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HISTOLOGICAL EVIDENCE AND CLINICAL CORRELATIONS OF RENAL TB-IRIS IN HIV-POSITIVE PATIENTS AND OUTCOMES

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Declaration

This research reported is based on independent work performed by the candidate, Dr Thania Kahn, and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university. This work has not been reported or published prior to registration for the abovementioned degree.

Abstract

THE ASSOCIATION BETWEEN RENAL HISTOLOGY AND CLINICAL "RENAL TB-IMMUNE RESCONSTITUTION INFLAMMATORY SYNDROME (IRIS)" IN HIV-POSITIVE PATIENTS WITH RENAL AND MORTALITY OUTCOMES

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Background
Tuberculosis immune reconstitution inflammatory syndrome [TB-IRIS] is a well described clinical entity in HIV-infected patients that can affect multiple organs. There is however a paucity of information regarding renal involvement. This study aimed to illustrate the clinical, biochemical and histopathological features of HIV patients with suspected renal TB-IRIS, and to assess the mortality and renal outcomes of these patients.

Methods
The study was an observational, retrospective review of two established HIV positive renal biopsy registries [Groote Schuur Hospital and Livingstone Hospital Port Elizabeth, Eastern Cape]. Renal biopsies were reviewed for the presence of granulomatous interstitial nephritis [GIN]. Patients' folders and laboratory records were reviewed for evidence of tuberculosis [TB] and TB-IRIS. They were also reviewed for other causes of GIN ie drugs, fungal infection, sarcoidosis and infection. The study was approved by the UCT research ethics committee. The data was then analysed comparing 3 groups: [TB : no IRIS] (all TB cases with no features of IRIS), [TB + IRIS] (all cases with features of TB-IRIS) and [Other] (other causes of GIN).

Results
68 HIV-positive renal biopsies were identified with GIN. The mean age was 37.5±9.1 years. There were 33 males (48.5%); 61 (89.7%) were of African black ethnicity, and there were no Caucasians in the study. 29 patients (43%) were noted to be on other medications known to cause GIN. The mean time from ART initiation to biopsy was 12 weeks, with the shorter average time being in the [TB + IRIS] group (6 weeks).
The mean CD4 at biopsy was 105cells/μL, with the lowest CD4 seen in the in the [TB + IRIS] group (81cells/μL) (P-value 0.0175). The granulomas in the [TB + IRIS] group were noted to be more well-formed, with the highest number of poorly formed granulomas found in the [TB : no IRIS] group (25%) Sixteen (25%) of subjects had died within 2 years of their biopsy, with the majority of deaths occurring in the [TB : no IRIS] group (12/48, 44%), (P-value 0.01).

Conclusion
This study is the largest series of renal TB-IRIS that adds to the very limited case reports in the literature. There is a clinical entity of TB renal-IRIS that is associated with GIN on renal biopsy. Significant findings were those of a shorter time from ART initiation to biopsy in the [TB + IRIS] group, a lower CD4 count at biopsy and nadir in the [TB + IRIS] group with more well-formed granulomas. The majority of deaths within 2 years were noted in the [TB : no IRIS] group. This entity seems to be in keeping with other TB-IRIS descriptions previously published.

Acknowledgments
I would like to thank my supervisor, Prof Nicola Wearne, for her unwavering support, guidance and assistance during this project.

List of Figures and Tables

Chapter 1: Introduction and Literature Review

1. TB and HIV in South Africa

South Africa (SA) continues to have the highest rate of human immunodefiency virus (HIV) infection world-wide, with an estimated 6.4 million people documented HIV positive in 2015, (11.2% of the total population).[1] According to the United Nations 2012 Global Report, 70% of the 34 million HIV-infected individuals globally, are located in sub-Saharan Africa (SSA).[2] In 2012, HIV/AIDS was the most common communicable disease leading cause of death in SA, causing death in 202 100 people.[1] In addition to this, SA has a co-existing tuberculosis (TB) epidemic, and is considered to be one of the "high burden" countries, ranking third in the world in terms of this burden.[1] According to the World Health Organisation (WHO), approximately 9 million new cases of TB occurs annually worldwide, with 31% of these cases in Africa.[3] South Africa ranks third in the world, after India and China, in terms of TB burden, with 400% increase in incidence over the past 15 years.[3]

The TB epidemic is fuelled by the HIV epidemic, with more than 70% of TB patients also being HIV-positive.[4] In 2009 the WHO declared that their biggest area of concern remained the dual epidemic of these two diseases.[4] The proportion of TB cases living with HIV was highest in the WHO African Region (31%), and exceeded 50% in parts of Southern Africa[5], with 65% of newly diagnosed sputum-positive TB patients being HIV-positive.[2] The Western Cape, in South Africa, has the second highest number of TB cases in the country, with the current annual risk of developing TB in HIV-infected individuals being at 30%.[4]

2. Spectrum of HIV renal disease

Renal disease is a common finding in HIV-positive individuals, and is associated with an increased morbidity and mortality.[6,7] HIV-positive patients are at an increased risk for a broad spectrum of renal disease, including pathologies as a direct consequence of HIV gene expression itself, as well as disease related to various comorbidities, anti-retroviral therapy (ART) effects, co-infections and immune impairment.[32] One of the largest renal biopsy series in HIV-positive patients, conducted in Cape Town (South Africa), described a wide spectrum of renal pathology in HIV-associated renal disease.[7] Aetiologies included opportunistic infections, drug toxicity, HIV-associated nephropathy (HIVAN) and immune complex disease

in the setting of HIV infection. The most common opportunistic infection was TB.[7] Tenofovir is a commonly used ART drug which has been shown to be associated with a decline in estimated glomerular filtration rate (eGFR), and proteinuria, with approximately 1-2% of patients developing a tubulopathy requiring discontinuation of the drug.[32] An increasing prevalence of non-communicable diseases, including hypertension, diabetes and glomerulonephritis was noted in the 2012 South African renal registry report, which has also contributed to renal disease seen in HIV-positive patients.[7,8] HIV-positive patients are living longer on ART and are therefore at higher risk of being exposed to these chronic diseases.[9] Swanepoel et al defined the spectrum of renal disease in the setting of HIV, into glomerular, tubulointerstitial, or vascular-dominant and other, in their 2017 convention of international panel of experts.[32] Glomerular entities include classic HIVAN, FSGS, minimal change diseases and immune complex-mediated diseases. The tubulointerstitial-dominant pathologies comprise of injuries in the setting of classic HIVAN, acute tubular injury or necrosis, drug-induced, direct parenchymal infection and immunologic dysfunction-related. The thrombotic micrangiopathies in the setting of HIV and arteriosclerosis account for vascular causes; and diabetic nephropathy and age-related nephrosclerosis make of the 'other' pathologies found on the setting of HIV.[32]

Wearne et al found HIVAN to be the most common histology seen in 57.3% of 221 cases in their study.[6] HIVAN consists of a range of histological findings which can affect the glomerulus, interstitium and tubules and is a diagnosis made on renal biopsy.[9] ART has been shown to decrease the mortality of HIVAN by 57%.[6]

Immune complex diseases in the setting of HIV is a heterogenous group of immune-complex-related renal diseases found in HIV-positive patients, and includes membranous nephropathy, membranoproliferative, mesangial proliferative, IgA nephropathy, and lupus-like glomerulonephritis.[7,9] The prevalence of this group of diseases in African biopsies is 17-40%.[9]

Tuberculosis is the most common opportunistic infection in HIV-infected individuals in the developing world, with a 10% mean annual risk of an HIV-positive patient developing TB.[7] In a recent retrospective review of renal biopsies demonstrating granulomata, TB-

granulomatous interstitial nephritis (GIN) was considered likely in 62.2% of patients, and 6 of the 45 cases were likely to be due to TB-IRIS.[11]

3. Granulomatous interstitial nephritis

Granulomatous interstitial nephritis (GIN), is seen as part of the spectrum of acute interstitial nephritis (AIN), which is characterized by an inflammatory infiltrate in the kidney interstitium.[12] GIN is a variant of AIN that demonstrates granulomas on histology, and in the developed world is reported as being a rare entity.[13,14] In the South African setting it is now becoming a more common diagnosis found on renal biopsies.[6,11] The prominent finding on renal biopsy is that of granulomata, which vary in morphology and may be isolated, extensive, and necrotising, and may be associated with other renal pathologies.[15] Causes of GIN include infections, drugs and sarcoidosis; however quite often the cause is unknown.[16] Mycobacterium tuberculosis is the most common infectious agent especially in endemic areas.[11] Causative drugs include antibiotics and non-steroidal anti-inflammatory drugs (NSAID).[6] A recent review of GIN amongst HIV-positive patients showed the majority of cases to be secondary to TB (60%), followed by drugs (20%), and less commonly infection and idiopathic.[11]

4. Tuberculosis and the kidney

Patients with HIV have a 20-37 times greater risk of TB than HIV-negative individuals, with TB being the most frequent opportunistic infection in HIV-infected individuals, and is associated with an increased mortality in these individuals.[17] Urogenital TB represents 27% of extrapulmonary TB, with renal involvement being the third most common form, and can lead to both acute and chronic kidney disease.[7,18] Granulomas have been noted to be poorly-formed in HIV-positive individuals, with a lesser degree of caseous necrosis.[19] However there is still little in the literature regarding renal TB incidence data in South Africa as well as its contribution to renal disease.

5. Immune Reconstitution Inflammatory Syndrome (IRIS)

The combined HIV/TB epidemic and the increased roll-out of ART, has brought with it the additional challenge of IRIS. It results from the unmasking of previously subclinical infection

or worsening of pre-existing partially-treated opportunistic infections, and is associated with a wide array of pathogens, most notably mycobacteria.[20,21]

Various studies estimate that 10-50% of HIV-positive patients starting ART develop IRIS.[22] Another case series noted IRIS in 25-35% of HIV-infected patients who are treated with ART.[23] The study showed the majority of IRIS cases occur within 2 months of ART initiation, and noted an association with lower viral load levels and increased CD4 counts after ART initiation. These IRIS patients seemed to demonstrate good long-term outcomes. They also demonstrated better viral load suppression, after 2 years of ART, compared to patients without IRIS.[23]

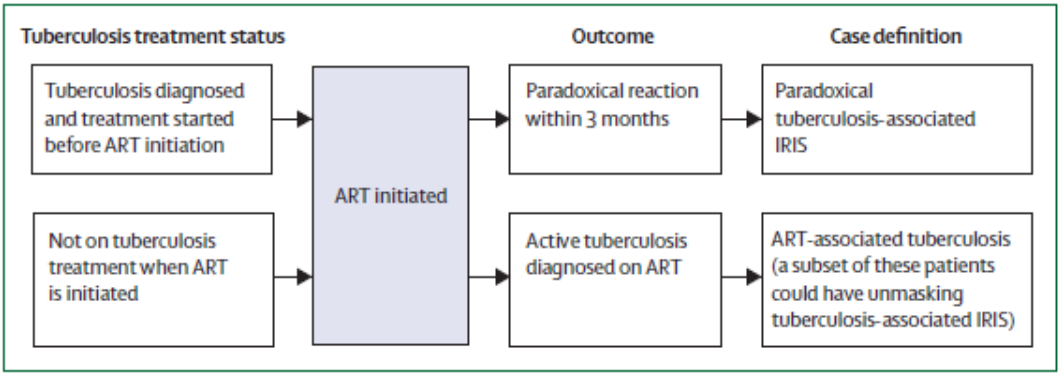
ART leads to viral load suppression and increased CD4 cell counts, which in turn causes a gradual restoration of immune responses.[22] This augmented immune system activation and response can result in the complication of paradoxical worsening of previously treated opportunistic infections or unmasking of subclinical, untreated infections.[22] Many diseases are associated with IRIS, including mycobacterial and fungal infections, and Kaposi's sarcoma.[22] This underlying immunopathological process is still not fully understood. Studies in humans have implicated this immune reconstitution process in the pathogenesis of TB IRIS, with the risk of developing IRIS being associated with the rate of peripheral blood lymphocyte recovery after initiating ART and TB treatment.[33] It has also been suggested that ART may activate local immune resconstitution by increased numbers of lymphocytes at the site of infection, which may not be detected in peripheral blood.[33] This hypothesis is supported by evidence that the main population of CD4 cells found in peripheral blood during the 3 months post-ART initiation are activated CD45RO+ memory cells, which redistribute from sites of sequestration with the possibility of exacerbating inflammatory processes.[33] Other processes of immune reconstitution that have been described include an increase in B and natural killer (NK) cell count and activation, T cell functional deficit recovery, high neutrophil counts and TNF alpha at infection sites and hypercytokinaemia.[33]

There are currently no definitive diagnostic tests for IRIS, and diagnosis of the syndrome is largely based on case definitions, including clinical and laboratory findings. Tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS) is an abnormal exaggerated

immune response against dead or viable mycobacteria tuberculosis that occurs in HIV-infected individuals, after ART initiation.[24] Meintjies et al[20] provided the following case definitions for TB-IRIS (Fig 1):

1) Paradoxical TB IRIS – Deterioration of pre-existing TB signs or symptoms or radiological manifestations, following initiation of ART, usually occurring within the first 3 months of treatment.
2) Unmasking TB-associated IRIS – when a patient presents with active TB within 3 months of starting ART
3) ART-associated IRIS - where a new diagnosis of TB is made following ART initiation

Figure 1. Schematic representation showing the different forms of TB-IRIS and ART-associated tuberculosis[20]



The clinical manifestations of TB-IRIS vary, and includes ongoing fevers, worsening lymphadenopathy and worsening dyspnoea. The main sites involved are the lymph nodes (68%), and the lungs (16%).[24] Pulmonary findings may involve new parenchymal lung lesions, new or worsening lymphadenopathy and new or progressive pleural effusions.[24] Lymph nodes can become larger and suppurate.[24] Abdominal TB-IRIS can occur in the form of hepatitis, intra-abdominal lymphadenopathy and peritonitis. Patients with the paradoxical form tend to exhibit features of worsening or recurring respiratory and constitutional symptoms, and may also show new or worsening chest x-ray changes.[24] Unmasking TB-IRIS involves TB that becomes clinically evident after ART initiation, and it often presents with augmented inflammatory characteristics. It is not as well described as the paradoxical type.[24]

There is no definitive diagnosis or confirmatory test for TB-IRIS. The following criteria need to be met in order to consider a diagnosis of TB-IRIS[24]:

i) An initial improvement of TB symptoms and/or radiological findings after an adequate period of TB treatment

ii) Subsequent deterioration of TB symptoms and/or radiological findings during or after TB treatment

iii) The absence of factors that may reduce the efficacy of the TB treatment, eg poor compliance, drug malabsorption, drug side effects

iv) And the exclusion of any other possible causes for the clinical deterioration

The diagnosis of TB-IRIS should only be considered once drug-resistant TB, malignancies and other opportunistic infections have been excluded. In SA, the most common alternative diagnosis drug-resistant TB.[24]

In 2010 Meintjies et al published their data from a randomised control trial assessing the treatment effect of prednisone in TB-associated IRIS.[25] They showed a clinical benefit in that prednisone reduced the need for hospitalisation with significantly greater symptom improvement and quality of life. The article noted the necessity of excluding drug-resistant TB and other possible causes of clinical deterioration before considering steroid administration.

6. Renal TB-IRIS

There is great paucity of information regarding renal involvement specifically due to TB-IRIS. The literature exhibits 6 documented cases of renal TB-IRIS.[26,27,28,29,30,31] And more recently, a South African review of HIV-positive renal biopsies, with GIN, documented another 6 cases of renal TB-IRIS.[11]

As discussed above, the dual HIV/TB epidemic in Africa has posed a tremendous burden on its health system. It has also been found that these pathologies have a notable association with renal impairment. With the improved rollout of ART, more cases of TB-IRIS are being diagnosed, which have been associated with impaired renal function. More information needs to be sought on a possible entity of renal TB-IRIS, as this may be respond to steroid therapy, as documented in previous trials.[10,25,32]

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Chapter 2: Publication-ready Manuscript

TITLE:

The association between renal histology and clinical "Renal TB-Immune Reconstitution Inflammatory Syndrome (IRIS)" in HIV-positive patients with renal and mortality outcomes

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INTRODUCTION:

South Africa [SA] continues to have the highest human immunodefiency virus (HIV) burden world-wide, with an estimated 7.52 million documented to be HIV positive in 2018 (12.4 percent of the total population).[1] Compounding this, SA has a co-existing tuberculosis [TB] epidemic. According to the World Health Organisation (WHO) SA ranks in the top 30 high burden TB countries with 675 per 100 000 population incident cases in 2017.[2] For the last 5 years it has been the leading cause of death from a single infectious agent, ranking above HIV.[2]

This study was undertaken in Cape Town in the Western Cape Province which has the second highest number of TB cases in the country.[2] The TB epidemic is fuelled by the HIV epidemic, with more than 70% of TB patients being co-infected with HIV.[2] In Cape Town, the current annual risk of developing TB in HIV co-infected patients is 30%.[3]

HIV-infected patients are at an increased risk of developing renal dysfunction.[4,25,26,27,28] Currently there are 607 HIV-positive patients of the 6464 patients on dialysis in South Africa ie 9.4%.[27] The renal unit at Groote Schuur Hospital [GSH], Cape Town, established a HIV renal biopsy registry in 2009 to document and assess the causes of renal failure in this high risk population. A retrospective review of 370 HIV-positive renal biopsies from this registry documented an exceedingly high rate of granulomatous interstitial nephritis [GIN] 45/370 [12.2%].[5] TB accounted for GIN in 62% of cases and contrasts the developed world where GIN is considered a rare entity observed in 0.5-0.9% of renal biopsies.[5,6,7] However, this is not an entirely appropriate comparison, as these series were conducted largely in HIV-negative populations. This highlighted the need to further investigate and characterise GIN specifically in the setting of renal TB- immune reconstitution inflammatory syndrome [IRIS].

The combined HIV/TB epidemic and the up-scaled rollout of anti-retroviral therapy (ART), has brought with it the additional challenge of IRIS. It results from the unmasking of previously subclinical infection or worsening of pre-existing partially-treated opportunistic infections. IRIS is associated with a wide array of pathogens, most notably mycobacteria.[8,9] There is very little information regarding TB-IRIS associated with kidney involvement. To our

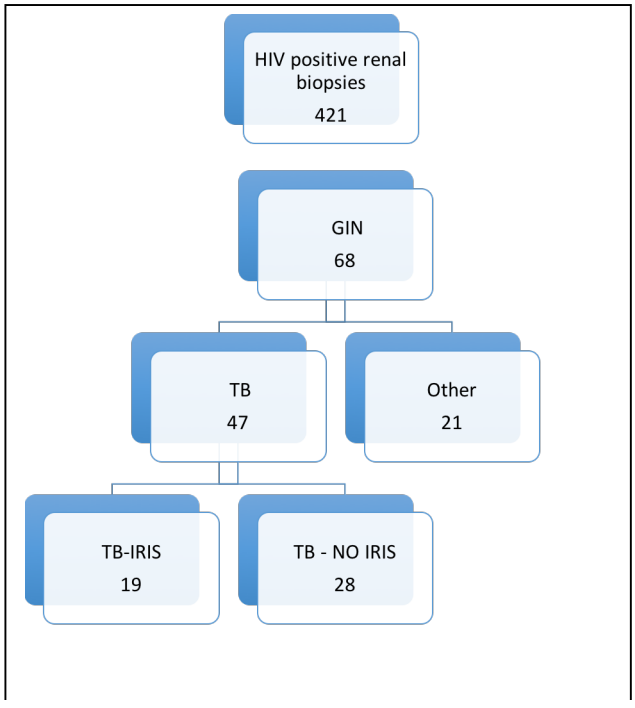
knowledge there are only 6 documented published case reports of biopsy-proven IRIS-related TB-GIN after initiation of ART.[10,11,12,13,14,15] And more recently another 6 cases of TB-IRIS with features of GIN, on biopsy, were described in a review done at GSH.[5] Hence it is an entity that is not well described.

Therefore the aim of this study was to document renal TB-IRIS in the presence of renal impairment. The primary objective of the study was to describe the clinical, biochemical and histological entity of renal TB-IRIS. The secondary objective was to assess the mortality and renal outcomes, specifically the follow-up creatinine done between 1 to 3 months post-biopsy.

METHODS

The study was an observational, retrospective review of two established HIV positive renal biopsy registries [GSH and Livingstone Hospital Port Elizabeth, Eastern Cape]. All biopsies in the registry were only performed as part of best clinical practice. This included unexplained renal failure, haematuria or proteinuria. The study was approved by the University of Cape Town Research Ethics Committee.[HREC 422/2015]. The inclusion criteria included all HIV-positive renal biopsies performed between 2009 to 2015 demonstrating histological evidence of GIN. (Figure 1)

Figure 1. Study profile



HIV : Human immunodeficiency virus
GIN : Granulomatous interstitial nephritis
TB : Tuberculosis
IRIS : Immune reconstitution inflammatory syndrome

The presence of TB-IRIS was documented in the clinical notes in most cases. In cases where it was not clear, a retrospective diagnosis was made from the medical records using the Meintjies criteria and was independently assessed by two experienced clinicians. Paradoxical and unmasking forms of IRIS were seen but are not recorded for the purposes of this study.

For all biopsies included in the study histological analysis occurred at the National Health Laboratory Service (NHLS) Division of Anatomical Pathology at GSH. Renal biopsies were processed for light microscopy with haematoxylin, eosin, methenamine silver and periodic acid-Schiff stains. Immunohistochemistry and electron microscopy was performed. GIN was defined by the presence of epithelioid granulomas in the renal interstitium with or without necrosis or multinucleate giant cells.[17] When GIN was noted, a Ziehl–Neelsen (ZN) stain was performed for acid fast bacilli (AFBs) and calcofluor stains for spores or fungi. Biopsies were also examined for other pathologies. Granulomas were assessed as being well-formed (granulomas consisting of activated macrophages evidenced by swollen eosinophilic cytoplasmic accumulation with or without giant cells), or poorly-formed (granulomas in which the macrophages are activated howevere they are not as swollen or eosinophilic but more so than normal macrophages).

Patients were assessed for the likelihood of active TB. Investigations included sputum (acid-fast bacilli (AFB) on gram stain, TB geneXpert [GXP] and TB cultures), urine (TB culture and lipoarabinomannan(LAM)), serum TB cultures, renal biopsy and radiological assessment (chest X-ray and abdominal ultrasound etc). Other supportive evidence for TB was also reviewed and included, such as pleural and pericardial fluid cultures, lymph node aspiration/biopsy and cerebrospinal fluid (CSF).

Patients were reviewed for the presence of renal TB-IRIS. Renal TB-IRIS was defined as renal biopsy histological findings of renal granuloma, in a patient demonstrating features of clinical TB-IRIS, using the consensus case definitions by Meintjies et al.[1] This included all HIV-positive patient who demonstrated clinical deterioration shortly after ART initiation, in which other causes of GIN were excluded. Histopathological findings on renal biopsies were then correlated with clinical and laboratory evidence of TB-IRIS.

Data collected at baseline was considered to be the time of renal biopsy. The following baseline parameters were obtained: demographic features (age, gender and ethnicity) and clinical features (ART and TB treatment, date of commencement of these treatments and the concurrent use of any other possible implicating drugs). Baseline laboratory parameters included CD4 count(cells/μL) and HIV viral load(copies/ml); renal function [serum creatinine (μmol/L), eGFR(mL/min/1.73m^2)]; urine protein/creatinine ratio (UPCR)(gm/mmol); and urine findings [dipstix and microscopy, culture and sensitivities (MC & S)]. The nadir CD4 count and prior baseline creatinine were also obtained. The nadir CD4 was the best creatinine prior to biopsy.

Histological evaluation included number and morphology of the granulomas (ie single, multiple, poorly-formed), ZN evaluation for AFBs as well as fungal stains. Other coexisting histological pathologies were also sought including evidence of HIV-associated nephropathy (HIVAN), acute tubular necrosis (ATN), eosinophilic interstitial nephritis, as well as ascending pyelonephritis. Information that could support another cause for the GIN, such as alternative opportunistic infections, drugs and other systemic diseases were also sought and this included serum cryptococcal latex antigen test [CLAT], fungal cultures, antineutrophil cytoplasmic antibodies (ANCA), serum angiotensin-converting enzyme (ACE).

Follow-up biochemical data (creatinine and UPCR) were obtained between 1-3 months. Mortality data was obtained from patient folders, electronic records and HIV clinics. Deaths within 2 years of the biopsy were recorded.

Continuous variables were summarised as mean ± standard deviations (normally distributed data) or medians with interquartile ranges (non-normally distributed data). Categorical variables were summarised as frequencies and percentages. Parametric and non-parametric tests were performed depending on the distribution of data. Comparison of continuous variables between TB with no IRIS and TB with IRIS groups were analysed using either two-sample t-test (normally distributed) or Wilcoxon rank-sum test (non-normally distributed data). For the primary comparison of three groups (TB with no IRIS, TB with IRIS and other), one-way ANOVA or Kruskal-Wallis test was performed. Chi-square test or Fisher's Exact test was used to test for associations between categorical variables. A $p<0.05$ was interpreted as statistically significant. All statistical analyses were performed using Stata (Version 14.2; Stata Corp, College Station, Texas, USA).

RESULTS

Sixty-eight renal biopsies were identified demonstrating GIN from 421 HIV positive renal biopsies from the combined registries during the defined trial period. The baseline characteristics of the 68 biopsies are reviewed in Table 1.

Table 1 – Baseline Data

		TB : no IRIS (A)	**TB + IRIS** (B)	**Other** (C)	**P-value** (A) vs (B) vs (C)
		n=28	**n=19**	**n=21**	**p-value**
Demographics	Total cohort*				
Age	37.5±9.1	36.7±10.2	39.3±9.0	37.1±7.9	0.621
Gender, male (N)	33 (49%)	14 (50%)	10 (53%)	9 (43%)	0.809
Ethnicity, black (N)	61 (90%)	24 (86%)	18 (95%)	19 (91%)	0.705
Clinical					
ART at biopsy (y)	31/60 (51.7%)	6 (24%)	15 (83%)	10 (59%)	<0.001
Time from ART initiation to biopsy (weeks)	12 (4-26)	28 (10-88)	6 (4-9)	26 (20-40)	0.002
TB treatment at biopsy (y)	35/47 (74.5)	19 (68%)	16 (84%)	NA	0.207
Time from TB treatment to biopsy (days)	6 (2-8)	5 (2-7)	7 (2-12)	NA	0.239
On drugs known to cause AIN (y)	29 (43%)	12 (43%)	8 (42%)	9 (43%)	0.998
On	18 (26%)	7 (25%)	7 (37%)	4 (19%)	0.433

Trimethoprim/Sulfamethazole					
On Penicillin	5 (7%)	2 (7%)	1 (5%)	2 (10%)	0.874
Biochemical					
CD4 at biopsy, (med, IQR) (cells/μL)	105 (56-281)	102 (42-233)	81 (59-101)	270 (90-475)	0.0175
CD4 nadir, (med, IQR) (cells/μL)	97 (52-183)	92 (19-167)	79 (55-121)	191 (86-336)	0.025
Creatinine baseline, (med, IQR)(μmol/L)	96 (71-169)	177 (72-259)	99 (71-139)	89 (69-102)	0.429
Creatinine at biopsy, (med, IQR) (μmol/L)	417 (177-901)	547 (195-1033)	287 (183-810)	333 (102-794)	0.146
UPCr at biopsy (med, IQR) (gm/mmol)	0.26 (0.16-0.51)	0.3 (0.2 - 0.6)	0.2 (0.1 - 0.3)	0.28 (0.16-0.51)	0.125
Urine culture positive (Bacteria and Fungus)	19/51 (37%)	5 (23.8)	6 (46.2)	8 (47.1)	0.266
Urine dipsticks: Leucocytes	25/53(47%)	12 (52%)	5 (36%)	8 (50%)	0.601
Red blood cells	36/53(68%)	18 (78%)	9 (64%)	9 (56%)	0.159
Protein	48/53(91%)	19 (83%)	13 (93%)	16 (100%)	0.342
Histological					
HIVAN	43/68(63%)	19 (68%)	12 (63%)	12 (57%)	0.744
Granuloma: single	25/68(37%)	13 (46%)	5 (26%)	7 (33%)	0.351
Granuloma: poorly formed	15/68(22%)	7 (25%)	1 (5%)	7 (33%)	0.075
Granuloma: multiple	43/68(63%)	14 (50%)	15 (79%)	14 (67%)	0.120
Pyelonephritis/Infection	15/68(22%)	6 (21%)	2 (11%)	7 (33%)	0.244

*n varies due to missing data
TB : Tuberculosis
IRIS : Immune Reconstitution inflammatory syndrome
ART : Antiretroviral therapy
Med : Median
IQR : Inter-quartile range
HIVAN : HIV-associated nephropathy
Med, IQR: Median, interquartile range

The GIN cohort comprised 33 (48.5%) males, the mean age was 37.5 years (SD+-9.1) and 61 (89.7%) were of black African ethnicity. There were 7 patients (10.3%) of mixed ethnicity with no Caucasians in the study. Thirty-one of 60 patients (51.7%) were on ART at the time of renal biopsy. The average time from ART initiation to biopsy was 12 weeks. Additional medications known to cause acute interstitial nephritis (AIN) were used in 29/68 of the cases (43%). Thirty-five patients were known to be on TB treatment at the time of biopsy, with the average time from TB treatment initiation to biopsy being 6 days. Table 2 demonstrates the investigations performed for TB diagnosis. The mean CD4 count at biopsy was 105cells/μL. The median creatinine at biopsy was 417μmol/L.

Table 2. Investigations in patients with confirmed TB

TB Investigation	n (%)
Urine Culture:	
Positive	4 (8.5)
Negative	10 (21.3)
Not Performed	33 (70.2)
Urine LAM:	
Positive	0 (0)
Negative	2 (4.3)
Not Performed	45 (95.7)
Sputum:	
Positive	15 (31.9)
Negative	13 (27.7)
Not Performed	18 (38.3)
Unknown Result	1 (2.1)
GeneXpert on biopsy:	
Positive	2 (4.3)
Negative	4 (8.6)
Not Performed	41 (87.1)
Overall Culture Result:	
Positive	15 (31.9)
Negative	14 (29.8)
Not Performed	18 (38.3)
Radiology:	
Positive	27 (57.5)
Negative	9 (19.1)
Not Performed	0 (0)
Unknown Result	11 (23.4)
Other:	
Abdominal	6 (12.8)
Pleural Effusion	5 (10.6)
Pericardial effusion	3 (6.4)
Lymph Node	3 (6.4)
Cold Abscess	1 (2.1)
CSF	1 (2.1)
Liver	1 (2.1)
Pus Swab	1 (2.1)
Urine AFB	1 (2.1)
MOT/MAC on Sputum	1 (2.1)

TB – tuberculosis
LAM - lipoarabinomannan
CSF – cerebrospinal fluid
AFB – acid-fast bacilli
MOT – mycobacteria other that tuberculosis
MAC – mycobacterium avium complex

On subgroup analysis of the [TB : no IRIS] and the [TB + IRIS] group, the mean age was 36.7 and 39.3 years respectively. Males made up approximately 50% of the cohort and the majority were African ethnicity. The highest proportion of ART use at time of biopsy was in the [TB-IRIS] group (83%) [p-value <0.001]. The average time from ART initiation to biopsy was 6 weeks vs 28 weeks in the [TB+IRIS] and [TB :no IRIS] group respectively (p-value 0.002). In the [Other] group the mean age was 37 years, 43% were males, and 91% were of African ethnicity. Fifty-nine percent of these cases were on ART at the time of biopsy, with the average time to ART commencement being 26 weeks. Forty-seven percent of the TB-IRIS cases were unmasking and 53% were paradoxical.

The baseline and nadir CD4 was lowest in the [TB + IRIS] compared to the comparison groups and had statistical significance, with a median baseline CD4 of 81cells/μL (p=0.0175) and nadir CD4 79cells/μL (p=0.025) in the [TB + IRIS] group. The median creatinine was almost double (547mmol/L) in the [TB : no IRIS] group compared to the comparison groups (287mmol/L in [TB + IRIS] and 333mmol/L in [Other]); however this was not statistically significant (p-value 0.146). The median UPCR at biopsy was 0.26gm/mmol, with no significant difference between the groups (p-value 0.125).

Twenty subjects had leucocytes on their dipstix at the time of biopsy, 15 of which grew an identifiable organism, and the remaining 5 had sterile pyuria ie growth <10000cfu. (Table 2) Of the 15 positive urine cultures, 4 were from the [TB + IRIS] group, 3 from [TB : no IRIS], and 8 were of the [other] group (Table 3). Of note, is the high rate of culture-positive infections in the [Other] group.

Table 3. Leucocyte-positive urine dipstix results

Leucocytes	TB : no IRIS	TB + IRIS	Other	Total
N	17 77%	9 69%	7 39%	33 62%
Y	5 23%	4 31%	11 61%	20 38%
Total	22 100%	13 100%	18 100%	53 100%

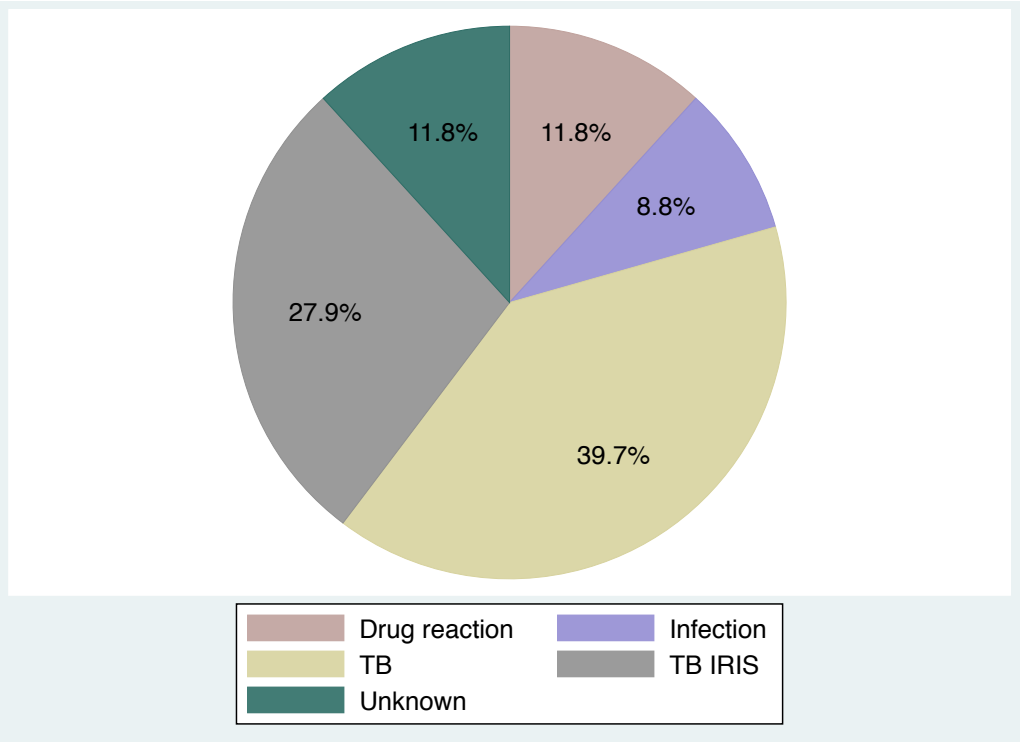
Table 4. Positive urine culture organism identification

Organism cultured	TB : no IRIS	TB + IRIS	Other
Escherichia Coli	1	1	4
Staphylococcus aureus	0	0	1
Gram-negative bacteria	0	2	1
Klebsiella pneumonia	2	1	0
Enterococcus faecalis	0	0	1
Yeast	0	0	1

Biopsy results showed the granulomas found in the [TB + IRIS] group to be relatively well-formed (p-value 0.075). This is in comparison to the finding of higher numbers of poorly formed granulomas in the [TB : no IRIS] group. Histological features of pyelonephritis were observed in 15 (22%) of the biopsies. HIVAN was noted in 43 (63%) of the biopsies, with the highest finding in the [TB : no IRIS] group)68%), but statistically insignificant (p-value 0.744).

Figure 2 shows the breakdown of aetiologies of GIN found in our study population. The main cause was TB accounting for 67.6% of all cases (39.7% of these due to TB alone, and 27.9% due to TB-IRIS). Drug reactions and infection accounted for 11.8% and 8.8% respectively. Causative drugs included bactrim and diuretics; and causative infections included bacterial pyelonephritis and fungal. The specific organisms identified are shown in Table 4. The remaining 11.8% was due to unknown causes, with no definitive aetiology found on biopsy or other investigations.

Figure 2. Causes of Granulomatour Interstitial Nephritis (GIN)



TB – tuberculosis
IRIS – immune reconstitution inflammatory syndrome

The secondary outcomes of the study were death within 2 years of biopsy and a follow-up creatinine within 1-3 months post-biopsy (Table 5). Sixteen subjects (25%) had died within 2 years of their biopsy, with the majority of deaths occurring in the [TB : no IRIS] group (12/28, 44%), (p-value 0.01). The follow-up median creatinine done at 1-3 months was 121mmol/L (85-488). Although not statistically significant the [TB + IRIS] group had the worst creatinine at this timepoint (344mmol/L). This is compared to a median creatinine of 141mmol/L in the [TB : no IRIS] group and 114mmol/L in the [Other] group (p-value 0.57).

Table 5 – Study Outcomes (Mortality and renal function)

		TB, no IRIS (A)	**TB + IRIS** (B)	**Other** (C)	**P-value** (A) vs (B) vs (C)
		n=28	**n=19**	**n=21**	**p-value**
Outcome	Total				
Death within 2 years post-biopsy	16/64 (25%)	12 (44%)	2 (11%)	2 (11%)	0.01
Follow-up creatinine at 1-3 months	121 (85-488) 45/68	141 (81-898)	344 (92-569)	114 (85-203)	0.57

Creatinine baseline (μmol/L)	96 (71-169)	177 (72-259)	99 (71-139)	89 (69-102)	0.429
CD4 nadir (cells/μL)	97 (52-183)	92 (19-167)	79 (55-121)	191 (86-336)	0.025

DISCUSSION

This observational retrospective study of HIV-positive renal biopsies assessed the existence of an entity of renal TB-IRIS, and its renal and mortality outcomes. We found this entity to follow the standard descriptions of TB-IRIS, ie the occurrence of new TB infection or worsening of symptoms, shortly after ART initiation, in HIV-positive patients with low CD4 counts. This study adds to the existing literature with a new observation of "well-formed' granulomas in the TB-IRIS patients. As far as we are aware this has not been described in the literature previously. These patients with renal TB-IRIS showed better mortality and renal outcomes compared to the other 2 groups.

Despite the significant increase in numbers accessing ART in SA, only half of the patients in the study were on ART at the time of biopsy [31/60, 51.7%). In 2015 the worldwide use of ART was 46%(43-50%).[19] SA has increased its ART coverage by more than 25% points from 2010 to 2015. This equated to 3,4 million people having access to ART in SA.[19]

Due to the increased rollout of ART in SA, IRIS has become an important early complication which needs to be considered in our setting.[8] IRIS is thought to result from immunological responses, that were previously subdued by the HIV infection. These responses become activated again once the host's immune system is restored.[9] The 3 main TB-IRIS syndromes consist of "paradoxical", "unmasking" and "ART- associated TB".[8] Paradoxical TB-IRIS occurs within 3 months of ART initiation in patients already receiving TB therapy, who initially demonstrated a response to TB treatment. In unmasking TB-IRIS the patient is not on TB treatment at the time of ART initiation, but then presents with active TB within 3 months of commencement of ART, with either worsening of clinical manifestations of TB or development of paradoxical complications. Finally, ART-associated TB occurs in patients not

on TB treatment when ART is started, and the diagnosis of active TB is made after ART initiation.[8]

Renal TB-IRIS to date has not been a well described entity. To our knowledge there are only 6 documented case reports to date of biopsy-proven IRIS-related kidney injury, in the form of TB-GIN after initiation of ART (Table 6).[10,11,12,13,14,15] Two of these cases were unmasking IRIS, in which renal dysfunction developed after the diagnosis of TB was made, after ART initiation. All 6 cases demonstrated low CD4 counts (25-88cells/μL), and non-suppressed viral loads (>56732 copies/ml). TB diagnoses were based on various parameters, including symptoms, pulmonary TB, pleural effusions, bone and liver lesions, and cutaneous TB, with 1 case being a proven mycobacterium avium complex (MAC). ART was initiated 2 weeks to 45 days after TB treatment in 3 of the cases, and from 2 days to 3 months before TB treatment in the other 3 cases. Importantly, studies have shown that TB-IRIS shows a good response with steroid treatment.[16] All 6 cases showed a prompt improvement after steroid therapy, and showed improvement of renal function at follow-up, ranging from 8-18 months. However, in the study done by Meintjies et al, not all patients with TB-IRIS responded to prednisone treatment.[16]

Table 6 Case reports of IRIS-related GIN

Case Report	CD4 count (cells/ul)	HIV VL (copies/ml)	TB diagnosis	ART initiation	Onset of renal disease	Treatment	Renal function improvement	Follow-up
Jehle 2004	69	12477886	Miliary, urinary	2 weeks after TB treatment	6 weeks after cART	Prednisone	Within 10 days	Healthy at 1 year
Daugus 2006	26	56732	Pleural effusion	1 month after TB treatment	4 weeks after cART	Steroids	Within 1 week	Normal renal function after 1 year
Izzedine et al 2007	37	>750000	Symptoms, bone/liver granulomas	3 months before TB treatment	5 months after cART	Prednisone	Over 2 weeks	Normal renal function at 10 months
Salliot et al 2008	88	177504	Pulmonary, hepatic, cutaneous TB	45 days after TB treatment	15 days after cART	Prednisone	Slow	Normal renal function at 8 months
Croucher et al 2010	79	61573	Pulmonary TB	2 days before TB treatment	50 days after re-starting ART	Prednisone	Within 24 hours	Normal renal function at 18 months
Martin-Blondel et al 2011	25	6.5 $\log^{10}$	MAC	34 days before MAC diagnosis and treatment	103 days after cART	Prednisone	Over 1 month	Normal renal function at 10 months

IRIS : Immune reconstitution inflammatory syndrome
GIN : Granulomatous interstitial nephritis

In a recent review of GIN in HIV-positive renal biopsies done at GSH, 6 cases were found in patients with TB-IRIS.[5]

In studies from developed countries, including USA, Europe and the UK, the most common causes of GIN are reported to be idiopathic, sarcoidosis and drug-induced, with TB being an uncommon cause.[19,20,21] In developing countries, including Africa and India, however, TB is the most common infectious cause of GIN.[17] In this study the majority of GIN was attributed to TB (67.6%)(Figure 2). Drug reactions and idiopathic GIN each contributed 11.8% to the causes of GIN. Of note though, is the rather significant number of cases thought to be due to TB-IRIS (27.9%). Interestingly there was not an increased percentage of drugs known to cause GIN in the [Other] group compared to the TB groups.

One of the recent modifications made to the 2008 TB-IRIS case definitions was the inclusion of a timeframe of initiation of ART within 3 months, for the diagnosis of TB IRIS to be made, as this is the time during which immune restoration takes place.[8] In our study, the mean time of ART initiation in the [TB + IRIS] group was 6 weeks (4-9 weeks), which is consistent with the above time-frame for TB-IRIS. This finding supports the occurrence of IRIS that is seen in other systems.

The [TB + IRIS] group showed a lower median nadir CD4 of 79cells/μL (p= 0.025) and biopsy CD4 of 81cells/μL (p= 0.0175) than the other 2 groups. However, another modification made to the TB-IRIS definitions was the omission of the laboratory parameters of CD4 and VL, specifically a rise in the CD4 count, as a necessary marker for the diagnosis of TB-IRIS.[8] This is due to the fact that TB-IRIS is often diagnosed shortly after ART initiation, before any significant rise in CD4 count occurs, and because there are probably other cellular mediators of IRIS, along with CD4 T-cells which also contribute to IRIS.[8]

It has been noted in previous literature that TB granulomas in HIV positive patients in other organ systems were poorly formed.[22,23] Another notable observation in our study was the detection of relatively well formed granulomas in the [TB + IRIS] group. This could possibly be attributable to activation of immunological responses required to form granulomas.

With regards to the mortality outcome in the study cases, [TB : no IRIS] appeared to denote a higher mortality, with a better outcome in the [TB + IRIS] group. The mortality rate was lowest in the [TB + IRIS] group.

The assessment of the renal outcomes in these patients, in the form of a follow-up creatinine, done within 1-3 months after biopsy, showed higher creatinines in the [TB + IRIS] group. The median creatinine in this group was 344mmol/L, compared to 141mmol/L and 114mmol/L in the [TB : no IRIS] and [Other] groups respectively, although this was not statistically significant (p-value 0.57). The TB-IRIS patients in our study were not treated with steroids, and this could have possibly contributed to the untreated inflammatory reaction with worsening fibrosis, and hence causing the higher creatinine seen at follow-up in this group. This is in contrast to the previously discussed 6 case studies from the literature, all of which showed improvement of their creatinine with steroid therapy. (Table 6)

Limitations in this study include the following: i) It was a retrospective review, ii) follow-up creatinines were not well documented after 3 months for most of the study participants, iii) more specific histological evaluation would have been helpful in assessing the degree of interstitial infiltration and fibrosis, and vi) the exact causes of death were not evaluated, ie patient mortality could have been affected by other non-related co-morbidities.

CONCLUSION

The ongoing increase in ART roll-out, may lead to increased occurrence of TB-IRIS. To date, there is marked paucity in the literature regarding the entity of renal TB-IRIS. This study demonstrated that renal TB-IRIS is found in the following clinical and histological settings. Firstly, in an HIV positive patient with low CD4 nadir, recent ART initiation, followed by clinical deterioration in renal function. Secondly with histological features of well-formed granulomas on renal biopsy. Finally other common causes of GIN should be excluded, including infection and specific drug use. Renal TB-IRIS is therefore an important entity to recognise in the setting of HIV and AKI, as it may respond to steroid therapy, which may

impact on renal outcomes. Further research could include better accuracy in testing for TB-GIN and further tests for supporting TB-IRIS.

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