TDF Week 48 results

| Treatment arm | TAF/FTC/ATV/r | TDF/FTC/ATV/r |
|---|---|---|
| HIV RNA <50 | 87% | 90% |
| Grade 3-4 Clinical AEs | 10% | 5% |
| Nausea (Gr 1-4) | 21% | 12% |
| Grade 3 / 4 Lab AEs | 25% | 17% |
| LDL elevations | 10% | 3% |

No clinically defined cases of proximal renal tubulopathy in either arm.

No discontinuations for renal adverse events.

**Sax et al, JAIDS 2014, 67:52-58**

# Phase 2 DRV/r trial: TAF versus TDF Week 48 results

| Treatment arm | TAF/FTC/DRV/c | TDF/FTC/DRV/c |
|---|---|---|
| HIV RNA <50, Wk 48 | 77% | 84% |
| Diarrhoea (Gr 1-4) | 21% | 26% |
| Fatigue (Gr 1-4) | 14% | 18% |
| Nausea (Gr 1-4) | 13% | 10% |
| Rash (Gr 1-4) | 12% | 8% |

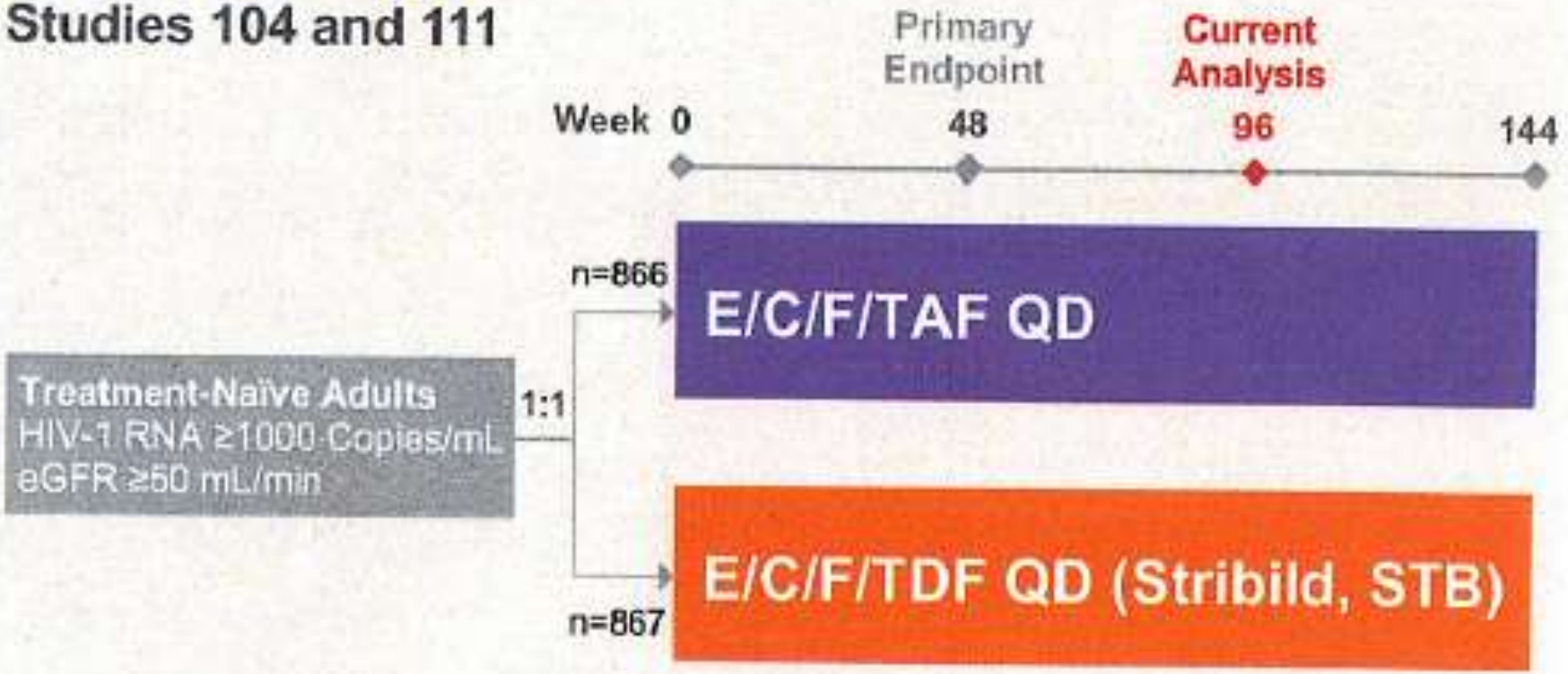
One clinically defined case of proximal renal tubulopathy in TDF arm.

Two discontinuations for adverse events in each arm.

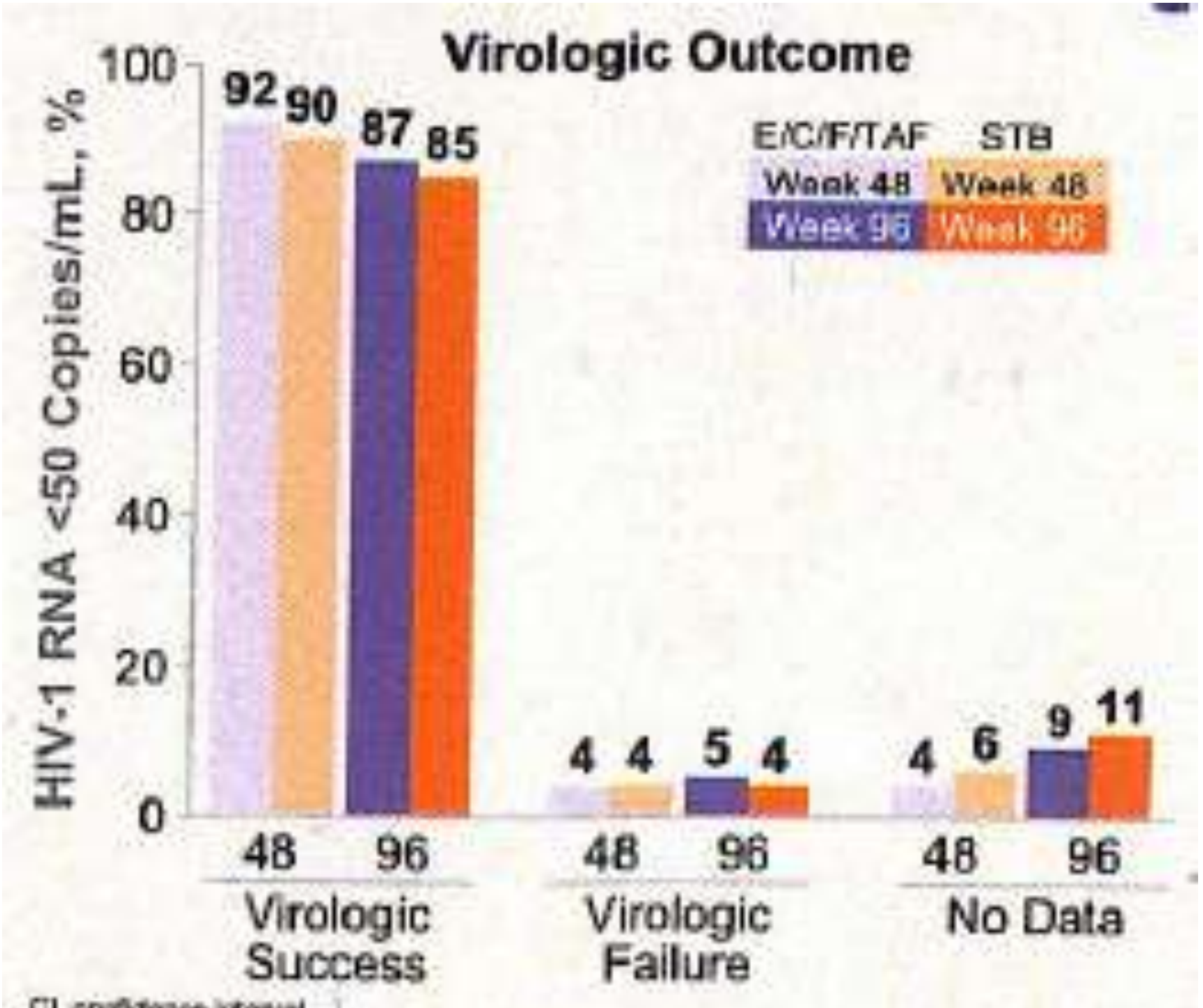
**Sax et al, JAIDS 2014, 67:52-58**

# Study Design

## Studies 104 and 111




E/C/F, elvitegravir/cobicistat/emtricitabine; eGFR, estimated glomerular filtration rate.


Virologic Outcome
HIV-1 RNA <50 Copies/mL, %
100
80
60
40
20
0
E/C/F/TAF
STB
Week 48
Week 96
Week 48
Week 96
92
90
87
85
4
4
5
4
4
6
9
11
48
96
48
96
48
96
Virologic Success
Virologic Failure
No Data

# Safety Summary

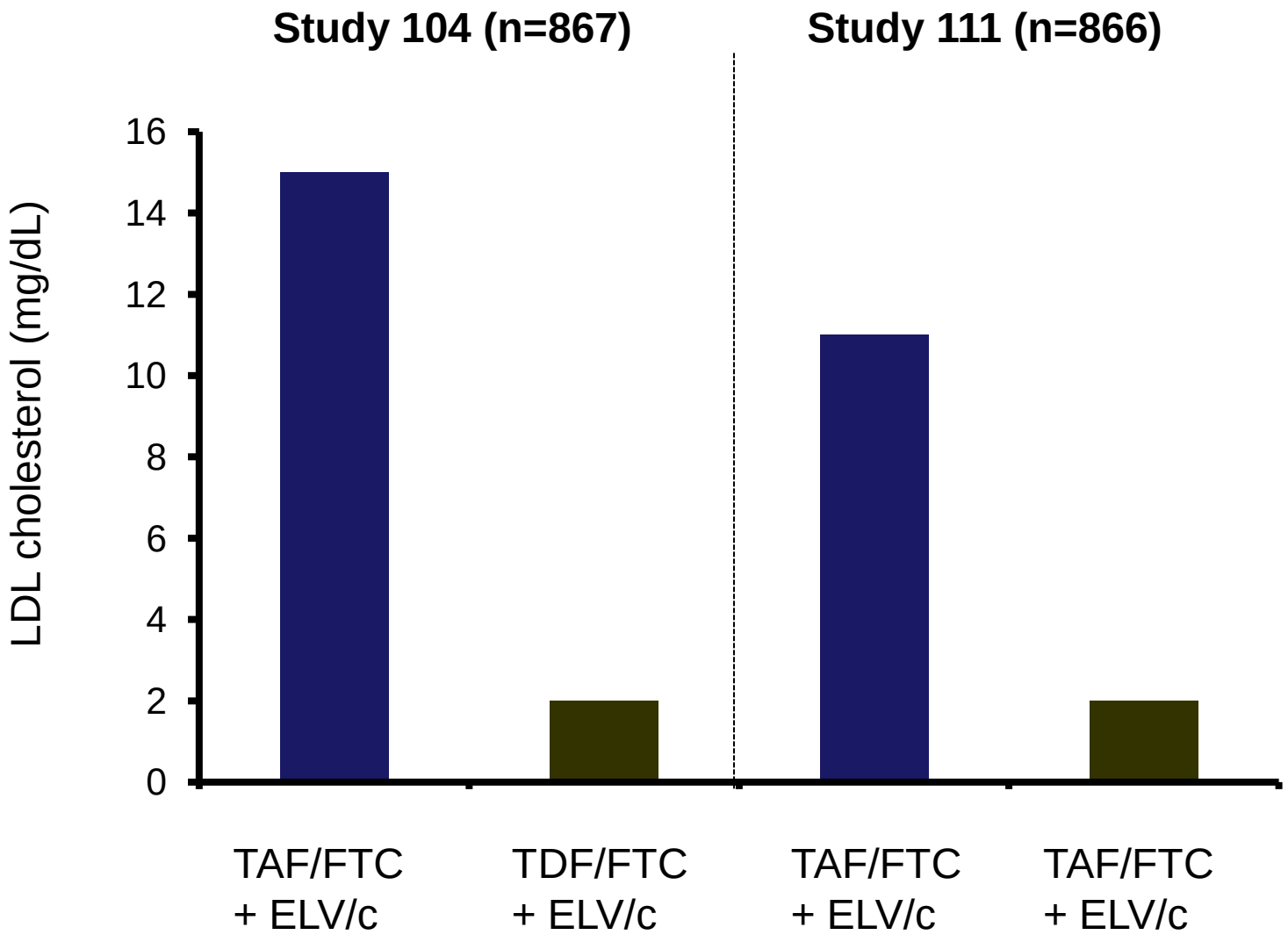
| Patients, % | E/C/F/TAF n=866 | STB n=867 |
|---|---|---|
| Any AE | 93 | 95 |
| Any drug-related AE | 42 | 46 |
| Grade 3 or 4 AE | 12 | 12 |
| Drug-related Grade 3 or 4 AE | 2 | 1 |
| Serious AE | 11 | 10 |
| Drug-related serious AE | 0.6 | 0.2 |
| AE-related discontinuation | 1 | 2 |
| Renal AE discontinuation, n | 0 | 6* |
| Death | 0.2† | 0.3‡ |

*p<0.03. †Stroke (n=1); alcohol intoxication (n=1); alcohol and drug intoxication (n=1); myocardial infarction (n=2); AE, adverse event.

**TDF versus TAF**

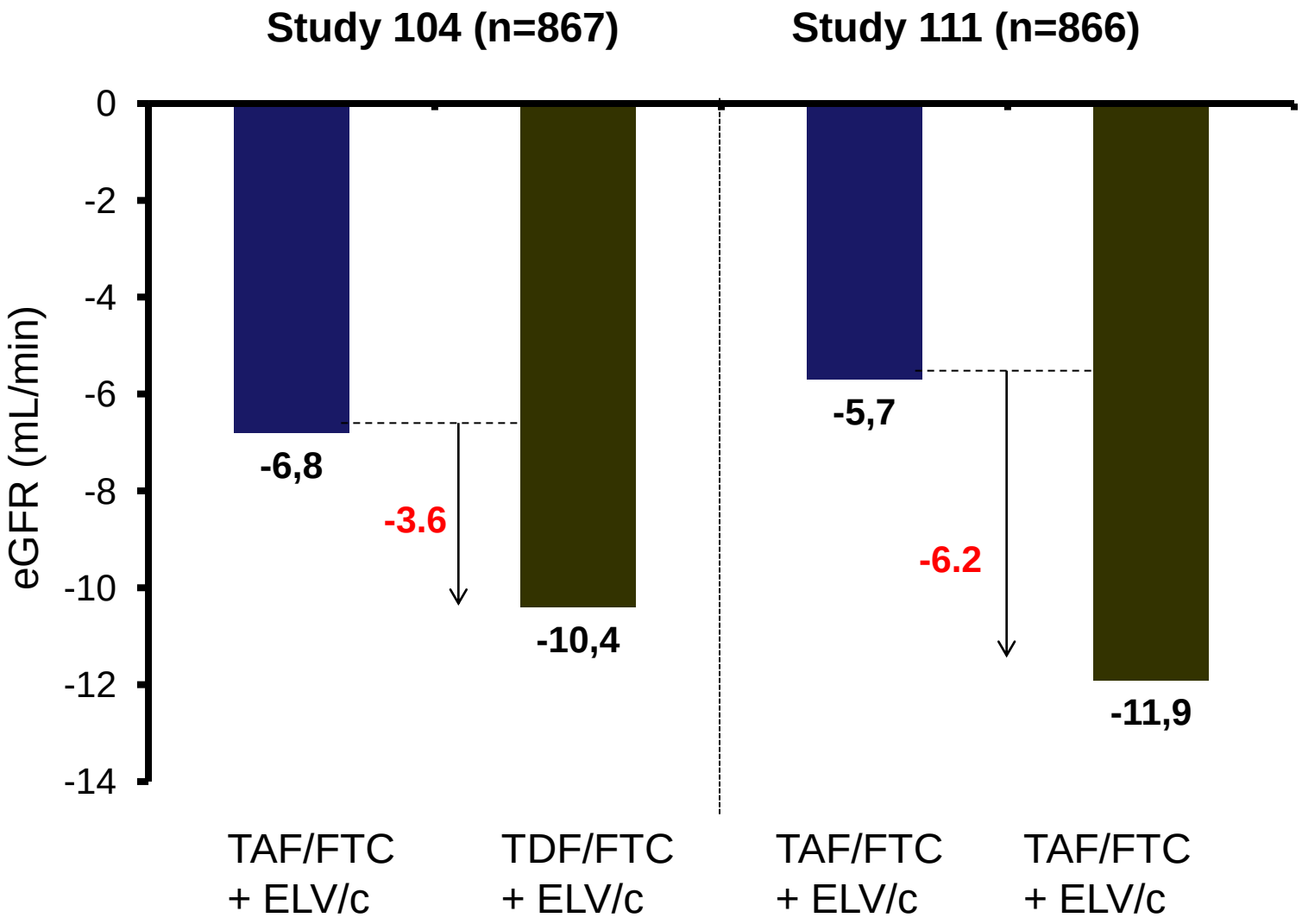
**Are we making a mountain out of a mole-hill?**

# Change in LDL to Week 48
# TAF versus TDF



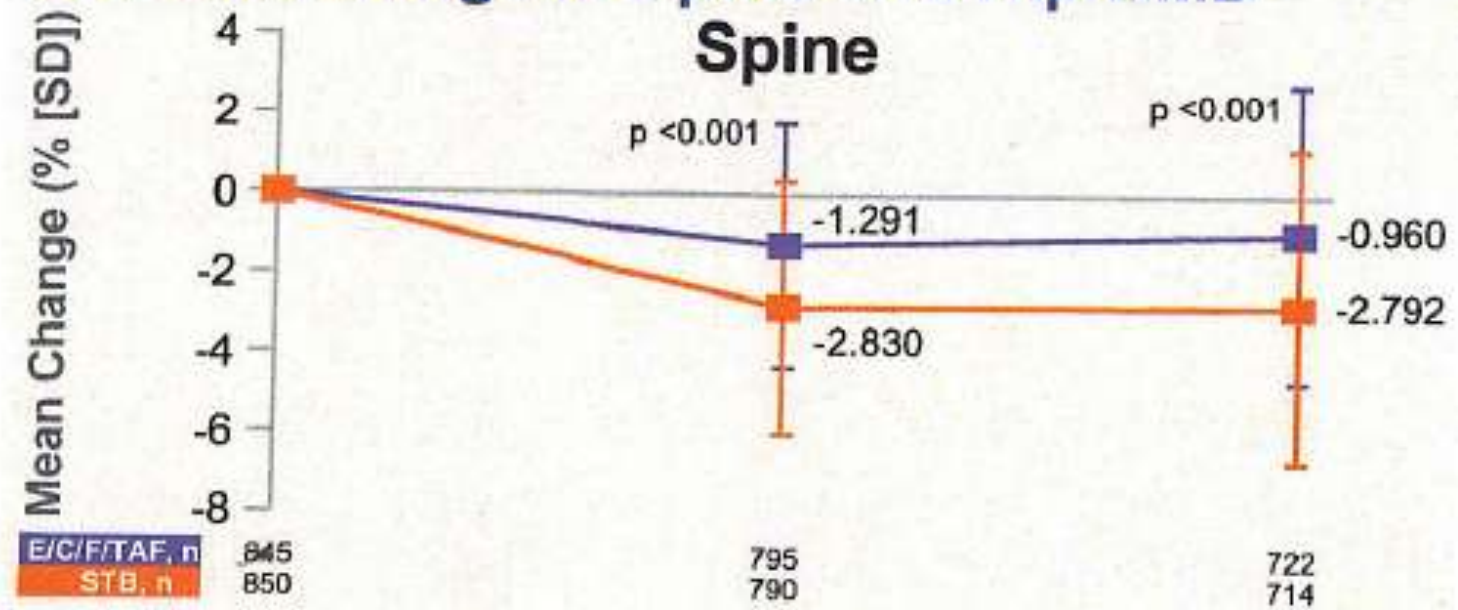

**Gilead press release, September 2014**

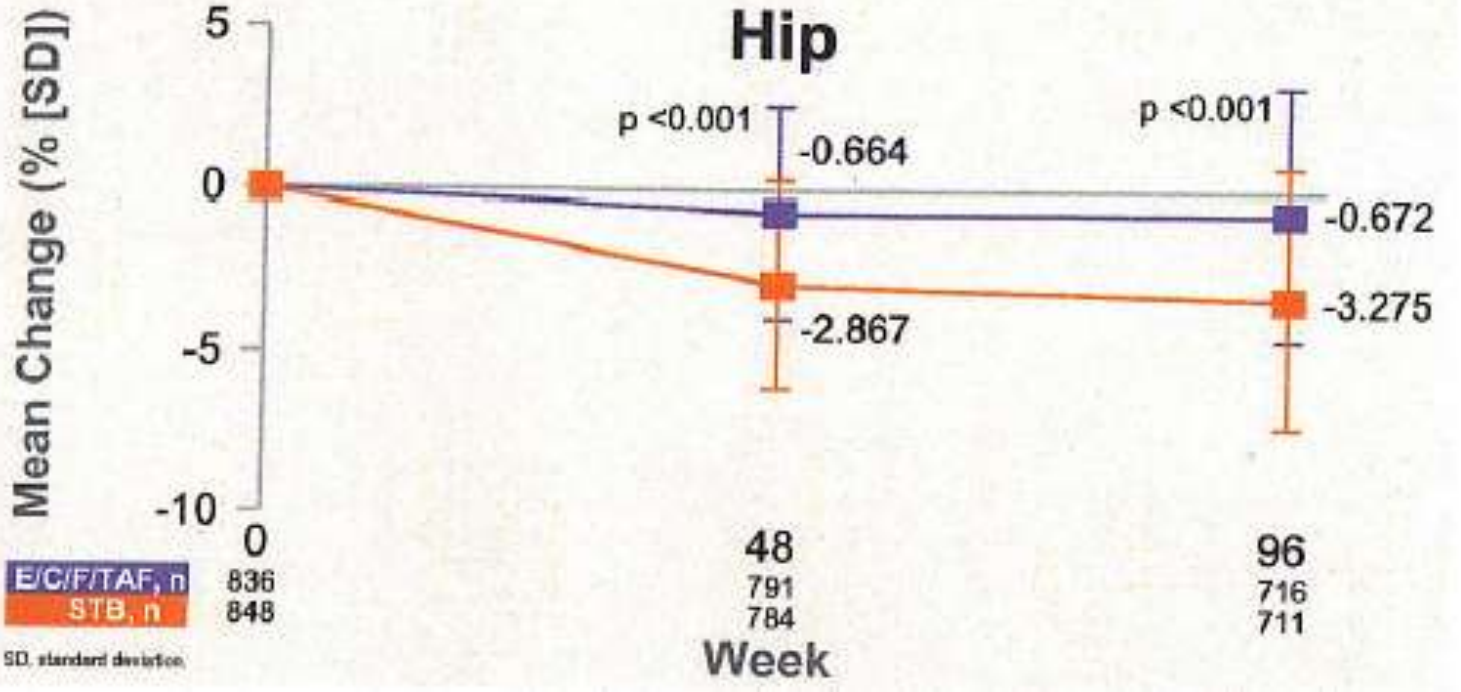
# Change in eGFR to Week 48
# TAF versus TDF



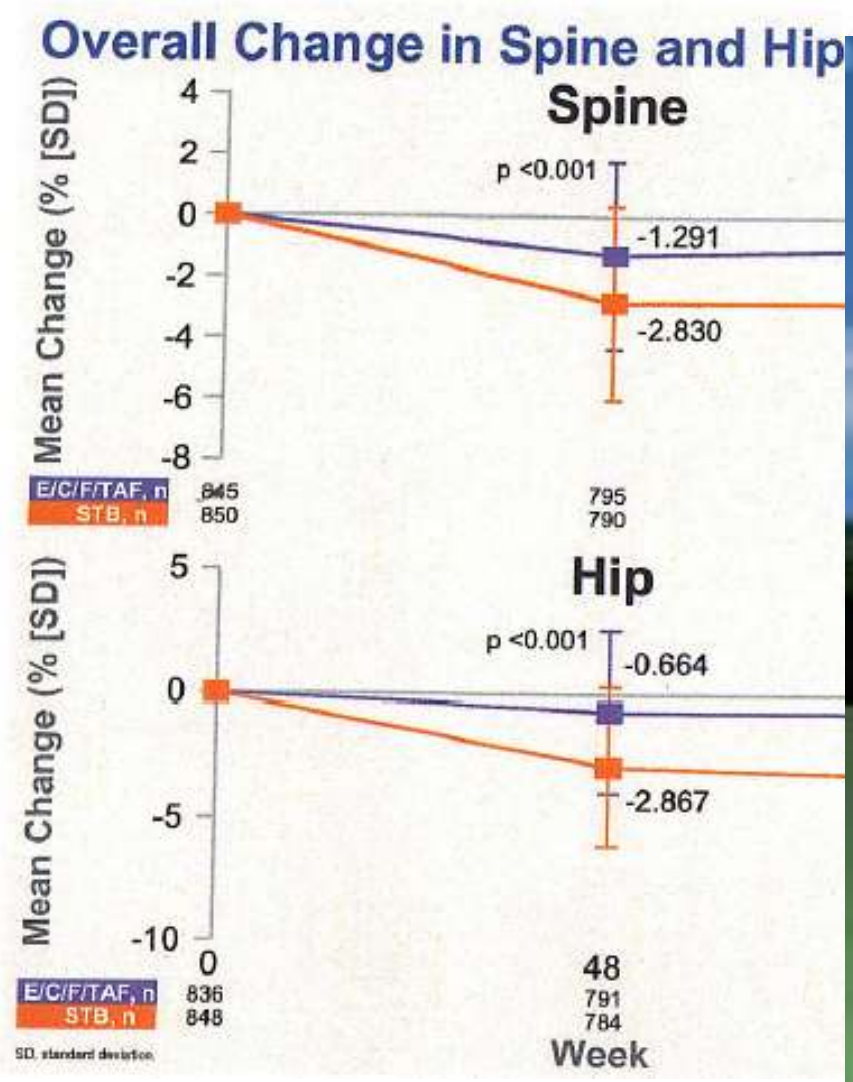

Gilead press release, September 2014

# Overall Change in Spine and Hip BMD




SD, standard deviation


Overall Change in Spine and Hip
Spine
Mean Change (% [SD])
4
2
0
-2
-4
-6
-8
p <0.001
-1.291
-2.830
E/C/F/TAF, n
STB, n
845
850
795
790
Hip
Mean Change (% [SD])
5
0
-5
-10
p <0.001
-0.664
-2.867
0
48
E/C/F/TAF, n
STB, n
836
848
791
784
SD, standard deviation
Week

# TDF versus TAF – Phase 3 trials

TAF/FTC/ELV/c versus TDF/FTC/ELV/c (104 and 111 trials)

1744 naïve patients, placebo-controlled

TAF vs TDF - same HIV RNA suppression (92% vs 90%)

- Grade 3 or 4 adverse events?
- greater rises in LDL, TCHOL, HDL
- smaller reductions in eGFR (CG)
- smaller reductions in bone mineral density

TAF boosted by cobicistat, so dose is reduced from 25 to 10mg

TDF also boosted by cobicistat – why not reduce TDF dose to 200mg?

Is TDF 300mg in these Phase 3 trials overestimating tox of tenofovir?

# Clinical significance? START study n=4685, 2.2 year follow up

| | Immediate ART | Late ART | |
|---|---|---|---|
| On ART | 95% | 15% | |
| On TDF | 79% | 15% | |
| Mean % change, Hip (36m) | -3.5% | -2.0% | |
| Mean % change, Spine (36m) | -2.0% | -0.5% | |
| Osteoporosis | 1.7% | 0.9% | n.s. |
| Bone fractures | 0.7% | 0.8% | n.s. |
| Minimal trauma fractures | 0.2% | 0.3% | n.s. |

Hoy et al. Adverse events Workshop, October 2015, Barcelona [ADRLH-62]

# TDF versus TAF – summary

Phase 3 trials have shown no efficacy improvements for TAF vs TDF

Safety results are mixed.  TAF shows slightly better renal and bone results, but slightly worse lipids.  One Phase 2 study shows excess nausea and elevations in LDL cholesterol.

There is no clear evidence that these small differences in laboratory markers will translate into clinical adverse events – (e.g. bone fractures, cardiovascular events).

# Next year, will TAF 10mg be worth a higher price versus generic TDF 300mg?

# TDF versus TAF – new trials

There are no current plans to conduct trials of TAF with EFV or DTG

Will TAF show any safety benefits over TDF, in this context?

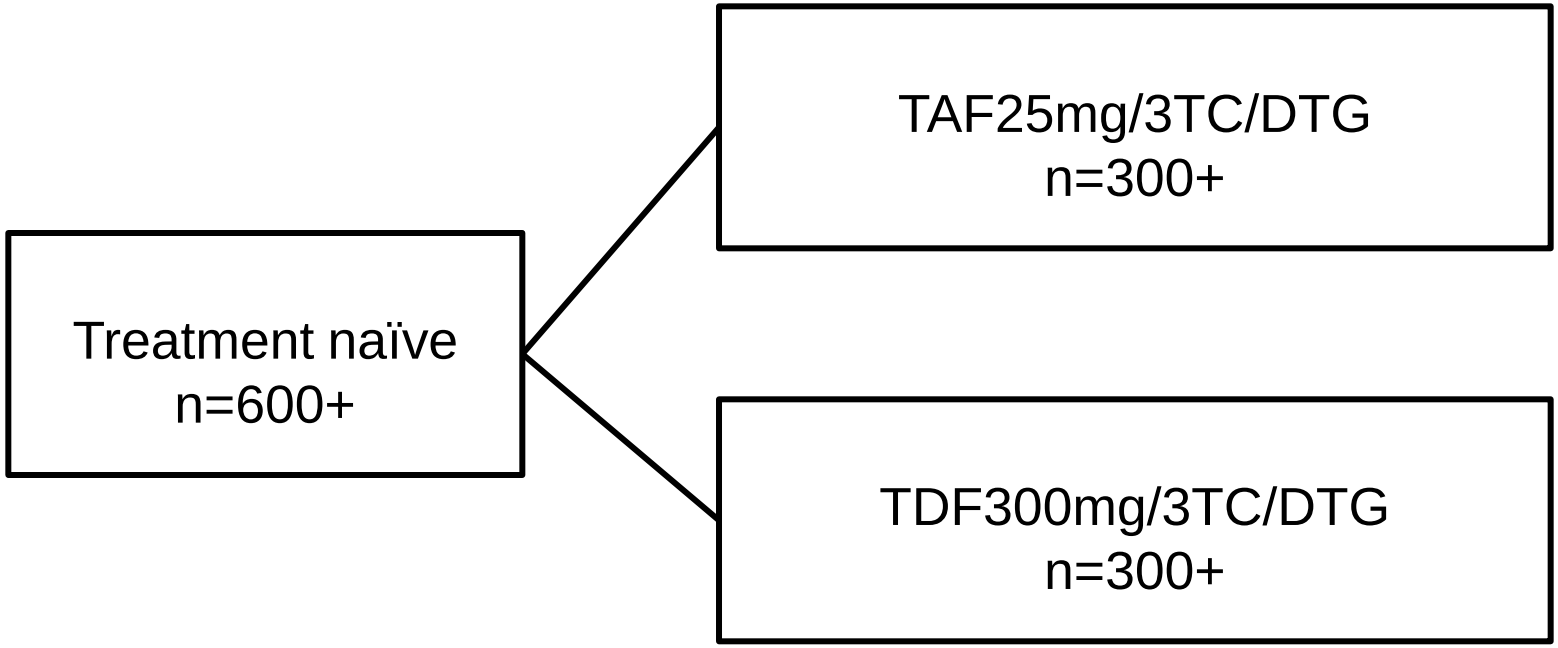
TDF would not then be boosted by ritonavir or cobicistat. Safety may be more favourable.

# Other problems with TAF

No clinical experience of TAF in pregnancy – but intracellular TDF-DP concentration is 4x higher than tenofovir-DF – could this have clinical consequences for foetal development?

TAF is a substrate for p-gp.  What about interactions with rifampicin?

# TDF vs TAF – new study needed
# Unboosted doses of each drug




Double-blinded, randomised
Primary endpoints: HIV RNA <50 copies/mL (FDA Snapshot)
Secondary endpoints: serum creatinine, bone density (hip/spine)

# Do we even need tenofovir, or is PI + 3TC (or DTG + 3TC) enough?

# 4 randomised trials of PI/r + 3TC versus PI/r + 2NRTIs HIV RNA <50 copies/mL (switch = failure endpoint)

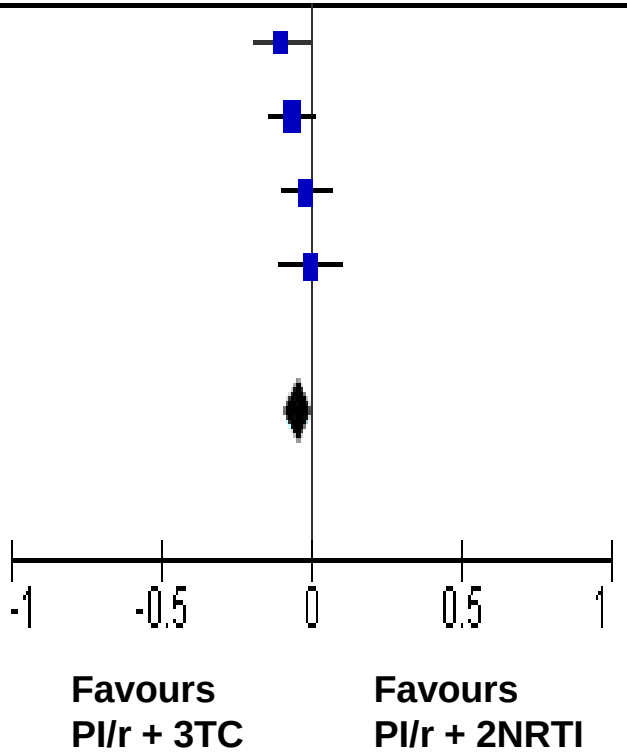
| Clinical trial | Treatment arms | Follow up time + inclusion | HIV RNA <50 Dual therapy | HIV RNA <50 Triple therapy |
|---|---|---|---|---|
| GARDEL | LPV/r + 3TC vs LPV/r+2NRTIs | 96 weeks Naïve | 195/217 (90%) | 176/209 (84%) |
| Ole | LPV/r + 3TC vs LPV/r+2NRTIs | 48 weeks Switch | 108/118 (92%) | 110/121 (91%) |
| SALT | ATV/r + 3TC vs ATV/r+2NRTIs | 96 weeks Switch | 99/143 (84%) | 99/1343 (78%) |
| ATLAS-M | LPV/r + TDF vs LPV/r + 2NRTIs | 48 weeks Switch | 120/133 (90%) | 106/133 (80%) |

# Benefits of PI/r + 3TC in 4 randomised trials
# HIV RNA<50 copies/mL at Week 48 or 96

| | PI/r + 1 NRTI | | Triple ARV Therapy | | | Risk Difference | Risk Difference |
|---|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| ATLAS-M | 12 | 119 | 22 | 111 | 21.5% | -0.10 [-0.19, -0.01] | |
| Gardel | 16 | 165 | 22 | 141 | 28.4% | -0.06 [-0.13, 0.02] | |
| OLE | 15 | 123 | 17 | 127 | 23.4% | -0.01 [-0.09, 0.07] | |
| SALT | 44 | 143 | 44 | 143 | 26.7% | 0.00 [-0.11, 0.11] | |
| **Total (95% CI)** | | **550** | | **522** | **100.0%** | **-0.04 [-0.09, 0.00]** | |
| Total events | 87 | | 105 | | | | |

Heterogeneity: Chi² = 2.72, df = 3 (P = 0.44); I² = 0%

Test for overall effect: Z = 1.76 (P = 0.08)



# Conclusions

1. TAF is boosted by ritonavir and cobicistat. The dose of TAF has been lowered from 25mg to 10mg once daily, to compensate.

2. TDF is boosted by ritonavir and cobicistat. The dose of TDF should be lowered to 200mg, to compensate for this boosting effect.

3. TDF tends to show worse safety when combined with PI/r or elvitagravir/cobistat, which both boost tenofovir levels

4. Safety comparisons of TAF 10mg with TDF 300mg may be biased when both are combined with ritonavir or cobicistat. The dose of TDF has not been adjusted, and so high TDF levels could worsen safety profile.

# The choices for the future

**TDF + 3TC + ATV/r – fully generic in 2017, very cheap**

**ATV/r + 3TC – equivalent efficacy as a maintenance option, fully generic**

**TAF/FTC/ELV/c – very expensive, but any real clinical benefits?**