Should the dose of tenofovir be reduced to 200mg/day, when combined with protease inhibitors or elvitegravir?

Andrew Hill
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Tenofovir – lower dose with PIs?

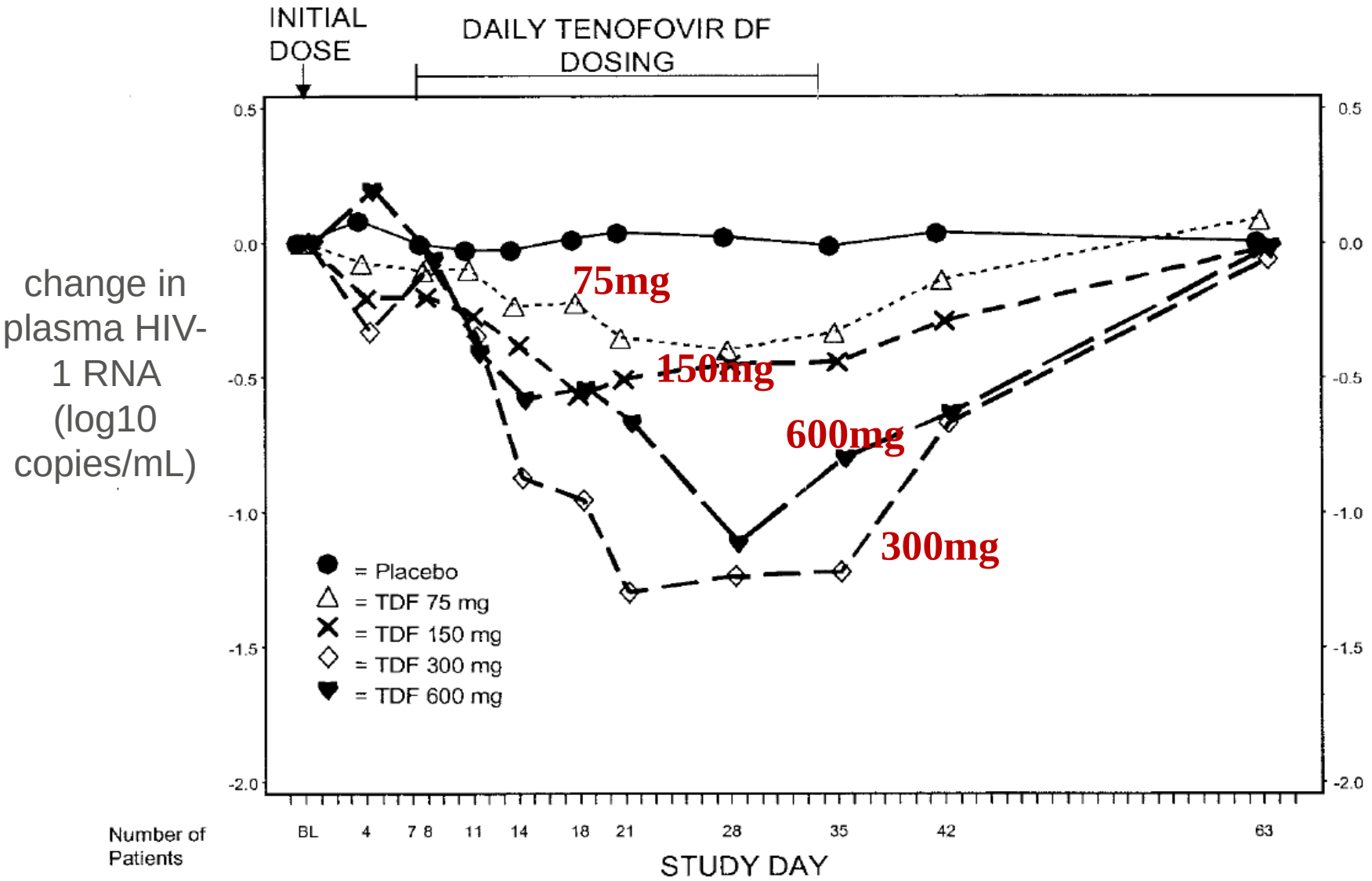
Tenofovir dose-ranging studies showed increase in efficacy from 75-300mg OD, then no rise to 600mg OD.

Efficacy of TDF was established in studies with efavirenz, which does not affect TDF drug levels

LPV/r, ATV/r and DRV/r all raise TDF levels. TDF causes renal toxicity, especially when combined with protease inhibitors.

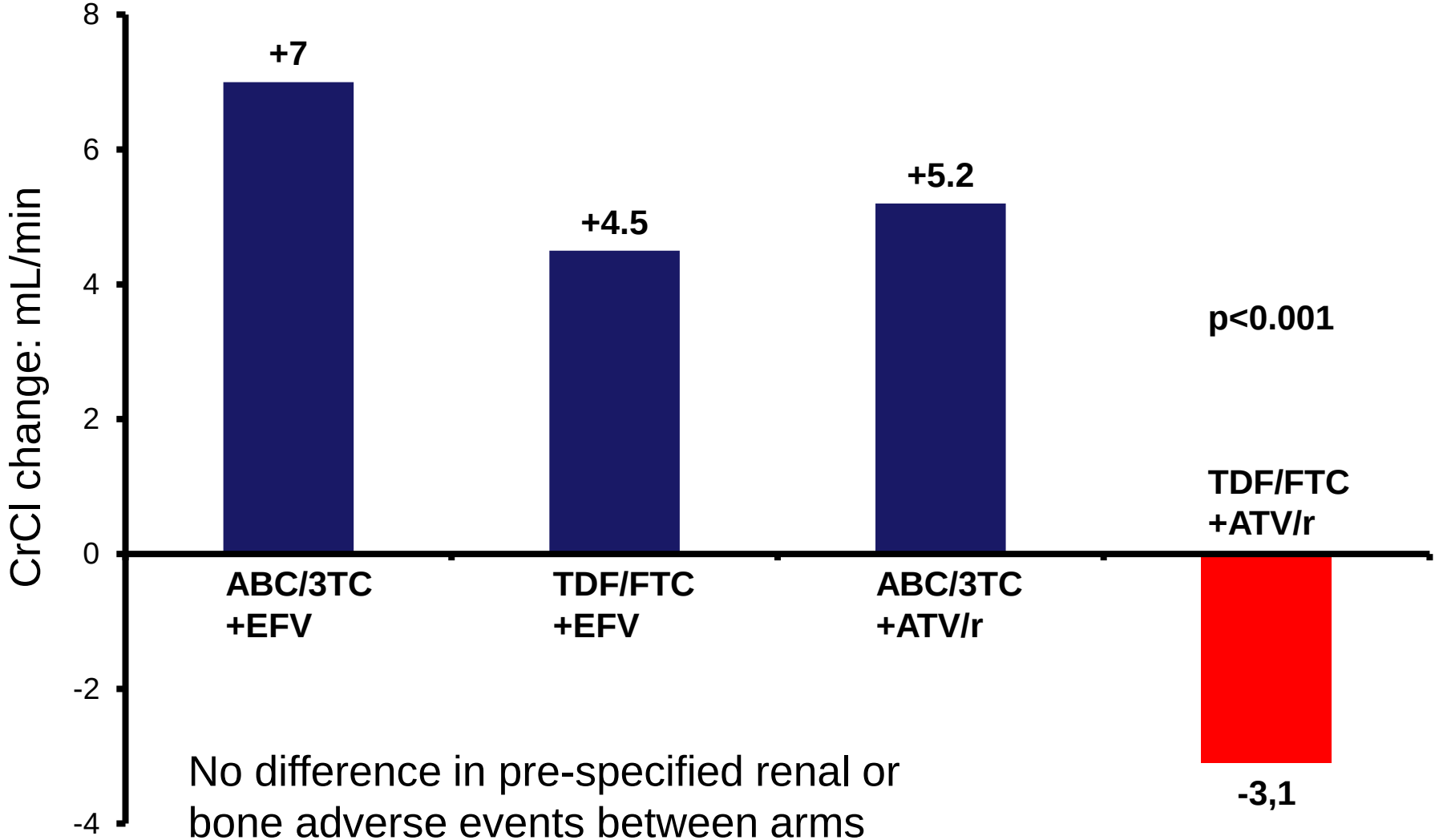
New paediatric TDF pills available, at 200mg and 250mg strength
Could lower doses of TDF cancel out these drug interactions?

TDF monotherapy: virological response over 4 weeks



Barditch-Crovo et al, AAC 2001

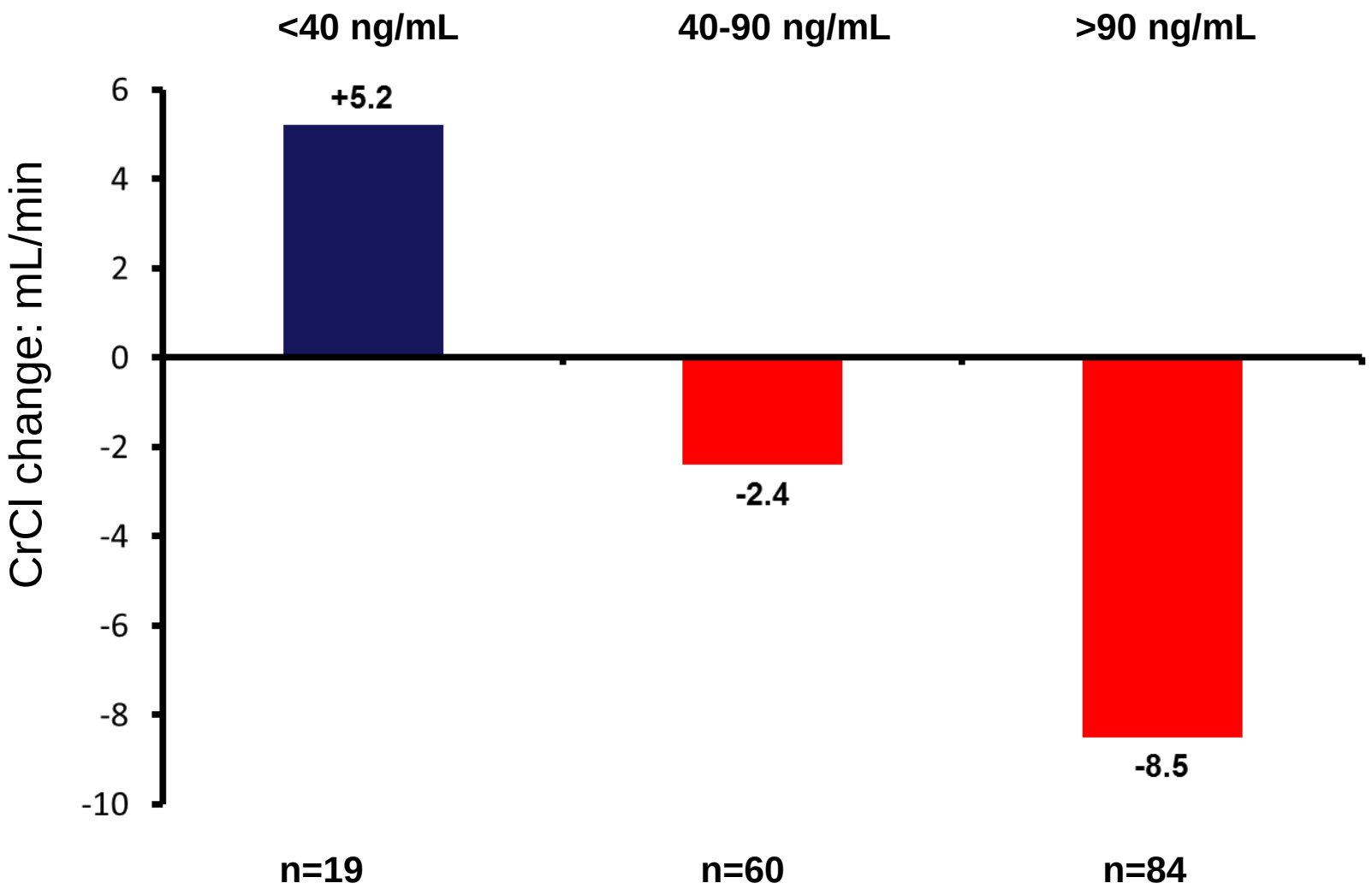
ACTG 5202: change in creatinine clearance from baseline to Week 96



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

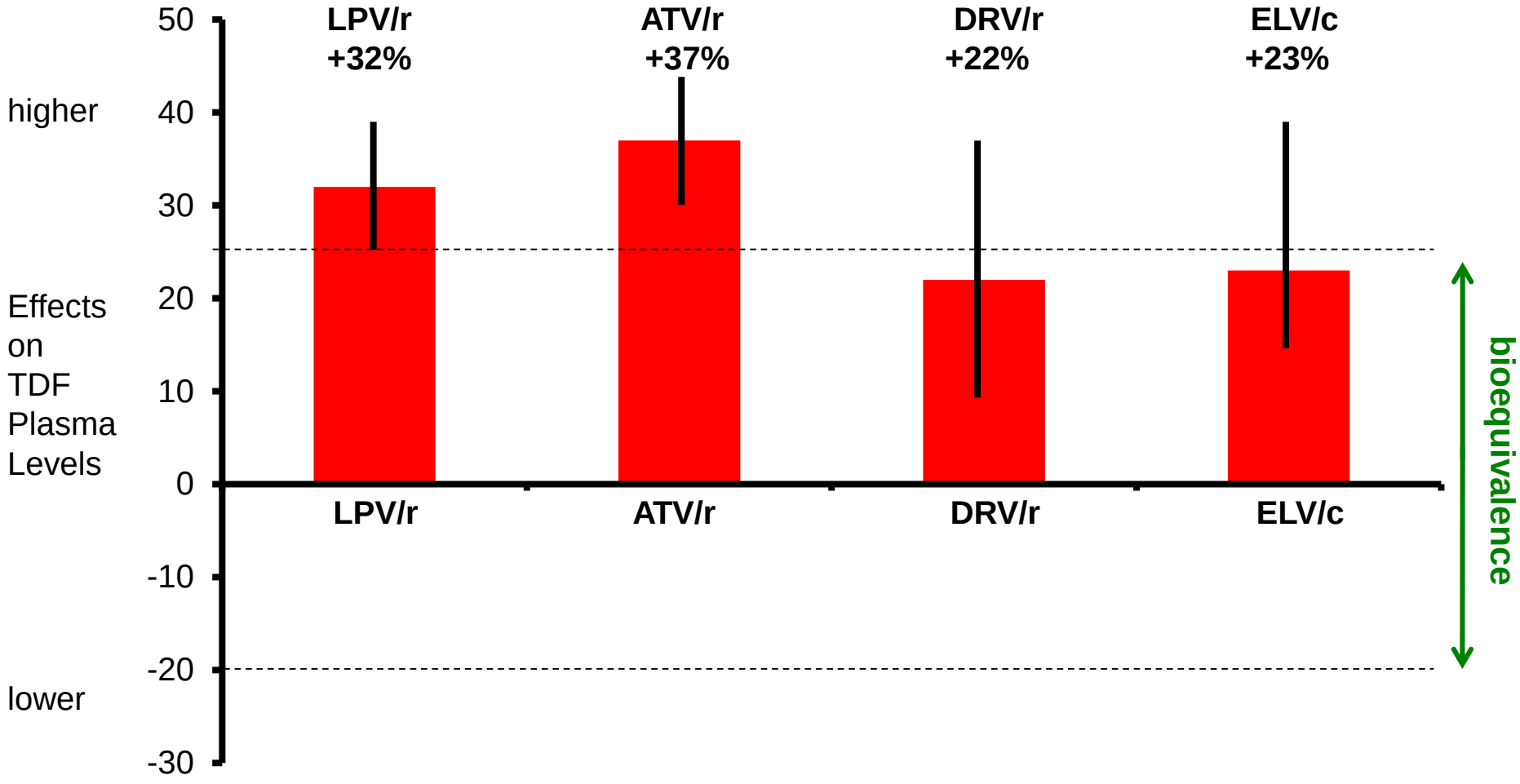
Sax et al. JID 2011, 204: 1191-1201

Change in creatinine clearance to Week 48 by TDF Ctrough

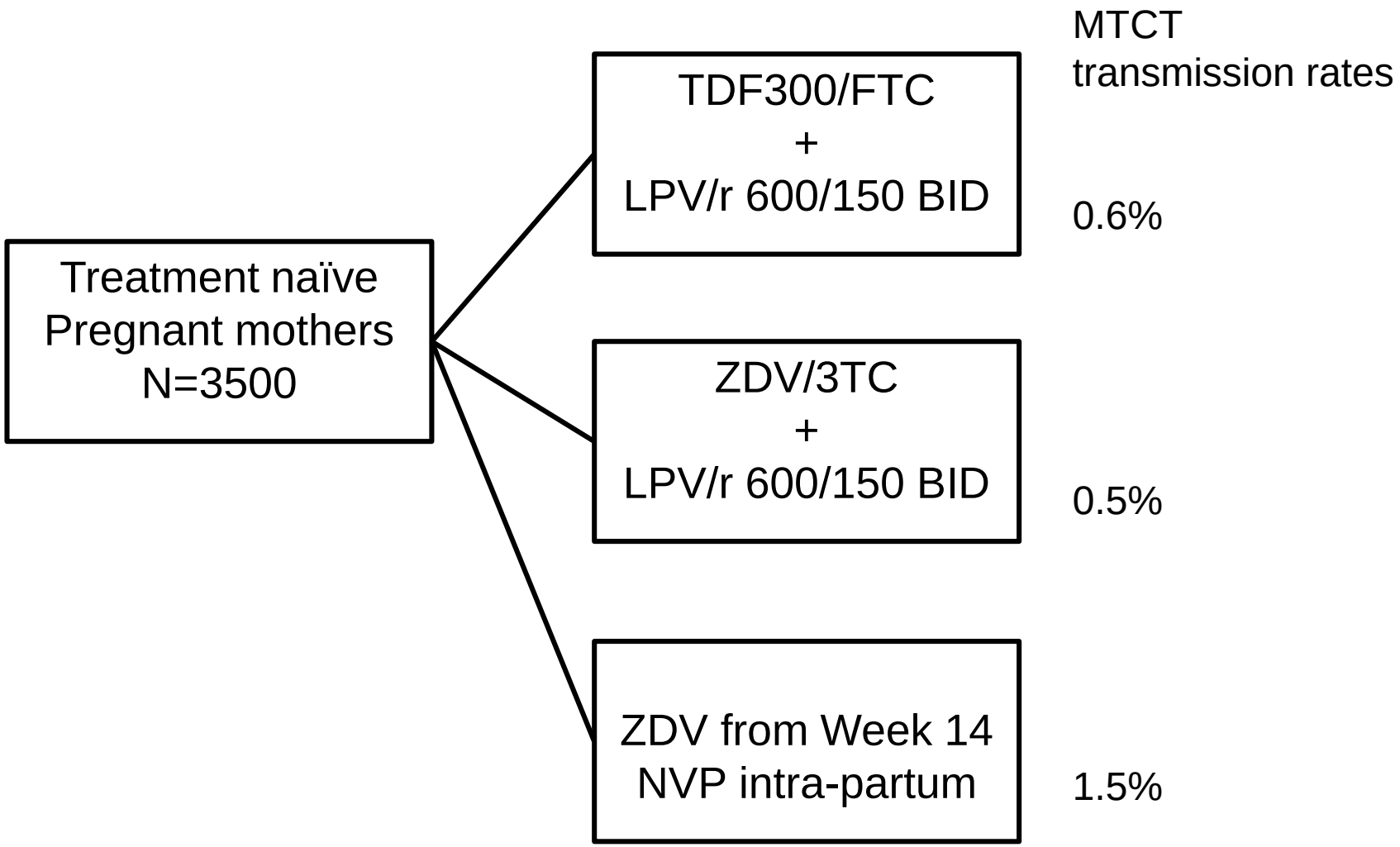


Poizot-Martin et al. JAIDS 2013

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



PROMISE study
US National Institutes of Health



NIH press release, November 2014

PROMISE study

Women taking tenofovir 300mg OD + 3TC + LPV/r 600/150 BID

More likely to show adverse pregnancy outcomes:

- very low birth weight
- very premature delivery
- stillbirth
- spontaneous abortion
- major birth defects

More babies on TDF/FTC/LPV/r died within 2 weeks of birth

Main cause of death was prematurity

Studies of TDF vs other NRTIs, with EFV eGFR (Cockroft-Gault)

Study	Comparison	Time	Renal safety		
		Weeks	TDF	NRTI	difference
Gilead 903	TDF vs d4T	144	124	122	+2 (p=n.s)
Gilead 934	TDF vs ZDV	96	119	118	+1 (p=0.51)
BICOMBO	TDF vs ABC	48	+0.6	+1.3	-0.6 (p=n.s.)
ACTG 5202	TDF vs ABC	48	+4.5	+7.0	-2.5 (p=n.s.)
ASSERT	TDF vs ABC	48	+1.2	+0.2	+1.0 (n.s.)

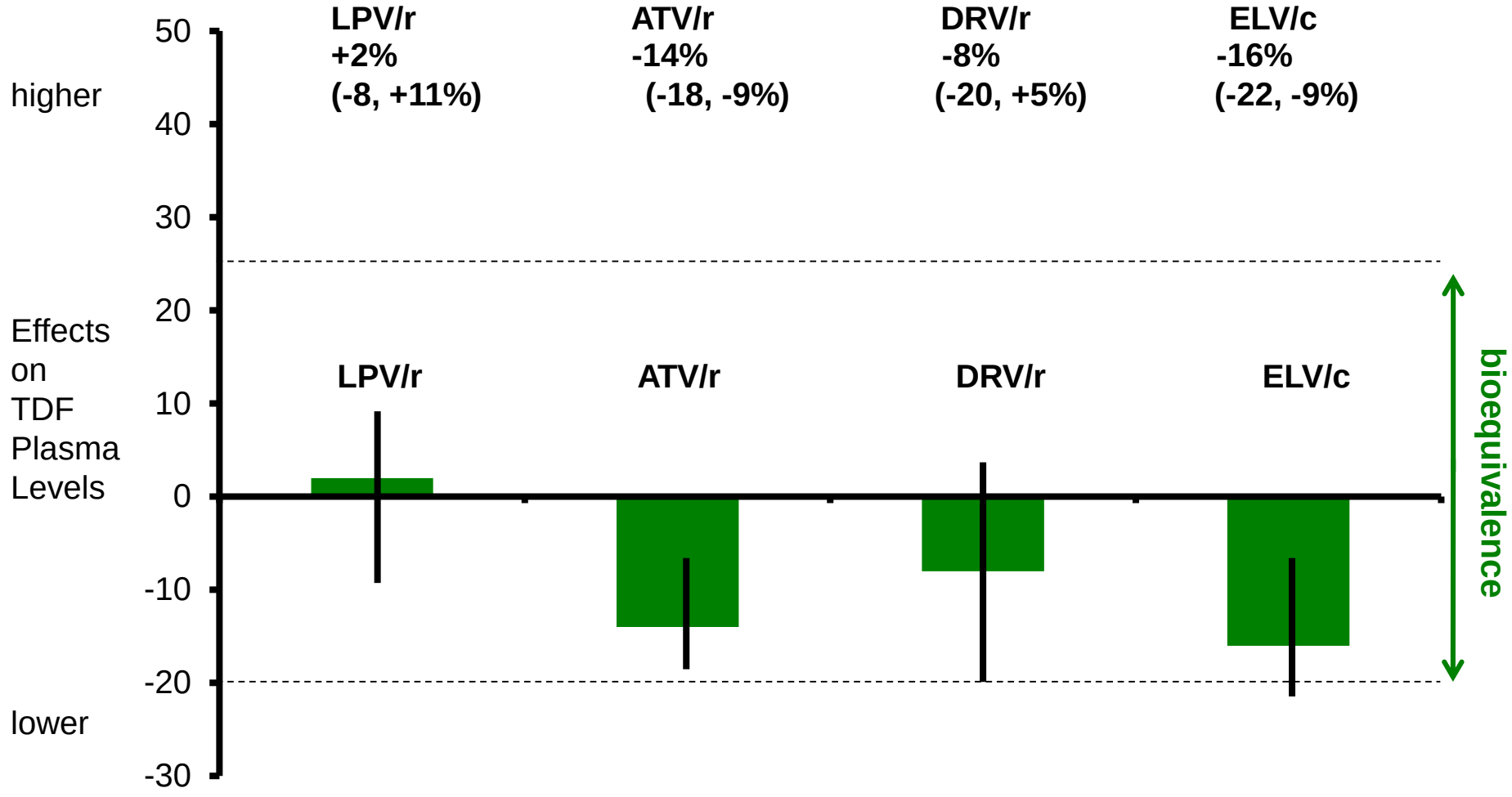
Studies of TDF vs other NRTIs, with PIs eGFR (Cockroft-Gault)

Study	Comparison	Time	Renal safety		
		Weeks	TDF	NRTI	difference
SWIFT	TDF vs ABC	48	-8.3	-4.8	-3.5 (p=0.012)
ACTG5202	TDF vs ABC	96	-3.1	+5.2	-8.3 (p<0.001)
HEAT	TDF vs ABC	96	+4	+7	-3.0 (p=n.s.)

PK trial to validate 200mg TDF dose when used with PIs or ELV/c

Cross-over PK trial.
Patients stable on TDF/FTC/RAL, HIV RNA <50 copies/mL
Measure PK after 2 weeks on each phase

Predicted Tenofovir Cmin (95% C.I.), using 200mg dose



Conclusions

Protease inhibitors and elvitegravir raise the Cmax and AUC of tenofovir by 25-55%, which could raise the risk of renal toxicities

There is no evidence that these higher tenofovir drug levels are improving efficacy.

Use of tenofovir at available lower doses (e.g. 200 OD) could compensate for this drug interaction, providing a safer dose while maintaining efficacy.

How can we interpret clinical trials comparing TAF 10mg versus TDF 300mg?

TDF versus TAF – summary

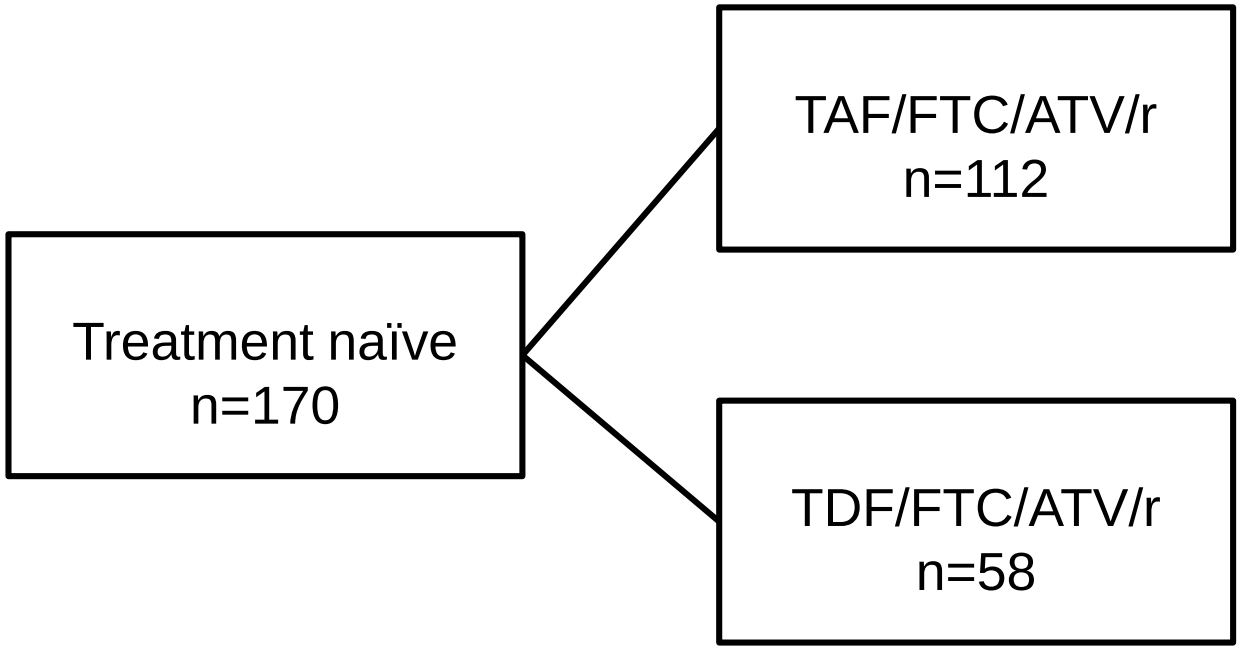
Phase 3 trials have shown no efficacy improvements for TAF vs TDF

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.

TDF already available as a cheap generic, in many co-formulations
TAF only being developed with ELV/c, and ATV/r which are currently not used first-line in low income countries. No trials with EFV or DTG.

Is TAF worth the additional cost, versus TDF at 200mg?

TDF vs TAF – Phase 2 study 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 trial: TAF versus TDF
Week 48 results

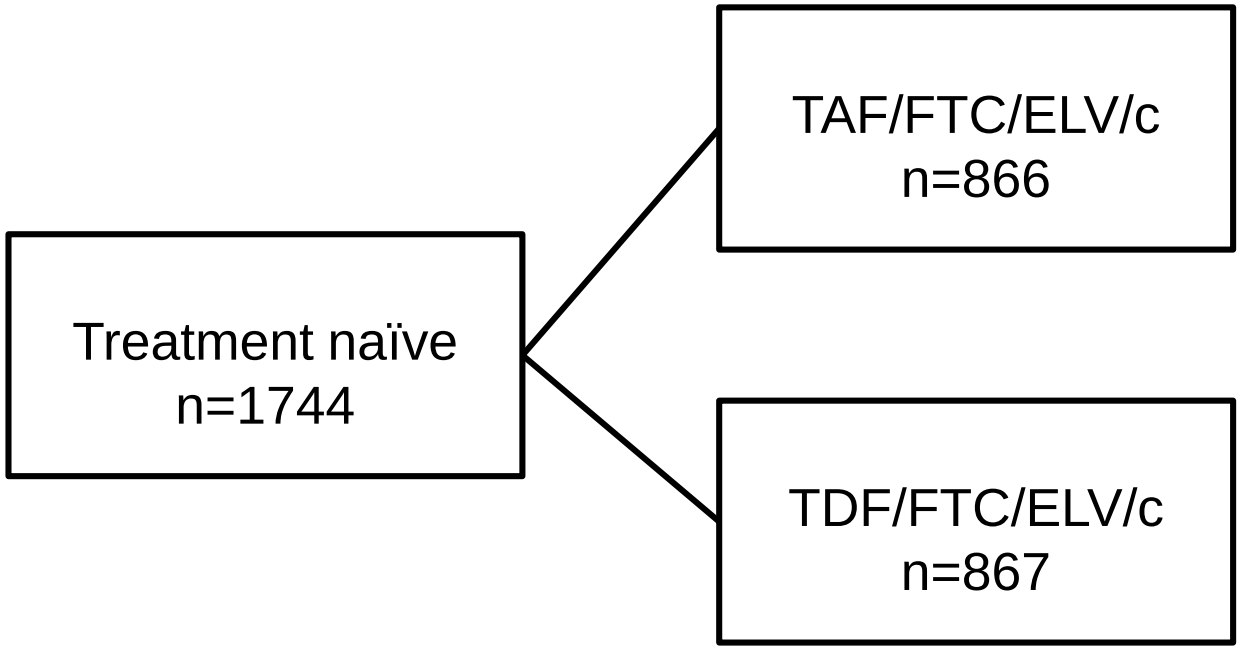
Treatment arm	TAF/FTC/ATV/r	TDF/FTC/ATV/r
HIV RNA <50	87%	90%
Grade 3-4 Clinical AEs	10%	5%
Nausea (Gr 1-4)	21%	12%
Grade 3 / 4 Lab AEs	25%	17%
LDL elevations	10%	3%

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

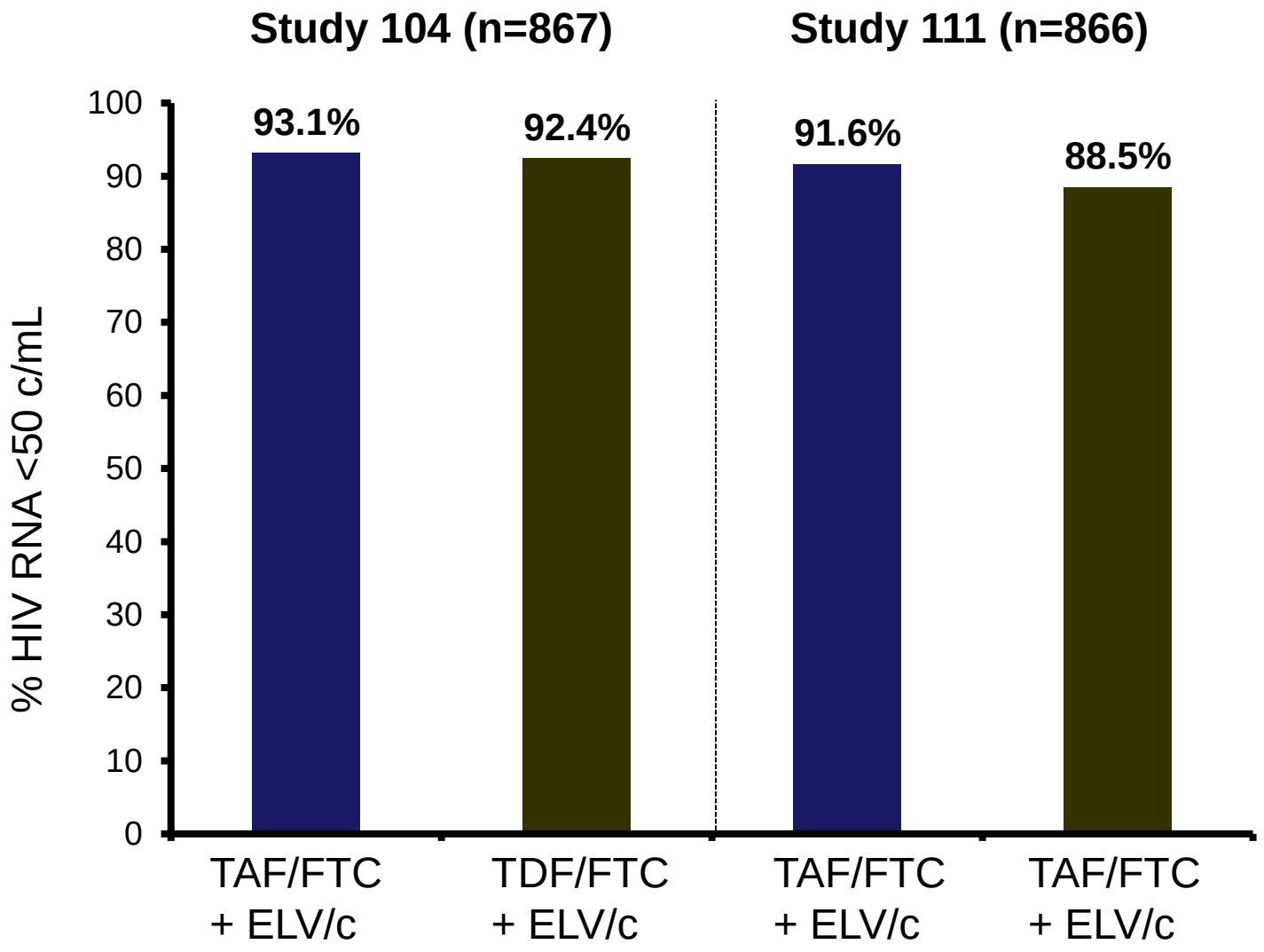
TDF vs TAF – Phase 3 studies 104 and 111



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

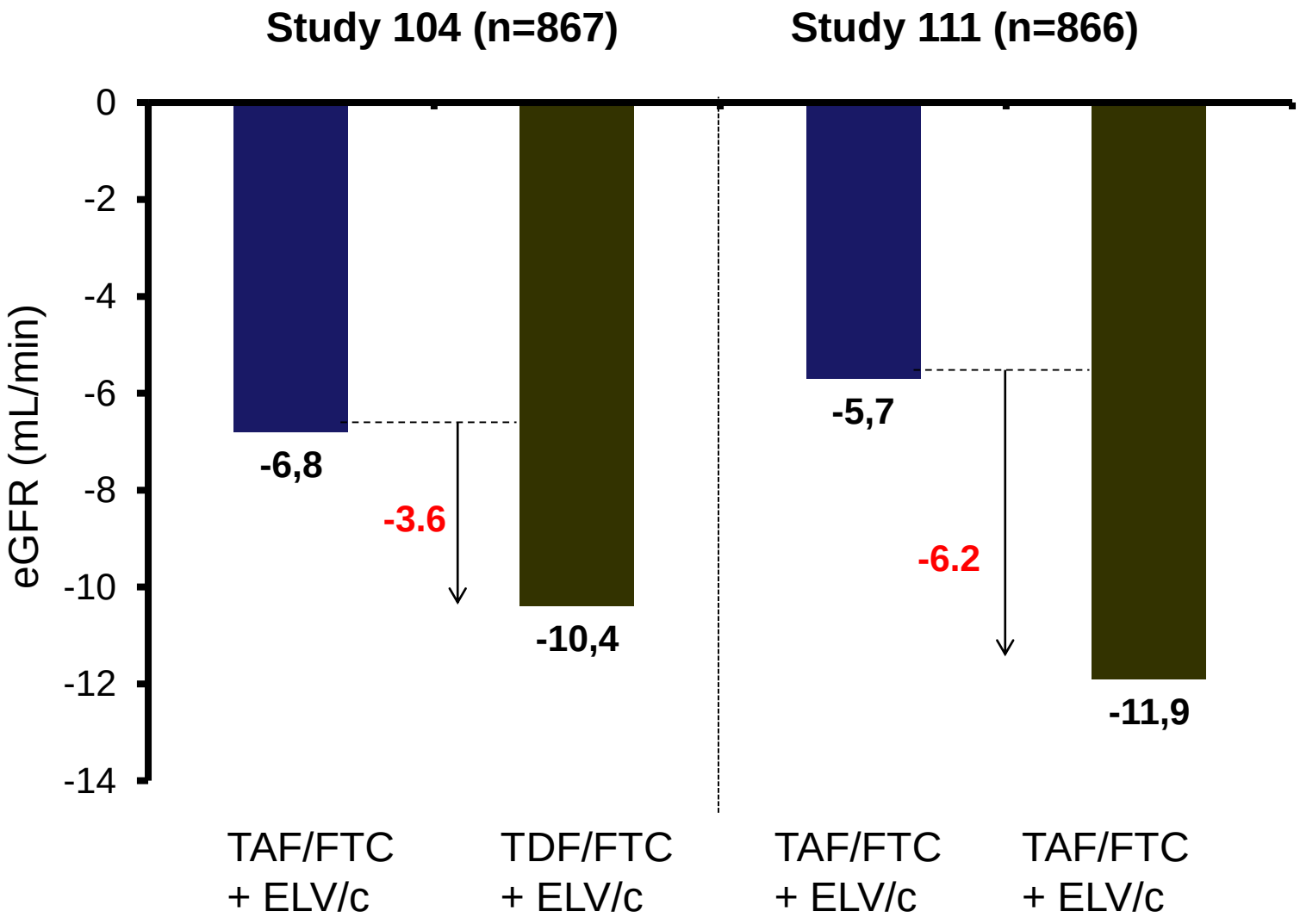
Gilead press release, September 2014

Non-inferior efficacy of TAF vs TDF, Week 48, 1st-line treatment



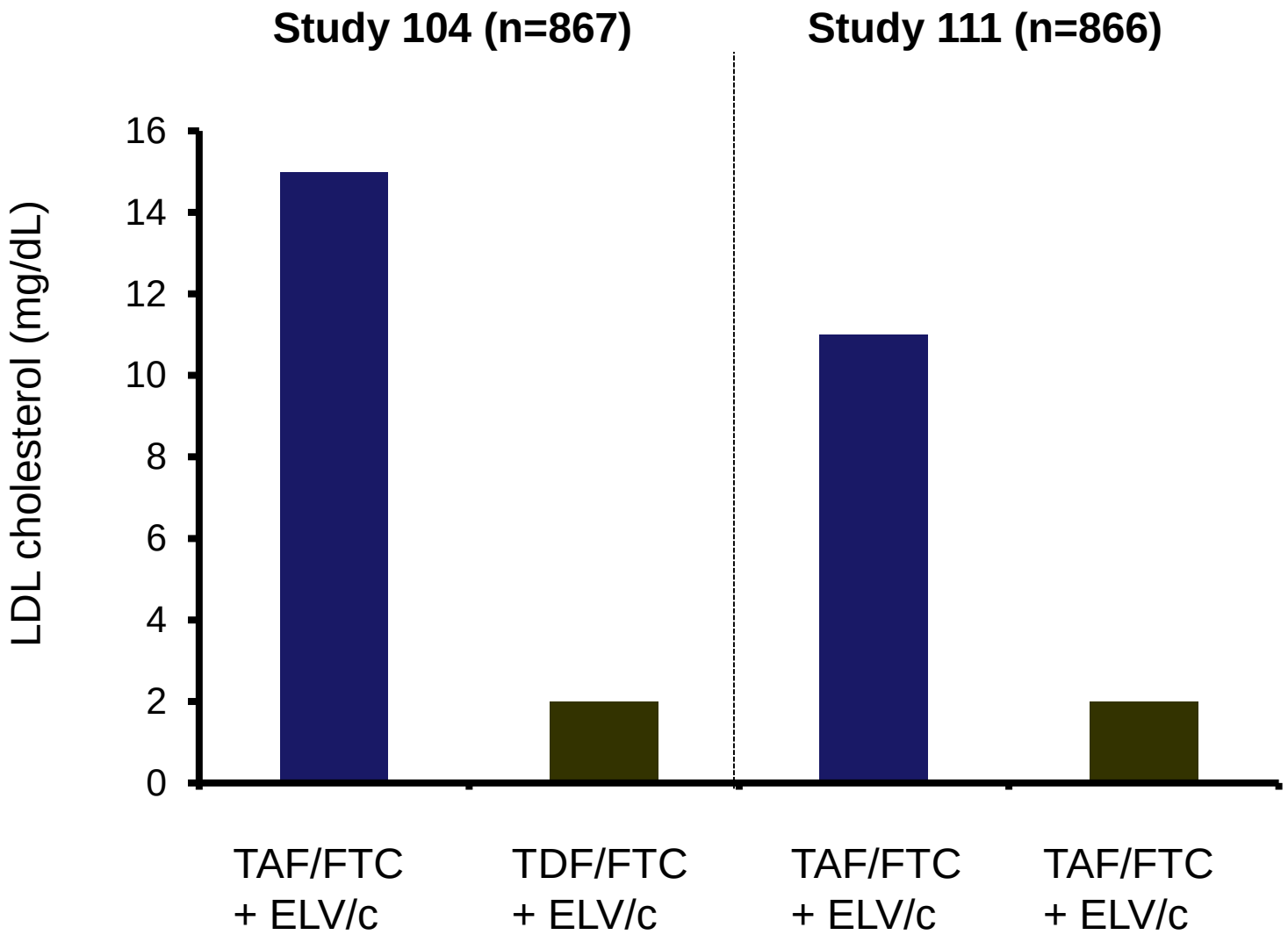
Gilead press release, September 2014

Change in eGFR to Week 48
TAF versus TDF



Gilead press release, September 2014

Change in LDL to Week 48
TAF versus TDF



Gilead press release, September 2014

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?

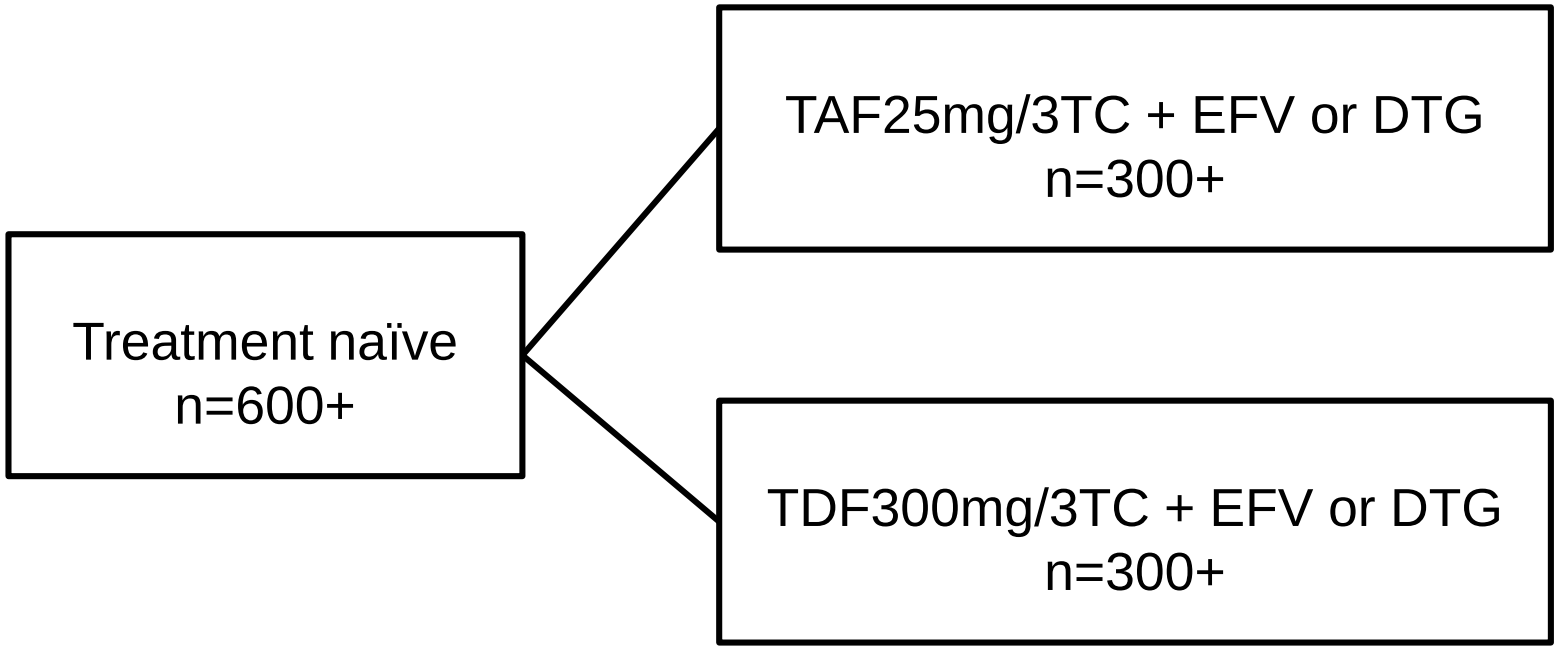
TDF versus TAF – new trials

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.

TDF vs TAF – new study needed



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

Patent Expiry dates: 2015-2019

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

2014: 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)

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

Prices of FDCs versus generics in 2016/7?

Single pill
Euro 5000-8000/year?

TAF/FTC/ELV/c

Three pills
Euro 1000/year?

Generic TDF 200mg

Generic 3TC

Generic EFV or PI/r

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.