Original Article

Proteinuria in HIV-Infected Children: Prevalence and Associated Risk Factors

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Abstract

Background: Renal abnormalities are increasingly recognised among children living with human immunodeficiency virus, even after the initiation of antiretroviral therapy. Proteinuria may be an early marker of HIV-related kidney injury and may develop before a measurable reduction in renal function. The aim is to determine the prevalence of proteinuria and identify associated clinical, immunological and treatment-related factors among children living with HIV. **Material and Methods:** This hospital-based cross-sectional study included 161 HIV-infected children aged 18 months to 16 years attending the Antiretroviral Therapy Clinic at the Indira Gandhi Institute of Child Health, Bengaluru, from January 2021 to July 2022. Demographic, clinical, immunological, virological and treatment-related data were collected. **Results:** The mean age was 12.2 years, and 54% of participants were female. Initial dipstick proteinuria was detected in 13 children (8.1%), while uPCR-defined proteinuria was present in 40 children (24.8%). Persistent dipstick proteinuria was identified in eight children (5.0%), whereas persistent uPCR-defined proteinuria was present in 19 children (11.8%). Advanced clinical stage at the time of study was significantly associated with initial proteinuria (P=0.00069). **Conclusion:** Proteinuria was common among children living with HIV and was detected more frequently by uPCR than by dipstick testing. Routine quantitative urine protein assessment and periodic renal-function monitoring are recommended, particularly for children with advanced HIV disease or prolonged tenofovir exposure.

Keywords: HIV; children; proteinuria; urine protein-to-creatinine ratio; antiretroviral therapy; tenofovir; renal dysfunction.

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Introduction

Human immunodeficiency virus (HIV) infection remains an important cause of illness and death among children, particularly in low- and middle-income countries. At the end of 2024, approximately 1.4 million children aged 0–14 years were living with HIV worldwide, but only about 760,000 were receiving antiretroviral therapy (ART).[1] Although the expansion of early diagnosis and ART has greatly improved survival, children living with HIV remain vulnerable to chronic complications involving the kidneys, cardiovascular system, bones and nervous system. Kidney disease is particularly important because its early stages may be clinically silent and may remain undetected until considerable renal damage has occurred.[2]

Renal involvement in paediatric HIV infection includes a wide range of abnormalities, such as transient proteinuria, persistent albuminuria, tubular dysfunction, acute kidney injury, HIV-associated immune-complex kidney disease and HIV-associated nephropathy (HIVAN). Among these manifestations, proteinuria is one of the earliest and most easily measurable indicators of glomerular or tubular injury. It may occur before a noticeable reduction in the estimated glomerular filtration rate or an increase in serum creatinine. HIVAN is generally characterised by persistent or heavy proteinuria, progressive loss of kidney function, focal segmental glomerulosclerosis or mesangial hyperplasia, and microcystic dilatation of renal tubules.[3] In severe cases, untreated disease can progress rapidly to kidney failure and death.[4]

The mechanisms responsible for proteinuria in children with HIV are complex. HIV can directly infect renal epithelial cells, including podocytes and tubular epithelial cells, resulting in cellular injury, loss of normal filtration-barrier function and leakage of proteins into the urine. Persistent viral replication may also promote inflammation, immune activation and the deposition of immune complexes within renal tissue. Other causes include opportunistic infections, dehydration, sepsis, malnutrition and exposure to potentially nephrotoxic medications. Genetic susceptibility is also important. Children of African ancestry appear to have a greater risk of HIVAN, partly because of risk variants in the apolipoprotein L1 gene. However, the presence of a genetic risk variant alone is not sufficient, and uncontrolled HIV replication may act as an important trigger for renal injury.[2,3]

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The reported prevalence of proteinuria among HIV-infected children varies considerably between countries and study populations. Differences in age, ethnicity, severity of HIV infection, access to ART, viral suppression, nutritional status and methods used to measure urinary protein may account for this variation. In a longitudinal cohort of 286 HIV-infected children, Chaparro et al. reported baseline proteinuria in 33%, including nephrotic-range proteinuria in 11.2%.[5] Proteinuria was also associated with greater mortality, while improvement in urinary protein excretion was related to reduction in HIV viral load. These findings indicate that proteinuria may serve not only as a marker of kidney injury but also as an indicator of disease severity and poor clinical outcome.

Studies from sub-Saharan Africa have reported similarly important, although variable, levels of renal involvement. A study conducted in Lagos, Nigeria, found proteinuria in 20.5% of HIV-infected children compared with 6% of HIV-negative controls.[6] Proteinuria was particularly common among children with advanced clinical disease and severe immunosuppression. Another Nigerian study reported a prevalence of 31.6% for HIV-associated nephropathy defined through persistent microalbuminuria and renal ultrasound findings.[7] In northern Tanzania, persistent microalbuminuria was identified in 28.8% of 330 HIV-infected children and was significantly associated with advanced clinical stage and a CD4 count below 350 cells/µL.[8]

Lower prevalence estimates have been documented in populations with greater access to ART and better virological control. In a Brazilian cohort, proteinuria was detected in 7% and microalbuminuria in 11.6% of HIV-infected children and adolescents.[9] A South African study involving predominantly virologically suppressed children receiving long-term ART found proteinuria in 6.6% and microalbuminuria in 8.5%.[10] Similarly, a contemporary United States cohort reported an overall prevalence of HIV-associated chronic kidney disease of 6%, although intermittent or persistent proteinuria remained an important feature among affected patients.[11] These differences suggest that early and effective ART may reduce the occurrence and progression of HIV-related kidney disease, but it does not completely eliminate the risk.

Several factors have been investigated as possible predictors of proteinuria and renal dysfunction in HIV-infected children. Advanced clinical stage, low CD4 cell count, severe immunosuppression, persistent viraemia and delayed initiation of ART have frequently been associated with urinary protein loss.[5,6,8] Older age and longer duration of HIV infection may increase cumulative exposure to viral replication, chronic inflammation and medications. Race and genetic background may also influence susceptibility. In a large paediatric cohort, Black race, Hispanic ethnicity and older age were associated with an increased risk of persistent renal abnormalities,[12] Exposure to tenofovir, indinavir, amphotericin B and certain antiviral or antimicrobial medications was also associated with renal dysfunction.[12] However, ART has a dual relationship with kidney health: successful viral suppression can prevent or improve HIV-related nephropathy, whereas some antiretroviral drugs may produce tubular or glomerular toxicity in susceptible children.

The association between ART and proteinuria therefore remains influenced by the drug regimen, treatment duration, adherence and degree of viral suppression. A Nigerian study involving 250 children reported HIV-associated nephropathy in 34% and found significant associations with age, ART status, duration of treatment, clinical disease severity and immunological stage.[13] Nevertheless, other studies have not found a significant relationship between ART duration and proteinuria.[6,7] These inconsistent findings highlight the need for locally generated evidence using clearly defined measurements of proteinuria and appropriate evaluation of HIV-related, treatment-related and demographic factors.

Routine screening for proteinuria provides a simple and relatively inexpensive method of identifying children who may require further renal assessment. Dipstick urinalysis is widely available, but positive findings should preferably be confirmed using a spot urine protein-to-creatinine ratio or albumin-to-creatinine ratio because transient proteinuria may occur during fever, exercise, dehydration or acute infection. Early identification of persistent proteinuria permits timely assessment of kidney function, blood pressure, HIV viral load, CD4 status, medication exposure and possible underlying renal disease. Therefore, determining the prevalence of proteinuria and identifying its associated risk factors among HIV-infected children are essential for developing appropriate screening practices, preventing progressive kidney damage and improving long-term clinical outcomes.

Materials and Methods

The following section was developed from the methodology reported on pages 65–66 of the supplied thesis. Details not available in the thesis extract, such as sample size calculation, sampling method, ethics approval number and the original statistical analysis plan, have not been invented.

Study design and setting: A hospital-based cross-sectional study was conducted among children and adolescents living with human immunodeficiency virus attending the Antiretroviral Therapy Clinic, Centre of Excellence, at the Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, India. The study was carried out over 18 months, from 1 January 2021 to 1 July 2022.

The study evaluated the prevalence of proteinuria and its relationship with demographic, clinical, immunological, virological and treatment-related characteristics among paediatric patients with confirmed HIV infection.

Study population: The study population comprised children aged 18 months to 16 years with confirmed HIV infection who attended the ART clinic during the study period. Children fulfilling the eligibility criteria were assessed after obtaining informed consent from their parents or legal caregivers.

Eligibility criteria

Inclusion criteria

Children were included when they:

1. Were aged between 18 months and 16 years.
2. Had a confirmed diagnosis of HIV infection.
3. Attended the ART clinic at the study institution.

4. Had informed consent provided by a parent or legal caregiver.

Exclusion criteria

Children were excluded when they had conditions that could independently cause transient or persistent proteinuria or interfere with the interpretation of urinary protein measurements. These included:

1. Current febrile illness.
2. Previously diagnosed chronic kidney disease.
3. Known autoimmune disease.
4. Current treatment with corticosteroids.
5. Treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.
6. Recent strenuous physical exercise.
7. Cardiac failure.
8. Hyperglycaemia.
9. Hypertension.
10. Urinary tract infection.

Confirmation of HIV infection: HIV infection was confirmed according to the diagnostic criteria applicable during the study period. For children older than 18 months, a positive HIV diagnosis was defined by two positive HIV antibody tests performed using enzyme-linked immunosorbent assay-based testing. Only children with an established diagnosis of HIV infection were enrolled.

Data collection: Demographic, clinical and treatment-related information was obtained through clinical assessment and review of the participants' medical records. The following variables were recorded:

- Age and sex.
- Age at HIV diagnosis.
- Duration since HIV diagnosis.
- Probable route of HIV transmission.
- Clinical stage at the time of diagnosis.
- Clinical stage at the time of study enrolment.
- Current ART regimen.
- Duration of ART.
- CD4 cell count.
- HIV viral load.
- Relevant clinical history and medication exposure.

Clinical staging was recorded from the available ART records and clinical evaluation. Information on CD4 count and viral load was obtained from recent investigations or blood samples collected during the study assessment.

Blood collection and laboratory investigations

Two venous blood samples of approximately 2 mL each were collected under aseptic conditions. One sample was used for the measurement of CD4 cell count and HIV viral load, while the second sample was used for serum creatinine estimation. Serum creatinine was used to estimate glomerular filtration rate using the bedside modified Schwartz equation. Renal function was classified as impaired when the estimated glomerular filtration rate was below 90 mL/min, as defined in the thesis protocol. For final publication, the investigators should confirm whether the reported eGFR value was standardised to a body surface area of 1.73 m^2 and provide the exact equation and laboratory calibration procedure used.

Urine collection and processing

A freshly voided spot urine sample was collected from each participant in a clean universal specimen container. Urine specimens were analysed within two hours of collection to minimise changes associated with prolonged storage.

The urine sample was initially assessed using AKON Lab urinalysis reagent strips. Dipstick protein results were categorised as:

- Negative.
- 1+: greater than approximately 30 mg/dL.
- 2+: greater than approximately 100 mg/dL.
- 3+: greater than approximately 300 mg/dL.
- 4+: greater than approximately 1,000 mg/dL.

Dipstick proteinuria of at least 1+ was considered significant. A dipstick result of 4+ was classified as nephrotic-range proteinuria.

Measurement of urinary protein and creatinine

Quantitative urinary protein and urinary creatinine concentrations were measured from the spot urine sample. Urinary protein was determined using an immunoturbidimetric method, while urinary creatinine was measured using the modified Jaffe method. The analyses were performed using a COBAS 6000 automated analyser.

The ratio was expressed as milligrams of protein per milligram of creatinine.

The age-specific normal uPCR values reported in the thesis were:

- Less than 0.5 mg/mg for children younger than 2 years.
- Less than 0.2 mg/mg for children aged 2 years or older.

A uPCR between 0.2 and 2.0 mg/mg was classified as proteinuria, while a uPCR greater than 2.0 mg/mg was classified as nephrotic-range proteinuria.

The thesis subsequently defines significant proteinuria as dipstick protein of at least 1+ and a uPCR above 0.2 mg/mg. Because the age-specific normal threshold for children younger than 2 years was stated as below 0.5 mg/mg, the final manuscript should clarify whether the threshold of 0.5 mg/mg or 0.2 mg/mg was used for participants aged 18–23 months.

Definition of study outcomes

The primary outcome was the prevalence of significant proteinuria among HIV-infected children.

Significant proteinuria was assessed using dipstick urinalysis and quantitative uPCR. Based on the thesis protocol, significant proteinuria was defined by:

- 1. Dipstick urinary protein of at least 1+; and/or
- 2. An elevated uPCR above the applicable age-specific threshold.

Nephrotic-range proteinuria was defined as:

- 1. Dipstick urinary protein of 4+; or
- 2. uPCR greater than 2.0 mg/mg.

Impaired renal function was defined as an estimated glomerular filtration rate below 90 mL/min according to the study protocol.

The potential factors evaluated in relation to proteinuria included age, sex, age at HIV diagnosis, duration of HIV infection, route of transmission, clinical stage, CD4 count, viral load, ART regimen, duration of ART, nutritional status and estimated renal function.

Confirmation of proteinuria

Participants with significant proteinuria on the initial evaluation, defined as dipstick proteinuria of at least 1+ and/or an elevated uPCR, underwent repeat urine analysis at least two months after the first assessment.

Proteinuria detected again during the repeat assessment could be classified as persistent proteinuria. However, the original thesis excerpt does not explicitly provide a formal definition of persistent proteinuria or state whether both dipstick and uPCR criteria were required at follow-up. This definition should be confirmed from the original data collection protocol.

Quality control

Urine specimens were processed within two hours of collection. Quantitative urinary protein and creatinine measurements were performed using automated laboratory methods. The use of both dipstick urinalysis and quantitative uPCR reduced dependence on a single screening method.

For a Q1-level manuscript, additional laboratory quality-control information should be reported, including analyser calibration, internal quality-control materials, inter-assay and intra-assay coefficients of variation, reagent manufacturer and lot details, limits of detection and participation in an external quality-assurance programme. These details were not present in the supplied thesis methodology.

Statistical analysis

The statistical analysis was not described in the supplied methodology. Therefore, the following is a recommended Q1-level analysis plan and should be revised to match the analyses actually performed.

Data should be entered into a validated database and analysed using the statistical software employed in the original study. Continuous variables should be assessed for normality using histograms, Q–Q plots and the Shapiro–Wilk test. Normally distributed variables should be presented as mean and standard deviation, whereas skewed variables should be reported as median and interquartile range. Categorical variables should be expressed as frequencies and percentages.

Univariable logistic regression should initially be used to estimate the association between each potential risk factor and proteinuria. Variables with clinical relevance or a univariable P value below 0.20 may then be entered into a multivariable binary logistic regression model. Associations should be reported as crude and adjusted odds ratios with 95% confidence intervals.

Potential collinearity among predictors should be evaluated using variance inflation factors or correlation analysis. Model fit may be assessed using the Hosmer–Lemeshow goodness-of-fit test, while model discrimination may be evaluated using the area under the receiver operating characteristic curve. A two-sided P value below 0.05 should be considered statistically significant.

Results

A total of 161 children and adolescents living with HIV were included in the analysis. All participants were receiving antiretroviral therapy at the time of enrolment.

The mean age of the participants was 12.2 years, with an age range of 3–16 years. Most participants were older than 10 years (120/161, 74.5%). Females accounted for 54.0% of the cohort, producing a male-to-female ratio of approximately 1:1.18.

The mean age at HIV diagnosis was 3.7 years. A total of 94 children (58.4%) had been diagnosed before 5 years of age, while only 15 (9.3%) were diagnosed after 10 years of age. Mother-to-child transmission was the predominant route of HIV acquisition, accounting for 156 cases (96.9%). At the time of the study, 103 participants (64.0%) had received ART for more than 5 years.

Table 1: Demographic and HIV-related characteristics of the study population

Characteristic	Category	Number (%)
Age at enrolment	<5 years	4 (2.5)
	5–10 years	37 (23.0)
	>10 years	120 (74.5)
Age, years	Mean; range	12.2; 3–16
Sex	Male	74 (46.0)
	Female	87 (54.0)
Age at HIV diagnosis	<5 years	94 (58.4)
	5–10 years	52 (32.3)
	>10 years	15 (9.3)
Age at diagnosis	Mean; range	3.7 years; 5 months–16 years
Route of HIV transmission	Mother-to-child transmission	156 (96.9)
	Blood transfusion	3 (1.9)
	Unknown or other	2 (1.2)
Duration of ART	<1 year	10 (6.2)
	1–5 years	48 (29.8)
	>5 years	103 (64.0)

At the time of HIV diagnosis, none of the participants were classified as clinical stage 1. Ninety-seven children (60.2%) were in advanced clinical stages 3 or 4. By the time of study assessment, only 11 participants (6.8%) remained in stages 3 or 4, while 150 (93.2%) were in stages 1 or 2.

Most participants had favourable immunological and virological findings. A CD4 count above 500 cells/mm³ was documented in 126 children (78.3%), and the mean CD4 count was 927 cells/mm³. Viral load was below 1,000 copies/mL in 148 participants (91.9%).

Twenty-three children had a recorded comorbid condition. Tuberculosis was the most frequent comorbidity, affecting 19 participants (11.8%). All participants were taking lamivudine. Dolutegravir was the second most frequently used medication, followed by abacavir, zidovudine and tenofovir.

Table 2: Clinical, immunological, virological and treatment characteristics

Characteristic	Category	Number (%)
Clinical stage at diagnosis	Stage 1	0 (0.0)
	Stage 2	64 (39.8)
	Stage 3	65 (40.4)
	Stage 4	32 (19.9)
Clinical stage at study assessment	Stage 1	73 (45.3)
	Stage 2	77 (47.8)
	Stage 3	10 (6.2)
	Stage 4	1 (0.6)
Comorbidities	None	138 (85.7)
	Tuberculosis	19 (11.8)
	Other	4 (2.5)
CD4 count	<200 cells/mm³	7 (4.3)
	200–349 cells/mm³	10 (6.2)
	350–499 cells/mm³	18 (11.2)
	≥500 cells/mm³	126 (78.3)
Viral load	<1,000 copies/mL	148 (91.9)
	≥1,000 copies/mL	13 (8.1)
BMI category reported in thesis	<18.5 kg/m²	120 (74.5)
	18.5–25.0 kg/m²	38 (23.6)
	>25.0 kg/m²	3 (1.9)
ART medication*	Lamivudine	161 (100.0)
	Dolutegravir	116 (72.0)
	Abacavir	66 (41.0)
	Zidovudine	54 (33.5)
	Tenofovir	39 (24.2)
	Lopinavir/ritonavir	37 (23.0)
	Efavirenz	4 (2.5)

*Participants received combination ART; therefore, medication percentages do not total 100%. BMI percentages were recalculated from the reported counts. Age- and sex-standardised paediatric BMI-for-age scores were not available.

Initial dipstick examination identified significant proteinuria of at least 1+ in 13 children, corresponding to a prevalence of 8.1% (95% confidence interval [CI]: 4.8–13.3%). Eight had 1+ proteinuria and five had 2+ proteinuria. No participant had 3+ or 4+ proteinuria on dipstick examination. Among the 13 children who underwent repeat dipstick examination, eight remained positive. Thus, persistent dipstick proteinuria was observed in 5.0% of the total cohort (95% CI: 2.5–9.5%) and in 61.5% of those who were initially dipstick-positive.

Quantitative uPCR assessment identified proteinuria in 40 participants, giving an initial prevalence of 24.8% (95% CI: 18.8–32.1%). The mean initial uPCR was 0.69 ± 1.19 mg/mg. At repeat assessment, 19 of the 40 initially positive children continued to have a uPCR above 0.2 mg/mg. The prevalence of persistent proteinuria was therefore 11.8% in the total cohort (95% CI: 7.7–17.7%) and 47.5% among children with initial uPCR-defined proteinuria.

Thirty-five participants (21.7%; 95% CI: 16.1–28.7%) had an eGFR below 90 mL/min/1.73 m². Five children had an eGFR between 45 and 59 mL/min/1.73 m². No participant had an eGFR below 45 mL/min/1.73 m².

Table 3: Urinary protein and estimated glomerular filtration rate findings

Renal assessment	Category	Number (%)
Initial dipstick, n=161	Negative	148 (91.9)
	1+	8 (5.0)
	2+	5 (3.1)
	3+ or 4+	0 (0.0)
Repeat dipstick among initial positives, n=13	Negative	5 (38.5)
	1+	5 (38.5)
	2+	3 (23.1)
Initial uPCR, n=161	≤0.2 mg/mg	121 (75.2)
	>0.2 mg/mg	40 (24.8)
Initial uPCR	Mean ± SD	0.69 ± 1.19
Repeat uPCR among initial positives, n=40	≤0.2 mg/mg	21 (52.5)
	>0.2 mg/mg	19 (47.5)
Repeat uPCR	Mean ± SD	0.48 ± 0.55
Overall persistent proteinuria	uPCR >0.2 mg/mg	19/161 (11.8)
eGFR category, n=161	>120 mL/min/1.73 m²	44 (27.3)
	90–120 mL/min/1.73 m²	82 (50.9)
	60–89 mL/min/1.73 m²	30 (18.6)
	45–59 mL/min/1.73 m²	5 (3.1)
	<45 mL/min/1.73 m²	0 (0.0)

eGFR: estimated glomerular filtration rate; SD: standard deviation; uPCR: urine protein-to-creatinine ratio.

The prevalence of initial uPCR-defined proteinuria increased across the current clinical stages. Proteinuria was present in 16.4% of children in stage 1, 26.0% in stage 2, 70.0% in stage 3 and in the single participant classified as stage 4. Current clinical stage was significantly associated with proteinuria (P<0.001).

The distribution of proteinuria also differed significantly across CD4 categories (P=0.005). However, a strictly linear inverse relationship was not observed. The highest prevalence occurred among children with CD4 counts of 200–349 cells/mm³, where 7 of 10 participants had proteinuria. Only one of the seven children with a CD4 count below 200 cells/mm³ had proteinuria.

Age, sex, age at diagnosis, ART duration, comorbidity status, viral load and eGFR category were not significantly associated with initial proteinuria in the unadjusted analyses.

Table 4: Unadjusted associations with initial uPCR-defined proteinuria

Variable	Proteinuria prevalence by category	Recalculated *P* value
Age	<5 years: 0/4 (0.0%); 5–10 years: 10/37 (27.0%); >10 years: 30/120 (25.0%)	0.601
Sex	Male: 15/74 (20.3%); female: 25/87 (28.7%)	0.273
Age at diagnosis	<5 years: 25/94 (26.6%); 5–10 years: 14/52 (26.9%); >10 years: 1/15 (6.7%)	0.243
Duration of ART	<1 year: 1/10 (10.0%); 1–5 years: 11/48 (22.9%); >5 years: 28/103 (27.2%)	0.475
Current clinical stage	Stage 1: 12/73 (16.4%); stage 2: 20/77 (26.0%); stage 3: 7/10 (70.0%); stage 4: 1/1 (100.0%)	<0.001
Comorbidity	Absent: 31/138 (22.5%); present: 9/23 (39.1%)	0.116
Viral load	<1,000 copies/mL: 37/148 (25.0%); ≥1,000 copies/mL: 3/13 (23.1%)	1.000
CD4 count	<200: 1/7 (14.3%); 200–349: 7/10 (70.0%); 350–499: 6/18 (33.3%); ≥500: 26/126 (20.6%)	0.005
eGFR category	>120: 11/44 (25.0%); 90–120: 19/82 (23.2%); 60–89: 5/30 (16.7%); 45–59: 3/5 (60.0%)	0.207

The stage 4 and eGFR 45–59 categories contained very small numbers; these estimates should therefore be interpreted cautiously.

Persistent proteinuria was strongly associated with the clinical stage at HIV diagnosis. Its prevalence increased from 4.7% among children diagnosed in stage 2 to 9.2% in stage 3 and 31.3% in stage 4 (P<0.001).

A similar relationship was found for the clinical stage at study assessment. Persistent proteinuria affected 1.4% of participants in stage 1, 13.0% in stage 2, 70.0% in stage 3 and the single participant in stage 4 (P<0.001).

Persistent proteinuria was also more frequent among children with comorbidities than among those without comorbidities: 34.8% versus 8.0%, respectively (P=0.001). Age, sex, age at diagnosis, duration of ART and viral-load category were not significantly associated with persistent proteinuria.

Table 5: Unadjusted associations with persistent uPCR-defined proteinuria

Variable	Persistent proteinuria by category	Recalculated *P* value
Age	<5 years: 0/4 (0.0%); 5–10 years: 5/37 (13.5%); >10 years: 14/120 (11.7%)	0.865
Sex	Male: 7/74 (9.5%); female: 12/87 (13.8%)	0.468
Age at diagnosis	<5 years: 11/94 (11.7%); 5–10 years: 7/52 (13.5%); >10 years: 1/15 (6.7%)	0.764
Duration of ART	<1 year: 1/10 (10.0%); 1–5 years: 5/48 (10.4%); >5 years: 13/103 (12.6%)	0.919
Clinical stage at diagnosis	Stage 2: 3/64 (4.7%); stage 3: 6/65 (9.2%); stage 4: 10/32 (31.3%)	<0.001
Current clinical stage	Stage 1: 1/73 (1.4%); stage 2: 10/77 (13.0%); stage 3: 7/10 (70.0%); stage 4: 1/1 (100.0%)	<0.001
Comorbidity	Absent: 11/138 (8.0%); present: 8/23 (34.8%)	0.001
Viral load	<1,000 copies/mL: 17/148 (11.5%); ≥1,000 copies/mL: 2/13 (15.4%)	0.653

Thirty-nine participants were receiving a tenofovir-containing regimen. Initial proteinuria was more frequent among children receiving tenofovir than among those not receiving tenofovir, 35.9% versus 21.3%, although the association was not statistically significant. Persistent proteinuria occurred in 15.4% of tenofovir-treated participants and 10.7% of those receiving other regimens.

Among participants receiving tenofovir, proteinuria was more frequent after more than 1 year of exposure than after less than 1 year of exposure: 52.9% versus 22.7%. Persistent proteinuria was similarly more frequent after more than 1 year of exposure, although neither association reached statistical significance.

Reduced eGFR was observed in 47.1% of children who had received tenofovir for more than 1 year compared with 13.6% of those treated for less than 1 year. Longer tenofovir exposure was associated with approximately 5.6-fold higher unadjusted odds of reduced eGFR.

Table 6: Tenofovir exposure and renal outcomes

Comparison	Outcome prevalence	Unadjusted OR (95% CI)	Exact *P* value
Tenofovir versus no tenofovir	Initial proteinuria: 14/39 (35.9%) vs 26/122 (21.3%)	2.07 (0.94–4.53)	0.088
Tenofovir versus no tenofovir	Persistent proteinuria: 6/39 (15.4%) vs 13/122 (10.7%)	1.52 (0.54–4.33)	0.406
Tenofovir >1 year versus <1 year	Initial proteinuria: 9/17 (52.9%) vs 5/22 (22.7%)	3.83 (0.96–15.19)	0.091
Tenofovir >1 year versus <1 year	Persistent proteinuria: 4/17 (23.5%) vs 2/22 (9.1%)	3.08 (0.49–19.29)	0.374
Tenofovir >1 year versus <1 year	eGFR <90: 8/17 (47.1%) vs 3/22 (13.6%)	5.63 (1.20–26.41)	0.033

CI: confidence interval; eGFR: estimated glomerular filtration rate; OR: odds ratio. Estimates are unadjusted and have wide confidence intervals because only 39 participants received tenofovir.

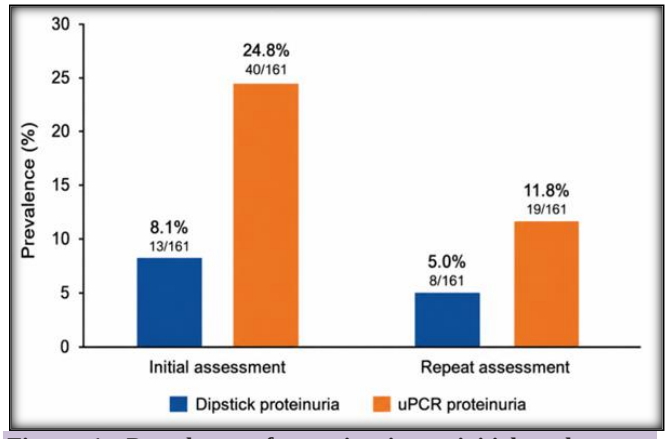

Figure 1: Prevalence of proteinuria at initial and repeat assessments among children living with HIV

[Figure 1] Bar chart comparing dipstick-defined and uPCR-defined proteinuria at the initial assessment and persistent proteinuria at the repeat assessment. Initial uPCR-defined proteinuria was identified in 40 of 161 participants (24.8%), while persistent uPCR-defined proteinuria was present in 19 participants (11.8%).

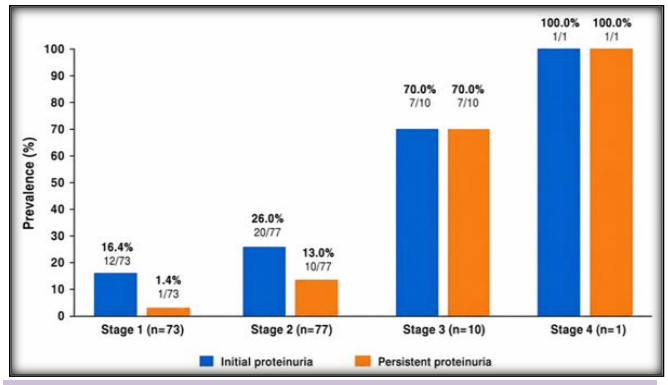

Figure 2: Initial and persistent proteinuria according to the current clinical stage of HIV infection

[Figure 2] showing the increasing prevalence of both initial and persistent proteinuria across clinical stages 1–4. Estimates for stage 4 should be interpreted cautiously because this category included only one participant.

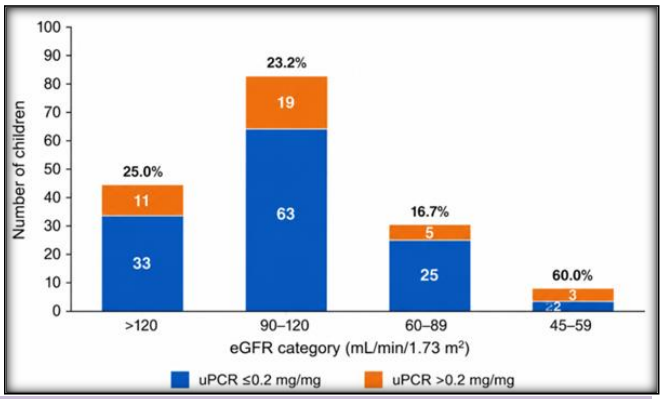

Figure 3: Distribution of proteinuria across estimated glomerular filtration-rate categories

[Figure 3] showing the numbers of children with and without uPCR-defined proteinuria across eGFR categories. Proteinuria was present in 60% of participants with an eGFR of 45–59 mL/min/1.73 m²; however, this category contained only five participants.

Discussion

The present study evaluated proteinuria and associated clinical factors among 161 children and adolescents living with HIV and receiving antiretroviral therapy. Most participants were older than 10 years, had acquired HIV through vertical transmission and had received ART for more than five years. Despite favourable virological control in most children, initial uPCR-defined proteinuria was detected in 40 participants, giving a prevalence of 24.85%. Persistent proteinuria was documented in 19 children, corresponding to 11.8% of the total study population. These findings show that clinically silent renal involvement remains common among children living with HIV, even when ART coverage, CD4 recovery and viral suppression are generally satisfactory.

The initial prevalence of 24.85% is comparable with the cumulative proteinuria prevalence of 22% reported by Purswani et al. among children and adolescents with perinatally acquired HIV in the United States.[14] It is also close to the 29% proteinuria prevalence recently reported among young people living with HIV in Uganda.[15] However, prevalence estimates vary widely across paediatric studies because of differences in age, ethnicity, ART exposure, HIV disease severity, urine sampling protocols and the criteria used to define proteinuria. For example, Deyà-Martínez et al. documented persistent proteinuria in 17.6% of HIV-infected paediatric patients,[16] whereas Dondo et al. reported persistent proteinuria in only 5% of ART-naïve children in Zimbabwe.[17] Thus, the prevalence observed in the present study lies within the broad range described in paediatric HIV populations.

The difference between dipstick and uPCR findings was clinically important. Only 13 children, or approximately 8%, had proteinuria of at least 1+ on the initial dipstick test, whereas 40 children, or 24.85%, had a uPCR above 0.2 mg/mg. Persistent dipstick proteinuria was present in eight children, compared with persistent uPCR-defined proteinuria in 19 children. This difference indicates that dipstick testing alone may fail to identify a considerable proportion of children with low-grade urinary protein loss. Dipsticks are affected by urine concentration, pH and the predominant type of urinary protein, while uPCR provides a quantitative estimate adjusted for urine creatinine. The findings support the use of quantitative uPCR after screening, especially in children at increased renal risk.

The clinical stage of HIV infection was one of the most important factors associated with proteinuria. At the time of study assessment, the prevalence of initial proteinuria increased from 16.4% in stage 1 to 26% in stage 2, 70% in stage 3 and 100% in the single child classified as stage 4. A statistically significant association was observed between advanced current clinical stage and initial proteinuria. Persistent proteinuria also increased with clinical stage both at HIV diagnosis and at the time of study assessment. These findings suggest that greater cumulative disease severity may contribute to sustained renal injury.

Advanced HIV disease can affect the kidneys through direct viral injury to renal epithelial cells, immune-complex deposition, chronic inflammation, opportunistic infections and exposure to potentially nephrotoxic medications.

The improvement in clinical staging between diagnosis and study assessment is also noteworthy. At diagnosis, approximately 60% of children were classified in stages 3 or 4, whereas only 6.8% remained in these stages during the study. This change probably reflects the clinical benefits of long-term ART. Nevertheless, the association between previous advanced disease and persistent proteinuria suggests that renal injury acquired during periods of severe HIV disease may not resolve completely after clinical and immunological recovery. Longitudinal follow-up is therefore important even in children who later achieve satisfactory viral suppression.

An association was identified between CD4 count category and initial proteinuria, with a reported P value of 0.0041. A Tanzanian study similarly found higher frequencies of proteinuria and microalbuminuria among children with a low CD4 percentage [18]. However, the category-specific pattern in the present study was not strictly linear. Proteinuria was most frequent in the CD4 range of 200–349 cells/mm³, while only one of seven children with a CD4 count below 200 cells/mm³ had proteinuria. This finding may have been influenced by the small number of children with severe immunosuppression. In addition, CD4 count was not significantly associated with persistent proteinuria. The results therefore support an association between immunological status and initial renal abnormalities but do not establish a consistent dose-response relationship.

Viral load was not significantly associated with either initial or persistent proteinuria. This may be explained by the high proportion of children with adequate virological control, as 91.9% had a viral load below 1,000 copies/mL. The small number of children with virological non-suppression reduced the statistical power to detect a meaningful difference. Furthermore, renal abnormalities may reflect historical exposure to uncontrolled viral replication rather than only the viral load measured at the time of study enrolment. Similar uncertainty has been reported in paediatric cohorts in which mild renal abnormalities persisted despite apparently controlled HIV infection.[16,19] Kruthika et al. found glomerular or tubular dysfunction in nearly half of ART-treated HIV-positive children, although serum creatinine and eGFR were normal in all participants.[19]

The study also demonstrated that proteinuria and reduced eGFR did not always occur together. Thirty-five children had an eGFR below 90 mL/min/1.73 m², but the association between eGFR category and proteinuria was not statistically significant. Three of the five children with an eGFR of 45–59 mL/min/1.73 m² had proteinuria, suggesting clinically important renal involvement despite the lack of overall statistical significance. Dondo et al. reported reduced eGFR in 34.6% of ART-naïve HIV-infected children in Zimbabwe [17], while Fredrick et al. found proteinuria in 7.1% and an eGFR of 30–59 mL/min/1.73 m² in 5.8% of children in Tanzania [18]. More recent evidence also shows that CKD prevalence can vary substantially according to the renal biomarker and estimating equation used [15]. Creatinine-based eGFR may be affected by muscle mass and nutritional status, which is particularly important in children with HIV and poor growth.

Tenofovir exposure deserves particular attention. Among 39 children receiving tenofovir, 14, or 35.8%, had initial proteinuria and six, or 15.4%, had persistent proteinuria. These proportions were higher than those observed among children not receiving tenofovir, although the differences were not statistically significant. Proteinuria was detected in 52.9% of children exposed to tenofovir for more than one year compared with 22.7% of those exposed for less than one year. This association approached statistical significance. More importantly, reduced eGFR was present in 47.05% of children exposed for more than one year compared with 13.6% exposed for less than one year, and this relationship was statistically significant.

These findings are consistent with evidence that cumulative tenofovir exposure may increase renal risk. Purswani et al. found that exposure for more than three years independently increased the odds of proteinuria among children and adolescents with perinatal HIV infection.[14] A Zimbabwean paediatric study also reported proteinuria and reduced eGFR among children receiving tenofovir and emphasised the need to evaluate proximal tubular function.[20] In a Ghanaian cohort, tenofovir use was associated with higher uPCR values and increased odds of tubular dysfunction.[21] Tenofovir is primarily eliminated through proximal tubular cells, where intracellular accumulation can cause mitochondrial injury, phosphate wasting, tubular proteinuria and a decline in filtration function.

Nevertheless, the tenofovir findings should be interpreted cautiously. Only 39 children were exposed to the drug, and the cross-sectional design could not establish whether tenofovir preceded the development of proteinuria or reduced eGFR. Baseline renal measurements before tenofovir initiation were unavailable. In addition, total uPCR cannot distinguish glomerular albuminuria from low-molecular-weight tubular proteinuria. Future studies should include urinary albumin-to-creatinine ratio, serum phosphate, fractional phosphate excretion, urine glucose in the presence of normal blood glucose and tubular biomarkers such as urinary β_2-microglobulin. Such measurements would help determine whether the observed abnormalities represent HIV-associated glomerular injury, tenofovir-related proximal tubular dysfunction or a combination of both.

The presence of comorbidities was associated with a numerically higher prevalence of initial and persistent proteinuria, although the relationship did not reach statistical significance in the thesis analysis. Tuberculosis was the most common comorbidity. Opportunistic infections may increase renal risk through systemic inflammation, dehydration, sepsis and exposure to nephrotoxic antimicrobial agents. However, the small number of children with comorbidities limited the precision of the analysis.

The current findings have practical implications. HIV kidney-disease guidance recommends regular assessment of renal function and urinary protein, with closer evaluation when abnormalities are detected.[22] Because proteinuria may occur before a major fall in eGFR, screening should not depend on serum creatinine alone. Children with advanced HIV stage, previous severe immunosuppression, comorbid illness, persistent

proteinuria or prolonged tenofovir exposure may require more frequent monitoring. Genetic susceptibility may also contribute to renal risk; APOL1 high-risk genotypes have been associated with increased odds of CKD among children and young people with perinatally acquired HIV.[23] Although genetic testing was outside the scope of the present study, it may help explain why only some children develop renal complications despite similar HIV and treatment exposures.

The study's strengths include the use of both dipstick urinalysis and quantitative uPCR, repeat urine assessment among initially positive participants and simultaneous evaluation of clinical, virological, immunological and treatment-related variables. However, several limitations must be considered. It was a single-centre cross-sectional study, and some clinically important subgroups contained very few participants. There was no HIV-negative comparison group, renal ultrasonography or kidney biopsy. Urinary albumin and tubular biomarkers were not measured, and the repeat assessment after at least two months did not fully establish chronic kidney disease persisting for three months or longer. The use of fixed adult BMI thresholds was also unsuitable for evaluating nutritional status across a wide paediatric age range. Finally, the analyses were largely unadjusted; therefore, the observed relationships should not be interpreted as independent causal risk factors.

Overall, proteinuria was a frequent renal abnormality among ART-treated children living with HIV. Advanced clinical stage was consistently associated with both initial and persistent proteinuria, while CD4 count was associated with initial proteinuria. Prolonged tenofovir exposure was significantly associated with reduced eGFR and showed a clinically important trend towards increased proteinuria. These findings support routine quantitative urinary protein assessment and periodic renal-function monitoring as part of long-term paediatric HIV care.

Conclusion

Proteinuria was a common renal abnormality among children and adolescents living with HIV in this study. Initial uPCR-defined proteinuria was present in 24.8% of participants, while persistent proteinuria was identified in 11.8%. Dipstick testing detected fewer cases than quantitative uPCR, indicating that dipstick urinalysis alone may miss children with low-grade urinary protein loss. Advanced HIV clinical stage was significantly associated with both initial and persistent proteinuria, while CD4 count was associated with initial proteinuria. Although viral load, age, sex, duration of ART and eGFR category were not significantly associated with proteinuria, clinically important renal abnormalities were still observed in several children. Longer exposure to tenofovir was significantly associated with reduced eGFR and showed a higher frequency of initial and persistent proteinuria, although the proteinuria associations were not statistically significant.

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Conflicts of interest

There are no conflicts of interest.

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