KIDNEY DISEASE IN AFRICANS WITH HIV AND TUBERCULOSIS

Short title: Kidney disease in Africans with HIV/TB

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Abstract

Objective: To describe the spectrum of kidney disease in African patients with HIV and tuberculosis (TB).

Methods: We used data from three cohorts: consecutive patients with HIV/TB in South London (UK, 2004-2016; n=95), consecutive patients with HIV/TB who underwent kidney biopsy in Cape Town (South Africa, 2014-2017; n=70), and consecutive patients found to have HIV/TB on autopsy in Abidjan (Cote d'Ivoire, 1991; n=100). Acute kidney injury (AKI) was ascertained using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. In the Cape Town cohort, predictors of recovery of kidney function at six months were assessed using Cox regression.

Results: In the London cohort, the incidence of moderate/severe AKI at 12 months was 15.1 (95%CI 8.6-26.5) per 100 person-years, and the prevalence of chronic and end-stage kidney disease (ESKD) 13.7% and 5.7% respectively. HIV-associated nephropathy (HIVAN) was diagnosed in 6% of patients in London, and in 6% of autopsy cases in Abidjan. Evidence of renal TB was present in 60% of autopsies in Abidjan and 61% of kidney biopsies in Cape Town. HIVAN and acute tubular necrosis (ATN) were also common biopsy findings in Cape Town. In Cape Town, 40 patients were dialyzed, of whom 28 (70%) were able to successfully discontinue renal replacement therapy. Antiretroviral therapy status, CD4 cell count, eGFR at biopsy and renal pathology, other than ATN, were not predictive of eGFR recovery.

Conclusions: Kidney disease was common in Africans with HIV/TB. Monitoring of kidney function, and provision of acute dialysis to those with severe kidney failure, is warranted.

Introduction

Sub-Saharan Africa is severely and disproportionally affected by the HIV and tuberculosis (TB) epidemics, with an estimated 19 million co-infected with HIV and *Mycobacterium tuberculosis* [1, 2]. HIV infection is a major risk factor for TB, and TB control programs across the continent have been overwhelmed by the increased case load attributable to HIV. TB in people with HIV is often disseminated and, in the absence of antiretroviral therapy (ART), a major cause of death [3, 4]. Widespread use of ART in sub-Saharan Africa has reduced the incidence of TB although the rates of TB in many countries remain among the highest reported worldwide [2].

Kidney disease in the setting of HIV is common, complex, and a clinically significant problem [5]. The spectrum of kidney disease encompasses acute kidney injury (AKI), HIV-associated nephropathy (HIVAN), immune-complex kidney disease, diabetic and hypertensive nephropathy, opportunistic infections in addition to TB (e.g. cryptococcus, candida), malignancy (e.g. B-cell lymphoma) and drug toxicity from ART, co-trimoxazole and other antimicrobial chemotherapy [6-8]. In the setting of HIV/TB, kidney injury may result from any of these conditions as well as immune reconstitution inflammatory syndrome (IRIS) and acute or chronic effects of TB or anti-tuberculous chemotherapy on the kidney. A kidney biopsy is often required to establish the diagnosis and guide therapeutic management, although this is rarely available outside selected major centres in sub-Saharan Africa.

The prevalence, incidence and pathology of kidney disease in African HIV/TB patients remain largely unreported. A cross sectional study from Cameroon evaluated renal function in 200 patients with HIV/TB and variable duration of TB treatment and reported that sixteen (8%) had impaired renal function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) [9]. An autopsy study from Uganda reported renal TB in eight (50%) of 16 patients with TB/HIV, HIVAN in three (19%) and other

abnormalities in four subjects; only one patient had normal kidneys [10]. We used observations from three distinct cohorts to describe the burden and spectrum of kidney disease in Africans with HIV/TB.

Methods

We used data from three cohorts: consecutive African patients with HIV/TB in London, United Kingdom; patients with HIV/TB who underwent kidney biopsy in Cape Town, South Africa; and an autopsy series of people with HIV/TB in the pre-ART era in Abidjan, Cote d'Ivoire. Regulatory approvals were in place for each of the three cohorts; individual consent was not required.

In London, we identified all black African patients diagnosed with HIV/TB between 2004 and 2016 at King's College Hospital on a prospectively maintained database. To be included, patients were required to have HIV-1 infection diagnosed prior to, or up to 1 month after TB diagnosis, and a positive culture for *Mycobacterium tuberculosis* or histology demonstrating granulomatous inflammation (with or without acid-fast bacilli). Demographic variables, HIV parameters, renal risk factors (hypertension and diabetes), details of TB treatment, and all available serum creatinine and proteinuria measurements and kidney biopsy reports were obtained. HIV parameters, TB outcomes, and renal function were evaluated up to 12 months post-TB diagnosis.

In Cape Town, we identified consecutive patients with a clinical diagnosis of TB from a prospectively maintained kidney biopsy database at Groote Schuur Hospital between 2015 and 2017. To be included, patients were required to have had HIV infection at the time of kidney biopsy, and TB as evidenced by positive culture, nucleic acid amplification, urine lipoarabinomannan (LAM), elevated adenosine deaminase (ADA) levels in pleural or peritoneal fluid, or granulomatous inflammation (with or without acid-fast bacilli) in any organ (including the kidney). Renal TB in this cohort was defined as the presence of granulomatous inflammation with or without acid-fast bacilli on kidney biopsy. Tenofovir toxicity was suspected in patients whose biopsies demonstrated acute tubular necrosis (ATN) with blebbing of the

proximal mitochondrial cell membrane on light microscopy and predominant mitochondrial structural abnormalities on electron microscopy. Demographic variables, HIV parameters, hypertension, diabetes, TB treatment, ART and renal function at the time of biopsy, and at three and six months, were recorded. As renal, HIV and TB care took place in different locations, limited information on TB and HIV outcomes was available for this cohort.

In Abidjan, we identified patients with HIV/TB on a prospectively maintained database of autopsies in the pre-ART era performed by a single pathologist (SBL) in 1991 in two hospitals [3]. To be included, patients were required to be HIV-1 and/or HIV-2 positive and to have pathological evidence of tuberculosis: acid-fast bacilli and/or (caseous or non-caseous) granulomatous inflammation in one or more organs. The diagnosis of TB in the kidney was histological: either non-reactive necrosis with numerous acid-fast bacilli (see Fig), or granulomatous inflammation with acid-fast bacilli, or granulomatous inflammation without acid-fast bacilli but TB in other organs and other infectious causes excluded.

Definitions

Acute kidney injury (AKI) was defined by increases in serum creatinine as per the Kidney Disease: Improving Global Outcomes (KDIGO) classification; Stage 1 was defined by a 1.5-1.9 fold or ≥26.5 µmol/L increase from baseline; Stage 2 by a 2.0-2.9 fold increase from baseline; Stage 3 by a $\geq$3 fold increase from baseline, a rise to ≥353.6 µmol/L, or the need for renal replacement therapy (RRT) [11]. To assess renal function at baseline and 12 months, creatinine values were converted to eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, with application of the factor 1.159 for black ethnicity [12]; CKD at 12 months was defined by an eGFR <60 mL/min/1.73m^2 for >3 months, subdivided into stages 3 (eGFR 30-59 mL/min/1.73m^2), 4 (eGFR 15-29 mL/min/1.73m^2) and 5 (eGFR <15 mL/min/1.73m^2). End stage kidney disease (ESKD) was defined by the need for permanent RRT.

Proteinuria was assessed on randomly collected samples and expressed as urine protein/creatinine ratio (uPCR, expressed in mg/mmol). The diagnosis of hypertension and diabetes was based on the use of medications to treat these conditions at the time of TB diagnosis or kidney biopsy.

Analyses

Demographic and clinical characteristics were described for each of the three cohorts, and kidney pathology for the Abidjan and Cape Town cohorts. The incidence of AKI was calculated for participants in the London cohort, with follow up included up to 12 months, the last clinic visit, or the date of the first AKI episode, whichever occurred earliest. In the Cape Town cohort, predictors of non-recovery of kidney function (eGFR <60 mL/min/1.73m^2 or <30 mL/min/1.73m^2 at six months) were analysed using Cox regression.

Results

A total of 265 Africans with HIV/TB were included: 95 from London, 70 from Cape Town, and 100 from Abidjan (Tables 1 and S1). The mean age across the three cohorts ranged from 36.4-39.1 years; most patients had advanced immunodeficiency and disseminated TB. Most patients in London were ART-naïve at TB diagnosis while in Cape Town most had initiated ART at the time of kidney biopsy; none of those in Abidjan had received ART. The TB diagnosis in Abidjan was made ante-mortem in 22% and at post-mortem in 78%; TB was the main cause of death in 89% and the sole cause of death in 61%.

In London at TB diagnosis, the median eGFR was 118 (Inter-Quartile Range [IQR] 88-129) mL/min/1.73m^2; 13 patients (13.7%) had an eGFR <60 mL/min/1.73m^2 (Table 2). Patients in Cape Town had severe, proteinuric kidney disease (median eGFR 8 [IQR 5-19] mL/min/1.73m^2, median urine protein creatinine ratio [uPCR] 247 mg/mmol). Application of the correction factor for ethnicity in the eGFR

calculation minimally affected the number of patients in each eGFR category in the London and Cape Town cohorts (data not shown). No information on renal function was available for the Abidjan cohort.

Acute kidney injury

The majority (71.7%) of patients co-infected with HIV/TB in the London cohort remained free of AKI; 14 (15.2%) developed stage 1 AKI, three (3.3%) stage 2 AKI, and nine (9.8%) stage 3 AKI in the first year after starting TB treatment (Table 2); eight AKI episodes required RRT, and 70% of AKI episodes occurred in those on ART. The incidence of moderate/severe (stage 2/3) AKI was 15.1 (95% CI 8.6-26.5) per 100 person-years and these episodes were due to, or occurred in the setting of, HIVAN (n=4), ATN (n=3), interstitial nephritis/drug toxicity (rifampicin/co-trimoxazole, n=2), drug-induced liver injury (n=2), and congestive cardiac failure (n=1). All 14 patients with stage 1 AKI had resolution of their kidney injury. Of the 12 patients who developed stage 2/3 AKI, three died, renal function normalised in four, partially recovered in three (allowing discontinuation of dialysis in two subjects) and did not recover with the need for permanent RRT in the remaining two patients.

Chronic kidney disease

In the London cohort at 12 months post TB diagnosis, the median eGFR was 107 (IQR 91-129) mL/min/1.73m^2 (Table 2). Eleven patients (12.6%) had CKD stage 3/4/5; at TB diagnosis all but one had an eGFR <60 mL/min/1.73m^2. Five patients (5.7%) presented with or progressed to ESKD. Seven patients had kidney biopsies; six showed HIVAN, one had interstitial nephritis, one had both HIVAN and interstitial nephritis, and none had granulomata.

Mortality and kidney failure

Five patients died within 12 months of TB diagnosis (Table S1). All five had kidney failure at the time of death: three had AKI with normal kidney function at TB diagnosis, and two had severe CKD (acute on chronic kidney failure, ESKD).

Kidney pathology in the Abidjan and Cape Town cohorts

Pathological evidence of renal TB, ranging from single granulomas to vast numbers of acid-fast bacilli in glomeruli and tubule-interstitium (Fig S1), was present in 61%, interstitial nephritis in 31% (14% vs. 36% in those with ante-mortem and post-mortem TB diagnoses respectively), and HIVAN in 6% of autopsy cases in Abidjan; only 17% of subjects in Abidjan had normal kidneys.

Many patients in Cape Town had multiple renal pathologies. Renal TB was diagnosed in 61%, and HIVAN, ATN and pyelonephritis in 41%, 69% and 17% respectively (Table 3 and S2). Tenofovir disoproxil fumarate (TDF) exposure was considered a contributing factor to the renal presentation in a single case. Immune complex kidney disease and amyloidosis were uncommon findings in either cohort.

Dialysis and reversibility of kidney failure in the Cape Town cohort

Access to dialysis in government hospitals in South Africa is restricted and generally reserved for those with AKI and carefully selected patients with ESKD. In the six months following kidney biopsy, 44 (63%) patients required RRT; of these four were considered to have ESKD with no or minimal potential for reversibility. Dialysis was provided to the remaining 40 (91%) patients, of who 28 (70%) subsequently successfully discontinued RRT (post-dialysis eGFR $\geq$60 [n=14], 30-59 [n=9], 15-29 [n=5] mL/min/1.73m^2). By six months, renal function had improved in the majority of patients (eGFR $\geq$60 mL/min/1.73m^2 in 33%, eGFR 30-59 mL/min/1.73m^2 in 30%), and ESKD was present in 16 (23%) of the 70 participants (Tables 2 and S2).

Age, gender, CD4 cell count, ART status and eGFR at biopsy were not predictive of eGFR recovery nor were the presence of hepatitis B co-infection, hypertension or HIVAN. The presence of ATN on biopsy was associated with reduced risk of eGFR <60 mL/min/1.73m^2 at six months (Hazard Ratio 0.56, 95%CI 0.31-0.99) (Table S3).

Discussion

We used data from three complementary cohorts to study the incidence of AKI and CKD (London cohort), histological findings in patient with TB/HIV undergoing renal biopsies for clinical reasons and outcome of patients undergoing RRT for AKI (Cape Town cohort), and kidney pathology of patients who died with HIV/TB in pre-ART era (Abidjan cohort). We report a high burden of kidney disease in African patients with HIV/TB. Data from London indicate that acute and chronic impairment of kidney function is common, and that 12% may require temporary or permanent RRT while receiving TB treatment. Data from London and Abidjan (comprising patients unselected for kidney disease) suggest that HIVAN may be present in about 6%, and that HIVAN is an important cause of ESKD in this population. Data from Cape Town (comprising patients with severe kidney disease) showed that HIVAN was common, acute and chronic kidney pathologies frequently co-existed, and that kidney failure may recover in the majority of patients.

Most subjects had severe immunodeficiency and disseminated TB with evidence of renal TB in 60% of cases. Immunodeficiency is a strong predictor of urine LAM positivity and mycobacteriuria which are indicative of haematogenous dissemination of TB to the kidneys (Fig S1) [13]. Immunodeficiency is also a major risk factor for AKI in the setting of HIV [14, 15]. The aetiology of AKI is often multifactorial, with infection, malignancy and liver disease compounded by reduced renal blood flow (hypotension or shock) and exposure to potentially nephrotoxic medications [14, 16]. Hence, the presence of TB in the kidneys should not be interpreted as TB being the sole cause of AKI or CKD. Kidney biopsies, where performed,

frequently show ATN as well as evidence of underlying chronic kidney pathology [17]. ART may contribute to (or cause) AKI through immune reconstitution inflammatory syndrome (IRIS) [18, 19] or direct ART nephrotoxicity, most commonly from TDF [20]. While TDF was widely used in London and Cape Town, proximal tubulopathy was not observed in the London cohort and in the Cape Town cohort TDF exposure was considered a contributing factor to the renal presentation in only one patient. A low rate of TDF toxicity is consistent with a previous study from our centre that did not find an association between TDF exposure and AKI [15], and a large UK cohort study of almost 16,000 patients that reported black individuals to be at 80% reduced risk of treatment-limiting TDF toxicity compared to those of (predominantly) white ethnicity [21].

The prevalence of CKD 3 - 5 in the London cohort after one year was 13%, a finding that is consistent with findings from a study from Cameroon in which 13% of those on ART had an eGFR <60 mL/min/1.73m^2 [9]. Data from the Cape Town cohort suggest that many of these individuals may have HIVAN, with or without sequelae of AKI and/or renal tuberculosis. The higher prevalence of HIVAN in the Cape Town vs. the London and Abidjan cohorts is likely explained by selection bias: participants in the Cape Town cohort all has severe kidney disease whereas the latter two cohorts comprised HIV/TB cases unselected for abnormalities of kidney function. As ART provides survival benefit in people with HIV/TB [22] as well as protection against kidney disease progression in individuals with HIVAN [7, 8, 23-25], fully suppressive ART is a particular priority for patients with impaired renal function and/or proteinuria. However, despite unrestricted access to ART, 6% of patients in the London cohort developed ESKD. The incidence of ESKD among HIV/TB patients who receive treatment in Africa without monitoring of renal function could be substantially higher, especially in West Africa where apolipoprotein L1 (APOL1) risk alleles which predispose to HIVAN are highly prevalent and rates of viral suppression remain well below those reported in Southern and East Africa [1, 5, 26].

Substantial reversibility of kidney failure was observed in the Cape Town cohort, even among those who required dialysis. This findings is consistent with a previous study of acute interstitial nephritis from Cape Town [27]. Specialist nephrology services are extremely sparse in sub-Saharan Africa and RRT is rarely available. Our results suggest that patients with HIV/TB may be appropriate candidates for acute dialysis in that 70% of those who received renal support regained native renal function and were able to subsequently discontinue dialysis. While haemodialysis and haemofiltration are the standard modalities of RRT for patients with AKI in resource-rich settings, these are generally not available in resource-limited health care settings [28]. However, acute peritoneal dialysis may be a lower-cost alternative providing life-saving renal support to patients with AKI [29]. Indeed, several acute peritoneal dialysis units have been successfully established across sub-Saharan Africa [30], although considerable scale up will be required to meet the needs of people with HIV/TB who develop AKI.

Uniquely this study benefits from three complimentary cohorts to provide insight into the prevalence, incidence and aetiology of kidney disease in Africans with HIV/TB. However, there are several limitations that should be acknowledged. Although subjects in the three cohorts were identified on prospectively maintained databases, data collection was retrospective and invariably some data was missing where tests had not been performed or results could not be obtained. In London, not all subjects with AKI or CKD underwent kidney biopsy, in Abidjan subject's antemortem renal function and CD4 cell counts were not available, and among subjects in Cape Town viral load data were unavailable for more than half. Diagnosis of renal TB in the Cape Town cohort was based on identifying granulomatous inflammation (with or without acid fast bacilli) in the kidney; this may have resulted in an underestimation of the prevalence of renal TB as those with advanced immunodeficiency may be unable to mount a granulomatous inflammatory response, or an overestimation of the prevalence of renal TB as in some cases this pathological abnormality may have been due to another infection, drug toxicity, or vasculitis. Additionally, this prevalence estimate may be under-estimated as (non-granulomatous) interstitial

nephritis was not considered diagnostic of renal TB. Although interstitial nephritis may be indicative of rifampicin or co-trimoxazole-induced renal toxicity [27], interstitial nephritis in the Abidjan cohort was more common in those with a post-mortem TB diagnosis (many also had HIV diagnosed post-mortem), suggesting this may also reflect a localised or systemic inflammatory immune response to TB in the kidney, in the setting of uncontrolled HIV replication. Finally, there may be a degree of overlap in clinical and pathological features of ATN from TDF toxicity and other causes such as sepsis; we may therefore have underestimated the contribution of TDF to the burden of kidney disease in the Cape Town cohort.

Conclusion

Acute and chronic kidney disease was common in Africans with HIV/TB in all three study cohorts, and approximately 10% of patients in London required dialysis. These data suggest that in much of sub-Saharan Africa where RRT is unavailable, kidney failure may be an important cause of death in patients with HIV/TB.

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Contributions

NW and FAP designed the study. NW, RH, RB, RS, AO, SA and FP assisted with data collection. SBL performed the autopsies in Abidjan. FI performed the statistical analyses. NW, RFM, JWB, SBL and FAP interpreted the data. FAP wrote the first draft of the paper. All authors contributed to and approved the final version of the manuscript.

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Conflict of Interest Statement

RFM reports personal fees and other from Gilead Sciences outside the submitted work; .JWB reports personal fees from Janssen Pharmaceuticals outside the submitted work; FAP reports grants and personal fees from Gilead Sciences, grants and personal fees from ViiV Healthcare, grants and personal fees from Janssen Pharmaceuticals, and personal fees from MSD outside the submitted work; All others report no conflicts of interest.

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Table 1 Clinical characteristics of the three cohorts

		London cohort (n=95), at TB diagnosis	Cape Town cohort (n=70), at kidney biopsy	Abidjan cohort (n=100), at death
Age (years)	mean (SD)	37.8 (10.4)	39.1 (8.5)	36.4 (10.2)
Gender (female)	n (%)	49 (51.6)	30 (42.9)	23 (23)
HBsAg positive	n (%)	17 (17.9)	8 (12.3)	Not available
HCV Ab positive	n (%)	2 (2.1)	Not available	Not available
Diabetes	n (%)	1 (1.1)	5 (7.1)	Not available
Hypertension	n (%)	7 (7.4)	14 (20.0)	Not available
ART naïve	n (%)	55 (57.9)	18 (25.7)	100 (100)
ART experienced - off ART	n (%)	12 (12.6)	7 (9.7)	0
ART experienced - on ART	n (%)	28 (29.5)	45 (64.3)	0
Time on ART (months)	Median (IQR)	13.1 (2.4-49.3)	2.1 (1.2-6.2)	Not applicable
CD4 cell count (cells per µL)	Median (IQR)	90 (26-199)	73 (34-161)	Not available
VL (log copies/mL)	Median (IQR)	5.1 (4.0-5.7)	2.8 (1.5-4.0)	Not available
VL<200 (copies/mL)	n (%)	17/94 (18.0)	9/26 (34.6)	Not available

TB=tuberculosis; ART=antiretroviral therapy; VL=HIV viral load

Table 2 Renal status of the participants

		London cohort		Cape Town cohort	
		at TB diagnosis	**at 12 months***	**at kidney biopsy**	**at 6 months***
eGFR	Median (IQR)	118 (88-129)	107 (91-129)	8 (5-19)	43 (16-82)
eGFR ≥60	n (%)	82 (86.3)	76/87 (87.4)	0	23 (32.9)
eGFR 30-59	n (%)	6 (6.3)	4/87 (4.6)	8 (11.4)	21 (30.0)
eGFR <30	n (%)	7 (7.4)	7/87 (8.0)**	62 (88.6)	26 (37.1)
Proteinuria (uPCR, mg/mmol)	Median (IQR)	32 (18-60)	Not assessed	247 (127-450)	Not assessed
Proteinuria (uPCR >30 mg/mmol)	n (%)	20/36 (55.6)	Not assessed	45/45 (100)	Not assessed
No AKI	n (%)		66/92 (71.7) ***		Not assessed
AKI (KDIGO stage 1)	n (%)		14/92 (15.2)		Not assessed
AKI (KDIGO stage 2)	n (%)		3/92 (3.3)		Not assessed
AKI (KDIGO stage 3)	n (%)		9/92 (9.8)		Not assessed
Dialysis (ever: acute/permanent)	n (%)		11 (11.6)		40 (55.6)****

*latest value in those who died/LTFU/discharged

**includes 2 ESKD deaths

***excludes 3 ESKD cases requiring dialysis throughout

****four patients were not offered dialysis

uPCR=urine protein creatinine ratio; AKI=acute kidney injury; LTFU=lost to follow up; ESKD=end-stage kidney disease

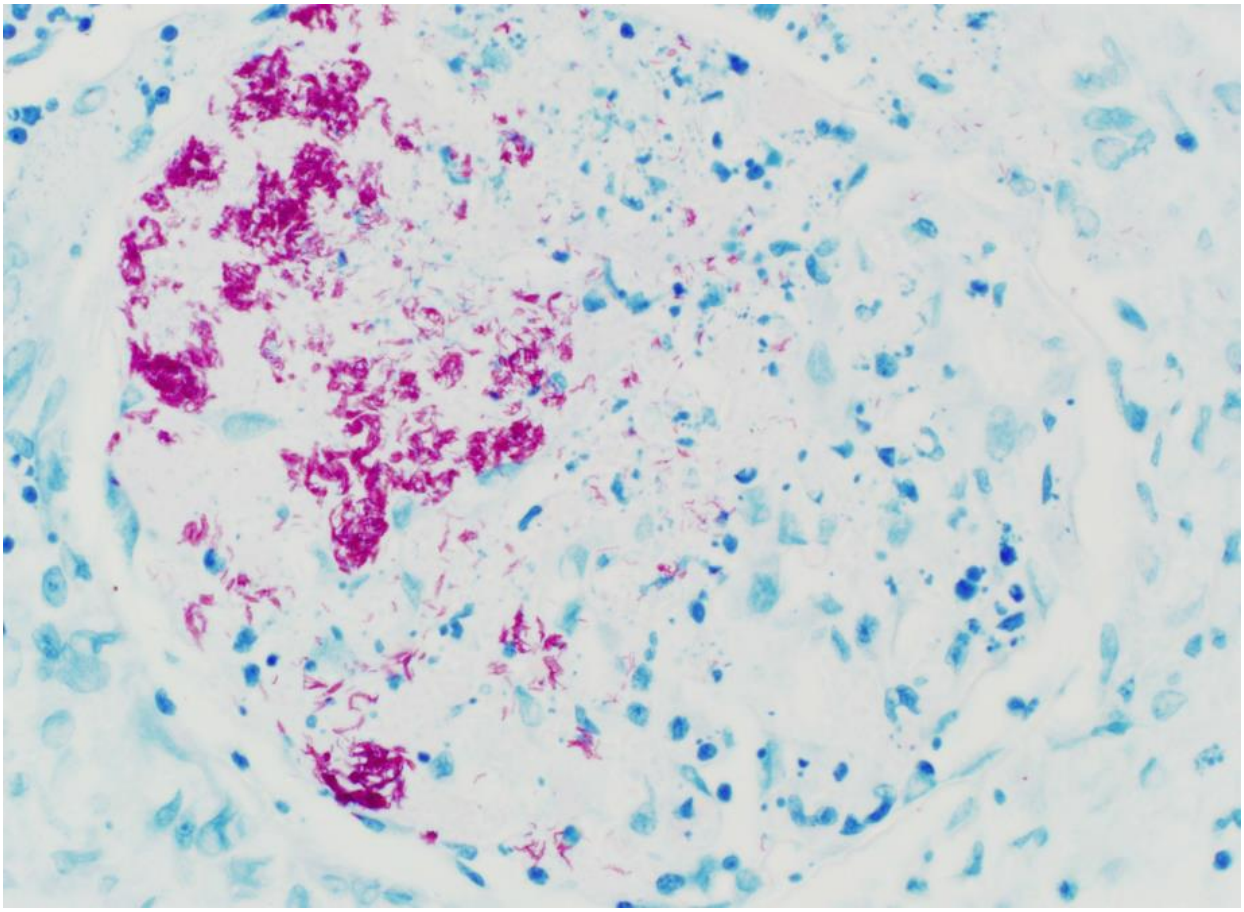
Table 3 Descriptive analysis of renal pathology

		Cape Town cohort (n=70), at biopsy	Abidjan cohort (n=100), at death
Pathological evidence of TB	n (%)	43 (61)*	60 (60)
HIVAN/FSGS	n (%)	29 (41)	6 (6)
Immune complex kidney disease	n (%)	7 (10)**	nil
Interstitial nephritis***	n (%)	10 (14)	31 (31)
Acute tubular necrosis	n (%)	48 (69)****	5 (5)
Other pathology			
Pyelonephritis (GNR)	n (%)	12 (17)	1 (1)
Cryptococcosis	n (%)	nil	1 (1)
Candidosis (kidney)	n (%)	1 (1)	nil
Hypertension	n (%)	7 (12)	nil
Ischaemia	n (%)	nil	2 (2)
Amyloid	n (%)	nil	1 (1)
Crescents	n (%)	1 (1)	nil
Cast nephropathy	n (%)	1 (1)	nil
DILS	n (%)	1 (1)	nil
Normal kidney	n (%)	nil	17 (17)

HIVAN = HIV-associated nephropathy; FSGS = focal and segmental glomerulosclerosis;
GNR = gram-negative rods; DILS = diffuse infiltrative lymphocytosis syndrome

*granulomas were poorly formed in n=31; caseous in n=2, and contained AFB's in n=3
**mesangio-capillary glomerulonephritis n=3; pauci-immune glomerulonephritis n=4
***other than granulomatous interstitial nephritis
****includes one case of possible tenofovir (TDF) toxicity

Figure S1 Renal tuberculosis in a post-mortem specimen from Abidjan



Glomerulus with abundant acid-fast bacilli (Ziehl-Neelsen stain, magnification x400).

Table S1 Additional clinical information about the participants in the three cohorts

			London cohort (n=95), at TB Diagnosis	Cape Town cohort (n=70), at biopsy	Abidjan cohort (n=100), at death
Black ethnicity		n (%)	95 (100)	100 (100)*	100 (100)
Region of origin					
	East Africa	n (%)	18 (18.9)	0	0
	Southern/Central Africa	n (%)	27 (28.4)	70 (100)	0
	West Africa	n (%)	50 (52.6)	0	100 (100)
HIV status					
HIV-1		n (%)	95 (100)	70 (100)	68 (68)
HIV-2		n (%)	0	0	11 (11)
HIV-1 and HIV-2		n (%)	0	0	21 (21)
TB diagnosis					
	MTB cultured/Gene Expert	n (%)	84 (88.4)	46 (65.7)	17 (17)
	AFB or granulomas	n (%)	11 (11.6)	16 (22.9)	83 (83)
	Urine LAM	n (%)	Not done	6 (8.6)	Not available
	Effusion adenosine deaminase (ADA)	n (%)	Not done	2 (2.9)	Not available
	RH-susceptible	n (%)	73/84 (86.9)	40/40 (100)**	Not available
	MDR-TB	n (%)	5/84 (6.0)	0	Not available
TB status					
	Time since TB diagnosis (days)	Median (IQR)	Not applicable	20 (0-64)	Not available
	Pulmonary TB	n (%)	24 (25.3)	22 (31.4)	6 (6)
	Extra-pulmonary TB	n (%)	16 (16.8)	10 (14.3)	3 (3)
	Disseminated TB	n (%)	55 (57.9)	38 (54.3)	91 (91)

TB treatment (see footnote 1)				
RHZ(E)/RH (throughout/at biopsy)	n (%)	68 (71.6)	58 (100)	Not available
Rbt (+HZE)	n (%)	7 (7.4)	0	Not available
Other, with fluoroquinolone*	n (%)	20 (21.1)	0	Not available
Other, with aminoglycoside*	n (%)	4 (4.2)	0	Not available
* not mutually exclusive				
HIV treatment (see footnote 2)				
On ART at TB diagnosis / continued ART	n / n (%)	28 / 28 (100)	Not available	0
Not on ART at TB diagnosis / restarted ART	n / n (%)	12 / 8 (66.7)	Not available	0
interval TB-ART (months)	Median (IQR)	4.1 (0.9-8.8)	Not available	Not applicable
ART naïve at TB diagnosis / commenced ART	n (%)	55 / 45 (81.8)	Not available	100 / 0
interval TB-ART (months)	Median (IQR)	2.2 (1.7-2.9)	Not available	Not applicable
ART regimen during TB treatment / at biopsy				
TDF	n (%)	53/81 (65.4)	32/45 (71.1)	Not applicable
ABC	n (%)	19/81 (23.5)	11/45 (24.4)	Not applicable
Other NRTI (not TDF)	n (%)	9/81 (11.1)	2/45 (4.4)	Not applicable
NNRTI	n (%)	62 (76.5)	41/45 (91.1)	Not applicable
PI	n (%)	13 (16.0)	4/45 (8.8)	Not applicable
INSTI	n (%)	6 (7.4)	0	Not applicable
TB and HIV outcomes (12 months)				
TB status				
treatment completed/cured	n (%)	75 (78.9)		
remains on TB treatment	n (%)	10 (10.5)		
transferred out	n (%)	5 (5.3)		
died	n (%)	5 (5.3)		
HIV status				
CD4 cell count	Median (IQR)	271 (150-391)		
CD4 >200	n (%)	54/79 (68.4)		
VL<200	n (%)	63/81 (77.8)		

*includes Coloureds (mixed race; n=5)
**susceptibility to R only

Foot notes
1. Non-standard regimens (containing fluoroquinolones and/or aminoglycosides) were used for TB drug resistance (n= 8) or TB drug toxicity (n=12)
2. In the London cohort, the following ART switches occurred: TDF to ABC n=3, NNRTI to PI n=2, NNRTI to INSTI n=2, INSTI to PI n=2, INSTI to NNRTI n=3
3. Cotrimoxazole was routinely prescribed to all patients unless their HIV was fully suppressed on ART

East Africa: Erithrea (6), Ethiopia (1), Rwanda (2), Somalia (1), Uganda (8)
Southern/Central Africa: Angola (1), Botswana (1), Cameroon (2), Congo (2), Gabon (1), Malawi (2), Mozambique (1), South Africa (3), Zambia (1), Zimbabwe (13)
West Africa: Ghana (2), Ivory Coast (12), Liberia (2), Nigeria (22), Sierra Leone (11), Togo (1)

Abbreviations:
TB=tuberculosis; MTB=*Mycobacterium tuberculosis*; AFB=acid-fast bacilli; LAM=lipoarabinomannan; MDR=multidrug-resistant; R/Rbt/H/Z/E=rifampicin/rifabutin/isoniazid/pyrazinamide/ethambutol; ART=antiretroviral therapy

Table S2 **Additional clinical information on participants with HIVAN, ATN and GIN in the Cape Town cohort**

		HIVAN (n=29)	ATN (n=48)	GIN (n=43)
Co-pathology				
HIVAN		not applicable	17	13
ICKD		4	5	4
AIN		3	6	7
Pyelonephritis		5	6	5
TB (GIN)		13	29	not applicable
ATN		17	not applicable	29
At biopsy				
ART status				
	naïve	13 (45)	9 (19)	10 (23)
	off ART	3 (10)	6 (13)	5 (12)
	on ART	13 (45)	33 (69)	28 (65)
CD4 cell count (cells/mm^3)		40 (19-103)	72 (34-128)	93 (48-237)
eGFR (mL/min/1.73m^2)		11 (5-14)	8 (5-14)	8 (5-14)
uPCR (mg/mmol)		470 (252-1200)	208 (104-410)	238 (110-444)
Dialysis				
Dialysis not needed		9 (31)	16 (33)	18 (42)
Dialysis not offered		4 (14)	2 (4)	1 (2)
Dialysed/(partial) recovery		13 (45)	23 (48)	15 (35)
Dialysed/no recovery		3 (10)	7 (15)	9 (21)
Status at 6 months				
Dead/LTFU with ESKD		6 (21)	10 (21)	8 (19)
Discharged/LTFU without ESKD		4 (14)	9 (19)	8 (19)
Alive		19 (66)	29 (60)	27 (63)
eGFR*				
	<15	7 (24)	9 (19)	10 (23)
	15-29	4 (14)	5 (10)	8 (19)
	30-59	10 (34)	12 (25)	12 (28)
	≥60	8 (28)	22 (46)	13 (30)

Data are N or N (%)

*latest value in those who died/LTFU/discharged

Abbreviations:
HIVAN=HIV-associated nephropathy; ATN=acute tubular necrosis; GIN=granulomatous interstitial nephritis
ICKD=immune complex kidney disease; ART=antiretroviral therapy; eGFR=estimated glomerular filtration rate
uPCR=urine protein/creainine ratio; LTFU=lost to follow up

Table S3 Results from the Cox regression analysis

Factors associated with non-recovery of kidney function (eGFR <60)

	HR	95%CI		P value
Age	0.97	0.94	1.01	0.155
Sex (male)	0.84	0.48	1.50	0.561
ART status				
ARTexp (on ART)	1.00			
ARTexp (off ART)	0.68	0.21	2.23	0.522
ART naïve	1.38	0.07	2.58	0.310
Hepatitis B	1.34	0.56	3.17	0.511
Diabetes mellitus	1.47	0.53	4.11	0.460
Hypertension	1.23	0.65	2.33	0.529
CD4 cell count	1.00	1.00	1.00	0.784
eGFR at biopsy	1.01	0.99	1.03	0.410
uPCR	1.00	1.00	1.00	0.107
HIVAN	1.09	0.61	1.93	0.779
ATN	**0.56**	**0.31**	**0.99**	**0.045**
TB kidney	0.97	0.53	1.75	0.909
Dialysis	1.09	0.62	1.95	0.759

Factors associated with non-recovery of kidney function (eGFR <30)

	HR	95%CI		P value
Age	1.01	0.96	1.06	0.704
Sex (male)	0.95	0.44	2.57	0.889
ART status				
ARTexp (on ART)	1.00			
ARTexp (off ART)	0.36	0.05	2.73	0.325
ART naïve	1.04	0.43	2.49	0.930
HBsAg	1.97	0.74	5.27	0.174
DM	**2.68**	**0.92**	**7.80**	**0.070**
HPT	1.82	0.81	4.10	0.146
CD4	1.00	1.00	1.00	0.749
eGFR at biopsy	0.99	0.96	1.03	0.775
uPCR	1.00	1.00	1.00	0.100
HIVAN	1.00	0.46	2.18	0.995
ATN	**0.52**	**0.24**	**1.12**	**0.096**
TB kidney	1.27	0.55	2.93	0.572
Dialysis	1.61	0.72	3.63	0.246

Abbreviations:
ARTexp=antiretroviral therapy experienced; HBsAg=hepatitis B surface antigen; DM=diabetes mellitus; HPT=hypertension
eGFR=estimated glomerular filtration rate; uPCR=urine protein/creainine ratio
HIVAN=HIV-associated nephropathy; ATN=acute tubular necrosis