Safety of tenofovir alafenamide in individuals with a history of tubulopathy on TDF

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Background

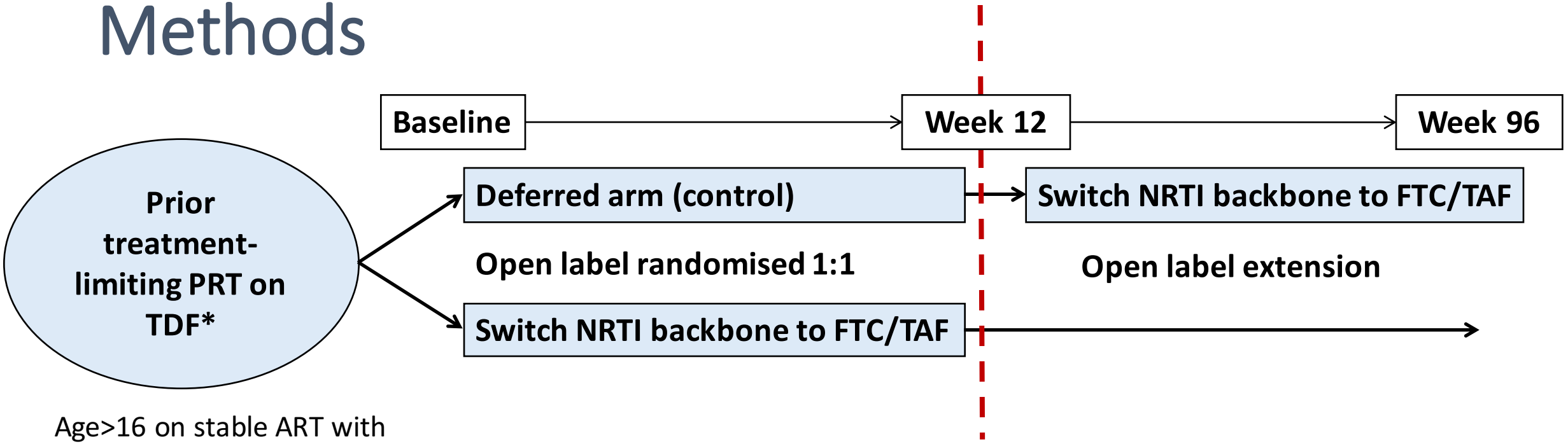
- Tenofovir disoproxil fumarate (TDF) is widely used but limited by its ability to cause renal toxicity.
  - An estimated 0.4% of recipients in the UK CHIC cohort developed treatment-limiting proximal renal tubulopathy (PRT) [1].
  - These individuals may be particularly sensitive to the effects of tenofovir on the kidney.
- Tenofovir alafenamide (TAF) results in 90% lower plasma tenofovir exposure, has an improved renal safety profile, and can be used in those with mild-moderate renal impairment.
  - The safety of TAF in individuals with previous TDF-associated treatment limiting PRT remains largely unknown.

[1] Hamzah L et al. J Infect 2017; 74(5): 492-500. [2] Gupta et al., IAC 2018

Study objective

To study the effects of TAF on kidney and bone in individuals who developed treatment-limiting PRT while receiving TDF

Methods

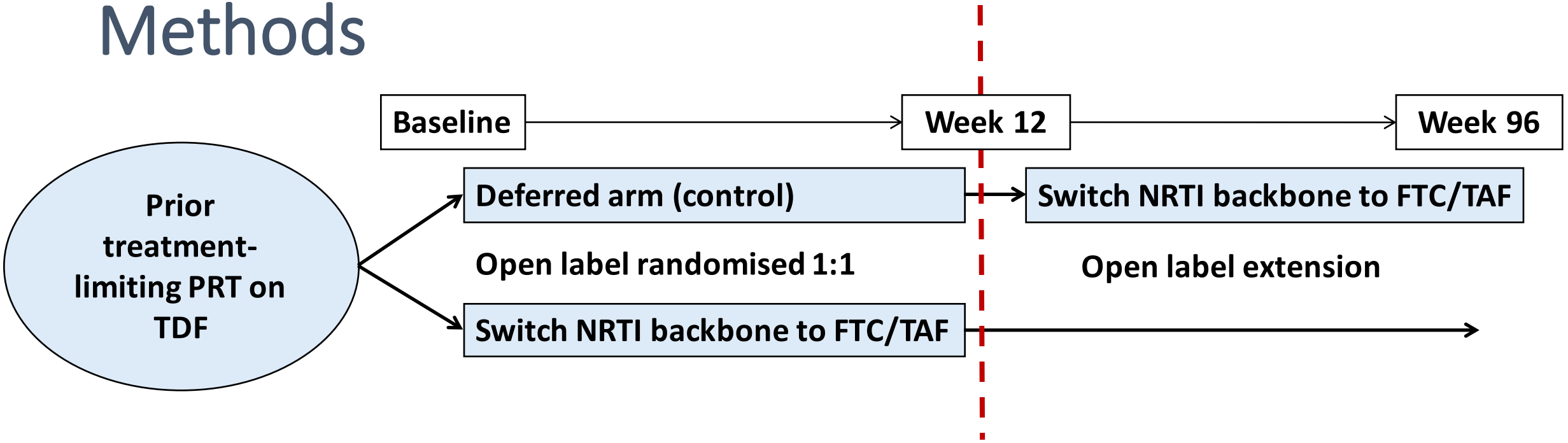


Age>16 on stable ART with VL<200 for last 6 months

***Defined by ≥2 of**

- Proteinuria (≥1+ on urinary dipstick or protein/creatinine ratio >30 mg/mmol)
- Normoglycaemic glycosuria (≥1+ on urinary dipstick)
- Hypophosphatemia (serum phosphate <0.64 mmol/L)
- Rapid eGFR decline (>5 mL/min/1.73m^2/year with >25% reduction from baseline)
- Renal biopsy showing acute tubular injury not explained by other causes

Methods



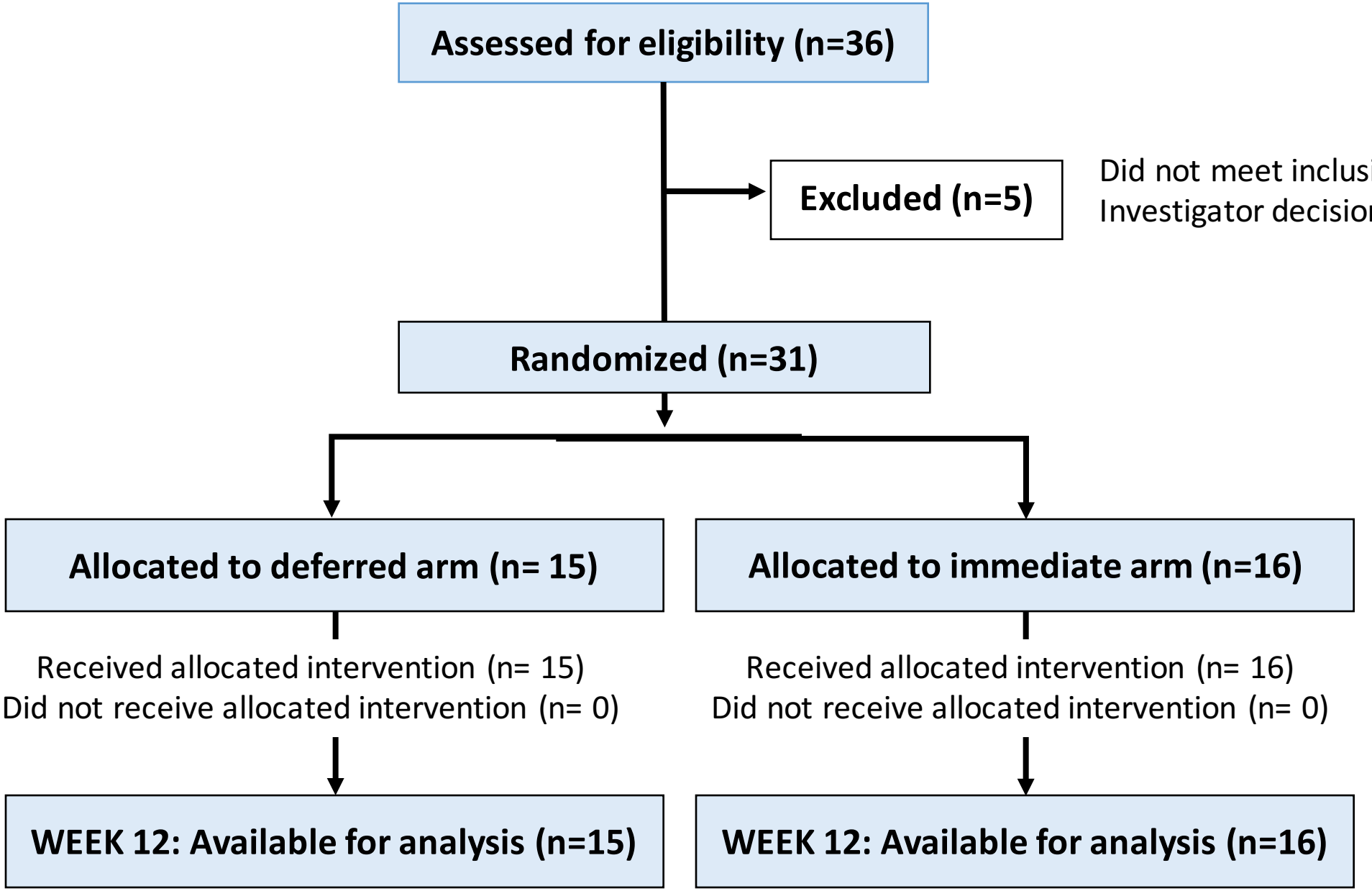
Primary outcome:

Change in retinol-binding protein/creatinine ratio (RBPCR) from baseline to week 12

Secondary endpoints:

Changes in other markers of kidney function and bone regulatory hormones

Incident proximal renal tubulopathy


Assessed for eligibility (n=36)
Excluded (n=5)
Did not meet inclusion criteria (n=4)
Investigator decision (n=1)
Randomized (n=31)
Allocated to deferred arm (n= 15)
Allocated to immediate arm (n=16)
Received allocated intervention (n= 15)
Did not receive allocated intervention (n= 0)
Received allocated intervention (n= 16)
Did not receive allocated intervention (n= 0)
WEEK 12: Available for analysis (n=15)
WEEK 12: Available for analysis (n=16)

Baseline demographics

	All N=31	**Deferred (control) arm** N=15	**Immediate (FTC/TAF) arm** N=16
Age (years)	52.4 [0.3]	52.4 [0.3]	52.2 [0.4]
Male sex	30 [96.8]	14 [93.3]	16 [100]
White ethnicity	28 [90.3]	13 [86.7]	15 [93.8]
Years since HIV diagnosis	20.1 [12.2, 27.5]	22.6 [12.6, 27.5]	18.7 [11.2, 28.8]
Years on ART	12.6 [7.5, 21.1]	17.7 [8.3, 21.9]	9.6 [7.0, 18.0]
Years since TDF discontinuation	6.8 [5.0, 10.1]	6.9 [3.7, 10.3]	6.5 [5.5, 7.6]
Nadir CD4 (cells/µl)	143 [66, 246]	167 [41, 246]	139 [69, 250]
Current CD4 (cells/µl)	553 [202]	504 [150]	600 [236]
HIV viral load <200 c/ml	31 [100]	15 [100]	16 [100]
Hepatitis B sAg positive	4 [15.4]	2 [14.3]	2 [16.7]
Hepatitis C Ab positive	1 [3.3]	1 [6.7]	0 [0.0]

Mean [SD], Median [IQR] or N [%]

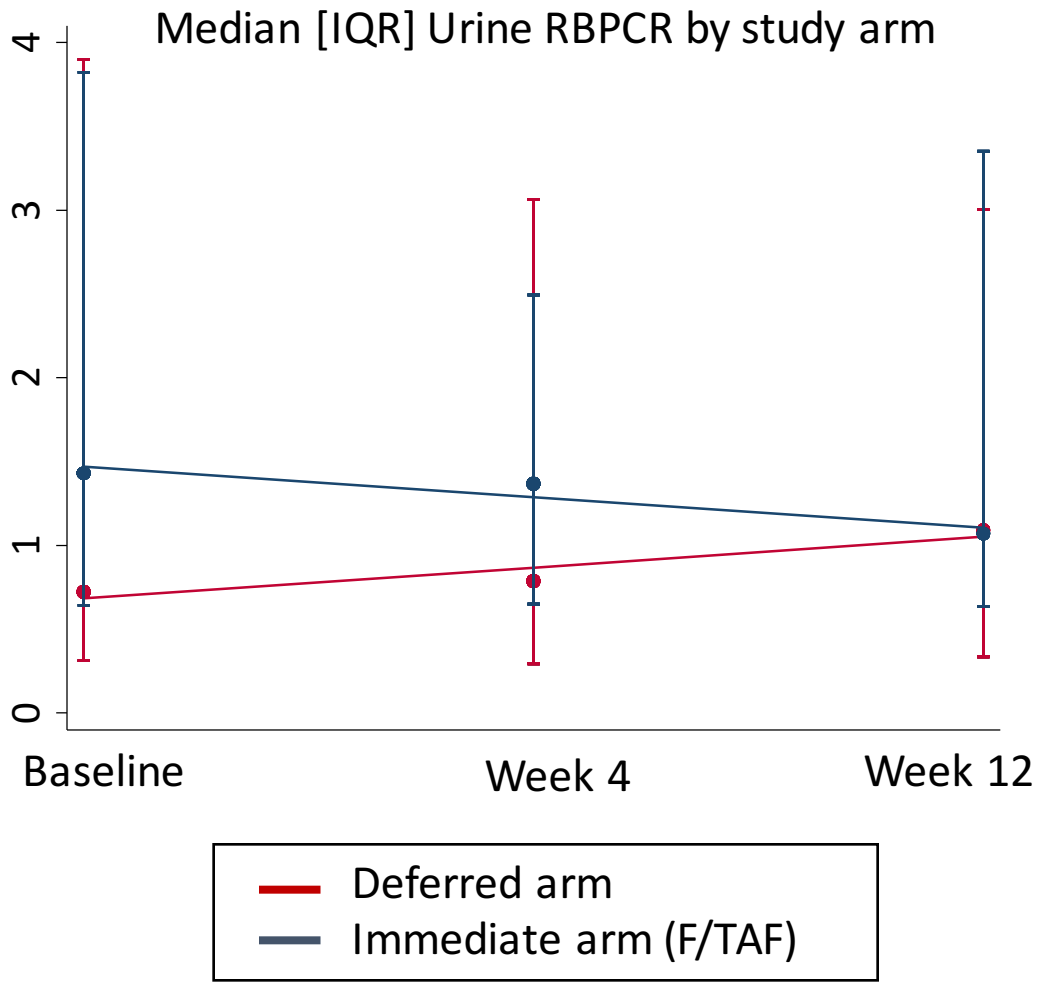
ART: antiretroviral therapy, TDF: tenofovir disosproxil fumarate, sAg: surface antigen, Ab: antibody

Prior PRT diagnosis

	All (n=31)	Deferred (control) arm (N=15)	Immediate (FTC/TAF) arm (N=16)
Proteinuria	29/31 [93.6]	14/15 [93.3]	15/16 [93.8]
• *uPCR median (range; mg/mmol)*	*72 [20, 1200]*	*64 [20, 823]*	*74 [35, 1200]*
Normoglycaemic glycosuria	12/16 [80.0]	6/8 [75.0]	6/7 [85.7]
Hypophosphataemia	22/28 [78.5]	12/14 [85.7]	10/14 [71.4]
• *Serum phosphate median (range; mmol/L)*	*0.55 [0.31, 1.09]*	*0.52 [0.31, 0.95]*	*0.56 [0.41, 1.09]*
Rapid eGFR decline	12/21 [57.4]	6/12 [50.0]	6/9 [66.7]
Acute tubular injury on biopsy	3/3 [100]	2 [14.3]	1 [6.25]
Alkaline phosphatase >ULN	10/24 [41.7]	6/11 [54.6]	4/13 [30.8]
• *ALP median (range; IU/L)*	*120 [96, 200]*	*160 [88, 629]*	*114 [74, 237]*

Proteinuria: Dipstick ≥1+ or protein/creatinine ratio >30 mg/mmol, Normoglycaemic glycosuria: Dipstick ≥1+, Hypophosphataemia: <0.64 mmol/L
Rapid eGFR decline: >5 mL/min/1.73m^2/year on TDF with >25% reduction from baseline

Primary outcome: change in urine RBPCR (baseline to week 12)



	Deferred (control) arm N=15			Immediate (FTC/TAF) arm N=16		
	BL	W 4	W 12	BL	W 4	W 12
Urine RBPCR	**0.72** [0.31, 3.90]	**0.79** [0.29, 3.06]	**1.09** [0.33, 3.00]	**1.43** [0.64, 3.82]	**1.37** [0.65, 2.49]	**1.07** [0.64, 3.35]

There was no change in urine RBPCR from baseline to week 12 :

β coefficient [95% CI] of the mean difference between arms: **19.6 [-35.3, 74.5] p=0.47**

RBPCR outlier analysis

Urine RBPCR category		Deferred (control) arm N=15			Immediate (FTC/TAF) arm N=16		
		Baseline	Week 4	Week 12	Baseline	Week 4	Week 12
<ULN	N [%]	10 [66.7]	11 [73.3]	11 [73.3]	11 [68.8]	12 [75.0]	12 [75.0]
1-5x ULN	N [%]	2 [13.3]	1 [6.67]	1 [6.67]	3 [18.8]	2 [12.5]	3 [18.8]
5x10x ULN	N [%]	1 [6.67]	-	-	1 [6.25]	-	-
>10x ULN	N [%]	2 [13.3]	3 [20.0]	3 [20.0]	1 [6.25]	2 [12.5]	1 [6.25]

Secondary outcomes: change in renal and bone biomarkers (baseline to week 12)

Secondary outcomes	Mean difference [95% CI] between arms	p-value
eGFR (creatinine)	3.66 [-5.59, 12.9]	0.44
eGFR (cystatin C)	-1.80 [-12.3, 8.71]	0.74
Urine ACR	-0.27 [-5.32, 4.79]	0.92
Urine PCR	4.41 [-15.1, 23.8]	0.66
TmPO4/GFR	0.01 [-0.11, 0.14]	0.82
FE-urea	-0.08 [-6.46, 6.30]	0.48
Urine osmolality	-59.9 [-208.6, 88.7]	0.43
PTH	6.64 [-7.51, 20.8]	0.36
P1NP	-12.6 [-31.3, 6.15]	0.19
CTX	-0.35 [-0.75, 0.04]	0.08

- **There were no changes in renal or bone biomarkers from baseline to week 12** (p>0.05 for all)
- No cases of PRT were reported

eGFR=estimated glomerular filtration rate (CKD-EPI); ACR=urine albumin/creatinine ratio; PCR=urine protein/creatinine ratio, TmPO4/GFR= ratio of tubular maximum reabsorption of phosphate to GFR; FE-urea=fractional excretion of urea; PTH=parathyroid hormone; P1NP=serum type 1 (N-terminal) procollagen; CTX=C-terminal telopeptide

Limitations

- Current analyses are restricted to the first 12 weeks of exposure to TAF, which may have been too short a period for changes in renal biomarkers to emerge.
- Small sample size limited the power to detect differences between the two groups.
- Recruitment did not reach target sample size (20 in each arm).
- Historic information to assess the presence or absence of all PRT criteria was incomplete, hence, not all participants had complete laboratory data to confirm the diagnosis of Fanconi syndrome.

Discussion

- We observed no change in renal and bone biomarkers during 12 weeks of exposure to TAF/FTC in 16 individuals with a history of TDF-associated treatment-limiting PRT.
- These data suggest there is no immediate effect of TAF on kidney function.
- Longer term safety data are required and this study will continue to follow all participants through 96 weeks.
- TAF may be a suitable treatment option for this population, potentially allowing ART regimens with enhanced potency, reduced pill burden, and activity against hepatitis B to be used.

Acknowledgements

- Study participants

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