Effects of HIV-1 And HIV-1/2 Coinfection on Patients with Asymptomatic Urinary Tract Infection Attending HIV Clinics in Benin City, Nigeria

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ABSTRACT

Conflicting reports exist on the effect of HIV types on disease progression and relation to opportunistic infections. This study aims to determine the effect of HIV types on the prevalence and aetiologic agents of urinary tract infection (UTI). A total of 485 subjects consisting of 335 HIV patients and 150 non-HIV subjects without symptoms of UTI were recruited for this study. The HIV patients comprised of 251 on HAART and 84 HAART-naive patients. Blood and urine specimens were collected from all subjects. The blood specimens were used to determine HIV type and CD4 count while significant microbial isolates were recovered from the urine specimens and identified using standard techniques. Only HIV patients on HAART had significantly higher prevalence of asymptomatic UTI compared with non-HIV subjects (p=0.0234). However, comparing the prevalence of asymptomatic UTI of the various HIV types with that of non-HIV subjects, the results showed only HIV-1 to be significantly associated with asymptomatic UTI (p<0.05). CD4 count <200 cells/µL was not associated with UTI. Generally, Staphylococcus aureus was the most common aetiologic agent of UTI. Among HIV patients (both HAART-naive and those on HAART) with HIV-1, Staphylococcus aureus was the most common cause of UTI, while among those with HIV-1/2 dual infection, Escherichia coli predominated. HIV types have an effect on the prevalence and aetiologic agents of asymptomatic UTI.

Keywords: HIV types; Urinary tract infection; Aetiologic agents; Benin City

INTRODUCTION

HIV pandemic is a continuing global health emergency[1] and HIV/AIDS is a major public health problem in Nigeria[2]. HIV is a retrovirus made up of two types- HIV-1 and HIV-2[3]. HIV-1 has a worldwide distribution in contrast to HIV-2 that is restricted to West Africa and countries with colonial ties to Portugal[4,5]. HIV-1 is more virulent than HIV-2[6-8]. However, available literatures show conflicting reports about the effect of dual HIV-1/2 infection. Some studies report that HIV-1/2 dual infection has slower progression to AIDS and longer survival time compared with people infected with HIV-1 mono-infection[9,10]. Others have reported higher mortality rates in persons infected with HIV-1/2 dual infection compared with HIV mono-infection[11]. Some authors have reported that the natural history of HIV disease in dually infected patients is similar to, and may be even more aggressive than that of HIV-1 infection alone[12-15]. This view is supported by a recent study that showed a 7-fold risk associated with tuberculosis for HIV-1/2 dual infection compared to 6-fold risk for HIV-1 and 2-fold risk for HIV-2 mono-infections[8].

Available literature on UTI and HIV/AIDS shows conflicting reports. The areas of conflict include the impact of HIV on the incidence of UTI, aetiologic agents and association with $CD4^+$ count[17].There is no report on the effect of HIV types on the prevalence of UTI in our environment. Hence, this study aimed to determine the effect of HIV serotypes on the prevalence of asymptomatic UTI. The effect of HIV types on the prevalence of aetiological agents of UTI as well as the effect of CD4+ count on the prevalence of UTI will be determined.

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MATERIALS AND METHODS

Study population

A total of 485 subjects consisting of 335 HIV positive patients (82 males and 253 females) and 150 (42 males and 108 females) apparently healthy HIV seronegative individuals, were used for this study. The HIV patients consisted of 251 patients on HAART (60 males and 191 females) and 84 HAART-naive patients (22 males and 62 females). All HIV patients were asymptomatic out-patients attending HIV clinics in the

University of Benin Teaching Hospital, Benin City; while their seronegative counterparts were from the surrounding community. The duration of HAART use among HIV patients were noted. Exclusion criteria included signs and symptoms of UTI, antibiotic usage within one week and large fluid in-take (less than one hour) before clinic attendance. Informed consent was obtained from all subjects or their parents/guardian in case of children prior to specimen collection. Approval for the study was given by the Ethical Committee of the University of Benin Teaching Hospital, Benin City. This study was carried out from March to June 2015.

Collection of specimens

Clean-catch mid-stream urine and 5 millilitre (ml) of venous blood were collected from each patient. The urine specimens were collected into sterile screw-capped universal container, containing few crystals of boric acid as preservative. The blood specimens were collected into ethylene diamine tetra-acetic acid (EDTA) bottles. The urine specimens were used to diagnose asymptomatic urinary tract infection while the blood specimens were used for determination of HIV type status and $CD4^+$ lymphocyte count.

Determination of HIV types

The HIV type was determined using an immunochromatographic kit-HIV 1.2.O Rapid Test Cassette (Global Devices, USA) following the manufacturer's instruction. Briefly, 25µL of patient's plasma (obtained by centrifuging the anticoagulated blood) was added to the specimen area of the cassette device. This was followed by the addition of 40µL of reagent buffer that came with the kit. Immediately after addition of the buffer, a timer was set. The result was read at 10mins and not more than 20mins. The presence of red lines in the control and HIV-1 (T1) area was taken as HIV-1 type. The appearance red lines in the control and HIV-2 (T2) area was interpreted as being positive for HIV-2 type, while the presence of red lines in the control, T1 and T2 areas was taken as positive for HIV-1/2 type.

Determination of CD4 lymphocyte count

CD4 lymphocyte counts were evaluated using the flow cytometry (Partec, Gmbh, Germany) following the manufacturer's instruction as previously described[18]. Briefly, 20µl CD4 phycoerythrin (monoclonal) antibodies was placed into a Partec test tube and 20 µl of well-mixed whole EDTA blood was added. The contents were mixed gently and incubated in the dark for 15 minutes at room temperature. This mixture was agitated during incubation every 5 minutes. Eight hundred microlitres of CD4 buffer was added to the mixture of antibody and sample and mixed gently. The counting of the cells was done by the flow cytometer.

Detection of asymptomatic urinary tract infection

Urine specimens were processed according to the method described by Akinloye *et al.*[19]. Briefly, a loopful (0.001ml) of well mixed un-centrifuged urine was streaked onto the surface of blood agar and cystine lactose electrolyte deficient (CLED) medium. The plates were incubated aerobically at 37^0C for 24hours and the count (pure colony) expressed as colony forming unit (cfu) per ml. A count of $\geq 10^5$cfu/ml was considered significant to indicate UTI.

Ten millilitre of each well mixed urine sample was centrifuged at 2000 x g for 5mins. The supernatant was discarded and a drop of the deposit examined microscopically using x 40 objective for pus cells, red blood cells, epithelial cells, cast, crystals, yeast-like cells and *Trichomonas vaginalis.* Pus cells $\geq$ 5 per high power field was considered significant to indicate infection.

Urinary tract infection was diagnosed if the bacterial or pus cell count, or both, were significant in an individual. The isolates were identified by standard microbiological methods[20].

Statistical analysis

The data obtained were analyzed using Chi square (X^2) test or Fisher's Exact test as appropriate for P value and odds ratio (OR) analysis. Statistical significance was set at $P < 0.05$. The statistical software INSTAT® (Graph Pad Software Inc., San Diego, CA, USA).was used for the analysis.

RESULTS

A prevalence of 12.00%, 19.05% and 21.51% among non-HIV subjects, HAART-naive HIV patients and HIV patients on HAART, respectively was observed (Table 1). HIV infection was a significant risk factor for acquiring UTI (OR = 1.937; 95% CI = 1.108, 3.387; P 0.0263) and this observation holds true for only HIV patients on HAART (OR = 2.010; 95% CI = 1.128, 3.581; P = 0.0234). The prevalence of UTI did not differ significantly (P = 0.7442) between HIV patient on HAART (21.51%) and HAART-naive (19.05%) (Table 1).

The effect of gender and duration of HAART use on the prevalence of asymptomatic UTI are shown in Table 2. In both HIV and non-HIV subjects, the prevalence of UTI were significantly higher (P < 0.05) in females compared with males, with the exception of HAART-naive HIV patients where the difference failed to reach statistical significance (P = 0.0891). Among HIV patients on HAART, the prevalence of UTI decreased from 15.79% in those on HAART for a year to 5.88% for those on HAART for 2 years. The prevalence of UTI then rose to 24.56% in those on HAART for ≥ 5years. However, duration of HAART use did not significantly (P = 0.3637) affect the prevalence of UTI among HIV patients on HAART.

The distribution of HIV types among HIV patients with UTI is shown in Table 3. In both HAART-naive HIV patients and those on HAART, the prevalence of UTI did not differ significantly between HIV-1 and HIV-1/2 (P = 0.0848 and P = 0.4091, respectively). Only HIV-1 was significantly associated with UTI when compared with non-HIV subjects among HAART-naive HIV patients (OR = 2.821; 95% CI = 1.170, 6.801; P = 0.0342) and those on HAART (OR = 2.222; 95% CI = 1.212, 4.076; P = 0.0133).

The combined effect of low CD4 count (<200cells/μL) and HIV types distribution did not significantly (P > 0.05) affect the prevalence of UTI among the HIV patients (Table 4).

A total of 98 microbial isolates were recovered in this study and majority (60.20%) was from HIV patients on HAART (Table 5). Generally, and among HIV patients on HAART, *Staphylococcus aureus* was the most prevalent microbial isolate. Among HAART-naive HIV patients, *Staphylococcus* aureus and *Candida albicans* predominated with a prevalence of 25.00% each, while among non-HIV subjects, *Candida albicans* was the most prevalent microbial isolate. *Pseudomonas aeruginosa* and *Trichomonas vaginalis* were only recovered from HAART-naive HIV patients, while *Proteus vulgaris* was recovered only from HIV patients on HAART (Table 5).

Among HAART-naive HIV patients infected with HIV-1, *Staphylococcus aureus* and *Candida albicans* were the most prevalent isolates (30.77% each) implicated in UTI. However, *Escherichia coli* were the predominant isolates among HAART-naive HIV patients infected with HIV-1/2 (Table 6). Among HIV patients on HAART, *Staphylococcus aureus* was the mostly implicated in UTI among those with HIV-1, while coagulase negative staphylococci and *Escherichia coli* predominated among those coinfected with HIV-1/2 with a prevalence of 20.00% each (Table 6).

Table 1:Prevalence of urinary tract infection among the study population

Subjects	No. tested	No with UTI (%)
Non -HIV	150	18(12.00)
HIV		
HAART-naive	84	16(19.05)
On HAART	251	54(21.51)

HIV vs non-HIV: OR = 1.937; 95% CI = 1.108, 3.387; P = 0.0263
HAART-naive vs non-HIV: OR 1.725; 95% CI = 0.828, 3.396; P = 0.2026
On HAART vs non-HIV: OR = 2.010; 95% CI = 1.128, 3.581; P = 0.0234
On HAART vs HAART-naive: OR = 1.165; 95% CI = 0.625, 2.171; P = 0.7442

Table 2: Gender distribution and duration of HAART use among HIV and non-HIV infected persons with urinary tract infection

Characteristics	No. tested	No. with UTI (%)	P value
Gender			
Non-HIV (control)			
Male	42	0 (0.00)	0.0111
Female	108	18 (16.67)	
HIV Infected			
HAART-naive			0.0891
Male	22	1 (4.55)	
Female	62	15 (24.19)	
On HAART			0.0002
Male	60	2 (3.33)	
Female	191	52 (27.23)	
Duration of HAART (years)			0.3637
1	19	3 (15.79)	
2	16	1 (5.88)	
3	22	3 (13.64)	
4	23	5 (21.74)	
≥5	171	42 (21.53)	

Table 3:Distribution of HIV types among HIV patients with urinary tract infection

Subjects/ HIV type	No. tested	No. with UTI (%)	P value
Non-HIV (control)	150	18(12.00)	
HIV Infected			
HAART-naive			
HIV-1	36	10(27.78)	0.0848
* HIV-2	1	1(100.00)	
HIV-1/2	47	5(10.64)	
On HAART			
HIV-1	172	40(23.26)	0.4091
HIV- 1/2	79	14(17.72)	

HAART-naive (HIV-1 vs non-HIV): OR = 2.821; 95% CI = 1.170, 6.801; P = 0.0342
(HIV-1/2 vs non-HIV): OR = 0.873; 95% CI = 0.306, 2495; P = 0.7997
On HAART (HIV-1 vs non-HIV): OR = 2.222; 95% CI = 1.121, 4.076; P = 0.0133
(HIV-1/2 vs non-HIV): OR = 1.579; 95% CI = 0.740, 3374; P = 0.3238; * HIV-2 was not included in statistical analysis

Table 4:Distribution of CD4 count and HIV types among HIV patients with urinary tract infection

HIV type	CD4 count (cells/µL)				
	< 200		> 200		
	No. tested	No. with UTI (%)	No. tested	No. with UTI (%)	P value
HAART-naive					
HIV-1	11	4(36.36)	25	6(24.00)	0.4539
HIV-1/2	16	4(25.00)	31	2(6.45)	0.1607
On HAART					
HIV-1	25	5(20.00)	147	29(19.73)	0.9048
HIV-1/2	7	3(42.86)	72	17(23.61)	0.5075

Table 5:Prevalence of urinary pathogens among HIV and non-HIV infected subjects

Organisms	Non-HIV (%)	HAART-naive (%)	On HAART (%)	Total (%)
Escherichia coli	4(21.05)	4(20.00)	10(16.95)	18(18.37)
*Klebsiella*species	1(5.26)	0(0.00)	2(3.39)	3(3.06)
Proteus vulgaris	0(0.00)	0(0.00)	1(1.69)	1(1.02)
Providencia species	1(5.26)	1(5.00)	6(10.17)	8(8.16)
Pseudomonas aeruginosa	0(0.00)	1(5.00)	0(0.00)	1(1.02)
Enterococcus faecalis	2(10.53)	2(10.00)	5(8.47)	9(9.18)
Staphylococcus aureus	4(21.05)	5(25.00)	13(22.03)	22(22.45)
Coagulase negative staphylococci	0	1(5.00)	13(22.03)	14(14.29)
Candida albicans	7(36.84)	5(25.00)	9(15.25)	21(21.43)
Trichomonas vaginalis	0(0.00)	1(5.00)	0(0.00)	1(1.02)
Total	19(19.31)	20(20.41)	59(60.20)	98

Table 6:Distribution of uropathogens in relation to HIV types among the patients

Organisms	HAART-naive			On HAART	
	HIV–1 (n = 13)	HIV–2 (n = 1)	HIV–1/2 (n = 5)	HIV–1 (n = 34)	HIV–1/2 (n = 25)
Escherichia coli	2(15.38)	-	2(40.00)	5(14.71)	5(20.00)
Klebsiella species	0(0.00)	-	0(0.00)	2(5.88)	0(0.00)
Proteus vulgaris	0(0.00)	-	0(0.00)	0(0.00)	1(4.00)
Providencia species	1(7.69)	-	0(0.00)	5(14.71)	1(4.00)
Pseudomonas aeruginosa	0(0.00)	-	1(20.00)	0(0.00)	0(0.00)
Enterococcus faecalis	0(0.00)	1(100.00)	0(0.00)	1(2.94)	4(16.00)
Staphylococcus aureus	4(30.77)	-	1(20.00)	10(29.42)	3(12.00)
Coagulase negative staphylococci	1(7.69)	-	0(0.00)	8(23.53)	5(20.00)
Candida albicans	4(30.77)	-	1(20.00)	6(17.65)	3(12.00)
Trichomonas vaginalis	1(7.69)	-	0(0.00)	0(0.00)	0(0.00)

DISCUSSION

The prevalence of asymptomatic UTI in this study was significantly higher (P = 0.0263) among HIV patients compared with the non-HIV infected persons. This is in agreement with the findings of Deokar and Bodhankar[21] and Omoregie and Eghafona[17]. However, the higher prevalence observed among HIV patients were statistically significant only in HIV patients on HAART. This agrees with previous reports[17,22].

The non-significant difference in the prevalence of UTI between HAART-naive and their non-HIV counterparts had previously been reported[17,22,23-25]. Studies that show significant difference in the prevalence of UTI between HIV (HAART-naive) and non-HIV subjects used either AIDS patients or HIV patients with symptoms of UTI[23,26,27]. The finding from this study showing that the prevalence of UTI did not differ significantly between HIV patients on HAART and those that were HAART-naive agrees with previous reports[17, 22, 28, 29].

In both HIV and non-HIV subjects, the prevalence of asymptomatic UTI was higher in females compared to males. This agrees with previous reports[16,17,27-31]. Close proximity of the female urethra meatus to the anus, shorter urethra and sexual intercourse have all been reported as factors that influence higher prevalence of UTI in females[32,33]. It is important to note that the higher prevalence of UTI in females observed in this study was not statistically significant among the HAART-naive HIV patients only and is consistent with a recent report from Osogbo, Nigeria[31].

The duration of HAART use did not significantly affect the prevalence of UTI in this study. This may indicate that it is the antiretroviral in the HAART regimen that affects the prevalence of UTI not the duration of use. However, a reduction in the prevalence of UTI between 1 and 2 years of HAART use followed by increase in the prevalence of UTI between 2 to ≥ 5years was observed. Although, not statistically, significant, further studies on the effect of HAART on UTI is needed to explain the higher prevalence of UTI among HIV patients on HAART. The antibacterial property of urine is based on its low pH, high urine urea concentration and osmolality[34]. It has been reported that some antiretrovirals used in the HAART regimen results in crystalluria, nephrolithiasis, decreased glomerular filtration rate and decreased urine osmolality[35]. This may affect the antibacterial property of urine and may explain the higher prevalence of UTI among HIV patients on HAART in this study.

In both HAART-naive HIV patients and those on HAART, prevalence of UTI was not related to HIV types. Comparing prevalence of UTI and HIV serotypes of both categories of HIV patients with prevalence of UTI among non-HIV subjects revealed that in both categories of HIV patients, only patients infected with HIV-1 had higher prevalence of UTI. Indeed, those with HIV-1 infection were significantly associated with UTI in both category of HIV patients compared with those with dual HIV 1 and 2 infection.

Irrespective of the treatment status, HIV type and CD4 count of HIV patients, the prevalence of UTI did not differ significantly. A central feature in the pathogenesis of HIV infection is the depletion of CD4 lymphocytes, and it is generally known that low CD4 count < 200 cells/μL predisposes HIV patients to opportunistic infections[36]. The finding in this study that CD4 count < 200 cells/μL was not associated with UTI agrees with a previous report[24] but contradicts other reports[26, 31]. Classical AIDS patients were used in the study of Evans *et al.*[26] as against asymptomatic HIV patients used in this study. This may explain the difference in the findings of this study and that of Evans *et al*.[26] No detail description of the HIV patients used in Olowe *et al.*[31] study was given. Hence, difficult to rationalize their findings with that of this study.

Among the aetiologic agents of UTI recovered in this study, *S.aureus* was generally the most prevalent isolate followed by *Candida albicans*. This is in agreement with a previous report[17]. Conflicting reports on the most prevalentaetiologic agent of UTI exist. Some authors have reported *Escherichia coli* as the predominant isolate.[21,25,27,28,29,31] Others have reported Enterococci[37], *Enterobacter* species[38], *Pseudomonas aeruginosa*[39] and *Staphylococcus aureus*[16,17,30] as the predominant isolate causing UTI in HIV patients. It is not clear whether geographical location or UTI symptomatic status could be the determinant factor of prevalence of these aetiologic agents among HIV patients.

Among non-HIV subjects, *Candida albicans* was the predominant isolate. This contradicts the finding of Omoregie and Eghafona[17] where *Staphylococcus aureus* predominated. In Nigeria, antibiotic use is unregulated[40]. Prescriptions of antibiotics without laboratory guidance and over the counter sales of antibiotics without prescription are rife[41]. This unregulated use of antibiotics may give rise to opportunistic Candida infections and may explain the findings in the study. The finding of *Trichomonas vaginalis* only among HAART-naive HIV patients agree with a previous report[17]. The reason of observing *T. vaginalis* only among HAART-naive HIV patients is unclear, although sexually transmitted infections, including trichomoniasis, increases the susceptibility of acquiring and transmitting HIV infection[42]. Specifically among HAART-naive HIV patients, *Staphylococcus aureus* and *Candida albicans* predominated (25% each) while among HIV patients on HAART, *Staphylococcus aureus* and Coagulase negative staphylococci were the most prevalent (22.03% each). The study of Omoregie and Eghafona[17] reported *Staphylococcus aureus* as the prevalent isolate in both HAART-naive HIV patients and those on HAART. *Escherichia coli* was reported as the predominant isolate recovered from antiretroviral therapy users and nonusers in Ethiopia[29]. The finding that more microbial isolates were recovered from HIV patients on HAART compared with their HAART naive counterpart agrees with a previous report[31].

The finding that *Staphylococcus aureus* was the most prevalent microbial isolates causing UTI among HIV (in both HAART-naive and HIV patients on HAART) patients with HIV-1 serotypes agrees with a previous study[16]. Similarly, the recovery of *Enterococcus faecalis* from the only case of HIV-2 mono-infected patient, agrees with a previous report where *Enterococcus faecalis* was among the isolates recovered as aetiologic agent of UTI[16]. In both HAARTnaive HIV patient and those on HAART, *Escherichia coli* was the most prevalent cause of UTI among those with HIV-1/2 coinfection. Coagulase negative staphylococci had the same prevalence as *Escherichia coli* among HIV patients on HAART with HIV-1/2 coinfection.

In conclusion, the prevalence of asymptomatic UTI was higher among HIV-1 patients irrespective of treatment status than non-HIV subjects while *Staphylococcus aureus* was generally the predominant aetiologic agent of UTI. HIV types appear to influence the aetiologic agents of UTI

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