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Review

Review of Treatments for Oropharyngeal Fungal Infections in HIV/AIDS Patients

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Abstract: HIV and AIDS patients are susceptible to opportunistic infections. Oral candidiasis or thrush is the primary manifestation of fungal infection in these patients. The primary objective of this literature review was to summarize established and novel treatment options for oropharyngeal fungal infections in HIV/AIDS patients. Azoles and polyenes are the two primary antifungal drug classes employed for the treatment of oral candidiasis. A literature review was conducted on Medline and Google Scholar in October of 2021 using the keywords "Oral", "Fungal", "HIV", and "Treatment". Included studies were clinical trials, meta-analyses, and randomized controlled trials. Nineteen studies regarding azoles, polyenes, and novel treatments for oropharyngeal fungal infections in HIV/AIDS patients were examined in this review. The primary concern demonstrated from these studies is increased reports of resistance to antifungals, especially development of fluconazole resistance. Additionally, studies demonstrated that fluconazole had different relapse durations comparative to other medications, and that posaconazole could possibly act as an alternate form of treatment. Nystatin was indicated as a first-line therapy for thrush in multiple studies but could be upstaged by miconazole nitrate in resource-poor settings. Amphotericin B was an effective treatment option and was shown to be resilient in terms of fungal resistance, however potent adverse side effects were reported. Alternative treatments, such as immunoglobulin antibodies and lemon grass, revealed promising antifungal effects for immunocompromised individuals. Taken together, this review provides a thorough summary of treatment options of oropharyngeal fungal infections in HIV/AIDS patients.

Keywords: fungal infections; thrush; oropharyngeal; oral; HIV; AIDS; antifungals; resistance

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1. Introduction

Human immunodeficiency virus (HIV) is a retrovirus that attacks the body's immune system. More specifically, HIV targets and destroys CD4 white blood cells which are essential in the prevention of infection or disease. The advanced form of HIV is referred to as acquired immunodeficiency syndrome (AIDS), and a CD4 cell count below 200 cells/mm^3 is one of the indicators used in the diagnosis of AIDS [1]. This stage of infection is acquired when the immune system has been significantly damaged or degraded. Therefore, persons with HIV/AIDS are vulnerable to opportunistic microbial infections [1,2]. This study will be focused on fungal microbes and treatment options associated with oropharyngeal infections in HIV/AIDS patients. Common fungal species associated with oropharyngeal infections in HIV/AIDS patients are presented in Table 1 and listed here: *Candida albicans*,

C. parapsilosis, *C. tropicalis*, *C. guilliermondii*, *C. krusei*, *C. glabrata*, *C. stellatoides*, and *Talaromyces marneffei* [2–9].

Table 1. Summary of oropharyngeal fungal strains associated with HIV and known antifungal resistance.

Fungus	Known Antifungal Resistance in the Literature
Candida sp.	Fluconazole [3,7,9], Itraconazole [7], Ketoconazole [7]
Candida albicans	—
Candida glabrata	Fluconazole [7,9]
Candida guilliermondii	—
Candida krusei	Fluconazole [7,9]
Candida parapsilosis	—
Candida stellatoides	—
Candida tropicalis	—
Talaromyces marneffei	—

Epidemiological estimates report that approximately 50% of AIDS-related deaths relate to invasive fungal infections, and this accounts for up to 1 million deaths per year [10]. The most commonly encountered form of fungal infection is known as thrush, or oral candidiasis, which occurs in 85–90% of cases [11]. Oral candidiasis is characterized by excessive growth of the *Candida* species in the superficial epithelium of the oral mucosa. Fungal overgrowth can cause creamy white lesions [2]. If left untreated, these lesions can directly contribute to the morbidity rates associated with HIV infections [10]. Fortunately, various drugs are in place to treat oropharyngeal fungal infections. Two primary forms of antifungal drug classes prescribed for the treatment of oral candidiasis in HIV patients include azoles and polyenes.

Azoles are fungistatic compounds that contain one or more azole rings bearing two to three atoms of nitrogen in five-membered ring heterocycles. The primary mechanism of antifungal action in azoles is related to the inhibition of the cytochrome P450 14α-demethylase. This enzyme converts fungal lanosterol to ergosterol, which participates in the synthesis of the fungal cell wall. The azole family includes imidazoles and triazoles. Imidazoles are distinguished from triazoles due to their azole ring carrying two atoms of nitrogen, whereas triazoles contain three [12]. The most commonly employed azoles are triazoles, and these include butoconazole, fluconazole, itraconazole, and econazole [13]. Additionally, compared to imidazoles, triazoles demonstrate greater target specificity, are more resistant to metabolic degradation, and have superior potency [12]. Azoles ordinarily have long half-lives at approximately 30 h, with the exception of voriconazole which has a half-life of 6 h [14].

Polyenes such as amphotericin B and nystatin are ionophores that are characterized as fungicidal and fungistatic antibiotics. These drugs contain a macrolide with a β-hydroxylated portion and a conjugated double-bond system in the lactone ring. Polyenes function by binding with fungal sterols in the cell membrane in an irreversible manner that results in the deterioration of the membrane integrity. This process causes changes in cell permeability leading to metabolic degradation, and ultimately leads to cell death [15]. The polyene amphotericin B has an initial half-life of 10–24 h, but after chronic use can last up to 15 days [16]. Nystatin is limited to treatment of cutaneous, mucocutaneous, and gastrointestinal fungal infections due to its poor absorption following oral or topical use. As nystatin is not metabolized to a significant extent, it is eliminated through the feces, and its elimination time is related to the gastrointestinal transit time [17].

The overall goal of this review article is to provide an overview of primary clinical research studies that have evaluated the effectiveness of antifungals in the management of oropharyngeal fungal infections in HIV/AIDS patients. In addition, this review will highlight novel treatment options, including intravenous immunoglobulin antibodies [18]. These novel forms of therapy are important in consideration of the arms race in successfully treating microbial infections while preventing the evolution of resistant strains. Like bacteria, fungi are constantly evolving and developing resistance to existing treatments and prophylaxis application.

2. Methodology

A literature review search was conducted in October of 2021 using Medline (PubMed) and Google Scholar, as previously described [19–21]. On PubMed, the advanced search function was used. Title and abstracts were searched for the keywords "Oral", "Fungal", and "HIV" using the "Add with AND" search function in between the keywords. The search was then narrowed to "Clinical Trial", "Meta-Analysis", and "Randomized Controlled Trial". Palliative, preventative, or curative drug therapies were considered, regardless of whether the control group received placebo treatment. No restrictions were made in regard to age, sex, or race. At this stage, the number of selected studies was 12. On Google Scholar, the ordinary search function was used and searched for the keywords "Oral", "Fungal", "HIV", and "Treatment". Seven more articles were selected based on the inclusion keywords. This concluded the article search with 19 total included studies.

3. Results

Overview of studies included in this review—Nineteen articles were extracted from PubMed and Google Scholar. Table 2 summarizes the key characteristics and conclusions from these studies. The total amount of participants in the collective studies was 3517. Of these, 3489 persons were HIV- or AIDS-positive. Of the 28 non-HIV subjects, two were immunosuppressed children. Trials were conducted in different countries of varying populations with different socioeconomic realities [19]. The countries included in this review article are Belgium, Canada, Chile, France, Mexico, Uganda, the United Kingdom, and the United States.

Of the 19 examined articles, 16 trials were performed with patients who had some manifestation of oropharyngeal candidiasis. Two trials were carried out with patients who presented with talaromycosis, and one study examined systemic fungal infections. Fifteen trials were performed on HIV- or AIDS-positive adults, one trial included both immunocompromised and HIV+ patients, one trial was performed with HIV/AIDS-positive children, one trial with immunosuppressed children, and one was unspecified.

Regarding drug class, in the 19 articles, azoles and polyenes were the primary drug families investigated for the treatment of oropharyngeal fungal infections in HIV/AIDS-infected persons. Sixteen studies investigated some form of triazole drug, of which three included an imidazole. Five studies investigated a polyene-based drug.

Below, the 19 primary articles will be summarized based on drug class. Here, the articles have been organized as triazole studies, polyenes studies, comparative studies (i.e., comparing one drug class to another), and novel therapies. The discussion section will highlight common points and/or themes identified from reviewing these studies.

Triazoles—Nine included papers focused on triazoles as treatment or therapy of oropharyngeal fungal infections in HIV- or AIDS-infected individuals. One multicenter study compared fluconazole to ketoconazole for treatment of oropharyngeal candidiasis in HIV+ children. Fluconazole-treated children exhibited higher clinical and mycological cure rates (88% and 71%, respectively) than ketoconazole-treated children at the conclusion of treatment (81% and 57%, respectively). Fluconazole and ketoconazole were shown to have similar effectiveness and safety [22].

Another multicenter trial by Vazquez et al. compared posaconazole and fluconazole in the treatment of oropharyngeal fungal infections in HIV- or AIDS-infected individuals. For

13 days, subjects were administered either 200 mg of posaconazole or fluconazole oral suspension. On day 14, clinical success was achieved in 91.7% of 169 posaconazole patients and 92.5% of 160 fluconazole patients, suggesting that posaconazole is comparable to fluconazole. On day 14, mycological success from treatment was the same (68%) in posaconazole and fluconazole treatment. However, posaconazole participants had considerably better mycological success than fluconazole users by day 42 (40.6% vs. 26.4%, respectively). Clinical recurrence was less common in posaconazole patients than in fluconazole patients (31.5% vs. 38.2%). Both treatments had comparable adverse effects [3].

One study examined the use of itraconazole capsules to prevent deep fungal infections in HIV-infected patients. Half of the patients received itraconazole and the other half received placebo capsules. Treatment with itraconazole reduced the frequency of oral candidiasis (25% vs. 48%) and the time it took for oral candidiasis to develop, but not the number of deep fungal infections (11 vs. 13) [23]. Saag et al. investigated treatment of fluconazole-refractory oropharyngeal candidiasis with itraconazole oral solution for HIV+ patients. Itraconazole oral solution was administered for 14 days to 74 HIV+ individuals with proven oropharyngeal candidiasis who had failed fluconazole treatment. Among these subjects, 55% had a clinical response to the treatment by day 28, with an average response time of 7 days. In this study, the authors linked inadequate adherence to the recommended regimen, increased medication metabolism, poor absorption, and excessive development of a treatment-resistant *Candida* species to refractory oral candidiasis. However, they mentioned that changes in *C. albicans* which contribute to treatment resistance are the most common and primary cause of refractory oral candidiasis in HIV patients [24].

A trial by Chariyalertsak et al. examined itraconazole for primary prophylaxis of systemic fungal infections for persons with AIDS. Oral itraconazole was administered to 63 patients, whereas a placebo was given to the other 66 patients. One patient (1.6%) who received itraconazole showed systemic fungal infection, compared to eleven patients (16.7%) with systemic infection in the placebo group. In the itraconazole prophylaxis group, the incidence of recurrent or refractory mucosal candidiasis was dramatically decreased [25].

A study from 1995 described the use of a fluconazole suspension in patients with AIDS for the treatment of esophageal candidiasis. After symptom remission, therapy was continued for another two weeks. Following the conclusion of treatment, a second endoscopy was completed. Symptom resolution was noted in all 41 evaluable patients, where 17 (41%) had resolution by 1 week, 37 (90%) by 2 weeks, and 40 (98%) by 3 weeks [26]. Goldman et al. compared the administration of fluconazole in a continuous vs. episodic manner in patients with AIDS and a history of oropharyngeal candidiasis. After 42 months, 4.1% of subjects in the continuous fluconazole arm developed a form of fluconazole-refractory oropharyngeal candidiasis, compared with 4.3% of subjects in the episodic fluconazole group [27].

Casjka et al. studied the population pharmacokinetics of fluconazole for the secondary prevention of oropharyngeal candidiasis in HIV+ patients. Serum drug concentration measurements were acquired over 37 months in patients not receiving highly active antiretroviral therapy. Average fluconazole concentration or time spent over minimal inhibitory concentrations did not improve the prediction of oropharyngeal infection recurrence or microbiological resistance in the clinical setting. Thus, the authors state that the relationship between fluconazole concentrations and secondary prevention of oropharyngeal candidiasis is weak. They note that, though preventive treatment has been shown to increase resistance to fluconazole, it has benefits in terms of cost, compliance, and medication interactions [28].

A trial investigated itraconazole as a method of relapse prevention concerning *Penicillium marneffei* infections in HIV-infected patients. Patients were administered either oral itraconazole or placebo as maintenance therapy. Within a year, none of the 36 patients on itraconazole experienced a relapse of *Penicillium marneffei* infection, but 20 of the 35 patients on the placebo (57%) relapsed. Moreover, prophylaxis with oral itraconazole

is well-tolerated and prevents relapses of *Penicillium marneffei* infection in HIV-infected individuals [8].

Polyenes—Two studies included in this review article solely investigated polyenes for the therapy of oropharyngeal fungus in HIV- or AIDS-infected persons. MacPhail et al. investigated the prophylaxis of HIV-associated oral candidiasis through the use of nystatin pastilles. This study demonstrated that prophylaxis using nystatin was significantly more effective than the placebo for delaying the contraction of oral candidiasis. However, the estimates for effectiveness of nystatin in the delay of oral candidiasis onset were based on a fairly small sample size (128 HIV+ subjects) and primarily on patients aged 27–50 (76% of patients) [29].

Comparative studies—Four studies compared a triazole vs. polyene treatment for therapy of oropharyngeal fungal infections in HIV- or AIDS-infected persons. One study mentioned triazoles, imidazoles, and polyenes. The study by Pons et al. compared the use of fluconazole (triazole) vs. nystatin (polyene) for the treatment of candidiasis in patients with AIDS. This randomized comparison used fluconazole vs. liquid nystatin using a swish–retain–swallow procedure, and 87% of the fluconazole-treated patients were clinically cured after two weeks, compared to 52% of the nystatin-treated patients. Fluconazole eliminated *Candida* organisms from the oral flora in 60% of cases, compared to just 6% with nystatin. On day 28 of the study, the fluconazole group had fewer relapses (18%) than the nystatin group, which had a 44% relapse rate. By day 42, the relapse disparity was non-existent. In this study, treatment of oral candidiasis in HIV-infected individuals with fluconazole oral suspension as a systemic therapy was more successful than liquid nystatin as a topical therapy and offered a longer disease-free interval before relapse [30].

A second study (from 1996) analyzed the risk factors associated with emerging azole-resistant oral candidiasis during HIV infection over a 12-month period. Twenty-four (37%) of the isolated strains of *Candida* species resisted fluconazole (triazole) and itraconazole (triazole). Here, five (8%) strains resisted fluconazole, and two (3%) strains resisted ketoconazole (imidazole). None of the isolated *Candida* strains resisted amphotericin B (polyene). The authors of this study concluded that due to the potential risk of emergence of azole-resistant *Candida* strains in AIDS patients, it is critical to cautiously identify an antifungal medicine for the treatment of moderate fungal infections. This study also states that HIV-infected individuals frequently experience chronic and/or recurring bouts of oral candidiasis, and oral candidiasis resistant to fluconazole has been recorded in both HIV-infected and other immunocompromised patients [7].

A trial in 2017 evaluated itraconazole and amphotericin B for the treatment of HIV-related talaromycosis. For 11 days, 440 randomly assigned HIV+ adults with talaromycosis were administered intravenous amphotericin B or itraconazole capsules. Following this period, all patients received maintenance therapy using itraconazole. Amphotericin B therapy had significantly more rapid clinical resolution and fungal clearance compared to itraconazole. Moreover, amphotericin B significantly lowered rates of immune reconstitution inflammatory syndrome and rates of relapse compared to itraconazole. In addition, the amphotericin B group had a 6.5% mortality rate, while the itraconazole group had a 7.4% mortality rate. At week 24, however, the amphotericin B group had an 11.3% death rate while the itraconazole group had a 21.0% death rate [6].

Three comparative studies focused on triazole vs. imidazole therapies for oropharyngeal fungal infections of HIV/AIDS patients. Van Roey et al. compared a mucoadhesive buccal slow-release tablet of miconazole nitrate to systemic treatment using ketoconazole tablets for the treatment of oropharyngeal candidiasis in HIV-infected persons. The analysis of 332 patients in this study showed that miconazole nitrate was comparable to ketoconazole treatment, with clinical response rates of 87% and 90%, respectively [31]. A multicenter trial examined the use of an oral itraconazole (triazole) solution compared to clotrimazole (imidazole) troches in immunocompromised subjects with oropharyngeal candidiasis. Significantly more subjects treated with itraconazole demonstrated negative cultures at the end of treatment compared to the clotrimazole group (60% vs. 32%, respectively).

Results were comparable for the clinical response success rate (53% vs. 30%, respectively). These results were similar in patients with HIV/AIDS. This study claims that, though they are inconvenient, nystatin and clotrimazole troches are typically the first-line therapy for oropharyngeal candidiasis [32].

In 2008, a clinical trial compared clotrimazole troches to an itraconazole oral solution for treatment of oral candidiasis in AIDS patients. After 1 week, 29 patients were randomly treated with itraconazole oral solution or clotrimazole troches. Clinical severity scores decreased in all patients until the end of therapy, but there was no statistically significant difference between the two groups. By the end of one week of therapy, 73.3% of clotrimazole patients and 66.7% of itraconazole patients had achieved clinical cure. In this study, Linpiyawan et al. indicate that suppressive treatment is not recommended because it increases the risk of developing clinical tolerance or medication resistance. They also note that azole agent resistance has been reported more frequently. However, itraconazole has so far been associated with a low rate of resistance, suggesting that it may be less frequent than ketoconazole and fluconazole in developing resistance [33].

Novel therapies—Two novel therapies were conducted for the treatment of oropharyngeal fungal infections of immunocompromised patients. Wright et al. examined the treatment of oral thrush in HIV or AIDS patients with lemon juice, lemon grass, and gentian violet. The 0.5% gentian violet group had 9 clinical successes and 8 failures, the lemon juice group had 16 clinical successes and 2 failures, and the lemon grass group had 15 clinical successes and 2 failures. Thirty individuals withdrew from the study. The individuals who finished the study were analyzed and both lemon treatments demonstrated superior results compared to the gentian violet aqueous solution for the treatment of oral thrush in HIV+ persons [34].

One study examined a novel form of therapy for two immunocompromised pediatric patients experiencing oral fungal infections. At the time of the study in 2018, the two patients were 8-year-old females with well-characterized primary immunodeficiencies that were prone to chronic mucocutaneous candidiasis (CMC). These two patients had previously been resistant to pharmacological treatments for CMC. In this study, the patients were administered commercial human polyvalent intravenous IgG (IV IgG) three times a day as a mouthwash over the course of two weeks. After 13 days, the IV IgG treatment diminished the *C. albicans* mouth infection by 98% in the first patient and 70% in the second patient. Following IV IgG therapy, complementary nystatin and caspofungin treatments were administered and complete fungal clearance was noted [18].

Table 2. Summary of studies included in this review. Acronyms: IRIS = immune reconstitution inflammatory syndrome; IV IgG = human polyvalent intravenous antibodies.

Study	Drug and Class	Target	Geography	Age (Mean)	Number of Participants	Findings	Year of Publication	PMID [Ref #]
1	Fluconazole (Triazole), Ketoconazole (Triazole)	Oropharyngeal candidiasis	Spain, France	Fluconazole: 4.6, Ketoconazole: 3.8	46 HIV/AIDS+	Fluconazole and ketoconazole are comparable for the treatment of oropharyngeal candidiasis in HIV+ children.	1994	8070443 [22]
2	Fluconazole Suspension (Triazole)	Esophageal candidiasis	United States	37 ± 2 years	41 AIDS patients	Fluconazole suspension was effective for the treatment of all 41 patients with esophageal candidiasis. 90% of patients had symptom resolution by the 2-week mark.	1995	8580277 [26]
3	Nystatin (Polyenes)	Oral candidiasis	University of California, San Francisco, United States	38	128 HIV+	Administration of prophylaxis Nystatin pastilles is effective in delaying time to oral candidiasis.	1996	8757423 [29]
4	Ketoconazole (Triazole), Fluconazole (Triazole), Itraconazole (Triazole), Amphotericin B (Polyenes)	Resistant oral candidosis	Italy	Case: 33 ± 5, Controls: 31 ± 6	64 HIV+	Twenty-four (37%) of the isolated strains were resistant both to itraconazole and fluconazole, five (8%) to fluconazole alone, and two (3%) to ketoconazole alone, while none of the isolated strains were resistant to amphotericin B.	1996	8937963 [7]
5	Fluconazole (Triazole), Nystatin (Polyenes)	Oropharyngeal candidiasis	United States	38	167 HIV+	Fluconazole is more effective than Nystatin for eradication of oral candidiasis and longer disease-free relapse time.	1997	9195083 [30]

Table 2. *Cont.*

Study	Drug and Class	Target	Geography	Age (Mean)	Number of Participants	Findings	Year of Publication	PMID [Ref #]
6	Itraconazole (Triazole), Clotrimazole troches (Imidazole)	Oropharyngeal candidiasis	Multicenter, United States	Itraconazole: 40 ± 11, Clotrimazole: 40 ± 11	Itraconazole: 75 patients (61 HIV+), Clotrimazole: 74 (62 HIV+), total = 149	Percentage of patients with negative cultures at the end of treatment was significantly greater in the itraconazole group than in the clotrimazole group (60% vs. 32%, respectively).	1997	9220211 [32]
7	Itraconazole (Triazole)	*Penicillium marneffei*	Thailand	Itraconazole: 29.7 (19–49), Placebo: 29.5 (19–49)	71 HIV+ finished the study	In HIV+ persons who completed successful primary treatment of *Penicillium marneffei* infection, secondary prophylaxis with oral itraconazole was well-tolerated and prevented relapses. 57% of the patients assigned to the placebo had relapse within the first year.	1998	9845708 [8]
8	Itraconazole oral solution (Triazole)	Oropharyngeal candidiasis	15 Centers in the United States	37 ± 8	74 HIV/AIDS+	Among patients with fluconazole-unresponsive oropharyngeal candidiasis, 55% achieved clinical response by day 28. All patients who followed the 6-week follow-up phase relapsed.	1999	10555103 [24]
9	Itraconazole Oral Solution (Triazole), Clotrimazole troches (Imidazole)	Oral candidiasis	Thailand	32 years (15–62 years)	29 AIDS patients (15 clotrimazole, 14 itraconazole)	Clinical cure rates for oral candidiasis when treated with itraconazole and clotrimazole troches were essentially equivalent (73.3% vs. 66.7%). Relapse rates also comparable, but slightly higher in clotrimazole group. Low incidence in resistance for itraconazole suggests it is less common than ketoconazole and fluconazole.	2000	11123451 [33]

Table 2. *Cont.*

Study	Drug and Class	Target	Geography	Age (Mean)	Number of Participants	Findings	Year of Publication	PMID [Ref #]
10	Itraconazole (Triazole)	Oral candidiasis	Australia, United Kingdom, Canada, South Africa, Belgium	Itraconazole: 37.8, Placebo: 37.6	Itraconazole: 187, Placebo: 187 (n = 374 HIV+)	Itraconazole reduced incidence of oral candidiasis and time to develop infection vs. placebo, but not the amount of deep fungal infections. Chronic itraconazole treatment well-tolerated in HIV+ persons. Insufficient deep fungal infections noted to determine if prophylaxis with itraconazole was effective for this condition.	2001	11737382 [23]
11	Fluconazole (Triazole)	Oropharyngeal candidiasis	Switzerland	37 years (26–63 years)	132 HIV+ patients (66 fluconazole, 66 placebo)	Average fluconazole concentration or time above minimal inhibitory concentrations did not clinically improve prediction of occurrence of oropharyngeal candidiasis relapse or microbiological resistance. Relationship between fluconazole concentrations and preventive effectiveness was poor.	2001	11829202 [28]
12	Itraconazole (Triazole)	Systemic fungal infections	Thailand	Itraconazole: 33.4, Placebo: 33.3	129 HIV+ patients (63 itraconazole, 66 placebo)	Prophylaxis significantly more effective with the itraconazole group than the placebo group for the treatment of mucosal candidiasis.	2002	11740718 [25]

Table 2. *Cont.*

Study	Drug and Class	Target	Geography	Age (Mean)	Number of Participants	Findings	Year of Publication	PMID [Ref #]
13	Miconazole Nitrate (Imidazole), Ketoconazole (Triazole)	Oropharyngeal candidiasis	Uganda, East Africa	18+	Miconazole: 178, Ketoconazole: 179 (n = 357 HIV+)	Miconazole nitrate is comparable to ketoconazole for treatment of oropharyngeal candidiasis in HIV+ persons. Higher rate of gastrointestinal and drug-related adverse events seen with ketoconazole treatment.	2004	14722446 [31]
14	Fluconazole (Triazole) in episodic vs. continuous therapy	Oropharyngeal candidiasis and esophageal candidiasis	United States	38 (19–71 years)	829 HIV+ patients	Administration of continuous fluconazole therapy not linked to increased relapse risk of oropharyngeal candidiasis or esophageal candidiasis, when compared to episodic fluconazole therapy. Studied patients had access to active antiretroviral therapy.	2005	16231260 [27]
15	Posaconazole (Triazole), Fluconazole (Triazole)	Oropharyngeal candidiasis	South Africa, USA, Mexico, Chile	Posaconazole: 36.4 ± 7.8, Fluconazole: 37.6 ± 9.1	350 HIV+	Posaconazole and fluconazole are comparable for treatment of oropharyngeal candidiasis. Posaconazole appeared more effective than fluconazole over time for mycological success and in delaying relapse.	2006	16575739 [3]
16	Lemon juice, Lemon grass, Gentian violet	Oral thrush	South Africa	75% under 34	52 HIV+ completed the study	Lemon juice and lemon grass > gentian violet in the treatment of oral thrush in HIV+ population. Additionally, lemon treatments leave no dental staining.	2009	19109001 [34]

Table 2. *Cont.*

Study	Drug and Class	Target	Geography	Age (Mean)	Number of Participants	Findings	Year of Publication	PMID [Ref #]
17	Itraconazole (Triazole), Amphotericin B (Polyenes)	Talaromycosis—*Talaromyces marneffei*	Vietnam, United Kingdom, United States,	Amphotericin B: 34 (30–38 years), Itraconazole: 34 (29–38)	435 HIV+ adults with talaromycosis	Treatment with amphotericin was associated with significantly faster clinical resolution and fungal clearance as well as significantly lower rates of relapse and IRIS than itraconazole.	2017	28614691 [6]
18	IVIg or Intravenous Immunoglobulin (Antibodies)	Chronic oral candidiasis	Mexico	8-year-old females (non-HIV but immuno-compromised)	2 non-HIV	Pediatric female patients with candidiasis responded to IV IgG mouthwash. Treatment significantly reduced mouth infection after 13 days, and fungal clearance was noted after complementary nystatin and caspofungin treatments.	2018	30627128 [18]
19	Fluconazole (Triazole), Nystatin (Polyenes)	Oral candidiasis	Dr. Soetomo Hospital, Indonesia	Unavailable	88 HIV/AIDS+ patients	Nystatin was the most administered oral antifungal to combat oral candidiasis. The most common drug-related problem for antifungal therapy was nausea.	2018	Unavailable [35]

4. Discussion

The accumulated results of the 19 reviewed studies demonstrated a few recurrent findings regarding antifungals, both generally and drug-specific. The principal drugs discussed were amphotericin B, fluconazole, itraconazole, ketoconazole, and nystatin. In the examined studies, antifungal resistance was a common theme, with recurrent mention to fluconazole. Additionally, we observed different fluconazole relapse durations comparative to other medications. Other points of discussion include first-line therapy, the efficiency of amphotericin B, and novel treatment options. The text below will provide further discussion points on the topics described above.

Antifungal resistance—The overall literature suggests a wide variety of factors that can lead to refractory and/or treatment-resistant candidiasis. Examples include poor prescription adherence, how commonly a drug is used, the length of treatment, and development of a treatment-resistant *Candida* species [7,24,28,32,33]. Another factor of concern is the use of long-term suppressive treatments, because these agents increase the risk of developing clinical tolerance or medication resistance [33]. The principal methods by which *Candida* strains acquire azole resistance are genetic alterations that allow overexpression of the ergosterol pathway (*ERG11*, *ERG3*, *ERG6*, *UPC2*) and mutations to transport genes (*CDR1*, *CDR2*, *MDR1*) that enhance export of azoles [9,36].

Three papers explicitly mention fluconazole as a subject of attention regarding fungal resistance [7,28,32]. Fluconazole is a low-cost triazole with benefits in terms of compliance, minimal medication interactions, and low rates of adverse effects. Fluconazole can be utilized for prophylaxis management of oropharyngeal candidiasis in HIV+ patients [28,35]. However, preventive treatment using fluconazole has been recorded to increase fungal resistance [28]. Persistent and/or relapse episodes of oral candidiasis have often been observed in HIV-infected patients who are unresponsive to fluconazole [7]. Seeing as fluconazole is one of the most administered antifungals for oral candidiasis in some regions, it is of no surprise that strains of *Candida*, such as *Candida glabrata* and *Candida krusei,* have become resistant [7,35]. It could prove useful to identify the species causing the fungal infection prior to choosing the antifungal for treatment.

In consideration of the development of treatment-resistant fungal species, it is becoming increasingly important to bring careful consideration in the selection of an appropriate antifungal treatment for oropharyngeal fungal infections in HIV/AIDS-infected persons [7,32,33]. Additionally, the increase in resistance to treatment demonstrates the need to develop different or new treatment options for oropharyngeal fungus infections [32], especially in HIV- or AIDS-affected individuals, where morbidity rates due to these infections are higher than in an unaffected population [10]. For example, in a study from France which described the cause of death in 924 HIV-infected individuals, 262 (27%) deaths were attributed to opportunistic infection [37]. It is in part for this reason that funding and furthering research on novel treatments of oropharyngeal fungus infections, such as intravenous immunoglobulin antibodies, is crucial [18]. It could be worthwhile for first-line or go-to treatments to change periodically to help fight conditions such as persistent and/or recurrent episodes of oral candidiasis in HIV/AIDS-infected patients. For example, lower rates of resistance with itraconazole compared to ketoconazole or fluconazole could make it a viable option for treatment [33]. Additionally, according to Saag et al., drug prescription regimen adherence is one of the factors leading to the development of drug-resistant *Candida* species [24]. Proper adherence to an antifungal prescription regimen, comparably to an antibiotic regimen, should be followed through to the end of treatment to minimize the possible development of a treatment-resistant fungus.

Fluconazole relapse compared to other drugs—Relapse times varied following fluconazole treatment of oropharyngeal-related candidiasis in HIV- or AIDS-infected individuals [3,22,30]. In one study, fluconazole was superior in the prevention of relapse compared to nystatin in the first 28 days, but this difference no longer existed after day 42 [30]. This indicated that fluconazole, as an oral suspension, was more successful than liquid nystatin in providing a longer disease-free time before infection recurrence. In another study

comparing fluconazole and ketoconazole for treatment of oropharyngeal candidiasis in HIV+ children, both patient groups showed comparable relapse rates two to four weeks following therapy [22]. Posaconazole and fluconazole demonstrated comparable mycological success after two weeks. However, noticeably better continuous mycological success was observed in the posaconazole group at day 42 [3]. These findings suggest that posaconazole could be an alternate option to the more commonly encountered fluconazole. Perhaps posaconazole could also be used in cases of chronic recurring candidiasis infections where fluconazole is no longer a viable treatment option.

First-line therapy—According to three studies, nystatin served as a first-line therapy for oropharyngeal candidiasis or oral fungal infections as a whole in HIV- or AIDS-infected individuals [31,32,35]. The World Health Organization (WHO) recommends 100,000 IU of nystatin orally 3 times daily for 7 days or gentian violet as first-line therapy of oropharyngeal candidiasis [31]. Though it is an efficient treatment when correctly followed, nystatin is inconvenient to use (which leads to a lack of prescription regimen adherence), has a bitter taste, and is accompanied by side effects [31,32]. Some common side effects with nystatin use include nausea and vomiting [35]. Here, treatment with topical miconazole nitrate could be considered as an alternative to nystatin, as it is one of the only medications administered once daily. This reduced daily administration can be beneficial in resource-poor settings where ease of use can maximize the odds of successful therapy [31].

Amphotericin B is very effective, however, it is associated with adverse side effects—The polyene amphotericin B was noted to serve as an efficient and resistant-free option for fungal infections in HIV or AIDS patients [5–7]. Tumbarello et al. examined resistance in *Candida* species to different drug treatments (fluconazole, itraconazole, and ketoconazole) and showed that none of the isolated species resisted treatment with amphotericin B [7]. Another study compared itraconazole to amphotericin B in the treatment of HIV-associated talaromycosis, and amphotericin B proved to achieve faster clinical resolution as well as fungal clearance than itraconazole. Amphotericin B also provided reduced rates of relapse and immune reconstitution inflammatory syndrome [6]. Taken together, amphotericin B appears to be a reliable form of treatment for oropharyngeal fungal infections of HIV- or AIDS-infected individuals. Unfortunately, notable side effects are associated with the use of amphotericin B [7]. For example, in one study, four patients needed to discontinue drug treatment due to abnormalities in liver function, hypokalemia, renal function impairment, and severe gastrointestinal tract reactions (including nausea and vomiting). Following discontinuation of treatment with amphotericin B, all patients experienced symptom relief [5]. In consideration of the severity of these side effects, amphotericin B could serve as a last-resort therapy for severe fungal infections in HIV- or AIDS-infected persons. The development of novel drugs with the efficacy of amphotericin B but without the side effects will be beneficial to the treatment of oral candidiasis.

Huang et al. demonstrated that voriconazole was an effective and safe induction therapy of HIV-associated disseminated talaromycosis compared to amphotericin B. Although talaromycosis predominantly affects the face and neck, the oropharyngeal region is also susceptible to this fungal species. This study examined voriconazole and amphotericin B as induction therapy for talaromycosis in HIV-infected patients. Enrolled patients had a confirmed infection and received either intravenous amphotericin B or voriconazole as induction therapy and received maintenance therapy by oral itraconazole thereafter. Response rates to both amphotericin B and voriconazole were similar at primary and follow-up efficacy evaluations. Few adverse reactions were noted in both drug groups. The hospital stay durations were shorter for the voriconazole group [5]. This finding suggests that voriconazole should be examined in the context of oropharyngeal fungal infections in HIV+ patients as this antifungal may result in reduced adverse effects compared to amphotericin B.

Alternative and novel treatments for candidiasis—Two alternate forms of treatment were examined in this review article. The development of alternate forms of treatment for oropharyngeal fungus infections is crucial to prevent stagnation in the race against

developing treatment resistance. Wright et al. investigated lemon juice and lemon grass (*Cymbopogon citratus*) vs. gentian violet for treatment of oral thrush in HIV+ persons. Results showed that treatment with gentian violet was inferior to lemon juice and lemon grass. Gentian violet also left noticeable and recognizable violet staining in the oral cavity, and this discoloration of the mouth is associated with HIV and AIDS [34]. Unfortunately, this discoloration brings about unwanted societal stigma against HIV-infected individuals. Thus, given that lemon juice and lemon grass options are non-staining and more efficient, the use of gentian violet should likely be avoided as a form of treatment.

The use of commercial human polyvalent intravenous IgG for treatment of recurring chronic mucocutaneous candidiasis in two immunocompromised pediatric patients was successful. Though these patients had been resistant to previous pharmacological therapies, IV IgG mouthwash successfully diminished *C. albicans* mouth infection [18]. This study is a primary example for the importance of continued research and development of novel antifungal therapies. Pedraza-Sánchez et al. demonstrated that alternative forms of treatments could be used to obtain fungal clearance in cases where patients resisted previous pharmacological therapies. Human polyvalent intravenous IgG combined with following nystatin and caspofungin complementary therapy could serve as a new standard for effective treatment of chronic mucocutaneous candidiasis.

5. Conclusions

This review article demonstrated that antifungal therapies have significantly different treatment efficacy regarding clinical success, infection relapse prevention, patient prescription regimen adherence, and potential for developing resistant fungal strains. Due to the different antifungal drug families and their different mechanisms of action, it is important to explore the potential of non-first-line therapies for oropharyngeal fungal infections in HIV+ or AIDS+ persons. Some studies demonstrate that a variety of factors (adherence, drug of use, length of treatment, etc.) contribute to refractory or treatment-resistant candidiasis, and that fluconazole should be treated with caution due to increased resistance. Unfortunately, due to the volatile and multi-factored nature of evolutionary or adaptive biology, it is difficult to pinpoint the cause and effect regarding developing antifungal resistance. This emphasizes the need for novel discoveries to combat increased antifungal resistance. Here, research into other types of intravenous immunoglobulin antibodies for treatment of oral candidiasis is beneficial and warranted.

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