academicJournals

Vol. 6(3), pp. 53-59, March, 2014
DOI: 10.5897/JAHR2013.0283
ISSN 2141-2359

http://www.academicjournals.org/JAHR

Journal of AIDS and HIV Research

Full Length Research Paper

Prevalence and utility of dipstick proteinuria in predicting renal insufficiency in treatment naive human immunodeficiency virus (HIV) infected Africans

Olufunmilayo A. Lesi[1]*, Oluwatosin O. Bamidele [2], Christiana O. Amira[1], Charles O. Okany [3] and Alani S. Akanmu[4]

[1]Department of Medicine, Gastroenterology and Hepatology Unit, College of Medicine, University of Lagos P.M.B 12003, Idi-Araba, Lagos, Nigeria.
[2]Department of Epidemiology, School of Public Health, University of Texas Health, Houston, USA.
[3]College of Medicine, University of Lagos (CMUL), Lagos University Teaching Hospital, AIDS Prevention Initiative, Nigeria.
[4]Department of Haematology and Blood transfusion, Lagos University Teaching Hospital, Nigeria.

Received 1 December, 2013; Accepted 27 January, 2014

This study investigated the prevalence and associated factors of proteinuria in treatment naive human immunodeficiency virus (HIV) infected individuals. It also evaluated utility of dipstick urinalysis for the detection of impaired renal function. Two hundred (200) HIV seropositive patients and 72 HIV seronegative subjects were evaluated and tested for proteinuria using dipstick reagent strips. Serum urea and creatinine, haemoglobin, CD4+ T-lymphocyte (CD4+ cell) count and HIV RNA viral load were performed. Cockroft-Gault (CG) equation was used to estimate glomerular filtration rate (eGFR). Dipstick proteinuria was detected in 85 (43%) of the seropositive population compared to 6 (8.3%) in HIV seronegative subjects (odds ratio (OR) 8.3, p < 0.001). One hundred (50%) HIV positive subjects had CD4+ cell < 200 cells at baseline and 63 (31%) had impaired renal function. Although dipstick proteinuria was associated with male gender, severe anaemia, elevated serum urea and creatinine, significantly lower CD4+ cell count and impaired renal function, only the inverse association of dipstick proteinuria and CD4+ cell count remained on logistic regression (OR 0.4, 95% CI: 1.6 to 5.2). We have documented the high prevalence of proteinuria in HIV subjects prior to anti retroviral therapy (ART), and the important role of proteinuria as a significant risk factor for severe immunosuppression. We also show that dipstick proteinuria is not sensitive for the identification of impaired renal function, but has moderate utility in excluding renal insufficiency in subjects negative for proteinuria on dipstick testing.

Key words: Proteinuria, estimated glomerular filtration rate, immunosuppression.

INTRODUCTION

Worldwide, chronic kidney disease (CKD) has become increasingly important as a complication of both HIV infection and anti-retroviral therapy, and is associated with significant morbidity, mortality and progression of HIV infection to AIDS (Lozano et al., 2012; Estrella and Fine, 2010). Reports from prospective studies in developed

*Corresponding author. E-mail: oalesi@cmul.edu.ng, fulesi2@yahoo.com.

developed countries suggest a marked racial predilection of human immunodeficiency virus associated nephropathy (HIVAN) for both black and Hispanic subjects (Estrella and Fine, 2010; Bickel et al., 2013; Ibrahim et al., 2012). This is a major concern as sub-Saharan African, a predominantly black population accounts for over 23 million people living with HIV who constitutes 69% of people living with HIV globally (UNAIDS, 2013).

Investigators from Congo, Ghana and various parts of Africa corroborate the importance of chronic kidney disease in HIV infected black Africans (Sarfo et al., 2013; Wools-Kaloustain et al., 2007; Franey et al., 2009; Longo et al., 2012). Histopathological evidence of glomerulosclerosis has been documented in a high proportion of HIV infected Nigerian patients with proteinuria and chronic kidney disease (Emem et al., 2008; Okafor et al., 2011). There is a need to identify subjects at risk of developing chronic kidney disease to ensure provision of early preventive measures to delay the onset and progression of renal dysfunction.

The current international guidelines recommend the determination of baseline renal function such as serum urea and creatinine, and evaluation of glomerular filtration rates prior to initiation of anti-retroviral therapy (ART) for the early identification of renal impairment and to guide selection of therapy (Gupta et al., 2005). These tests are however not readily available in resource limited areas and rural primary health centres in many parts of sub-Saharan Africa. As such, initiation of ART is often done without prior baseline renal function tests. The implication of this practice is the delayed identification of patients with pre-existing renal impairment who may require more intensive monitoring or may require alternative therapy.

Proteinuria, an early marker of renal disease, is often associated with chronic kidney disease and has been consistently documented in HIV associated nephropathy (HIVAN). Detection of proteinuria may therefore serve as a guide and surrogate marker for the identification of renal impairment in HIV infected populations. Point of care testing using urine dipstick is an efficient and inexpensive screening tool. It is relatively sensitive to detect proteinuria and can also measure the urine protein concentration semi-quantitatively. The aims of current study is thus set out to determine the prevalence of proteinuria in subjects with HIV infection using urine dipstick and explore the association of proteinuria with renal function tests and other HIV related factors.

METHODOLOGY

Study design

This prospective observational cross-sectional study was carried out at the HIV/AIDS treatment clinic of a tertiary care university hospital in Lagos, Nigeria, between July and December, 2011. The treatment centre is part of the 'President's Emergency Plan For AIDS Relief (PEPFAR)' supported sites, and provides general care of HIV/AIDS patients, including free ART.

Two hundred and seven consecutive ART naïve patients presenting for HIV care constituted the study population. Seven had incomplete data and were omitted from further evaluation. 72 random HIV sero-negative blood donors were recruited to serve as the control group for the evaluation of proteinuria. The study subjects were eligible for enrolment if they were at least 18 years of age and provided informed consent. Exclusion criteria were patients with pre-diagnosed hypertension, diabetes mellitus, tuberculosis, pregnancy, chronic kidney disease, liver disease, cardiac disease or any acute disease state within the past week. HIV status of all patients were confirmed by Western blot testing.

Fresh urine samples were obtained from all patients and tested for proteinuria using dipstick reagent strips (Atlas Medical, UK). Proteinuria was defined by the presence of ≥ 1+ protein on dipstick. The severity of proteinuria was classified according to the manufacturer's instruction (1+ mild proteinuria of > 30 mg/dl/day, 2+ is moderate proteinuria of > 100 mg/dl/day, and 3+ is severe proteinuria > 300 mg/dl/day). Subjects with dipstick testing < 30 mg/dl showed no colour change on dipstick and were considered negative for proteinuria.

Blood samples were also taken from the HIV seropositive subjects for haemoglobin (Autohaematology analyser, Mindray medical, China). Severe anaemia was defined as haemoglobin (Hb) values below 10 g/dl (Beutler and Waalen, 2005). Serum urea and creatinine were performed using the Roche Hitachi automatic analyser. Normal values for Urea and Creatinine were 2.6 to 7.9 µmol/L and 50 to 140 µmol/L, respectively as determined by the laboratory standards. The creatinine clearance was calculated using the Cockcroft-Gault formula (CGF) as an estimated Glomerular Filtration Rate (eGFR) (Cockcroft and Gault, 1979). This eGFR is recommended by the Infectious Disease Society of America (IDSA) guideline as the basis for dose modification of therapy in HIV subjects (Gupta et al., 2005). The estimated GFR of < 60 mls/min^{-1}. 72 m^2 was classified as renal impairment. Severity of immunosuppression was determined using the CD4+ T-lymphocyte count (Partec Cyflow, Germany). HIV RNA Viral load evaluation was done using the Roche Amplicor version 1.5.

Data was analyzed with statistical package for social sciences (SPSS) Version 20 (SPSS Inc, Chicago, IL USA). Proportions were expressed as percentages. Categorical variables were compared using chi-square with statistical significance level set at $P < 0.05$. Variables associated with proteinuria, with a p-value < 0.05 in univariate analysis were included in a multivariable analysis. The sensitivity and specificity of proteinuria was calculated using eGFR as the gold standard for renal function.

RESULTS

A total of 272 patients were screened for proteinuria, of which 200 were HIV positive subjects undergoing pre-treatment evaluation and 72 were randomly selected HIV negative blood donors. Overall, there were 180 females and 92 males. The mean age ± SD of the HIV positive subjects was 36.7 ± 9.14 years and was similar to the mean age of the 72 HIV uninfected blood donors. The prevalence of proteinuria was 42.5% in HIV positive subjects compared to 8.3% in HIV negative subjects (OR = 8.3, $p < 0.001$). The demographic characteristics of the study subjects based on HIV status are shown in Table 1.

Baseline laboratory characteristics of HIV seropositive subjects

Mild proteinuria with dipstick 1+ was common and seen in

Table 1. Demographic characteristics of subjects based on HIV status.

Patient characteristic	HIV seropositive subjects	HIV seronegative subjects	P-value
	N = 200 (%)	N = 72 (%)	
Mean Age (SD)	36.73 (9.14)	36.39 (10.7)	
Age group			
< 29	38 (19)	5(6.9)	0.2
30-39	104 (52)	33(45.8)	
40-49	36 (18)	22(30.6)	
>50	22 (11)	12(16.7)	
Sex			
Female	133 (66.5)	47 (65.3)	
Male	67 (33.5)	25 (34.7)	0.9
M/F rate	2:1	1.8:1	
Proteinuria			
No	115 (57.5)	66 (91.7)	<0.001* , *OR=8
Yes	85 (42.5)	6 (8.3)	

*OR: odds ratio.

Table 2. Baseline laboratory characteristics of HIV positive subjects.

Laboratory parameter	HIV seropositive subjects (n = 200)
Median Urea (IQR)	3.5 (2.8-4.6) mmol/l
Median serum creatinine (IQR)	100.6 (86.7-119.6) umol/l
Median hemoglobin (IQR)	10.5 (9-11.8) g/dl
Median CD4+ cells IQR	199 (87-344) ul
<200	100 (50%)
201-350	53 (25.6%)
351-499	31 (14.9%)
>500	17 (8.5%)
eGFR median (IQR)	67.8 (55.8-78) ml/min/1.73m^2
GFR <60 mls/min/1.72m^2	63 (31%)
Proteinuria present (all cases)	85 (42.5%)
+1 (>30 mg/dl)	56 (66%)
+2 (>100 mg/dl)	21 (24.7%)
+3 (>300 mg/dl)	8 (9.4%)
Plasma HIV RNA median (IQR)	69289 (4407-241,729) copies/ml
>50,000 copies/ml	110 (55%)

56 (65.8%) of the HIV subjects with proteinuria. Moderate and severe proteinuria with dipstick 2+ and 3+ were noted in 21 (24.7%) and 8 (9.4%), respectively. The baseline laboratory values for haemoglobin concentration, serum urea and creatinine are shown in Table 2. One hundred (50%) of the population had marked immunosuppression with CD4+ cells less than 200, median HIV RNA was 69,289 copies/ml. 63 (31.5%) subjects had renal insufficiency with eGFR < 60 mls/min/1.72 m^2.

Table 3. Relationship between proteinuria and baseline characteristic.

Patient characteristic	Univariate analysis			Multivariate Analysis	
	All proteinuria (≥1+)	Nil proteinuria	P value	OR (95% CI)	P value
	n=85, (%)	N=115, (%)			
Gender					
Female	48 (36.1)	85 (63.9)	0.007	1.9 (0.9-3.7)	0.053
Male	37 (55.2)	30 (44.8)			
Urea > ULN	9 (10.7)	2 (1.8)	0.007	3 (0.5-18)	0.3
Serum. Creatinine > ULN	17 (20)	8 (7.0)	0.005	2.1 (0.6-6.5)	0.2
HB <10g/dl	43 (50.6)	40 (34.8)	0.018	0.6 (0.3-1.2)	0.23
CD4+ cells (ul/ml) < 200 cells/mL	55 (64.7)	45 (39.1)	0.0002	0.4 (0.2-0.7)	*0.0058
eGFR < 60mls/min/1.72m^2	35 (41.2)	28 (24.3)	0.008	0.6 (0.3-1.4)	0.29
Plasma HIV RNA > 50,000 copies/ml (n,%)	53 (62.4)	57 (49.6)	0.048	-	-

Urea upper limit of normal (ULN- 7.9 umol/l), creatinine upper limit of normal (ULN-140 umol/l).

Factors associated with proteinuria

The factors found to be significantly associated with dipstick proteinuria on univariate analysis were male gender (p = 0.007), urea (p = 0.007), serum creatinine (p = 0.005), Hb < 10 g/dl (p = 0.018), and CD4+ cells < 200 (p = 0002) as shown in Table 2. Subjects with proteinuria were significantly more likely to have renal insufficiency than subjects without proteinuria, 35 of 85 (41.2%) and 28 of 115 (24.3%), respectively (p = 0.008). Nevertheless, most (50 of 85, 58%) of the subjects with proteinuria had apparently normal eGFR. Overall, 35 (17.5%) of the HIV infected subjects in this study had both proteinuria and renal insufficiency. In the multivariate regression analysis, only the inverse association between CD4+ cell and proteinuria remained significant (OR = 0.4, p = 0.006).

As shown in Table 3, the sensitivity and specificity of dipstick proteinuria to predict reduced eGFR was 55.5 and 63%, respectively. Significant proteinuria comprising of moderate (> 2+) and severe (> 3+) dipstick proteinuria was associated with a sensitivity and specificity of 19 and 88%, respectively. The negative predictive value of dipstick proteinuria to identify renal insufficiency was 75.2%.

DISCUSSION

The prevalence of dipstick proteinuria was 42.5% in our study population of HIV seropositive patients undergoing pre ART treatment evaluation. These subjects had a significant 8-fold higher incidence of dipstick proteinuria compared to the HIV seronegative blood donors. This high prevalence of baseline proteinuria in this population is consistent with reports from other parts of sub Saharan Africa, and ranges from 26.1% in Western Kenya, 38 to 48% in Nigeria and 15% in Congo (Sarfo et al., 2013; Wools-Kaloustain et al., 2007; Longo et al., 2012; Okafor et al., 2011). Studies that include antiretroviral medicines (ARV) consistently reported lower prevalence of proteinuria in their study populations. Other reasons for these differences in the prevalence of proteinuria are related to the clinical and immunological stage of patient at presentation and methodology of protein evaluation.

The lower prevalence of dipstick proteinuria in the HIV seronegative study subjects is consistent with reports from normal subjects (Jotwani et al., 2012). In these populations, proteinuria is mostly physiological and transient, and caused by factors such as dehydration, emotional stress, fever, intense activity or inflammation that have minimal implications on morbidity and mortality. In longitudinal studies, repeat dipstick testing is done to identify subjects with persistent proteinuria at higher risk for chronic kidney disease. In the current study, we excluded individuals who were known have acute illness other than related to HIV seropositivity. We also excluded patients with risk factors for chronic kidney disease such as diabetes and hypertension, and pregnancy. However, we did not explore the role of emotional stress, dehydration or inflammation caused by asymptomatic urinary tract infection to exclude subjects with benign proteinuria.

Dipstick proteinuria and renal Insufficiency

Evidence from prospective longitudinal studies suggests that in HIV-positive individuals, the combination of proteinuria and renal insufficiency are associated with faster progression to AIDS and death (Bickel et al., 2013; Beutler, 2005). In our study, 35 (17.5%) of the overall HIV infected study subjects had both proteinuria and renal

Table 4. Sensitivity and Specificity of dipstick proteinuria to identify renal insufficiency in HIV positive study subjects.

Parameter	All proteinuria ≥1+	Significant proteinuria ≥2+
Sensitivity	0.55 (0.4-0.7)	0.19 (0.1-0.3)
Specificity	0.63 (0.5-0.7)	0.87 (0.8-0.9)
PPV	0.41 (0.3-0.5)	0.41 (0.25-0.61)
NPV	0.75 (0.6-0.8)	0.70 (0.6-0.7)

PPV - positive predictive value, NPV - Negative predictive value.

insufficiency. This subgroup thus have a higher risk for chronic kidney disease (CKD) and drug toxicities, and require more intensive monitoring for appropriate dosage adjustment of ART such as tenofovir.

Many HIV clinicians commonly regard the presence of proteinuria to be an early marker of HIV associated nephropathy (HIVAN). Consistent with this observation, renal insufficiency occurred more commonly in subjects with proteinuria. However, over half (58%) of our study subjects with dipstick proteinuria had no evidence of renal insufficiency and had a normal eGFR. The role of dehydration, stress and asymptomatic infections that cause benign proteinuria even in normal populations was not pursued in this study but require further evaluation. Additionally, the presence of renal tubulo-interstitial disease that characteristically causes minimal or no proteinuria despite renal insufficiency requires further evaluation (Bickel et al., 2013).

It is notable that the sensitivity and specificity of urine dipstick to identify renal insufficiency were poor (Table 4). However, the specificity increased in subjects with moderate to severe proteinuria. Our finding corroborate the report of Gupta et al. (2009) and Siedner et al. (2008), and suggests that there are variably other causes of proteinuria aside from renal dysfunction (Drumheller et al., 2012). The role of other tests like urinary protein-creatinine ratios (uPCR) and association with renal insufficiency require further evaluation. It is important that all patients with significant proteinuria should have further examination of urinary sediment and renal function tests along with nephrology consultation.

Proteinuria and immunosuppression

Although proteinuria was associated with various factors including male gender, elevated levels of urea and creatinine, severe anaemia, low CD4+ cells and reduced creatinine clearance, only the association of proteinuria with CD4+ count remained significant on multivariate analysis (Table 3). Our study therefore suggests that proteinuria is an independent risk factor for immunosuppression and possibly disease severity in HIV. The significant inverse association of proteinuria with CD4+ cell count identified in our study corroborates studies done both locally and internationally (Gupta, 2009; Janakiraman et al., 2008). Gupta et al. (2009) suggested that proteinuria may be a surrogate measurement of greater systemic inflammation in patients at an advanced stage of immunosuppression. Consistent with this observation, severe CD4+ cell depletion has been associated with microbial translocation from the gut or opportunistic infections, some of which will affect the urinary tract leading to proteinuria independent of any HIV associated nephropathy (Brenchley et al., 2006). Resolution of proteinuria and immune restitution on commencement of ARV supports the role of systemic inflammation in the aetiology of proteinuria (Kalayjian et al., 2008). In this African population with severe immunosuppression, it is plausible that the high prevalence of dipstick proteinuria seen in over one-third of patients prior to initiation of ART may be largely due to systemic inflammation associated with low CD4+ cell counts. Longitudinal studies post ARV commencement and the association of proteinuria and immune activation needs further evaluation.

We identified some limitations to our study. Although urine dipsticks are considered effective screening tools for proteinuria, they may be less sensitive than newer tests such as uPCR. False negative results may occur with dilute urine or with proteinuria consisting primarily of proteins other than albumin as dipsticks detect albumin only. Similarly, false positive tests may be seen in the presence of severe haematuria. The Cockcroft-Gault formula has been used commonly in clinical practice and is widely used to adjust drug dosing for kidney function. However, serum creatinine-based estimated GFR among HIV-infected persons may be particularly biased due to associated altered metabolism, malnutrition and body mass abnormalities.

Conclusion

Our study has shown that prior to initiation of ART, HIV infected subjects have significantly more proteinuria than seronegative subjects. We have documented the important role of proteinuria as a significant and independent

risk factor for severe immunosuppression. As a screening tool, dipstick proteinuria is not sufficiently sensitive or specific to identify renal insufficiency in HIV positive individuals. Nontheless, it is useful in identifying renal insufficiency in subjects with moderate to severe proteinuria, and in excluding renal insufficiency in subjects negative for dipstick proteinuria. In the absence of better screening tools in resource poor and rural centres, all HIV positive patients should have dipstick proteinuria in the phase of pre-treatment evaluation and periodically during follow up to identify subjects with significant or persistent proteinuria. This will encourage early detection, prompt intervention and possibly reversal of the renal impairment. Detailed renal investigation and nephrology review is important for all subjects with significant or persistent proteinuria.

Conflict of Interests

The author(s) have not declared any conflict of interests.

REFERENCES

Beutler E, Waalen J (2005). The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? Blood 107 (5):1747-50

Bickel M, Marben W, Betz C, Khaykin P, Stephan C, Gute P, Haberl A, Knecht G, Wolf T, Brodt HR, Geiger H, Herrmann E, Jung O (2013). End-stage chronic kidney disease and dialysis in HIV-positive patients: observations from a long-term cohort study with a follow-up of 22 years. HIV Med. 14(3):127-35.

Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, Kazzaz Z, Bornstein E, Lambotte OL, Altmann D, Blazar BR, Rodriguez B, Teixeira-Johnson L, Landay A, Martin JN, Hecht FM, Picker LJ, Lederman MM, Deeks SG, Douek DC (2006). Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nature Med. 12:1365-71

Cockcroft DW, Gault MH (1976). Prediction of creatinine clearance from serum creatinine. Nephron 16;31–41.

Drumheller BC, McGrath M, Matsuura AC, Gaieski DF (2012). Point-of-care urine albumin:creatinine ratio is associated with outcome in emergency department patients with sepsis: a pilot study. Acad. Emerg. Med. 19(3):259-64.

Emem CP, Arogundade F, Sanusi A, Adelusola K, Wokoma F, Akinsola A (2008). Chronic kidney disease in HIV- seropositive patients in Nigeria: an assessment of prevalence, clinical features and risk factors. Nephrol. Dialysis Transpl. 23:741-746

Estrella ME, Fine DM (2010). Screening for Chronic Kidney Disease in HIV-Infected Patients. Advances in Chronic Kidney Dis. 17(1): 26-35.

Franey C, Knott D, Barnighausen T, Dedicoat M, Adam A, Lessells R, Newl ML, Cooke, GS (2009). Renal impairment in a rural African antiretroviral programme. BMC Infect. Dis. 9:143.

Gupta SK, Eustace JA, Winston JA, Boydstun II, Ahuja TS, Rodriguez RA, Tashima KT, Roland M, Franceschini N, Palella FJ, Lennox JL, Klotman PE, Nachman SA, Hall SD, Szczech LA (2005). Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin. Infect. Dis. 40(11):1559–1585.

Gupta SK, Komarow L, Gulick RM, Pollard RB, Robbins GK, Franceschini N, Szczech LA, Koletar SL, Kalayjian RC. (2009) Proteinuria, creatinine clearance, and immune activation in antiretroviral-naive HIV-infected subjects. J. Infect. Dis. 15;200(4);614-8.

Ibrahim F, Hamzah L, Jones R, Nitsch D, Sabin C, Post FA (2012). UK Collaborative HIV Cohort (CHIC)/CKD Study Group. Baseline kidney function as predictor of mortality and kidney disease progression in HIV-positive patients. Am. J. Kidney Dis. 60(4):539-47.

Janakiraman H, Abraham G, Matthew M, Kuruvilla S, Panikar V, Kumaraswamy SS, Seshan SV, Lesley N (2008) Correlation of CD4 counts with Chronic kidney disease in HIV Positive Patients. Saudi J. Kidney Dis. Transpl. 19(4):603-607

Jotwani V, Li Y, Grunfeld C, Choi AI, Shlipak MG (2012) Risk factors for ESRD in HIV-infected individuals: traditional and HIV-related factors. Am. J. Kidney Dis. 59(5): 628-35.

Kalayjian RC, Franceschini N, Gupta SK, Szczech LA, Mupere E, Bosch RJ, Smurzynski M, Albert JM (2008). Suppression of HIV-1 replication by antiretroviral therapy improves renal function in persons with low CD4 cell counts and chronic kidney disease. AIDS 22(4): 481-7

Longo AL, Lepira FB, Sumaili EK, Makulo JR, Mukumbi H, Bukabau JB, Mokoli VM (2012). Prevalence of low estimated glomerular filtration rate, proteinuria, and associated risk factors among HIV-infected black patients using Cockroft-Gault and modification of diet in chronic kidney disease study equations.K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification J. Acquir. Immune Defic. Syndr. 59(1):59-64.

Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA (2012) Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet.15:380(9859):2095-128.

Okafor UH, Unuigbe EI, Ojogwu LI, Oviasu E, Wokoma FS (2011). Chronic kidney disease in HIV infected patients at University of Benin Teaching Hospital in Nigeria. Afr. Health Sci. 11(Supplement1): S28 - S33

Sarfo FS, Keegan R, Appiah L, Shakoor S, Phillips R, Norman B, Hardy Y, Bedu-Addo G, Longstaff L, Chadwick DR. (2013) High prevalence of renal dysfunction and association with risk of death amongst HIV-infected Ghanaians. J. Infect. 67(1):43-50

Siedner MJ, Atta MG, Lucas GM, Perazella MA, Fine DM (2008). Poor validity ofurine dipstick as a screening tool for proteinuria in HIV-positive patients J. Acquir. Immune Defic. Syndr. 47(2):261-263.

UNAIDS (2012). Report on the Global AIDS Epidemic 2010. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_unaids_global_report_2012_with_annexes_en.pdf. Retrieved 26 Nov 2013 .

Wools-Kaloustain K, Gupta SK, Muloma E, Owino-ong W, Sidle J, Aubrey RW, Shen J, Kipruto K, Zwickl BE, Goldman M (2007). Chronic kidney disease in an antiretroviral-naïve HIV-infection outpatient population in Western Kenya. Nephrology Dialysis Transplantation 22(8):2208-2212.