

Invasive Fungal Infections in People Living with HIV/AIDS

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Abstract

The increased incidence of invasive and opportunistic mycoses is probably related to the growth of the immunocompromised population, such as people living with HIV. This study is a literature review that aims to analyze the frequency of invasive fungal infections in people living with HIV. In most studies evaluated, *Pneumocystis* pneumonia was the most frequent invasive fungal infection among people living with HIV, and cryptococcosis was the second most frequent. Invasive fungal infections are associated with greater morbidity and mortality in people living with HIV. The most important highlighted information is that the lack of epidemiological data on fungal infections in the studied populations was reported by most studies. Therefore, there is a need for further studies to assess the frequency of invasive fungal infection in people living with HIV, which may serve as subsidies for the implementation of strategies for the prevention and management, with a consequent increase in the quality of life and reduction of morbidity/mortality in this population.

Keywords

Invasive Fungal Infections, HIV, Epidemiology, Invasive Mycoses, *Pneumocystis*, Opportunistic Mycoses

1. Introduction

Human immunodeficiency virus (HIV) infection is still a public health problem, despite the global effort to reduce new cases of infection, discrimination, and mortality related to Acquired Immunodeficiency Syndrome (AIDS) [1]. The

overall incidence of HIV infection reached its peak in 1997, with 3 million new cases. There was a decline between 1997 and 2005, and after that period, the annual incidence remained relatively constant. However, the number of people living with HIV has steadily increased, reaching 38.8 million in 2015 worldwide [2].

The year 1996 represented a milestone in the history of the treatment of HIV infection due to the availability, in several countries, of highly active antiretroviral therapy (HAART) with a combination of several antiretroviral medications, which provided a reduction of mortality with a decrease from 1.8 million deaths in 2005 to 1.2 million in 2015 in world statistics [1].

By contrast, although many countries have experienced decreases in mortality and in new HIV/AIDS cases, others have increased incidence of infection [2]. In Latin America, 79,000 to 130,000 people acquired HIV in 2018, a 7% increase compared with 2010. Increases in incidence were seen in Brazil (21%), Costa Rica (21%), Bolivia (22%) and Chile (34%), according to UNAIDS [3].

In the Clinical Protocol and Therapeutic Guidelines for the Management of HIV Infection in Adults updated in 2017, the Ministry of Health of Brazil points out the emergence of opportunistic infections and neoplasms as defining characteristics of AIDS. These included pneumonia, neurotoxoplasmosis, cryptococcal meningitis, atypical or disseminated pulmonary tuberculosis, and retinitis caused by cytomegalovirus [4].

The epidemiology of invasive fungal infections (IFI) is not completely known when compared to other infections, but the subject deserves special attention due to its increased incidence, mainly in relation to diseases that cause immunodepression, such as AIDS [5]. More than 90% of the deaths arising from fungal infections are associated with species of one of the genera *Cryptococcus*, *Candida*, *Aspergillus*, or *Pneumocystis* [6].

According to Armstrong-James *et al.* [7], there are more than one million new cases of invasive fungal infection related to HIV-AIDS per annum and mortality reaches 500,000 worldwide. The mortality rate varies between 30% and 70% for cryptococcal meningitis, 10% - 60% for histoplasmosis, 10% - 30% for *Pneumocystis* pneumonia and 10% - 33% for talaromycosis according to the place and study [7] [8]. Another infection, oral candidiasis, is common in untreated patients and has a high degree of morbidity [7].

The increased incidence of some of the invasive mycoses is probably related to the growth of the immunocompromised population, the increase in the number of solid organ and bone marrow transplants, and the use of immunosuppressive drugs [9] associated with the improvement of diagnostic technologies. In the era HAART, the IFI still occur in patients with HIV, mainly in those with low CD4+ count ($<200 \text{ mm}^3$); the existing clinical challenge is perceived in relation to fungal infections in patients that are severely immunocompromised [10].

In this way, the epidemiology of IFI in people living with HIV is important to direct the actions focused on their diagnosis, prevention, and treatment, being a

strategy for improving the quality of life of this population. The present study aimed to approach the frequency of IFI in people living with HIV and the main fungal species evolved.

2. Methodology

2.1. Type of Study

This study consists of an integrative review of literature, that is a method of bibliographical research, which allows scientists to gather and summarize the scientific knowledge available on the subject in research. This type of study makes possible the evaluation and synthesis of the available scientific evidence that will contribute to the development of conclusions on the discussed thematic [11]. Six steps have been taken to prepare this study: establishing the guiding question and objectives of the research; definition of criteria for inclusion and exclusion of publications; search in the literature; analysis and categorization of studies; and presentation and discussion of results [11]. The question for this review was: “How frequent are invasive fungal infections in people living with HIV?” Based on the guiding question, the PRISMA flow-chart model was used (Figure 1).

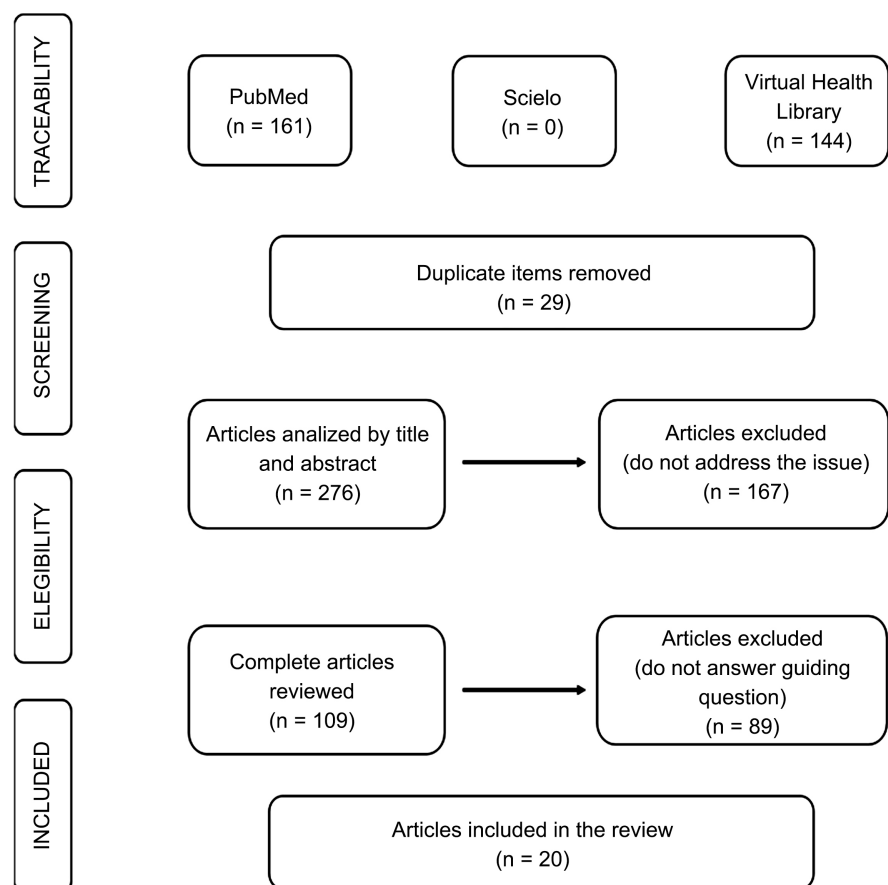


Figure 1. Flow of the selection process of the studies for the integrative literature review, elaborated based on the PRISMA recommendations.

2.2. Course of the Selection of Articles

The search took place in May 2018 in the following databases and/or digital libraries: Virtual Health Library, Scientific Electronic Library Online (SciELO), and the PubMed portal; the Medical Literature Analysis and Retrieval System Online (Medline) from the association of descriptors in Health Sciences and Medical Subject Headings (MeSH) by means of the Boolean operator “AND”: epidemiology; invasive fungal infections; and HIV. In the Medline/Pubmed search process, by the characteristics of this database, only the English descriptors were used. All the identified studies were initially evaluated by way of analysis of the titles and summaries. In the studies in which the reading of the title and summary was not sufficient for the application of the criteria of inclusion and exclusion, the article was read for inclusion or exclusion in the study.

The inclusion criteria were: publications that addressed invasive fungal infections in people living with HIV; published or available online in the period from January 2007 to April 2018 (10-years period); in the Portuguese, English, or Spanish languages; and were available free of charge for full Internet reading. Studies were excluded that did not fill in the previous requirements; literature review papers, case reports, dissertations, theses, book chapters, supplements or editor comments; articles that did not address the search theme; and the duplicate articles should be considered for posting only once. A data collection instrument was developed that met the following inclusion criteria: 1) year of publication, 2) authors, 3) country where the study took place, 4) study type, and 5) IFI more frequent in people living with HIV.

3. Results

The path traveled in the identification and selection of study components was described in **Figure 1**. The selective reading of the 305 articles found in Medline and Virtual Health Library were initially made with review by title and summary. Thirty-seven studies were selected from Medline, according to titles and summaries. Then, the full and critical reading of these texts was conducted, and six articles were selected. From the search conducted at the Virtual Health Library, 72 articles were chosen after reading titles and summaries, which were read. Among the articles, 14 were selected. Of the 109 articles selected in the two databases, 89 were excluded when the pre-established exclusion criteria for the study were applied. So, 20 articles composed the *corpus* of work.

Characteristics of the Studies

Nineteen (95.0%) studies were published in the last 5 years. A broad geographical distribution is noted in the included studies, since three (15.0%) were carried out in Africa, four (20.0%) in Latin America, one (5.0%) in North America, six (30.0%) in Europe, and six (30.0%) in the Asian continent (**Table 1**). Sixteen (80.0%) studies were epidemiological descriptive, two (10.0%) were retrospective descriptive, one (5.0%) prospective descriptive, and one (5.0%) randomized.

Table 1. Most frequent invasive fungal infections in people living with HIV according to different studies.

Year	Publications	Local	Type of study	Most frequent IFI	Candidiasis (not invasive)*	Use of HAART
2009	[14]	Italy	Descriptive retrospective	<i>Pneumocystis pneumonia</i>	not	-
2014	[42]	France	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	not	-
2014	[10]	North America	Descriptive prospective	Cryptococcosis	not	-
2015	[15]	Belgium	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	-
2015	[43]	Czech Republic	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	not
2015	[16]	Denmark	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	-
2015	[44]	Mexico	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	yes
2015	[17]	Nepal	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	not
2015	[18]	Qatar	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	-
2015	[19]	Russia	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	not	-
2015	[20]	Senegal	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	not
2016	[12]	South Africa	Randomized	Cryptococcosis	not	-
2016	[21]	Kenya	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	no
2016	[13]	Mexico	Descriptive retrospective	Histoplasmosis	not	-
2017	[22]	Philippines	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	-
2017	[23]	Chile	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	-
2018	[24]	Malaysia	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	yes
2018	[45]	Uruguay	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	yes
2018	[25]	Romania	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	-
2018	[26]	Jordan	Descriptive epidemiological	<i>Pneumocystis pneumonia</i>	yes	yes

*Recurrent vulvovaginal candidiasis and oral candidiasis. -: They did not mention.

The most frequent IFI in people living with HIV was *Pneumocystis* (Table 2); only two studies highlighted cryptococcosis as the most frequent infection [10] [12], and one histoplasmosis as the most common severe fungal disease among people living with HIV [13]. In this last study, *Histoplasma capsulatum* was the most prevalent etiological agent (36 [27.2%] of the 132 evaluated individuals) in Mexico, between 2005-2014, after *Candida* spp. Of the total, 83 patients (62.9%) were infected by HIV [13]. However, this study neither pointed out whether the infection by *H. capsulatum* occurred only in people living with HIV nor mentioned the cases of *Pneumocystis pneumonia*.

Table 2. Study characteristics in which *Pneumocystis* pneumonia was the most frequent IFI in people living with HIV.

Year	Publications	Results (<i>Pneumocystis</i> pneumonia)
2009	[14]	297 people living with HIV. 131 cases of <i>Pneumocystis</i> pneumonia
2014	[42]	35,876 invasive fungal infections in the general population. 26.1% cases of <i>Pneumocystis</i> pneumonia: majority in HIV carriers.
2015	[15]	15 cases/year
2015	[43]	Estimate: <i>Pneumocystis</i> pneumonia in 40% of HIV cases in 2012. <i>Pneumocystis</i> pneumonia in 12 of the 30 new cases of HIV.
2015	[16]	15 cases/year
2015	[44]	Prevalence: 5,130/year.
2015	[17]	Estimate: 990/year. Incidence: 3.6/100,000
2015	[18]	15 cases/year. Incidence: 0.8/100,000
2015	[19]	1,414 cases/year. Incidence: 0.99/100,000
2015	[20]	1,149 cases/year. Incidence: 8.2/100,000
2016	[21]	17,000 cases/year. Incidence: 43/100,000
2017	[22]	391 cases/year. Incidence: 0.40/100,000
2017	[23]	766 cases/year. Incidence: 4.3/100,000
2018	[24]	1,286 cases/year. Incidence: 4.2/100,000
2018	[45]	48 cases/year. Incidence: 1.4/100,000
2018	[25]	30 cases/year. Incidence: 0.18/100,000
2018	[26]	6 cases/year. Incidence: 0.1/100,000

In the retrospective study conducted in North America, 159 (52.5%) of 303 HIV carriers presented with cryptococcosis. Of these, 77.9% showed a CD4+ count of less than 50 cells/mm³ [10]. In research conducted in South Africa, where four (12.0%) of the 34 patients necropsied presented with cryptococcosis, the CD4+ count ranged from 1 cells/mm³ to 56 cells/mm³, and in two of these patients, *Cryptococcus neoformans* was identified [12].

Identification of the *Cryptococcus* species was described by three (15.0%) studies [12] [13] [14]. In a study carried out in Mexico, 132 cases of fungal diseases were identified, of which 28 were caused by *C. neoformans*, one by *C. laurentii*, one by *C. albidus*, and one by *C. uniguttulatus* [13]. The studies carried out in Italy and South Africa identified only *C. neoformans* as the cryptococcal agent, which was responsible for 62 (20.9%) of 297 cases of fungal infections and 4 (12.0%) of 34 cases of fungal infections, respectively [12] [14]. The infection of the meninges (cryptococcal meningitis) was indicated in 12 (60.0%) of the studies [15]-[26].

4. Discussion

The most common IFI among people living with HIV was *Pneumocystis* pneumonia. Despite the decline in mortality from HIV infection, *Pneumocystis* pneumonia is still a worrisome disease and, in most developing countries [27]. *Pneumocystis* pneumonia is caused by *P. jirovecii* and, in many cases, this disease defines AIDS in people living with HIV, occurring more often when the CD4+ count is less than 200 cells/mm³ and when the patient was not using anti-retrovirals [10] [21] [28] [29] [30].

Candidiasis was the fungal infection (although it is not invasive) that stood out in most studies evaluated due to its high prevalence. According to literature, oropharyngeal candidiasis is still a common problem in the people living with HIV, even with the availability of HAART [31]. Esophageal candidiasis affects about 20% of AIDS patients not using antiretrovirals and 5% of those who are under antiretroviral therapy [20]. Candidiasis can become severe when it spreads to deep organs and causes candidemia, increasing the mortality rate.

Cryptococcosis, the second most frequent IFI in people living with HIV, has a relevant role, because it is considered one of the most common mycoses, especially affecting the central nervous system [31]. Cryptococcal meningitis emerged firstly as one of the main causes of infectious morbidity and mortality in patients with AIDS, since the beginning of the spread of HIV in the world [32]. In the last two decades, there have been advances in the prevention, diagnosis, therapy, and results of patients with cryptococcal meningitis. However, efforts are still needed in order to implement these strategies, mainly in low-income populations [33]. The low incidence of cryptococcal meningitis found in some countries such as Romania, which has an estimated rate of 0.09/100,000 inhabitants, may have as a justification the broad coverage of HAART [25].

Histoplasmosis, an infection caused by *H. capsulatum*, first presents an acute pulmonary form, from where the fungus spreads through the hematogenic pathway. Disseminated histoplasmosis was rare until the emergence of AIDS, occurring only at extremes of age and in individuals immunocompromised by neoplastic diseases or by the use of immunosuppressant therapy [34]. However, the annual incidence of histoplasmosis is still unknown in many countries, even if endemic [35].

Disseminated histoplasmosis was observed in 23 patients, of which 12 (52.2%) presented with HIV/histoplasmosis coinfection, among patients admitted in a hospital of high complexity in Mato Grosso do Sul, State of the Central-Western region of Brazil from 2011 to 2016. The average CD4+ count was 19 cells/mm³, and 56.5% of the patients died [36]. Another study conducted in a university hospital in the interior of the state of Minas Gerais, Brazil, highlighted 113 cases of histoplasmosis in 20 years, and of them, 103 (91.1%) were associated with AIDS [37].

HAART have improved the cellular immunity of AIDS patients, and also the rate of response to the treatment of histoplasmosis, as observed in a study con-

ducted in Colombia, by Tobón *et al.* [38]. In this study, all who received HAART responded to the antifungal treatment as well as the non-HIV patients, compared with 47% among those who did not receive antiretroviral therapy [38]. HAART has an important impact on reducing mortality, vertical transmission, and treatment of serious comorbidities [31]. For instance, a study carried out in China from 2014 to 2015 evaluated 954 HIV infected patients and concluded that the two most important factors for hospital mortality were the CD4+ count <100 cells/mm³ and the non-use of HAART [39]. To promote restoration of the immune system is important for the treatment and prevention of all types of infection.

Early diagnosis of any type of infectious disease is extremely important for proper treatment. Delayed diagnostic of fungal diseases exacerbates the problem of empirical use of antimicrobials, with consequent risk of increased antimicrobial-resistant microorganisms [40]. The diagnosis of a fungal disease, especially in an immunocompromised patient, is not always obvious. It depends on the local epidemiology, the technical capacity of the healthcare team, the availability of diagnostic tests, whether serological, microscopic and culture, or molecular tests, such as PCR. The causes of death in patients with aids are tuberculosis and other associated infections, as fungal, bacterial or toxoplasmosis, and a team prepared for these diagnoses is not always available in all countries, especially in developing ones [41].

Most of the studies reported lack of reliable data and records on the frequency of IFI. Even with the limitation of epidemiological data, there is high mortality among people living with HIV related mainly to one of the following IFI: cryptococcosis, *Pneumocystis pneumonia*, histoplasmosis, or aspergillosis, which can be significantly reduced by investment in timely diagnosis and appropriate antifungal treatment [35].

Even in the current world effort scenario to increase access to HAART [1], it is necessary to improve the registration of IFI so that we can have access to actual data of these diseases in the population in addition to the greater availability of appropriate diagnostic and therapeutic methods. As a result, IFI can be identified early and have correct handling, which is important in preventing related mortality caused by fungi in people living with HIV [35].

In addition to the findings, opportunistic fungal infections affect not only HIV/AIDS patients, but also others who have immunocompromised, such as patients with hematological diseases, solid organ transplant and chronic obstructive pulmonary disease, among others [7]. Often infections by *P. jirovecii* are confused with other lung diseases, and as the microbiological diagnosis by culture is not performed, it can often not be confirmed, which may mask their real prevalence. Other fungi that affect HIV/AIDS-infected patients, such as *Aspergillus* species and *Talaromyces marneffeii* species [7] [8] are often forgotten. We believe that studies on fungi that affect this population that is more susceptible to opportunistic fungal infections are poorly disseminated, or are restricted to

regional publications. Thus, access to the literature is not possible, and the real prevalence of the different etiologic agents involved may remain unknown.

5. Conclusion

Invasive fungal infections are associated with greater morbidity and mortality in immunocompromised individuals. In most of the studies evaluated, the most frequent IFI in people living with HIV was caused by *Pneumocystis jirovecii*. However, there is a lack of reliable data regarding its frequency, as well as for other fungal infections, like histoplasmosis. There is a need for further studies to assess the frequency of IFI in people living with HIV, which may serve as subsidies for the implementation of strategies for the prevention and management, in order to improve the quality of life and reduction of morbidity and mortality in this population.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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