Original Article

A Comparative Study of *Mycobacterium Tuberculosis* in Hospitalised Adult HIV Infected Patients with Normal and Abnormal Renal Function at the University Teaching Hospital, Lusaka, Zambia

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ABSTRACT

Background: *Mycobacterium tuberculosis (TB)* remains a leading cause of mortality and morbidity worldwide, including Zambia, especially among those infected with the Human Immunodeficiency Virus (HIV). Both kidney dysfunction and *TB* have been shown to be highly prevalent among hospitalised HIV infected patients.

Little is known about how *TB* and kidney dysfunction impact each other in HIV patients, and whether there is any association between the occurrence of kidney dysfunction and active *TB* infection in this population. This study was aimed at determining the prevalence and risk factors of active *TB* infection in HIV positive patients with and without kidney dysfunction.

Methods: This was an analytical cross-sectional study. Using simple random sampling, HIV positive patients on the medical wards were recruited in two arms (74 with & 59 without kidney dysfunction). Urine Lipoarabinomannan (LAM), *TB* blood culture, sputum culture and genexpert MTB/Rif were used for *TB* diagnosis. Data was analysed using STATA version 13.

Results: *TB* prevalence in all HIV positive hospitalized patients was 45%, and more prevalent in the kidney disease than non-kidney disease group (54% vs 35.59%; p=0.034). *TB* diagnosis pick up was comparable in the kidney disease and the non-kidney disease group using urine LAM and blood culture at 31.1% vs 22.2% and 8.9% vs 3.1% respectively, but lower using sputum culture; 12.5% vs 24.1%.

Among kidney disease patients, a higher CD4 count > 200cells/µl was protective for active *TB* (P = 0.011). Severe immunosuppression (CD4 count < 200cells/µl) was 18.64% higher in the kidney dysfunction group compared to the non-kidney disease group (P=0.026). The only factor associated with active *TB* was male gender (P = 0.029); while Proteinuria in a *TB* patient was strongly associated with kidney disease (P < 0.001). Patients with WHO stage III/IV were likely to present with *TB* in both groups (P=0.004, 95% CI 1.47 - 7.20).
Kidney dysfunction severity (measured by estimated glomerular filtration rate), age, antiretroviral therapy status and duration on combination antiretroviral therapy, history of *TB* contact and current cough, had no significant association with active *TB* in the two groups.

Conclusion: Patients with kidney disease are more likely to present with active *TB* infection than HIV infected

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patients with no kidney disease. Among patients with active *TB*, urinalysis can help predict renal dysfunction; while determinants of active *TB* in the general population are not similar to those in kidney disease patients.

INTRODUCTION

Mycobacterial tuberculosis remains a leading cause of mortality and morbidity worldwide, including Zambia, especially among those infected with the Human Immunodeficiency Virus (HIV).[1,2,3] Both kidney dysfunction and Tuberculosis (TB) have been shown to be highly prevalent among hospitalised HIV infected patients.[4]

Ayles *et al* estimated HIV prevalence in Zambia to be between 12.5 and 14.3%; while HIV infection alone, was shown to have an attributable risk for *TB* of 36% in the general population.[1,5] Other studies estimate the prevalence of TB in HIV infected populations at the University Teaching Hospital (UTH) to be between 14% and 56%.[10, 11, 12, 13] Among HIV patients with pulmonary disease at UTH in Lusaka, Mateyo *et al* found a *TB* prevalence of 55.8%; [12] while Muchemwa *et al*, in a study of Zambian HIV infected patients admitted with severe sepsis in UTH, found a prevalence of TB bacteraemia was 34.8%.[11]

On the other hand, kidney dysfunction is on the rise with an estimated 500 million individuals globally reported to have CKD, while the incidence of acute kidney injury (AKI) is as high as 2,000 – 3,000 per million in hospitalised patients globally.[2, 3, 6, 7, 8, 9] The prevalence of kidney dysfunction is very high in HIV infected individuals in African settings. Studies in Sub-Sahara Africa estimate the burden of kidney disease to be in the range of 17% to 30% among HIV positive patients. [2, 6, 14, 15] Banda *et al* estimated the prevalence of kidney dysfunction at 42% among hospitalised HIV infected patients compared to 27% among uninfected patients at UTH in Lusaka, Zambia.

A few studies have reported an association between AKI requiring dialysis and long term risk of TB.[7, 16, 17] A study by Wu V.C *et al*, in low HIV prevalence population in China, demonstrated a relative risk of active *TB* in AKI to be 7.71 compared to the general population.[16] Another study by Moore, *et al* in England and Wales, showed that patients requiring dialysis had a 100-fold incidence of *TB* compared to the general population. This was most evident among migrant populations in the United Kimgdom.[20]

The risk of *TB* in kidney disease seems to be higher with increasing stage of AKI. Patients with AKI requiring dialysis have a higher risk than AKI patients not requiring dialysis.[18] This may be explained by the fact that renal patients tend to be more immunosuppressed than the general population, due to alterations in T-cell immune responses caused by both uraemia and dialysis.[16, 18, 19] This may be true among populations with a high HIV burden like Zambia.

The routine employment of rapid diagnostic techniques with good sensitivity and specificity such as genexpert mycobacteria/Rifampicin (MTB/Rif) for TB diagnosis in HIV infected individuals should be used. However, this can be very challenging in sputum scarce patients like those with severe kidney dysfunction and sepsis.[7, 21] In a multi-centre study by Peter J.G, *et al* use of a bedside "Lipoarabinomannan" (rapid urine test strip) LAM-guided initiation of anti-tuberculosis treatment in HIV-positive hospitalised patients with suspected *TB* was associated with a reduced 8-week mortality.[22] In work by Peter *et al* the LAM test strip to detect active *TB* infection had both sensitivity and specificity of 66% (95% CI 57-74%) on urine specimen from patients with advanced HIV disease.[23] Significant predictors of urine positivity in studies included severe immunosuppression with CD4 counts < 50 cells/µl , elevated protein-to-creatinine ratio (a biomarker of kidney dysfunction) and LAM ELISA (Enzyme-linked immunosorbent assay) positivity.[23]

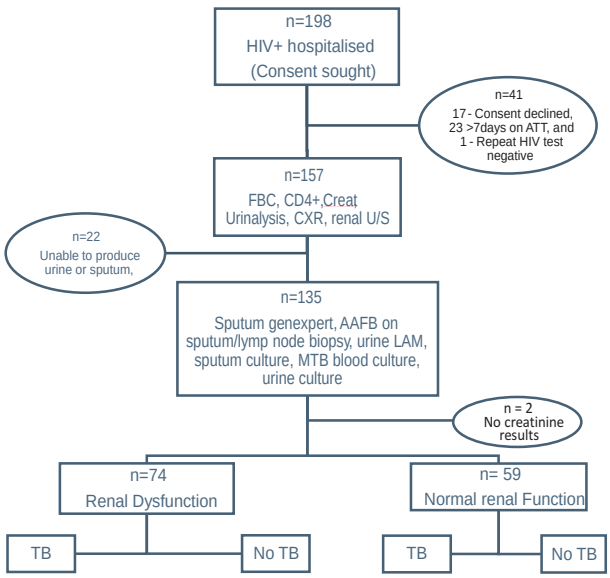
Little is known about how TB and kidney dysfunction impact each other in HIV patients, and whether there is any association between the occurrence of renal dysfunction and active *TB* in HIV infected people. This study aimed to determine the prevalence and determinants of active *TB* infection in HIV positive patients with and without kidney dysfunction.

MATERIALS AND METHODS

This was a cross-sectional, analytical study. One hundred and thirty-four patients was the calculated sample size using STATA, 2011 with the following assumptions; two-

sided test, estimated prevalence of 13% *TB* among HIV patients with normal renal function, and 37% among the HIV patients with renal dysfunction with a proportional difference of 24%, 90% power and 95% confidence interval in a 1:1 ratio Using simple random sampling, 133 HIV positive patients on the medical wards were recruited in two arms (74 with & 59 without kidney dysfunction) following the inclusion and exclusion criteria as elaborated in figure 1.

Figure 1. Study Algorithm



Data was analysed using STATA version 13. Continuous variables following the normal distribution were expressed as means with standard deviations, while skewed data was expressed as medians with interquartile ranges; and categorical variables were expressed as percentages or proportions. Unpaired Student T-test or the Mann – Whitney test were used for continuous variables based on the degree of skewness of data. Either a *Chi square* or *Fishers exact test* were used (where applicable) for comparison of categorical variables. Outcome variables were dichotomised (e.g. active *TB* or no *TB*) to determine association with exposure (e.g. kidney disease). P value of < 0.05 was taken as statistically significant, with a confidence interval of 95%.

Urine Lipoarabinomannan (LAM), *TB* blood culture, sputum culture, gene-xpert MTB/Rif and lymph node biopsy were used for *TB* diagnosis.

Blood was tested for anti-HIV antibodies using two sequential rapid tests; Alere Determine™ and Unigold™. Serum Creatinine were processed using the Beck Man Coulter AU480™ with Beck Man Coulter AU480 Reagent™, while estimated glomerular filtration rate (eGFR) was calculated using the Modified Diet in Renal Disease (MDRD) formula. CD4 T-cell count was performed using flow cytometry. The process was done using a Becton Dickinson Facs Count machine with BD Facs Count Reagent™.

Blood culture for *Mycobacterium tuberculosis* was performed using BACTEC 9120 blood culture machine. The positive cultures were offloaded from which a smear was prepared and stained using the Ziehl Neelsen method for the presence or absence of acid-fast bacilli (AFB). Where AFB were observed, the culture was reported as being positive. For cultures flagged positive for growth by the instrument but no AFB were observed during microscopy, the result was reported as contaminated and a simple morphological description of the organisms observed was reported as a comment. The cultures that were negative at the end of the 42 days were reported out as negative.

About 5mls of mid-stream urine for *TB* – LAM was collected, and a rapid test strip using Alere LAM Determine™ was done.

Two sputum samples (spot and morning) for genexpert and *TB* culture were collected on enrolment. *TB* culture was performed on expectorated sputum according to standard protocols. After neutralization with para-amino-salicylic acid (PBS) followed by centrifugation and re-suspension of the deposit, 0.5ml of the deposit was inoculated into a Mycobacterial Growth Indicator Tube (MGIT) (Becton Dickinson) for culture.

The Genexpert MTB/RIF assay was performed on 1ml of thawed unprocessed sputum samples. Sample treatment buffer was added to sputum samples and a defined volume of this mixture was then transferred to the sample chamber of the cartridge. The cartridge was then inserted in the

Genexpert™. From this point on, all steps were automated till final results were obtained on the monitor.

Radiological procedures included posterior-anterior chest X-rays and abdominal ultra-sounds which were performed and reported on by experienced radiologists, while lymph node biopsy was performed by surgeons.

Ethical Approval:

The study was approved by the Ethics Research Committee of ERES CONVERGE IRB, I.R.B. No. 00005948; Ref. (Approval) No. 2014 – Oct – 009. Permission was also obtained from the office of the Senior Medical Superintendent of the University Teaching Hospital, Lusaka.

RESULTS

There were 135 participants enrolled and 133 analysed in two arms (kidney disease and non-kidney disease groups). Of these 74 (55.64%) had kidney dysfunction and 59 (44.36%) had normal renal function). The recruitment and exclusion of participants were as outlined in the study flow chart in figure 1.

The mean ages in the kidney disease and non-kidney disease groups were 39.38 years (SD ± 10.34) and 37.61 years (SD ± 10.67) respectively (Table 1). More patients were on combination antiretroviral therapy (cART) in the kidney disease group; 45 (60.81%) compared to 27 (45.76%) in the non-kidney disease group (Table 1). In both groups, over 96% of participants had HIV WHO stage III/IV defining conditions.

The mean estimated glomerular filtration rate (eGFR) was 31.41mm^3/minute (SD±26.61) in the kidney disease group and 153.64mm^3/minute (SD±49.48) in the non-kidney disease group (Table 1). Proteinuria, haematuria and glucosuria were more prevalent among patients with kidney disease compared to those without, although only proteinuria was statistically significant, P < 0.001 (Table 1). Severe anaemia (Hb<7.0g/dl) was more common in the kidney disease group than the normal kidney group (48% against 18.64%) (Table 1).

Table 1. Baseline characteristics of study population by kidney function

Characteristic	Kidney Disease Group (n = 74; 55.64%)	Non-Kidney Disease Group (n=59; 44.36%)	P Value
Mean AGE (SD)	39.38 (10.34)	37.61 (10.67)	0.671
Gender			0.710
Female	45 (60.81)	34 (57.63)	
Male	29 (39.19)	25 (42.37)	
cART Status			**0.022***
Pre - cART	23 (31.08)	31 (52.54)	
On cART	45 (60.81)	27 (45.76)	
cART defaulters	6 (8.11)	1 (1.69)	
WHO HIV Staging			
I	-	1 (1.69)	0.697
II	2 (2.7)	1 (1.69)	
III	44 (59.46)	38 (64.41)	
IV	28 (37.84)	19 (32.2)	
Urinalysis			
Proteinuria ≥	15 (20.55)	1 (1.75)	**0.001***
Haematuria	22 (30.14)	7 (12.23)	0.491
Glucosuria	8 (10.96)	2 (3.51)	0.184
Haemoglobin – g/dl (SD)	7.3 (2.4)	9.5 (3.2)	**0.038***
CD4 Count			**0.026***
CD4 count <200 cells/mm^3	54 (78.26)	31 (59.62)	
Creatinine µmol/L (IQR)	465.92 (78.3 - 2074.3)	61.14 (28.3 – 100.5)	
eGFR ml/min (SD)	31.41 (26.61)	153.64 (49.48)	**<0.0001***

** Statistically significant with P value < 0.05*
All values are mean unless stated otherwise

Associations of Active *Mycobacterium tuberculosis* Infection and Kidney Disease

Microbiological *TB* prevalence in all HIV positive hospitalised patients was 25%, and 45% when radiological diagnosis was included. *TB* was more prevalent in the kidney disease group at 54% compared to the non-kidney disease group at 35.59% (p=0.034) (Table 2 and Figure 2). Patients in WHO stage III/IV were likely to present with *TB* in both groups (P=0.004, 95% CI 1.47 - 7.20).

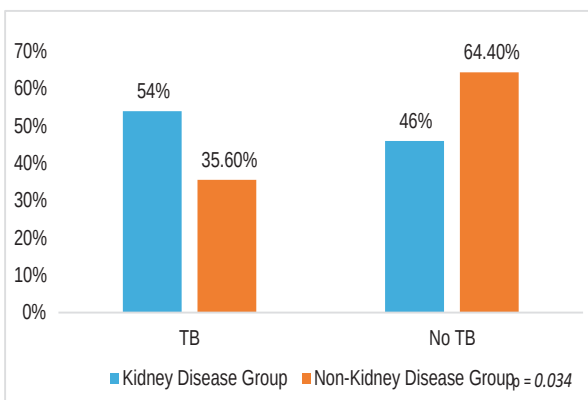
Table 2. Tuberculosis Diagnostic Pick-up according to kidney disease status

	Kidney Disease Group (n = 74; 55.64%)	Non-Kidney Disease Group (n=59;44.36%)	P Value
Lab MTB diagnosis	**18 (25)**	**14 (25)**	**0.964**
Urine LAM	**14 (31.1)**	8 (22.2)	
Sputum culture	5 (12.5)	**7 (24.1)**	
Blood culture	**7 (9)**	1(3.1)	
MTB diagnosis (Includes chest X ray)	40 (54)	21 (35.59)	**0.034***

**statistically significant with P value < 0.05*

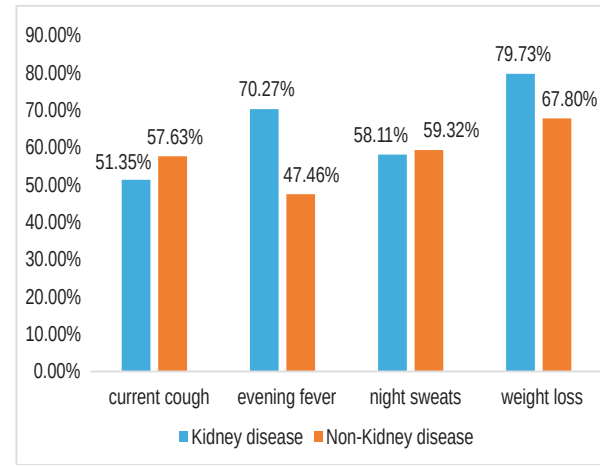
Note: *not all patients submitted all three samples used for diagnostics. Kidney disease group: Urine LAM - 45/74, Sputum culture - 40/74, Blood culture - 45/74. Non – kidney disease group: Urine LAM - 36/59, Sputum culture - 29/59, Blood culture – 32/59.*

Figure 2. Prevalence of active *Mycobacterium tuberculosis* infection according to kidney function



In patients with kidney disease, evening fever and weight loss occurred more frequently than in the non-kidney disease group (Figure 3). On the other hand, the frequency of current cough of any duration and night sweats, were almost similar in both groups (Figure 3).

Figure 3. Frequency of constitutional symptoms according to kidney function



In the bivariate analysis (Table 3); active *TB* among the kidney disease group, had significant association with evening fever and male gender (OR 2.44, 95% CI 1.00 – 5.95, P = 0.049) and (OR 2.44, 95% CI 1.09 – 5.46, P =

Table 3. Determinants of active TB among patients with Kidney disease

Characteristic	Crude OR (95% CI)	P Value	Adjusted OR (95 % CI)	P Value
Gender				
Female	1		1	
Male	2.44 (1.09- 5.46)	**0.030***	4.57 (1.17- 17.82)	**0.029***
cART				
Pre – cART	1		1	
On cART	0.86 (0.37- 1.98)	0.719	0.36 (0.04- 3.51)	0.398
Duration on cART				
<6 months	1		1	
>6 months	0.8 (0.36- 1.77)	0.581	4.19 (0.42- 41.98)	0.223
CD4 count <200 cells/µl	1		1	
CD4 count ≥200 cells/µl	0.19 (0.05- 0.69)	**0.011***	0.04 (0.00- 0.45)	**0.009***
Evening Fever				
Yes	2.44 (1.00- 5.95)	**0.049***	2.14 (0.27- 4.59)	0.386
Weight Loss				
Yes	3.05 (0.98- 9.44)	**0.054**	2.03 (0.39- 10.53)	0.399

**statistically significant with P value < 0.05*

0.030) respectively. However, the significance was lost for evening fever on adjusting for confounding, but was strengthened for male gender (OR 4.57, 95% CI 1.17 - 17.82, P = 0.029). Weight loss on the other hand, was 11.93% more common in the kidney disease group than the non-kidney disease group, but not statistically significant (p = 0.054).

Renal dysfunction severity (as measured by eGFR), age, cART status, duration on cART, history of *TB* contact and current cough, had no significant association with active *TB* in the kidney disease group.

A CD4 count > 200 cells/µl was protective of active TB among HIV infected individuals with kidney disease {P = 0.011, OR 0.19, 95% CI 0.05 – 0.69}(Table 3). Severe immunosuppression (CD4 count < 200 cells/µl) was more prevalent in the kidney disease group than the non-kidney disease group. The median CD4 T-cell count was 85 cells/µl (1 – 670 cells) in the kidney disease group, compared to 124 cells/µl (4 – 1353cells) in the non-kidney disease group.

Renal dysfunction was strongly associated with proteinuria (P < 0.001), especially among patients with active *Mycobacterium tuberculosis* compared to the non-kidney disease group.

DISCUSSION

This study found higher rates of active TB among patients with kidney dysfunction (54%) comparable to that found by Mateyo *et al.* (55.8%) in a study that focussed on HIV patients presenting with pulmonary disease where broncho-alveolar lavage specimens were used.[12] This is also consistent with a meta-analysis by Gao, *et al* which found TB prevalence among HIV populations of between 2.93% to 72.34% in most African and Asian countries excluding China.[14]

Studies in Asia report much lower rates of active TB of between 9 to 12% among patients with kidney disease, but these rates were still higher than in the general population.[7, 16, 24] These studies were mostly conducted in countries with low HIV prevalence compared to our setting. Our study has demonstrated that the relative risk of having active TB is higher among HIV patients with kidney disease than in the general HIV infected population (RR 1.52). Even though these findings showed a lower relative risk compared to an Australian/New Zealand study by Dobler *et al* which demonstrated an adjusted relative risk of active TB among dialysis patients of 7.8, they support the evidence that kidney disease poses a risk of TB in this population.[25]

Our study showed that patients with kidney dysfunction had lower immunity as evidenced by lower CD4 T-cell counts using a cut-off 200 cells/µl, compared to the general HIV infected population (78.26% vs 59.62%, p = 0.026); a factor that independently increases the risk of active TB. Although uraemia causes profound alterations in immune responses of individuals presenting with kidney disease, this may be confounded by underlying immunosuppression among HIV infected patients alongside other factors like; malnutrition due to dietary restrictions, cART regimen and duration of cART.[16] During literature search, we unfortunately could not find studies that had looked at patient groups that had both kidney disease and HIV infection, while the only studies close to ours was in patient populations with a very low HIV prevalence, mostly in East Asia.[16]

TB diagnosis in special populations, like those with HIV, diabetes mellitus and renal disease remains challenging as often time these patients are sputum scarce, or too ill to expectorate any sputum.[7] This can be overcome by using methods that do not require sputum for diagnosis (like urine and venous blood samples). TB diagnostic pick up was higher in the kidney disease than non-kidney disease group using urine LAM and blood culture at 31.1% vs 22.2% and 7% vs 3.1% respectively, though not statistically significant. On the other hand, sputum culture had a higher pick up rate in the non-kidney disease group 24.1% vs 12.5% probably owing to the poor quality of sputum and low immune status among renal patients.

Although majority of the study participants were females, male gender had a significant association with active TB, similar to what was shown by Rao *et al.* (68.7% of positive TB cases being among male patients, p = 0.002).[7] However, we could not find a plausible scientific explanation for this finding. Determinants of TB in our study were slightly different compared to studies in non-HIV infected populations where diabetes mellitus, past TB infection, and a higher mean age were noted.[7, 16, 24, 25] Of

the traditional constitutional symptoms associated with TB infection, only evening fever was statistically significant at bivariate level. However, at multivariate level, the significance was lost when comparing patients having the symptom in both groups. On the other hand, symptoms like current cough, weight loss and night sweats which are considered to be strong predictors when screening for active TB in general population surveys had no statistical significance in our study.[26]

Renal dysfunction was strongly associated with proteinuria ($P < 0.001$), especially among patients with active TB compared to the non-kidney disease group. This has been shown to be true in studies that utilised measurement of the urine protein-to-creatinine ratio, where it was demonstrated that an elevated ratio was predictive of a positive TB LAM.[22, 23, 28] It therefore implies that detection of proteinuria in patients with active TB may strongly predict likelihood of kidney dysfunction. However, our study did not establish any correlation between presence of proteinuria, haematuria or glucosuria and active TB infection in patients with kidney disease.

The study could not draw causal association between kidney disease and active TB due to none utilisation of renal biopsies. Furthermore, the absence of urine TB cultures on our diagnostic panel made it challenging to draw conclusions on causal associations between TB and kidney disease.

CONCLUSION

From our study, we may thus conclude that patients with kidney disease are more likely to present with active TB infection than HIV infected patients without kidney dysfunction. Furthermore, tests like the Urine LAM may be very helpful diagnostics in HIV patients with renal disease, who are often times sputum scarce and severely immunosuppressed. We further showed that among patients with active TB, urinalysis can help predict renal dysfunction; and that determinants of active TB in the general population are not similar to those in kidney disease patients.

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REFERENCES

1. World Health Organization. Global Tuberculosis Report, 2013. WHO/HTM/TB/2013.15
2. Kidney Disease: Improving Global Outcomes (KDIGO): KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Volume 3 | issue 1 | January 2013. http://www.kidney-international.org
3. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney inter.*, Suppl.2012; 2: 1–138.
4. World Health Organization. Global tuberculosis control: a short update to the 2009 report. http://www.who.int/tb/publications/ global report/2009.
5. Ayles H, Schaap A, Nota A, Sismanidis C, Tembwe R. Prevalence of Tuberculosis, HIV and Respiratory Symptoms in Two Zambian Communities: Implications for Tuberculosis Control in the Era of HIV. *PLoS ONE* 4(5): e5602; 2009. doi:10.1371/journal.pone.0005602.
6. Wali RK. Aspirin and the Prevention of Cardiovascular Disease in Chronic Kidney Disease: Time to Move Forward? *J Am Coll Cardiol* 2010, 56:966–968.
7. **Manmadha T. Rao, Ram R, Swarnalatha G, Santhosh Pai B.H, Ramesh V, Shyam Sunder Rao**

C. *et al*. Tuberculosis in Haemodialysis Patients: A Single Centre Experience. *http://www.indianjnephrol.org*, 2013, 23 (5): 340 - 345.

8. Tandi E Matsha, Yandiswa Y Yako, Megan A Rensburg, Mogamat S Hassan, Andre P Kengne and Rajiv T Erasmus. Chronic Kidney Diseases in Mixed Ancestry South African Populations: Prevalence, Determinants and Concordance between Kidney Function Estimators. *BMC Nephrology* 2013, 14:75 http://www.biomedcentral.com/1471-2369/14/75.
9. Hoste EA, Schurgers M. Epidemiology of acute kidney injury: how big is the problem? *Critical Care Medicine*. 2008 Apr; 36(4 Suppl):S146-51. Doi: 10.1097/CCM.0b013e318168c590.
10. Banda J, Mweemba A, Siziya S, Mweene M, Andrews B, Lakhi S. Prevalence and Factors Associated with Renal Dysfunction in HIV Positive and Negative Adults at the University Teaching Hospital, in Lusaka. *Medical Journal of Zambia*, 2010; 37 (3).
11. Muchemwa L, Lakhi S, Andrews B, Bwalya M. High Prevalence of Mycobacterium Tuberculosis Bacteraemia among a cohort of HIV-infected patients with Severe Sepsis in Lusaka, Zambia. *Int J STD AIDS*. 2016 Mar 21. pii: 0956462416640963. [Epub ahead of print].
12. Mateyo K, Lakhi S, Guffey B, Chi B, Mweemba A, Andrews B. Pulmonary Disease in HIV-infected Patients at the University Teaching Hospital, Lusaka, Zambia. *Medical Journal of Zambia*, 2014 41(2): 50 - 58.
13. Andrews B, Muchemwa L, Lakhi S, Bwalya M, Mabula C , Chipili G, Heimburger D.C, Bernard G.R. Validation of a Clinical Risk Score and Performance of Urine LAM Test for Detecting Tuberculosis Bacteraemia in HIV-Positive Patients with Severe Sepsis. (In publication, 2014).
14. Gao J, Zheng P, Fu H. Prevalence of TB/HIV Co-Infection in Countries except China: A Systematic Review and Meta-Analysis. *PLoS ONE* 8(5): e64915. doi:10.1371/journal.pone.0064915.
15. Sumaili EK, Cohen EP, Zinga CV, Krzesinski JM, Pakasa NM, Nseka NM. High prevalence of undiagnosed Chronic Kidney Disease among at-risk population in Kinshasa, the Democratic Republic of Congo. *BMC Nephrology* 2009, 10:18 http://www.biomedcentral.com/1471-2369/10/18.
16. Wu VC, Wang CY, Shiao CC, Chang CH, Huang HY, Huang TM, *et al*. Increased Risk of Active Tuberculosis following Acute Kidney Injury: A Nationwide, Population-Based Study. *PLoS ONE*; 2013 8(7): e69556. doi:10.1371/journal.pone.0069556.
17. Yang Wen-fang, Han Fei, Zhang Xiao-hui, Zhang Ping, Chen Jiang-hua. Extra-pulmonary Tuberculosis Infection in the Dialysis Patients with End stage Renal Diseases: Case Reports and Literature Review. *Journal of Zhejiang University-Science B (Biomed & Biotechnol)* 2013 14(1):76-82.
18. Daher EdeF, da Silva Junior GB, Guarda˜o Barros EJ. Review: Renal Tuberculosis in the Modern Era. *Am. J. Trop. Med. Hyg.*, 2013, 88(1), 54–64 doi:10.4269/ajtmh.2013.12-0413.
19. Daher Ede F, Silva Junior GB, Damasceno RT, Santos GM, Corsino GA, Silva SL, Gutie´ rrez-Adrianze´n OA. End-stage Renal Disease due to Delayed Diagnosis of Renal Tuberculosis: A Fatal Case Report. *Brazilian Journal of Infectious Diseases*; 2007; 11: 169–171.
20. Moore DAJ, Lightstone L, Javid B, Friedland JS. High Rates of Tuberculosis in End-Stage Renal Failure: The Impact of International Migration. *Emerging Infectious Diseases,* 2002; 8(1).
21. Lawn SD, Kerkhoff AD, Vogt M, Wood R. HIV-associated Tuberculosis: Relationship between Disease Severity and the Sensitivity of new Sputum-based and Urine-based Diagnostic Assays. http://www.biomedcentral.com/1741-7015/11/231.
22. Peter JG, Zijenah LS, Chanda D, Clowes P, Lesosky M, Lombard CJ, Kadzirange G, Bandason T, Chansa A, Liusha N, Mangu C, Mtafya B, Msila H, Mtafya B, Rachow A, Hoelscher M, Mwaba P, Theron G, Dheda K. Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial. *The Lancet*, 2016, 387 (10024): 1187–1197,. http://dx.doi.org/10.1016/S0140-6736(15)01092-2.

23. Peter JG, Theron G, Muchinga TE, Govender U, Dheda K. The Diagnostic Accuracy of Urine-Based Xpert MTB/RIF in HIV-Infected Hospitalized Patients Who Are Smear-Negative or Sputum Scarce. *PLoS ONE*; 2012, 7(7): e39966. doi:10.1371/journal.pone.0039966.
24. Oliveira JL, Silva Junior GB, Daher EF. Tuberculosis Associated Chronic Kidney Disease. *American Journal of Tropical Medicine and Hygiene*. 84: 843–844.
25. Dobler CC, Mc Donald SP, Marks GB. Risk of tuberculosis in dialysis patients: A nationwide cohort study. *PLoS ONE*; 2011, 6 (12): e29563. Doi.10.1371/journal pone. 0029563.
26. World Health Organization: Global tuberculosis control. Bulletin of the World Health Organization. Past Issues. 2010, 88: 1-80. http://www.who.int/entity/bulletin/volumes/88/en/.
27. The Global Fund to fight AIDS, Tuberculosis and Malaria. Programme Scorecard, Zambia HIV/AIDS, 2013.
28. Peter JG, Theron G, van Zyl-Smit R, Haripersad A, Mottay L, Kraus S, Binder A, Meldau R, Hardy A, Dheda K. Diagnostic Accuracy of a Urine Lipoarabinomannan strip-test for TB Detection in HIV-infected Hospitalised Patients. *European Respiratory Journal.* 2012; 40(5):1211-20. Doi: 10.1183/09031936.00201711.
29. Guidelines for the prevention and management of Mycobacterium Tuberculosis Infection and Disease in Adult Patients with Chronic kidney Disease: http://www.renal.org/docs/default-source/guidelines-resources/BTS_TB_guidelines_in_renal_disease.pdf?sfvrsn=0.
30. Unsal A, Ahbap E, Basturk T, Koc Y, Sakaci T, Arar AS, Sevinc HKM: Tuberculosis in Dialysis Patients: A Nine – year Retrospective Analysis. http://www.jidc.org/index.php/journal/article/viewFile/23492998/841.
31. Sing Leung Lui, Sydney Tang, Fu Keung Li, Bo Ying Choy, Tak Mao Chan, Wai Kei Lo and Kar Neng Lai. Tuberculosis Infection in Chinese Patients Undergoing Continuous Ambulatory Peritoneal Dialysis. *American Journal of Kidney Diseases*, 2001: 38(5); 1055-1060.
32. Ahmed AT, Karter AJ. Tuberculosis in California Dialysis Patients. *Int J Tuberc Lung Dis* 2004; 8(3):341–345.
33. Hillemann D, Rüsch-Gerdes S, Boehme C, Richter E. Rapid Molecular Detection of Extra pulmonary Tuberculosis by the Automated GeneXpert MTB/RIF System. *Journal of Clinical Microbiology*. 2011, 49(4):1202. DOI 10.1128/JCM.02268-10.
34. Green C, Huggett JF, Talbot E, Mwaba P, Reither K, Zumla AI. Rapid Diagnosis of Tuberculosis through the Detection of Mycobacterial DNA in Urine by Nucleic Acid Amplification Methods. *Lancet Infect Dis*. 2009 Aug; 9(8):505-11. doi: 10.1016/S1473-3099(09)70149-5.
35. Shigidi M, Farouk N, Abulikailik RI, Alsir RT, Abu-Aisha H. Active Tuberculous Infection among Adult Sudanese Patients on Long Term Peritoneal Dialysis. *Arab Journal of Nephrology and Transplantation*. 2012 Sep;5(3):135-40.
36. Singh J, Sankar MM, Kumar S, Gopinath K, Singh N, Mani K, Singh S. Incidence and Prevalence of Tuberculosis among Household Contacts of Pulmonary Tuberculosis Patients in a Peri-Urban Population of South Delhi, India, *PLoS ONE* 2013; 8(7).
37. National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. *Am J Kidney Dis* 2012; 60(5):850-886.
38. Zeka AN, Tasbakan S, Cavusoglu C: Evaluation of the GeneXpert MTB/RIF Assay for Rapid Diagnosis of Tuberculosis and Detection of Rifampin Resistance in Pulmonary and Extra pulmonary Specimens. *Journal of Clinical Microbiology*. 2011; 49(12):4138. DOI: 10.1128/JCM.05434-11.