A SYSTEMATIC REVIEW OF THE MANAGEMENT OF ORAL CANDIDIASIS ASSOCIATED WITH HIV/AIDS

By

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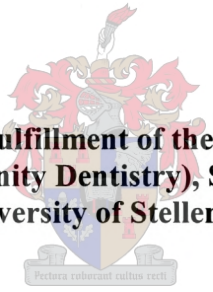

Thesis submitted in partial fulfillment of the requirement for the Degree of MSc Dental Science (Community Dentistry), School of Oral Health Sciences, University of Stellenbosch.

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March 2002

DECLARATION

I, HANY AHED ALBOUGY hereby declare that the work contained in this thesis is my own original work and has not previously in its entirety or in part, been submitted at any university for a degree.

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.....19....day of ....feb.....2001

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ABSTRACT

The purpose of this review was to investigate the management of oral candidiasis in HIV/AIDS patients and to evaluate the different guidelines that are available for its management. To achieve this aim, three objectives were identified: (i) to identify and report on the different interventions used to manage oral candidiasis, in patients with HIV/AIDS, (ii) to determine the efficacy of these interventions, and (iii) to provide guidelines for management. A thorough systematic search of the literature was carried out and all relevant papers were graded into three levels of evidence (A, B, and C) and scored for quality according to set criteria.

A number of topical and systemic antifungal medications are used to treat oral candidiasis in HIV-positive patients. These include the poleyne antibiotics, nystatin and amphotericin B. Milder episodes of oral candidiasis respond to topical therapy with nystatin, clotrimazole troches or oral ketoconazole. Fluconazole has been extensively evaluated as a treatment for candidiasis. With HIV-infection, a cure rate of 82% has been achieved with a daily oral dose of 50 mg. Fluconazole was found to be a better choice of treatment for relapsing oropharyngeal candidiasis, resulting in either better cure rates or better prevention of relapse. Intravenous amphotericin B has been found to be effective therapy in azole refractory candidiasis where it was shown to be safe and well tolerated.

Topical therapies were found to be effective treatment for uncomplicated oropharyngeal candidiasis, however patients relapsed more quickly than those treated with oral systemic antifungal therapy. Overall, nystatin appears less effective than clotrimazole and the azoles in the treatment of oropharyngeal candidiasis. With regard to the

resolution of clinical symptoms, clotrimazole was found to be just as effective as the azoles, except when patient compliance was poor. Fluconazole-treated patients were more likely to remain disease-free during the fluconazole follow-up period than with those treated with other interventions.

Relatively few studies were qualified to address the provision of guidelines for the management of oral candidiasis in primary health care settings. Most of the studies found were of moderate and low quality level of evidence. These studies included the assessment of different guidelines for identification, treatment and dental needs. They stressed that patients with HIV need dentists who will act as primary health care providers, together with other providers to ensure adequate overall care.

Given the level of interest and importance of candidiasis associated with treatment of HIV-positive patients, it is surprising to find that little high quality research has been undertaken. As such, it is hoped that this review would provide researchers, oral health care workers and other health care providers with an overview of the management of oral candidiasis associated with HIV/AIDS.

OPSOMMING

Die doelstelling van die oorsig was om ondersoek in te stel na die hantering van orale kandidiase in HIV/AIDS pasiënte asook om die verskillende beskikbare riglyne vir die behandeling daarvan te evalueer. Ter verwesenliking van hierdie doelstelling is drie doelwitte geïdentifiseer: (i) om die intervensies wat gebruik word in die hantering van orale kandidiase behandeling te identifiseer, (ii) om die effektiwiteit van hierdie intervensies te identifiseer en (iii) om op grond hiervan riglyne vir die hantering voor te stel. 'n Sistematiese literatuursoektog is uitgevoer en alle relevante artikels is in drie groepe geklassifiseer (A, B en C) op grond van die data kwaliteit.

'n Verskeidenheid topikale en sistemiese antifungale middels word gebruik om orale kandidiase in HIV-positiewe pasiënte te behandel. 'n Sukseskoers van 82% is met die gebruik van 'n daaglikse dosis van 50 mg medikament gerapporteer. Fluconazole was die beter keuse van middel vir die behandeling van terugkerende orofaringeale kandidiase.

Topikale behandeling was effektief in die behandeling van ongekompliseerde orofaringeale kandidiase, hoewel die kans op terugkeer van die toestand groter was as met die sistemiese middels. Pasiënte wat met flukonasool behandel is, het 'n groter kans gehad om siektevry te bly vergeleke met pasiënte op die ander intervensies.

Meeste van die studies was van middelmatige tot lae kwaliteit en gevolglik was dit moeilik om behandelingsriglyne te stel. Wat egter wel duidelik is, is dat HIV pasiënte primêre mondsorg benodig wat saam met ander versorging omvattende sorg sal verseker.

DEDICATION

I would like to dedicate this thesis to my parents and my family for their support and encouragement.

ACKNOWLEDGEMENTS

It is a great pleasure to thank the following people for their help and support. Special thanks to:

- Professor Usuf Chikte, Associate Dean: Faculty of Health Sciences for his support and encouragement.
- Professor Sudeshni Naidoo, Department of Community Dentistry, for her encouragement and valuable advice.
- Professor A J Louw, Head of Community Dentistry Department.
- Dr V Yengopal for his advice given with a friendly manner.
- Dr S Akasha for his patience, effort and advice.
- Ms M Mullar, MRC for her advice and support.
- Staff of the Department of Community Dentistry.
- The librarians of Medical School Library, University of Stellenbosch, for their kindness and valuable help with obtaining references.
- To my family for their tolerance during my absence.

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CHAPTER 1

Introduction

Fungi are ubiquitous organisms. They live in soil, water, animals, and human beings. The earliest exposure to fungi that most humans experience occurs during birth while passing through the vaginal canal. In human beings, fungi can inhabit a variety of habitats. Yeast, such as *Candida albicans* is frequently isolated from the oral cavity. Oral candidiasis has been recognized as a clinical entity since the time of Hippocrates (Lynch, 1994), who described it in association with severe underlying disease in his treatise "Epidemics" which was published in the 4th century BC.

Candida species (Candida spp.) are omnipresent, and certain species, most notably *Candida albicans* (*C.albicans)* are present in the natural flora of humans. These species routinely inhabit mucosal tissues and skin and co-exist in an innocuous manner as a saprophytic colonizer or commensal. In times of stress, and when the body's immune defence systems are compromised and the normal balance altered, these organisms can emerge as pathogens (Samaranayake, 1992).

Candidiasis is the name used to describe infections caused by yeast species of the genus *Candida*. *Candida spp.* may cause mild superficial mucocutanous infections and rarely, invasive life-threatening disease. The latter is usually due to invasion by endogenous colonizing strains of *Candida spp.* in the presence of lowered host defence mechanisms. *C.albicans* is the species responsible for the majority of these infections (Reef and Mayer, 1995). Oral candidiasis is a frequent and early manifestation of disease associated with the human immunodeficiency virus (HIV) (Samaranayake, 1989) and has been reported in

more than 90% of patients with acquired immunodeficiency syndrome (AIDS) (Phelan, Saltzman, Friendland and Klein, 1987). Candidiasis may occur as a clinical sign and symptom of HIV (Van Meter, Gallo, Garcia-Rojas, Tan and Silverman, 1994), most commonly presenting as pseudomembranous candidiasis, erythematous candidiasis, or angular cheilitis.

Although oral candidiasis can occur at any stage of HIV infection, it is most common in patients with low CD_4 counts (Greenspan, 1994a). *Candida* infection of the oral cavity in many cases, is simply treated with topical antifungal agents and the removal of any predisposing factors (Odds, 1988). Numerous oral and systemic therapeutic agents are used to treat oral candidiasis. The efficacy, safety and cost effectiveness of the agent must be considered when prescribing for the treatment of oral candidiasis (Greenspan, 1994a).

The management of oral candidiasis is an important part of the care of an HIV infected individual. The high frequency of oropharyngeal candidiasis in immunocompromised patients has led many institutions to develop guidelines for the use of antifungal agents as a line of treatment. However, few specific recommendations have been made regarding the management of oropharyngeal candidiasis in patients infected with HIV (Powderly, Mayer and Pefect, 1999a). The purpose of this study was to investigate, through a systematic review, the management of oral candidiasis associated with HIV/AIDS.

CHAPTER 2

2. Literature Review

2.1 Biology of Candida albicans

Candida albicans is frequently found as a commensal in the oral cavity, gastro-intestinal and vaginal mucosa. Infection is usually endogenous, although cross-infection can occur, e.g., from mother to baby and from baby to baby. *C.albicans* exists as a dimorphic yeast and grows as spherical to oval budding yeast cells (blastospores), 3-5 to 5-10 microns in size, or as cylindrical, multinucleated hyphae. Germ-tube formation leading to hyphal development is considered important to the pathogenesis of candidal infection (Odds, 1988). It is usually present as a harmless asymptomatic commensal but can manifest as a pathogen. The organism has been described as the most common and serious fungal pathogen of man (Shepherd, Poulter and Sullivan, 1985).

2.1.1 Taxonomy

At least 20 genera and nearly 90 species of yeasts have been isolated and classified from human beings. The genus *Candida* is a collection of about 150 asporgenus yeast species. They are classified among the fungi imperfecti in the class Deuteromycetes (Shepherd, Poulter and Sullivan, 1985). Seven *Candida spp.* are of major medical importance and of these, *C.albicans*, *C.tropicalis* and *C.glabrata* are the most frequently isolated. The other pathogenic *Candida spp.* are *C.parpasilosis, C.stellatoidea, C.guilliermondi, C.krusei* and *C.pseudotropicalis*. Within the class Deuteromycetes, the distinguishing feature of the *Candida spp.* is their ability to form pseudohyphae, the only exception being C.glabrata (Shepherd, Poulter and Sullivan, 1985).

The taxonomic classification of *C.albicans* remains a subject of great debate as a result of different morphologic forms of the organism (Lynch, 1994). *C.albicans* is antigenically divided into two groups: A, which it shares with *C.tropicalis*, and B, which is shared by *C.stellatoidea*. *C.albicans* can be divided into a number of biotypes, which are important in studies of the epidemiology of outbreaks of disease and in clusters of cases in restricted areas. Certain biotypes may be more virulent than others and spread through hospital units just as particular Staphylococcal types or Pseudomonas types are known to spread (Rippon, 1988). The main feature of the genus *Candida* is the absence of any teleomorphic forms and the genus is therefore placed in the subdivision Deuteromycotina (see Table 1).

There are a number of techniques described to type *C.albicans* strains, and these include sereotyping, resistogram typing, morphotyping, killer typing, biotyping, immunoblotting, electrophoretic karyotyping and DNA finger printing. However, it is generally accepted that none of these methods are ideal (Tsang, Samaranayake, Philipsen, McCullough, Reichart, Schmidt-Westhausen, Scully and Porter, 1995). The current data indicate that there are many different sub-strains of oral *C.albicans* present in HIV-infected patients. Korting et al., (1988) found biotypes of 61 oral *C.albicans* isolates from HIV infected individuals, with or without signs of candidiasis.

Table: 1

Classification of the genus Candida (Barnett, Payne and Yarrow, 1990)

Kingdom: Fungi

Division: E umycotina

Subdivision: Ascomycotina

Subdivision: Basidiomycotina

Subdivision: Deuteromycotina

Class: Blastomycetes

Family: Sporoblomycetacea

Family: Cryptococcacea

Genus: Candida

Species: albicans.

2.1.2 Oral Carriage

Reports of oral carriage of *C.albicans* vary greatly in the literature, although most investigators (Arendrof and Walker, 1980; Odds, 1988; Schmid, Voss and Soll, 1990) agree that yeasts are commonly found in the oral cavity of healthy people and that a significant percentage of the species found are *C.albicans* (Lynch, 1994). The mean carriage rates of *C.albicans* for normal people and for patients are 18% and 41%, respectively. Carriage of yeast is also influenced by age. The highest incidence is approximately 50% in infants from 1 week to 18 months of age, followed by adults with a mean carriage rate of 20%. Neonates and children have the lowest carriage rates at 16% and 9% respectively (Odds, 1988). It is important to note that the isolation of *C.albicans* or other *Candida spp.* from the oral cavity, in the absence of lesions, does not constitute evidence of clinical candidiasis (Cannon, Holmes, Mason and Monk, 1995).

Healthy subjects who are *Candida* carriers have approximately 300 to 500 colony-forming units per ml of saliva (Arendrof and Walker, 1980). The number of colony-forming units has a diurnal variation, with higher counts in the early morning and late afternoon (Schmid, Voss and Soll, 1990). The highest numbers of *Candida spp.* are thought to be present on the dorsum of the tongue, followed by the palate and buccal mucosa.

2.2 Pathogenesis

Candidiasis is caused primarily by *C.albicans* and less frequently, by other species, e.g. C.parpsilosis and C.tropicalis. The disease itself generally takes two forms: superficial (mucosa) and invasive (disseminated). *C.albicans* can infect virtually every tissue in the human body, but by far the most common manifestation of candidiasis are superficial lesions of the mucosa surfaces (Shepherd, Poulter and Sullivan, 1985). The commensal

nature of these organisms implies that the vast majority of oral candidiasis are endogenous in origin and that eradication of the organism from the human host by antifungal therapy is difficult. The latter has obvious implications in the management of oral candidiasis, because maintenance therapy may be required to keep infection at bay, particularly in immunocompromised patients (Samaranayake, 1992).

Factors which play a role in the transformation of *Candida* from commensal to pathogen include hyphal formation, thigmotropism, protease secretion, adherence, and phenotypic switching. *C.albicans* is pathogenic both in the yeast form and in the pseudohyphea form. Thigmotropism is the ability of the organism to sense and penetrate mucosal surfaces via intercellular junctions that may be more readily breached (Sweet, 1997). One of the key pathogenic mechanisms is the secretion of aspartyl proteases, which have a broad specificity. These enzymes can act as keratinases, which can penetrate orthokeratinized mucosa. They are also capable of degrading salivary lactoferrin, lactoperoxidase, mucin and secretory immunoglobulins. The protease activity is lost above pH 5. *Candida* overcomes this problem by producing organic acids at the tips of its pseudohyphea there by acidifying the microenvironment. The selection of phenotypically altered strains may be enhanced by a phenomenon known as switching which occurs especially in response to stress. The binding of *C.albicans* to oral mucosa is the first step in the infectious process. The adhesion of *C.albicans* to the buccal mucosa of HIV positive patients seems to be enhanced at a time before immunosuppression becomes obvious.

In superficial candidiasis, the histopathological change is a chronic mucositis with the yeast confined to the stratum corneum. Netrophils can be seen traversing the epithelial layer from the underlying lamina propria. When the organisms invade visceral tissue,

microabcesses are formed. Both yeast and hyphal forms are present. The initial reaction is neutrophil invasion. Histocytes, giant cells, and epithelioid cells appear early, and the reaction may take the form of a granulomatous response. In severely immunocompromised individuals the immune response may be minimal or nonexistent, leaving the abscess comprised only of candidal organisms and necrotic tissue.

2.3 Clinical presentation

Oral candidiasis can assume a variety of clinical forms and various classification schemes have been proposed to describe them (Odds, 1988). The most commonly used scheme divides clinical lesions into three broad categories of acute, chronic, and mucocutaneous. Acute candidiasis is further subdivided into pseudomembranous and atrophic forms. Chronic candidiasis includes atrophic and hyperplastic variants. Mucocutaneous candidiasis can be localized, familial, or syndrome related.

2.3.1 Acute pseudomembranous candidiasis (thrush)

Acute pseudomembranous candidiasis is a disease of the newborn, old and debilitated persons or those who are medically compromised. This condition is also known colloquially as thrush. Thrush is often seen in medically compromised patients, particularly in those infected with the HIV (Marsh and Martin, 1992). It presents as superficial, confluent fungal colonies or plaques on the oral mucosa. These plaques can be wiped off to reveal an erythematous, occasionally bleeding base. This clinical sign is useful in distinguishing acute pseudomembranous candidiasis from leukoplakia, which by definition, cannot be rubbed off (Lynch, 1994).

The incidence of acute pseudomembranous candidiasis is less than 5% in otherwise healthy populations. Neonatal colonization initially occurs from a number of sources, including

breast-feeding, health care worker's hands, and pacifiers (Lynch, 1994). Commonly affected areas are the soft palate, oropharynx, tongue, check and gingiva. The symptoms include tenderness, burning sensation and dysphagia (Flaitz and Hicks, 1999).

2.3.2 Acute atrophic candidiasis

Acute atrophic candidiasis differs from thrush in that the superficial plaques are absent, with only an erythematous, painful, frequently burning, stomatitis clinically evident (Lynch, 1994). It is caused by the suppression of the oral bacterial micro flora by broad-spectrum antibiotics, typically tetracyclines and corticosteroid therapy. There is a concomitant overgrowth by the oral fungi, in particular, *C.albicans*. The mucosa of the tongue and cheeks becomes thin, inflamed and atrophic in appearance (Marsh and Martin, 1992).

2.3.3 Chronic atrophic candidiasis

This condition often called denture sore mouth, or denture stomatitis, is the most common form of oral candidiasis (Marsh and Martin, 1992). Characteristically, the lesions appear as an asymptomatic, extremely erythematous mucositis, limited exclusively to the denture-bearing mucosa.

2.3.4 Candidal leukoplakia (Chronic hyperplastic candidiasis)

This condition first appears as a white patch (leukoplakia) intraorally, usually on the buccal mucous membrane near the commissures. Lesions can be extensive, are usually bilateral, do not have a surface that is easily removed. This condition is important in that 5-11% of all these lesions have a propensity to become cancerous (Marsh and Martin, 1992).

The chronic hyperplastic candidal variant in HIV–positive or AIDS patients should be clearly distinguished from hairy leukoplakia lesions (Samaranayake and Pindborg, 1989). Indeed, on histopathologic examination candidal hyphea can be demonstrated within the superficial epithelium of hairy leukoplakia lesion and *Candida spp.* can be recovered from its surface (Greenspan, Pindborg and Schiodt, 1990). However, close examination of the epithelium should enable its differentiation from hyperplastic candidiasis due to the characteristic histopathologic features (eg. presence of koilocytes) (Greenspan, Pindborg and Schiodt, 1990).

2.3.5 Angular cheilitis

Angular cheilitis (angular stomatitis) is a disease of multifactorial aetiology, and it may be infective or non infective in origin (Samaranayake, 1992). It is frequently seen in association with chronic atrophic candidiasis. Traditionally, the occurrence of angular cheilitis has been attributed to vitamin B complex deficiency, decreased vertical dimension, or focal Candidal infection, either alone or in combination (Lynch, 1994). Clinically the lesions manifest as red, fissured crusts with or without ulceration and could be accompanied by subjective symptoms of soreness, tenderness burning, or pain (Ohman, Dahlen and Moller, 1985). Although the infection is generally caused by *Candida spp.* and/or Staphylococcus aurius the extent of involvement of the latter organisms in HIV–induced angular cheilitis remains to be determined.

2.3.6 Median rhomboid glossitis

Median rhomboid glossitis (central papillary atrophy) represents a unique form of oral candidiasis, which in the past was considered to be a developmental defect. However, a high percentage of median rhomboid glossitis lesions show a superficial invasion of *C.albicans*. There continues to be debate as to whether *C.albicans* causes median rhomboid glossitis or whether it is simply an opportunistic organism that invades tissue that has been altered through other mechanisms. This tongue lesion is characterized by a specific location–anterior to the circumvalate papilla, and has a specific shape–rhomboid. The lesion surface may vary from nodular to fissured to smooth and depapillated. Typically this lesion is a symptomatic (Flaitz and Hicks, 1999).

2.4 Diagnosis of Oral Candidiasis

As is the case in other infectious disease, confirmation of a clinical diagnosis of oral candidiasis depends on the laboratory identification of the pathogen by mycologic and/or histopathologic techniques. Due to a variety of clinical forms of candidiasis a number of differing specimens such as smears, swabs, imprint samples, salivary samples, oral rinse samples and biopsy specimens can be taken (Table 2) (Samaranayake and Holmstrup, 1989).

The diagnosis of oropharyngeal candidiasis generally is not difficult to make, as it has identifiable characteristics on visual examination and can be cultured from scrapings of oropharyngeal lesions (Powderly, Mayer and Perfect, 1999a). In addition to clinical signs and symptoms, which are generally sufficient to enable diagnosis, candidiasis may be confirmed either by a positive potassium hydroxide (KOH) wet mount, Gram-stained smear, or a cacofluor stain of specimens obtained from the lesion by swabbing or scraping.

Fungal cultures are rarely necessary to make a diagnosis of oral candidiasis, but they are helpful if identification of *Candida spp.* is desired or colony counts are required. Biopsy specimens of oral lesions may be useful to distinguish certain forms of leukoplakia and oral herpetic ulcers similar in appearance to certain *Candida* variants (Powderly, Mayer and Perfect, 1999a; Reef and Mayer, 1995).

The development of oropharyngeal candidiasis reflects immunologic impairment or deterioration in the host. In the case of HIV-positive patients, the occurrence of oropharyngeal candidiasis should trigger questions about the adequacy and effectiveness of their current antiretroviral treatment regimen and determination of their CD_4^+ cell counts and HIV plasma RNA assays. Once assessed and antiretroviral treatment is initiated or adjusted, an appropriate medication should be selected for treatment of the oropharyngeal candidiasis. The range of therapeutic options is wide and includes topical applications, local and systemic therapy with azoles and intravenous therapy with amphotericin B (Powderly, Mayer and Pefect, 1999a).

Biopsy may be considered appropriate in certain cases to exclude neoplasia and to diagnose hyperplastic candidiasis definitively. Haematological investigations are also important to assess any underlying predisposing factors such as deficiency of iron, vitamin B_{12} or folate (Table 2).

Table 2: Appropriate laboratory investigations for oral candidiasis (McIntyre, 2001)

Condition	Swab	Smear	Oral rinse	Biopsy	Blood tests*
Pseudomembranous	+	+	+	-	-
Erythematous	+	+(-)	+	-	-
Hyperplastic	+	+(-)	+	+(-)	+
Candida-associated denture stomatitis	+	+	+	-	+
Angular cheilitis	+	+	+	-	+
Median rhomobiod glossitis	+	+	+	+(-)	+(-)

*Blood tests include iron, vitamin B_{12}, folate, and glucose
+: Useful; - not useful; +(-) may be useful

CHAPTER 3

Aim and Objectives

Aim:

The aim of this study was to systematically review the management of oral candidiasis associated with HIV/AIDS.

Objectives:

To achieve the aim of this study three objectives were identified:

Objective 1: To identify all interventions used for topical and systemic treatment of oral candidiasis.

Objective 2: To compare the efficacy of the different interventions of treatment of oral candidiasis in HIV patients.

Objective 3: To provide guidelines for the management of oral candidiasis in primary health care settings.

CHAPTER 4

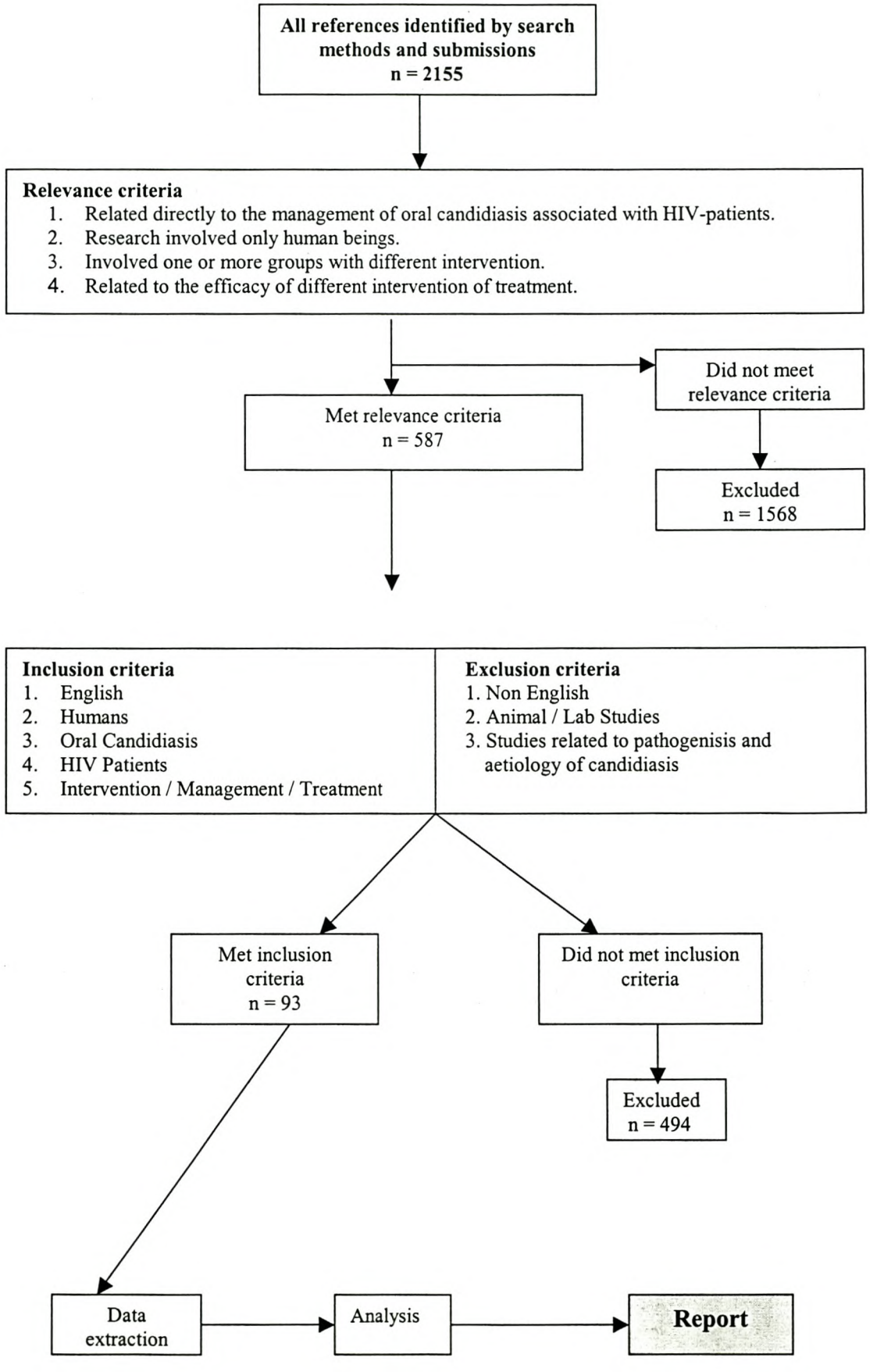
Methodology

4.0 Introduction

The foundation for the evidence-based approach is the systematic literature review, which differs significantly from the traditional narrative review. Narrative reviews are usually broad in scope and are often informed and subjective, supporting the author's views. Reviews by different authorities may arrive at different conclusions, leaving the reader wondering what the outcome really is. While narrative reviews are useful for providing a general perspective on a topic and are appropriate for describing the history of a problem or its management, their selection of studies is subject to bias and the overall conclusions may not be accurate. On the other hand, systematic reviews use explicit standards for evidence retrieval, assessment and synthesis. The methodology of the systematic review is thoroughly documented and reproducible. The strengths of systematic reviews include a clearly defined question, a comprehensive search strategy, explicit inclusion criteria, assessment of methodological quality of the included studies, synthesis of the data and a summery of the results.

The term "overview" is often used to describe a systematic review, whether it is qualitative or a quantitative. The preparation of a systematic review is a major undertaking, requiring considerable time and expertise. Traditional reviews of the literature tend to ignore the variable quality of studies and are therefore unlikely to present a reliable summary. Ideally, systematic reviews concentrate on studies that provide the strongest evidence. All the journals were hand-searched for articles. A diagram illustrating the stage of this systematic review's methods is presented in figure 1.

Figure: 1 Review methodology



4.1 Search Strategy

4.1.1. Preliminary search

A preliminary search was undertaken to provide information on available reviews of candidiasis and management on the effects of candidiaisis in HIV seropositive patients. The preliminary search was carried out in several stages:

- Identification and collection of reviews of candidiasis.
- Medline search using a methodology filter strategy to identify the scope of systemic reviews and Meta-analysis literature.
- Due to time constraints and budget pressures, the decision was taken to review the literature from 1990 to present. A preliminary search indicated that most of the research that reported on interventions for the management of oral candidiasis in HIV/AIDS was published during this period.
- The Medline database was searched using Winspirs/Silver platter software, the MESH words were used are oral candidiasis, management and AIDS. Appropriate filters and limits were used to limit fields of search that match inclusion criteria for this review.

4.1.2. Hand search

Hand searching of the Index Medicus was undertaken from August 2001 back to 1990. The bibliographies of the eligible papers were also searched. The reference list of each retrieved paper was reviewed for hitherto unretrieved papers. All relevant papers were then also retrieved and the process repeated. To expand this literature process, any journal appearing in the reference list was added to a list of journals to be hand searched. The following journals, which are likely to provide the bulk of the data used in this review were hand searched to identify any relevant studies for inclusion:

a. Antimicrobial Agants chemotherapy 1990-2001

b. Clinical Infectious Diseases 1990-2001

c. The Journal of Infectious Diseases 1990-2001

d. AIDS 1990-2001

4.2 INCLUSION CRITERIA

4.2.1. Methodology and Quality criteria

The following methodological issues were considered when assessing studies for inclusion: patient selection, confounding, and measurement. Study designs are often graded hierarchically according to their quality, or degree to which they are susceptible to bias. The hierachy indicates which studies should be given most weight in a synthesis. In this review, the degree to which each study dealt with the methodological issues was graded into three levels of evidence. Patient groups that were exposed to medication for candidiasis may differ in respect to factors other than candidiasis itself. Some of these differences may be related to the outcomes under investigations (type of candidal disease, *Candida spp.* involved, level of immunity etc.) and also confound any observed relationship and thus should be controlled for in the analysis. Confounding factors are factors that can cause or prevent the outcome of interest. In the case of management of candidiasis these are likely to include age, other disease, resistant, pharmacogenetic factors, socioeconomic status, and level of CD4. Factors likely to modify the effect of medication on the outcomes, such as type of candidiasis and condition of the patient before the introduction of medication should also be considered.

A specific set of inclusion criteria for each level was developed so that literature of similar quality or methodological rigour could be grouped together. The inclusion criteria of 3

levels A, B and C were developed using previous systematic reviews as guidelines, together with guidelines developed by Cochrane-type systematic reviews (Kay and Locker, 1998; McDonagh, Whiting, Bradley, Cooper, Sutton, Chestnutt, Misso, Wilson,Treasure and Kleijnen, 2000). Quality criteria differed according to the different study design. The quality criteria in this review was assessed in three levels (A, B, and C) and each paper was scored for quality according to set criteria (Kay and Locker, 1998) (see Table 3).

Papers selected for this review were classified as level A where all these criteria were met and level C, were none was met. Level B articles met some of the quality criteria of level A, but not all (see Table, 4).

4.3. ASSESSMENT OF PAPERS FOR INCLUSION

4.3.1. Relevance assessment

Decisions about the inclusion of studies were made according to the following pre-determined criteria related directly to the management of oral candidiasis:

- Research involved only human beings.
- Involved two or more groups of interventions.
- HIV/AIDS studies.

A full report of titles and abstracts found to be relevant to the review were obtained for assessment for inclusion criteria.

4.3.2. Assessment of papers for inclusion criteria

An inclusion criteria was assessed for each of the objectives separately.

4.4 Exclusion criteria

- Papers in languages other than English were excluded.
- Animal and/or laboratory studies were excluded.
- Papers involving reviews were excluded.
- Papers looking at other aspects of intervention or management of oral candidiasis were excluded.

Table 3: Criteria for assessment

Level A (High quality of evidence)	Level B (Moderate quality of evidence)	Level C (Low quality of evidence)
• Randomized control study design (RCT), quasi RCT- where there was an experimental and/or control group. • The research aims were clearly defined. • Criteria were given for inclusion / exclusion of subject. • The paper gave details for non-compliance rates, or drop out. • There was a control, or reference group. • The numbers of participants in each group were given. • The paper defined the outcome measures objectively. • The length of follow-up period was stated.	• Non-RCT type study. • The search aims were clearly defined. • Criteria were given for inclusion / exclusion of subject. • The paper did not give details of non-compliance rates, drop out. • The number of participants in each group was not given. • The length of follow-up period was not stated.	• Research aim was not clearly defined. • No criteria were given for the inclusion / exclusion of subject. • No control or reference group. • No numbers of participants were given in each group. • Paper did not define the outcome measures. • The length of follow-up period was not stated. • No comments from the authors on the clinical significance of the findings.

Table: 4 References and quality levels.

No	Authors	Study design RCT	The search aims clearly defined.	Inclusion exclusion criteria	Details of non-compliance or drop out rate.	Control, or reference group.	No of participants in each group.	Outcome measures.	Follow-up.	Variations	Quality level
1	Graybill et al., 1998	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
2	Phillips et al., 1998	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
3	Blomgren et al., 1998	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
4	Moshi et al., 1998	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
5	Wilcox et al., 1997	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
6	Pons et al., 1997	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
7	Murray et al., 1997	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
8	Barbaro et al., 1996	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
9	MacPhail et al., 1996	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
10	Flynn et al., 1995	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
11	Barbaro et al., 1995	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
12	Banting et al., 1995	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
13	Konsberg, Axell, 1994	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
14	Cartledge et al., 1994	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
15	Hernandez-Sampelayo et al., 1994	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
16	Pons et al., 1993	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
17	Marriott et al., 1993	✓	✓	✓	✓	✓	✓	✓	✓	✓	A

CAont'd Table: 4

No	Authors	Study design RCT	The search aims clearly defined	Inclusion/ exclusion criteria	Details of non compliance or drop out rate	Control, or reference group	No of participants in each group	Outcome measures	Follow-up	Variations	Quality level
18	Rindum et al., 1993	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
19	Laine et al., 1992	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
20	Redding et al., 1992	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
21	Stevens et al., 1991	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
22	Smith et al., 1991	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
23	Koletar et al., 1990	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
24	Leen et al., 1990	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
25	De Wit et al., 1990	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
26	De Wit et al., 1989	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
27	Dupont and Drouhet, 1988	✓	✓	✓	✓	✓	✓	✓	✓	✓	A
28	Fichtenbaum et al., 2000		✓	✓	✓		✓	✓	✓	✓	B
29	Saag et al., 1999		✓	✓	✓		✓	✓	✓	✓	B
30	Plettenberg et al., 1999		✓	✓	✓		✓	✓	✓		B
31	Cartledge et al., 1998		✓	✓	✓		✓	✓	✓		B
32	Cross et al., 1998		✓	✓	✓	✓	✓	✓	✓		B
33	Hegener et al., 1998		✓	✓	✓	✓	✓	✓	✓		B
34	Revankar et al., 1998		✓	✓	✓		✓	✓	✓	✓	B

Cont'd Table: 4

No	Authors	Study design RCT	The search aims clearly defined	Inclusion exclusion criteria	Details of non compliance, or drop out rates	Control or reference group	No of participants in each group	Outcome measures	Follow-up	Variations	Quality level
35	Cartledge et al., 1997		✓	✓	✓	✓	✓	✓	✓	✓	B
36	De Wit et al., 1997		✓	✓	✓	✓	✓	✓	✓		B
37	Hoppe et al., 1997		✓	✓	✓	✓	✓		✓	✓	B
38	Tumbarello et al., 1997		✓	✓		✓	✓	✓		✓	B
39	Phillips et al., 1996		✓	✓	✓	✓	✓	✓	✓	✓	B
40	Dronda et al., 1996		✓	✓	✓	✓	✓	✓	✓	✓	B
41	Silverman et al., 1996		✓	✓	✓	✓	✓	✓	✓	✓	B
42	Guennec et al., 1995		✓	✓	✓		✓	✓	✓		B
43	Dios et al., 1995		✓	✓	✓	✓	✓	✓	✓		B
44	Laufen, et al., 1995		✓	✓		✓	✓		✓		B
45	Plettenberg et al., 1994		✓	✓	✓		✓	✓	✓		B
46	White and Goetz, 1994		✓	✓			✓	✓	✓		B
47	Millon et al., 1994		✓	✓	✓	✓	✓	✓	✓	✓	B
48	Laine, 1994		✓	✓	✓	✓	✓	✓	✓	✓	B
49	Chavanet et al., 1994		✓	✓	✓	✓	✓	✓	✓		B

Cont'd Table: 4

NO	Authors	Study design RCT	The search aims clearly defined	Inclusion exclusion criteria	Details of non compliance or drop out rate	Control or reference group	No of participants in each group	Outcome measures	Follow-up	Variations	Quality level
50	Vuffray et al., 1994		✓	✓	✓	✓	✓	✓	✓	✓	B
51	De Wit et al., 1993		✓	✓	✓		✓	✓	✓	✓	B
52	Just-Nubling et al., 1990		✓	✓	✓		✓	✓	✓		B
53	Thorsen and Marthiesen, 1990		✓	✓	✓		✓	✓	✓		B
54	Hay, 1990		✓	✓			✓	✓	✓		B
55	Weig and Muller, 2001										C
56	Jabra-Risk et al., 2000										C
57	Flaitz and Hicks, 1999										C
58	Chow et al., 1999										C
59	Powderly et al., 1999a										C
60	Powderly et al., 1999b										C
61	Ghannuoum and Elewski, 1999										C
62	Hood et al., 1999										C
63	Hood et al., 1998										C
64	Valdez et al., 1998										C
65	Webb et al., 1998										C
66	Darouiche, 1998										C
67	Cartledge et al., 1997										C

Cont'd Table 4

No	Authors	Study design RCT	The search aims clearly defined	Inclusion exclusion criteria	Details of non compliance or drop out rate	Control or referance group	No of participants in each group	Outcome measures	Follow-up	Variations	Quality level
68	Ruhnke et al., 1997										C
69	Greenspan and Shirlaw, 1997										C
70	Redding et al., 1997										C
71	Hoppe, 1997										C
72	Glick and Burris, 1997										C
73	Green, 1997										C
74	Barry and Brown, 1996										C
75	Revankar et al., 1996										C
76	Millus and Martin, 1996										C
77	Maenza et al., 1996										C
78	Reef and Mayer, 1995										C
79	Chryssanthou et al., 1995										C
80	Garcia-Hermosa et al., 1995										C
81	Dewsnup, Stevens, 1994										C
82	Van Meter et al., 1994										C

Cont'd Table: 4

No	Authors	Study design RCT	The search aims clearly defined	Inclusion exclusionon criteria	Details of non compliance or drop out rate	Control or reference group	No of participants in each group	Outcome measures	Follow-up	Variations	Quality level
83	Redding et al., 1994										C
84	Newman et al., 1994										C
85	Greenspan, 1994										C
86	Greenspan, 1994b										C
87	Cameron et al., 1993										C
88	Sanguineti et al., 1993										C
89	Glatt, 1993										C
90	Vander Bijl and Arendorf, 1993										C
91	Lewis et al., 1991										C
92	Lucatorto et al., 1991										C
93	Blatchford, 1990										C

CHAPTER 5

RESULTS

5.1 OBJECTIVE 1: To identify all interventions used for topical and systemic treatment of oral candidiasis.

5.1.1 Topical and systemic treatment

A total of 14 studies on the effect of antifungal medications on oral candidiasis were found. Thirteen studies assessing the topical and systemic antifungal agents achieved evidence level A and one evidence level B. The response and the effect of the topical and systemic antifugals used in the main analysis were changes in different parameters (clinical cure, colonization, relapse, sign and symptoms) before and after treatment. Table 5 shows the 14 studies that were included in assessing objective one. In this table, the main differences of the effect of the topical and systemic antifungal medications are shown. All the studies in Table 5 show variance (95% Confidence intervals or standard deviations) except one study which is level B quality of evidence.

Oral candidiasis has traditionally been treated with topical antifungal therapy, such as nystatin suspension or clotrimazole troches, nystatin pastilles, or the oral systemic agent ketoconazole for more persistent or difficult cases (Pons, Greenspan, Debruin and the Multicenter Study Group, 1993) (Tables 6 and 7). The polyene antibiotics, nystatin and amphotericin B, bind to sterols present in fungal cell membranes causing membrane leakage of the cellular contents that lead to cell death (Redding, Farinacci, Smith, Fothergill and Rinaldi, 1992). Nystatin can be used topically as treatment for thrush and is available as a suspension or pastille. One or two pastilles (200 000 U/ pastille) are dissolved in the mouth 4-5 times a day. Nystatin oral suspension (100 000 U/ ml) is used as a mouth rinse, with 1-5 ml of the suspension held in the mouth for 1 minute, 4 times a day

(Greenspan and Shirlaw, 1997). Dosing is 4 times daily and side effects, often mild, include nausea, vomiting and diarrhea.

Amphotericin B is available as a 100 mg ml suspension and as a 10 mg Lozenge (Fugilin). The suspension is used as a mouth rinse, 1 ml four times daily, swished around the mouth, held and then swallowed. Amphotericin B Lozenges are held in the mouth for 15-20 minutes, while they dissolve. It is rarely used to treat thrush because of it's significant toxicity including fever, vomiting, renal, cardiovascular and neurological toxicity.

The synthetic broad-spectrum antiphenols, the azoles, include ketoconazole and clotrimazole. These agents exert their fungistatic effect by disrupting synthesis of ergostrol, which changes membrane permeability. Ketoconazole is given orally once daily and has been proven effective in the treatment of thrush. Unfortunately it requires an acidic gastric pH for absorption often lacking in patients with HIV/AIDS thus limiting its effectiveness. Clotrimazole troches have proven effective and currently is the most commonly used therapy for thrush associated with HIV infection. It is used only as a topical medication dissolved in the mouth five times daily. Side effects are minimal, but compliance can be a problem because of frequency of dosing and the fact that some patients object to the "gritty" feeling of the troches. Clotrimazole troches contain dextrose, which may promote dental caries. In addition, patients with HIV/AIDS and symptomatic xerostomia complain of difficulty in dissolving the intraoral troches. For individuals with angular cheilitis, topical gels and creams such as sugar-free miconazole oral gels (Daktarin), nystatin and triamcinolon acetonid cream, 1% clotrimazole cream or 2% ketoconazole cream can be applied to the lesion 3 times daily. When treating patients who wear dentures their prosthesis must also be included in the antifungal regimen.

Miconazole gel applied to the fitting surface 4 times daily can be recommended (Greenspan and Shirlaw, 1997).

A second generation of azoles or triazoles contains the drug fluconazole. This drug possesses several properties which makes it well suited to treat thrush. The mechanism of action is similar to ketoconazole; however, fluconazole is a thousand times more selective as an inhibitor of fungal cell wall sterol biosynthesis. It is considerably more water-soluble than the earlier azoles resulting in less protein binding and allowing more unbound drug to reach the site of infection. It does not require an acidic environment for absorption and readily crosses the blood brain barrier. Fluconazole is not metabolized by the liver as are the other azoles, so it reaches systemic circulation largely intact. Its oral bio-availability is greater than 90% and plasma concentration peak two hours after dosing, the route of elimination is via urine and, to a lesser extent, through the faeces, largely as an unchanged drug. Fluconazole has been extensively evaluated as a treatment for thrush. With HIV infection, a cure rate of 82% was reported with a daily oral dose of 50mg (Redding, Farinacci, Smith, Fothergill and Rinaldi, 1992).

Milder episodes of oral candidiasis may respond to topical therapy with nystatin, clotrimazole troches or oral ketoconazole. As the patient's immune competence declines, the severity of disease worsens and recurrences occur at more frequent intervals, systemic therapy may be necessary. Ketoconazole and clotrimazole are less effective than fluconazole for the treatment of thrush. Fluconazole has been increasingly relied upon for the management of thrush. When these preparations are used in tablet or capsule forms, they may be difficult for patients with an advanced stage of AIDS, to swallow, particularly when marked dysphagia secondary to candidiasis is already present (Graybill et al, 1998).

Itraconazole is an azole antifungal agent indicated for the treatment of aspergillosis, blastomycosis, histoplasmosis and recently it has been approved for use in onychomycosis. Itraconazole has a broad spectrum of activity in-vitro, including a wide variety of *Candida spp*. In addition, it has demonstrated in-vitro activity against *Candida spp*. that are fluconazole-susceptible or fluconazole-resistant.

Ketoconazole and itraconazole capsules have been shown to be effective in treating oropharyngeal candidiasis in AIDS patients. However, absorption may be variable in some HIV-infected patients who have been found to be hypochlohydric. Preliminary clinical studies in AIDS patients with several episodes of oral candidiasis, have shown that itraconazole oral solution (100 mg twice daily) produced a 100% clinical cure rate after 6 days of treatment and was more effective than topical therapy with clotrimazole troches. Ketoconazole was the first oral antifungal drug shown to be effective for the treatment and prevention of oropharyngeal candidiasis, but it has been largely replaced by fluconazole for several reasons. In a number of studies comparing fluconazole with ketoconazole, fluconazole was a better choice for the treatment of relapsing oropharyngeal candidiasis producing either better cure rates or better prevention of relapse. The doses of fluconazole were 50 or 100 mg/day, while those of ketoconazole were higher (200 or 400 mg/day). Various studies suggest that a daily dose of 100 or 200 mg for 2-4 weeks is effective, but few comparative data are available (De Wit, Doherty, Vroey and Clumeck, 1998).

Table 5: Intervention for topical and systemic treatment.

No	Author	Study design	No & Characteristics of patients	Intervention	Results and Comments	Quality level
1	Graybill et al 1998	Open label, third party –blind clinical trial.	179 HIV+ patients	Itraconazole oral solution (200 mg/daily for 7 days or 14 days); flucanozole tablets, 100 mg/daily for 14days.	179 patients available for efficacy; 97% clinical response after 14 day of itraconazole and 87 % after 14 day of fluconazole. 97.5% instead of 95% confidence intervals (CI) of the difference in response rate were used in the determination of equivalence.	A
2	Flynn et al., 1995	Randomized double blind, multicenter.	182 immunocompromised children 5-14 y of age.	Fluconazole suspension 4 mg/(kg. day) loading dose, then 2 mg/(kg. day) for 13 days (n=86); nystatin suspension USP 400,000 units 4 times a day for 14 days (n=73).	91% clinical cure with fluconazole versus 51% with nystatin (P<0.001). 76% mycological cure with fluconazole versus 11% with nystatin. The difference in outcomes were statistically significant (P<0.001). There was no significant difference in the clinical efficacy between two dosage of fluconazole.	A
3	Pons et al., 1993	Randomized single blind.	334 HIV+ patients with oral candidiasis .	Fluconazole 100 mg daily for 14 days (n=176); clotrimazole (10 mg) 5 times daily for 14 days (n=158).	98% of available fluconazole-treated patients and 94% of available clotrimazole-treated patients were cured or showed improvement (P= not significant). Fluconazole was more effective in eradicating *Candida* from oral flora than clotrimazole by the end of therapy (65% versus 48%) (P= 0.005).	A
4	Redding et al., 1992	Randomized double blind.	24 HIV+ patients with thrush.	Fluconazole 100 mg tablets once/day (n=13), or clotrimazole 10 mg troches five times/day (n=11) for 14days.	100% clinical cure with fluconazole versus 73% with clotrimazole; 15% colonization of fluconazole versus 38% clotrimazole. Non of these differences was statistically significant using the Student's t Chi-square test.	A
5	Pons et al., 1997	Randomized open-label.	167 HIV+ patients with oropharyngeal candidiasis.	Fluconazole suspension 100 mg (10 ml) once daily for 14 days with 200 mg (20 ml) loading dose on day 1 (n=83); nystatin 5 ml (500,ooo U) 4 times daily for 14 days (n=84).	138 patients available for clinical outcome; 87% clinical cure with fluconazole versus 52% with nystatin (p<.001); mycological eradication of *Candida* spp. at 14 days was 60% with fluconazole versus 6% with nystatin (P<.001); 18% relapse rate with fluconazole versus 44% with nystatin at the 4 Week follow up-visit (P<.001).	A

Cont'd Table: 5

No	Author	Study design	No & Characteristics of patients	Intervention	Results and comments	Quality level
6	Koletar et al.,1990	Randomized, open-label.	39 HIV+ patients and oral candidiasis.	Fluconazole 100 mg for 14 day (n=17); clotrimazole troche (10 mg) 5 times daily for 14 days (n=19).	Among 36 available patients, clinical resolution rates were 100 and 65% respectively (P=0.018). Mycological eradication rates were 75 and 20%, respectively (P=0.004). Fluconazole treated patients were disease free during follow-up than those treated with clotrimazole (P=0.014 at 2 weeks). After 14 days of therapy, fluconazole was clinically more efficacious and resulted in significantly better mycological eradiation than clotrimazole.	A
7	De Wit et al., 1993	Randomized open-label trail.	40 HIV+ patients and oropharyngeal candidiasis.	Fluconazole 150 mg daily (n=20) or Itraconazole 100 mg once daily for 7 days (n=20). (Day 8 and 30 follow up).	37 patients available for clinical evaluation; 75% clinically cured, with fluconazole versus 20% with itraconazole. At follow-up, 30% relapse. The difference was not significant (Fisher's exact test, two-tailed test).	A
8	Smith et al., 1991	Randomized double blind study.	111 HIV+ patients with candidiasis or ARC 85 with OPC, 26 with esophageal candidiasis	Itraconazole 200 mg once a day (n=59) ketoconazole 200 mg twice a day for 28 days (n=52).	Clinical cure with ketoconazole and itraconazole at 1 week were not significantly different (82 and 75%, respectively; P=0.4497); however, the average clinical response rate risen to 93% for each drug by week 4 (P=0.859). When the mycological response for all the groups of patients was combined, this was significantly greater for ketoconazole than for itraconazole at 7 days (92 and 68%, respectively; (P=0.0028). However, after 4 weeks of therapy there was no significant difference (85 and 83%) in the ketoconazole and itraconazole groups; respectively.	A
9	Hernandez-Sampelayo and the Multicenter Study Group, 1994	Randomized open label.	46 HIV+ infants and children 0-14 y of age.	Fluconazole 3 mg/kg per day (n=24); ketoconazole 7 mg/kg per day (n=22), duration from 5 to 49 days.	88% clinical cure with fluconazole versus 81% with ketoconazole; 71% mycological cure with fluconazole versus 57% with ketoconazole; 50% of fluconazole-treated patients versus 41% of ketoconazole treated patients were treated failures at 4-week follow-up visit. (No variance reported).	B
10	De Wit et al., 1989	Randomized double blind.	37 HIV+ patients or patients with AIDS.	Fluconazole 50 mg/day for 2 -42 days (n=18); ketoconazole 200 mg/day for 2 –28 days (n=19).	17 available episodes in fluconazole treated patients and 16 available episodes in ketoconazole treated patients; 100% clinical cure with fluconazole versus 75% with ketocoazole (P=.045); 87% culture negative with fluconazole versus 69% with ketoconazole (P= Not significant).	A

Cont'd Table: 5

No	Author	Study design	No & Characteristics of patients	Intervention	Results and comments	Quality level
11	Murray et al.,1997	Open label, evaluator-blinded.	162 immunocompromised patients (83% with HIV or ARC).	Itraconazole oral solution (10 mg/ml) 200 mg per day for 14 days (n=75); clotrimazole troches (10 mg) 5 times daily (n=74).	149 patients available for efficacy; 77% clinical response with itraconazole versus 70% with clotrimazole (P= Not significant); 60% mycological cure with itraconazole versus 32% with clotrimazole (P<.001); 53% clinical response plus mycological cure with itraconazole versus 30% with clotrimazole (P=.006); 46% of itraconazole versus 60% of clotrimazole recent relapsed by the 28 day follow-up visit (P=.10).	A
12	Banting, Greenhorn, and McMinn, 1995	Randomized clinical trial.	650 patients with symptoms of oral candidiasis.	48 ml nystatin; (100,000 IU/ml) dissolved in 432 ml of distilled water producing 10,000 IU nystatin ml sol. versus nystatin vaginal lozenge (100,000 IU/g) dissolve in mouth 3 times daily for 7 days.	Clinical sign and symptoms were cleared within 7 days. Nystatin denture soaking solution was not shown to provide any additional benefit in this study. The difference between test and control groups in the rate of positive smears for *C.albicans* over the three observation period was not statistically significant (M-H Chi Square =0.021, P=0.886)	A
13	Konsberg and Axell, 1994	Randomized double blind controlled clinical trail.	36 patients with denture stomatitis.	Miconazole 1 mg (approximately 1 ml).	A single application of a miconazole denture lacquer considerably reduces the number of *C.*yeasts for a substantial period of time. Miconazole denture lacquer was statistically significantly better than placebo (P<0.001).	A
14	Blomgren, Berggren, and Jontell, 1998	Randomized, blind study.	71 patients diagnosed with oral candidiasis.	Fluconazole 50 mg/day for 7 days (n=36). Nystatin 4 times daily for 21 days (n=35).	87% improvement with fluconazole and 80% with nystatin. 8 patients in fluconazole group and 12 patients in nystatin group were exhibited relapse within 6 months. No statistical difference in the outcome of treatment was revealed between the two groups as assessed by clinical scoring.	A

Table 6: Topical agents available for treatment of oral candidiasis

Drug	Forms	Strength	Use
Nystatin	Pastille	200,000 units	Dissolve 1-2 pastilles 4 times daily
Nystatin-triamcinolone	Powder (for oral use)	---	Apply to denture 2-3 times daily
Nystatin	Ointment / cream	---	Apply to commisures 3 times daily
Clotrimazole	Oral troche	10 mg	Dissolve 1 troche 5 times daily
Ketoconazole	Cream	2 %	Apply to commisures 3 times daily
Clotrimazole	Cream	1 %	Apply to commisures 3 times daily

Table 7: Systemic agents available for treatment of oral candidiasis

Drug	Forms	Strength	Use
Ketoconazole	Tablet	200 mg	Once daily
Fluconazole	Tablet	100 mg	Once daily
Itraconazole	Capsule	100 mg	200 mg daily
Amphotericin B	Suspension	100 mg	1 ml 4 times daily

5.1.2 Recurrent and Refractory oral candidiasis

A total of 6 studies on the treatment of recurrent and refractory oral candidiasis were found. The studies assessed the intervention for treatment achieved evidence level B (n= 5) and level C (n= 1). Table 8 shows the 6 studies that were included in assessing the intervention for recurrent and refractory oral candidiasis. In this table, the main differences in the interventions for recurrent and refractory oral candidiasis is shown. Of the 6 studies, only 3 studies reported variance (95% Confidence intervals or standard deviations - Table 8).

The cause of refractory oral candidiasis in HIV patients is multifactorial and includes incomplete adherence to the regimen, poor absorption, increase metabolism of drug and overgrowth of a *Candida spp.* that is less responsive to therapy. However, the most commonly cited reason for the development of this disorder is alteration in the structure of *C.albicans* that leads to drug resistance.

The development of antifungal agents that could be used to treat HIV-positive patients with recurrent and, in particular refractory oropharyngeal candidiasis, has gained considerable interest. The overall tolerability of itraconazole oral solution, the combined topical and systemic effect of the liquid formulation, and its activity against fluconazole-refractory disease establish this drug as a primary alternative to intravenous amphotericin B in the treatment of this disorder. To achieve the most durable effect, itraconazole requires prolonged administration, perhaps as chronic suppressive therapy, in conjunction with highly active antiretroviral therapy. However, the potential for drug-drug interactions with some of the antiretroviral agents used in highly active antiretroviral therapy (HAART) regimens and the development of recurrent disease, even while receiving chronic suppressive therapy, remains a concern (Saag, 1999).

Table 8: Intervention for recurrent and refractory oral candidiasis.

No	Author	Study design	No & characteristics of patients	Intervention	Results and comments	Quality level
1	Saag et al., 1999	Open-label, multicenter trial.	74 HIV+ patients with confirmed OPC who failed fluconazole therapy.	100 mg of Itraconazole oral solution twice daily (200 mg/day) for 14 days.	74 patients were available for efficacy. 41 (55%) achieved a clinical response with 95% two-sided confidence intervals indicating a response range of 43% to 67%. Among the 74 patients, 12 did not have mycologic assessment data on day 14 or day 28. On day 28, eight (11%) patients had negative cultures.	B
2	Phillips et al., 1996	Prospective, open label, intervention.	36 HIV+ patients clinically diagnosed of typical pseudomembranous lesions on oral examination.	Itraconazole solution 200 mg daily dose for 14 days, followed by suppressive therapy.	34 patients were available, clinical response to itaraconazole solution was 65%, response was complete in 24% and partial in 41% of patients, relapse rate 36% within 2 months *(No variance was reported).*	B
3	Fichtenbaum et al., 2000	Multicenter, prospective.	832 Patients with advanced HIV infection 36 had confirmed episode of fluconazole refractory infection and 35 had oral candidiasis and 1 had esophageal candidiasis.	200 mg of fluconazole daily dose for 14 days.	78% treatment-response for the initial episode of fluconazole, 54% continued receiving fluconazole after clinical failure. The continuous use of fluconazole was significantly associated with fluconazole failure when compared with no use (p=.005). In contrast, there was no significant association between the intermittent use of fluconazole and the development of fluconazole failure (p=.12). In addition, the total dose of fluconazole was not significantly associated with the development of refractory infection.	B

Cont'd Table: 8

No	Author	Study design	No &characteristics of patients	Intervention	Results and comments	Quality level
4	Millon et al., 1994	Longitudinal study.	30 patients, 21 was confirmed with OPC	50 mg of fluconazole per day. and if no improvement was observed within 1 week, the dose was increased to 100 mg/day.	Fluconazole therapy selected resistance mutans for which MIC increased with total dose. This resistance characteristic is genetically stable after several cultures. The successive increase in the MICs of fluconazole suggest that there were several events or independent events associated with different targets. *(No variance was reported).*	B
5	Revankar et al., 1998	Prospective randomized trail.	128 patients with active thrush	200 mg daily or intermittent therapy with fluconazole.	It is suggested that combination of antiretroviral regimens containing protease inhibitor may have little impact in OPC recurrence rates unless accompanied by both significance viral load suppression and a sustained rise in CD4 cell counts. There was no statistically significant difference in the OPC recurrence rate before and after initiation of HAART (0.52 versus 0.41 episodes per month; p= 0.22).	B
6	Lucatorto et al., 1991	Case report.	One HIV+ patient with a thick, white, cheesy plaque, characteristic of oral candidiasis.	Fluconazole 200 mg per day orally with a loading dose of 200 mg twice daily for 1 day.	The oral mucosa showed no evidence of candidal infection. The patient was completely free of oral or pharyngeal pain. *(No variance was reported).*	C

Fluconazole has been widely used in HIV-related candidiasis since its release in 1990. However, fluconazole-resistant oropharyngeal candidiasis has become a significant management problem, and it is estimated to occur in approximately 5% of patients with advanced HIV-disease. Intravenous amphotericin has been effective as a salvage therapy in azole-refractory candidiasis, but this approach is both inconvenient and associated with potential toxicities. Experience with itraconaozole capsules for fluconazole-resistant oropharyngeal candidiasis has been disappointing. Itraconazole shares several pharmacologic properties with ketoconazole including a requirement for gastric acidity for optimal absorption, a high degree of protein binding and being lipophilic with limited penetration of aqueous body fluid compartments, and is equally effective as ketoconazole in HIV-related mucosal candidiasis (Phillips et al, 1996).

Voriconazole is a new potent broad-spectrum triazole antifungal agent. The synergism of viroconazole (VRC) and terbinafine (TRB) was studied by Weig and Muller, (2001) using 39 genotypically defined clinical *C.albicans* isolates that were cross-resistant to fluconazole, and VRC and serial isolates that gradually developed azole resistance. Synergy was noticed in 100% of the strains that were resistant to VRC. Antagonism was not observed. They were able to demonstrate effective synergism between VRC and TRB *in vitro* against clinical isolates of *C.albicans* from HIV-infected patients.

Recurrent oropharyngeal candidiasis in HIV-infected patient is common. The majority of the recurrent episodes respond to conventional therapy. However, recurrence of oropharyngeal candidiasis should be considered a warning sign of possible HIV progression and prompt a re-evaluation of the patients on highly active antiretroviral therapy, with determination of viral load and CD4 cell counts (Powderly, Mayer and

Perfect, 1999a). It is recommended that each episode of oropharyngeal candidiasis be treated acutely until further data are available, provided that the infection is limited to the oropharyngeal cavity and the patients CD4 cell count is above 50 cell / mm.^{3} It is recommended that treatment of recurrence with clotrimazole troches continues for as long as the drug remains effective. However, the importance of compliance needs to be stressed, as treatment failure may be due to the patients unwillingness or inability to adhere to the dosing regimen rather than a true reflection of drug efficacy. When a patients does not respond or is unable to follow the treatment regimen, an alternative approach must be adopted (Powderly, Mayer and Perfect, 1999a).

After consideration of the immune status of the patient and any warranted adjustments to the highly active antiretroviral therapy regimen, the patients past exposure to antifungal agents and current medications should also be taken into account prior to selection of the most suitable azoles. Phillips (1996) concluded that itraconazole solution appeared to be an effective treatment for fluconazole-refractory oropharyngeal candidiasis, and suggested that it may be active both topically and systemically.

5.1.3 Summary

Objective 1 attempted to assess the effect of antifungal medications on oral candidiasis. The response and the effect with topical and systemic antifungal used in the main analysis were of the change in different parameter (clinical cure, colonization, relapse, sign and symptoms) before and after treatment. For this objective, the quality of studies found was mainly of a high quality (level A). A large number of studies were excluded because there were case-studies and therefore did not meet inclusion criteria of being evidence (level B) or above.

Antifungal medications do appear to manage oral candidiasis especially among HIV-positive patients (Table 8). Fluconazole is the most effective among others antifungals in the management of oral candidiasis. Only 3 studies showed 100% clinical cure with fluconazole. The other studies showed statistically significant positive effect with other antifungal agents. Most of the studies used a single dose of antifungal agents for a short period. The relapse rate with topical antifungal among some of the studies was high. The results suggest that a daily single-dose is effective, but few comparative data are available.

All of the studies shown in Table 8 achieved evidence level B and level C. In one study the successive increase in the mean inhibitory concentrations of fluconazol suggest that there were several events or independent events associated with different targets (Millon et al., 1994). Other studies suggested that a combination of antiretroviral regimens containing protease inhibitors, may have little impact in oropharyngeal candidiasis recurrence rates unless accompanied by both significant viral load suppression and a sustained raised in CD4 cell counts. Intravenous amphotericin B has been effective salvage therapy in azole-refractory candidiasis, but this approach is both inconvenient and associated with toxicities. In 3 studies, a common approach to management has been to progressively increase the dose of fluconazole.

5.2 Objective 2: To compare the efficacy of the different interventions of treatment of oral candidiasis in HIV-positive patients.

5.2.1 Comparison of available therapy

A total of 20 studies looking at the effect of antifungal drugs and a comparison of their actions met the inclusion criteria. Most of these studies treated HIV-seropositive patients. Of these, 12 studies achieved evidence level A, 5 achieved evidence level B and 3 achieved evidence level C. The efficacy of different interventions was compared in the treatment of HIV-positive patients. Table 9 shows level A studies that were included in assessing the efficacy of different intervention of treatment of oral candidiasis in HIV-patients. In this table, a comparison of different interventions is shown.

In general, topical therapies, especially clotrimazole, are effective treatments for uncomplicated oropharyngeal candidiasis (mild-moderate clinical symptoms with no esophageal involvement) although patients treated with topical therapies tend to relapse more quickly than those treated with oral systemic antifungal therapy. Overall, nystatin appears less effective than clotrimazole and the azoles in the treatment of oropharyngeal candidiasis. With regard to the resolution of clinical symptoms, clotrimazole is similarly effective to azoles, except when patient compliance is poor (Philips et al, 1998).

Table 9: Comparison of available intervention.

No	Authors	Study design	No & characteristics of patients	Intervention	Results and Comments	Quality level
1	Graybill et al., 1998	Randomized, third-party-blind multicenter trial.	179 HIV+ patients with OPC.	Itraconazole sol. 200 mg/day for 7 or 14 days. Fluconazole tab. 100 mg/day for 14 days.	97% clinical response after 14 days of itraconazole and 87% of fluconazole after 14 days, 7 days itraconazole oral solution was equivalent to fluconazole treatment for 14 days, one half of patients in all three groups relapsed by 1 month after completion of treatment. Itraconazole oral solution was well tolerated and offers an alternative at least as effective as fluconazole in the treatment of OPC.	A
2	Koletar et al., 1990	Randomized control trail.	39 HIV+ patients with oral candidiaisis.	Fluconazole caps. 100 mg/day for 14 day. Clotrimazole troche. 10 mg 5 times/day for 14 days.	Fluconazole-treated patients were more likely to remain disease free during follow-up than those treated with clotrimazole. Clinical resolution rates were 100 and 65% respectively. Fluconazole were more effective than clotrimazole troches in the treatment of HIV-infected patients with oral candidiasis.	A
3	Flynn et al., 1995	Randomized control trail.	182 immunocompromised infants & children with signs of oral thrush.	Fluconazole susp. 2-3 mg/kg per day for 14 days. Nystatin 400,000 U 4 time's daily for 14 days.	Clinical cure was demonstrated in 91% of the subject in fluconazole group and 51% of the subject in the nystatin group. Fluconazole susp. was more effective than nystatin in the treatment of thrush in immunocompromised children.	A

Cont'd Table: 9

No	Author	Study design	No & characteristics of patients	Intervention	Results and Comments	Quality level
4	Pons et al., 1997	Randomized control trail.	167 HIV+ patients with OPC.	Fluconazole 100 mg/day for 14 days. Nystatin susp. 500,000 U 4 times daily for 14 days.	87% clinical cure with fluconazole and 52% with nystatin. Fluconazole oral suspension as a systemic therapy was more effective than liquid nystatin as a topical therapy in the treatment of oral candidiasis in HIV+ patients and provided a longer disease free interval before relapse.	A
5	Philips et al., 1998	Double-blind randomized control trail.	244 HIV+ patients with OPC.	Itraconazole sol. 100 mg twice daily for 14 days. Fluconazole caps. 100 mg once daily for 14 days.	These results showed that in the treatment of OPC, itraconazole oral solution and fluconazole capsule at a 100 mg single daily dose for 14 days were equally effective.	A
6	Laine et al., 1992	Randomized trial.	169 AIDS patients.	Fluconazole 100 mg/day or Ketoconazole 200 mg/day for 15 days.	Endoscopic cure occurred in 91% of patients with fluconazole and 52% with ketoconazole. Fluconazole was associated with significantly, greater rate of endoscopic and clinical cure than ketoconazole in-patients with AIDS and C.oesophagitis.	A
7	Smith et al., 1991	Randomized control trail.	111 HIV+ patients.	Itraconazole 200 mg/day or Ketoconazole 200 mg twice day for 28 days.	75% clinical response of itraconazole and 82% of ketoconazole after 1 week, after 4 weeks of treatment this had risen to 93% in each group.	A
8	DeWit, Goossens, and Clumeck, 1993	Randomized control trail.	40 HIV+ patients with OPC.	Fluconazole 150 mg single dose or itraconazole 100 mg/day for 7 days.	A single dose 150 mg of fluconazole may be a safe, effective, and convenient therapy for HIV-positive patients with OPC.	A

Cont'd table: 9

No	Authors	Study design	No &characteristic of patients	Intervention	Results and Comments	Quality level
9	Pons et al., 1993	Randomized multicenter.	334 HIV+ patients with oral candidiasis.	Fluconazole 100 mg once daily or Clotrimazole 10 mg 5 time's daily for 14 days.	This study showed that 5 times daily dosing with clotrimazole was as effective in achieving clinical cure as once daily oral dosing with 100 mg fluconazole taken for 2 weeks. Fluconazole was shown to be more effective in eradicating *Candida* from the oral pharynx at the end of 2 weeks therapy.	A
10	Redding et al., 1992	Randomized control.	24 HIV+ patients with thrush.	Fluconazole tabs. 100 mg once daily or Clotrimazole troche. 10 mg 5 times/daily for 14 days.	Fluconazole tablets and clotrimazole troches were effective in treating thrush in-patients with HIV infection. Multiple doses versus once per day dosing, however would appeared to favour fluconazole as a choice for this infection.	A
11	Barbaro et al., 1995	Double-blind randomized control trail.	123 HIV+ patients.	Fluconazole 100 mg once daily or Itraconazole 100 mg once daily for 1-2 week.	Fluconazole was associated with higher rate of endoscopic cure than is itraconazole.	A
12	Barbaro et al., 1996	Double-blind, multicenter placebo-control.	85 HIV+ patients.	Fluconazole 3 mg/kg daily. Itraconazole 3 mg/kg day. Flucytosin association 100 mg/kg daily for 2 week.	Both fluconazole and itraconazole + flucytosine association were efficacious in short-term treatment of oesophageal candidiasis in AIDS patients. Itraconazole + flucytosine association may represent an alternative therapeutics regimen for patients with fluconazole resistant C.oesophagitis.	A

Of the available systemic azoles, ketoconazole was found to be the least effective, and until recently, fluconazole was considered the most reliable. However, the newer oral suspension of itraconazole, which avoids the erratic absorption and uncertain bioavilability associated with prior formulations, seems to be as effective as fluconazole for the treatment of oropharyngeal candidiasis (Philips et al, 1998). Itraconazole has been shown to be effective in patients with recurrent or persistence oropharyngeal candidiasis. In the study by Flynn et al., (1995) fluconazole was significantly more effective than nystatin for achieving clinical and mycological cure. In a recent randomized, open-label study of HIV-infected patients with oropharyngeal candidiasis, the superiority of fluconazole oral suspension to nystatin oral suspension was confirmed (Pons et al, 1997).

Oral itraconazole was compared with oral ketoconazole in the treatment of HIV-infected patients with oropharyngeal candidiasis in several studies (Smith et al, 1991; de Repentigny, Ratelle and the HIV Itraconazole Ketoconazole Project Group, 1996). In a randomized double-blind study (Smith et al., 1991) in which a 4-week course therapy with oral itraconazole was compared with oral ketoconazole, oral itraconazole was better tolerated than ketoconazole. It combined the beneficial effects of topical application to the oral mucosa with the systemic availability of the oral drug following absorption, and it was easier to swallow than capsules or tablets for patients with oropharyngeal candidiasis.

Several studies (Murray et al, 1997; Phillips et al, 1996) conducted on patients with oropharyngeal candidiasis have demonstrated the efficacy of itraconazole oral solution as the first line therapy for oropharyngeal candidiasis as well as its effectiveness in patients with fluconazole refractory oropharyngeal candidiasis. Murray et al., (1997) compared the efficacy of troches in immunocompromised patients, the majority of whom had HIV

infection or AIDS and had received prior antifungal treatment. The clinical response was not significantly higher among patients treated with itraconazole oral solution versus clotrimazole troches. Treatment with the former drug produced significantly higher rates of mycological cure and clinical response. Itraconazole oral solution was associated with a statistically insignificant lower rate of relapse at the end of the 28-days follow up period. In addition to its higher efficacy, itraconazole oral solution had the added benefit of a once daily oral administration, whereas the clotrimazoel troches required dosing five times daily. In studies by Graybill et al (1998) and Greenspan and Shirlaw (1997), HIV-infected patients were randomized to itraconazole oral solution for 7 or 14 days or to treatment with oral fluconazole for 14 days. The majority of patients had received prior antifungal therapy for treatment of oropharyngeal candidiasis, however, treatment with 7-day course of itraconazole produced lower rates of mycological cure and lower rates of relapse-free clinical cure at the end of 28 days follow-up period when compared with the other two groups.

Impaired gastric acid secretion of HIV-infected patients and those with AIDS, may have important pharmacokinetic, and hence, clinical implications, as the absorption of antifungal drugs may be impaired under conditions of achlohydria. The absorption of ketoconazole is markedly reduced under hypochlorohydric conditions, and as a result, some patients may actually be suboptimally or inadequately treated, even when high-dose therapy is administered. The absorption and consequently, the serum concentrations of azole antifungal agents can also be affected by interactions with a variety of drugs. For example, the concurrent use of rifampicin can reduce the serum concentrations of ketoconazole, while the use of ketoconazole can decrease the serum concentrations of theophylline. The concurrent use of rifampicin, phenytoin, cabamazepine, or phenobarbital

with itraconazole may reduce the plasma concentrations of itraconazole, possibly leading to clinical failure or relapse.

Darouiche (1998) reported that because both ketoconazole and itraconazole are potent inhibitors of the hepatic cytochrome p450 enzyme system, the drug-drug interactions with these two azole agents are generally similar to co-administration of either azole agents with other drugs primarily metabolized by the p 450 enzyme system and may result in increased plasma concentration of the latter drugs, often requiring adjustments in the dosing of those drugs. For instance, the co-administration of either ketoconazole or itraconazole can potentially increase the plasma concentrations of cyclosporine (possibly requiring a 50% reduction in the daily dose of cyclosprine), dioxin possibly requiring a 60% -75% decrease in the daily dose of digoxine), HIV-protease inhibitors saquinavir, indinavir, nelfinavir, and ritonavir, phenytoin, some antihistamines (terfanadine and astemaizole), certain sedatives (midazolam) and cisapride.

Another issue related to the pharmacokinetics of azole antifungal agents is the correlation between salivary and serum concentrations of these drugs and their antifungal efficacy. Ketoconazole is reportedly more active *in-vitro* against *C.albicans* than fluconazole, and fluconazole is generally more clinically active in the treatment of oropharyngeal and esophageal candidiasis. Drugs that achieve high concentrations in the oral cavity and/or saliva, such as fluconazole, might have a local effect (as is achieved with topical antifungal agents) in the treatment of oropharyngeal and esophageal candidiasis. The salivary concentration of fluconazole is considerably higher and more sustained than those of ketoconazole. The relatively high concentration of fluconazole in saliva can be explained by the fact that fluconazole has a low degree of protein binding, is relatively hydrophilic

(with good penetration of saliva), and is largely non-ionized under physical conditions. Although the mean plasma concentration of fluconazole in healthy subjects were reported to be virtually identical for the oral suspension and the capsule form, fluconazole oral suspension achieves higher drug levels at the local site of infection and therefore, may offer at least some theoretical advantages in the treatment of oropharyngeal candidiasis (Laufen et al, 1995).

Some cases of oropharyngeal candidiasis treated with oral fluconazole are considered to represent clinical or mycological failures because of diminished *in-vitro* susceptibility of *Candida* isolates to fluconazole as a result of previous exposure to the drug. It is also possible that low drug concentration in saliva, in association with diminished salivation, may play a role in cases of therapeutic failure.

In a study by Garcia-Hermosa et al (1995) conducted on 16 patients with AIDS and oropharyngeal candidiasis who had been treated with fluconazole for at least 7 days, salivary drug levels were found to correlate well with the dosage of fluconazole, but not with the therapeutic response. There was also a poor correlation between the drug concentration in saliva and those in serum, which was again independent of the clinical response to treatment. Drug levels in saliva were consistently below the mean inhibitory concentration (MICs) for patients who failed to respond to therapy. These findings indicate that the presence of a resistant organism, rather than low salivary concentration of fluconazole, was the more likely cause of treatment failure.

5.2.2 Drug–resistance and interaction

The common and long-term use of any drug may promote the development of, or select for resistant strains and thus complicate therapy. There are three possible ways in which a patient might acquired resistance (i) a colonizing or infecting organism is initially susceptible but mutates and becomes resistant, (ii) the patient is colonized or infected with multiple strains or species and an inherently resistant strain or species is selected, or (iii) the patient is initially colonized or infected with an inherently resistant species. Concomitant with the wide spread use of triazoles, in particular, fluconazole, there have been increasing reports of fluconazole-resistant *C.albicans* strains. The likelihood of resistance development increases when patients are on azoles for an extended period (Ghannoum and Elewski, 1999).

18 studies carried out to examine different antifungal resistance were found. Of these, 4 achieved evidence level B and 14 achieved evidence level C. The resistance of different antifungal medications and the treatment of drug-resistance candidiasis were evaluated. Table 10, shows drug-resistant candidiasis, methods of treatment and *Candida* isolates in relation to therapy. The growing incidence of resistance to some of the most widely used antifungal agents is of particular concern. Currently, there are many effective therapeutic options for oropharyngeal candidiasis. The newer azole antifungal compounds are commonly used because of their high rate of efficacy ease of administration and low toxicity. Fluconazole, the most commonly used newer azole, has been found to be extremely effective and well-tolerated. As a result, it has been widely used to treat oropharyngeal candidiasis, both for acute episodes (intermittent therapy) and for prophylaxis (continuous therapy) (Revankar et al., 1996).

Table 10: Drug-resistance and interaction.

No	Authors	Study design	No& characteristics of patients	Intervention	Improvement	No improvement	Results and comments	Quality level
1	Cartledge, 1998	Multicenter study.	26 HIV+ patients with OPC.	D0870 Fluconazole 150 mg/day Initial dose & 25 mg/day for 6 days.	17 = 65%	9 = 35%	D0870 showed promise in the treatment of resistant OPC and excellent efficacy in non-resistant HIV-related candidiasis.	B
2	Thorsen and Mathiesen, 1990	Randomized double-blind study.	16 HIV+ patients with OPC. 13 patients with ketoconazole resistance OPC.	Fluconazole 50-200 mg/day. Ketoconazole 200 mg/day.	11 = 84%	3 = 27%	HIV infected patients with OPC attained complete or partial remission on 50-200 mg fluconazole per day Fluconazole appeared to be a suitable choice of drug in this respect.	B
3	Newman, 1994	Descriptive study.	8 HIV+ patients with mucosal candidiasis.	Fluconazole 400-800 mg/day.	———	8 = 100%	The appropriate prophylactic use of fluconazole to prevent fungal infection in-patients with low CD4 lymphocyte counts needed to be better defined.	C
4	Revankar, 1996	Cohort study	50 HIV+ with severe immunosuppressed.	Fluconazole	48 = 96%	2 = 4%	Fluconazole-resistant *C.albicans* & non-*C.albicans* yeast infection were common in patients with advance immunodeficiency, but clinical efficacy of fluconazole remained high.	C

Cont'd Table: 10

No	Authors	Study design	No & Characteristics of patients	Intervention	Improvement	No improvement	Results and comments	Quality level
5	Dewsnup, and Stevens, 1994	Case report.	2 HIV+ patients with oral thrush	Amphotericin B 1 mg/5 ml of 5% dextrose in water with cherry syrup/dose 4 times daily. 200 mg Fluconazol daily previous treatment.	2 = 100%	_____	Oral amphotericin B therapy in-patients with azoles-resistance thrush were efficacious, safe & well tolerated.	C
6	Hegener, et al., 1998	Pilot study.	12 patients suffered from end-stage AIDS disease.	Voironazole 200 mg twice / day.	10 = 83%	2 = 17%	The efficacy of 200 mg twice daily in patients with fluconazole-refractory candidiasis, switching to voriconazole were effective in the majority of the patients after 7 days of therapy.	B
7	Dupont, Drouhet, 1988	Open study.	61 HIV+ patients with candidiasis.	Fluconazole 50 mg once daily.	100%	_____	The results suggest that fluconazole is an appropriate treatment for OPC, particularly in AIDS patients. The efficacy of fluconazole treatment appeared to be as good as ketoconazole & better than for topical agents, with which patient's compliance is poor.	A

Although, it is clear from published reports that resistance is associated with prior use of fluconazole, the risk factors for the development of resistance have been well characterized. Development of fluconazole resistance has been reported after years of continuous suppressive fluconazole therapy, after only one month of suppressive therapy, after multiple courses of intermittent therapy, and after reported exposures to single doses of fluconazole. It cannot be determined from the available data how best to use oral azoles in the management of HIV-infected patients to avoid later resistance. Most descriptive reports of fluconazole resistance have been in patients with advanced immunosuppression (Maenza et al, 1996).

Recently, the occurrence of oral candidiasis not responsive to fluconazole which has been related to the emergence of fluconazole resistance strains of *Candida* and, in particular, of C.glabrata and C.krusi, have been recorded (Tumbarello et al, 1997).

Predisposing factors for oral infection with fluconazole-resistant *Candida spp.* showed that it appears to occur more frequently among patients with some identifiable risk factors, viz., previous use of fluconazole therapy, advanced stage of HIV-infection and a high number of episodes of oral candidiasis in the previous years. Some of these factors are strongly co-related one to the other (Tumbarello et al., 1997). In addition, regardless of the above-mentioned factors, the extensive use of fluconazole is the most likely cause for the emergence and increasing prevalence of fluconazole-resistant *Candida spp.* as it was found to be the only independent factor selected by multiple logistic regression analysis. In order to face the potential risk of the emergence and selection of fluconazole resistant- strains of *Candida* in patients with AIDS, it is important to consider carefully the selection of the

antifungal drug and in particular of fluconazole, for the therapy of mild fungal infection (Tumbarello et al., 1997).

Vuffray et al., (1994) confirmed and observed the emergence of resistant *C.albicans* strains during fluconazole therapy for oropharyngeal candidiasis. They suggested that resistance was accrued by the initially susceptible *C.albicans* strain during flucoanzole-exposure. Clinically, cross-resistance between fluconazole and other azoles might also occur. The large number of HIV-infected patients at risk for oropharyangeal candidiasis and oesophageal candidiasis mandates that physicians be aware of the epidemiology and potential determinants of infection with *C.albicans* that has decreased susceptibility to fluconazole resistance (White and Goetz, 1994).

The increased prevalence of *C.albicans* strains with decreased *in-vitro* susceptibility to azoles may substantially reduce the prophylactic and therapeutic effectiveness of these agents against mucosal candidiasis in HIV-infected patients and necessitate the use of more complex and toxic therapeutic options. Given the increasing incidence of nosocomial *C.albicans* infection and sexual transmission of *C.albicans*, such decreased susceptibility could also have substantial import for other patient populations (White and Goetz, 1994).

According to Sanguineti et al., (1993) physicians must consider resistance in cases of apparent fluconazole failure, and cautions against the indiscriminant use of this important drug. The mechanism of resistance remains to be elucidated, but the common long-term use of fluconazole will certainly result in more frequent recognition of therapeutic failure due to fluconazole-resistant *C.albicans.*

The epidemiology and clinical significance of fluconazole resistance were assessed by Revankar et al (1996) in a cohort of HIV-infected patients with recurrent oropharyngeal candidiasis. Fifty patients were prospectively evaluated using a novel method of detecting fluconazole resistance with chromogenic media containing fluconazole. Previous fluconazole use and severe immunosuppression were risk factors for resistance. However, 5 of 26 patients had resistant isolates with no prior fluconazole use, and all were severely immunosuppressed. Despite the high prevalence of resistance, 48 patients clinically responded to fluconazole. Fluconazole-resistant *C.albicans* and non-*C.albicans* yeast infections are common in-patients with advanced immunodeficiency, but clinical efficacy of fluconazole remains high.

The problem of fluconazole resistance seems closely linked to advanced AIDS and the cumulative dose of azoles, resistance to fluconazole dose not appear to develop during the shorter courses of therapy used for invasive *Candida* infections. Microbiologic resistance of *C.albicans* and non-*C.albicans* yeast in oropharyngeal candidasis in HIV positive patients is common, especially in those of immunosuppression and previous fluconazole use.

5.2.3 Summary

This objective assessed the efficacy of different interventions of treatment of oral candidiasis in HIV-positive patients. A number of differences were found. The quality of studies found was mainly high (level A). All the included studies show a comparison between two different interventions for the treatment of oral candidiasis in HIV-positive patients are shown in Table 9.

It shows that a 100% clinical resolution rate with fluconazole-treated patients was achieved and that patients were more likely to remain disease-free during the fluconazole follow-up period than those treated with clotrimazole. Although fluconazole was more effective than clotrimazole troches in treatment of HIV-infected patients with oral candidiasis, one study showed that the treatment of oropharyngeal candidiasis with itraconazole oral solution and fluconazole capsule at 100 mg single daily dose for 14 days are equally effective. Another showed that itraconazole oral solution is well tolerated and offers an alternative at least as effective as fluconazole in the treatment of oropharyngeal candidiasis.

Table 9 shows that clinical cure by fluconazole is significantly higher than with ketoconazole in patients with AIDS and C.oesophagitis. In other studies fluconazole is associated with a higher rate of endoscopic cure than itraconazole. Table 10 shows 7 studies that assess drug-resistance and interaction. The quality of studies were moderate (level B), low (level C) and only one was of high quality (level A).

The long-term use of any drug promotes the development of resistance. The development of fluconazole resistance has been reported after years of continuous suppressive fluconazole therapy. Table 10 shows that the efficacy of 200 mg twice daily in patients with fluconazole-refractory candidiasis, switching to voriconazole were effective in the majority of the patients after 7 days of therapy. The efficacy of fluconazole treatment appears to be as good as ketoconazole and better than for topical agents where patient compliance is poor. Oral amphotericin B therapy in patients with azole resistant thrush was efficacious, safe and well tolerated.

5.3 Objective 3: To provide guidelines for the management of oral candidiasis in primary health care settings.

A total of 9 studies of the suggested guidelines of therapy of oral candidiasis associated with HIV were found. The studies assessed different guidelines for identification, treatment, dental needs and regimen. Of these, 8 studies achieved evidence level C, and 1 study achieved evidence level A. Oral health care has been an integral part of the management of HIV infection and AIDS since the disease was first identified in the early 1980s. The spectrum of HIV-associated opportunistic disease occurring in the oral cavity propelled oral health care providers to the forefront of patient care. Oral candidiasis was one of the opportunistic infections in the first reported cases of AIDS (Glick and Burris, 1997).

Oral manifestations have been shown to be reliable markers for immune deterioration and disease progression to AIDS. Furthermore, many of these oral changes interfere with daily activities and ultimately, influence the patient's quality of life. It is imperative that the oral health care providers recognize oral pathologies, diagnose and treat oral lesions or make appropriate referrals (Glick and Burris, 1997). Oral health needs may directly influence changes in medical practice. Oral pain, a common complaint among persons with HIV, can result in impaired oral nutritional intake and oral administration of medications. Oral health care workers may be the first to diagnose the oral manifestations of HIV.

Identification of the medications taken by the patient will also help to establish the medical status of HIV-seropositive patients. Immunocompetent HIV-seropositive patients may not take any medications, others may be taking medication to prevent or treat opportunistic disease. As HIV-associated immune deficiency progresses, the number of medications taken may increase.

Oral lesions such as candidiasis and hairy leukoplakia may be the initial sign of progressive immune deficiency or may be signs of disseminated opportunistic disease. The dental and periodontal examination for HIV-seropositive patients is the same as for all patients. Treatment planning considerations may be quite different for HIV-seropositive immunocompetent patient than from those with mild, moderate or severe immune deficiency.

Identifying an HIV patient's medication is particularly important because of the potential for interactions between medications. These include hypersensitivity type reactions and decreased effectiveness or enhanced activity of some medications when prescribed together. For example, the antiviral drug didanosin (ddl) may decrease the effectiveness of ketoconazole, an antifungal drug, and the effectiveness of ketoconazole may be reduce by rifampin, a drug used to treat tuberculosis. Adverse drug reactions in HIV-infected individuals are often not predictable. Therefore, as when prescribing any medication for a patient, the health care worker must be familiar with the known adverse effects of the medication prescribed. In addition, the patient's primary medical care provider should be informed of medications prescribed, and instructions to the patients should include the potential for an adverse side effect when any drug is prescribed.

It is increasingly recognized that the development of oropharyngeal candidiasis reflects immunologic impairment or deterioration in the host. In the case of HIV-positive patients, the occurrence of oropharyngeal candidiasis should trigger questions about the adequacy and effectiveness of their current antiretroviral treatment regimen, if any, and determination of their CD4 cell counts and HIV plasma RNA assays. Once assessed and antiretroviral treatment is initiated or adjusted, an appropriate medication should be selected for treatment of oropharyngeal candidiasis episode (Powderly et al, 1999b).

The most commonly employed topical applications for the treatment of oropharyngeal candidiasis are nystatin and clotrimazole. An oral suspension of amphotericin B is also available, but it is used to a much lesser extent. With regards to oral systemic therapy, three drugs are commonly prescribed in tablets or capsule for the treatment of oropharyngeal candidiasis: ketoconazole, itraconazole and fluconazole. While varying doses and treatment patterns have been employed for these drugs, the most common approach involves a single daily dose (Darouiche, 1998). Intravenous amphotericin B is inconvenient and associated with severe dose-limiting toxicity, so it is not routinely used in the treatment of oropharyngeal candidiasis. However, because resistance to amphotericin B is extremely rare, it remains the drug of choice for patients with severe or recurring disease and those with oesophageal involvement (Darouiche, 1998; Flynn et al and the Multicenter Fluconazole Study Group, 1995). Fluconazole suspension, 6 mg/kg loading dose followed by 3 mg/kg per day, should be considered as acceptable therapy for oropharyngeal thrush in immunocompromised children.

Many factors have been found to complicate or confound the treatment of immunocompromised patients with oropharyngeal or esophageal candidiasis. For

example, it is difficult to eradicate *Candida spp.* from mucous membranes because these organisms constitute the normal oral flora. Therefore, most treatment regimens are directed at controlling symptoms rather than at eradicating the causative pathogens, an approach that is reinforced by the fact that most antifungal agents (e.g., the azoles) are fungistatic rather than fungicidal. In addition, chronic suppressive or intermittent treatment may foster the development of resistance not only in *C.albicans* but in non-albicans strains of *Candida* as well. Treatment is further impeded by the fact that many patients are inadvertently under-treated because of impaired absorption or drug interactions. Traditional antifungal agents such as the topical polyenes and imidazoles may be satisfactory for the treatment of relatively mild and transient episodes of oropharyngeal candidiasis (e.g., thrush), the clinical utility of these agents ultimately can be compromised by numerous encumbrances. Similarly, although ketoconazole has a long history of use for the treatment of oropharyngeal and esophageal candidiasis, concerns about potentially serious side effects have favored the use of alternative antifungal agents instead.

The most optimal results, based on both clinical and mycological criteria, are achieved with the newer triazole agents. Both fluconazole and itraconazole offer clinical efficacy at least comparable to that of the traditional topical and oral antifungal agents, together with a highly favorable mycological cure rate. In some cases, there also appears to be more prolonged response to treatment and lower relapse rate with these newer compounds. The recent introduction of novel oral formulations of both itraconazole and fluconazoel offers an important alternative to traditional oral formulations of antifungal agents. In addition to addressing the problem of poor absorption of the drug in the traditional dosing forms, these new formulations deliver high concentrations of the drug

directly to the site of the infection. Moreover, oral solutions are better tolerated, with fewer drug-drug interactions and more convenient dosing schedules and are easier to administer than tablets or capsules to patients with severe oral lesions, restricted oral intake, or inability to swallow (Darouiche, 1998).

5.3.1 Summary

This objective assessed the guidelines for the management of oral candidiasis in primary health care settings. Relatively few studies were qualified to address this issue. No included study specifically provided clear guidelines except for one study which had a high quality of evidence (level A), all the other studies were of moderate (level B) and low quality (level C) of evidence. The small number of studies, the differences between them and their low quality rating, suggests caution when interpreting the results. These studies included and assessing different guidelines for identification, treatment, dental needs and regimen. A major weakness generally was the lack of control for any possible confounding factors, many of which were highlighted by the study author. The high frequency of candidiasis in HIV-patients has led to many authors to develop protocols to guide the use of antifungal agents in the treatment of this opportunistic infection. However, few specific recommendations have been made regarding the management of candidiasis in patients infected with HIV.

Access to oral health care is an essential need for all patients, particularly for individuals with complex medical conditions. The oral health care worker and the patient may well establish a strong relationship of trust particularly when the patient has to come repeatedly for dental treatment.

The strong casual link between HIV-infection and development of oropharyngeal candidiasis would suggest that anyone presenting with symptoms and without other known risk factors be assessed for risk of HIV-infection. Patients should be educated to recognize the symptoms of the oral candidiasis variants commonly observed in HIV-infected patients, as well as other oral conditions associated with HIV-infection, such as Hairy leukoplakia and Kaposi's sarcoma.

The present goal of therapy is re-evaluation of the patient's antiretroviral therapy and alleviation of clinical symptoms of oropharyngeal candidiasis. In the HIV-infected patients with oropharyngeal candidiasis exhibiting no oesophageal involvement and with a $CD4^+$ cell count above 50 cell/mm^3, topical agents such as clotrimazole troches are excellent choices for initial treatment. In the patient with esophageal involvement and/or a $CD4^+$ cell count of 50 cells/mm^3 or less, a systemic oral azole may be appropriate. In HIV-infected patients with recurrent candidiasis, acute treatment of each episode is preferred pending further studies. In recognition of the potential for development of drug resistance, chronic oral antifungal therapy is not generally recommended except for patients in whom candidal episodes become frequent and/or severe.

CHAPTER 6

CONCLUSIONS

Oral candidiasis is a frequent and early manifestation of HIV infection (Samaranayake and Holmstrup, 1989) and has been reported in more than 90% of patients with AIDS (Phelan, Saltzman, Friendland and Klein, 1987). Topical treatment of initial or recurrent episodes of oropharyngeal candidiasis is appropriate, provided the clinical symptoms are not severe and there is no risk of esophageal involvement. The oral azoles, which are effective therapies, could be reserved for use in more serious cases of oropharyngeal candidiasis. This approach would assist in preventing unnecessary fluconazole exposure and reducing the incidence of drug-resistant candidiasis. Selection of a particular azole should be made after consideration of a number of variables, including a patient's medications, past history of oropharyngeal candidiasis and previous azole exposure, immune status and general health. In the majority of cases, fluconazole is likely to be the most suitable candidate, since fewer drug interactions have been demonstrated for this compound.

The new generation of oral triazole antifungal agents-flucoaznole and itraconazole are an important advance with respect to both efficacy and safety in the management of candidal infections. Fluconazole is generally safe and well tolerated and has been shown to produce a rapid clinical and mycological response. Fluconazole posseses several properties, which make it well suited to treat thrush. With HIV-infection, a cure rate of 82% was achieved with a daily oral dose of 50 ml (Redding et al, 1992). Ketoconazole and clotrimazole are less effective than fluconazole for treatment of thrush (Graybill et al., 1998). Fluconazol and itraconazole have widespread use, in part because of their ease

of administration and the lack of toxicity. However, neither drug is the perfect antifungal agent and both have notable drawbacks.

An emerging problem that has arisen due to fluconazole being more widely used, is the development of resistance. The judicious use of the azole antifungal drugs is clearly beneficial to many patients, but indiscriminate or inappropriate use is associated with increasing antimicrobial resistance. Ketoconazole was the first oral antifungal drug shown to be effective for the treatment and prevention of oropharyngeal candidiasis, but it has been largely replaced by fluconazole. Itraconazole has been less thoroughly evaluated in the setting of HIV-related oropharyngeal candidiasis. Various studies suggested that a daily dose of 100 mg or 200 mg for 2-4 week is effective, but few comparative data are available (De Wit et al, 1998).

Treatment of refractory disease remains difficult. At present, the most viable approach for the treatment of refractory disease, of severe or unresponsive episodes of oropharyngeal candidiasis, and of patients with deep tissue infections, continues to be intravenous amphotericin B. It is hoped, however, that the widespread use of effective antiretroviral agents and therapeutic approaches will greatly decrease the incidence of severe and/or refractory oropharyngeal candidiasis.

During the course of HIV-disease there is a great demand and need for oral health care. Oral health care workers can act as a primary health care provider, sharing responsibility with other health care providers to ensure adequate overall care for HIV-patients. The vast majority of HIV-patients are asymptomatic and many are unaware of their status. Oral health care workers should be able to recognize oral manifestations, diagnose, treat

and make appropriate referrals (Glick and Burris, 1997). Treatment planning for HIV-seropositive patients may vary. Oral health care workers should be aware that unusual and adverse drugs reaction and interaction also occurs in HIV-seropositive patients. For many developing countries (including South Africa), HIV prevention is the only means of containing the epidemic. Preventive approaches include education, change in behavior (sexual and drug use) and the use of barrier techniques. Diagnosis of HIV is difficult in the developing world, where there is little access to laboratory techniques, and the cost of such assessments are exhorbitant. In such a setting, the evaluation of patients, including oral findings and oral examination screenings, become useful marker for HIV-AIDS recognition and diagnosis (Epstein and McCarthy, 1996).

The relationship of oral health to the progression of HIV disease and the most appropriate preventive oral health care for HIV-infected individuals remains to be studied. These studies are likely to further emphasize the importance of oral health care in the management of patients with HIV infection. Dental treatment for HIV-infected dental patients should be appropriately planned after a thorough evaluation. Alterations to policies for the rational use of antifungal agents and appropriate surveillance may be necessary to recognize and deal with the changing spectrum of candidiasis in the future (Reef and Mayer, 1995). As the treatment of oropharyngeal candidiasis reflects immunologic impairment or deterioration in the host, any HIV-infected patients presenting with symptoms should be assessed for adequacy and effectiveness of antiretroviral treatment and immunodeficiency status.

Treatment for refractory disease remains difficult, and in many ways, unsatisfactory. At present, the most viable approach for the treatment of refractory disease, of severe or unresponsive episodes of oropharyngeal candidiasis, and of patients with deep tissue infection continues to be intravenous amphotericin B. Further clinical studies are required to understand the impact of new antiretroviral treatment and viral loads, the prevalence of opportunistic infections, and the development of drug resistance.

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