Renal Tubular Dysfunction Among People Living with HIV on Tenofovir Disoproxil Fumarate in Uganda: A Hospital-Based Cross-Sectional Study

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Abstract

Background

Tenofovir Disoproxil Fumarate (TDF), the most commonly prescribed antiretroviral drug globally is associated with renal tubular dysfunction (RTD) whose magnitude is poorly understood in resource-limited settings. Our goal was to describe the prevalence and factors associated with renal tubular dysfunction in Uganda's people living with HIV(PLHIV) taking TDF-containing regimens.

Methods

We enrolled adult PLHIV receiving TDF-containing antiretroviral regimens from the HIV clinic at Mbarara Regional Referral Hospital. Socio-demographic, clinical and laboratory data were collected from each participant. Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula was used to estimate glomerular filtration rate (eGFR) and participants who had any two of, raised urinary excretion of phosphate, uric acid and glycosuria in non-diabetic normal glycemic were said to have renal tubular dysfunction. Logistic regression analysis was done to identify the factors that were independently associated with renal tubular dysfunction.

Results

Of the 145 participants enrolled, 84 (57.9%) were female, and the mean age was 46 (± 9) years. The mean serum creatinine was 0.77 (± 0.12) mg/dl and the mean eGFR of 112 (±24) mL/min/1.73m2. A total of 116/145 (80%) participants had at least one abnormality in parameters of tubular dysfunction; 26 (17.9%) and 3 (2.1%) of the participants had a combination of two or more parameters, respectively. In our study, the prevalence of renal tubular dysfunction was 20% (29/145) (95% CI 14.2-27.3). Female gender was statistically significantly associated with tubular dysfunction, adjusted odds ratio (AOR): 2.75, 95% (CI. 1.05-7.19), p=0.03.

Conclusion

The prevalence of renal tubular dysfunction is high and can occur in patients receiving TDF despite normal serum creatinine. We recommend using urinary abnormalities other than isolated serum creatinine in the detection of renal tubular dysfunction.

Background

In the Antiretroviral Therapy (ART) era, mortality in people living with HIV (PLHIV) was attributed to aging and non-communicable diseases(1). Kidney diseases in PLHIV can be due to HIV-associated nephropathy(HIVAN), drug-induced, HIV-associated immune complex kidney disease(HIVICK), and HIV

thrombotic microangiopathy(1). Tenofovir Disoproxil Fumarate (TDF), a Nucleotide Reverse Transcriptase Inhibitor (NRTI), is part of the first-line drugs for the treatment of HIV and was reported to have a good safety profile (2–6). However, it has been associated with renal dysfunction, particularly, a rise in serum creatinine which is expressed as reduction of estimated glomerular filtration rate (eGFR) (7–11), and one large study reported a 33% increased risk of developing CKD for each year of using TDF (12). Other studies mention serum creatinine to be a late and less sensitive marker of TDF nephrotoxicity (13–16).

TDF mainly affects the proximal renal tubule, and studies have reported the presence of tubular proteinuria, urinary phosphate wasting and other parameters of renal tubular dysfunction resembling the Fanconi syndrome in PLHIV taking TDF-containing regimens (6, 17–24). TDF renal toxicity occurs as early as 3 to 6 months (25) and is thought to have the spontaneous resolution in 24 months (6). Despite normal glomerular function, TDF-induced renal tubular dysfunction causes decreased bone density, which subsequently impairs the patient's quality of life and productivity(26).

Factors that have been associated with TDF renal tubular dysfunction include; co-morbidities; such as hepatitis C and diabetes mellitus; low body weight, older age, concomitant administration of nephrotoxic drugs; low CD4 count, duration of therapy, and genetic (21, 27, 28).

We hypothesize that RTD is common among adult PLHIV in Uganda who are receiving TDF-containing ART, and this can happen in patients with normal serum creatinine. Further, we hypothesize that the use of parameters defining Fanconi syndrome can diagnose TDF nephrotoxicity early before the rising of serum creatinine.

The main goal of this study was to establish the burden and risk factors for renal tubular dysfunction among PLHIV on TDF-containing regimens in Uganda. The study may engender an approach for screening for TDF side effects in sub-Saharan Africa, particularly Uganda, where we still use isolated serum creatinine as a screening tool for TDF nephrotoxicity.

Methodology

Study Design, Setting and Population

This was a cross-sectional study conducted in the HIV clinic of Mbarara Regional Referral Hospital (MRRH). MRRH serves as a teaching hospital for Mbarara University of Science and Technology and is located in Mbarara district, South-western Uganda, about 260 km from the capital city of Uganda, Kampala. The MRRH HIV clinic was established in November 1998 and is under the governance of MRRH as well as the Uganda Ministry of Health. It provides both pediatric and adult HIV care services to over 4 million people from southwestern Uganda (29). Since its inception, it has provided care to approximately thirty thousand patients. The clinic runs from Monday to Thursday, attending to approximately 200 to 250 clients per day, of whom the majority come for drug refills. Patients who are starting a new ART regimen are usually given monthly drug refills for the first six months and adherence is monitored by using self-reported and electronic adherence calculations, using the pill count method. During every visit,

patients are monitored based on clinical characteristics, while laboratory tests like serum creatinine, fasting, and random blood sugar, liver function test, and enzymes, CD4 count are taken whenever they are needed by the clinicians, viral load six months after initiation of ART then annually. Patients' information at this HIV clinic was previously documented only on paper but, currently, all patient information is stored in an Electronic Medical Records system (EMRS) which started in 2007. All information that was previously stored in paper files had been transferred to the database. The paper files are still used as daily clinical review forms and data from these files is entered into the open EMRS by qualified data personnel. The team performs routine data quality control procedures and all queries are corrected within 24 h. (30)

The study was conducted for 3 months, from 1st June 2021 to 31st August 2021. It is known the median time to develop RTD on TDF is 3 to 6 months(6, 17–24), and it is thought that this effect only occurs in the early months of using TDF and resolute at 24 to 31 months hence the rationale to explore the prevalence at 24 months(6). Participants meeting the inclusion criteria were adult PLHIV on TDF for 24 ± 2month attending an HIV clinic at MRRH on routine follow-up.

The following individuals were excluded from the study: Individuals with an incomplete history of antiretroviral treatment, including date of commencement of ART and combination of ART; persons who were known and/or newly diagnosed with Diabetes Mellitus; persons with documented hyperparathyroidism, persons who were pregnant or lactating; persons who were newly diagnosed and who had documentation of preexisting renal dysfunction measured by drop eGFR less than 60 mL/min/1.73m^2 (eGFR was calculated by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) and those who declined to consent.

Sampling and Recruitment

The MRRH ISS clinic database was used to identify the study sample population. The clinic was expected to attend at least 200 participants a day, but the study took place at the time of the COVID-19 National lockdown; hence the number of patients was reduced significantly. We changed the sampling method to consecutive enrollment of any patient who attended the clinic and fulfilled the inclusion and exclusion criteria. The nature and purpose of the study were explained to each participant and written consent was sought from these patients. We enrolled a maximum of 10 patients per day. Details of participants' recruitment are illustrated in **Figure 1**.

Data Management Collection

Variables collected

We obtained data by using a standardized questionnaire through a face-to-face interview. Individual patient records and forms were kept in files after data collection. Basic/demographic characteristics (age, sex, address, marital status, religion, employment status, education status), anthropometric measurement (weight and height) were obtained by using one weighing scale which was calibrated every day, and a height/length measuring board. We obtained clinical characteristics (CD4, Viral Load, clinical staging, time on TDF, type of TDF regimen, whether PI or non-PI containing) of all the patients who were on TDF-

based regimen for 24 ± 2 months from their file records and database. These data enabled us to determine the factors associated with renal tubular dysfunction in HIV patients who were 18 years and above on TDF for 24 ± 2 months.

Participants were asked to collect midstream spot urine samples. In the fasting state, 4mls of blood were drawn and 10mls of urine samples were collected for laboratory tests. Samples were sent to Mbarara University's clinical research laboratory on the same day. Beckman Coulter AU480 Chemistry Analyzer machine was used to measure serum glucose, creatinine, uric acid, and phosphate as well as urine glucose, creatinine, uric acid, and phosphate, while CD4 T cell count was measured by PIMA machine (PIMA Alere Inc., Waltham MA.).

Fraction Excretion of Phosphate was calculated using the following formula;

$$FEphos = \frac{(Urine\ Phosphate\ \times Serum\ Creatinine)}{(Serum\ Phosphate\ \times Urine\ Creatinine)} \times 100\%$$

Fraction Excretion of Uric Acid was calculated by using the following formula;

$$FE\ Of\ Uric\ Acid = \frac{(Urine\ Uric\ acid\ \times Serum\ Creatinine)}{(Serum\ Uric\ acid\ \times Urine\ Creatinine)} \times 100\%$$

Estimated Glomerular Filtration Rate (eGFR) by CKD-EPI formula (31)

$$eGFR = 141 * \min\left(\frac{Scr}{k}, 1\right)^{\alpha} * \max\left(\frac{Scr}{k}, 1\right)^{-1.209} * 0.993Age * 1.018(if\ female) * 1.159(if\ black)$$

where:

Scr is serum creatinine in mg/dL.

κ is 0.7 for females and 0.9 for males.

α is -0.329 for females and -0.411 for males.

min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m² body surface area, which is an accepted average adult surface area.

Renal tubular dysfunction

The renal tubular dysfunction can present as Fanconi Syndrome, which is the global dysfunction of the proximal tubule leading to excessive urinary excretion of amino acids, glucose, phosphate and other solutes handled by the proximal segment of the nephron. This can lead to electrolytes imbalance, acidosis, rickets and Osteomalacia (32)

Fanconi-like Syndrome is a proximal tubule disease characterized by tubular proteinuria, hypophosphatemia, euglycemic glycosuria, hypouricemia, hypokalemia and metabolic acidosis (33–35). In this study, renal tubular dysfunction in people living with HIV who were on TDF for 24 ± 2 months was defined by the presence of at least two of the following parameters; Phosphate wasting: F.E Phos of >20% among patients with normal serum phosphate levels (2.7–4.5 mg/dL or 0.87-1.45mmol/L) or >10% among patients with hypophosphatemia (serum phosphate of <2.7 mg/dL or 0.87mmol/L) (24), Uric acid wasting: FE of Uric acid >10% in presence of decreased plasma uric acid level (Men <0.20mmol/L, Women <0.15mmol/L) (18), Glucosuria: Urine glucose>1.7mmol/L with plasma glucose <10mmol/L (18)

Statistical analysis

Collected data was summarized on an Excel 2016 (Microsoft Corporation, Redmond, USA) spreadsheet and was imported to STATA-13 (Stata Corp, Lakeway Drive, College Station, Texas 77845 USA) for analysis. The normally distributed continuous variables were summarized by means (SD) and the skewed continuous variables by medians (IQR). Categorical variables were presented by frequencies and percentages.

We computed the proportion of patients who fulfilled our study definition to determine the prevalence of renal tubular dysfunction among HIV patients 18 years and above on TDF for 24 ± 2 months. Bivariate and multivariate logistic analysis models were used to determine the factors independently associated with renal tubular dysfunction among HIV patients 18 years and above on TDF for 24 ± 2 months. A $P<0.05$ was considered to indicate a statistically significant association.

Data Quality Control

All the anthropometric measurements were done using the same equipment and the weighing scale was calibrated before weighing each of the study participants. The laboratory tests were analyzed in the Mbarara University clinical research laboratory which is rated 3 stars by Strengthening Laboratory Management Toward Accreditation (SLMPTA), has standardized internal quality control protocols and participates in external quality control programs by the National Health Laboratory Service Epi Center South Africa.

Results

In this study, 145 participants, were enrolled from June 2021 to mid-August 2021. All participants were HIV-positive, aged 18 years, and were on a TDF-containing regimen for 24 ± 2 months, with different durations of HIV diagnosis.

Characteristics of study participants

The majority of participants involved in this study were female 84 (57.9%) and the mean age was 46 (± 9). 73 (50.3%) of participants had a normal Body Mass Index (BMI). Participants had a median CD4 that was 227c/µl (IQR 128-335) at the time of TDF initiation. All of our participants had undetectable viral loads with a mean of 69.7 (± 45.9). Only 13 participants had hypertension as a comorbidity. In the past 1 year from the date of the study, only 9 (6.2%) of participants reported a history of using herbs for more than 2 months **(**Table 1**).**

Table 1
; Participants' baseline characteristics

VARIABLE	TOTAL (N=145)
Gender, n (%)	
Female	84 (57.9)
Male	61 (42.1)
Age, Mean (Sd)	46 (±9)
Age category, years n (%)	
18-45	70 (48.3)
Above 45	75 (51.72)
BMI Kg/m^2, n (%)	
Under Weight (below 18.5)	9 (6.2)
Normal Weight (18.6 – 24.9)	73 (50.3)
Over Weight (25 – 29.9)	48 (33.1)
Obese (above 30)	15 (10.3)
PI-containing ART, n (%)	7 (4.8)
Baseline CD4, Mean (Sd)	240 (159.6)
Current CD4, Mean (Sd)	617.4 (239.4)
Current Viral Load, Mean (Sd)	69.7 (45.9)
Comorbidity, n (%)	
No	130 (89.6)
Hypertension	13 (8.9)
Other (Asthma)	2 (1.3)
Drug History, n (%)	
No	136 (93.8)
Herbs	9 (6.2)
BMI; Body Mass Index, **ART;** Antiretroviral Therapy	

All participants had a normal renal function, with a mean serum creatinine of 0.77 (± 0.12) mg/dl and eGFR of 112 (±24) mL/min/1.73m2 calculated by CKD-EPI Creatinine formula. The mean and standard deviation for other serum parameters were 0.6 (±0.6) mmol/L, 0.197 (±0.1) mmol/l, 5.3 (±1.3) mmol/L for

Phosphate, Uric acid and glucose respectively. The mean and standard deviation for the urine parameters were 44.3 (±38.1) mg/dl,4.3 (±3.6) mmol/l,1.6 (±1.1) mmol/l, 0.3 (±1) mmol/l for creatinine, phosphate, uric acid and glucose respective (Table 2).

Table 2
; Laboratory Characteristics

VARIABLE	TOTAL (N=145)
Serum chemistry, Mean (Sd)	
Creatinine, mg/dl	0.77 (0.12)
Phosphate, mmol/L	0.7 (0.2)
Uric Acid, mmol/L	0.25 (0.15)
Glucose, mmol/L	5.3 (1.3)
eGFR (mL/min/1.73m^2)	112 (24)
Urine chemistry, Mean (Sd)	
Creatinine, mg/dl	44.3 (38.1)
Phosphate, mmol/L	4.0 (3.6)
Uric Acid, mmol/L	1.5 (1.1)
Glucose, mmol/L	0.3 (1)
Fraction Excretion (%)	
F.E of Uric Acid, Median (IQR)	8.9 (7.2 – 25.2)
F.E of Phosphate, Median (IQR)	8.9 (6.8 - 13.0)

Prevalence of renal tubular dysfunction.

A total of 116 (80%) participants had abnormalities in parameters of tubular dysfunction. A single parameter abnormality was found in 37 (25%), 15 (10%), and 3 (2%) participants, for fraction excretion of uric acid, fraction excretion of phosphate and normal glycemia glucosuria respectively, while 26 (17.9%) and 3 (2.1%) participants had a combination of two or more parameters respectively thus fulfilling the study definition of renal tubular dysfunction (Table 3). Hence, the prevalence of renal proximal tubular dysfunction among people living with HIV who are above 18 years on TDF for 24 ± 2 months attending Mbarara Regional Referral Hospital HIV clinic was **20% (29/145) (95% CI 14.2-27.3).** The Venn diagram (Figure 2), represents the relationship of parameters used to define renal tubular dysfunction.

Table 3
; Prevalence of renal proximal tubular dysfunction based on the definition of each parameter and combination.

Single Parameters	**N (%)**	**95% CI**	**Std. Err**
F.E of Uric Acid	65 (44.8)		
F.E of Phosphate	44 (30.3)		
Normal Glycemia Glycosuria	7 (4.8)		
Two Parameters			
F.E of Uric Acid and Glycosuria	0	0	0
F.E of Phosphate and Glycosuria	1(0.7)	0.9-4.8	0.6
F.E of Uric Acid and F.E of Phosphate	25 (19.3)	13.6-26.6	3.2
Three Parameters			
F.E of Phosphate, F.E of Uric Acid and Glycosuria	3 (2.07)	0.65-0.62	1.1
Prevalence of renal proximal tubular dysfunction	**29 (20)**	**14.2-27.3**	**3.3**

N; Number of people, **F.E of Uric Acid;** Fraction excretion of uric acid, **F.E of Phosphate;** Fraction excretion of phosphate

The Factors Associated with renal tubular dysfunction

The univariate analysis of anticipated risk factors was not significant. We ran a multivariate analysis considering all factors that had p-values less than 0.05 in univariate analysis and other factors that have been reported to have a significant association or with biological explanations to cause or associate with renal tubular dysfunction. After controlling for age, time from diagnosis of HIV, baseline CD4 at the initiation of TDF, current CD4, concomitant use of protease inhibitors (PI), presence of comorbidities, use of herbs and body mass index (BMI), the odds of female participants on TDF to develop renal tubular dysfunction was 2.7 (95% C.I, 1.057-7.19, p=0.038) times higher than male participants. The details of the analysis are shown in Table 4.

Table 4
; Factors associated with proximal tubular dysfunction in patients on Tenofovir Disoproxil Fumarate

Variable	Bivariate Analysis			Multivariate Analysis		
	Unadjusted Odds Ratio	p-value	95% CI	Adjusted Odds Ratio	p-value	95% CI
Age	Ref	0.215	0.735-3.898	2.074	0.116	0.835-5.147
18-45	1.693					
>45						
Gender	Ref	0.082	0.904-5.391	**2.758**	**0.038**	**1.057-7.19**
Male	2.208					
Female						
Time with HIV	Ref	0.677	0.526-2.688	-	-	-
Below 150 months	1.189					
Above 150 months						
Baseline Cd4	Ref	0.507	0.317-1.762	-	-	-
Above 200	0.748					
Below 200						
Current Cd4	Ref	0.860	0.457-2.548	-	-	-
Above 500	1.080					
Below 500						
Use of P.I	Ref	0.140	0.681-15	2.722	0.233	0.525-14.10
No	3.230					
Yes						
Comorbidity	Ref	0.894	0.291-4.100	-	-	-
No	1.093					
Hypertension						
Herbs Use	Ref	0.073	0.889-14.18	3.006	0.147	0.678-13.31
No	3.552					
Yes						

HIV; Human immunodeficiency virus, **CD4**; Cluster of differentiation 4, **P.I**; Protease Inhibitor, **BMI**; Body mass Index

Variable	Bivariate Analysis			Multivariate Analysis		
	Unadjusted Odds Ratio	p-value	95% CI	Adjusted Odds Ratio	p-value	95% CI
BMI	Ref	0.418	0.283-20.81	-	-	-
Under Weight	2.428	0.677	0.114-14.63			
Normal Weight	1.6	0.577	0.175-22.79			
Over Weight	2					
Obese						

HIV; Human immunodeficiency virus, **CD4**; Cluster of differentiation 4, **P.I**; Protease Inhibitor, **BMI**; Body mass Index

Discussion

There has been an equipoise on the safety profile of TDF, following the emergence of case series and studies that report features of RTD among patients on TDF.(7, 8, 16–24, 34). Histological renal changes associated with TDF are not uncommon (36). Our study shows the presence of parameters of Fanconi syndrome, which is in keeping with TDF-associated RTD in PLHIV taking TDF-containing regimens. In this study group, all participants had normal renal glomerular function measured by eGFR calculated by CKD-EPI which has been reported in previous studies as well (13–16). It is of crucial note that these are patients, by current practice, are normally left to continue taking TDF. To the best of our knowledge, this is the only study in East Africa that shows the RTD in PLHIV on TDF by measuring the parameters of Fanconi syndrome.

Our study found that the prevalence of RTD in PLHIV on TDF-containing regimens for at least 24 months was 20% with about 116 (80%) participants with abnormalities in parameters of tubular dysfunction. Unlike our study, Nyende et al report the prevalence of renal dysfunction to be 2.52% (11). This is mainly due to the difference in the operational definition used to diagnose renal dysfunction in patients on TDF. This study used eGFR, dipstick proteinuria and glycosuria, while in our study we used the combination of parameters used to define Fanconi syndrome. The effect of TDF on eGFR has been documented to be mild with no change in dipstick albuminuria in HIV or non-HIV patients (16).

The prevalence of RTD that we found in this study is similar to previous studies considering our confidence interval of 14 to 27.3 (17, 27). The possible explanation of the slight difference in exact prevalence could be due to small differences in the definition of RTD, the minimum duration of TDF and maybe the geographical and genetic predisposition. Our study used a spot sample of urine instead of 24 hours urine collection and the RTD definition did not include tests like α1-microglobulin, β2-microglobulin and measurement of retinol-binding protein which are not readily available in many resource-limited settings, making this method more applicable for clinical practice in Sub Saharan African countries.

In our study, being female was significantly associated with RTD after controlling for age, concomitant use of protease inhibitors, and use of herbs for more than 2 months in the previous one year from the time of the study. We couldn't find a scientific explanation to explain this finding, but we postulate it could be due to polymorphisms in genes encoding drug transporters (27). Previous studies report multiple factors to be associated with the development of RTD in a patient taking TDF these includes, that older age, lower body weight and homozygosity for the C allele at position 24 of ABCC2(27) concomitant use of protease inhibitors (lopinavir/ritonavir), reduced renal clearance of TDF, female gender, advanced HIV infection with CD4 below 200 were associated with renal tubular dysfunction in HIV patients on TDF (34, 35, 37, 38).

Limitations

This study used a combination of parameters defining Fanconi syndrome to diagnose renal tubular dysfunction following prolonged exposure to TDF. These values can be affected by several other factors other than tubular dysfunction. An increase in serum parathyroid hormone can increase urine phosphate levels. Multiple myeloma can present as Fanconi syndrome as well. We did not screen or rule out multiple myeloma. Exclusion of diabetic patients because of different thresholds of glycemia known to cause glucosuria, will reduce generalization of the study results. In this study, we did not do the renal biopsy, which is the gold standard for the diagnosis of the effect of TDF on renal proximal tubules.

The study was conducted during a period of COVID-19 country lockdown and since it was done in a regional referral hospital, we may have enrolled much sicker patients who came to the clinic. This may overestimate our study findings.

Conclusions And Recommendations

Renal tubular dysfunction in HIV patients who are on TDF-containing regimens, can occur in asymptomatic patients with normal eGFR and is associated with electrolytes and micro nutrient wasting. Female gender was significantly associated with renal tubular dysfunction in patients taking TDF. Factors associated with TDF tubulopathy are nonspecific and differ from study to study.

Therefore, we recommend a comparative study between renal biopsies and parameters of Fanconi syndrome on screening for TDF side effects. Since in some cases the side effects of TDF have been reported to be permanent, we therefore recommend a consideration of substitution of TDF to Abacavir (ABC) or Tenofovir Alafenamide (TAF).

List Of Acronyms And Abbreviations

AIDS : Acquired Immuno-Deficiency Syndrome

AKI : Acute Kidney Injury

ART : Anti-Retroviral Therapy

CKD : Chronic Kidney Disease

ESRD: End Stage Renal Disease

FE of Uric acid : Fraction Excretion of Uric Acid

F.E Phos : Fraction Excretion of Phosphate

HIV : Human Immunodeficiency Virus

MRP : Multidrug Resistance Protein

MRRH : Mbarara Regional Referral Hospital

NRTIs : Nucleoside Reverse Transcriptase Inhibitors

PIs : Protease Inhibitors

PLHIV : People Living with HIV

RTD : Renal Tubular Dysfunction

SLMPTA : Strengthening Laboratory Management Toward Accreditation

TB : Tuberculosis

TD : Tubular Dysfunction

TDF : Tenofovir Disoproxil Fumarate

UPCR : Urine Protein Creatinine Ratio

Declarations

Ethics approval and consent to participate

This study was approved by the Mbarara University of Science and Technology Faculty of Medicine Research Committee (MUST-FRC) and Mbarara University Research Ethics Committee (MUST REC) under the reference number MUST-2021-65.

Investigators sought permission to access patient records from the ISS clinic data management committee. Study numbers rather than patient names were used for confidentiality.

We obtained informed consent from all respondents and confidentiality was maintained throughout the study. Access to data was limited to only those who were involved directly in the study and the clinical

team who assisted in the management of those patients. The consent form was translated into the local language (Runyankore) and the participants were allowed to pull out of the study at any point without any penalty and that did not affect the standard service. The blood sample was drawn once for both the study and the routine laboratory tests to minimize the number of pricks.

Results of the tests were communicated to the participants at the earliest time (within one week) either by phone call or text message.

The test results were also communicated to the managing clinicians to allow them make necessary medication adjustments if required.

All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during this study are not publicly available due to the fact that they contain client clinic identification number which we used to merge the information from the patient to the database for reliability, quality assurance and consistence of information as well as during communication of study results from clinic clinicians. Moreover, there is still ongoing analysis to answer different research question. But all data are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

All authors named in this manuscript have contributed substantially to this work and meet the criteria for authorship. JPN, RM and WM took part in initial concept design, proposal writing, data collection, data interpretation, manuscript writing/revision, and approval of final work. EN contributed towards data interpretation, revision of the manuscript, and approval of final work. MK contribute in sampling procedure and data analysis.

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Figures

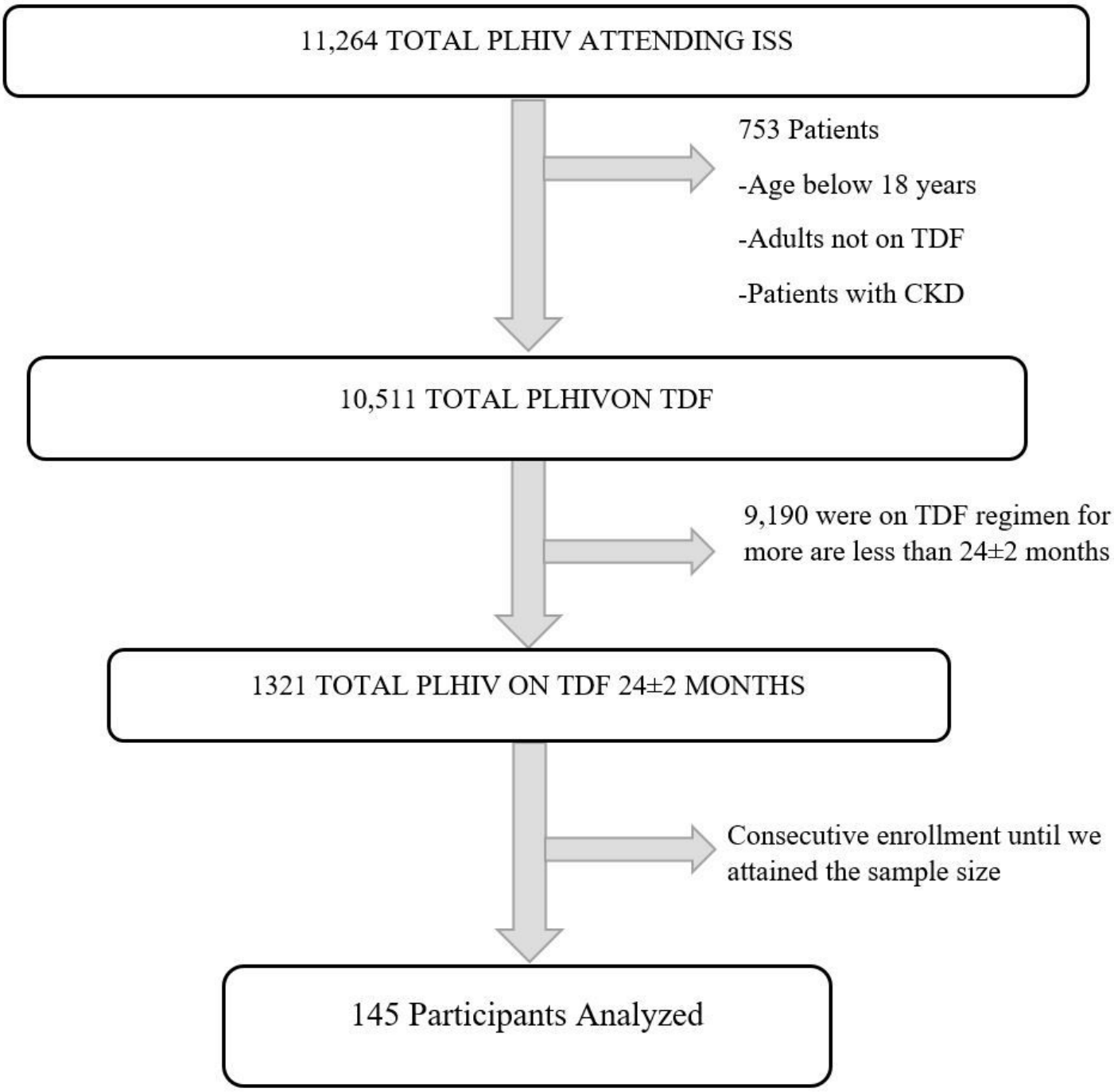

Figure 1

Study flow diagram

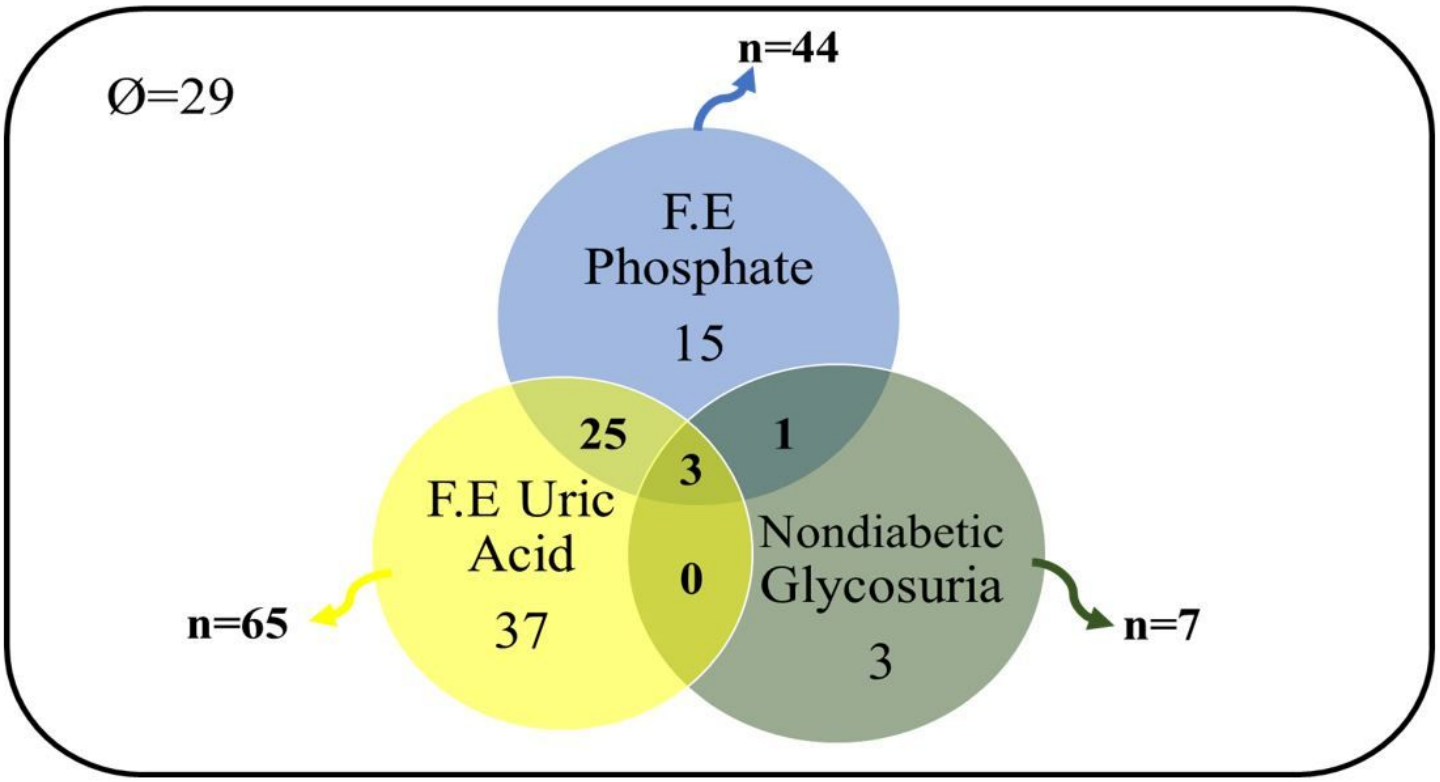

Figure 2

Parameters indicating renal tubular dysfunction

Ø; Number of participants who did not meet any parameter used in the definition of renal tubular dysfunction.