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BHIVA 'Best of CROI' Feedback Meetings

London | Birmingham

Haydock | Newcastle

Cardiff | Wakefield

Edinburgh

Opportunistic infections and complications

Dr Frank Post

King's College London

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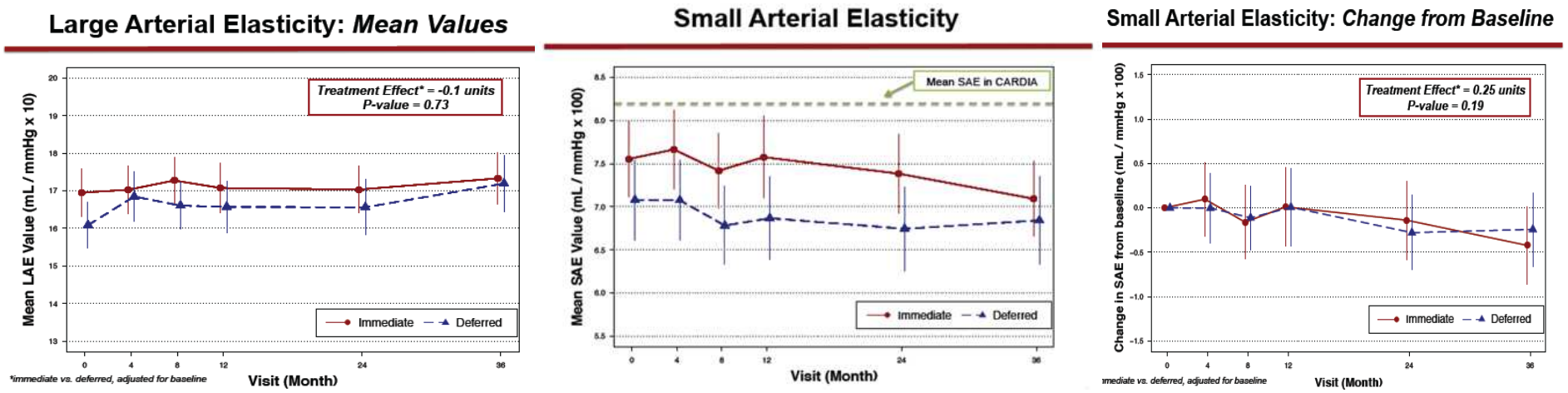
MI and vascular disease

Early antiretroviral therapy does not improve vascular function: a START sub study



- START sub-study (n=332)
- Mean age 35 years, 70% male, 66% non-white, 30% smokers, low CVD risk
- Two groups were matched.
- FU through 36 months.
- Immediate ART did not improve arterial elasticity compared with deferred ART

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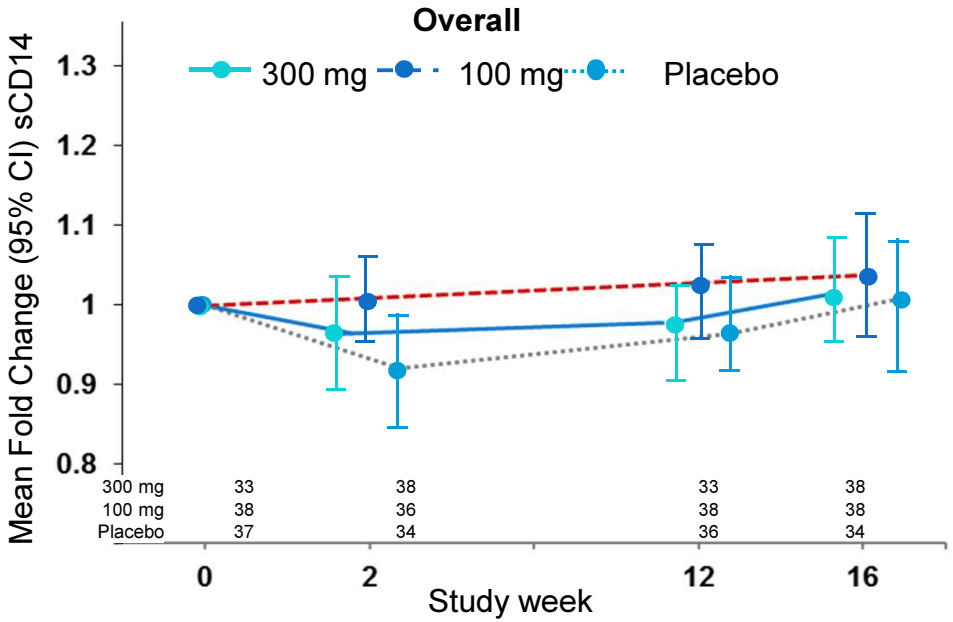
Baker, JV et al, CROI 2016, Oral #41

Aspirin fails to impact immune activation or endothelial function in treated HIV

- ACTG A5331 - double-blind RCT
- Randomized to daily aspirin (100 or 300mg) or placebo for 12 weeks
- No major impact on immune activation (sCD14), endothelial function (FMD) or coagulation (d-dimer) when added to fully suppressive ART
- This study does not support the use of aspirin as anti inflammatory in HIV patients



O'Brien ML, et al, CROI 2016, #44LB

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CNICS Cohort (1996-2014)

Comparing Cardiovascular Disease Risk Scores in HIV

Population: 10,832 HIV+ pts with 229 incident MIs, FU: 4.3 yrs
Outcomes: Discrimination and calibration

AUC	Framingham	DAD	ATP3	ASCVD
	AUC	AUC	AUC	AUC
Type 1 MI	0.73*	0.74*	0.73*	0.72
Type 2 MI	0.63*	0.63*	0.62*	0.72
All MI	0.68*	0.69*	0.63*	0.74

All Myocardial Infarctions Expected vs observed event rates for 4 risk scores: Framingham, ATP-3, ACC/AHA ASCVD, D:A:D

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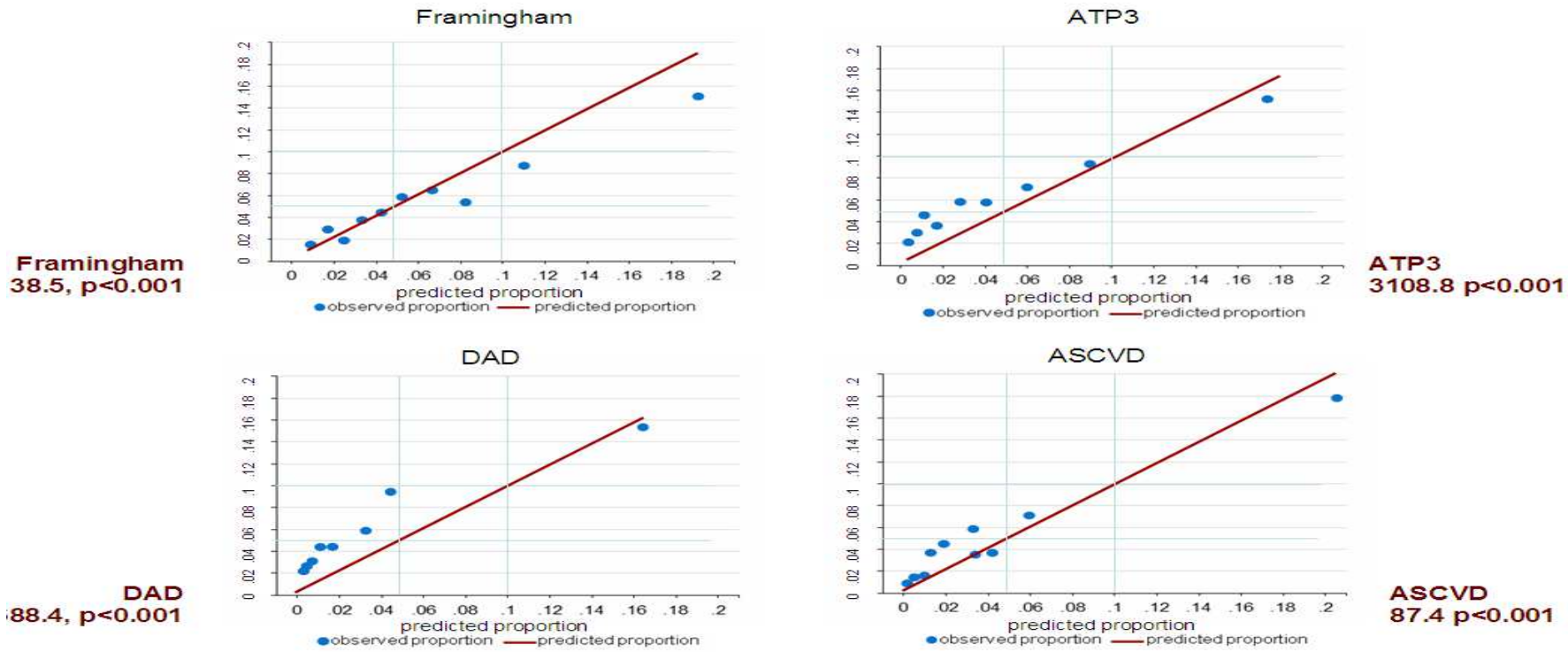
Crane H, et al. CROI 2016; Boston #O42; Clement ME, et al. CROI 2016. Poster 642

CNICS Cohort (1996-2014)

Comparing Cardiovascular Disease Risk Scores in HIV



- The DAD score underestimates the observed risk of CVD
- The addition of HIV-specific variables as in the DAD score did not improve discrimination compared with ASCVD

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Crane H, et al. CROI 2016; Boston #O42; Clement ME, et al. CROI 2016. Poster 642

ABC Use and Recurrent Myocardial Infarction

Retrospective analysis (1999-2014) on 816 pts of D:A:D cohort with a MI (baseline)

- A total of 102 recurrent MI occurred over 3863 PY (rate 2.64/1000 PY; 95%CI:2.13, 3.15)
- Rate of recurrent MI was 3.47 (95%CI:2.37, 4.57)/1000 PY for pts currently receiving ABC post-MI vs. 2.31 (95%CI:1.75, 2.88)/1000 PY for those who were not in ABC

Associations between use of ABC at initial MI, current post-MI use and cumulative exposure to ABC post-MI and risk of recurrent MI

Univariate analysis	Relative hazard	P-Value
Receipt of ABC at initial MI	1.07 (0.72, 1.59)	0.74
Current post-MI use of ABC	1.50 (1.00, 2.24)	0.05
Cumulative exposure to ABC (/5 years)	0.88 (0.65, 1.19)	0.41

The association between post-MI exposure to ABC and recurrent MI appeared to be largely explained by ABC use in earlier years

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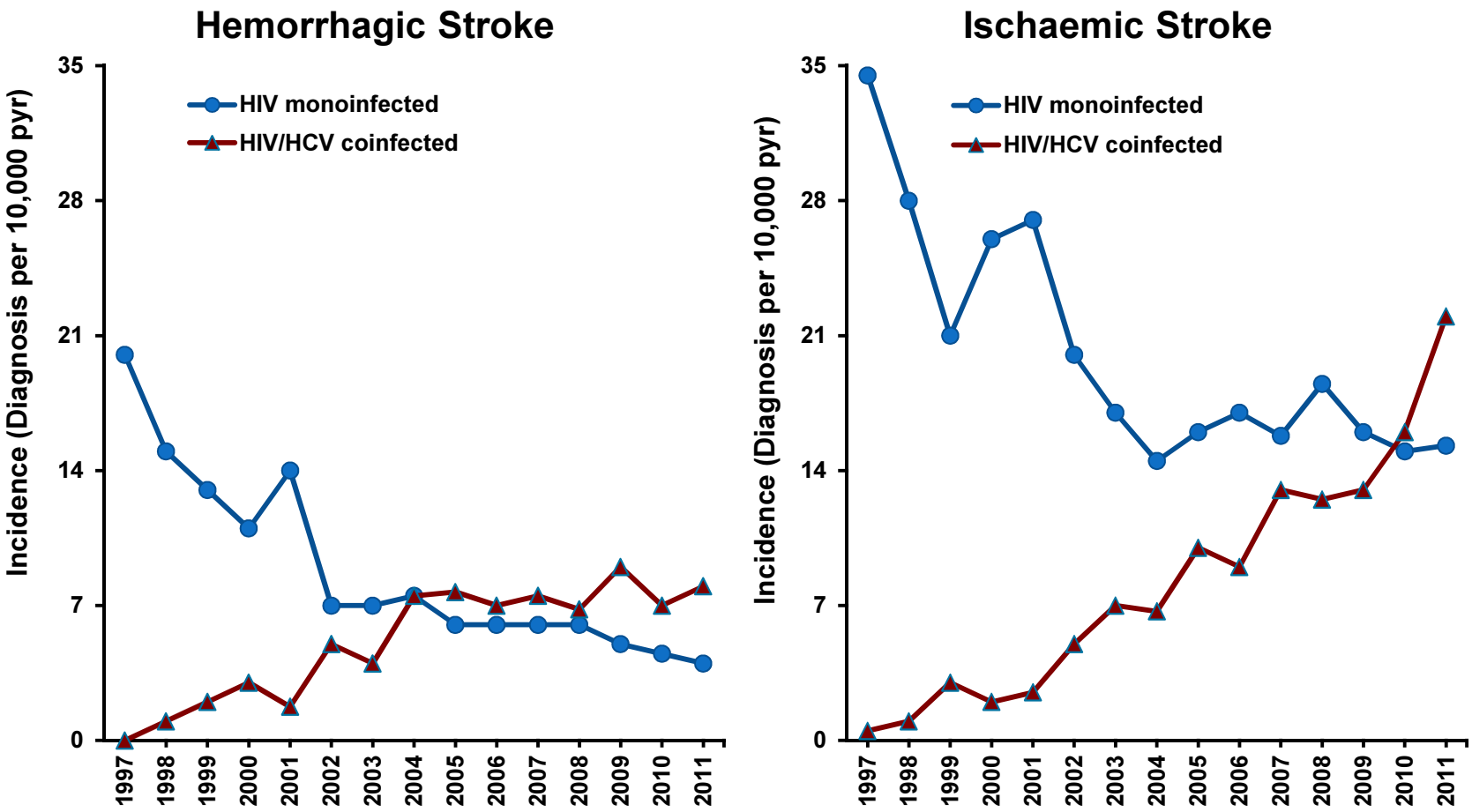
O'Brien ML, et al, CROI 2016, #44LB

Incidence of Stroke in HIV-Infected Patients in Spain (1997-2011) Stratified by HCV Status



Berenguer J, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 639.

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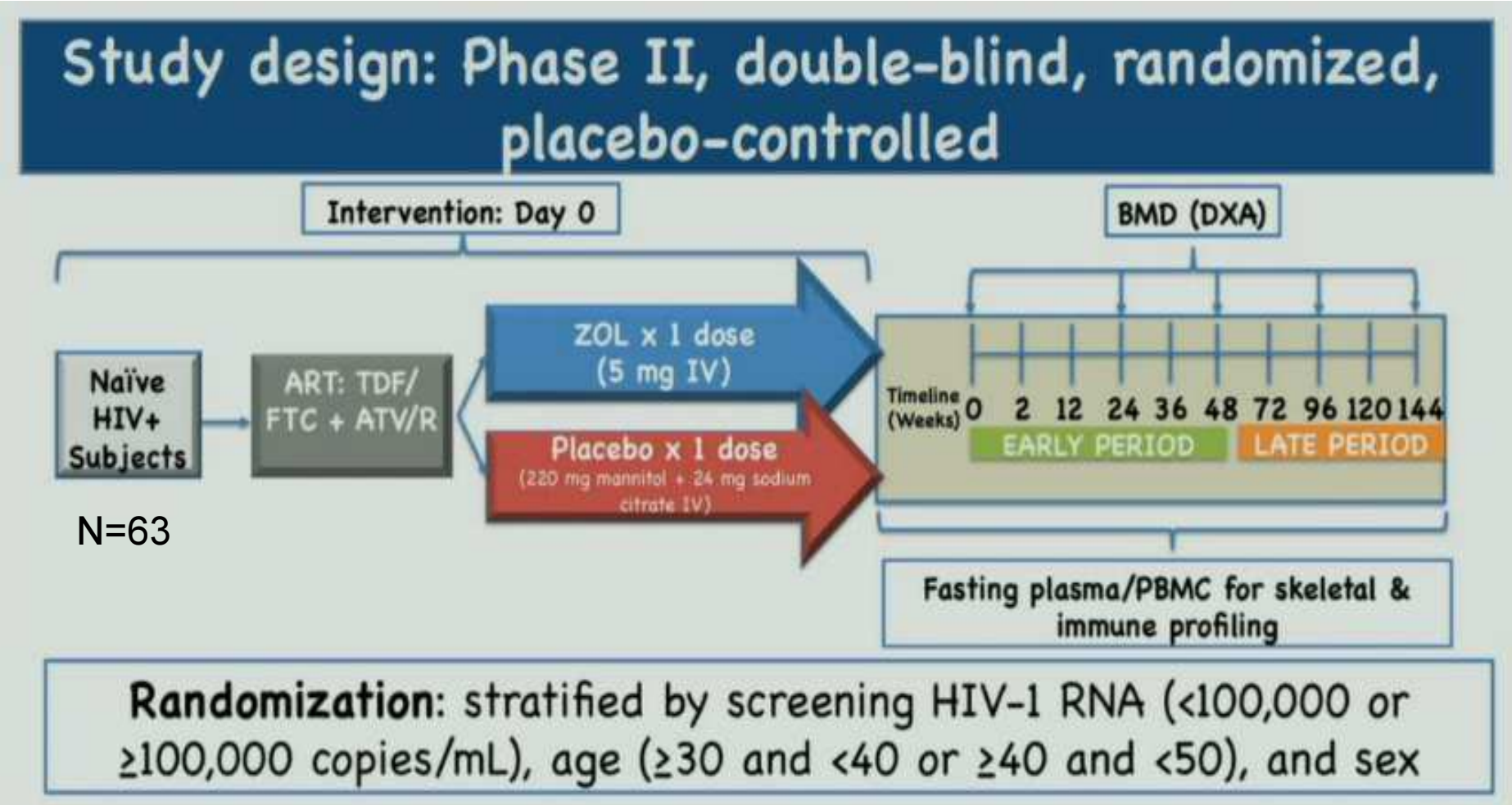
CVD: Take-home messages

- No benefit from early ART or aspirin in low risk patients with preserved CD4 cell count
- Superiority of DAD CVD risk score not confirmed
- The incidence of stroke has declined in HIV+ patients who do not have HCV

Bone disease and fractures

Single dose zoledronic acid prevents antiretroviral-induced bone loss (O-47)



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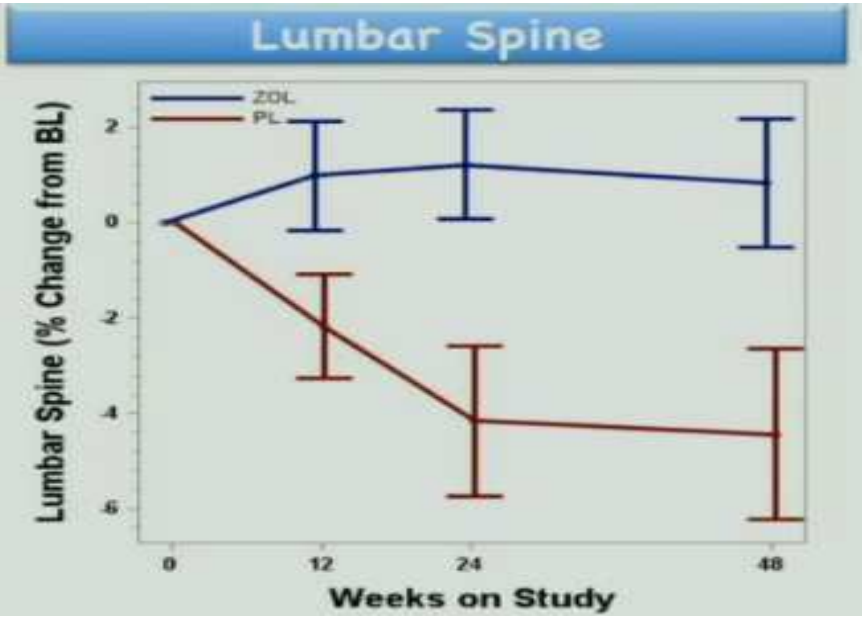
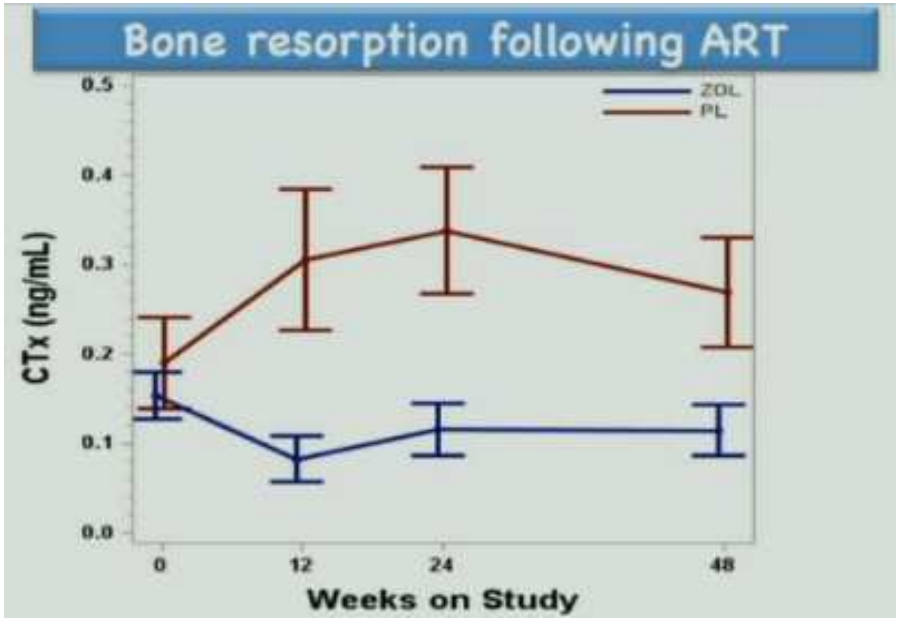
Zolendronate prevents BMD loss by inhibiting bone resorption.





LS BMD at 48 weeks: +1.8% vs. -4.4%

74% reduction in CTx at 12 weeks

- Significant trends were also observed at the hip and femoral neck.
- Similar rates of virologic suppression and mean CD4 T cell increase over 48 weeks
- No major side effects.

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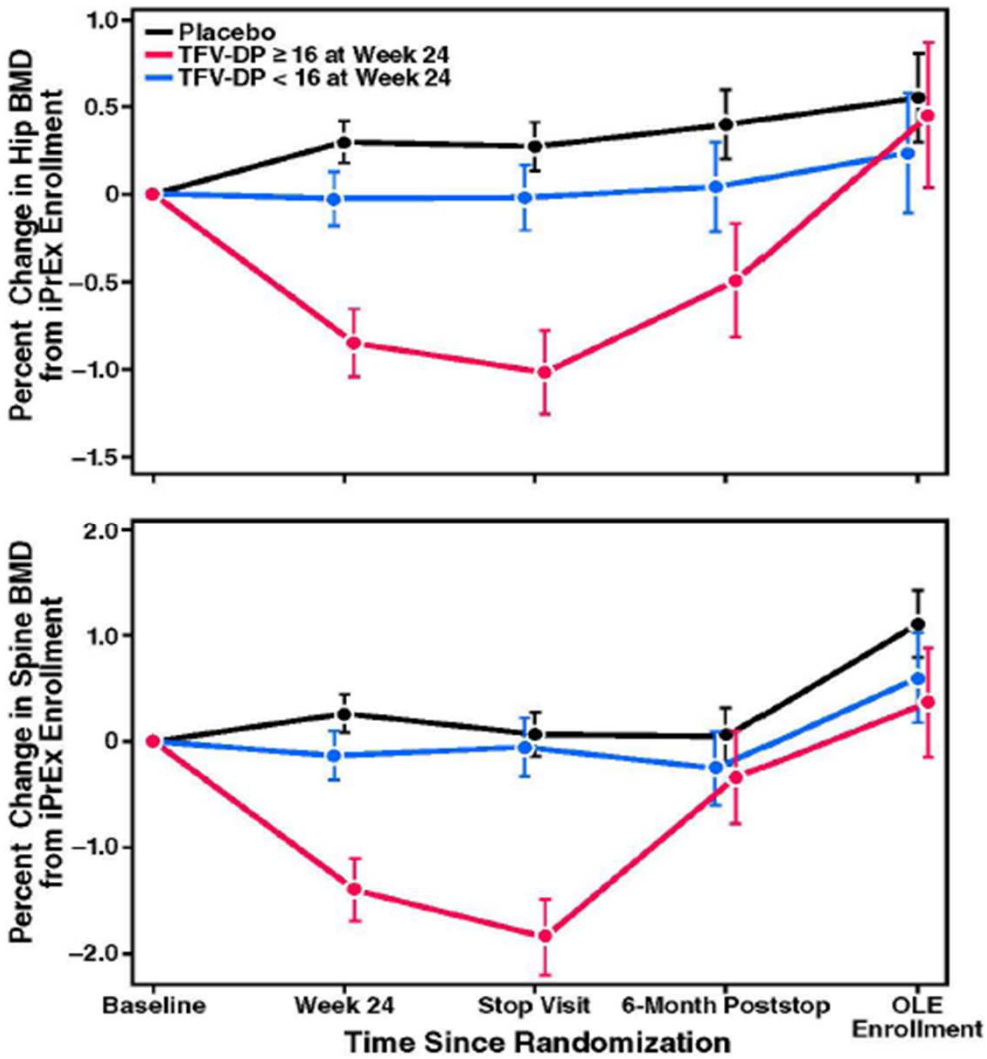
BMD recovery after stopping TDF/FTC PrEP



- Patients with TFV-DP concentrations ≥16 fmol/10^6 cells experienced 1-2% reductions in BMD
- BMD changes were reversible after TDF/FTC discontinuation

Grant et al. 48LB

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Risk factors for fractures and osteonecrosis in EuroSIDA

- 11820 HIV+ patients: 86118 PYFU
- Baseline characteristics
  - Median age 41y, 75% male, 86% white, median CD4 440/mm^3 and 70.4% virologically suppressed
- 618 fractures: incidence 7.2 (6.6-7.7) per 1000 PYFU
- 89 cases of osteonecrosis: incidence 1.0 (0.8-1.3) per 1000 PYFU

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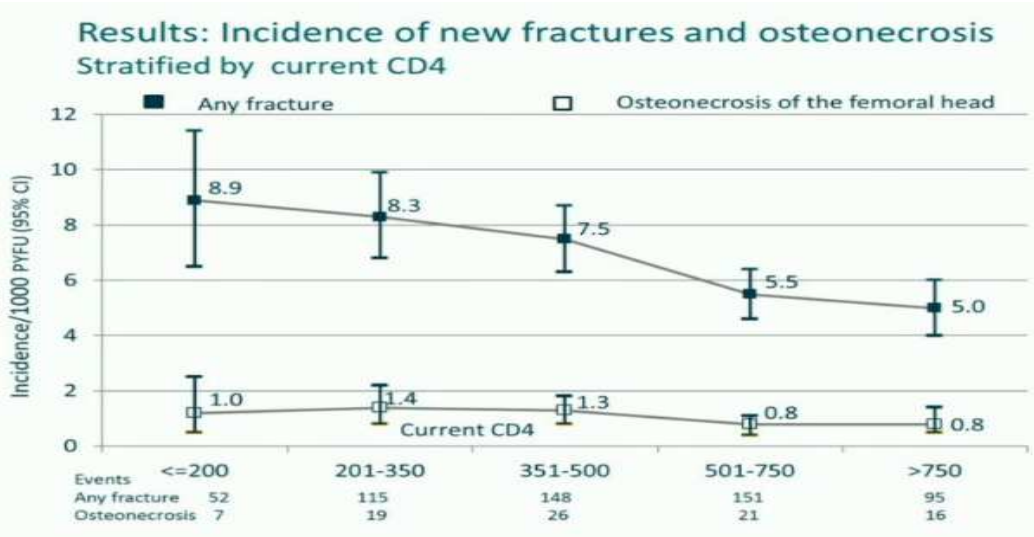
Antiretrovirals, fractures and osteonecrosis in a large European HIV cohort (EuroSIDA) (O-46)



TDF exposure	Any Fractures IRR (95% CI) Univariate	Any Fractures IRR (95% CI) Multivariate [b]	Osteoporotic fractures [a] IRR (95% CI) Multivariate [b]
Ever vs never TDF	**1.71** (1.42-2.06)	**1.40** (1.15-1.70)	1.10 (0.76-1.58)
On vs off TDF	**1.38** (1.16-1.64)	**1.25** (1.15-1.70)	1.12 (0.79-1.60)
Cumulative TDF exposure/ 5 years	**1.28** (1.13-1.50)	1.08 (0.94-1.25)	0.99 (0.69-1.43)

IRR: incidence rate ratio. **P< 0.05 for IRR (95% CI) written with bold letters**
[a] grouped as fractures of the spine, arm, wrist and hip
[b] adjusted for demographics, HIV-specific variables and co-morbidities

After adjustment, fractures were associated with:

- Older age, white race, lower BMI, IV drug use, lower baseline CD4, HCV-coinfection, prior osteonecrosis, prior fracture, recent non-AIDS cancer and recent cardiovascular disease (last 12 months), TDF exposure

Osteonecrosis was associated with

- White race, lower nadir CD4, prior osteonecrosis, prior fracture and prior AIDS

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Vitamin D and calcium supplementation

- ACTG A5280 is an RCT of the effects of Ca+/Vit D supplementation on BMD in patients starting Atripla
- Daily supplementation with vitamin D3/calcium attenuated the loss in bone mineral density (BMD) by approximately 50% over 48 weeks.
- Effect of ART initiation and ART plus vitamin D/calcium supplementation on bioavailable 25OHD in blacks and non-blacks in ACTG A5280

Yin et al, poster 700

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Vitamin D and calcium supplementation

Table 2. Baseline and Absolute Change from 0 to 48wks by race [Median (Q1, Q3)]

Variables	Baseline & Change 0-48 week	Placebo				Vitamin D/calcium			
		N	Black	Non-black	P	N	Black	Non-black	p
Total 25OHD (ng/mL)	Baseline	65	20.2 (16.0, 27.3)	29.8 (22.2, 35.6)	0.004	64	23.0 (14.6, 25.1)	34.7 (23.1, 40.5)	0.001
	Change		-2.5 (-6.3, 4.3)	1.3 (-5.5, 4.7)	0.25		32.2 (14.3, 42.6) *	22.5 (14.2, 34.1) *	0.27
VDBP (ug/mL)	Baseline	63	179 (92, 299)	272 (181 ,353)	0.007	60	93 (77, 255)	313 (216 , 408)	<0.001
	Change		25.9 (-4.8, 40.6) *	11.2 (-6.9, 38.7)	0.43		9.4 (-0.2, 28.3)	27.0 (0.0, 60.0) *	0.098
Bioavailable 25OHD (ng/mL)	Baseline	61	2.6 (1.4, 4.3)	2.0 (1.4, 3.3)	0.53	59	4.4 (1.8, 5.3)	2.1 (1.6, 2.6)	0.014
	Change		-0.1 (-1.4, 0.1)	0.1 (-0.4, 0.5)	0.063		3.9 (1.4, 7.3) *	1.1 (0.4, 2.2)*	<0.001#
PTH (pg/mL)	Baseline	69	28.9 (25.9, 34.0)	27.1 (21.3, 33.1)	0.44	65	27.5 (22.5, 35.5)	28.0 (25.4, 32.4)	0.89
	Change		5.9 (-0.4, 12.2) *	4.3 (-1.4, 12.3) *	0.49		-0.9 (-8.2, 4.2)	1.7 (-1.9, 7.2)	0.11

* p<0.05 within race group change from baseline.
\# p<0.05 difference between race groups (black vs. non-black) in change from baseline.

- Bioavailability of 25(OH)D similar in black vs. other participants
- PTH responses to TDF were similarly abrogated in these patients

Yin et al, poster 700

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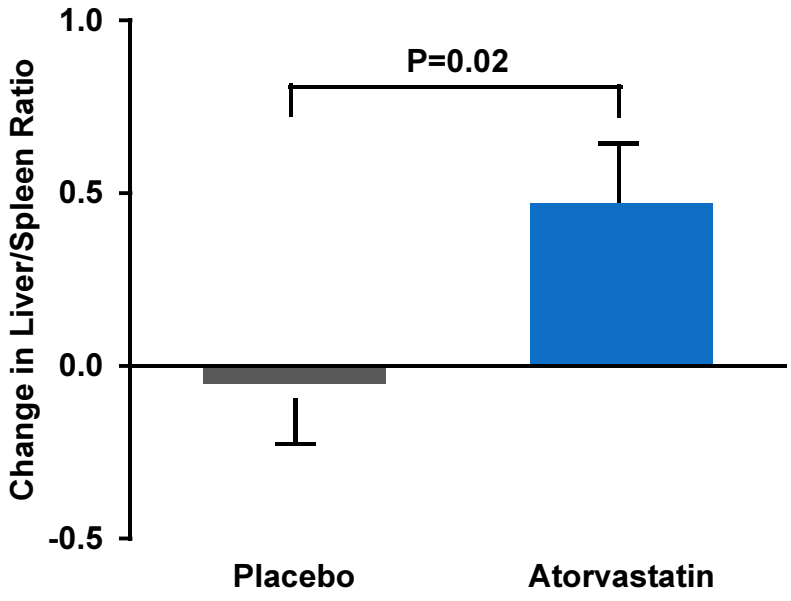
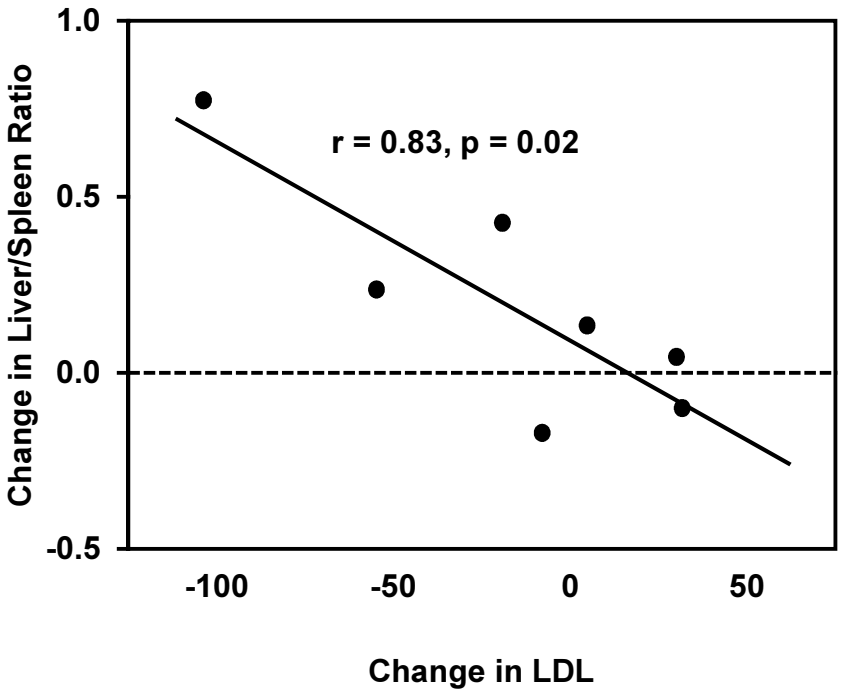
BMD and Fractures: Take-home messages

- Bone loss with initial ART can be prevented with bisphosphonates
- Effect of TDF-PrEP on BMD is reversible upon discontinuation
- Fracture risk in increased with immunodeficiency and TDF exposure

Liver disease and cancer

Statins Reduce Liver Fat in NAFLD Over 12 Months





In HIV/HCV patients, statin use was associated with a reduced incidence of:

- Liver cirrhosis (aHR 0.73, CI 0.58-0.92) [2]
- Hepatocellular carcinoma (aHR 0.51, 95% CI 0.36, 0.72) [3]

1. Lo J, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 553;
2. Oliver N, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 550;
3. Simon T, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 551.

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Risk factors for liver fibrosis progression (FIB-4 ≥3.25) in subjects without significant liver disease (FIB-4 <1.45) at BL

Table. Factors Associated with Progression to Advanced Liver Fibrosis Among Patients with Baseline FIB<1.45

	Overall (n=14,198)			HIV-monoinfected (n=12,532)			HCV-coinfected (n=1,666)		
Factor	aHR	95% CI	*P* Value	aHR	95% CI	*P* Value	aHR	95% CI	*P* Value
Male sex	1.02	0.88-1.17	0.82	1.00	0.85-1.18	0.97	1.09	0.84-1.42	0.53
Race (reference: White)									
Black	0.93	0.83-1.05	0.26	0.91	0.79-1.04	0.18	1.00	0.79-1.27	1.00
Hispanic	0.95	0.80-1.14	0.59	0.96	0.79-1.16	0.68	0.82	0.53-1.28	0.39
Other	0.76	0.56-1.04	0.09	0.74	0.51-1.05	0.09	0.88	0.47-1.63	0.69
Chronic hepatitis C	1.85	1.63-2.11	<0.001	--	--	--	--	--	--
Chronic hepatitis B	1.45	1.17-1.81	0.001	1.54	1.21-1.96	<0.001	1.08	0.64-1.82	0.77
Alcohol use disorder	1.36	1.17-1.58	<0.001	1.43	1.18-1.72	<0.001	1.30	1.01-1.68	0.04
Diabetes mellitus*	1.87	1.56-2.25	<0.001	2.01	1.64-2.47	<0.001	1.30	0.82-2.03	0.26
CD4 count*, cells/mm^3									
≥500 (referent)	--	--	--	--	--	--	--	--	--
350-500	1.29	1.10-1.53	0.002	1.31	1.07-1.59	0.007	1.23	0.89-1.72	0.22
200-349	1.90	1.62-2.24	<0.001	1.89	1.57-2.29	<0.001	1.80	1.33-2.45	<0.001
100-199	2.88	2.39-3.48	<0.001	3.29	2.66-4.08	<0.001	1.75	1.29-2.79	0.001
<100	6.93	5.80-8.27	<0.001	7.93	6.48-9.71	<0.001	3.97	2.71-5.82	<0.001
HIV viral level*, copies/ml									
<500 (referent)	--	--	--	--	--	--	--	--	--
500-9999	1.27	1.07-1.52	0.007	1.43	1.17-1.74	<0.001	0.83	0.56-1.24	0.36
10,000-99,999	1.43	1.22-1.66	<0.001	1.40	1.17-1.68	<0.001	1.45	1.09-1.93	0.01
≥100,000	2.60	2.19-3.08	<0.001	2.76	2.27-3.35	<0.001	2.04	1.41-2.94	<0.001
Baseline FIB-4 per unit	3.89	3.23-4.69	<0.001	4.30	3.47-5.32	<0.001	2.66	1.81-3.91	<0.001

* Time-varying

Kim et al, poster 558

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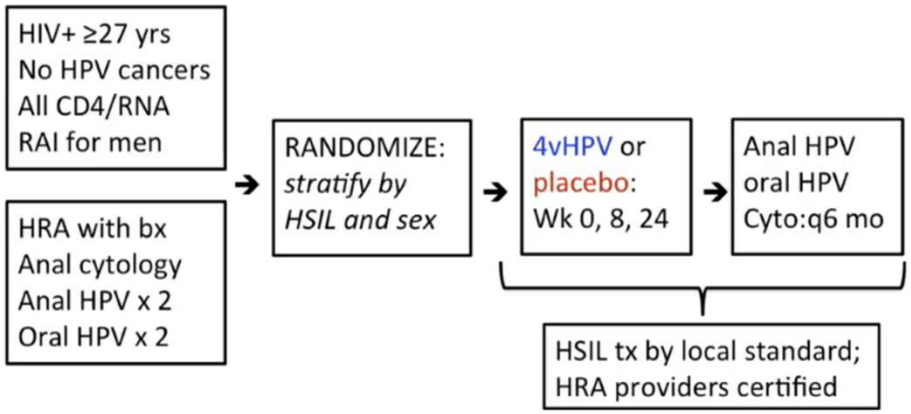
Quadrivalent HPV vaccine in older HIV+ Adults (O161)

Does HPV vaccination prevent persistent anal infection with vaccine types in HIV+ MSM and women without infection at baseline?



Outcome	4vHPV (n)	Placebo (n)	HR (95.1% CI)
Persistent anal HPV, or single detection at last visit[1]	26	33	0.75 (0.45, 1.26)
Persistent anal HPV[1]	13	17	0.73 (0.36, 1.52)
Anal HSIL Week 52 or later (histology)[2]	46	45	1.0 (0.69-1.44)

Outcome	4vHPV (n)	Placebo (n)	HR (95.1% CI)
Persistent oral HPV, or single detection at last visit	7	10	0.68 (0.26, 1.80)
Persistent oral HPV	1	8	0.12 (0.02, 0.98), *P*=.019

- N=575, Age 47, 18% female, 46% white
- CD4 602, VL 90%<200 cpm
- B/L Infection: Anal 60%, Oral 11% ≥ 1 4vHPV type

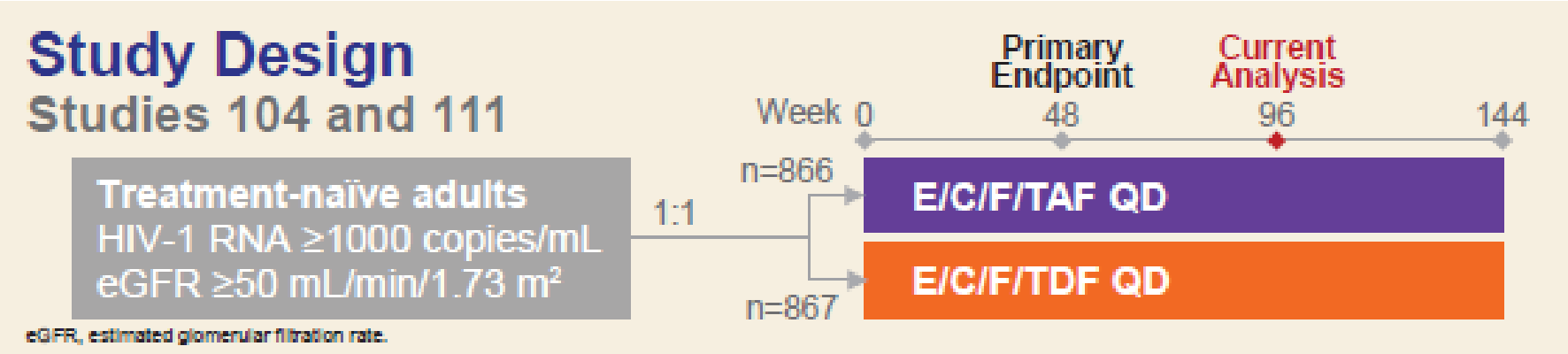
- DSMB stopped early (2.6 yrs FU)
- No safety issues

ACTG AIDS CLINICAL TRIALS GROUP

Study did not support routine vaccination of older HIV+ adults for prevention of anal HPV infection or improving anal HSIL outcomes

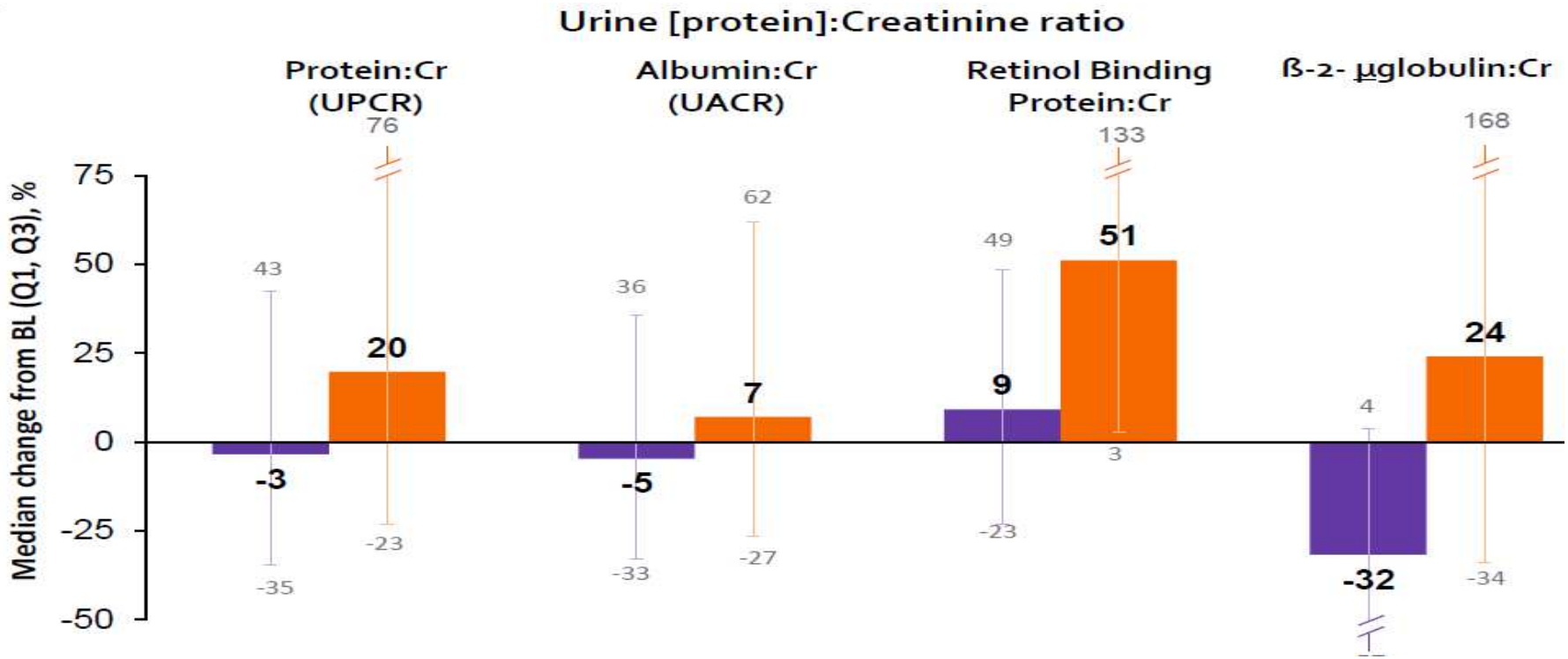
Renal disease

Comparison of renal outcomes with ECF-TAF vs. ECF-TDF in ART-naïve patients (GS-0104/0111)



1733 patients

Comparison of renal outcomes with ECF-TAF vs. ECF-TDF in ART-naïve patients (GS-0104/0111)



	ECF-TAF	ECF-TDF	P value
Acute kidney injury	3	11	0.06
Chronic kidney disease (albuminuria or eGFR <60)	3	17	
Renal discontinuations	0	6	0.03

1733 patients

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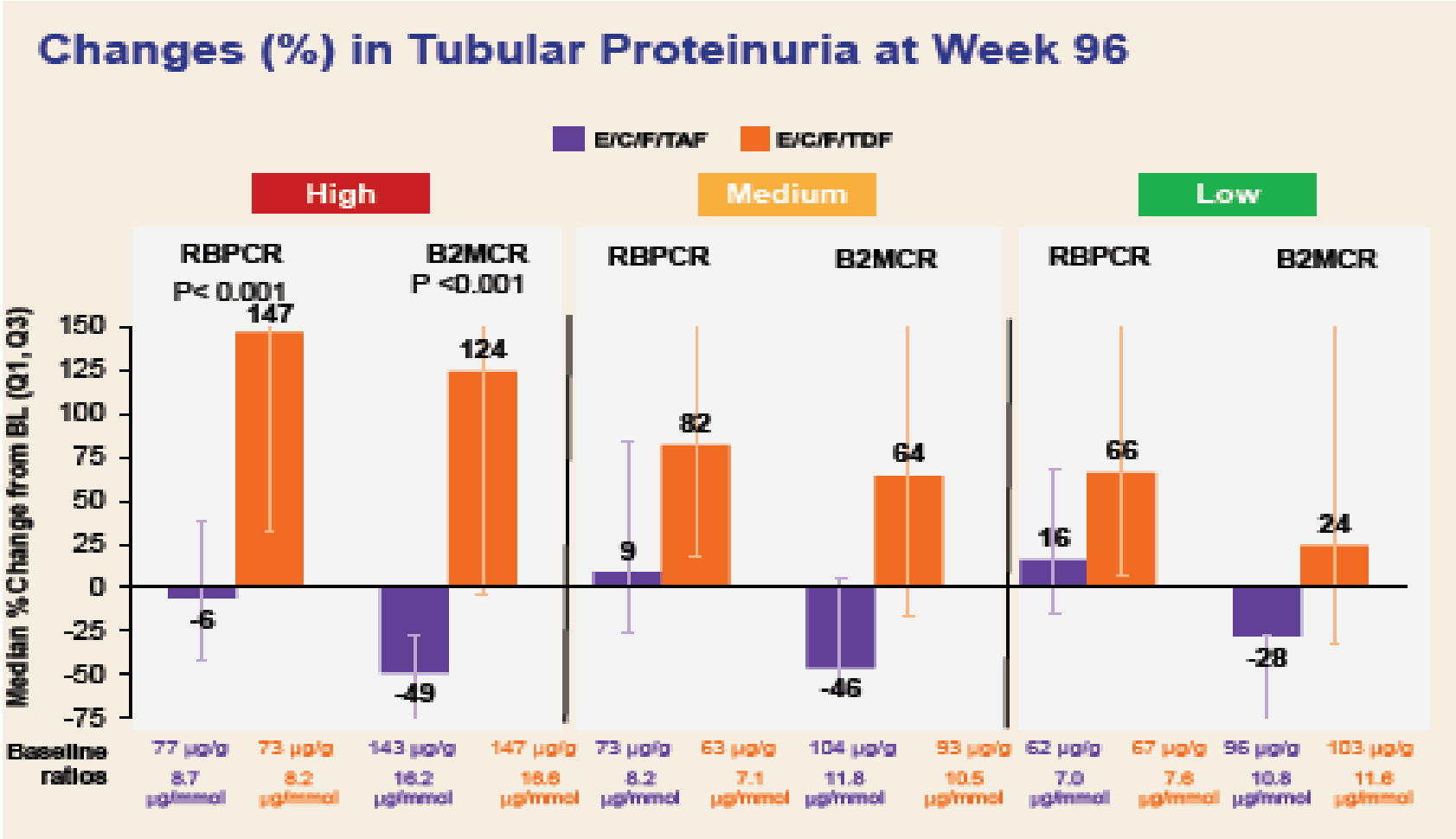
Comparison of renal biomarkers with ECF-TAF vs. ECF-TDF in patients stratified by D:A:D CKD risk score (GS-0104/0111)



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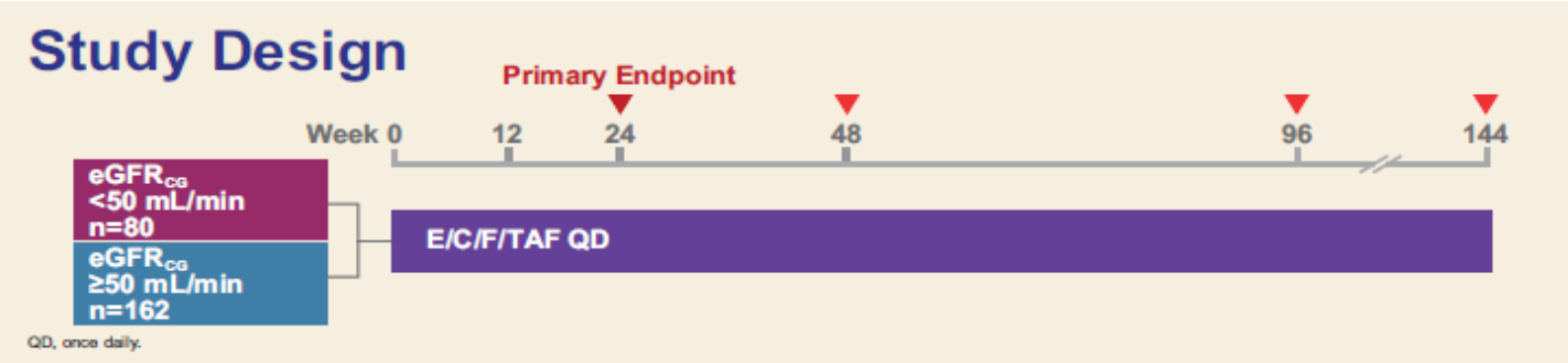
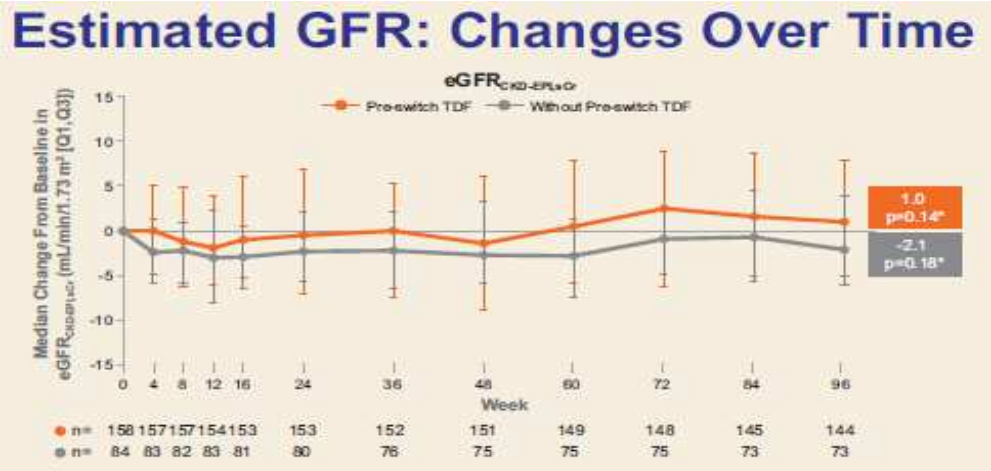
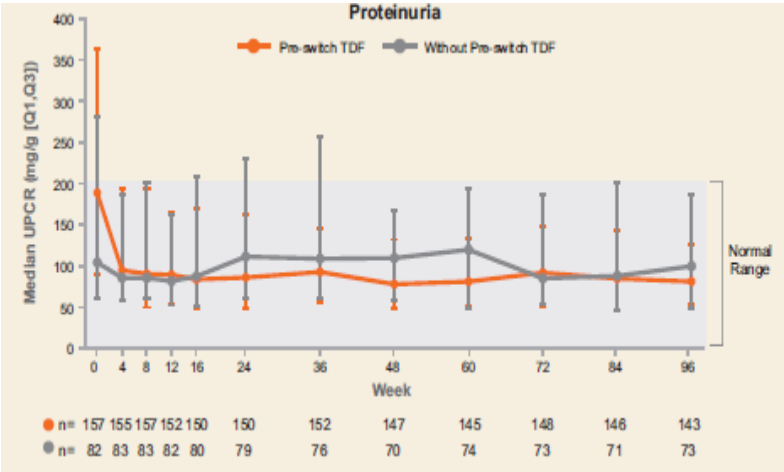
Safety of ECF-TAF in patients with renal impairment (GS-0112)

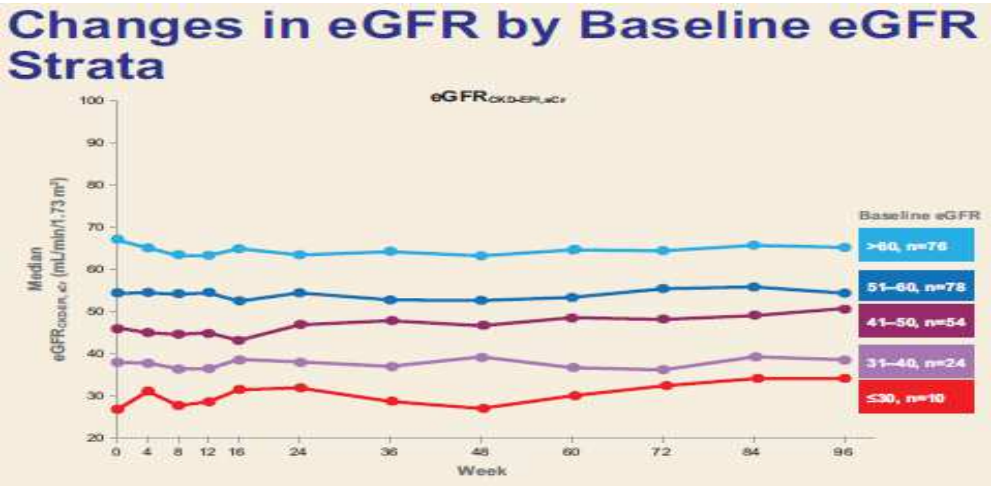


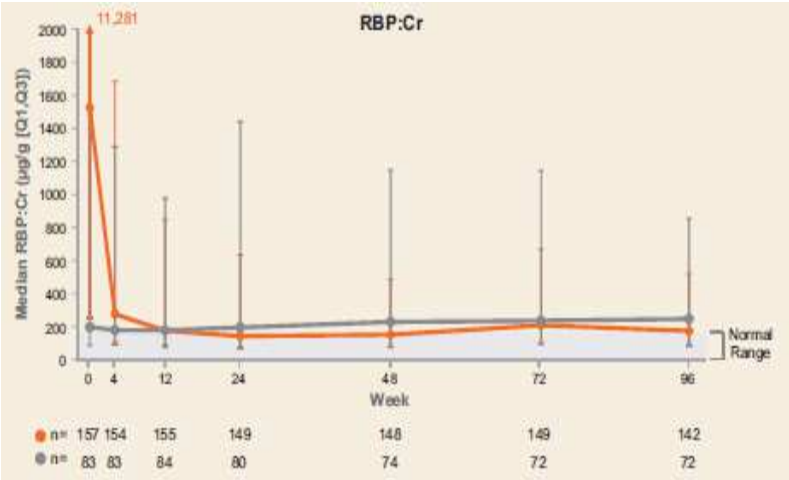
242 patients

Safety of ECF-TAF in patients with renal impairment (GS-0112)









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Risk Factors for severe Tenofovir (TDF)-Associated Renal Tubulopathy (Fanconi syndrome)

Objective:

- To define the risk factors for treatment-limiting renal tubulopathy in patients receiving tenofovir (TDF)

Methods:

- Retrospective case ascertainment
  - Proximal tubulopathy
    - ≥2 of: normoglycaemic glycosuria, hypophosphataemia <0.64 mmol/L, protein-creatinine ratio >300 mg/mmol
  - Acute tubular injury on kidney biopsy

- Poisson regression (using data from the UK CHIC cohort)

Risk Factors for severe Tenofovir (TDF) Associated Renal Tubulopathy

- 15983 subjects received TDF for >4 weeks between Oct 2002-July 2013
  - 69 (0.4%) developed tubulopathy (PT: n=52; ATI: n=17) after a median (IQR) of 43 (26, 67) months of TDF exposure
  - At presentation, 83% were taking ritonavir-boosted PI
    - 44% lopinavir, 35% atazanavir, 16% darunavir, 5% other

Table 1: Factors associated with developing TDF associated renal tubulopathy

	Univariate			Multivariate$		
	RR	95% CI	P-value	RR	95% CI	P-value
Age at baseline	**1.30**	**(1.16, 1.46)**	**<0.0001**	**1.33**	**(1.18, 1.50)**	**<0.0001**
Ethnicity (black vs. white/other)	**0.28**	**(0.12, 0.64)**	**0.003**	**0.27**	**(0.12, 0.63)**	**0.003**
Calendar year at TDF start						
2000-2003	1			1		
2004-2007	0.46	(0.26, 0.81)	**0.007**	0.60	(0.33, 1.07)	0.083
2008-2010	0.31	(0.15, 0.63)	**0.001**	0.54	(0.25, 1.17)	0.116
2011-2014	0.39	(0.15, 0.97)	**0.043**	0.72	(0.26, 2.00)	0.532
Time on TDF (per year increase)*	**1.11**	**(1.01, 1.21)**	**0.025**	**1.12**	**(1.01, 1.23)**	**0.026**
Years on ARVs at TDF start	1.06	(1.01,1.11)	**0.030**	1.00	(0.94, 1.05)	0.900
ARV regime (PI based vs NNRTI based)*	**4.05**	**(2.44, 6.72)**	**<0.0001**	**3.99**	**(2.38, 6.68)**	**<0.0001**
CD4 cell count (per 50 cell increase)*	**0.93**	**(0.88, 0.98)**	**0.006**	**0.92**	**(0.88, 0.97)**	**0.003**

Predicting Drug Discontinuation in TDF-Tolerant Patients: A Prospective PK/PG Study

Methods:

- Adult HIV-positive patients on TDF-containing HAARTs (>6 months), with CrCl >60 ml/min and no significant comorbidity were included
- Tenofovir (TFV) plasma and urinary concentration were measured (LC/MS)
- Single nucleotide polymorphisms in: *ABCB1, ABCC2, ABCC4, ABCC10, SLC22A6, SLC28A2.*
- Patients were followed prospectively for drug discontinuations due to renal toxicity (eCrCl <60 ml/min, nephrolithiasis, persisting 24h urine abnormalities)

Results:

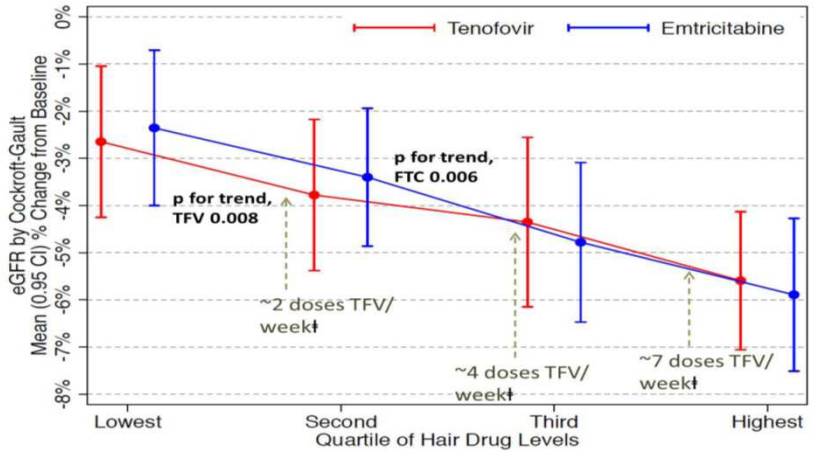
- 310 patients (73% male, 85% Caucasian, median age 46 years, BMI 23.5 kg/m^2, median CrCl 91 (80-107) ml/min) - median follow up of 20.6 months
- 24 patients interrupted TDF for renal toxicity
- Factors associated with TDF discontinuation (multivariate):
  - Age (p=0.005), male gender (p=0.047), PI use (p=0.002) and *ABCB1* (encoding P-glycoprotein) TT genotype (p=0.0042)

Higher Cumulative TFV/FTC Levels Associated With Decline in Renal Function (iPrEX trial)

Results:

- Hair data and creatinine measures were available for 1144 person-visits in 202 participants followed for a median of 16.8 months
- Median age 29 years (19-70); 91% MSM
- Baseline CrCl of 112 mL/min (99-128)
- Greater reductions in eGFR were observed with increasing quartiles of hair level for TFV (p 0.008) and FTC (p 0.006)

Figure: Relationship between % change in eGFR from baseline (calculated by Cockcroft Gault*) and hair concentration** of either TFV (red) or FTC (blue)



*Similar findings were seen when creatinine clearance or GFR was estimated either by the Cockcroft Gault or Modification of Diet in Renal Disease (MDRD) equation.
**Hair assays of TFV and FTC in UCSF lab peer-reviewed and approved by the DAIDS Clinical Pharmacology and Quality Assurance (CPQA) program
‡Median hair levels for 2, 4 and 7 doses/week of tenofovir estimated from the STRAND study (Liu A et al. PLOS ONE 2014. PMID 25296098)

- Mean % eGFR change from baseline :
  - -2.6 (SE 0.8) ml/min at visits with TFV Q1 levels
  - -5.6 (SE 0.7) ml/min at visits with TFV Q4 levels

- The odds of CrCl <70 ml/min (6.1% of sample) increased with increasing quartile of TFV/FTC concentration (OR 4.4 [1.1-17.4] for Q4 vs. Q1 TFV)

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Renal: Take-home messages

- TAF associated with fewer clinically significant renal events
- TAF appears safe in patients with renal impairment up to 96 weeks
- Older age, white ethnicity and PI use are risk factors for TDF-induced Fanconi syndrome
- Greater renal function decline during PrEP with greater TFV exposure

BHIVA 'Best of CROI' Working Party 2016

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- Dr David Asboe
- Dr Sanjay Bhagani
- Dr Daniel Bradshaw
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