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ORIGINAL RESEARCH

Evaluation of Antifungal Activity Against *Candida albicans* Isolates From HIV-Positive Patients with Oral Candidiasis in a Major Referral Hospital, West Java, Indonesia

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Purpose: Oral candidiasis remains prevalent in HIV patients, with growing concern over antifungal resistance. This study aimed to identify *Candida* species in HIV patients with oral candidiasis and assess the antifungal susceptibility of the predominant species.

Materials and Methods: A cross-sectional study was conducted at a referral hospital in West Java, Indonesia, involving 30 HIV patients aged ≥18 years, with no prior antifungal therapy and a confirmed diagnosis of oral candidiasis. Oral rinse samples were collected and cultured on CHROMagar *Candida* for species identification and CFU/mL quantification. Antifungal activity was assessed using disk diffusion against nystatin, fluconazole, itraconazole, and voriconazole. Inhibition zone diameters were recorded, while categorical susceptibility interpretation was applied only to fluconazole and voriconazole based on CLSI guidelines. The Friedman test and Fisher's exact test were used, with $p < 0.05$ considered statistically significant.

Results: *Candida* (*C*). *albicans* was the predominant species (100%), consistent with previous findings. Non-*Candida albicans Candida* (NCAC) species, including *C. glabrata* (10%), *C. krusei* (3.3%), and *C. tropicalis* (3.3%), were also identified, aligning with reports of emergence. Inhibition zone diameters varied significantly ($p < 0.001$). Voriconazole had the widest zone (34.0 ± 10.7 mm), followed by fluconazole (33.0 ± 9.3 mm), itraconazole (29.5 ± 5.5 mm), and nystatin (27.9 ± 5.0 mm). For fluconazole and voriconazole, categorical interpretation showed 90.0% and 86.7% susceptibility, respectively, with no significant difference ($p = 1.00$). Since no interpretive breakpoints exist for nystatin and itraconazole, only inhibition zone diameters were reported.

Conclusion: *C. albicans* predominated, with fluconazole and voriconazole showing high susceptibility, while nystatin and itraconazole demonstrated inhibition zones but could not be categorically interpreted due to the absence of established breakpoints. Routine species identification and susceptibility testing remain essential to guide therapy and monitor emerging resistance in immunocompromised populations, highlighting the need for further validation studies.

Keywords: *Candida albicans*, antifungal susceptibility, oral candidiasis, HIV, disc diffusion

Introduction

Oral candidiasis is one of the most common opportunistic fungal infections in HIV-positive patients and often serves as an early clinical indicator of immunosuppression, particularly in individuals with a low CD4+ T cell count.[1,2] Although *Candida albicans* remains the primary pathogen responsible for oral candidiasis, non-*Candida albicans Candida* (NCAC) species such as *C. glabrata, C. krusei, C. tropicalis*, and *C. dubliniensis* have also been identified as causative agents. The clinical relevance of these species has grown due to their rising prevalence and their potential resistance to antifungal therapies.[3–5]

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The emergence of antifungal resistance, particularly resistance to azole-based therapies such as fluconazole, poses a significant challenge to the successful treatment of oral candidiasis.[6] Azoles are widely used as first-line therapy because of their broad-spectrum antifungal activity and favourable safety profiles, however, the increasing resistance of both *C. albicans* and NCAC species has led to persistent and recurrent infections, leading to poor clinical outcomes and increased healthcare burdens. A recent systematic review analyzing 2564 *Candida* isolates from HIV-positive patients with oral candidiasis revealed high pooled resistance rates to azoles and 5-flucytosine, while most isolates remained susceptible to nystatin, amphotericin B, and caspofungin. These findings suggest that reliance on azoles for initial treatment may be inadequate in certain settings and that polyenes or echinocandins may be more appropriate alternatives.[5] These findings underscore the potential inadequacy of azoles as first-line agents in certain settings and suggest that polyenes or echinocandins may be more effective alternatives.

The challenge of treating fungal infections is further compounded in resource-limited settings, where access to diagnostic laboratories is often restricted, and empirical treatment without susceptibility testing is frequently practiced. A survey of 241 mycology laboratories in seven Asian countries by the Asia Fungal Working Group (AFWG) found limited access to advanced fungal diagnostics and antifungal susceptibility testing, especially in Indonesia, Philippines, and Thailand. This suggests limited availability of comprehensive fungal diagnostic services in these countries.[7] In the United States, a study reported that although 95% of hospitals offered antifungal susceptibility testing (AFST) in 2015, only 28% performed the test in-house or through affiliated centres, and just 33% provided reflexive AFST, indicating that despite improvements since 2011, significant gaps in AFST availability remain.[8] Limited access to trained personnel in clinical mycology remains a major barrier, as many laboratories lack adequately trained staff to perform or interpret AFST. Additionally, the low number of clinical fungal isolates being tested is partly since most hospitals do not perform AFST in-house and often outsource testing, primarily due to high costs and limited laboratory infrastructure. These limitations contribute to a lack of clinical awareness of the value of timely AFST, with minimal formal training programs in medical mycology.[9] Furthermore, standardized AFST methods, such as CLSI, are often impractical for routine use due to their complexity, need for technical expertise, and slow turnaround (48–72 hours), limiting access to species-specific susceptibility data essential for guiding antifungal therapy.[9,10]

Besides the difficulties in treatment and limited access to diagnostic laboratories, the number of fungal infections worldwide keeps increasing, especially among people with weakened immune systems, including those living with HIV, and due to the growth of drug-resistant fungal strains.[11,12] Although the clinical impact is significant, studies on the types of *Candida* species and their antifungal resistance patterns in HIV-positive patients in Indonesia, specifically in West Java, remain very limited. This lack of local data makes it hard to create treatment guidelines and limits clinicians' options for selecting the most appropriate antifungal therapy, which can lead to treatment failure and the spread of resistant strains. To add more data from Indonesia and to address this gap, this study was carried out to identify *Candida* species found in HIV-positive patients with oral candidiasis and to assess the resistance patterns of the most common species to commonly used antifungal agents. The findings are expected to support better treatment decisions and improve the management of oral candidiasis in HIV-positive patients in Indonesia.

Materials and Methods

Study Design

This cross-sectional study involved HIV-positive outpatient clinic and inpatients diagnosed with oral candidiasis at a major referral hospital in West Java, Indonesia. The inclusion criteria included HIV-positive patients aged 18 years or older, those clinically diagnosed with oral candidiasis through subjective assessment and clinical examination by an oral medicine specialist, with confirmation by a 10% potassium hydroxide (KOH) test, and who had not received any antifungal treatment before sample collection. The exclusion criteria were patients who were in poor general condition or unconscious at the time of examination, and those who were unable to sit upright and perform an oral rinse procedure for sample collection. In addition to age and gender, other patient characteristics, such as oral hygiene status, clinical stage of the disease, antiretroviral therapy (ART) status, total lymphocyte count (TLC), and comorbidities, were also recorded.

Saliva samples were obtained using a convenience sampling method from patients who met the inclusion criteria until a total of 30 samples were reached. Samples were collected using the oral rinse technique as described in previous studies,[13] which is a well-established, non-invasive, and effective method for isolating *Candida* species from the oral cavity. Each subject was instructed to rinse their mouth vigorously with 10 mL of sterile phosphate-buffered saline (PBS) for 60 seconds, and the rinse sample was collected into sterile tubes for further laboratory analysis.

Candida Species Identification

Candida species were identified based on colony morphology and pigmentation using CHROMagar™ Candida medium (CHROMagar, Paris, France), which allows rapid differentiation of common clinical isolates, including *C. albicans, C. tropicalis, C. glabrata*, and *C. krusei*.[14]

To quantify colony-forming units (CFU), a 100 µL aliquot of each saliva sample was also plated onto Sabouraud Dextrose Agar (SDA) and incubated at 37°C for 48 hours. Colonies with identical morphology were counted, and the results were expressed as CFU/mL of saliva.

Antifungal Susceptibility Testing

Candida species that predominated in the sample were subcultured onto Sabouraud Dextrose Agar (SDA) plates and incubated at 37°C for 24–48 hours. Well-grown colonies were harvested and suspended in sterile saline to achieve turbidity equivalent to a 0.5 McFarland standard (approximately 1.5×10^6 CFU/mL). The suspension was homogenized and vortexed thoroughly prior to testing. Antifungal susceptibility was determined using the disk diffusion method on Mueller-Hinton Agar (MHA) supplemented with 2% glucose and 0.5 µg/mL methylene blue, as recommended by the Clinical and Laboratory Standards Institute (CLSI).[10,15] Disks impregnated with antifungal agents were commercially manufactured and obtained from Oxoid™ (Thermo Fisher Scientific, UK). The antifungal disks used included nystatin (100 U), fluconazole (25 µg), itraconazole (10 µg), and voriconazole (1 µg). After incubation at 35°C for 24 hours, the inhibition zone diameters were measured in millimeters using a digital caliper and interpreted according to CLSI M44-A2 guidelines, which categorized as Susceptible (S), Intermediate (I), or Resistant (R), based on zone diameter breakpoints specific to each antifungal agent and Candida species. And the results were expressed as n (%). For nystatin and itraconazole, no CLSI or EUCAST interpretive criteria exist for disk diffusion. Therefore, results are reported only as observed inhibition zone diameters without categorical classification.

Statistical Analysis

Normality of the inhibition zone data was first tested using the Shapiro–Wilk test ($n<50$). Since the results showed $p<0.05$, indicating non-normal distribution, the data were analyzed using the Friedman test (non-parametric). A p-value of < 0.05 was considered significant.

Results

A total of 30 subjects met the inclusion and exclusion criteria for this study. The majority of the subjects were male (93.3%), with ages ranging from 18 to 65 years and a mean age of 32.7 years. A total of 63.4% of the subjects had poor oral hygiene status. Clinically, most subjects (66.7%) were classified as Stage IV, indicating advanced disease progression. Regarding ART, the majority (66.7%) had not started treatment at the time of data collection, as they had only recently been diagnosed with HIV-positive. However, more than half of the subjects (56.7%) had normal or elevated TLC values (≥1200 cells/µL). Several subjects were also reported to have comorbid conditions, such as pulmonary tuberculosis (Table 1).

The majority of cases were diagnosed as acute pseudomembranous candidiasis in 23 patients (76.7%), followed by erythematous candidiasis in 7 patients (23.3%). Figure 1 shows the clinical features of oral candidiasis observed in the study subjects. Among those with pseudomembranous candidiasis, several cases also presented with angular cheilitis. Table 2 shows the results of *Candida* species identification. *C. albicans* was isolated from all samples (100.0%). The median colony count for *C. albicans* was 270 CFU/mL, with a range from 1 to 460 CFU/mL. In addition to *C. albicans*, other *Candida* species were also detected in several samples. The median colony count for NCAC species was 353 CFU/

Table 1 General Characteristics of Study Subjects

Characteristics	Number of Patients n (%)
Gender	
• Male	28 (93.3)
• Female	2 (6.7)
Age (years), Mean ± SD (51,6 ± 12,0)	
• 18-30	15 (50,0)
• 31-40	8 (26,7)
• 41-50	7 (23,3)
• 51-65	-
Oral hygiene, Median (Interquartile Range)	3,2 (2,6–3,8)
• Good	1 (3.3)
• Moderate	10 (33.3)
• Poor	19 (63.4)
HIV Stage	
• Stage I	4 (13.3)
• Stage II	3 (10.0)
• Stage III	3 (10.0)
• Stage IV	20 (66.7)
TLC level (cells/u/L), Median (Interquartile Range)	1305 (850–2032)
• <1200 cells/mL	13 (43.3)
• ≥1200 cells/mL	17 (56.7)
On ART	
• Yes	10 (33.3)
• No	20 (66.7)

Abbreviations: TLC, Total lymphocyte count; ARV, Antiretroviral.

mL, with a range from 10 to 670 CFU/mL. The median colony count for NCAC species was 353 CFU/mL (range: 10–670 CFU/mL), with *C. glabrata* identified in 3 samples (10.0%), *C. krusei* in 1 sample (3.3%), and *C. tropicalis* in 1 sample (3.3%).

The results of the antifungal susceptibility testing for four antifungal agents are summarized in Table 3. The mean diameter of the inhibition zones differed significantly among the tested antifungal agents, with voriconazole exhibiting the highest mean inhibition zone (34.0 ± 10.7 mm), followed by fluconazole (33.0 ± 9.3 mm), itraconazole (29.5 ± 5.5 mm), and nystatin (27.9 ± 5.0 mm). These differences were statistically significant ($p<0.001$). Figure 2 shows the results of the disk diffusion antifungal susceptibility testing, where *C. albicans* isolates appeared green on CHROMagar, and clear inhibition zones were observed around the antifungal disks, indicating antifungal activity. The inhibition zone diameters for nystatin and itraconazole were reported as raw values (mm) only, since no CLSI or EUCAST interpretive

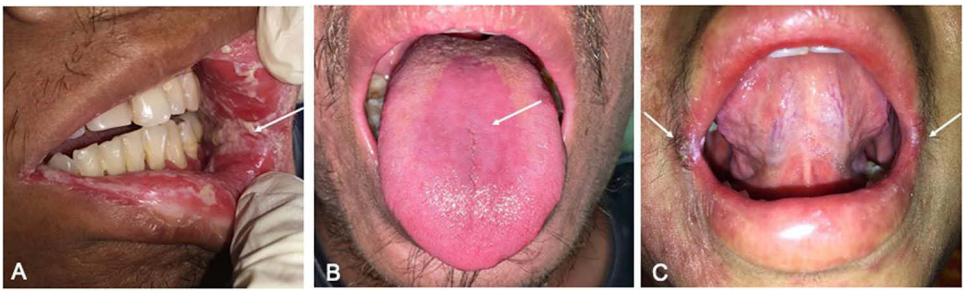

Figure 1 The clinical features of oral candidiasis observed in the study subjects. (**A**). Acute pseudomembranous candidiasis, characterized by the presence of removable white plaques on the labial and buccal mucosa; (**B**) Median rhomboid glossitis, representing an erythematous form of candidiasis that typically affects the midline of the tongue; (**C**) Angular cheilitis, marked by inflammation at the corners of the mouth, which presents with erythema, fissures, and the presence of white exudate.

criteria are available. For fluconazole and voriconazole, categorical interpretations were retained according to CLSI M44-A2 guidelines.

Discussion

This study showed that acute pseudomembranous candidiasis was the most prevalent type of oral candidiasis. This finding aligns with previous studies that have consistently identified pseudomembranous candidiasis as the most frequent clinical presentation in HIV-positive individuals, ranging from mild, curd-like white plaques to more chronic and treatment-resistant forms.[16–18] The demographic characteristics of the participants reflected global patterns, with younger adult males most commonly affected. Many patients also presented with advanced-stage HIV, had not yet received ART, had low TLC suggestive of immune suppression, poor oral hygiene, and risk behaviors such as smoking and alcohol use, all of which are known to increase susceptibility to fungal infections, particularly candidiasis. Notably, the prevalence of oral candidiasis was higher among untreated patients than those receiving HAART, reinforcing the role of immunosuppression and behavioral factors in the development of these infections.[1,17–20]

Previous studies over the past decade have consistently identified *C. albicans* as the most common species associated with oral candidiasis in HIV-positive patients, with reported prevalence rates ranging from 37.2% to 95.2%.[21,22] In line with these findings, the present study also identified *C. albicans* as the predominant species. However, some research has reported a shift toward NCAC species as the dominant isolates in HIV-positive individuals. Paul et al found *C. tropicalis* to be the most frequently isolated species.[23] Moreover, this study detected the presence of NCAC species, including *C. glabrata, C. krusei*, and *C. tropicalis*. Several reports have further documented that mixed colonization by *C. albicans* and NCAC species among HIV patients ranges from 16.5% to 23.7%.[1,21,24,25]

In this study, most *C. albicans* isolates exhibited good sensitivity to the tested antifungal agents, including nystatin, fluconazole, itraconazole, and voriconazole. However, resistance was detected in a subset of samples, specifically against voriconazole, fluconazole, nystatin, and itraconazole. These findings are consistent with global reports, which show low but increasingly recognized resistance rates among clinical isolates of *C. albicans*.[26] Since CLSI or EUCAST has

Table 2 Identification of *Candida* Species

***Candida* Species**	**n (%)**	**Growth (CFU/mL) Median (Range)**
C. albicans	30 (100.0)	270 (1–460)
Non-*Candida albicans Candida*		353 (10–670)
• *C. glabrata*	3 (10.0)	
• *C. krusei*	1 (3.3)	
• *C. tropicalis*	1 (3.3)	

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Table 3 Comparative Analysis of Sensitivity and Inhibition Zone Diameters of Antifungal Agents

	Antifungal Agents				p-value
	Nystatin	**Fluconazole**	**Itraconazole**	**Voriconazole**	
The inhibition Zone Diameter					
• Mean ± SD	27.9 ± 5.0	33.0 ± 9.3	29.5 ± 5.5	34.0 ± 10.7	<0.001*
• Range	6.0–35.6	6.0–52.0	20.2–46.0	6.0–52.0	
Interpretation of Results, n (%)					
• Susceptible	-	27 (90.0)	-	26 (86.7)	1.00
• Intermediate	-	-	-	-	
• Resistant	-	3 (10.0)	-	4 (13.3)	

Notes: *p<0.05 was considered statistically significant. For inhibition zone diameters (Mean ± SD, Range), comparison among four antifungal agents was analyzed using the Friedman test. For categorical comparison (Susceptible vs Resistant), only fluconazole and voriconazole were included, analyzed using Fisher's exact test (two-sided). No official breakpoints are available for nystatin and itraconazole in disk diffusion. Therefore, inhibition zones are reported only as raw values (mm).

established no clinical breakpoints for nystatin and itraconazole, no categorical interpretation of susceptibility or resistance was performed. This study reports only the observed diameters (mm) and recommends future validation using broth microdilution (CLSI M27) to correlate inhibition zones with MICs.

In particular, this study observed fluconazole resistance in 10% of isolates, which falls within the globally reported resistance range of 1% to 24.8%. By comparison, higher resistance rates to other azoles have been reported in previous studies, for example, resistance to itraconazole (20.0%) and voriconazole (20.0%).[5,6,23,27,28] In contrast, Paul et al reported fluconazole resistance as high as 63.3% and voriconazole resistance at 18.3% among HIV-positive patients.[23] Antifungal susceptibility patterns can vary across countries, influenced by differences in geographic variation in patient populations, patterns of antifungal use, differences in testing methodologies, the regional distribution of specific fungal species, and variations in immune status among patients.

Antifungal susceptibility testing (AFST) primarily aims to determine the minimum inhibitory concentration (MIC) of antifungal agents against fungal pathogens, using methods such as broth microdilution, disk diffusion, and gradient diffusion strips. In this study, the disk diffusion method was employed, which offers several advantages, including simplicity, affordability, ease of interpretation, and the capacity to test multiple microorganisms and antifungal agents simultaneously.[10,29] This technique is a valuable tool in both clinical and research settings, enabling efficient and cost-effective evaluation of antifungal susceptibility.

Beyond laboratory methods, demographic and clinical characteristics, such as patient age, underlying medical conditions, socioeconomic status, and antibiotic usage, can also influence the distribution of fungal infections and

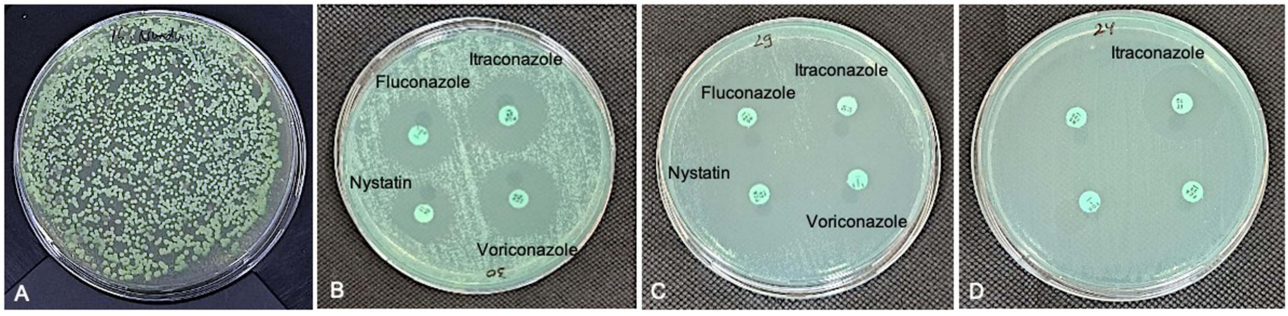

Figure 2 The results of the disk diffusion antifungal susceptibility testing. (**A**) *C. albicans* isolates grown on CHROMagar, appearing green in color; (**B** and **C**) Clear inhibition zones were observed around all four antifungal agents; (**D**). An inhibition zone was observed only around itraconazole, indicating selective susceptibility.

antifungal resistance. For example, countries with a higher proportion of immunocompromised individuals, including those living with HIV, often report a greater burden of fungal infections and may display distinct antifungal susceptibility patterns compared to regions with fewer such cases.[30–32]

Another important consideration is the shifting prevalence of fungal species, which raises concerns about accurate species identification and the emergence of antifungal resistance.[33] Over time, NCAC species, such as *C. glabrata, C. parapsilosis*, and *C. tropicalis*, have increasingly been reported as major pathogens in candidiasis, replacing *C. albicans* as the dominant species in certain regions.[34,35] These NCAC species tend to show higher resistance rates to commonly used antifungal drugs, especially fluconazole, particularly in areas where species surveillance and antifungal resistance monitoring are well established.

Additionally, prolonged exposure to azole antifungals, especially among immunocompromised patients, has been linked to cross-resistance within the azole class, including fluconazole, itraconazole, and voriconazole.[5,23] This trend may be explained by a combination of factors, including extended fluconazole use, patient immunosuppression, the presence of comorbid conditions, and the increasing global prevalence of NCAC species.

Azole resistance in *C. albicans* remains a significant clinical challenge, largely driven by the widespread and prolonged use of azole-based antifungal agents. This resistance is typically associated with decreased intracellular drug accumulation, which can result from reduced drug uptake, enhanced efflux activity, or genetic alterations in the drug's primary target, lanosterol 14α-demethylase (Erg11). In some cases, resistance arises from overexpression of the ERG11 gene or structural mutations that lower the enzyme's binding affinity for azole compounds. Additionally, *C. albicans* can adapt through modifications in sterol biosynthesis pathways or the activation of alternative survival mechanisms. Cross-resistance among azoles, where resistance to one agent, such as fluconazole, also reduces susceptibility to other azoles like itraconazole and voriconazole, has been well documented.[36] In general, azole resistance in *Candida* species can be attributed to three primary mechanisms: structural or expression changes in 14α-demethylase, impaired drug accumulation caused by active efflux or limited uptake, and defects in C5-6 desaturase, which allow the fungus to bypass azole-mediated inhibition by synthesizing alternative sterol compounds.[37–39]

This study also found that nystatin resistance occurred in 6.7% of *C. albicans* isolates, a rate notably higher than those reported in earlier studies, which ranged from 0.8% to 4.9%.[5] Nystatin resistance is commonly linked to alterations in ergosterol biosynthesis, particularly mutations in ERG3 and ERG6, as well as increased activity of efflux pumps. Moreover, biofilm formation significantly contributes to reduced susceptibility, as biofilm-associated fungal cells are shielded by a protective extracellular matrix and exhibit altered metabolic activity, both of which impair antifungal efficacy. Nystatin exerts its antifungal action by binding to ergosterol within the fungal cell membrane, forming pores that disrupt membrane integrity and ultimately cause cell death. Resistance mechanisms can counteract this process by either reducing ergosterol availability for binding or by actively exporting the drug from the cell.[38]

The novelty of our study lies in providing localized data from West Java, Indonesia, a region where epidemiological and antifungal resistance data remain scarce. Although the topic of *Candida* infections in HIV-positive individuals has been covered globally, very few studies in our country have analyzed both species distribution and antifungal resistance using primary clinical isolates. By contributing regional data, our study supports more contextualized and evidence-based treatment guidelines, especially in a healthcare setting where diagnostic limitations and empirical prescribing remain common. This is crucial given the rising clinical impact of NCAC species, which are often intrinsically less susceptible to azoles and are now recognized by the WHO as fungal priority pathogens.

This study has several limitations. The relatively small sample size and single-center design may restrict the generalizability of the results. However, our institution treats a large number of HIV-positive patients annually, and this study provides a foundational dataset that reflects a subset of this population. We acknowledge that CHROMagar *Candida*, although widely used in resource-limited laboratories, has limited sensitivity and specificity for distinguishing closely related NCAC species, such as *C. glabrata, C. parapsilosis*, and *C. auris*, which can share colony morphology. More advanced identification methods, such as Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) or molecular techniques, were not used due to resource constraints, a limitation that highlights the difficulties faced by laboratories with limited equipment or funding. Future studies involving larger, multi-centre samples, incorporating both *C. albicans* and NCAC species, and applying molecular techniques alongside

standardized quantitative susceptibility testing to provide a more comprehensive understanding of antifungal resistance trends in HIV-positive populations are recommended.

Conclusion

This study demonstrated that *C. albicans* remains the most frequently identified species responsible for oral candidiasis in HIV-positive patients. Among the antifungal agents evaluated, voriconazole produced the broadest inhibition zones, reflecting its potent antifungal activity.

In contrast, nystatin and itraconazole demonstrated inhibition zones but could not be categorically interpreted due to the absence of established CLSI/EUCAST breakpoints. A small percentage of *C. albicans* isolates exhibited resistance to fluconazole and voriconazole, suggesting the emergence of antifungal resistance in this immunocompromised population. These results underscore the importance of implementing routine species identification and antifungal susceptibility testing to guide therapy, enhance treatment outcomes, and monitor emerging resistance in HIV-positive individuals.

Data Sharing Statement

The data used in the current study are available from the corresponding author upon reasonable request.

Ethical Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran (Ethical Clearance No: 81/UN6.KEP/EC/2024). Written informed consent was obtained from all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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