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CANDIDURIA AMONG HIV- INFECTED PATIENTS ATTENDING A TERTIARY HOSPITAL IN BENIN CITY

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ABSTRACT

Background: Candiduria is a common finding. However, in immunocompromised patients like HIV-infected individuals, it has high risk of morbidity and mortality as it could be a pointer to systemic candidiasis. Unfortunately, there are no clear criteria for differentiating between colonization and infection or between upper or lower urinary tract infections.

Objective: This study focused on determining the spectrum of *Candida* species implicated in candiduria among HIV-infected individuals and their susceptibility to fluconazole and voriconazole in a tertiary hospital.Methods: A total of 300 subjects comprising of 200 HIV patients and 100 non-HIV individuals were used for this study. Clean catch midstream were collected from each individual and processed using standard microbiological techniques. Emergent *Candida* isolates were identified with CHROMagar Candida and sugar fermentation tests.Results: The overall prevalence of candiduria among HIV patients was 13.5%. HAART-naive patients had a significantly higher prevalence (OR=4.165, 95%CI=1.602, 10.828; P=0.0038) than their counterpart on highly active antiretroviral therapy (HAART). Female gender was a significant risk factor for acquiring candiduria. Age had no significant effect on the prevalence of candiduria in this study. A CD4+ count <200 cells/µl was a significant risk factor for acquiring candiduria only among HAART-naive patients (OR=11.711; 95%CI=3.943, 34.780; P= 0.0001). The three species of *Candida* recovered from this study were *C. albicans, C. krusei and C.parapsilosis. C. albicans* (64.52%, 83.36%) and *C. krusei* (66.67%, 100.00%) were resistant to fluconazole and voriconazole respectively.Conclusion: There is a significant relationship between antiretroviral therapy, CD4+ counts, and the prevalence of candiduria among the study population.

Keywords:HAART, HAART-naive, candiduria, CD4+ counts, Candida, prevalence.

CANDIDURIE CHEZ DES MALADES VIVANT AVEC LE VIH DANS UN HOPITAL TERTIAIRE DANS LA VILLE DE BENIN

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RÉSUMÉ

Contexte: La candidurie est un problème commun de sante publique. Cependant, chez les patients immunodéprimés comme les individus infectés par le VIH, elle présente un risque élevé de morbidité puisqu'elle peut évoluer vers la candidose systémique. Malheureusement, il n'existe pas de critères clairs permettant de distinguer la colonisation et l'infection de même que les infections des voies urinaires supérieures et inférieures.

Objectif: Cette étude a porté sur la détermination du spectre d'espèces de *Candida* impliqués dans la candidurie chez les personnes infectées par le VIH et leur sensibilité au fluconazole et voriconazole dans un hôpital tertiaire. Methodes : Un total de 300 sujets comprenant 200 patients atteints du VIH et 100 personnes non -VIH ont été utilisés dans cette étude. Les echantillons d'urine ont été collectées auprès de chaque personne par la methode de ''Clean catch midstream''et traitées en utilisant des techniques microbiologiques standard. Les isolats émergents de *Candida* ont été identifiés avec CHROMagar Candida et les tests de fermentation de sucre. Résultats : La prévalence globale du VIH chez les patients atteints de candidurie était de 13,5%. Les patients en naïfs de la multithérapie HAARTavaient une prévalence significativement plus élevée (OR = 4,165, IC à 95% =

1,602, 10,828, p = 0,0038) par rapport a leurs homologues sous traitement antirétroviral hautement actif (HAART) . Le sexe féminin était un facteur de risque important d'acquisition de candidurie. L'âge n'avait pas d'effet significatif sur la prévalence de candidurie dans cette étude. Un compte de CD4 + < 200 cellules / µl n'a été un facteur de risque important pour l'acquisition de candidurie que chez les patients en multithérapie naïfs (OR = 11,711 ; IC à 95% = 3, 943, 34, 780, p = 0,0001). Les trois espèces de Candida récupérés de cette étude étaient *C. albicans*, *C. krusei* **et** *C.parapsilosis***. *C. albicans*(64,52%, 83,36 %) et** *C. krusei* **(66,67%, 100,00 %) étaient résistants respectivement au fluconazole et voriconazole. Conclusion: Il existe une relation significative entre le traitement antirétroviral, CD4 +, et la prévalence de candidurie parmi la population de l'étude.**

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Mots-clés: multithérapie HAART , naïfs , candidurie , CD4 + , Candida , prévalence .

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) cause by human immunodeficiency virus (HIV) is the most important public health problem of modern times (1). HIV/AIDS continues to spread globally and remains a worldwide pandemic affecting about 40 million people (2). The pandemic is the leading cause of death in sub-Sahara Africa and the fourth leading cause of mortality worldwide and over 95% of these deaths have occurred among young adults in the developing world (3-4).

Fungal infections caused by yeast pathogens remain quite common in immunocompromised host, especially in HIV-infected individuals (5). These infections are playing an increasing important role in the morbidity and mortality of HIV/AIDS patients (6). Although the use of highly active antiretroviral therapy (HAART) has decreased the incidence of fungal infections (7-8), candidiasis continues to afflict HIV-infected individuals in HAART era (6, 9). Unfortunately, prolong use of antifungal among this population has led to increased incidence of resistance (10).

The healthy urinary tract is sterile so the presence of *Candidaspecies* in urine or candiduria represent a variety of clinical situations (11-13), such as contamination of urine specimen, colonization of bladder due to indwelling catheters, infection of upper or lower urinary tract, and primary or disseminated candidiasis (13-15).

Candidaspecies are the most commonly recovered fungi from urine (16) with *C. albicans* being the most frequently isolated, accounting for 50-70% of isolates in various studies (15, 17). Others non-albicans such as *C. glabrata* and *C. tropicalis* are the next most common species while *C. parapsilosis* is commonly found in urine of neonates and is usually associated with systemic infection in this population (18).

Conditions that predispose to candiduria includes immunosuppresion, use of broad spectrum antibiotic, gender, age, diabeties mellitus, chronic renal failure, malignancy, urinary tract abnormalities, pregnancy, and neutropenia (16, 19-23).

Asymptomatic candiduria is usually benign in most patients and do not require antifungal medication (24). However, in immunocompromised patients, it has a high risk of morbidity and mortality (25). There is little or no report on candiduria among HIV-infected individuals in our locality, thus this study focused on determining the spectrum of *Candida* species implicated in candiduria among HIV-infected individuals and their susceptibility to fluconazole and voriconazole.

MATERIALS AND METHODS

Study Area

The study was carried out in the University of Benin Teaching Hospital, Benin City, Nigeria. It is located in the South-South geopolitical zone of Nigeria. It serves as a referral hospital to about six to ten states in Nigeria. It is a centre for Institute of Human Virology, Nigeria and US President's Emergency Plan for AIDS Relief (PEPFAR) HIV/AIDS interventions in the zone.

Study Population

A total of 300 individuals consisting of 200 HIV patients and 100 (42 males and 58 females) apparently healthy, aged-matched, non-HIV individuals were recruited for this study. The patients consists of 100 (31 males and 69 females) HAART-naïve patients and 100 (22males and 78 females) HIV patients on HAART for 3-6 months. The HAART regimen included stavudine, zidovudine, and nevirapine. The HIV patients were out-patients and asymptomatic. Informed consent was obtained from all individuals prior to specimen collection. The Ethical Committee of the University of Benin Teaching Hospital approved the protocol for this study.

Specimen collection and processing

Venous blood (5ml) was collected into ethylene diamine tetraacetic acid (EDTA) container and mixed. Clean-catch mid-stream urine was collected into sterile universal container containing few crystals of boric acid as preservative (26).

The blood specimens were used for CD4 counts using flow cytometry (Partec, Germany) following

manufacturer's instruction. A loop-full (0.001ml) of well mixed un-centrifuged urine was streaked onto

the surface of Saboraund's Dextrose Agar (SDA) and Brain Heart Infusion Agar (BHIA) containing 5µg/ml gentamicin. The plates were incubated aerobically at 370C for 24-48 hours and counts were expressed in colony forming unit per ml. A count of ≥ 105 cfu/ml was considered significant to indicate asymptomatic candiduria. The urine specimens were centrifuged at 2000 g for 5minutes. The supernatant was discarded and a drop of the deposit was examined microscopically at high magnification for pus cells. Pus cells ≥5 per high power field were considered to indicate infection (26).

Emergent yeast colonies were stored for identification. All *Candida* isolates were identified with CHROMagarTM*Candida* (Paris, France) as previously described (27) and sugar fermentation tests as described by Forbes *et al.,* (28).Antifungal susceptibility test was performed using the CLSI (29) disc diffusion methods. Voriconazole disc (1µg)and fluconazole disc (25µg) (Oxoid, England) were used for this study.

RESULTS

The prevalence of candiduria among HIV and non-HIV individuals is shown in table 1. HIV status was a significant risk factor for acquiring candiduria (OR=3.746; 95%CI=1.273, 11.025; P=0.0189). Considering HIV status, the prevalence of candiduria among HAART-naïve patients was significantly higher than HIV patients on HAART (P= 0.0038). Female gender was significantly associated with candiduria.

TABLE 1: PREVALENCE OF CANDIDURIA AMONG HIV AND NON-HIV INDIVIDUALS.

	Male		Female		Total		
Status	**No. Sampled**	**No. Infected (%)**	**No. Sample**	**No. Infected (%)**	**No. Sampled**	**No Infected (%)**	**Fungal Isolates**
Non HIV	**42**	**-**	**58**	**4 (6.70)**	**100**	**4 (4.00)**	*C. albicans*
Mixed Infection HIV patients	**42**	**-**	**58**	**-**	**100**	**-**	**-**
HAAT naive×	**31**	**1 (3.23)**	**69**	**20 (28.99)**	**100**	**21 (21.00)**	*C. albicans, C. parapsilosis*
Mixed Infection	**31**	**-**	**69**	**3 (4.35)**	**100**	**3 (3.00)**	*C. krusei , C.albicans*
On HAART$^{\beta,\alpha}$	**22**	**-**	**78**	**6 (7.69)**	**100**	**6 (6.00)**	*C. albicans, C. krusei*
Mixed Infection	**22**	**-**	**78**	**1 (1.28)**	**100**	**1 (1.00)**	

HIV versus non-HIV: OR=3.746; 95%CI=1.273, 11.025; P=0.0189; βOn HAART versus non-HIV: OR=1.532; 95%CI=0.4187, 5.604; P=0.7475. ×HAART naive versus non-HIV: OR=6.380; 95%CI=2.102, 19.362; P=0.0006. αHAART naive versus on HAART: OR=4.165, 95%CI=1.602, 10.828; P=0.0038

Only one male among HAART-naive HIV patient had candiduria. The prevalence of candiduria did not differ significantly (P= 0.7475) between HIV patients on HAART and non-HIV individuals.

Table 2 show *Candida* isolates recovered from HIV and non-HIV individuals. *C. albicans* was still the most prevalent and the only isolate recovered from non-HIV individuals. *C. krusei* was recovered from HIV patients on HAART and HAART-naïve while *C. parapsilosis* were recovered only from HAART-naïve HIV patients.

TABLE 2: CANDIDA ISOLATES RECOVERED FROM URINE OF HIV AND NON-HIV INDIVIDUALS

Organisms	Non-HIV (%)	HAART-naïve (%)	On HAART (%)	Total (%)
C. albicans	4 (100.00)	20 (86.96)	7 (87.50)	31 (88.57)
C. krusei	-	2 (8.70)	1 (12.50)	3 (8.57)
C. Parapsilosis	-	1 (4.45)	-	1 (2.86)

TABLE 3: *CANDIDA* **ISOLATES RECOVERED FROM URINE OF HIV AND NON-HIV INDIVIDUALS IN RELATION TO GENDER**

Organisms	Non-HIV		HAART-naive		On HAART			
	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
C. albicans	-	4 (100.00)	1 (100.00)	19 (82.61)	4 (80.00)	7 (87.50)	1 (100.00)	30 (85.71)
C. krusei	-	-	-	2 (8.70)	-	1 (12.50)	-	3 (8.52)
C. parapsilosis	-	-	-	1 (4.35)	-	-	-	1 (2.86)

Table 3 show Candida isolates recovered from HIV and non-HIV individuals in relation to gender.

All *C. albicans* recovered from non-HIV individuals were from female. Similarly, *C. krusei*, and *C. parapsilosis* were recovered from female HIV patients.

TABLE 4: PREVALENCE OF CANDIDURIA AMONG HIV AND NON-HIV INDIVIDUALS IN RELATION TO AGE

Age	Non-HIV		HAART-naive		On HAART	
Years	No. sampled	No. infected (%)	No. sampled	No. infected (%)	No. sampled	No. infected (%)
11-20	5	-	-	-	-	-
21-30	40	2 (5.0)	15	2 (13.3)	14	-
31-40	34	1 (2.9)	48	15 (31.3)	47	4 (8.5)
41-50	17	1 (5.9)	32	5 (15.6)	29	2 (6.9)
51-60	3	-	4	1 (25.0)	7	1 (14.3)
61-70	1	-	1	-	3	-

Non-HIV; P=0.9810; HAART-naïve; P=0.4160; On HAART; P=0.7329

TABLE 5. EFFECT OF CD4 COUNTS ON PREVALENCE OF CANDIDURIA AMONG HIV INDIVIDUALS

CD4 Counts (Cells/μl)	No. sampled	No. infected (%)	OR	95%CI	P. value	*Candida* isolates
HAART naïve						
<200	32	17(53.13)	11.711	3.943, 34.780	0.0001	*C. albicans*
≥200	68	6(8.82)	0.085	0.029, 0.254		*C. albicans*, *C. parapsilosis*
Mixed Infection						
<200	32	4(12.50)	21.632	1.127, 415.35	0.0152	*C. albicans*, *C. krusei*,
≥200	68	-	0.046	0.002, 0.888		
On HAART						
<200	12	2(16.67)	3.320	0.567, 19.426	0.4260	*C. albicans*
≥200	88	5(5.68)	0.301	0.052, 1.762		*C. albicans*
Mixed Infection						
<200	12	1(8.33)	23.087	0.886, 601.310	0.2399	*C. albicans*, *C. krusei*
≥200	88	-	0.043	0.002, 1.128		

Age had no significant effect on the prevalence of candiduria in this study (Table 4).

CD4 <200cells/µl was significantly associated with candiduria. However, among HIV patients on HAART, CD4<200cells/µl did not significantly affect the prevalence of candiduria (Table 5).

Among the yeasts recovered, more *C. albicans* and *C. krusei* were resistant to fluconazole and voriconazole. The only isolate of *C. parapsilosis* was susceptible to both antifungal agents (Table 6).

TABLE 6: ANTIFUNGAL SUSCEPTIBILITY PROFILE OF *CANDIDA* ISOLATES

Organisms	FLUCONAZOLE			VORICONAZOLE		
	S (%)	S-DD (%)	R (%)	S (%)	S-DD (%)	R (%)
C. albicans	9(29.03)	2(6.45)	20(64.52)	10(90.91)	2(100.00)	19(83.36)
C. krusei	1(33.33)	-	2(66.67)	-	-	3(100.00)
C. parapsilosis	1(100.00)	-	-	1(100.00)	-	-

DISCUSSION

Fungal infections are playing an increasing important role in the morbidity and mortality of HIV/AIDS patients (6). Although the use of highly active antiretroviral therapy (HAART) has decreased the incidence of fungal infections (7-8), candidiasis continues to afflict HIV-infected individuals in HAART era (6, 9).

Recent studies have shown that candiduria is getting increased due to immunocompromised patients; prolong hospitalization, uncontrolled use of antibiotic, prophylaxis by antifungal agents, urinary tract surgeries (11, 30-31). Candiduria accounted for up to 10% of UTIs and has resulted in increased rate of mortality during the last decades due to use of new treatments, surgery and transplantation (14, 32-33).

In this study, the overall prevalence of candiduria among HIV-infected individual was 13.5%. This is lower than 22% reported in Brazil among hospitalized patients (35). HIV status was significantly associated with candiduria (OR=3.746; 95%CI=1.273, 11.025; P=0.0189). HIV results in immunosuppression which has been reported as a risk factor for acquiring candiduria (11). However, in regard to treatment status, the prevalence of candiduria among HIV patients on HAART (6%) have no significant different with non-HIV (4%) individuals. This indicates that candiduria in HAART-naïve HIV patients contributed to the significant difference in prevalence among HIV and non-HIV individuals. Thus as, HAART improves immunity, candiduria decreases to almost the same prevalence with that of non-HIV individuals.

Candida albicans (88.57%) was the most predominant isolate recovered. This agrees with the report of previous investigators (11, 16, 24). Other species of Candida recovered includes *C.krusei* (8.57%) and *C. parapsilosis* (2.86%). These species of *Candida* have previously been reported as causes of candiduria (16, 35).Irrespective of HIV status and treatment status, the female gender was associated with candiduria in this study. This is in agreement with the report of previous investigators (14, 19, 22).In this study, increased age had no significant effect on the prevalence of candiduria. This does not agree with the report of Kauffman, (14). The reason for this is unclear.

Among HAART-naïve HIV patients, CD4<200cells/µl was associated with candiduria (Table 5). It has been reported that fungal agents such as *Candida* takes advantage of the immune suppression seen in HIV among HIV patients as a result of CD4 T cells depletion (35). This may explain the findings in this study. It has also been reported from a number of experimental studies that acquired resistant to *Candida* infection is dependent upon the participation of T-lymphocytes (35). HAART causes a decline in the incidence of some opportunistic infection in AIDS and this decline is currently attributed to restoration of immunity and anti *Candida* activity of protease inhibitors among the HAART regimen (35). This may explain the non significant difference in the prevalence of candiduria among HIV patients on HAART with CD4<200cells/µl and CD4≥200cells/µl. However, protease inhibitors were not among the HAART regimen for our HIV patients on HAART. This may therefore indicate that immune

reconstitution may account for the observed results among HIV patients on HAART in relation to candiduria.Most of *C. albicans* (64.52%, 83.36%) and *C. krusei* (66.67%, 100.00%) were resistant to fluconazole and voriconazole respectively. It has been reported that *Candida* species from HIV patients are more resistant to antifungal agents (36-37). Prolong used of antifungal among HIV patients has been reported as predisposing factor (10).

In conclusion, there is a significant relationship between antiretroviral therapy, CD4+ counts, and the prevalence of candiduria among HIV patients. Therefore candiduria should be verified by obtaining a second specimen and appropriate therapy instituted after antifungal susceptibility teststo prevent systemic candidiasis amongthis population.

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