Urinary Screening Abnormalities in Antiretroviral-naive HIV-infected Outpatients and Implications for Management—A Single-center Study in South Africa

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Few urinary screening studies have been performed to determine the incidence of urinary abnormalities in antiretroviral therapy-naive, HIV-infected outpatients. From published data, the incidence appears to be high, particularly when compared with populations outside sub-Saharan Africa. In South Africa, urinary screening in antiretroviral therapy clinics is not routinely practiced. The aim of this descriptive study was to screen antiretroviral therapy-naive, HIV-infected outpatients attending the HIV clinic for urinary abnormalities, namely leukocyturia, microscopic hematuria, and microalbuminuria/proteinuria. This study showed that 84% of the screened population had AIDS (CD4 count <200 cells/mm^3), and the incidence of abnormalities on urinary dipstick testing was high: 30% had leukocyturia, 33% had microscopic hematuria, and 44% had microalbuminuria/proteinuria. In patients with leukocyturia, an infective organism was cultured in only 29.1% of cases, predominantly *Escherichia coli* (70%) with sterile leukocyturia comprising the remainder. There may be an association with tuberculosis (TB) or sexually transmitted infections (STI) in the sterile leucocyturia group, but this remains to be confirmed. In those with a culture positive result the most common organism was E.Coli (70%), which exhibited 90% resistance to cotrimoxazole, demonstrating that cotrimoxazole prophylaxis is not effective to prevent urinary tract infection in this group. On the basis of these findings, it has been proposed that urinary screening be considered standard of care in HIV clinics in South Africa. An algorithm has been proposed for use in antiretroviral therapy clinics in South Africa to guide clinicians regarding the cost-effective management of urinary dipstick abnormalities. (*Ethn Dis*. 2009;19[Suppl 1]:S1-80-S1-85)

Key Words: HIV, Antiretroviral Therapy, Urinary Screening, Proteinuria, Leukocyturia, Microscopic Hematuria, Kidney Disease

INTRODUCTION

Few data exist on urinary screening of antiretroviral (ART)-naive, HIV-infected patients for early kidney disease, especially in sub-Saharan Africa. Statistics in the United States estimate the incidence of HIV-associated nephropathy to be 3.5%–12.0%.[1] If this were to be extrapolated to sub-Saharan Africa, with an estimated 22.5 million people infected with HIV, 788,000–2.7 million people would be expected to have HIV-associated nephropathy. Given the current paucity of resources available for managing end-stage renal disease in this region, the emphasis on early detection and treatment of HIV-associated chronic kidney disease (HIVCKD) must assume prime importance. A few studies have revealed that when screening for proteinuria in HIV infection, additional abnormalities such as leukocyturia and microscopic hematuria, have been found.[2–7] The relevance of these findings has not been investigated further, nor is the pathogenesis understood. Because of the paucity of data in sub-Saharan African countries, we undertook a urinary screening study in ART-naive, HIV-infected outpatients attending the HIV clinic at Johannesburg Hospital, South Africa. The aim was to detect early kidney disease in this population by screening for proteinuria (including microalbuminuria). It soon became apparent that additional abnormalities (leukocyturia/microscopic hematuria) were prevalent. Because of the potential relevance of these findings, they have been included in this description of urinary abnormalities in this population.

METHODS

Ethics approval was obtained from the Human Research Ethics Committee, University of the Witwatersrand, clearance certificate number M040929. All specimens that required laboratory analysis were processed by the Johannesburg Hospital laboratory, National Health Laboratory Services. The study was conducted at the HIV outpatient clinic at Johannesburg Hospital from February through December 2005. The study sample was recruited from a pool of patients that were referred from the Johannesburg Hospital inpatient service or from surrounding healthcare facilities. Initial urinary screening was performed on new patients attending the HIV outpatient clinic who were not yet on ART. Demographic data (age, sex, race) and clinical data (CD4 count, viral load, weight) were recorded when possible at the screening visit.

The screening was initially intended only to detect of proteinuria, but because of the high prevalence of additional abnormalities, these data have been included. Since the aim of this screening study was initially only to detect proteinuria, a clean-catch technique was not advised for urine collection. It was not part of the study protocol to ask about the presence of

hematuria, dysuria, urinary frequency/urgency, the presence of sexually transmitted infections (STIs) or menstruation. The manufacturer states that a test strip can be positive for 3 days before and after menstruation in women. Women were not asked about this 3-day interval. Urine specimens were held at room temperature for <2 hours before testing.

Urine dipstick tests were performed with Combur 9 test strips (Roche Diagnostics GmbH, Mannheim, Germany). These test strips detect leukocytes, nitrites, pH, protein, glucose, ketones, urobilinogen, bilirubin, intact erythrocytes (blood), hemoglobin, and myoglobin. Both hemoglobin and myoglobin are catalyzed by the same reaction and are therefore not differentiated from one another on the test strip. The test strips were stored at room temperature, per manufacturer recommendations. If the test strip was positive for nitrites or leukocytes, the urine specimen was sent for microscopy, culture, and sensitivity (MCS). If the test strip was positive for protein, the specimen was sent for quantification as a spot protein: creatinine ratio (g/mmol) (turbidimetric method with benzathonium chloride, Cobas, Roche Diagnostics GmbH). If the test strip was negative for protein, the urine was screened for microalbuminuria. The microalbumin test strips used were Micral-Test (Roche Diagnostics GmbH). The test strips were stored at 4°C per manufacturer recommendations. If the test strip for microalbumin was positive, it was sent for quantification as a spot microalbumin-to-creatinine ratio (mg/mmol) (immunoturbidimetric method with anti-albumin antibodies, Cobas, Roche Diagnostics GmbH). All test strips were used before the expiration date.

Statistics

Data were analyzed by using Microsoft Office Excel 2007 and Statsoft, Statistica 8 (licensed to University of the Witwatersrand). For analysis of the microalbuminuria dataset with respect to correlation with patient weights, the data were exported to the statistical package Stata version 8.0 (StataCorp LP, College Station, Texas) and analyzed at the Biostatistics Unit, Medical Research Unit of South Africa.

RESULTS

Demographic data

In total, 585 patients were screened. Data were incomplete in 7 patients, leaving 578 patients for inclusion. The racial representation was as follows: 560 Black (97.0%), 10 mixed ethnicity (1.7%), 6 White (1.0%), and 2 unknown (0.3%); 217 (37.5%) were men, and 361 (62.5%) were women. The mean age was 37 years (range 16–70 years), and mean CD4 count was 130 cells/mm^3 (range 1–828 cells/mm^3). On first presentation to the clinic, 482 of 576 patients (84%) were classified as having AIDS (CD4 count <200 cells/mm^3).

Urinary Dipstick Abnormalities

Leukocytes

A total of 175 (30.3%) samples were positive for leukocyturia. All positive specimens were sent to the laboratory for MCS. Of the specimens sent, results for 175 are available. Some specimens were not received at the laboratory and others were not processed because of laboratory error (spillage). Initially, we assumed that most cases of leukocyturia were caused by urinary tract infection (UTI), but only 29.1% of specimens cultured isolated an organism; 38.3% of specimens were culture-negative, and 32.6% showed mixed organisms of doubtful relevance. In the group with mixed organisms, 6 had tuberculosis (TB), 1 had a high-grade cervical squamous intraepithelial lesion on Papanicolau test, and 1 was on chemotherapy for Kaposi sarcoma. In the group with culture-negative leukocytosis, 8 had sexually transmitted infections (STIs), including 4 cases of syphilis, and 6 had TB. None of the urine samples from these 2 groups were sent for TB culture; the diagnosis of TB was made on the basis of findings outside of the urogenital tract. Of the 12 cases with mycobacterial infection, 4 were sputum-positive (1 with multiple-drug-resistant TB), 3 had been started on TB treatment before referral to the clinic, and 1 each had *Mycobacterium avium* complex on blood culture, tuberculous lymphadenitis, and central nervous system tuberculoma. In the group with culture confirmed UTI, 70% were caused by *Escherichia coli*, and 90% of isolates were resistant to cotrimoxazole. Of note, 3 cases of extended-spectrum β-lactamase (ESBL)-producing organisms were detected, and 2 of these patients had recently been admitted to a hospital, which was the most likely source of infection.

Erythrocytes (Microscopic Hematuria)

Microscopic hematuria was found in the urine of 191 (33.1%) of the 578 patients; 55 were men and 136 were women. The menstrual status was unknown in 79% of women screened. Because it was not considered within the scope of this study to investigate causes of microscopic hamaturia, no further investigations were performed, in particular, urine microscopy for dysmorphic red cells/red cell casts and urine culture for fungi, viruses, fastidious organisms, and tuberculosis. It would be considered acceptable for microscopic hematuria to be present in confirmed cases of UTI (22% of specimens), but it is noteworthy that in the mixed-organism and culture-negative groups, the prevalence of hematuria was 10.9% and 20.4%, respectively.

Proteinuria (Including Microalbuminuria)

Of the 578 patients, 253 (43.7%) had urine dipsticks positive for proteinuria. Of the 253, 193 (76.3%) were confirmed by the laboratory. The following definitions of proteinuria were used according to local laboratory

reference ranges: microalbuminuria, microalbumin-to-creatinine ratio 3.4–33.9 mg/mmol independent of sex; overt proteinuria, protein-to-creatinine ratio of 0.03–0.3 g/mmol; nephritic-range proteinuria, protein-to-creatinine ratio >0.3 g/mmol. After applying these definitions 158 of 193 specimens were included in the dataset; 34 specimens were excluded from analysis as their levels of microalbumin were too low for inclusion in the study. The microalbuminuric group was the largest, with overt and nephrotic-range proteinuria forming progressively smaller proportions: microalbuminuria, 107 (18.5%); overt proteinuria, 37 (6.4%); nephrotic-range proteinuria, 14 (2.4%).

In the microalbuminuric group, the prevalence of co-morbid disease was high. Infection was present in 52 of 107 (49%) patients with TB (50%), UTI (31%), and STI (7%) in decreasing frequency. Other co-morbidities were cardiovascular disease (14%), diabetes mellitus (4.6%), and malignancy (1.8%). When co-morbid disease was treated appropriately in the microalbuminuric group, microalbuminuria resolved in 17% of patients. Unfortunately the proportion lost to followup was high (26%). In the group with overt proteinuria, the infection rate was 30% with TB, UTI, and viral infection in the form of hepatitis B and C. Hypertension (10%), diabetes (6%), and malignancy (3%) were the remaining co-morbid diseases. The proportion lost to followup was 22%. In the nephrotic group, there was little co-morbid disease. Of note, there was no infection and equal prevalence of hypertension, diabetes, and malignancy (6.6% each). The numbers in this group were small, and 21% were lost to follow up.

Definition of Microalbuminuria

Depending on the definition used, the prevalence of microalbuminuria in the screened sample is shown in Figure 1. There appears to be little difference between the definitions applied to the
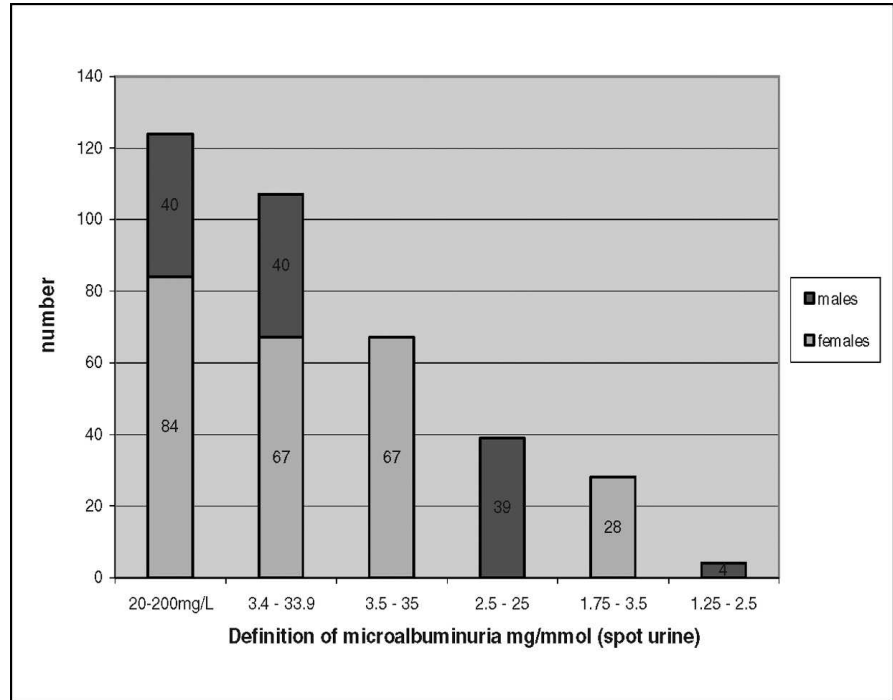

Fig 1. **Prevalence of microalbuminuria on screening according to definition used. 20–200 mg/L: international guidelines[8]. 3.4–33.9 mg/mmol: local laboratory. 3.5–35 mg/mmol: international guidelines for females[8]. 2.5–25 mg/mmol: international guidelines for males[8]. 1.75–3.5 mg/mmol: high normal range microalbuminuria: international guidelines for females[8]. 1.25–2.5 mg/mmol: high normal range microalbuminuria: international guidelines for males[8]**

data with respect to sex and whether the albumin-to-creatinine ratio or albumin concentration alone is used. With regard to the high-normal ranges of albuminuria that have been more recently recommended, the data showed an additional 32 patients that would have been screened if these criteria were applied.[8] If a prescreening value >10 mg/L albumin were used, which has been recommended for screening in those at risk for cardiovascular disease, 142 (as opposed to 107) patients would have been included in the microalbuminuric dataset.[8] Regression analysis was performed to determine whether a correlation existed between creatinine (a marker of muscle mass) and weight in the microalbuminuric group. No correlation was found between microalbumin concentration (mg/L) versus weight and microalbumin-to-creatinine ratio versus weight.

DISCUSSION

This study found a high prevalence of leukocyturia and microscopic hematuria in addition to proteinuria on urinary screening of ART-naive, HIV-infected outpatients. With regard to leukocyturia, the high prevalence of 30.3% was second only to a Ugandan study that showed a prevalence of 44.1%.[3] It appears that HIV-infected patients in African countries have a much higher prevalence (16.0%–44.1%) of leukocyturia than do patients in developed countries (1%–11%), but no studies have investigated why this occurs or its potential relevance.[3,4,9]

On the basis of current literature, this is the only African study that has investigated leukocyturia on dipstick by performing urine MCS. Specimens submitted for culture yielded an organism in 29.1% of cases, unlike the

findings from the HIV Epidemiology Research Study, which identified an organism in 60% of cultures.[9] The corollary may be more significant in that 70.9% of urine cultures were sterile in this study, compared with 40% in the HIV Epidemiology Research Study, which offered no explanation for the findings. No published studies to date have investigated the causes of (sterile) leukocyturia in HIV infection. In HIV-infected patients an additional potential cause of sterile leukocyturia may be interstitial nephritis, which can be directly due to HIV infection or caused by drugs used in its management (cotrimoxazole, atazanavir, tenofovir, indinavir, efavirenz) through a hypersensitivity reaction.[10] In advanced disease, opportunistic genitourinary pathogens (parvovirus B19, herpesvirus, cytomegalovirus, polyomavirus, *Candida* spp, *Aspergillus* spp.) may be implicated.[11]

During screening, it became apparent that certain infections were associated with sterile leukocyturia, namely TB (16.6%) and STI (11.1%). In those screened, only the group with sterile leukocyturia was asked about symptoms and signs of STI and TB. This introduced selection bias, which makes the results difficult to interpret as there are no data on symptoms and prevalence of TB and STI in those screened without sterile leukocyturia. In addition, those with suspected STI were treated syndromically, and no genital swabs or cultures were done to confirm the clinical diagnosis. It is interesting to note that in those with a diagnosis of TB and sterile leukocyturia, TB was diagnosed from organs other than the genitourinary tract. Hematuria, sterile leukocyturia, and proteinuria have been described in association with genitourinary TB in HIV.[12–14] Because urine was not sent for TB culture, we could not determine whether there was concomitant genitourinary TB in these patients, possibly as part of disseminated disease.

Many causes of sterile leukocyturia exist, but whether these are different in the HIV-infected population is unknown. While this study suggests that there may be an association with concomitant infection (TB, STI), these data can only propose this as a hypothesis that needs to be explored in further research. Sterile leukocyturia may act as a clinical indicator for screening for easily treatable conditions in this subgroup of patients.

The reasons why leukocyturia is more common in ART-naive, HIV-infected Africans, compared with studies from non-African countries, is not clear. From published studies, a potential explanation may be that African patients tended to have more advanced HIV disease at screening. This would be supported by the fact that in this study, 84% of patients had AIDS, potentially making them more susceptible to opportunistic genitourinary pathogens.[2–4,9] Microscopic hematuria occurred in 33.1% of those screened, a high prevalence when compared with other studies: 1.6%,[4] 15.5%,[7] 25%.[15] This finding is considered acceptable in the presence of a urinary tract pathogen.

Isolated microscopic hematuria has been described in HIV infection. In one study, after investigation, no serious pathology was found in young asymptomatic patients with normal renal function.[15] In a single study, cystoscopy in 9 patients with dysuria, urinary frequency, and hematuria without demonstrable urinary tract infection (including cytomegalovirus) showed congested bladder mucosa in all patients; the authors implicated HIV in the pathogenesis, but bladder biopsy with testing for HIV protein was not performed.[16] Uncontrolled HIV replication in uroepithelial tissue may be a source of isolated microscopic hematuria, but this has not been proven.

A positive urine culture prevalence of 7.1% was found in this study. This is low compared with published rates of 7%–50% in patients with AIDS.[11,17] This low prevalence may be ascribed to the outpatient population setting, compared with many published studies, which were hospital-based. In the culture-positive group, organisms identified in this study were *E coli* (70%), *Klebsiella* species (12%), *Staphylococcus aureus* (5%), and small percentages of *Enterobacter* species, *Enterococcus faecalis*, *Proteus mirabilis*, *Streptococcus agalactiae* and *S viridans* (2.5% each). A similar spectrum of organisms has been reported in other studies.[11] In contrast however, the following organisms were not seen in this sample: *Pseudomonas aeruginosa*, *Acinetobacter*, *Serratia*, and *Salmonella*.[11] This finding may reflect patterns of local pathogen exposure or the difference between inpatient versus outpatient populations. High levels of cotrimoxazole resistance occurred with *E coli* and *Klebsiella* species (90% and 80%, respectively). These findings concurred with published results, confirming that cotrimoxazole prophylaxis may not protect against UTI, most likely because of rapid emergence of uropathogen resistance, in spite of its efficacy against of bacterial pneumonias.[11,18,19]

There are few published studies on screening for detection of proteinuria (even fewer with microalbuminuria) in ART-naive, HIV-infected populations, particularly in Africa. In Kenya, 23 (6.2%) of 373 outpatients tested ≥1+ for proteinuria on dipstick (equivalent to ≥300 mg/L of proteinuria), which correlated with findings in this study of 8.8%. The mean CD4 count in the Kenyan study was 391 cells/mm^3, and 21.9% of patients had a CD4 count <200 cells/mm^3.[6] In a study from Uganda, 60 of 299 (20%) outpatients tested ≥1+ for proteinuria on dipstick, and although CD4 counts were not done, 67.6% were classified as World Health Organization clinical stage 3 disease. In a Tanzanian study, albuminuria was present in 28.4% of HIV-infected versus 16.8% of HIV-noninfected patients, and the mean CD4 count in HIV-infected patients was 289 cells/mm^3.[4] In these studies, participants were at less severe

stages of HIV infection than in this study, in which 84% had AIDS, and the mean CD4 count was 130 cells/mm^{3}. Despite the fact that these studies seemed to represent populations at differing stages of their HIV disease, the prevalence of proteinuria was similar. These findings may suggest that risk for HIV-associated renal disease is not necessarily related to disease progression. Unfortunately microalbuminuria/proteinuria was not quantified in any of these studies. The surprising feature in the Tanzanian study was the prevalence of albuminuria of 16.8% in the HIV-noninfected group, the causes of which were not mentioned.

Microalbuminuria was found in 107 of 578 (18.5%) patients screened, which is similar to results of other studies, although the numbers in this study are much larger. Two studies showed microalbuminuria in 14 of 72 (19.4%) and 9 of 48 (19%) patients.[20,21] Microalbuminuria in another study correlated with lower CD4 and leukocyte counts and higher levels of tumor necrosis factor alpha and β2-microglobulin, suggesting an association between AIDS progression and microalbuminuria.[20] The study by Monje et al corroborated these findings with a positive correlation between microalbuminuria, HIV p24 antigenemia, and levels of β2-microglobulin.[21] Unfortunately levels of tumor necrosis factor alpha and β2-microglobulin were not measured in our study.

The definitions of microalbuminuria we used have not been validated in Black Africans or in HIV-infected populations. In this study, with specific regard to microalbuminuria, there appeared to be little difference between various definitions applied to the data (Figure 1), particularly the use of albumin concentration (mg/L) versus the microalbumin-to-creatinine ratio (mg/mmol). The reason for including creatinine in the ratio is to correct for differences between men and women and conditions with severe muscle wasting—as seen in advanced HIV disease.[8] Analysis was performed

on the microalbuminuric group to assess whether there was any correlation between weight (as a surrogate marker for muscle bulk) and albumin concentration or weight and the microalbumin:-to-creatinine ratio, and no correlations were found. These data were not sufficiently powered to undergo analysis for significance between various definitions used, but they do suggest that further studies should be done to evaluate various definitions of microalbuminuria in Black African, HIV-infected populations. Of most significance from these data is that urinary albumin concentration was equivalent to the albumin-to-creatinine ratio, but albumin concentration testing is cheaper, easier to perform, and may be sufficient for mass screening programs, particularly in resource-limited settings.

There are numerous limitations to this study. It would have been useful to investigate the causes of all dipstick abnormalities more aggressively with better history taking, physical examination, and clean-catch techniques for urine collection, especially in light of the unexpected levels of (sterile) leukocyturia and microscopic hematuria, but this was not the aim of the initial study design With regard to microscopic hematuria, the absence of data on the menstrual status of women is disappointing. Additional factors that weaken the capacity to draw conclusions from the data are the numbers lost to followup and the absence of control groups. Ideally, the screening should have included those with HIV infection and higher CD4 counts (those who do not have AIDS) and an HIV-negative control group from the same ethnic population. In order to explore a potential association between sterile pyuria and co-morbid TB or STI, the prevalence of these conditions in a control group of HIV-infected people without leukocyturia is essential. In those with sterile leukocyturia it would be useful to exclude fastidious organisms, sexually transmitted and opportunistic pathogens, fungi, viruses, and tuberculosis. Followup of those screened with

urinary abnormalities would have further strengthened the findings of this study to determine whether resolution/reversal of urinary screening abnormalities occurred with appropriate treatment (antimicrobials and ART). This applies not only to leukocyturia and microscopic hematuria but also to the persistence or resolution of proteinuria, including microalbuminuria.

Conclusion

This urinary screening study has shown that urinary abnormalities in HIV-infected, ART-naive outpatients are common. These data form the basis for a well-designed prospective study to investigate, in more detail, the exact nature and potential etiologies of these urinary abnormalities and their relative prevalence in HIV-noninfected populations. At present, urinary screening in ART clinics in South Africa is not considered standard practice. With regard to leukocyturia, this means that 28.5% of patients had an abnormality that would not have been investigated or treated, and the same applies for microscopic hematuria (33.1%). Untreated UTI could be a source for ascending infection in the urinary tract and septicemia in the immunocompromised host. In those with sterile leukocyturia, common and easily treatable conditions such as STI or TB could be detected and treated, with obvious benefit to patients. With the high prevalence of dipstick abnormalities found in this study, these data suggest routine urine screening of all new patients attending ART clinics in South Africa should be considered standard practice. Further studies comparing findings in this cohort with urine findings of those with less profound immunodeficiency and those who are HIV-negative may yield deeper understandings about the impact of immunodeficiency on the genitourinary tract.

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