REVIEW PAPER

Human immunodeficiency virus and *Candida albicans* co-infection in Iran: a systematic review

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Abstract

Candidiasis is one of serious problems in immunosuppressed patients, including HIV patients. *Candida albicans* is a fungi causing different humans diseases. Immunosuppression is a hallmark of HIV infection, and its' deficiency can introduce complications through impairment of immune cells, such as CD4+ lymphocytes.

The aim of the current review was to investigate the importance of candidiasis co-infection in HIV Iranian patients. In addition, it focused on prognosis, prevention, and management of candidiasis since this infection could have a large scale of mortality in people living with HIV and AIDS (PLWHA).

For the current systematic review, multiple electronic bibliographic databases were searched, including PubMed, EMBASE, Scopus, Web of Science, Google Scholar, and Iranian databases from 1 January 2011 until 24 February 2020.

Majority of articles (n = 11) investigated oral and oropharyngeal candidiasis (OPC) with a prevalence range of 16.5% to 43.82% in HIV-positive patients. Apart from oral candidiasis, one reference also evaluated vagina, nail, and skin candidiasis. *C. albicans* isolates were the most prevalent species, with a 34.42%, 52.2%, and 82.2% frequency rate in three studies, while in other papers, there was a fluctuation in *C. albicans* prevalence.

Candidiasis is the most prevalent opportunistic infection in AIDS patients. Due to high prevalence rate of oropharyngeal candidiasis, routine screening of HIV patients is recommended. Since CD4+ T cells count decreased in HIV patients, periodic examinations are necessary. Fluconazole is most commonly used azole to treat *Candida* due to its mechanism; however, anti-fungal prophylaxis needs more investigation to reduce mortality and morbidity associated with mucosal candidiasis.

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Introduction

Human immunodeficiency virus (HIV) is considered one of the significant epidemics worldwide, with a substantial impact on human, social, and economic conditions [1]. According to an estimation, in 2018, almost 37.9 million people were living with HIV worldwide [2]. HIV is an asymptomatic chronic infection and can remain essentially unchanged during years [1]. During 8-10 years of infection, a vast majority of infected people (70-80%) undergo a chronic form of the disease, while in rapid progressor (RPs) consisting of 10-15% of HIV-infected persons, CD4+ T cells decline more rapidly within first years of infection [3]. Immunosuppression is considered to be the HIV infection hallmark [4]. Different complications arise from this situation [1]. Through impairment of immune cells, such as CD4+ and lymphocytes [5], the incidence of numerous opportunistic infections (OIs), malignant tumors, and dysfunction of various body organs increase [6].

OIs are infections that are more frequent and severe among people with defective immune systems, including people living with human immunodeficiency virus (PLHIV). HIV-associated OIs prevalence and incidence differ widely [2]. *Candida albicans*, *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, *Pneumocystis carinii* (syn. *P. jiroveci*), and *Toxoplasma gondii* in fewer reports, are microorganisms that are responsible for opportunistic infections [7]. In developing countries, the most prevalent OIs are oral candidiasis, tuberculosis (TB), pneumocystis pneumonia, varicella-zoster virus, bacterial pneumonia, dermatophyte infections, and herpes zoster [2]. *Candida albicans* can turn into an opportunistic pathogen with remarkable morbidity in immunodeficient patients [8].

Fungi comprise of almost 7% (611,000 species) of all eukaryotic species on the Earth, which among them only about 600 species can infect humans [9]. Naturally, fungi are not dangerous and colonize different parts of the human body, such as mucosa and skin. Nevertheless, when defense mechanism of the human body is repressed, especially cellular response of the immune system, these commensals turn into parasite pathogens [10].

More than 40 known *Candida* species are being related to human infections. In a worldwide study conducted on invasive candidiasis from 1997 to 2003, the top eight species were *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. guilliermondii*, *C. kefyr*, and *C. lusitaniae* [11].

C. albicans is one of the very few fungal species causing disease in humans [12]. Candidiasis is a fungal infection with a wide range of clinical manifestations. These clinical signs range from mucosal-cutaneous infections to life-threatening invasive diseases, which relate to high mortality rates. The fourth leading agent causing nosocomial bloodstream infections (BSI) in the USA is *Candida*, especially in neutropenic or immunocompromised patients [13].

Candida species can cause acute or chronic infections that generally limit skin and mucous membranes, but they can cause severe systemic problems. Candidiasis is divided into different types, such as mucosal candidiasis, oropharyngeal candidiasis (OPC), cutaneous candidiasis, vulvovaginal candidiasis (VVC), and systemic or disseminated candidiasis (candidemia) [14].

Different factors can make individuals more susceptible to candidiasis, including pregnancy, folate or iron deficiencies, endocrine disturbances, carbohydrate-rich foods, broad-spectrum antibiotic, steroid usage and xerostomia, and inherent or acquired immune system impairments [4]. *Candida* spp. is one of the serious problems in immunosuppressed individuals, including HIV-positive patients [12]. OIs are considered the main reasons for morbidity and mortality among HIV-infected patients, responsible for 94.1% of HIV-related deaths [2]. In the United States, the crude mortality rate of *Candida* spp. causing acquired systemic infections reaches up to 50% [9]. *Candida* infection is the most prevalent OI. In people with HIV (PLWH), the oropharyngeal, esophageal, vaginal, and cutaneous forms of candidiasis are prevalent. At various levels of AIDS, almost 90% of patients manifest oropharyngeal candidiasis, and invasive forms of fungal blood infections are life-threatening [15].

Therefore, the current review briefly examined the importance of candidiasis and HIV co-infection in Iranian patients. In addition, it focused on prognosis, prevention, and management of candidiasis, since this infection could have a large scale of mortality in PLWH.

Material and methods

Study question

This study was designed to address the pattern of HIV and *C. albicans* co-infection in Iran.

Search strategies

We searched multiple electronic bibliographic databases for the current systematic review, including Scopus, PubMed, Web of Science, EMBASE, Google Scholar, and Iranian databases from 1 January 2011 until 24 February 2020. Medical subject headings (MeSH) were applied to determine keywords for this study. The keywords and their combination included 'HIV' AND 'Human immunodeficiency viruses' OR 'AIDS' OR 'Acquired immunodeficiency syndrome' AND 'Candida albicans' OR 'Candida' OR 'C. albicans' OR 'Candidiasis' OR 'Co-infection' OR 'Drug resistance' AND 'Iran' OR 'Iranian'. Our search was restricted to English and Persian publication languages. Two independent reviewers did the search, and a third researcher verified the found results (Figure 1).

Study selection

The analysts assigned a list from titles and abstracts of the existing databases articles. At this phase, cross-sectional studies, cohort, and case series studies investigating

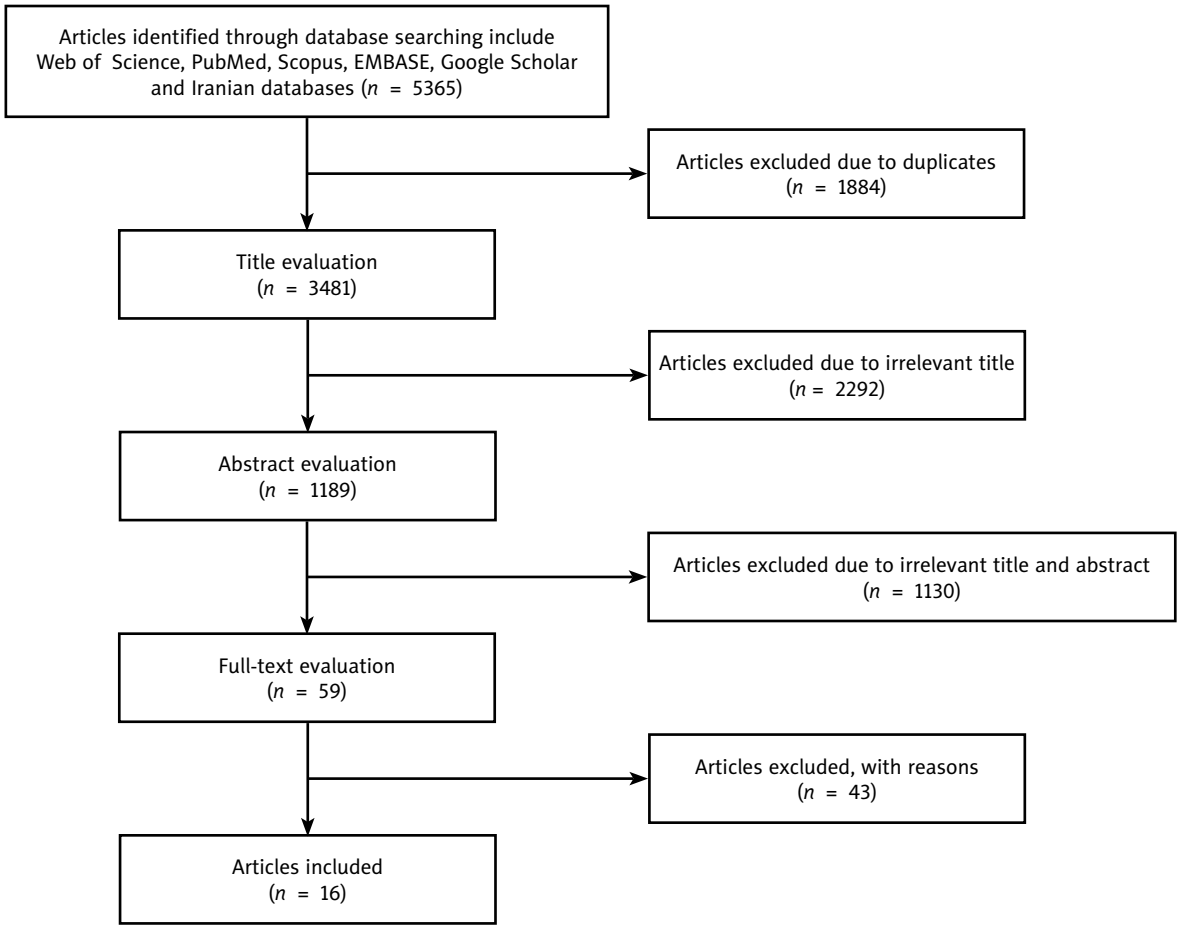

Figure 1. Flow chart of studies selection

HIV/*Candida* co-infection were included in the essential list. Next, articles, which shared duplicate titles were excluded. Finally, abstracts and full-text of the recorded articles were surveyed to obtain related papers.

Inclusion criteria

The original articles reporting HIV/*C. albicans* co-infection covering cutaneous candidiasis, oral candidiasis, and vulvovaginal candidiasis in HIV or AIDS stage patients were included from January 2011 to February 2020.

Exclusion criteria

We excluded articles irrelevant to this study's subject or those not meeting eligibility criteria. Articles with distorted study population and those using non-standard estimation methods were avoided. Articles that assessed *C. albicans* infection separate and without HIV or AIDS were also excluded. We removed studies conducted without Iranian patients or samples, literature review papers (literature reviews were examined to find relevant citations), congress abstracts, and letters to the editor.

Quality assessment

Articles' quality was assessed with a developed checklist, modified based on our records data, including study type, study design, number of patients, infection type, sample type, sample size, detection method, drug resistance, data collection tools, and analysis of the results. Each article was given a score of 0-12, and a score of ≥ 8 was considered satisfactory from methodological quality viewpoint.

Data extraction

Two reviewers were recruited to screen the conclusive search results based on titles, abstracts, and full texts according to inclusion and exclusion criteria to prevent publication bias. A third expert researcher was recruited to resolve disagreements between two reviewers. A data extraction Excel sheet software covering first author's name, publication year, province, study design, HIV-positive patient number, background medical condition, age range, gender, sampling, *C. albicans* infection type, examination methods, drug resistance, and studies main results were used to summarize the extracted data of the included articles.

Results

Search results

Searching of scientific databases included Scopus, PubMed, Web of Science, EMBASE, Google Scholar, and Iranian databases, and resulted in 5,365 studies. After we removed duplicate studies, 3,481 unique papers remained. Title screening revealed 1,189 studies, and in the following abstract screening, 59 articles based on the inclusion criteria were found. Final screening by full-text evaluation resulted in 16 studies, which were included for the study's data extraction. The included citations were published from 2011 to 2018. After that, information was extracted by carefully verifying summaries and full-texts. In the screening procedure, 5,349 studies were excluded, based on duplicate data, including those not containing any HIV/*Candida* co-infection, and any significance and relevant data reports.

Consequently, the 16 studies suitable for inclusion in systematic review of qualitative assessment were imported to Endnote library and Excel sheet software. Table 1 and Supplement 1 outlines extraction details and main results of the selected studies. Search strategy and study selection flow charts are presented in Figure 1.

Demographic data

The 15 cross-sectional studies and one case-control investigation were performed in different regions of Iran, and majority of them were conducted in Tehran (n = 9) [16-24], while three studies were reported from Kerman [25-27]. Although several studies did not include any age and gender information, other studies contained a diverse range of ages from 16 to 66 years old, involving 490 males and 140 females. In two studies, which reported genders in percentage, the overall male percentage was over 80, and female percentage was lower than 20 [20, 28]. Various citations declared their enrollment time, about one to two years.

Samples collection

In total, 16 studies were analyzed in our study. These papers provided patients' samples investigating different body parts, including oral scrapping swabs, nails, wounds, and vagina. Meanwhile, some studies did not include clear data about sample sizes. A large number of samples in each screened article were dedicated to HIV/*Candida* co-infected individuals.

Type and prevalence of candidiasis

The majority of articles (n = 11) investigated oral and oropharyngeal candidiasis (OPC), with a prevalence range of 16.5% to 43.82% in HIV-positive patients. One paper also evaluated vagina, nail, and skin candidiasis, apart from oral candidiasis. Regarding pseudo-membranous candidiasis, one data was available with a 26% prevalence rate in HIV-positive patients with CD4+ count greater than 200 [28]. *C. albicans* was the most prevalent species, with a 52.2%, 82.2%, and 34.42% frequency rate in three studies [22, 26, 27], while in other references, there was a fluctuation in *C. albicans* prevalence.

Risk factors and underlying diseases

Five studies evaluated the multiple risk factors and background diseases in patients, such as tobacco smoking, drug

Table 1. Studies conducted on HIV and *Candida albicans* co-infection prevalence in Iran

First author	Year of publication	Enrollment time	Province	Study design	Ref.
Pour	2018	–	Kerman, Iran	Case-control	[25]
Farahbakhsh	2018	–	Tehran, Iran	Cross-sectional	[16]
Hamzehee	2019	2017-2018	Kerman, Iran	Cross-sectional	[26]
Khedri	2018	2016-2017	Tehran, Iran	Cross-sectional	[17]
Salehi	2018	–	Tehran, Iran	Cross-sectional	[18]
Taghipour	2018	–	Iran	Cross-sectional	[31]
Shokri	2017	–	Iran	Cross-sectional	[30]
Salari	2016	–	Tehran, Iran	Cross-sectional	[20]
Sharifzadeh	2016	–	Iran	Cross-sectional	[29]
Katiraee	2015	–	Tehran, Iran	Cross-sectional	[19]
Shekari Ebrahim Abad	2015	–	Tehran, Iran	Cross-sectional	[22]
Pakfetrat	2015	2008-2010	Iran	Cross-sectional	[28]
Ashrafi Tamai	2014	–	Tehran, Iran	Cross-sectional	[21]
Katiraee	2014	–	Tehran, Iran	Cross-sectional	[23]
Khatibi	2011	–	Tehran, Iran	Descriptive cross-sectional	[24]
Mousavi	2012	2009-2010	Kerman, Iran	Cross-sectional	[27]

injection, hepatitis, denture stomatitis, CD4+ T lymphocyte decreased counts, high-risk sexual activity, mother-to-child transmission, HBV, HCV, HTLV-1 infection, purulent discharge, erythematous candidiasis, and perleche, severe periodontitis, and xerostomia, showing that each of them could affect the prevalence of HIV/*Candida* co-infection rate directly or indirectly.

Detection methods

Distinct methods were used to determine *Candida* genotypes and drug resistances prevalence, including direct microscopic examination, urease and assimilation test, sugar fermentation, germ-tube test, CHROMagar, beta glucosidase, disk diffusion testing, minimum inhibitory concentration (MIC) test, anti-fungal susceptibility testing, multiplex PCR, PCR-RFLP, real-time PCR, and multi-locus sequence typing (MLST) technique.

Candida genotypes

Only in one study, various *Candida* genotypes were examined using genotyping techniques and specific PCR primers of 25S, rDNA, and RPS genes [21]. Therefore, A, B, and C genotypes frequencies were 66 (66%), 24 (24%), and 10 (10%), respectively. Moreover, genotypes E and D were not found. A total number of 66 A genotypes were divided into A2 (14%), A3 (30%), A2/3 (20%), and A3/4 (2%). The total number of 24 B genotype isolates were categorized as B2 (4%), B3 (6%), B2/3 (10%), and B3/4 (4%), and among 10 C genotype, the isolates were classified into C2 (6%) and C2/3 (4%) genotypes.

Efficacy of anti-fungal medications

Of the 16 articles analyzed, seven studies reported anti-fungal susceptibility profiles for some anti-fungal medications, including amphotericin B, caspofungin, fluconazole, itraconazole, voriconazole, ketoconazole, clotrimazole, luliconazole, and nystatin. Two studies evaluated various substances' anti-fungal ability, including honey samples and plant oils against *Candida* isolates [29, 30]. Although the results showed many variations in determining anti-fungal susceptibility patterns, fluconazole-resistant rate (n = 16, 17.6%) was higher than itraconazole (n = 15, 16.7%) in one study [17]. Furthermore, the least drug resistance prevalence was reported in caspofungin (1.8%) in two citations [19, 23]. In another article, more than half of *Candida* isolates (n = 57) were susceptible to fluconazole [20]. Based on one study report on the activity of caspofungin, 8 (7.4%) of fluconazole-resistant isolates showed caspofungin resistance, with MICs of > 64 µg/ml and MIC rate of 1 (12.5%) in caspofungin non-susceptible isolates; in fluconazole-resistant isolates, it was more than 2 µg/ml. Moreover, 7 (87.5%) of caspofungin susceptible isolates in fluconazole-resistant isolates showed less than 2 µg/ml MIC rate [22]. According to Taghipour *et al.* study investigating the anti-fungal activity of luliconazole against different strains of *Candida* species, *C. albicans* MIC rate was reported 0.5 µg/ml [31]. One study reported that *Saccharomyces boulardii* extract exposure could change the *C. albicans* susceptibility pattern against ketoconazole and itraconazole. Therefore, ketoconazole increased *Candida* isolates susceptibility from 53.3% to 73.3%, and also, the sensitivity to itraconazole increased from 6.7% to 26.7% [18]. Based on Sharifzadeh *et al.* study evaluating the effects of plant oils on FLU-resistant and FLU-susceptible strains, the inhibitory effect of these oils was found, and demonstrated MIC values ranging from 300 to 3,200 µg. ml-1 for FLU-resistant strains, and 300 to 3,000 µg. ml-1 for FLU-susceptible strains [29]. Regarding the anti-fungal effect of honey samples against *C. albicans*, one study reported that all honey samples had anti-fungal activity against FLU-resistant *Candida* species [30].

Discussion

This systematic review investigated human immunodeficiency virus and *C. albicans* co-infection among the Iranian population. Data used in the current review was restricted to Tehran and Kerman province of Iran, from 2011 to 2020, and further studies are not available from other regions. Since candidiasis infections are the most common and recurrent opportunistic infections in AIDS patients, particularly in the early and advanced stages of AIDS, it is an important and challenging issue in managing these patients. The number of AIDS patients has been increasing in all Middle Eastern countries, and according to UNAIDS data, in 2018, about 61,000 people were living with AIDS in Iran.

The prevalence of AIDS in men is more than in women, although its' has also increased in women in recent years. Some studies suggest that OPC is more prevalent in women than in men. OPC has been represented to be expected in HIV-positive patients with a mean age of 34 years [32, 33]. However, other studies show that the highest prevalence of OPC in HIV patients in age range of 60-70 years, is due to weakened immune system in immunocompromised patients [34]. Typical manifestations of OPC are pseudo-membranous, erythematous, and angular cheilitis. Although OPC is easily treated, it can be a serious problem when accompanied by a defect in the immune system, especially in HIV-positive patients, and it can also be painful. Additionally, OPC may predispose patients to progression of more invasive diseases, such as esophageal candidiasis, which in 3-10% of HIV patients was observed as the first opportunistic infection. *C. albicans* is most frequent and responsible for 80% of esophageal candidiasis cases [35].

Oropharyngeal and esophageal candidiasis are early markers to predict and evaluate the progression and prognosis of HIV infection. A period of about 10 to 15 years exists between sero-conversion to HIV and full-blown AIDS [36]. During this period, oral candidiasis lesions, a decrease in CD4+ cell counts, and night sweats can be observed in patients related to HIV infection [37]. The presence of OPC

can most likely indicate progressive cellular immunodeficiency and initiate AIDS. In more than 50% of patients, during about 3 years after manifestation of oral *Candida* lesions, HIV infection becomes AIDS [38]. Since OPC and oral candida lesions are mostly seen in the advanced stages of HIV, even with unknown CD4+ cell counts level, they can be indirect markers of immunosuppression. Therefore, regular oral examinations are important for physicians in HIV-infected patients, particularly in those with uncertain status or CD4+ cell counts [39]. On the other hand, the increased risk of OPC and esophageal candidiasis in HIV infection is in significant contrast to the prevalence of vaginal candidiasis in HIV-infected women [40, 41].

A new molecular-based method leads to determining various *Candida* strains, providing an essential tool to predict the progression of HIV infection [42]. In patients with OPC, majority are infected with *C. albicans*, and the rest are infected with non-albicans species of *Candida* alone or in combination with *C. albicans*. Studies show that through each episode of OPC, many patients are infected with a unique strain of *C. albicans*, and in a minority of patients, the strain change with a new genotype of *C. albicans*, or change to non-albicans species of *Candida*. Furthermore, *C. albicans* strain from HIV patients indicates different karyotypes in comparison with those isolated from healthy individuals [43]. Many HIV patients represent several strains of *C. albicans* with different susceptibility to fluconazole. The incidence of fluconazole resistance shows a variable pattern in HIV patients. The gain of a new resistance genotype of *C. albicans* or progression in a previously susceptible strain may cause resistance to fluconazole. Clinically, because patients exhibit a different response to anti-fungal agents, concurrent presence of various strains of *C. albicans* has an important role in treating candidiasis. Accordingly, HIV patients and other individuals with candidiasis should be strongly monitored for the existence of multiple *C. albicans* strains during disease progression.

Several techniques have been used for the assessment of different strains of *C. albicans*, such as pulsed-field gel electrophoresis (PFGE), restriction fragment length polymorphism (RFLP), random amplification of polymorphic DNA (RAPD), and Southern blot assays. These methods facilitate determination of sub-types of colonization and strains of *C. albicans* during multiple infective episodes in HIV-infected patients. The evidence show that aging is a significant risk factor of oral candidiasis among HIV patients. With increasing age, the risk of colonization also increased in patients. Smoking, alcohol consumption, diabetes, nutritional deficiencies, immunosuppression, antibiotics, and clinical stage of AIDS, are other risk factors associated with oral candidiasis in HIV patients [44].

Several anti-fungal agents are used for candidiasis treatment, including fluconazole, amphotericin B, nystatin, and flucytosine. Fluconazole is the most commonly used azole for treatment of Candida infection due to low cost and toxicity [45]. There are two limitations to using fluconazole for the management of candidiasis in HIV patients: firstly, it reduces the sensitivity of *C. albicans* strains to this drug, and secondly, it can cause *C. albicans* to shift to other *Candida* species, such as *C. krusei* and *C. glabrata*, which are less susceptible to fluconazole [46]. Anti-fungals' resistance significantly increase, and is a common phenomenon while using fluconazole, particularly in HIV patients in recurrent and prolonged treatment. Due to broad spectrum of activity of itraconazole in patients who failed response to fluconazole, a higher dose of itraconazole can be used as well as in immunocompromised fluconazole-resistant patients [44]. Compared to fluconazole and itraconazole, ketoconazole is more effective, but because of drug interactions and hepatotoxicity, it is not recommended to treat candidiasis, especially in elderly patients [47]. Prophylaxis with various anti-fungal agents has successfully reduced the incidence of candidiasis infections. Although some anti-fungal drugs, such as fluconazole, could be an effective option, due to low rate of morbidity and mortality related to mucosal candidiasis, anti-fungal prophylaxis to prevent candidiasis is not recommended [48, 49]. In order to estimate the pattern of different microbial co-infections types among HIV-positive patients and in terms of limitations of the current study, it could refer to lack of evaluation of other microbial agents other than *C. albicans* in HIV-positive and AIDS patients. Meanwhile, clinical trials and meta-analysis studies could be suggested to determine the prevalence of different co-infections types and drug resistance patterns among these groups of patients.

Conclusions

Candidiasis infections are the most prevalent opportunistic infections in AIDS patients, especially at the early and advanced stages of the disease. Therefore, it is an important and challenging issue in managing these groups of patients. Due to the high prevalence rate of oropharyngeal candidiasis, routine screening among HIV-positive patients is recommended. Since CD4+ T cells count decrease in HIV patients, the clinician's periodic examinations of *Candida* infection symptoms are necessary. Additionally, serological and molecular laboratory detection methods for following *C. albicans* infection could reduce candidiasis progression. Prophylaxis with various anti-fungal agents has been successful in reducing the incidence of candidiasis. Fluconazole is the most commonly used azole to treat *Candida* due to its mechanism. However, anti-fungal prophylaxis is an arguable choice for preventing candidiasis infection, because of low morbidity and mortality related to mucosal candidiasis.

Conflict of interest

The authors declare no conflict of interest.

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