

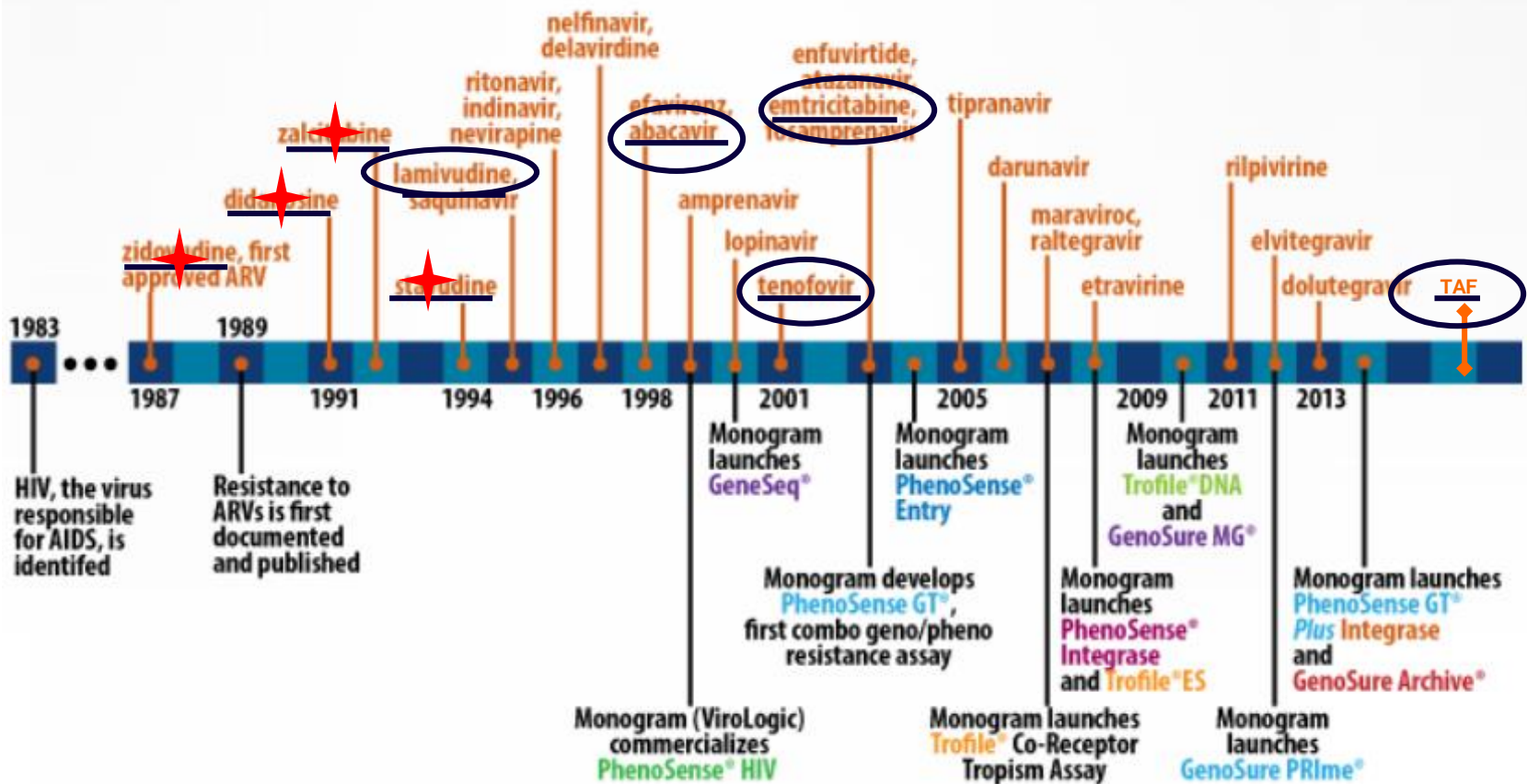
Update: NRTIs

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Acknowledgements: Raj Gandhi (slides), Richard Lessells (discussions)

- NRTIs are used in first, second and third line regimens:
 - Residual activity despite presence of signature mutations – resistance is not absolute.
 - Good efficacy in PI based 2nd line ART even when recycled.



AZT was first drug registered for the treatment of AIDS

Several NRTIs (AZT, d4T, ddI, ddC) have been put to pasture due to toxicity

ABC, 3TC, **TAF**, FTC, and **TDF** currently recommended guidelines in developed countries. – TAF is the workhorse TFV formulation.

AZT, d4T, ABC, 3TC, FTC, and TDF

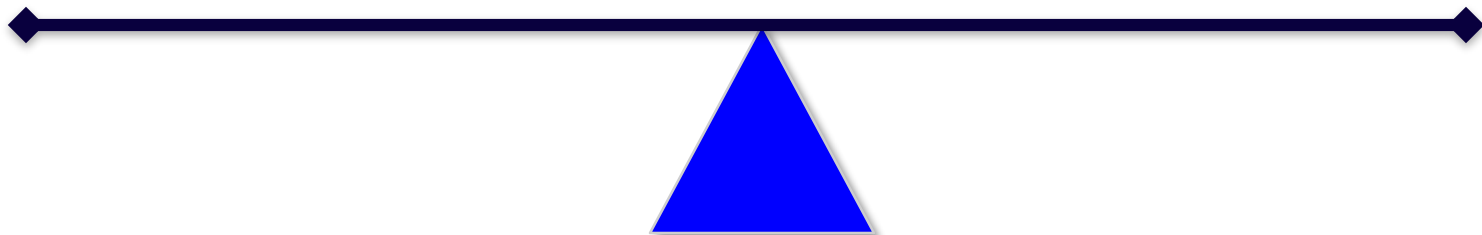
TFV is here to stay

**Argue that we should seriously consider
TAF to replace TDF in the SA?**

**Compare and Contrast TAF and TDF
Renal disease, Bone Disease.**

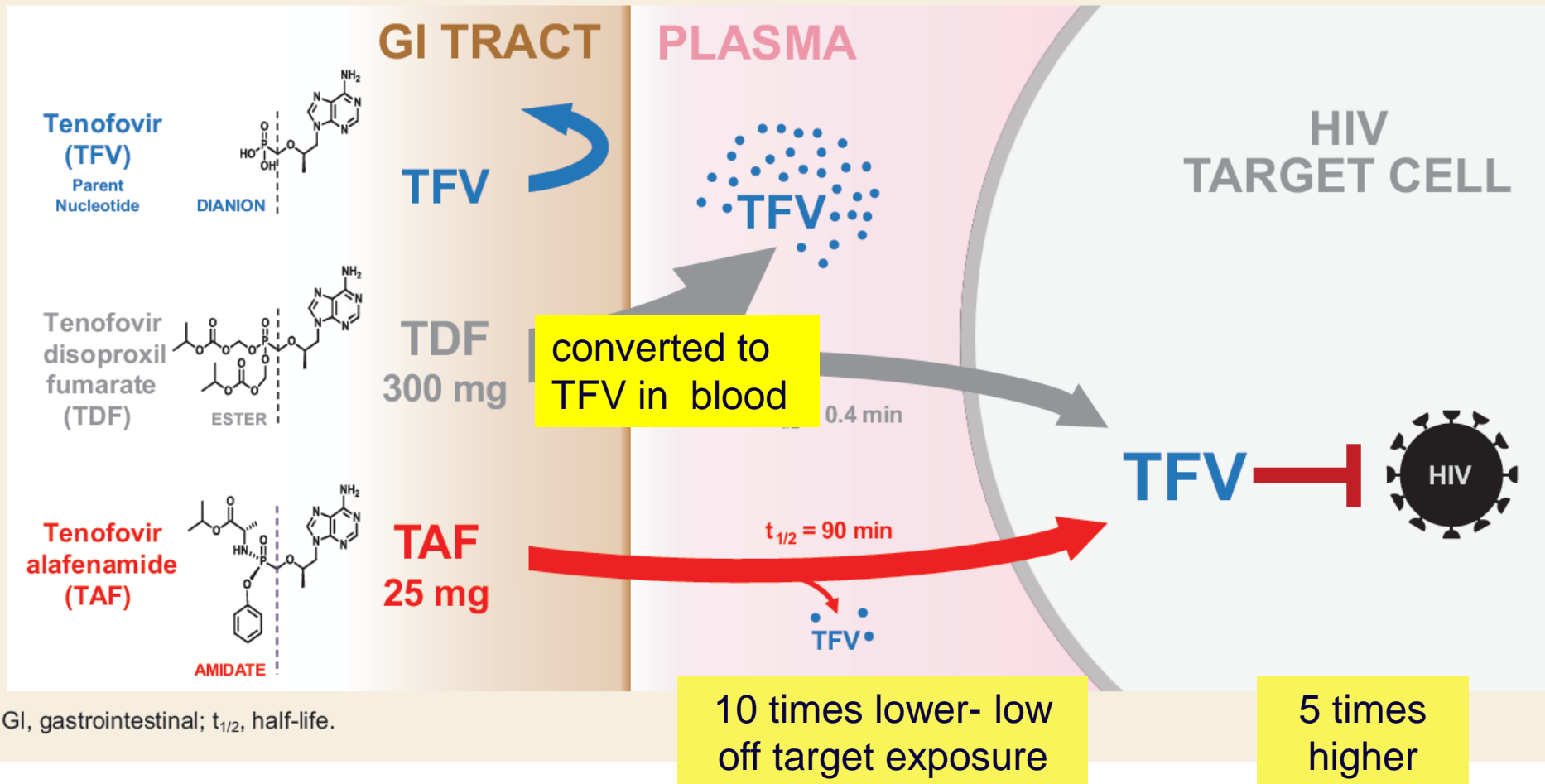
Reasons to choose TAF

Reasons to choose TDF



TAF & TDF – TFV prodrugs

Mechanism of Action: TAF vs TDF¹⁻⁶



HIV and Renal Disease: Role of TDF

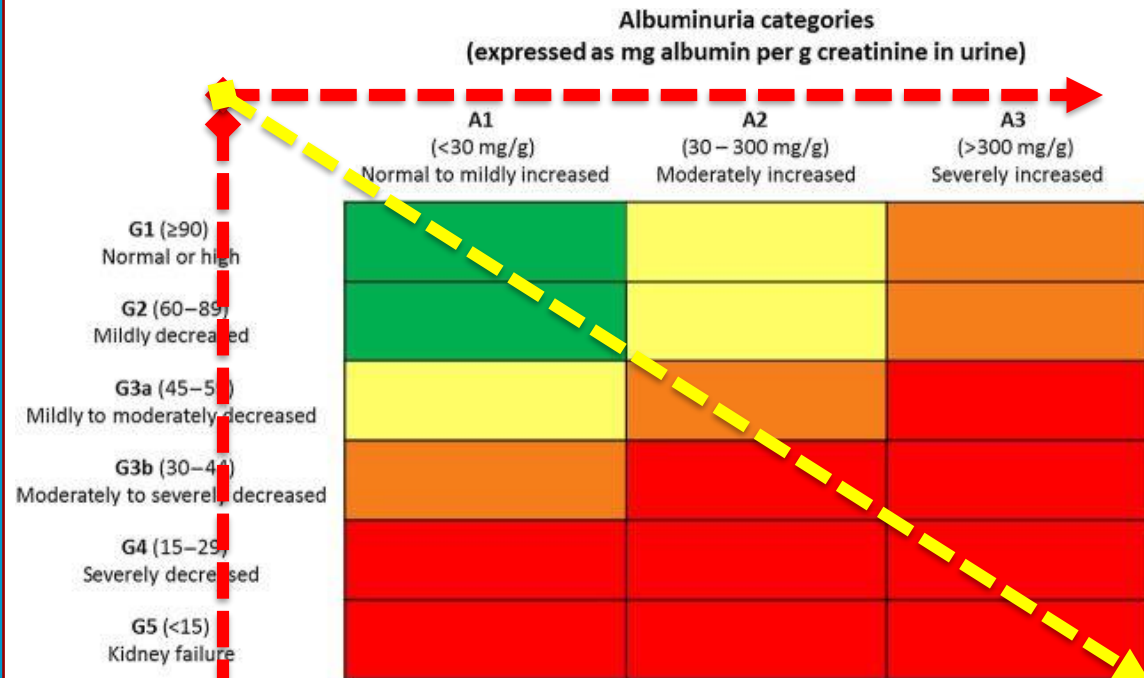
- *HIV is a risk factor for CKD and ESRD
- Prevalence of CKD (GFR <60 mL) 4.7% - 9.7%, higher rates if include proteinuria
- Factors associated with increased risk of CKD:
 - Older age, female sex, DM, HPT, previous AKI
 - Lower CD4, specific ARVs, and higher VL
- TDF associated with 16-55% increase incidence, 2-5 excess cases per 1000 person years¹

Decreased GFR and Proteinuria Predict Poor Clinical Outcomes

* In general population, low GFR and increased proteinuria is associated with **ESRD, CVD, all cause mortality**¹

Surrogate Markers

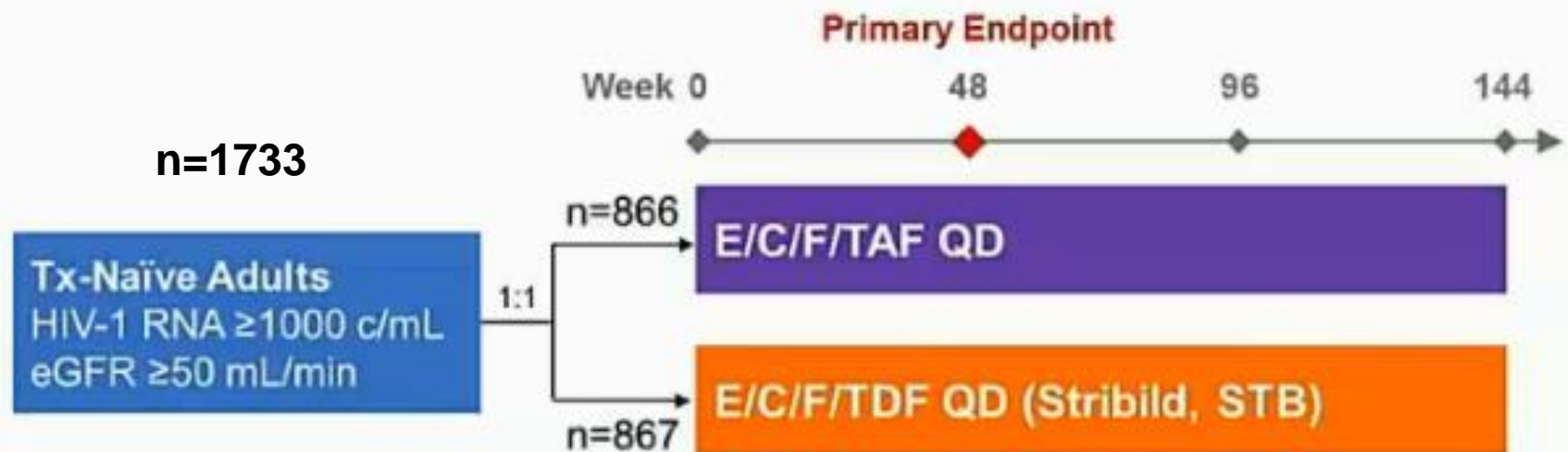
A positive impact on these is desirable.



Chronic kidney disease categorized by eGFR & albuminuria. Colors reflect risk for clinical outcomes: **ESRD, CVD, all cause mortality**. **Green: low risk**; **yellow: moderate risk**; **orange: high risk**; **red: very high risk**

TAF vs. TDF in Treatment-Naïve Patients

*2 randomized double-blind phase 3 trials compared safety & efficacy of EVG/c/**TDF**/FTC & EVG/c/**TAF**/FTC - 1733 ART-naïve with eGFR ≥ 50

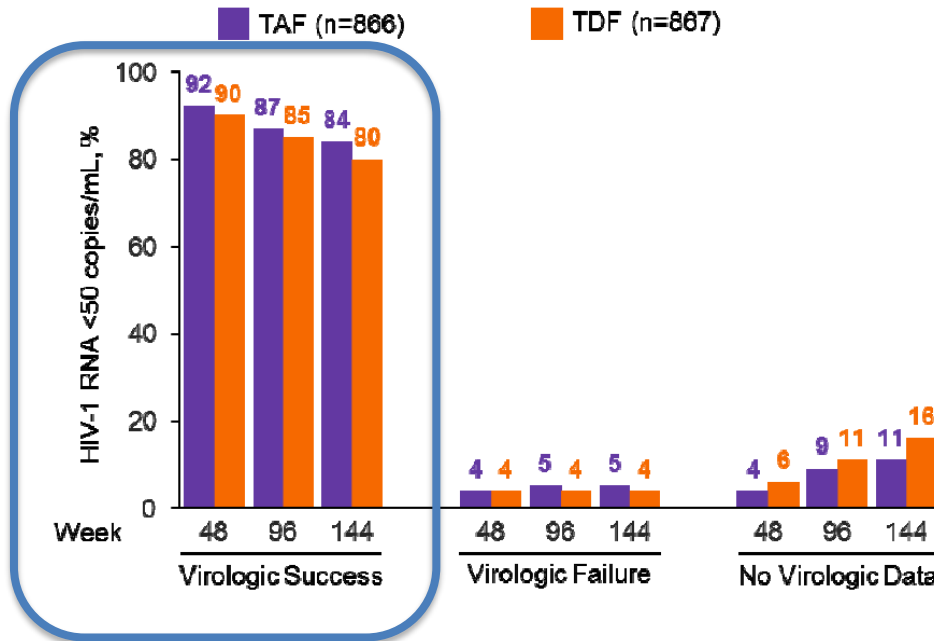


- Median age ≈ 34 yr
- Median CD4 ≈ 405
- Median eGFR ≈ 115

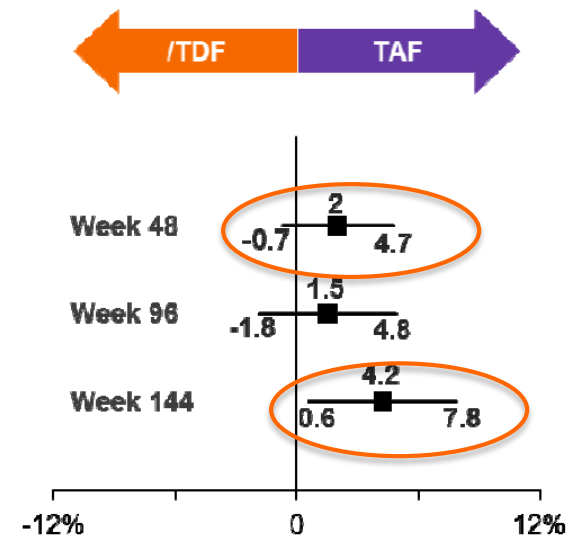
Randomized 1:1 to once-daily TAF 10 mg vs TDF 300 mg- with co-formulated EVG, COBI, & FTC 200 mg (E/C/F).

TAF vs. TDF in Treatment-Naïve Patients

Virologic Outcome



Treatment Difference (95% CI)



- At 48/52- VL <50 in 92% on TAF and 90% on TDF (TAF was non-inferior)
- At 144 weeks TAF was superior to TDF (VL <50 in 84.2% on TAF vs. 80% on TDF) largely d/t higher treatment discontinuation in the TDF arm.
- Virologic failure with resistance was uncommon in both groups (1.4%)

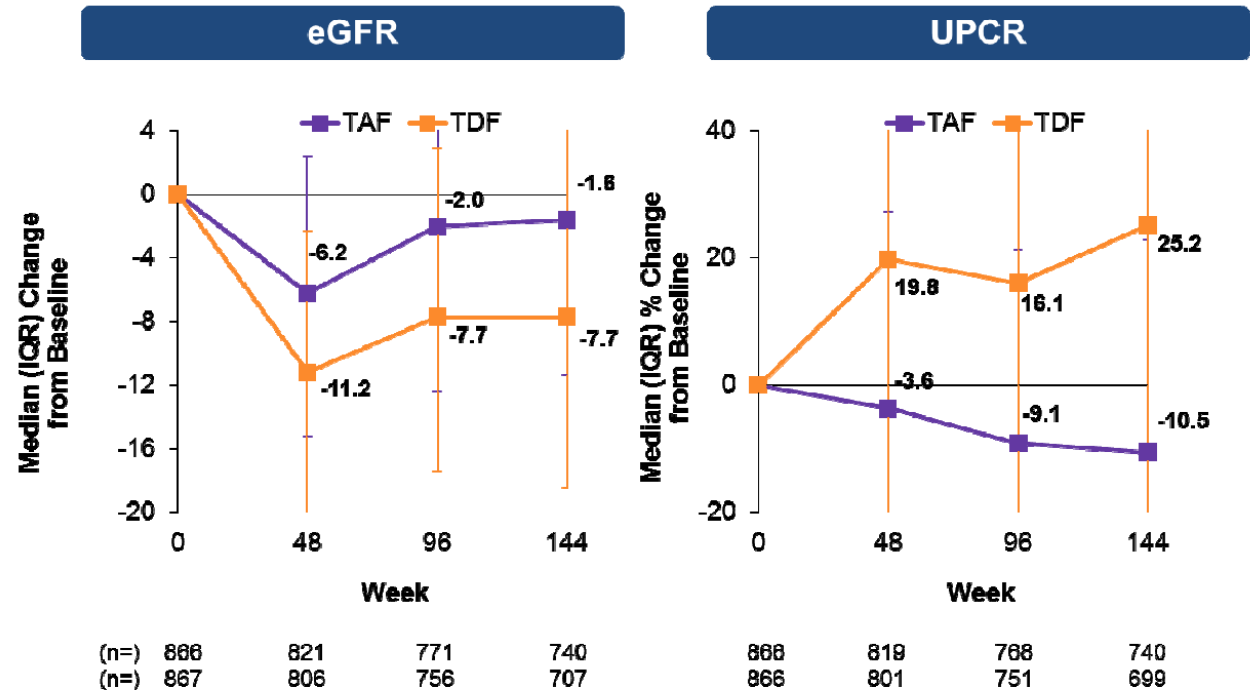
Adverse Effects TAF vs. TDF

- More discontinuations - **TDF (29/3.3%) vs. TAF (11/1.3%)**
- ***12 renal events** \Rightarrow Rx discontinuation - TDF, none - TAF
proximal tubulopathy (4); \uparrow sCr (3); RF (2); nephropathy (1); proteinuria (1); bladder spasm (1)
- 7 patients on TDF developed lab criteria for renal tubulopathy, **none on TAF**
- 6 patients on TDF had bone events that led to Rx discontinuation, **none TAF**
- **Not adequately powered to assess RF & fractures**

**TAF is as effective as TDF, possibly better
due to less toxicity**

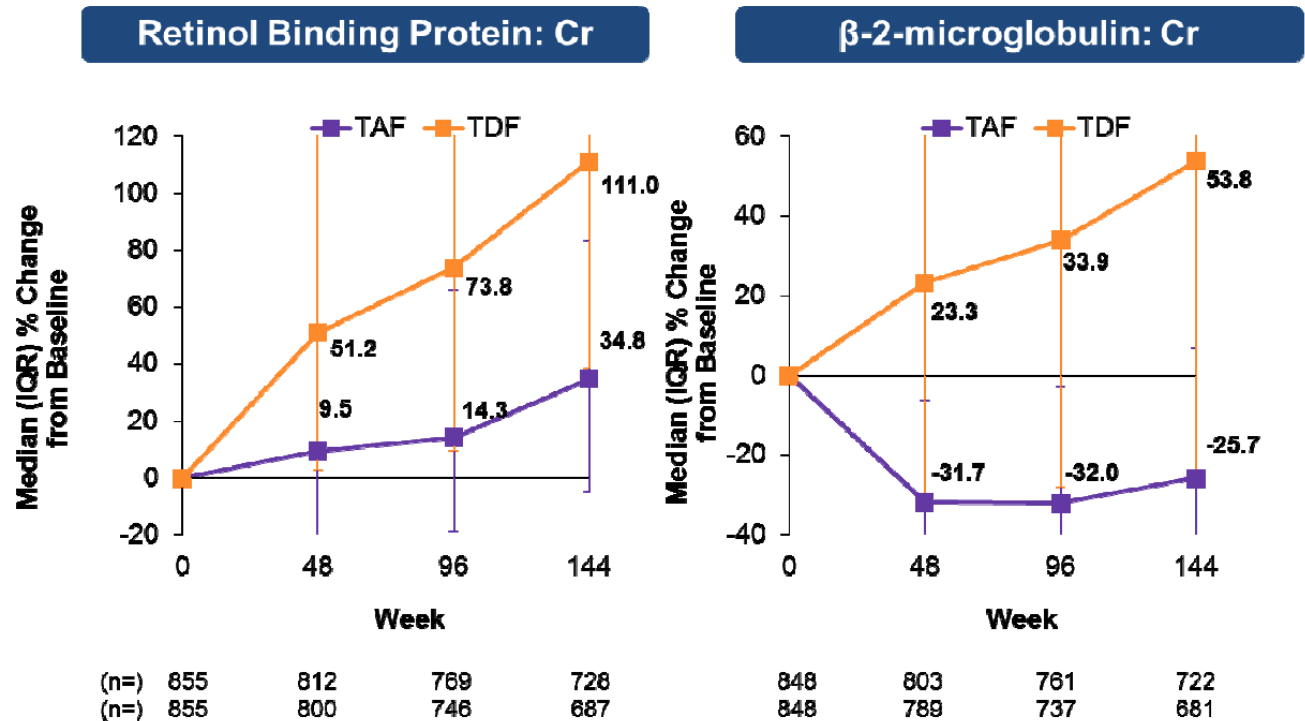
*Pts on TAF developed less reduction in GFR and less proteinuria

eGFR & UPCR
favored TAF



*Proximal tubular proteinuria less in patients initiating E/C/F/TAF than in those starting E/C/F/TDF

Renal tubular function was less affected by TAF



Advantages of TAF might seem small in an individual, but on a population level benefits may be substantial and increase over time

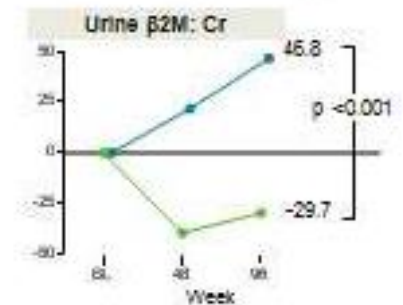
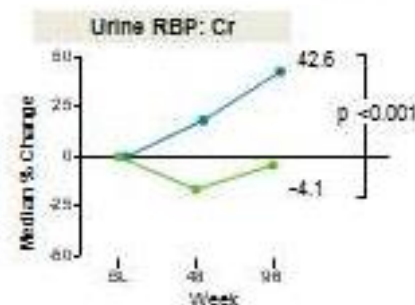
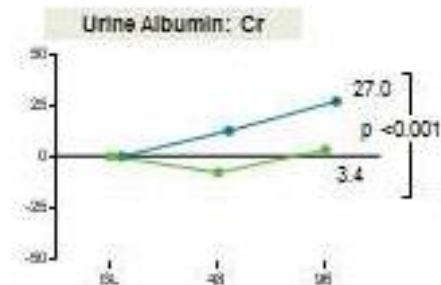
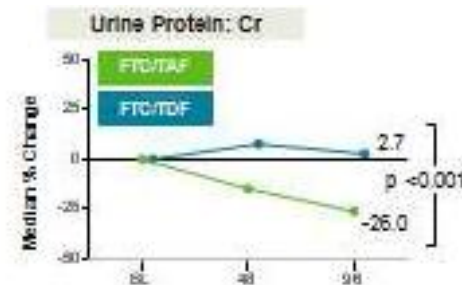
Is there any benefit to switching
from TDF to TAF in patients with
normal renal function?

Proteinuria Decreases When TDF/FTC switched to TAF/FTC

- N=663 virologically suppressed
- **Baseline CrCl 100**
- Randomized: cont. TDF/FTC (330) switch to TAF/FTC (333)
- Median age 49 yr
- Significant improvement in albuminuria and tubular proteinuria after switch to TAF

	TAF	TDF	P
Baseline UPCR >200	29 (9%)	28 (8%)	
Baseline UACR >30	37 (11%)	31 (9%)	
Wk 48 UPCR Change >200 to <200	21/28 (75%)	7/24 (29%)	0.0019
Wk 48 UACR Change >30 to <30	20/37 (54%)	3/30 (10%)	0.0002

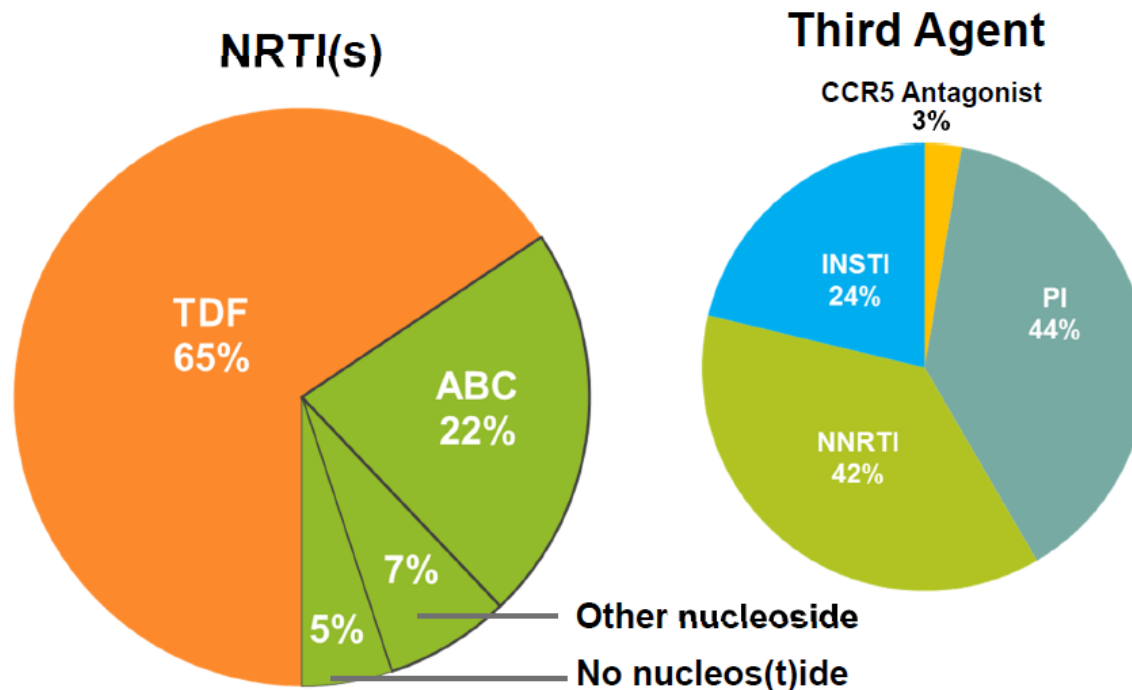
Renal effect of TDF appears to be lifted by switching to TAF.



Is there any benefit to switching to
TAF in patients at high risk of
kidney

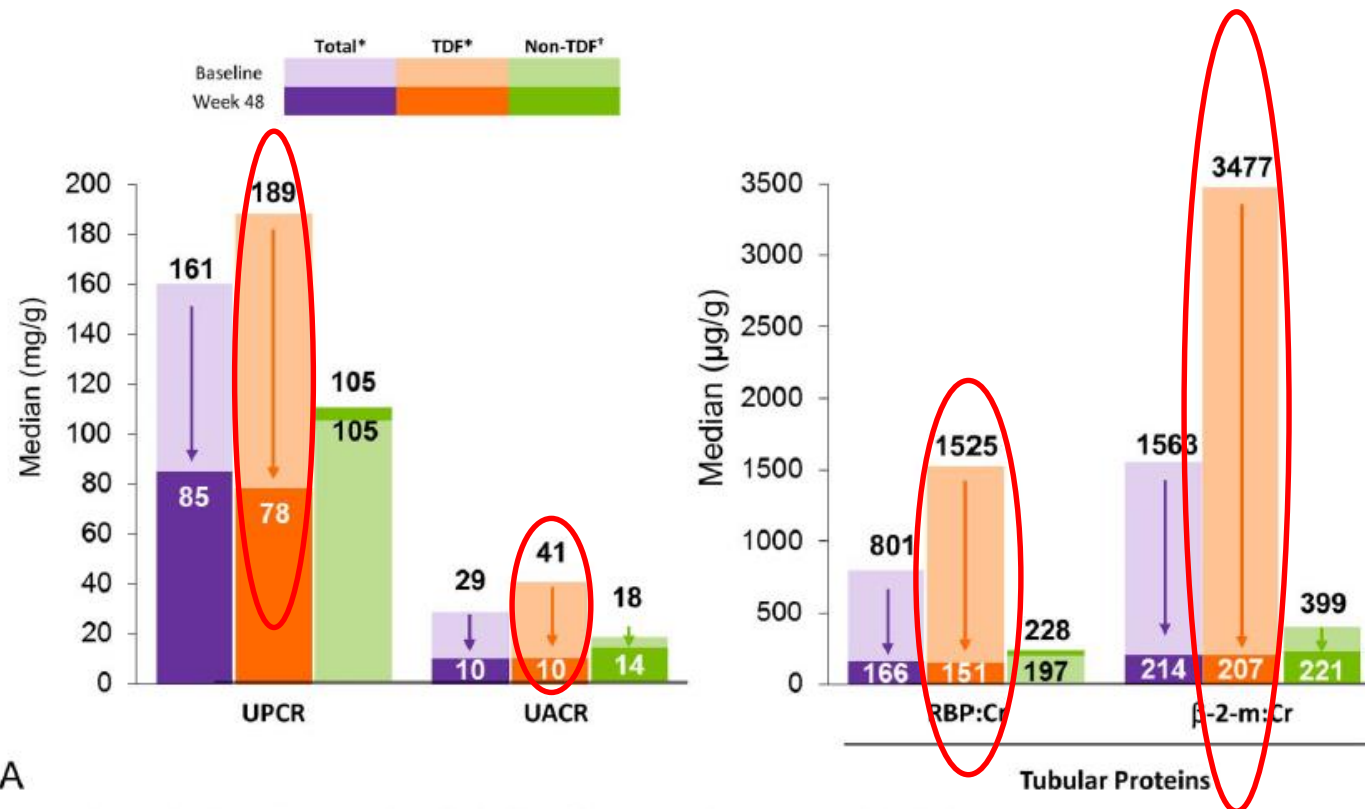
* Patients with mild/moderate renal impairment Switched to TAF

- eGFR of 30–69 mL/min
- Switch from different ART regimens – **mostly TDF**
- Single-arm, open-label study, switch to E/C/F/TAF.



Switching to TAF: mild to moderate renal impairment.

- ***No significant change in eGFR**
- Significant improvement in proteinuria, albuminuria, tub. Proteinuria in the entire group and those switched from TDF but not in those switched from non-TDF containing regimens.



*All Total and TDF changes statistically significant; †all non-TDF changes not statistically significant.

FIGURE 1. A, Proteinuria: change from baseline to week 48.

Moving away from TDF results
in an improvement in the
associated renal toxicity
markers without TAF adding to
that burden

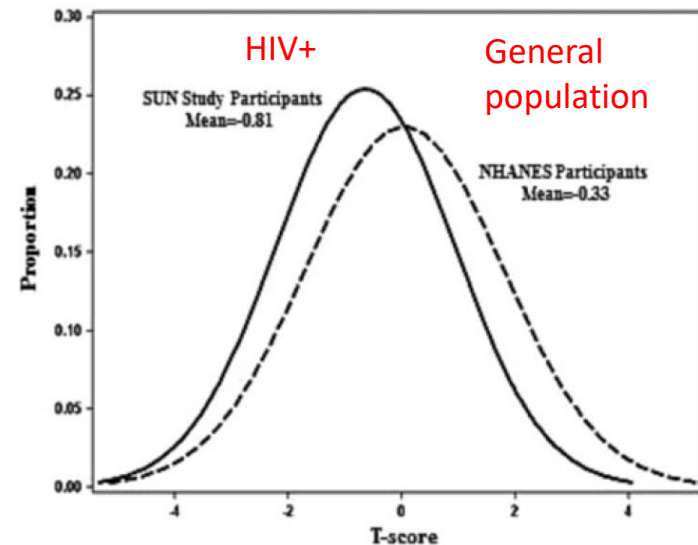
HIV and Bone Disease

- In the older general population, risk of fracture approximately doubles for each standard deviation decrease below young normal mean BMD

- **In HIV**

- High prevalence of osteopenia (40-62%), osteoporosis (14-42%) and fractures¹
- Osteopenia & osteoporosis is about twice more common compared to HIV neg. matched controls (age, sex, race, and BMI)¹

LOW BMD AND PROGRESSIVE BONE LOSS



¹Escota GV et al, ARHR, 2016,²Bedimo R et al, AIDS 2012; ³Borges A et al, CID, 2017

ART and Bone Disease

- *The majority on ART have stable BMD over time
- Significant no. continue to experience bone loss >5% BMD over 4 years despite suppressed viremia:
 - Similar to that seen with 1 year of corticosteroid Rx
 - More than that seen in HIV neg peri/post-menopausal women & older men.

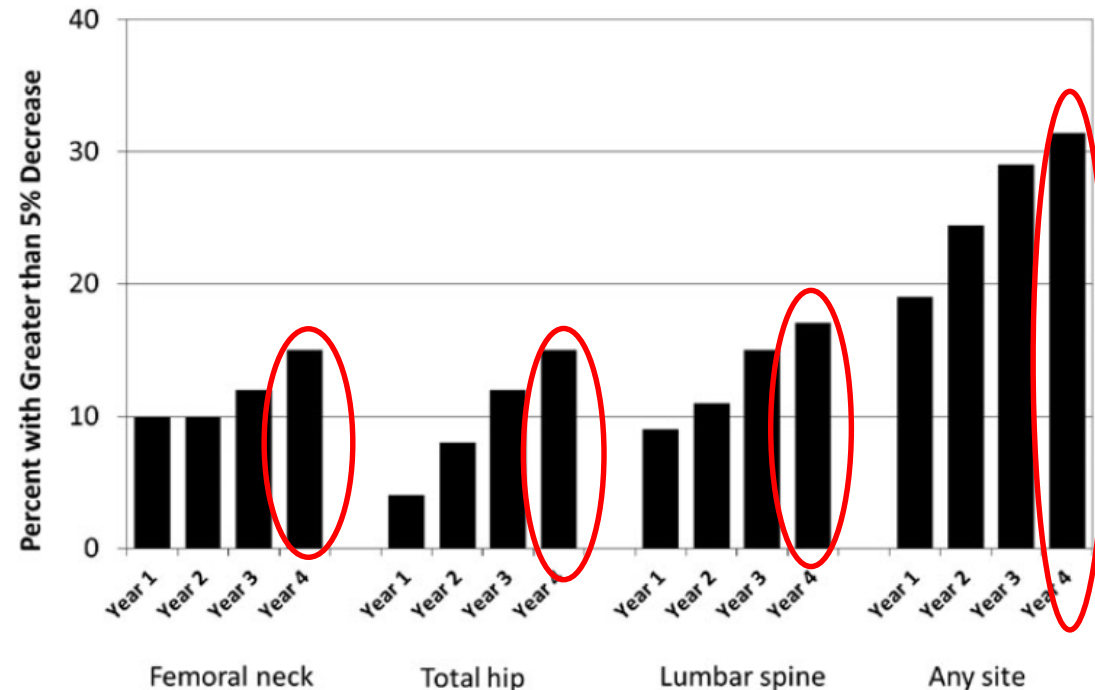


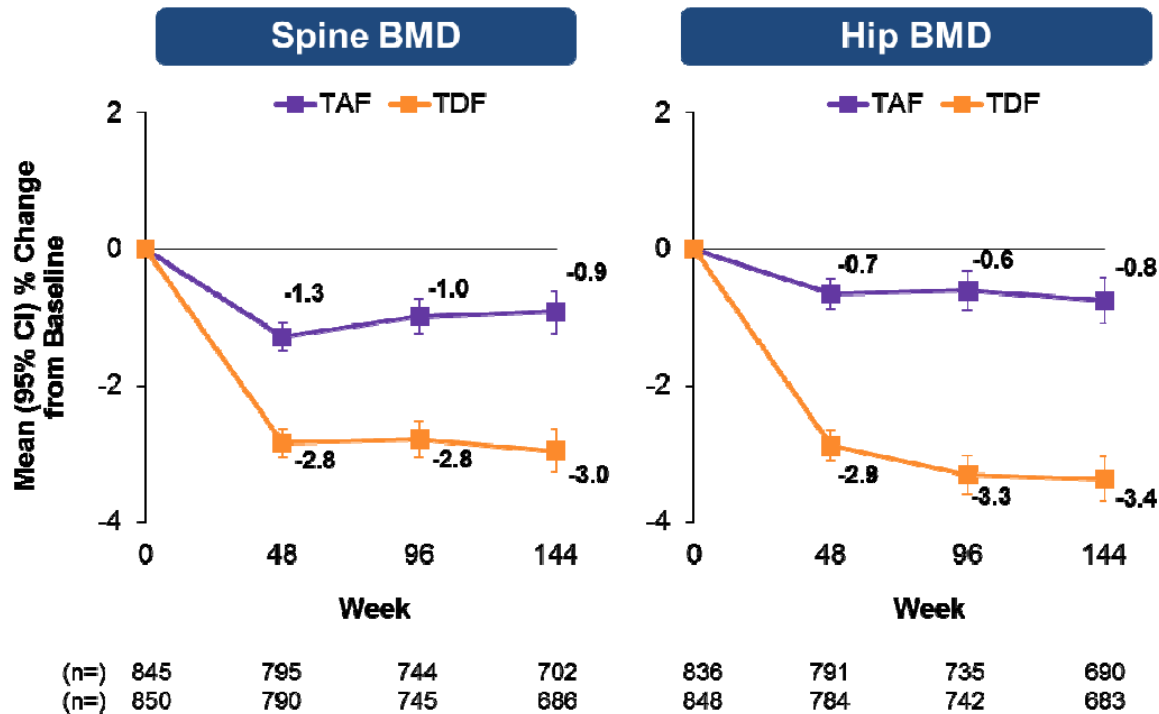
FIG. 2. Proportion with at least 5% loss in BMD over 4 years in subjects with virologic suppression (n = 170). At yr 4 **15% - femoral neck, 15% - total hip, 17% lumbar spine and 31% at one or more relevant sites.**

TDF and Bone Disease

- *TDF associated with greater bone loss \Rightarrow 2-4 % decrease in BMD – which is similar to bone loss during menopause.
- TDF associated with increased rate of fractures^{2,3}
 - 12% higher risk per year of exposure³
- Concomitant exposure to rPI associated with greater fracture risk²

Treatment naïve comparing TAF with TDF

Mean change in BMD is less and fewer on TAF had significant reduction in BMD



Difference between TAF and TDF: 1.99%

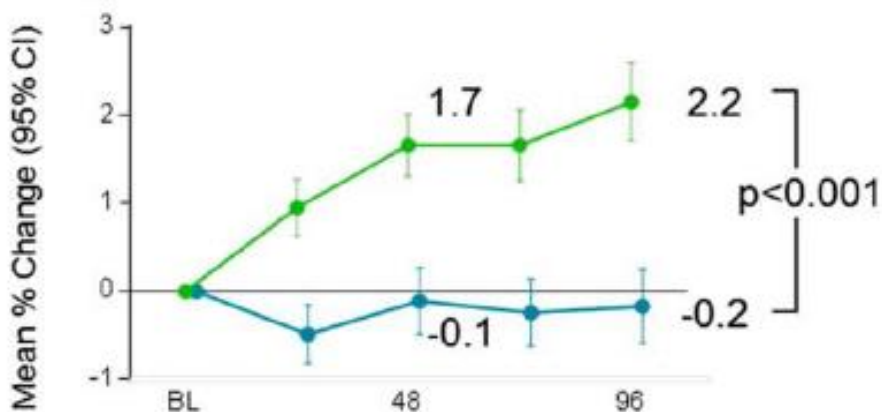
Difference between TAF and TDF: 2.61 %

Wk 144	TAF	TDF
Spine BMD decline $\geq 5\%$	15%	29%
Hip BMD decline $\geq 7\%$	15%	29%

- Fractures rare: all due to trauma
- No discontinuations due to BMD with TAF.
- 6 men discontinued TDF because of a $>5\%$ decrease in BMD

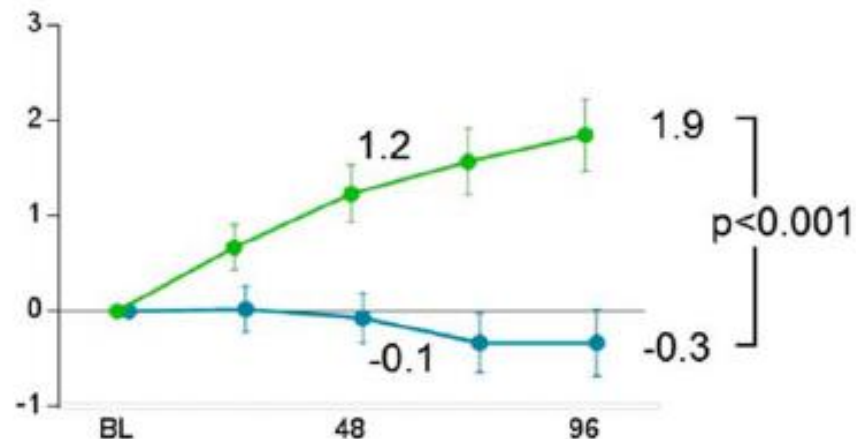
Switching from TDF/FTC to TAF/FTC: >2% ↑ in BMD

Spine BMD



Improvement after switching from TDF to TAF: 2.4%

Hip BMD



Improvement after switching from TDF to TAF: 2.2%

BMD gain after alendronate in HIV negative pts with osteoporosis: 4-6% → 50% reduction fracture rate.

Without adding a drug, switching TDF to TAF has **an effect almost ½ as great as starting bisphosphonate.**

TAF has far less bone effects than TDF

TAF vs. TDF: Lipid Effects

Lipids: ART naïve initiating E/C/F/TAF or E/C/F/TDF

*TAF is associated with greater increases in median TC, LDL, HDL & TGA than TDF

Lipids	TAF	TDF	TAF % Change	TDF % Change
Total cholesterol (Baseline to Wk 144)	+31 (160 → 191)	+13 (163 → 176)	+19%	+8%
LDL (Baseline to Wk 144)	+19 (101 → 120)	+6 (104 → 110)	+19%	+5.7%
HDL (Baseline to Wk 144)	+6 (44 → 50)	+2 (44 → 46)	+13.6%	+4.5%
TG (Baseline to Wk 144)	+20 (95 → 115)	+12 (100 → 112)	+21%	+12%
TC:HDL ratio (Baseline and Wk 144)	3.7	3.7		

Lipid lowering effect of TDF/FTC: TULIP



The Lipid-Lowering Effect of Tenofovir/Emtricitabine: A Randomized, Crossover, Double-Blind, Placebo-Controlled Trial

José R. Santos,^{1,2} María Saumoy,³ Adrian Curran,^{2,4} Isabel Bravo,¹ Josep M. Llibre,^{1,2} Jordi Navarro,^{2,4} Carla Estany,¹ Daniel Podzamczar,³ Esteban Ribera,^{2,4} Eugènia Negredo,^{1,5} Bonaventura Clotet,^{1,2,5,6} and Roger Paredes^{1,2,5,6}, for the Tenofovir/emtricitabine influence on Lipid metabolism (TULIP) Study Group

¹Lluita contra la SIDA Foundation, Germans Trias i Pujol University Hospital, ²Universitat Autònoma de Barcelona, ³HIV Unit, Infectious Diseases Service, Bellvitge University Hospital, Bellvitge Biomedical Research Institute, Hospitalet de Llobregat, ⁴Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Barcelona, ⁵Universitat de Vic–Universitat Central de Catalunya, Vic, and ⁶IrsiCaixa AIDS Research Institute, Barcelona, Spain

CID, 2015

- TDF/FTC added to PI monotherapy in subjects with TC: ≥ 5 or LDL ≥ 3.3 and not on lipid lowering agents

- TDF has an intrinsic lipid-lowering effect:
 - Reduced mean levels of TC, LDL, HDL
 - Decreased proportion of subjects:
 - TC ≥ 5 mmol/L from 86.7% to 56.8% (P = .001)
 - LDL ≥ 3.3 mmol/L from 87.8% to 43.9% (P < .001).

When switching from TAF to TDF need to closely monitor lipids

Achilles heel

Drug - Drug interactions

Drug-Drug Interactions

- TAF is a substrate of drug transporters (p-gp)
- Inhibitors of p-gp (rit & cobicistat) increase plasma concentrations
- Inducers of p-gp may decrease plasma of TVF:
Coadmin with Rif not recommended
- No significant interactions between TAF and DTG or RPV (25 mg/d)

Once-daily TAF with rifampicin

- PK study of TAF OD with RIF was compared directly with TDF in healthy volunteers
- Measured plasma TAF, TFV, FTC & IC TFV-DP/FTC-TP
- IC TFV DP after OD TAF + RIF achieved a concentration of that was 82% of that achieved by standard dose TDF.
- Data supports further studies of TAF co-administered with RIF in HIV and TB coinfection

Should TAF replace TDF?

Reasons to choose TAF

- TAF is as effective as TDF, perhaps slightly more so because of less toxicity.
- TAF is associated with less deleterious effects on eGFR and proteinuria than TDF.
- TAF is associated with smaller declines in BMD than TDF.
- Switching from TDF to TAF results in less proteinuria, increase BMD
- Benefit of TAF may be greater in pts at high risk for kidney & bone disease.

Reasons to choose TDF

- Compared with TAF, more and longer-term data with TDF.
- TDF associated with smaller increase in LDL than TAF → lipid monitoring needed
- TDF-cost lower
- Dosing with rifampicin established

