**GAFFI Fact Sheet**

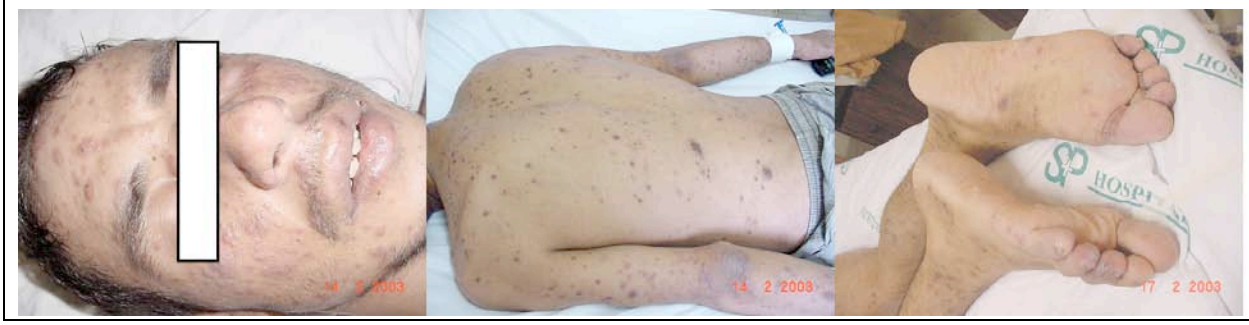
## Disseminated histoplasmosis

Disseminated histoplasmosis is a sub-acute infection especially in - infants and AIDS patients with a 100% mortality if untreated. It is acquired from inhalation of dust contaminated with *H. capsulatum* in highly localized areas. The clinical features are non-specific and diverse. The organism grows very slowly, so diagnosis is often delayed, or requires biopsy. A highly sensitive antigen test (ELISA format) is available enabling same day diagnosis in a few laboratories. There is a 90% survival if diagnosed and treated with liposomal amphotericin B or itraconazole.

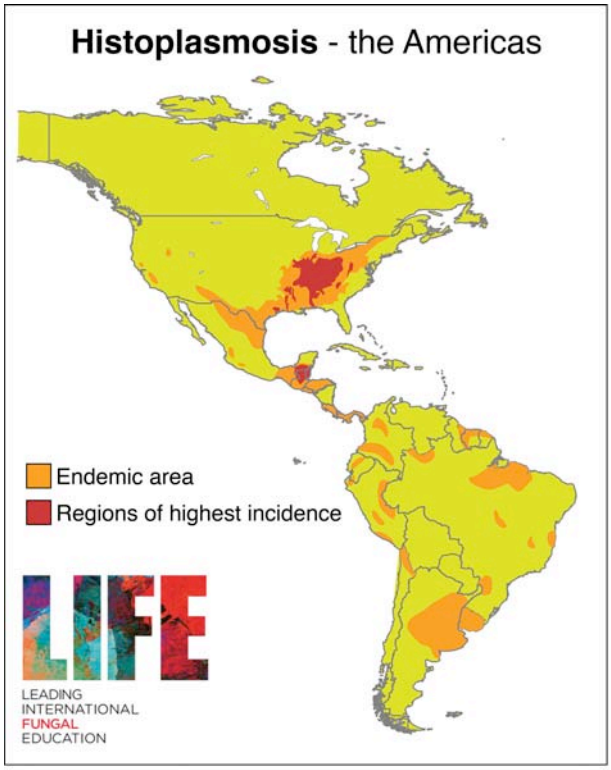
Disseminated histoplasmosis in AIDS patients

In endemic areas, attack rates of disseminated histoplasmosis in AIDS patients usually range from 5% to 20% and patients with CD4 counts of <150 cells/μL are at highest risk. A recent cohort study conducted in French Guiana found an incidence rate of 15.4/1000 HIV infected persons. More than 90% of HIV-infected persons with histoplasmosis develop the disseminated form of the disease and it is often an AIDS-defining illness. The global burden of histoplasmosis is not known.

Disseminated histoplasmosis in an AIDS patient: multiple skin lesions (papules and macules), some of them resembling Kaposi sarcoma. Skin lesions are seen in more than 50% of AIDS patients with histoplasmosis in Latin America, but are uncommon in US patients.



Over the course of days to weeks, patients develop fevers, chills, night sweats, fatigue, weight loss and eventually respiratory and gastrointestinal symptoms. Clinical suspicion is usually facilitated by the coexistence of mucocutaneous lesions with hepatosplenomegaly and lymphadenopathy. Of note, skin lesions are frequently found in cases reported in Latin America (30-80%), but they are uncommon in US cases (<10%). Lung involvement is common, typically manifest as bilateral reticulonodular infiltrates. A sepsis syndrome occurs in 10-20% of patients who develop hypotension, renal and hepatic failure, respiratory distress syndrome and coagulopathy. Laboratory abnormalities frequently include anemia, leukopenia, thrombocytopenia, hepatic enzyme elevation, increased ferritin, and/or adrenal insufficiency. Mortality rates during hospital admission range from 6 to 50%, and higher rates have been reported in Brazilian and Guatemalan patients than in US patients.



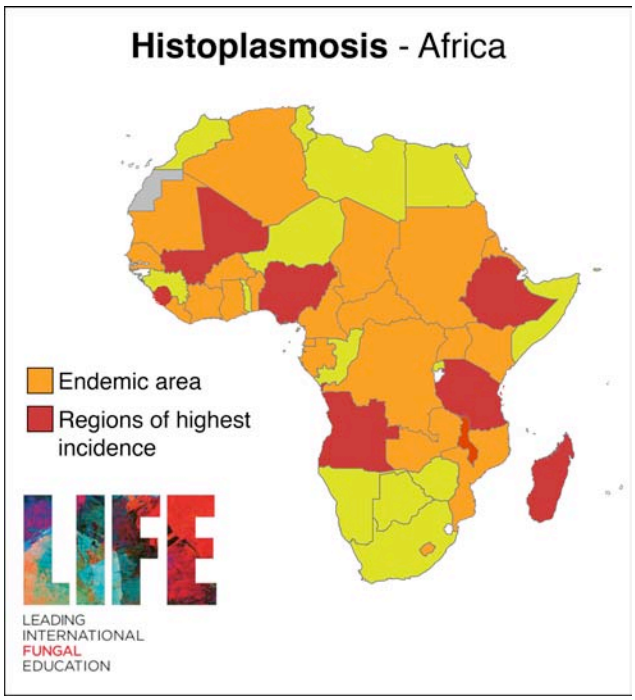

If clinicians seeing AIDS patients with prolonged fever in endemic areas don't consider the diagnosis, clinical hesitation and delays in starting appropriate antifungal therapy greatly increase the chance of death. Patients with comorbidities associated with immunosuppression such as cancer, organ transplant recipients, and those exposed to corticosteroids and TNF-alpha antagonists may also develop disseminated histoplasmosis.

Diagnosis

The best approach in the diagnosis of disseminated histoplasmosis is the detection of histoplasma antigen in urine, which is positive in over 90% of cases. Unfortunately this test is not readily available and one test is approved by the FDA. Systematic testing on all ill HIV positive patients is the best approach in areas of high prevalence. A Wright's stain on a blood film or bone marrow aspiration may demonstrate intracellular yeast-like organisms. Skin, mucosal or lymph node biopsies will also reveal characteristic intracellular yeasts visible with fungal stains. Positive cultures are usual in disseminated histoplasmosis (>70%), especially for blood and bone marrow cultures, but are slow (10-20 days and occasionally longer) and requires adequate laboratory infrastructure for handling class 3 pathogens. The sensitivity of diagnostic testing is greatest in patients with clinical manifestations, and impaired immune status, reflecting a higher tissue fungal burden.

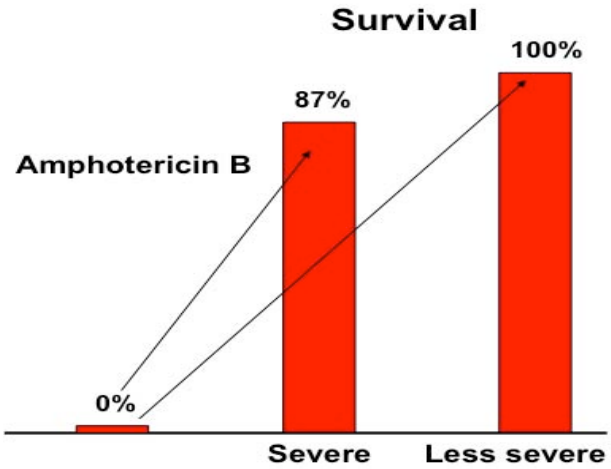
Treatment

Induction therapy with intravenous liposomal amphotericin B (Ambisome) in daily doses of 3mg/Kg, for 2 weeks, is the treatment of choice for patients with moderate to severe disseminated histoplasmosis. Patients who respond to induction therapy with liposomal amphotericin B may be changed to consolidation therapy with oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily), which should be continued for a total of 12 months, until recovery of CD4 cell counts on antiretroviral therapy.



Therapeutic drug monitoring is desirable for itraconazole but frequently difficult to perform in endemic areas such as in Latin America. Early antiretroviral therapy in new AIDS cases is helpful and recommended. Furthermore, in AIDS patients, secondary prophylaxis with itraconazole should be used to avoid relapses. For clinically stable patients with mild-to-moderate disease (without CNS involvement), therapy may be initiated with itraconazole, 200 mg 3 times daily for 3 days and then twice daily for at least 12 months, as long as the patient is not also treated with rifampicin for possible tuberculosis, with which histoplasmosis may be confused. The IDSA guidelines provide more detail.

Impact of therapy on **disseminated histoplasmosis** in AIDS




*Histoplasma capsulatum*

Two varieties of *H. capsulatum* cause human disease: *H. capsulatum* var. *capsulatum* , which has a worldwide geographic distribution and areas of high endemicity located in North, Central and South Americas , and *H. capsulatum* var. *duboisii*, which is restricted to Africa. Here we focus on diseases caused by *H. capsulatum var capsulatum,* soon to be called *H. capsulatum.*

*Histoplasma capsulatum* usually grows in soils enriched with organic nitrogen sources, especially bird or bat excrement. Consequently, exposure of human hosts to the fungi usually occurs during cleaning accumulated animal excrements, attics or barns as well as caving or participating in construction projects in contaminated areas, especially during remodeling or demolition of old buildings. The large majority of normal hosts who are exposed to *H. capsulatum* (>95%) remain asymptomatic, or develop only mild symptoms, that are never recognized as being due to histoplasmosis. Skin test surveys in populations reveal the extent of 'natural' exposure without disease, and serves to identify hyperendemic regions.

A small number of hosts infected in endemic areas will develop one of the clinical forms of histoplasmosis. There is a large spectrum of clinical presentations, which are strongly influenced by the extent of exposure and possibly virulence of different *H. capsulatum* strains, age and immunological status of the host, as well as the presence of chronic

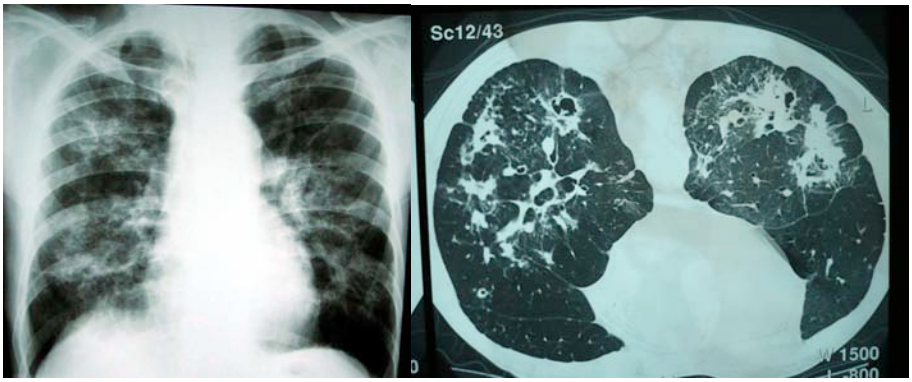
pulmonary disease prior to fungal infection. Outbreaks of histoplasmosis involving a large number of patients have been reported worldwide.

Other clinical forms of histoplasmosis

People newly exposed to *H. capsulatum* may became symptomatic and develop **Acute Pulmonary Histoplasmosis**, presenting with fever, chills, cough, dyspnea and pulmonary nodular infiltrates or consolidation on chest imaging. In the case of heavy exposure, diffuse pulmonary disease and respiratory failure may occur. Antifungal therapy should be used only in patients who are highly symptomatic or have moderate to severe clinical presentations. Methylprednisolone (0.5–1.0 mg/kg daily intravenously) during the first 1–2 weeks of antifungal therapy may be required for patients who develop hypoxemia and respiratory failure.

Elderly normal hosts with underlying structural lung disease such as emphysema may develop **Chronic Pulmonary Histoplasmosis** exhibiting signs and symptoms resembling tuberculosis or chronic pulmonary aspergillosis with cavitary lesions and fibrosis. Unfortunately, most cases of chronic histoplasmosis are misdiagnosed as tuberculosis. Serology for detecting specific anti-*H capsulatum* antibodies may be helpful in the diagnosis of acute and chronic pulmonary histoplasmosis (sensitivity >80%). Patients with chronic pulmonary histoplasmosis should receive at least 12 months of oral itraconazole (200 mg 3 times daily for 3 days and then once or twice daily). Due to the high rates of relapses, some authors suggest at least 18–24 months of antifungal therapy.

Chest radiograph and CT scan of a middle-age smoking male with chronic pulmonary histoplasmosis showing bilateral cavitary infiltrates.




After disseminated histoplasmosis, the most severe clinical manifestation of this endemic mycosis is **Progressive (Subacute) Disseminated Histoplasmosis** that occurs in patients at extremes of ages, who have subtle immunosuppression. Adrenal or intestinal masses or lymphadenopathy are the commonest manifestations of subacute disseminated histoplasmosis, but CNS involvement and endocarditis may occur. Itraconazole or liposomal amphotericin B are the treatments of choice.

Sequelae are frequently documented in patients with CNS and adrenal involvement, as well as in patients with chronic pulmonary histoplasmosis.

Research needs for disseminated histoplasmosis:

- Areas of hyperendemicity are not well defined, especially in Africa. Skin test surveys are required to develop a much more detailed geographical understanding of the distribution of disease. No maps have been drawn for Asia or Australasia to define the areas infected with *H. capsulatum*.
- The frequency and latency of pulmonary histoplasmosis in HIV infected patients is not known. The proportion of patients with community acquired pneumonia caused by *H. capsulatum* in endemic areas needs to be documented.
- The histoplasma antigen test needs be better studied in multicenter studies to ascertain its comparative performance.
- A simpler lateral flow like device for histoplasma antigen on urine needs to be developed and tested in multiple locations.
- Shorter, and possibly higher dose, liposomal amphotericin B regimens need to be trialled to shorten the current standard of 2 weeks, if possible.

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April 2013