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REVIEW

# The impact of sporotrichosis in HIV-infected patients: a systematic review

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**Abstract** Sporotrichosis is a fungal infection of man and animals caused by *Sporothrix* complex. It usually presents as a lymphocutaneous form, but disseminated disease may occur. Given the paucity of data about HIV/AIDS and sporotrichosis co-infection, a systematic review of reported cases of HIV-associated sporotrichosis found via Pubmed (1984–2013) was done. A total of 39 papers were included, and 58 patients' data analyzed. Thirty-three (56.9 %) cases were from Brazil and 18 (31 %) from the USA. Patients' mean age was 37.8 ± 10.4 years; males predominated (84.5 %). The median $CD4^+$ cell count was 97 cells/mm$^3$. The most common clinical forms were disseminated and disseminated cutaneous with 33 (56.9 %) and 10 (17.5 %) patients, respectively. There was a correlation between $CD4^+$ count and clinical categories ($p = 0.002$). Mortality was 30 % and there was a correlation between central nervous system involvement and death ($p < 0.001$).

**Keywords** Sporotrichosis · AIDS · Neglected diseases · HAART · Systematic review

## Introduction

Sporotrichosis, classically known as rose gardener's disease, is an infection of man and animals caused by the dimorphic fungus—*Sporothrix* complex—which included four distinct species: *S. globosa, S. brasiliensis, S. Mexicana* and *S. schenckii* [1]. It may present as an acute or chronic and cutaneous or lymphocutaneous, as well as disseminated disease, especially in immunocompromised hosts. It usually manifests in isolated cases or as outbreaks related to specific occupational exposure [2]; however recently, it has reached epidemic proportions in some parts of Latin America [3–6], India [7] and Northeastern China [8]. The clinical, demographic and epidemiologic features vary within regions. The disease affects predominantly tropical and subtropical regions, being the most prevalent subcutaneous mycosis in South America.

The mechanisms of transmission include traumatic inoculation of fungal elements from soil, plants and organic matter contaminated with *S. species*. Other modes of transmission (i.e., inhalation of conidia) are rare. In contrast, zoonotic transmission is common in hyperendemic areas and associated with scratches or bites from animals such as mice, armadillos, squirrels, dogs and cats [4, 9]. Importantly, there has been increased recognition of this condition affecting human immunodeficiency virus (HIV)-infected individuals through the years. Interaction between HIV and other endemic tropical diseases is associated with poor outcome; this is clearly the case of Chagas disease and visceral leishmaniasis [10]. Reports of sporotrichosis in the HIV population describe the skin as the most commonly

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affected organ [11]; nevertheless, multi-organ dissemination is more frequent in this scenario, probably due to underlying HIV-related immunosuppression [12]. Not infrequently, tropism for the central nervous system (CNS) occurs and is almost always fatal.

Data on HIV and sporotrichosis co-infection is scanty. Thus, we aim to systematically analyze all reported cases of HIV-associated sporotrichosis. In addition, we describe the demographic data, clinical profile, antifungal efficacy and survival outcome of those patients.

## Methods

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used for this systematic review [13]. A Pubmed literature search was performed using the search string "Sporotrichosis" or "*Sporothrix schenckii*" and "HIV" or "AIDS", which yielded 80 results on June 16, 2014. Results were limited to human studies and no language restrictions were imposed. All abstracts and titles published between April 1984 and December 2013 were reviewed. Articles were included if dated from 1984 onward, to coincide with the emergence of HIV infection. Reference lists of all records were also screened. One unpublished case from our center was further added to this systematic review.

Studies were considered eligible if they described sporotrichosis in an HIV-infected patient. Case series, case reports or cohort studies were eligible for inclusion. Exclusively original review articles were excluded. Studies were considered inappropriate when describing sporotrichosis infection in immunocompetent subjects or referring to treatment guidelines.

Two blinded reviewers independently assessed records for eligibility. Disagreements between reviewers regarding study inclusion were resolved through consensus and, when consensus was not possible, through the consultation of a third reviewer.

### Data extraction

Data were extracted and entered into a database for aggregate analyses. The following variables were extracted from the selected publications: country of publication, age, gender, clinical presentation, $CD4^+$ cell count, culture positive site (s), treatment plan and outcome.

### Definitions

Clinical presentations of sporotrichosis were classified according to Freitas: localized (fixed cutaneous and lymphocutaneous), cutaneous disseminated and disseminated [11].

Highly active antiretroviral therapy (HAART) was defined as a combination of three or more antiretroviral drugs, which generally included two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and a potent third agent, generally a nonnucleoside reverse transcriptase inhibitor (NNRTIs), a ritonavir-boosted protease inhibitor (PI/r), an integrase strand transfer inhibitor (InSTI) or a CC chemokine receptor blocker (CCR5) [14].

Immune reconstitution inflammatory syndrome (IRIS) was defined according to previous authors [15, 16], as a clinical reaction driven by excessive pathogen-specific immune recovery in a significant subset of HIV-infected patients starting HAART. It may present either as an unmasking of an already present infection or de novo depending on if the opportunistic pathogen's presence was previously known in the patient.

### Statistical analysis

Analyses for the categorical variables were expressed as counts and proportions, whereas the central tendency for age was expressed as mean ± standard deviation and for $CD4^+$ cell count as median, due to its skewed distribution. Comparisons of categorical variables were performed with Fisher's exact test. Kruskal–Wallis test was used to compare $CD4^+$ cell count within different sporotrichosis clinical forms. All analyses were conducted with SPSS version 22.0, on the basis of a two-sided type I error with an alpha level of 0.05.

## Results

Our research yielded 84 hits, and 39 titles were fully reviewed, summarizing 58 patients' data. The remaining 45 articles were excluded as described in "Methods". Four patients overlapped in two studies [17, 18]. Table 1 describes the demographic, clinical, immunologic, treatment and survival features of the included patients. Thirty-three (56.9 %) cases were from Brazil, 18 (31 %) from the USA, 2 (3.4 %) from Peru and 1 (1.7 %) each from Spain, Italy, Mexico, the UK and Congo.

The mean age of patients on presentation was 37.8 ± 10.4 years. There was a male predominance (84.5 %). The median $CD4^+$ cell count was 97 cells/$mm^3$ (Table 2).

Although detailed descriptions of sporotrichosis regarding the source of acquisition was not available in all reports, the majority of cases reported from Brazil were due to zoonotic transmission by infected cats and, less often, dogs.

The most common clinical presentation categories were disseminated and disseminated cutaneous with 33 (56.9 %) and 10 (17.2 %) patients, respectively. Sporotrichosis was the initial presentation of HIV infection in 16

**Table 1** Summary of data from patients with HIV/sporotrichosis co-infection, 1984–2013

| First author, year, reference | Country of Origin | Gender | Age | Clinical presentations | CD4 cell count at presentation (cell/ul) | Culture positive site(s) | Therapy | Outcome |
|---|---|---|---|---|---|---|---|---|
| Lipstein-Kresh (1985) [19] | USA | Male | 34 | Disseminated (cutaneous and osteoarticular) | N/A | Skin biopsy and synovial fluid | Initially treated with AmBd (1,9 g, total dose) + 5-FC; followed by SSKI | Dead |
| Bibler (1986) [20] | USA | Female | 71 | Disseminated (cutaneous, osteoarticular and pulmonary) | 140 | Skin biopsy | AmBd (950 mg, total dose) | Dead |
| Kurosawa (1988) [21] | USA | Male | 30 | Disseminated (cutaneous and endophthalmitis) | N/A | Skin biopsy and aqueous humor aspirate | AmBd (IV and intravitreal) and SSKI | Alive |
| Fitzpatrick (1988) [22] | USA | Male | 43 | Disseminated (cutaneous, pulmonary) | N/A | Skin biopsy, sputum, anterior nares and soft tissue abscess | Initially treated with AmBd (1410 mg, total dose); then switched to KTC | Alive |
| Shaw (1989) [23] | USA | Male | 30 | Disseminated (cutaneous and osteoarticular) | N/A | Skin biopsy and synovial fluid | Initially with SSKI + AmBd, followed by KTC and 5-FC | Alive |
| Keiser (1991) [24] | USA | Male | 41 | Fixed cutaneous | N/A | Skin exudate from cystic mass | AmBd and surgical excision | Alive |
| Heller HM (1991) [25] | USA | Male | 49 | Disseminated (cutaneous, bloodstream, eye, osteoarticular and pulmonary) | 11 | LN, lungs, esophagus, colon, testes, synovial, bone, blood, BM, sputum and skin | Initially treated with AmBd (2350 mg, total dose) + 5-FC, then switched to ITC and SSKI | Dead |
| Oscherwitz SL (1992) [26] | USA | Male | 38 | Disseminated (cutaneous and osteoarticular) | N/A | Synovial fluid | ITC | Alive |
| Penn (1992) [27] | USA | Male | 43 | Disseminated (cutaneous and meningoencephalitis) | 56 | Skin biopsy and CSF | AmBd (972 mg, total dose) | Dead |
| Donabedian (1994) [28] | USA | Male | 22 | Disseminated (cutaneous, meningoencephalitis, oral mucosa and pulmonary) | 17 | Skin, CSF and lung tissue | Initially with AmBd (750 mg, total dose) + FLC, then switched to ITC and SSKI | Dead |
| Bolao (1994) [29] | Spain | Male | 30 | Disseminated (cutaneous and pulmonary) | 63 | Skin biopsy and sputum | Initially treated with KTC, followed by SSKI, FLC, AmBd (750 mg), and finally switched to ITC as a maintenance therapy | Alive |
| Dong (1995) [30] | USA | Male | 31 | Disseminated (cutaneous + oral mucosa + meningoencephalitis) | 58 | Skin biopsy, oral swab and CSF | Initially treated with AmBd (400 mg total dose), followed by ITC | Dead |
| Rotz LD (1996) [31] | USA | Male | 32 | Disseminated (cutaneous, kidneys, meningoencephalitis, pulmonary) | 10 | Skin biopsy, urine, lung, meninges and CSF | AmBd (4 g total dose), followed by 5-FC | Dead |
| Morgan (1996) [32] | USA | Male | 49 | Sinus | 19 | Nasal sinuses | ITC | Alive |
| Gori S (1997) [33] | Italy | Male | 37 | Pulmonary | 345 | Sputum | AmBd (2.5 g total dose) then switched to ITC | N/A |

**Table 1** continued

| First author, year, reference | Country of Origin | Gender | Age | Clinical presentations | CD4 cell count at presentation (cell/ul) | Culture positive site(s) | Therapy | Outcome |
|---|---|---|---|---|---|---|---|---|
| Al-Tawfiq (1998) [34] | USA | Male | 47 | Disseminated (cutaneous, bloodstream and osteoarticular) | 9 | Skin biopsy and blood | AmBd (2,5 g, total dose) followed by maintenance with ITC | Alive |
| Neto RJP (1999) [35] | Brazil | Male | 30 | Disseminated cutaneous | 81 | Skin exudate biopsy | Initially treated with AmBd (355 mg), then switched to L-AmB (1690 mg). KTC was added as maintenance therapy later | Alive |
| Ware AJ (1999) [36] | USA | Male | 42 | Disseminated (cutaneous + bloodstream + osteoarticular + oral/nasal mucosa) | 10 | Skin, blood, synovial fluid and biopsy of subcutaneous nodule | AmBd then switched to ITC. ABLC was added later on. | Alive |
| Goldani LZ (1999) [37] | Brazil | Female | 34 | Disseminated cutaneous | 104 | Skin fragments biopsy | AmBd + FLC primarily, then switched to ITC | Dead |
| Edwards C (2000) [38] | USA | Male | 43 | Disseminated (cutaneous + bloodstream + osteoarticular) | N/A | Skin biopsy, blood and synovial fluid | AmB¶ (2.5 g, total dose) | Alive |
| Bonifaz (2001) [39] | Mexico | Male | 28 | Disseminated (cutaneous and bloodstream) | N/A | Skin biopsy and blood | Primarily treated with KTC, then switched to ITC | Alive |
| Aarestrup (2001) [40] | Brazil | Male | 28 | Disseminated (cutaneous + oral mucosa + osteomyelitis) | N/A | Skin exudate and periodontal tissue biopsy | AmBd (3 g, total dose), then switched to ITC and Terbinafine | Dead |
| Rocha MM (2001) [41] | Brazil | Male | 29 | Disseminated cutaneous | 228 | Skin biopsy | AmB¶ | Dead |
| Carvalho (2002) [42] | Brazil | Male | 24 | Disseminated cutaneous | 62 | Skin biopsy | ITC | Alive |
| Losman (2004) [43] | USA | Male | 53 | Pulmonary | 8 | BAL | ITC | Alive |
| Hardman (2005) [44] | UK | Male | 35 | Disseminated (cutaneous + meningoencephalitis) | 30 | Skin biopsy and CSF | L-AmB and 5-FC | Dead |
| Silva-Vergara (2005) [45] | Brazil | Male | 29 | Disseminated (cutaneous + meningoencephalitis + LN + BM + Genital + GIT) | 73 | Skin, CSF, testicles, LN, BM, epididymides and pancreas | ITC primarily, then switched to AmBd | Dead |
| Callens (2006) [46] | Congo | Male | 11 | Pulmonary | 33 | Sputum | FLC | Alive |
| Fontes (2007) [47] | Brazil | Male | 38 | Disseminated (nasal/oral mucosa + cutaneous) | N/A | Skin and oral lesions biopsy | Initially AmB¶ (1.5 g, total dose); followed by ITC | Alive |
| Vilela (2007) [48] | Brazil | Male | 34 | Disseminated (cutaneous, LN and meningoencephalitis) | 91 | Skin nodule biopsy, LN and CSF | AmBd (650 mg, total dose) | Dead |
| Bustamante (2009) [49] | Peru | Female | 30 | Disseminated (cutaneous + osteoarticular) | 134 | Skin ulcer exudate, synovial fluid and BM | AmBd then switched to ITC | LFU |
| | | Male | 27 | Lymphocutaneous | 83 | Skin and subcutaneous tissue biopsy | Primarily treated with AmBd, followed by ITC and FLC | Alive |

**Table 1** continued

| First author, year, reference | Country of Origin | Gender | Age | Clinical presentations | CD4 cell count at presentation (cell/ul) | Culture positive site(s) | Therapy | Outcome |
|---|---|---|---|---|---|---|---|---|
| Gutierrez-Galhardo (2010) [18] | Brazil | Female | 46 | Disseminated (cutaneous + osteoarticular + oral/nasal mucosa) | 70 | Skin nasal biopsy | AmBd (1 g, total dose) followed by ITC | Alive |
| | | Male | 47 | Disseminated (cutaneous, tenosynovitis and osteoarticular) | 157 | Skin exudate | AmBd (1 g, total dose) followed by ITC | Alive |
| Gutierrez-Galhardo (2010) [17] | Brazil | Male | 37 | Disseminated (cutaneous and meningoencephalitis) | 97 | Skin and CSF | AmBd then ITC + FLC | Alive |
| | | Male | 27 | Disseminated (cutaneous, pulmonary, GUT and meningoencephalitis) | 178 | Skin biopsy, CSF, sputum and urine | AmBd (2.5 g, total dose) followed by ITC | Dead |
| Freitas (2011) [11] | Brazil | Male | 42 | Lymphocutaneous | 726 | Skin exudate | ITC | Alive |
| | | Male | 46 | Disseminated (oral and nasal mucosa) | N/A | Nasal and oral biopsy | ITC | Alive |
| | | Male | 53 | Lymphocutaneous | 307 | Skin biopsy | ITC | LFU |
| | | Female | 46 | Fixed cutaneous | 237 | Skin biopsy | ITC | Alive |
| | | Male | 59 | Disseminated (cutaneous and conjunctival mucosa) | 488 | Skin exudate + conjunctival swab | ITC | Alive |
| | | Male | 24 | Lymphocutaneous | 483 | Skin exudate | ITC | LFU |
| | | Female | 29 | Fixed cutaneous | 524 | Skin exudate | ITC | Alive |
| | | Male | 42 | Disseminated cutaneous (bilateral ear + neck) | 212 | Skin biopsy | ITC | Alive |
| | | Female | 45 | Disseminated cutaneous | 111 | Skin exudate | ITC | Alive |
| | | Male | 38 | Lymphocutaneous | 725 | Skin exudate | ITC | Alive |
| | | Male | 44 | Disseminated (Skin and nasal mucosa) | 22 | Skin exudate, nasal swab | AmBd (2.5 g, total dose) | Alive |
| | | Male | 44 | Disseminated cutaneous | 110 | Skin exudate | AmBd (2.3 g, total dose) | Alive |
| | | Male | 41 | Lymphocutaneous | 201 | Skin biopsy | AmBd (1.6 g, total dose) followed by ITC | Alive |
| | | Male | 39 | Disseminated cutaneous | 86 | Skin biopsy | AmBd (2 g, total dose) | Alive |
| | | Male | 45 | Lymphocutaneous | 747 | Skin exudate | N/A | Alive |
| | | Male | 28 | Disseminated cutaneous | N/A | Skin exudate/ biopsy + blood | N/A | Dead |
| | | Female | 55 | Lymphocutaneous | 1100 | Skin exudate | ITC | Alive |
| Mello (2011) [50] | Brazil | Male | 44 | Disseminated (cutaneous and oral mucosa) | N/A | Skin and palate fragment biopsy | N/A | N/A |
| Silva-Vergara (2012) [51] | Brazil | Male | 32 | Disseminated (cutaneous, endocarditis and uveitis) | 560 | Subcutaneous nodule and mitral valve fragment biopsy | Primarily treated with ITC, then switched to AmBd and later on to L-AmB. Maintenance therapy with ITC | Alive |
| Chang (2013) [52] | USA | Male | 41 | Disseminated cutaneous | 208 | Skin biopsy | ITC | Alive |

**Table 1** continued

| First author, year, reference | Country of Origin | Gender | Age | Clinical presentations | CD4 cell count at presentation (cell/ul) | Culture positive site(s) | Therapy | Outcome |
|---|---|---|---|---|---|---|---|---|
| Moreira (2014) [53] | Brazil | Male | 38 | Disseminated (cutaneous and nasal mucosa) | 50 | Skin biopsy | Primarily treated with AmBd, then followed by ITC as maintenance therapy | Alive |
| Paixão (2014) Submitted | Brazil | Female | 21 | Disseminated (cutaneous, pulmonary, meningoencephalitis, osteoarticular) | 50 | Skin biopsy, sputum, CSF | Initially treated with AmBd, terbinafine and ITC. Later on L-AmB was added. Maintenance therapy was with PCZ | Dead |

*AmBd* amphotericin B deoxycholate, *ABCD* amphotericin B colloidal dispersion, *L-AmB* liposomal amphotericin B, *USA* United States of America, *LN* lymph node, *BM* bone marrow, *GIT* gastrointestinal tract, *GUT* genitourinary tract, *CSF* cerebrospinal fluid, *BAL* bronchoalveolar lavage, *NA* not available, *KTC* ketoconazole, *FLC* fluconazole, *ITC* itraconazole, *PCZ* posaconazole, *5-FC* flucytosine, *SSKI* saturated solution of potassium iodide, *LFU* lost to follow-up

¶ Means AmB formulation not specified

**Table 2** HIV-associated sporotrichosis cases: demographics, clinical categories and survival outcome

| | |
|---|---|
| Demographics | |
| Male no. (%) | 49 (84.5) |
| Female no. (%) | 9 (15.5) |
| Mean age ± standard deviation (years) | 37.8 ± 10.4 |
| Median CD4 + cell count [IQR] (cells/mm$^3$) | 97 [50–232.5] |
| Clinical categories no. (%) | |
| Disseminated | 33 (56.9) |
| Disseminated cutaneous | 10 (17.2) |
| Lymphocutaneous | 8 (13.8) |
| Fixed cutaneous | 3 (5.2) |
| Other | 4 (6.9) |
| Survival outcome no. (%) | |
| Dead | 16 (30.2) |
| Alive | 37 (69.8) |
| Unknown | 5 (8.6) |

Other refers to three cases with primary pulmonary involvement and one with only sinus disease

*IQR* Interquartile range

cases (27.5 %). Unusual manifestations of sporotrichosis included meningitis (ten cases), endophthalmitis (three cases), primary pulmonary disease (three cases), IRIS associated with *S. schenckii* (four cases), endocarditis (one case) and primary sinus disease (one case).

### IRIS-associated sporotrichosis

There were four cases (7.5 %) of IRIS-associated sporotrichosis; all patients were HAART-naïve, severely immunosuppressed (i.e., CD4 < 200 cells/ul) and had a high HIV viral load at baseline. Appearance of new disease manifestations occurred in two patients. Conversely, reactivation of preexisting lesions occurred in the other two cases. The median time from HAART initiation to developing IRIS was 4 weeks. IRIS-related *Sporothrix* meningitis was also noted in two patients.

### Meningeal sporotrichosis

There were ten cases (17.2 %) and nine of these resulted in death directly attributable to *S. schenckii* meningitis. All were associated with advanced HIV infection and multisystem involvement. The symptoms of CNS sporotrichosis resembled those of fungal meningitis such as fever, confusion, stiff neck and vomiting. Meningitis resulted from hematogenous spread of *S. schenckii*, with other organs also being affected (i.e., skin and osteoarticular lesions). CSF abnormalities were nonspecific. Finally, there was association between mortality and neurological disease ($p < 0.001$).

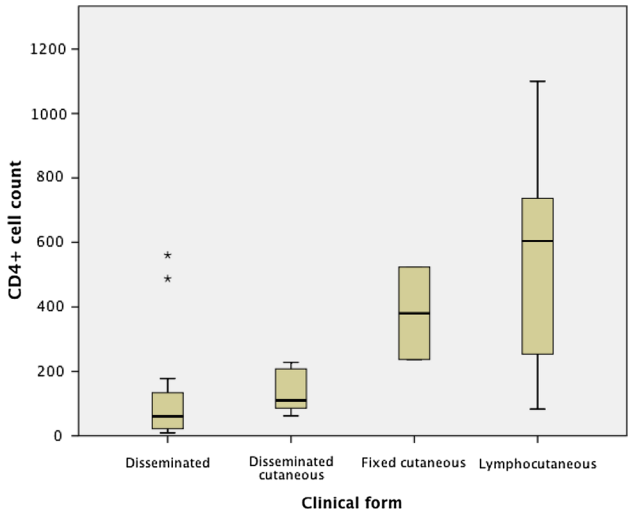


**Fig. 1** *Box plot* of $CD4^+$ cell count distribution within clinical categories in patients with sporotrichosis/HIV co-infection

Overall, 37 (70 %) patients survived and 16 (30 %) died. Data for five cases were unavailable in the reports. Thirteen (25 %) and three (6 %) patients with disseminated and cutaneous disseminated disease died, respectively. Overall, there was no association between clinical presentations of sporotrichosis and survival outcome ($p = 0.235$).

There were six cases of fungemia and no difference in mortality could be shown between groups with and without it ($p = 1.00$).

The distribution of $CD4^+$ cell count was associated with clinical categories ($p = 0.002$). Figure 1 shows the $CD4^+$ cell count distribution in HIV co-infected sporotrichosis patients.

The key diagnostic investigations are summarized in Table 3. Skin biopsy and cerebrospinal fluid were the most frequently culture-positive sites (89.7 and 17.5 % respectively).

The most common antifungal regimens prescribed were amphotericin B (AmB) plus azole(s) in 20 patients (34.5 %) followed by azole monotherapy in 19 patients (32.8 %). Itraconazole was the azole of choice and was prescribed to 37 patients (63.8 %). Fifteen patients (27.7 %) who received primarily itraconazole monotherapy for sporotrichosis had no documented relapse. Itraconazole drug serum levels were not routinely measured, so dose adjustments were made according to clinical responses. Itraconozale was also the preferred drug for maintenance therapy at a dose of 100–200 mg/day. Conversely, AmB deoxycholate was the AmB formulation of choice in the majority of cases; it was administered in 33 patients (61 %) at a total dose that varied between 0.4 and 4 g. Administration of a saturated solution of potassium iodide as add-on therapy was described for five patients (8.6 %). Posaconazole was used for just one patient. Data referring to treatment were unavailable for four patients.

**Table 3** Sample type and culture positivity for *S. schenckii* in HIV-positive patients

| Sample type | No. (%) |
|---|---|
| Skin biopsy | 52 (89.7) |
| CSF | 10 (17.5) |
| Sputum | 7 (12.3) |
| Synovial biopsy | 6 (10.5) |
| Blood | 6 (10.5) |
| Autopsy | 4 (7.0) |
| Oral tissue biopsy | 4 (7.0) |
| Nasal biopsy | 3 (5.3) |
| Bone marrow biopsy | 2 (3.5) |
| Urine | 2 (3.5) |
| Other[a] | 6 (10.8) |
| Total | 102 |

*CSF* Cerebrospinal fluid

[a] Other diagnostic samples used included nasal sinus biopsy, aqueous humor aspirate, bronchoalveolar lavage, lymph node biopsy, conjunctival swab and mitral valve fragment biopsy. Total numbers are not equivalent to 100 %, since more than one site per patient may have been culture positive

**Table 4** Survival outcome according to treatment modalities in HIV/sporotrichosis co-infected patients

| Treatment modalities[a] | Survival outcome | | |
|---|---|---|---|
| | Alive | Dead | Total |
| AmB without azole | 6 | 7 | 13[§] |
| AmB with azole | 13 | 6 | 19 |
| AmB with azole and 5-FC | 1 | 1 | 2 |
| Azole monotherapy | 16 | 1 | 17 |

[§] Five patients were treated with both SSKI and AMB

[a] Data regarding seven patients' treatment regimens and outcomes were unavailable. *AmB* amphotericin B, *5-FC* flucytosine

Regarding antifungal susceptibilities testing, it was not routinely performed in all patients, but described in just two cases [36, 44].

Survival outcomes of various treatment modalities are described in Table 4. There was a statistically significant association between prescribed antifungals and survival outcome ($p = 0.022$). Seven patients using AmB monotherapy and six patients with AmB plus azole died compared with one patient who used azole only.

With respect to antiretroviral (ARV) therapy and sporotrichosis mortality, 53 patients had survival outcome data; of these, 14 (26.4 %) were treated in the pre-ARV era (before 1996) and 39 (73.5 %) in the current ARV period (from 1996 onward), respectively. There were no differences between their mortality in the two time periods evaluated ($p = 0.09$).

## Discussion

Sporotrichosis is an endemic mycosis in some regions of the world [4–8]. Moreover, it has re-emerged in recent years with distinct patterns of transmission. While in Brazil, it has re-emerged as a zoonotic-transmitted mycosis related to domestic cats [4], in China it has appeared in rural regions of the northeast, associated with contact with wood for house heating during winter [8]. The HIV/AIDS epidemic also has distinct patterns worldwide, and in some countries there may be an overlap of the two entities. Since the 1980s, some case reports have been published discussing this co-infection [19–52].

In this systematic review, 58 patients were catalogued with their demographic, clinical and laboratory profiles, as well as the treatment outcome. The predominance of men may be related to the HIV/AIDS epidemic profile, since this gender is the most affected, especially if we consider the epidemiology of Brazil and the USA—the countries with the highest number of case reports analyzed here [54, 55].

The findings that more than 70 % of the patients presented disseminated forms of sporotrichosis, low median $CD4^+$ count and a substantial proportion of sporotrichosis as the initial presentation of AIDS draw attention to the importance of *Sporothrix* sps as an opportunistic pathogen. However, we must consider that there may have been a diagnostic bias leading to the suspicion of HIV co-infection in these more complex and severe cases. Possibly, other patients with localized forms of sporotrichosis were not tested for HIV due to the uncomplicated, classical clinical presentation. However, in our previous work [56], where we had tested the stored blood samples of 850 subjects registered in our clinical database, only 1 sample was positive for HIV (0.12 %). The lymphocutaneous and fixed cutaneous forms have been recognized as the most prevalent clinical presentations in immunocompetent subjects, but HIV serology is not routinely requested for them [3]. Another bias to consider is the reporting bias, as physicians tend to report the most relevant and unusual cases [51]. Thus, the real proportion of patients with disseminated forms of sporotrichosis among HIV subjects may be lower than found in the indexed publications studied.

CNS involvement was relatively common (~17 %) and associated with a poor outcome, expressing the severity of this kind of dissemination. It was related to the advanced level of immunosuppression of these patients, as shown by their low $CD4^+$ counts (median $CD4^+$ count 66 cells/ul). We reinforce the importance of performing lumbar puncture for every patient with sporotrichosis and HIV as a way to search for CNS dissemination of the fungus. We also agree with the previous suggestion of including disseminated sporotrichosis as an AIDS-defining illness in areas endemic in this mycosis [17, 56]. Therefore, testing for HIV serology in patients with extensive skin involvement and disseminated sporotrichosis should be routinely done.

It is clear that HIV-sporotrichosis co-infections place an immense burden on health-care systems. Recently, we showed that sporotrichosis–HIV co-infected subjects were more often hospitalized due to sporotrichosis dissemination, compared with uninfected subjects (28 vs 41 %, $p < 0.00001$) [56]. In addition, death attributable to sporotrichosis occurred 45 times more frequently in the HIV-infected group ($p < 0.05$).

The antifungal treatment of patients included oral and intravenous drugs. The data on the outcome of the patients should be interpreted with caution. Although we found that patients treated with azoles alone had a higher survival rate when compared with the ones treated with a combination of azoles and AmB, it seems reasonable to think that patients with more severe clinical pictures evolve with the need for hospitalization and the use of AmB. Thus, the high number of deaths in the group of patients treated with AmB should not be attributed to the drug itself, but to the severity of illness of these patients. For the less severely affected patients, the guideline is to treat orally with azole [57], which explains the successful outcome in this group of patients, with more than 94 % survival. Additionally, we found that AmB deoxycholate continues to be the preferred AmB formulation for therapy of HIV-related sporotrichosis, although the former is associated with a marked increase in renal toxicity compared with the liposomal preparations. Moreover, liposomal preparations allow greater doses to be administered, thereby shortening the treatment time.

HAART is the cornerstone of therapy in HIV-infected subjects during opportunistic infection (OI). However, the impact of HAART implementation during sporotrichosis is unknown and the reports studied did not describe this aspect in detail, which is a limitation of this discussion. Interestingly, we didn't find any difference in outcome, when compared the mortality between co-infected patients treated in the pre-HAART vs post-HAART era.

The optimal HAART combination in the context of sporotrichosis remains to be investigated, as several drug–drug interactions exist between common antifungals used to treat sporotrichosis and antiretroviral drugs (i.e., AmB and tenofovir; itraconazole and ritonavir). Whether short-term use of a simplification HAART regimen (i.e., nucleosides sparing regimens, INsTI monotherapy) might play a role in this scenario remains elusive.

The best time for HAART initiation during sporotrichosis infection is unknown. We believe that HAART should be delayed in high-risk subjects (CNS disease, low $CD4^+$ cell count and high viral load) due to predisposition to

IRIS-related meningeal sporotrichosis. Moreover, data extrapolated from HIV-associated cryptococcal and tuberculous meningitis trials do not support early HAART administration in contrast to other non-CNS opportunistic infection [58, 59].

Our study has several limitations. First, this is a systematic review and all cases studied refer to what is available in the literature; hence, it probably may not adequately mirror the real burden of sporotrichosis in HIV-infected patients. Second, bias is present, as more severe or unusual cases get to be published. Finally, we were unable to evaluate the impact of HAART on sporotrichosis, due to fact that the majority of studies did not describe this feature.

## Conclusions

Information on sporotrichosis in HIV patients is scarce. Based on predominantly Brazilian and North American studies, we conclude that co-infection may present in a severe, disseminated manner contrasting with uninfected subjects, in whom the localized, lymphocutaneous form predominates. The prognosis is worse if CNS is affected, being associated with lower $CD4^+$ counts. In areas endemic in both conditions, HIV testing should be routinely performed in patients presenting with disseminated disease and in cases where the skin is extensively affected. Disseminated sporotrichosis in HIV-positive individuals should be classified as an AIDS-defining illness. Also, the best timing of HAART administration in patients with severe forms, especially CNS disease, is unknown, and the risk of IRIS should be strongly considered. Finally, our study represents the first systematic review available on this topic, and further research will need to address whether the policy of using HAART for all HIV-infected patients would affect the outcome of HIV-associated sporotrichosis.

**Conflict of interests** All authors declare no competing interests relevant to this article.

## References


1. Marimon R, Cano J, Gene J, Sutton DA, Kawasaki M, et al. *Sporothrix brasiliensis, S. globosa,* and *S. Mexicana*, three new *Sporothrix* species of clinical interest. J Clin Microb. 2007;45:3198–206.
2. Lopes-Bezerra LM, Schubach A, Costa RO. *Sporothrix schenckii* and sporotrichosis. An Acad Bras Cienc. 2006;78:293–308.
3. Schubach A, Barros MBL, Wanke B. Epidemic sporotrichosis. Curr Opin Infect Dis. 2008;21:129–33.
4. Barros MB, Schubach ADO, do Valle AC, Galhardo MCG, Conceicao-Silva F, Schubach TM, et al. Cat-transmitted sporotrichosis epidemic in Rio de Janeiro, Brazil: description of a series of cases. Clin Infect Dis. 2004;38:529–35.
5. Mata-Essayag S, Delgado A, Colella MT, Landaeta-Nezer ME, Rosello A, Perez de Salazar C, et al. Epidemiology of sporotrichosis in Venezuela. Int J Dermatol. 2013;52:974–80.
6. Pappas PG, Tellez I, Deep AE, Nolasco D, Holgado W, Bustamante B. Sporotrichosis in Peru: description of an area of hyperendemicity. Clin Infect Dis. 2000;30:65–70.
7. Devi KR, Devi MU, Singh TN, Devi KS, Sharma SS, Singh LR, et al. Emergence of sporotrichosis in Manipur. Indian J Med Microbiol. 2006;24:216–9.
8. Song Y, Li SS, Zhong SX, Liu YY, Yao L, Huo SS. Report of 457 sporotrichosis cases from Jilin province, northeast China, a serious endemic region. J Eur Acad Dermatol Venereol. 2013;27:313–8.
9. Kauffman CA. Sporotrichosis. Clin Infect Dis. 1999;29:231–6.
10. Karp CL, Auwaerter PG. Coinfection with HIV and tropical infectious diseases. I. Protozoal pathogens. Clin Infect Dis. 2007;45:1208–13.
11. Freitas DF, de Siqueira Hoagland B, do Valle AC, Fraga BB, de Barros MB, de Oliveira Schubach A, et al. Sporotrichosis in HIV-infected patients: report of 21 cases of endemic sporotrichosis in Rio de Janeiro, Brazil. Med Mycol. 2012;50:170–8.
12. Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW. Residual immune dysregulation syndrome in treated HIV infection. Adv Immunol. 2013;119:51–83.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
14. Thompson MA, Aberg JA, Hoy JF, Telenti A, Benson C, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA. 2012;308:387–402.
15. Huis in't Veld D, Sun HY, Hung CC, Colebunders R. The immune reconstitution inflammatory syndrome related to HIV co-infections: a review. Eur J Clin Microbiol Infect Dis. 2012;31:919–27.
16. Armstrong WS. The immune reconstitution inflammatory syndrome: a clinical update. Curr Infect dis Rep. 2013;15:39–45.
17. Galhardo MC, Silva MT, Lima MA, Nunes EP, Schettini LE, de Freitas RF, et al. *Sporothrix schenckii* meningitis in AIDS during immune reconstitution syndrome. J Neurol Neurosurg Psychiatry. 2010;81:696–9.
18. Gutierrez-Galhardo MC, do Valle AC, Fraga BL, Schubach AO, Hoagland BR, Monteiro PC, et al. Disseminated sporotrichosis as a manifestation of immune reconstitution inflammatory syndrome. Mycoses. 2010;53:78–80.
19. Lipstein-Kresch E, Isenberg HD, Singer C, Cooke O, Greenwald RA. Disseminated *Sporothrix schenckii* infection with arthritis in a patient with acquired immunodeficiency syndrome. Rheumatol. 1985;12:805–8.
20. Bibler MR, Luber HJ, Glueck HI, Estes SA. Disseminated sporotrichosis in a patient with HIV infection after treatment for acquired factor VIII inhibitor. JAMA. 1986;256:3125–6.
21. Kurosawa A, Pollock SC, Collins MP, Kraff CR, Tso MOM. *Sporothrix schenckii* endophthalmitis in a patient with human immunodeficiency virus infection. Arch Ophthalmol. 1988;106:376–80.
22. Fitzpatrick JE, Eubanks S. Acquired immunodeficiency syndrome presenting as disseminated cutaneous sporotrichosis. Int J Dermatol. 1988;27:406–7.
23. Shaw JC, Levinson W, Montanaro A. Sporotrichosis in the acquired immunodeficiency syndrome. J Am Acad Dermatol. 1989;21:1145–7.
24. Keiser P, Whittle D. Sporotrichosis in human immunodeficiency virus-infected patients: report of a case. Rev Infect Dis. 1991;13:1027–8.
25. Heller HM, Fuhrer J. Disseminated sporotrichosis in patients with AIDS: case report and review of the literature. AIDS. 1991;5:1243–6.

26. Oscherwitz SL, Rinaldi MG. Disseminated sporotrichosis in a patient infected with human immunodeficiency virus. Clin Infect Dis. 1992;15:568–9.
27. Penn CC, Goldstein E, Bartholomew WR. *Sporothrix schenckii* meningitis in a patient with AIDS. Clin Infect Dis. 1992;15:741–3.
28. Donabedian H, O'Donnell E, Olszewski C, MacArthur RD, Budd N. Disseminated cutaneous and meningeal sporotrichosis in an AIDS patient. Diagn Microbiol Infect Dis. 1994;18:111–5.
29. Bolao F, Podzamezer D, Ventin M, Gudiol F. Efficacy of acute phase and maintenace therapy with itraconazole in an AIDS patient with sporotrichosis. Eur J Clin Microbiol Infect Dis. 1994;13:609–12.
30. Dong JA, Chren MM, Elewski BE. Bonsai tree: risk factor for disseminated sporotrichosis. J Am Acad Dermatol. 1995;33:839–40.
31. Rotz LD, Slater LN, Wack MF, Boyd AL, Scott EN, Greenfield RA. Disseminated sporotrichosis with meningitis in a patient with AIDS. Infect Dis Clin Pract. 1996;5:556–8.
32. Morgan M, Reves R. Invasive sinusitis due to *Sporothrix schenckii* in a patient with AIDS. Clin Infect Dis. 1996;23:1319–20.
33. Gori S, Lupetti A, Moscato G, Parenti M, Lofaro A. Pulmonary sporotrichosis with hyphae in a human immunodefiency virus-infected patient. A case report. Acta Cytol. 1997;41:519–21.
34. Al-Tawfiq JA, Wools KK. Disseminated sporotrichosis and *Sporothrix schenckii* fungemia as the initial presentation of human immunodefiency virus infection. Clin Infect Dis. 1998;26:1403–6.
35. Neto RJP, Machado AA, Castro G, Quaglio ASS, Martinez R. Esporotricose cutanea disseminada como manifestação inicial da síndrome da imunodeficiencia adquirida—relato de caso. Rev Soc Bras Med Trop. 1999;32:57–61.
36. Ware AJ, Cockerell CJ, Skiest DJ, Kussman HM. Disseminated sporotrichosis with extensive cutaneous involvement in a patient with AIDS. J Am Acad Dermatol. 1999;40:350–5.
37. Goldani LZ, Aquino VR, Dargel AA. Disseminated cutaneous sporotrichosis in an AIDS patient receiving maintenance therapy with fluconazole for previous cryptococcal meningitis. Clin Infect Dis. 1999;28:1337–8.
38. Edwards C, Reuther WL 3rd, Greer DL. Disseminated osteoarticular sporotrichosis: treatment in a patient with acquired immunodeficiency syndrome. South Med J. 2000;93:803–6.
39. Bonifaz A, Peniche A, Mercadillo P, Saúl A. Successful treatment of AIDS-related disseminated cutaneous sporotrichosis with itraconazole. AIDS Patient Care STDs. 2001;15:603–6.
40. Aarestrup FM, Guerra RO, Vieira BJ, Cunha RMC. Oral manifestation of sporotrichosis in AIDS patients. Oral Dis. 2001;7:134–6.
41. Rocha MM, Dassin T, Lira R, Lima EL, Severo LC, Londero AT. Sporotrichosis in patients with AIDS: report of a case and review. Ver Iberoam Micol. 2001;18:133–6.
42. Carvalho MT, de Castro AP, Baby C, Werner B, Filus Neto J, Queiroz-Telles F. Disseminated cutaneous sporotrichosis in a patient with AIDS: report of a case. Rev Soc Bras Med Trop. 2002;35:1–5.
43. Losman JA, Cavanaugh K. Cases from the Osler Medical Service at Johns Hopkins University. Diagnosis: *P. carinii* pneumonia and primary pulmonary sporotrichosis. Am J Med. 2004;117:353–6.
44. Hardman S, Stephenson I, Jenkins DR, Wiselka MJ, Johnson EM. Disseminated *Sporothrix schenckii* in a patient with AIDS. J Infect. 2005;51:e73–7.
45. Silva-Vergara ML, Maneira FR, De Oliveira RM, Santos CT, Etchebehere RM, Adad SJ. Multifocal sporotrichosis with meningeal involvement in a patient with AIDS. Med Mycol. 2005;43:187–90.
46. Callens SF, Kitetelef F, Lukun P, Van Rie A, Behets F, et al. Pulmonary *Sporothrix schenckii* infection in a HIV positive child. J Trop Pediatr. 2006;52:144–6.
47. Fontes PC, Kitakawa D, Carvalho YR, Brandao AA, Cabral LA, Almeida JD. Sporotrichosis in an HIV-positive man with oral lesions: case report. Acta Cytol. 2007;51:648–50.
48. Vilela R, Souza GF, Fernandes G, Mendoza L. Cuatenous and meningeal sporotrichosis in a HIV patient. Rev Iberoam Micol. 2007;24:161–3.
49. Bustamante B, Lama RJ, Mosquera C, Soto L. Sporotrichosis in human immunodeficiency virus infected peruvian patients. Infect Dis Clin Pract. 2009;17:78–83.
50. Mello CX, Schubach ADO, Madeira MDF. Can yeast-like form of *Sporothrix schenckii* confuse the diract parasitological diagnosis of american cutaneous leishmaniasis? Rev Soc Bras Med Trop. 2011;44:127.
51. Silva-Vergara ML, Camargo ZP, Silva PF, Abdalla MR, Sgarbieri RN, Rodrigues AM, et al. Case report: disseminated *Sporothrix brasiliensis* infection with endocardial and ocular involvement in an HIV-infected patient. Am J Trop Med Hyg. 2012;86:477–80.
52. Chang S, Hersh AM, Naughton G, Mullins K, Fung MA, Sharon VR. Disseminated cutaneous sporotrichosis. Dermatol Online J. 2013;19:8.
53. Moreira J, Quintella LP, Carvalho M, Lamas CC, Lyra MR. Disseminated sporotrichosis as the initial presentation of AIDS. Clin Res HIV/AIDS. Forthcoming 2015.
54. Ministério da Saúde do Brasil, Secretária de Vigilância em Saúde 2013. Boletim Epidemiológico Aids e DST [in Portuguese]. Available from: http://www.aids.gov.br/publicaco/2013/boletim-epidemiologico-aids-e-dst-2013. Accessed 12 June 2014.
55. Lansky A, Brooks JT, di Nenno E, Heffelfinger J, Hall HI, Mermin J. Epidemiology of HIV in the United States. J Acquir Immune Defic Syndr. 2010;55:S64–8.
56. Freitas DF, Valle AC, da Silva MB, Campos DP, Lyra MR, de Souza RV, et al. Sporotrichosis: an emerging neglected opportunistic infection in HIV-infected patients in Rio de Janeiro, Brazil. PLoS Negl Trop Dis. 2014;8:e3110.
57. Kauffman CA, Bustamante B, Chapman SW, Pappas PG. Clinical practice guidelines for the management of sporotrichosis: 2007 update by the Infectious Diseases Society of America. Clin Inf Dis. 2007;45:1255–65.
58. Boulware DR, Meya DB, Muzoora C, Rolfes MA, Huppler Hullsiek K, Musubire A, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N Engl J Med. 2014;370:2487–98.
59. Torok ME, Yen NT, Chau TT, Mai NT, Phu NH, Mai PP, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. Clin Infect Dis. 2011;52:1374–83.