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REVIEW

HIV-Associated Histoplasmosis: Current Perspectives

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Abstract: Histoplasmosis is an endemic mycosis caused by *Histoplasma capsulatum*. Infection develops by inhalation of microconidia from environmental sites inhabited by birds and bats. Disseminated disease is the usual presentation due to impaired cellular immunity. Common clinical manifestations include fever, fatigue, malaise, anorexia, weight loss, and respiratory symptoms. *Histoplasma* antigen detection is the most sensitive method for diagnosis. The sensitivity of the MVista® Quantitative *Histoplasma* antigen enzyme immunoassay is 95–100% in urine, over 90% in serum and bronchoalveolar lavage (BAL) antigen and 78% in cerebral spinal fluid (CSF). A proven diagnosis can be established by culture or pathology with sensitivities between 70% and 80%. The sensitivity of antibody detection by immunodiffusion or complement fixation was between 60% and 70%. Diagnosis using molecular methods has not been adequately validated for implementation and FDA cleared assays are unavailable. Liposomal amphotericin B should be used for 1–2 weeks followed by itraconazole for at least one year until CD4 counts are above 150 cells/mm3, HIV viral load is below 400 copies/mL and *Histoplasma* urine antigen is negative. Serum itraconazole level should be monitored to avoid drug toxicity. Antigen should be measured periodically to establish that treatment is effective and to assist in identifying relapse. The incidence of immune reconstitution inflammatory syndrome is low but it must be considered in patients who are thought to be failing antifungal treatment as it does not respond to changing antifungal agents but rather to initiation of corticosteroid therapy. In this review, we discuss pathogenesis, clinical manifestations, diagnosis and treatment based on personal experience and relevant publications.

Keywords: histoplasmosis, HIV

Introduction

Histoplasmosis is an endemic mycosis, caused by *Histoplasma capsulatum*. It is a dimorphic fungus that displays different morphologies depending on environmental conditions: a mold in the soil and a budding yeast in the mammalian host. The mold (saprophytic form) grows best in soils with a high nitrogen content associated with the presence of bird and bat guano. Demolition, construction, farming, raising chickens, archaeological digging and spelunking have been associated with an increased risk of infection.[1] Risk factors for disseminated histoplasmosis include AIDS,[2] primary immunodeficiencies,[3] other immunosuppressive disorders,[4,5] immunosuppressive drugs[6] and extreme ages.[4,7]

Histoplasmosis can be found worldwide in AIDS patients from the Americas and parts of Asia,[8] Southeast Asia[9] and Africa.[10] Histoplasmosis also occurs in non-endemic areas in individuals who have previously lived in or traveled to endemic areas.[11]

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In the United States, the most commonly implicated species in AIDS patients is *Histoplasma capsulatum var capsulatum*, an organism with a geographic region surrounding the Ohio and Mississippi River valleys.[12] However, another species, *Histoplasma capsulatum var. duboisii*, is rarely described in HIV infected patients in Africa (African histoplasmosis).[13,14]

It was estimated that annual incidence of disseminated histoplasmosis was ~100,000 cases globally in 2017.[15] The estimated incidence of histoplasmosis in 2012 was 1.48 cases per 100 people living with HIV in Latin America. It ranged from 0·003 cases per 100 people living with HIV in Chile to 4·16 cases per 100 people living with HIV in Guatemala.[16] In another report, histoplasmosis was reported the most common opportunistic infection among AIDS in Latin America with an incidence of 0.15 per 100,000 person-years.[17] The incidence data is limited in Africa despite the burden of HIV disease.[18]

The first reported case of histoplasmosis in AIDS occurred in a homosexual patient who presented in October 1980 with peripheral lymphadenopathy.[19] Lymphocyte studies showed markedly reduced T-lymphocyte function. Disseminated histoplasmosis was diagnosed in August 1981. He died in June 1982 and autopsy revealed invasive pulmonary aspergillosis, disseminated *Mycobacterium avium-intracellulare* (MAI) infection and disseminated histoplasmosis.

The earliest case occurred during an outbreak of histoplasmosis in Indianapolis in 1980.[20] Diagnosis of disseminated histoplasmosis was made by positive urinary *Histoplasma* antigen. *H. capsulatum* and MAI were isolated from multiple organs at autopsy. The patient was presumed to have acquired histoplasmosis in Indianapolis during the second Indianapolis outbreak.[20] The concomitant diagnosis of AIDS was first considered when cases began to be recognized in Indianapolis in 1983. AIDS was the predisposing condition in about one-third of cases of culture-proven histoplasmosis during a third Indianapolis outbreak in 1988.[20]

A study in the United States identified working with bird or bat droppings as a risk factor in patients with AIDS.[21] Age, sex and CD4 count below 100 cells/mm^3 were not associated with an increased risk. Recipients of antiretroviral therapy or fluconazole were protective.[21] Another study evaluated risk factors for severe or fatal disease. Several baseline laboratory abnormalities were associated with disease severity.[22] But multivariate analysis showed that creatinine greater than 2.1 mg/dL and albumin less than 3.5 g/dL were associated with increased risk and zidovudine therapy with decreased risk. Black race was associated with risk by univariate but not by multivariate analysis. *Histoplasma* antigen above 4 units was not associated with increased risk.

Pathogenesis

Histoplasmosis is acquired by inhalation of microconidia aerosolized from environmental sites containing *Histoplasma* microconidia and mycelial fragments[23] After conidia reach alveolar spaces, they bind to the CD11-CD18 family of integrins and are engulfed by neutrophils and macrophage.[24] The mycelial fragments are transformed into the pathogenic yeast form in alveolar macrophages.[25] While neutrophils emigrate early into infected foci of lungs which inhibit the growth of yeast cells,[26] macrophages and dendritic cells are the principal effector cells in host resistance to *Histoplasma*.[27] *H. capsulatum* replicates within macrophages until the T cells are activated. The release of cytokines such as interferon-γ (IFN-γ) from T cells activate mononuclear phagocytes which, in turn, produce tumor necrosis factor-α (TNF-α) and other cytokines that control the primary infection.[28]

Infected macrophages induce granuloma formation. However, macrophages from HIV-infected individuals do not mount an effective immune response.[24] A direct correlation exists between the CD4+ T-cell count and the capacity of macrophages to bind yeast cells. CD4$^+$ cells are very important in controlling primary infection.[29] The more common histopathologic appearance of tissue in HIV/AIDS patients is a massive influx of macrophages with scattered lymphocytes. Well-circumscribed granulomas are infrequently present, and the lack of an organized inflammatory response is indicative of an impaired cellular immunity.[30]

Reactivation of latent organisms is considered by some to be the common mode of infection in immunocompromised patients.[31] One report presumed reactivation of latent infection was the mode of acquisition in 4 patients from New York City who immigrated from Latin American countries.[32] However, this presumption of reactivation is challenged by other potential sources of exposure. The date of immigration and whether the patients had returned home since immigration was not described. Also, histoplasmosis is endemic in parts of New York. Of Navy recruits from New York, 2.6% were skin test positive and skin test positivity ranged between 5% and 15% in 3 of 12 New York economic areas.[33] Also, histoplasmosis has

been reported from states outside its recognized endemic area: central New York, Staten Island, the South Bronx, Idaho, Alaska, California, Colorado, New Mexico, Arizona, Montana and Florida.[34]

Another study from Kansas City, where skin test reactivity among Navy groups was 43%[33] stated "the pathophysiology of histoplasmosis in patients with AIDS involves reactivation of latent infection in some cases."[1] However, the annual incidence among patients with CD4 counts <150 cells/μL that were felt to have been exposed to *Histoplasma* previously (reactive skin test, pulmonary calcifications or positive serology) was no different than in those with no prior exposure, 15.9% and 13.5%, respectively. They concluded that "the incidence of histoplasmosis was too low to determine whether a reactivation occurred more frequently than dissemination of exogenously acquired infection".

The evidence does not support reactivation. For example, none of 449 solid organ transplant patients from Indianapolis developed histoplasmosis, including 0 of 48 with positive serologic tests for histoplasmosis in pretransplant screening.[35] Histoplasmin skin test reactivity was 55% among Navy recruits from Indiana indicating a high potential risk for reactivation if latent infection occurred. Cases presumed to be caused by a reactivation may represent reinfection or unrecognized infection that was present at the time of diagnosis of AIDS[20] or onset of immunosuppression.[36]

A multicenter study of histoplasmosis in transplant patients reported a disproportionate number of cases (34%) during the first year following transplantation.[36] These may represent reinfection or progression of unrecognized histoplasmosis that was present at the time of transplantation.[36] Ongoing exposure occurs in residents of endemic areas but does not cause disease in healthy immune subjects. Progressive disease is expected in patients with chronic diseases that impair cellular immunity or who are immunocompromised.

An autopsy study in Cincinnati evaluated lungs containing granuloma from patients not identified to have histoplasmosis.[37] Fungal stain of granulomas demonstrated *Histoplasma* organisms in 66.7% of patients (70 of 105). Fungal cultures were performed in 57.1% (40 of 70) of specimens in which yeast were seen and did not grow *Histoplasma* or induce histoplasmosis when injected into mice. Skin test reactivity in Navy recruits was 53% in Cincinnati.[33] A study at a Veteran's Hospital in Memphis, Tennessee examined 100 consecutive autopsies containing calcified foci in the lungs and/or hilar lymph nodes.[38] Organisms resembling *Histoplasma* were demonstrated in 63.9% (71 of 111) but inflammation was absent. *Histoplasma* was isolated from 1 of 100 specimens. Authors concluded that "It is highly unlikely that a calcified focus of the sort observed could ever breakdown and produce a recurrent local or disseminated disease due to *Histoplasma capsulatum*".

Clinical Features

Most AIDS patients with CD4 counts <150 cells/μL present with disseminated histoplasmosis (PDH) when infected. Isolated pulmonary involvement without dissemination occurs only in less than 5% of cases.[20,39] There are only a few studies describing patients with HIV and histoplasmosis who have CD4 counts greater than 200 cells/μL.[40,41]

Common clinical manifestations include fever, fatigue, malaise, anorexia, weight loss, and respiratory symptoms. Physical examination frequently reveals lymphadenopathy, hepatomegaly, and/or splenomegaly, with skin and oral lesions less common.[20] Skin lesions are described more frequently in cases that originate in Latin America[42] which is likely due to a delay in diagnosis.

Laboratory tests usually show anemia, leukopenia, thrombocytopenia, and elevated bilirubin and hepatic enzymes.[4] Elevated lactate dehydrogenase[43] and ferritin[44] are nonspecific but suggestive of PDH. There were reported case series of hypercalcemia in PDH.[45] Creatinine value >2.1 mg/dL and an albumin value <3.5 g/dL were associated with an increased risk of severe disease.[22] Shock with hepatic, renal, and respiratory failure (including ARDS) and coagulopathy may complicate severe cases and may be mistaken for bacterial sepsis.[20,46] Most common sites of involvement are liver, spleen, gastrointestinal tract, and bone marrow. Dissemination can also be seen in skin, adrenal glands, central nervous system, and endocardium.[47] Meningitis, cerebritis, and focal brain or spinal cord lesions occur in 5% to 10% of cases, as either manifestations of widely disseminated infection or isolated findings.[48] Pulmonary imaging is characterized by diffuse reticulonodular, interstitial, or miliary infiltrates but may be unrevealing in 10% to 50% of the cases.[49]

A high suspicion index is required from clinicians because of the nonspecific nature of the clinical presentation and radiological features of histoplasmosis. Given the nonspecific subjective and objective clinical findings

associated with histoplasmosis, it may be difficult to distinguish the clinical presentation from that of tuberculosis in high endemic areas. There are report cases of disseminated histoplasmosis mimicking extrapulmonary or miliary tuberculosis.[50]

There are some reports of co-infection with other opportunistic infections such as tuberculosis,[51] *Pneumocystis jirovecii*[52] and cryptococcal infection.[53] In one cohort from Columbia, co-infection with other opportunistic infection was found in 51% of the patients with disseminated histoplasmosis. Tuberculosis was the main co-infection (70%), followed by pneumocystosis (13%), cryptococcosis (13%) *Salmonella* infection (9%), and *Cytomegalovirus* (CMV) infection (9%).[54]

The mortality rates of HIV-associated disseminated histoplasmosis range from 17.5% within one month of treatment,[55] 39% within 3 months of diagnosis[40] to 45% at 30 days after antifungal therapy initiation.[56]

Diagnosis

Culture and Pathology

The gold standard for the diagnosis of histoplasmosis is the isolation of *H. capsulatum*. A general performance of cultures in the diagnosis of histoplasmosis showed a sensitivity of 89.5%, histopathology, 78.3% in one study.[58] Fungal blood cultures were positive in 73.9% (54 of 73) of patients enrolled in the prospective study comparing treatment with liposomal amphotericin B and amphotericin B deoxycholate[59] The sensitivity of the blood cultures ranges between 72% and 81%[60] Bone marrow cultures were positive in 36.6% (11 of 30).

Antigen Detection

The first *Histoplasma* antigen detection test was a radioimmunoassay (RIA) developed at Indiana University School of Medicine in 1985.[61] The first study evaluating 69 cases in patients with AIDS during outbreaks in Indianapolis reported a sensitivity of 97.1% (67 of 69) in urine and 83.0% (39 of 46) in serum.[20] The first *Histoplasma* antigen enzyme immunoassay (EIA) was developed in 1976.[62] Pretreatment of serum to eliminate interference caused by immune complex formation and improve sensitivity was introduced in 2008 at MiraVista Diagnostics (MVista® second-generation *Histoplasma* antigen EIA).[63] The third-generation MVista® Quantitative *Histoplasma* antigen EIA laboratory develop test (LDT) was introduced in 2007.[64] As an LDT rather than an FDA cleared test, the MVista® Quantitative *Histoplasma* antigen EIA can only be performed at MiraVista Diagnostics.

A multicenter study in which pretreatment of serum was incorporated into the assay reported sensitivity in urine of 100% (84 of 84) and serum of 94.2% (16 of 17).[58] Results for all patients in whom urine and serum were tested for antigen between 2014 and 2018 and at least one urine or serum specimen type was positively analyzed. The serum was positive, but urine was negative in 17.3% (13 of 75) (unpublished, MiraVista Diagnostics). Both urine and serum should be tested for the highest sensitivity.

Antigen also may be detected in bronchoalveolar lavage fluid (BAL) and cerebrospinal fluid (CSF) using the MVista® EIA. A study of 31 patients, 21 of which were immunocompromised including 11 with AIDS, reported antigen in BAL in 93.5% (29 of 31).[65] Antigen was detected in the CSF in 78% (39 of 50) of patients with meningitis.[66]

Cross reactions are universal in blastomycosis and occur in over 80% of patients with *Talaromyces marneffei* and *Paracoccidioides brasiliensis* infection.[64] These organisms have the same class of cell wall galactomannan.[67] Cross reactions occur in about 10% of patients with coccidioidomycosis,[68,69] in less than 5% with aspergillosis[64] and not with cryptococcosis.[70]

An FDA cleared polyclonal-based *Histoplasma* antigen EIA in vitro device (IVD) produced by ImmunoMycologics (IMMY; Norman, Oklahoma) was introduced in 2007. IMMY replaced the IVD with a non-FDA approved monoclonal antibody-based *Histoplasma* antigen assay using analyte-specific reagents (ASR) in 2013. The first comparison of the IMMY ASR and the MVista® LDT reported positive agreement in 64.5% (40 of 62) of specimens and negative agreement in 99.8% (937 of 939).[71] A second comparison study reported positive agreement of 90.4% (19 of 21) and negative agreement of 90.5% (79 of 82).[72] The third study that evaluated proven and probable cases and controls reported the sensitivity of the IMMY ASR to be 72% (36 of 50) and specificity 98% (49 of 50).[72]

The role of antigen detection has been evaluated in Latin America. Dr Gutierrez and colleagues evaluated MVista® Quantitative *Histoplasma* antigen EIA[64] in a prospective study of culture-proven cases in patients with AIDS.[73] Patients were enrolled at one institution in Panama and specimens were shipped to MiraVista Diagnostics for antigen detection. The sensitivity in urine

was 95.2% (20 of 21) and in serum was 94.7% (18 of 19). Specificity was not evaluated.

Subsequent studies have been conducted in Latin America using assays other than the MVista® *Histoplasma* antigen LDT. Results of 18 studies were evaluated in a meta-analysis that determined that antigen detection provided the most accurate method for diagnosis of progressive-disseminated histoplasmosis in advanced HIV, with a sensitivity of 95% and a specificity of 97%.[60] However, the study combined results using multiple different assays, including those shown to be less sensitive.

The two most thorough studies observed divergent findings. The first was a retrospective multicenter study that evaluated specimens obtained between 2000 and 2014 that had been stored at −80°C.[74] That study reported sensitivity of 98% evaluating 63 culture-proven cases and specificity of 97% evaluating 526 controls using the IMMY ASR.[74] The second study was prospective and reported sensitivity of 56.4% (44 of 78) in culture-proven cases using the IMMY ASR.[75] Although there were 447 controls in that study, they did not report specificity. The authors suggested that the sensitivity may have been reduced because of treatment with antifungal medications for at least 7 days before testing in 39.7% (35 of the 74) of cases. Studies using the MVista® LDT reported persistent antigenuria for >12 weeks during successful treatment with amphotericin B or itraconazole[76] showing that prior antifungal therapy was an unlikely cause for the lower sensitivity of the IMMY ASR. MVista® LDT has not been evaluated in Latin America because it is only offered at MiraVista Diagnostics, a requirement of LDT assays.

Histoplasma antigen serum lateral flow assay developed at MiraVista Diagnostics was evaluated showing a sensitivity of 95.8% (23 of 24) and a specificity of 90.2% (46 of 51).[77] Serum specimens were stored from culture-proven cases enrolled in a prospective study from May 2008 to August 2011 in Medellin, Columbia. The LFA was performed at the Centers for Disease Control in 2019. Many of the controls had other endemic mycoses known to be cross-reactive in the MVista® LDT EIA. However, serum is not ideal because special processing is needed to dissociate antigen from antibody and denature the antibody to reduce its inhibitory effect on detection of antigen in serum.[57] The equipment required for this pretreatment step is only available in diagnostic laboratories. Also, turnaround time is longer testing serum rather than urine.

The development of the serum LFA was abandoned and a new MVista® *Histoplasma* antigen LFA was developed for urine that does not require pretreatment for any equipment. A study in Argentina of culture-proven cases observed a sensitivity of 94% (16 of 17) and specificity of 100% (31 of 31) (Andreani Mariana, Laboratory of Microbiology, Mycology, Hospital General de Agudos, 2019, unpublished).

Serology

Detection of antibodies also is useful for diagnosis of histoplasmosis. Methods include complement fixation (CF),[78] immunodiffusion (ID),[78] and MVista® IgG, IgM EIA[66,79] and Western blot.[80] Among cases in patients with AIDS identified during the Indianapolis outbreaks, ID was positive in 58.3% (21 of 36) and CF in 70.6% (24 of 34).[48] More recent studies reported that ID or CF was positive in 69.2% of cases (9 of 13) in AIDS patients.[57] Antibody production was impaired in immunocompromised patients in that study. In a subsequent study in patients with AIDS, the sensitivity of ID or CF was 88.5% (23 of 26).[58] A Colombian study reported antibody to be positive in 58% of patients but included methods other than ID or CF that are not used clinically. A Brazilian study reported 19.6% (8 of 41) of patients had detected antibodies against *H. capsulatum*.[75] Another Brazilian study reported testing Western blot using deglycosylated histoplasmin antigen with sensitivity of 90%, specificity of 90.9% and accuracy of 90.3%.[80]

Molecular

A study evaluated PCR in urine from patients with high-level antigenuria in the second-generation *Histoplasma* antigen LDT observed low sensitivity.[81] Urine was cultured for *Histoplasma* at MiraVista Diagnostics and stored at −80° C for PCR testing. Five of the 51 specimens grew *Histoplasma* and the PCR was positive in four yielding a sensitivity of 7.8% (4 of 51). The antigen concentration was above the upper limit of the assay in those five specimens.

Among hundreds of reports using PCR, except for the urine study,[81] none established their role for diagnosis. Inadequate numbers of patients were studied, insufficient numbers of individual specimen types (BAL, sputum, body fluids, tissue) were tested, and validation was inadequate to establish precision and reproducibility. Also, FDA cleared devices are unavailable. The only established role for molecular methods is

identification of organisms isolated from culture.[82] A meta-analysis evaluating results from five studies in Latin America reported sensitivity of 95.4% and specificity of 98.7% but concluded that the available studies were inadequate to recommend PCR.[60]

In 2017, the WHO recognized histoplasmosis as a significant opportunistic infection and a major cause of death in patients with advanced HIV disease, especially in the hyperendemic areas. In 2019, the WHO included *Histoplasma* antigen tests on the second edition of the EDL (Lists of Essential In Vitro Diagnostics).

Representatives from most of Latin America met in March 2019 and made an announcement, The Manaus Declaration on Histoplasmosis in the Americas and Caribbean, "By 2025, every country should have access to rapid testing for histoplasmosis (antigen or PCR/molecular)".[83]

Diagnosis of Meningitis

A retrospective multicenter study reported that culture or pathology of CSF, brain, meninges or spinal cord were positive in 37.7% (26 of 69) of patients. 71.4% of the patients were immunocompromised.[84] Antigen was detected in the CSF in 66.0% (35 of 53), antibody by ID or CF in 59.4% (19 of 32) and antigen or antibody in 75% (43 of 57). Detection of antigen in the serum or urine was the basis for diagnosis in 20.1% (16 of 77) in patients with negative findings in the CSF or other CNS tissue. CSF volumes of 10 to 20 mL must be cultured to achieve the highest sensitivity.[84] Patients with meningitis may have negative culture, pathology, antigen and antibody in CSF findings but positive results from other sites.[84] Repeat antigen and antibody testing and culture or central nervous system (CNS) tissue culture and histopathology may be needed to establish a diagnosis in some patients.

Another study assessed the role of the MVista® IgG and IgM antibody EIA[66] and of 1,3-beta-D-glucan detection[85] in CSF for diagnosis of meningitis. Culture of CSF was positive in 19.1% (9 of 47). Antigen was detected in 78% (39 of 50), IgG or IgM antibody in 82.2% (37 of 45) and antigen or antibody in 98% (48 of 49).[66] The sensitivity for detection of antibody by ID was 44.2% (19 of 43) and by CF was 50% (5 of 10). Specificity of antigen detection in CSF was 96.6% (140 of 145) and IgG or IgM antibody detection was 92.8% (142 of 153). The lower sensitivity (54.8% [23 of 42]) and specificity (87.6% [134 of 153]) of 1,3-beta-D-glucan detection did not support its role for diagnosis of *Histoplasma* meningitis.[85]

Treatment

The approach to treatment depends upon the severity of disease as well as the presence of CNS involvement. Treatment is indicated for all AIDS patients with histoplasmosis.[86] The natural history of untreated acute-disseminated infection is progressive and 100% fatal.[87] Treatments should focus on administration of effective antifungal therapy and starting HIV medication.

Liposomal amphotericin B should be used in patients who are sufficiently ill to require hospitalization.[86] A randomized trial showed that induction therapy with liposomal amphotericin B produced better outcomes than the deoxycholate formulation.[59] Liposomal or deoxycholate amphotericin B was more effective in AIDS patients with histoplasmosis (excluded those with CNS involvement) than amphotericin B lipid complex, with one-year survival of 81% and 56%, respectively. The mean survival time was 11 months in patients treated with liposomal or deoxycholate amphotericin B compared to 8 months with amphotericin B lipid complex. Amphotericin B should be transitioned to itraconazole. Dose reduction of amphotericin B or earlier transition to itraconazole may be needed in patients who develop renal impairment or other significant toxicities. Most patients respond quickly to liposomal amphotericin B and then can be transitioned to itraconazole after one to two weeks.[59,86] The transition to itraconazole should occur after the patient becomes afebrile (or at least demonstrates consistent improvement in fever), no longer requires blood pressure or ventilatory support or intravenous fluids; and is able to take oral medications.

Itraconazole is the treatment of choice in patients with non-life-threatening manifestations of histoplasmosis.[86] A prospective study reported that 84.7% (50 of 59) of AIDS patients responded to treatment.[88] However, only 1 of the 9 failures was caused by progression of histoplasmosis. Itraconazole also is the treatment of choice for step down therapy in patients with severe disease who responded to amphotericin B.[86] A prospective study in patients with AIDS who responded to initial therapy with amphotericin B observed successful suppression during treatment with itraconazole 96.9% (39 of 42).[89]

Generic FDA approved itraconazole is less expensive than Sporanox capsules. Itraconazole capsules should be administered with food 200 mg three times daily for three days to achieve steady-state serum concentrations more

rapidly, and then 200 mg twice daily. Acid-blocking drugs should be avoided, and an acidic beverage (such as a non-diet cola) can be administered with the tablets to increase gastric acidity. Itraconazole blood levels should be determined and the dosage should be adjusted to achieve concentrations between 2 and 10 μg/mL.

The liquid formulation of Sporanox achieves 30% higher blood concentrations. However, Sporanox solution is much more expensive than generic capsules. Also, the solution is often stopped because of poor palatability or toxicity.[90] Gastrointestinal upset and fluid retention occur more commonly with the solution than the capsules. Itraconazole solution should be given on an empty stomach to achieve the highest serum concentration.

Itraconazole blood levels should be measured after two weeks of therapy[86] to assure they are therapeutic[91] and not potentially toxic.[92] Levels should also be determined if adherence to treatment is uncertain or drug interactions are suspected. The minimum inhibitory concentration for itraconazole in 90% of strains of *H. capsulatum* is 0.06 mcg/mL.[93] The therapeutic concentration is >1–2 mcg/mL measured by bioassay[86] or the sum of the itraconazole parent drug and the hydroxyl metabolite measured by high-performance liquid chromatography (HPLC).[91] However, data are not available to support that opinion. Bioassay levels average twice combined itraconazole and hydroxy itraconazole levels measured by HPLC[94] but the actual ratio varies considerably among isolates. The causes for subtherapeutic levels include improper dosage, nonadherence, absence of gastric acidity (acid reducers, lack of food or acidic beverage with itraconazole), and drug interactions increasing hepatic metabolism of itraconazole. Itraconazole is metabolized by and affects the hepatic cytochrome P450 (CYP) enzymes to varying degrees.[95] Potential for drug interaction should be assessed before starting therapy. Itraconazole and other triazoles may interact with antiretroviral agents.

One study reported that bioassay levels above 17.1 mcg/mL were associated with a 53.9% likelihood for toxicity and levels above 5 mcg/mL with a 26% likelihood.[92] Levels >10 mcg/mL by bioassay and combined itraconazole and hydroxy itraconazole levels above 5 mcg/mL by HPLC should be avoided to reduce risk for toxicity. Of note, toxicity occurred with bioassay levels between 5 and 10 mcg/mL. Furthermore, these high levels are unnecessary for treatment of histoplasmosis considering MICs are 0.06 mcg/mL or less in 90% of strains.[93]

Posaconazole is the preferred treatment if itraconazole cannot be administered. *Histoplasma* is highly susceptible (MICs less than 0.007 mcg/mL)[96] and does not become resistant to posaconazole.[96] Posaconazole was highly effective in experimental model and immunocompromised mice[97] and in patients who failed other treatments.[98] In that study, 6 patients responded favorably, including one with CNS infection. The CNS case failed treatment with amphotericin B, fluconazole, and voriconazole and was subsequently cured with posaconazole.

Fluconazole is not as active in vitro (median MIC ≥ 0.62 μg/mL in 96.9% (63 of 65)) of isolates[99] as itraconazole and has not been as effective when used for treatment.[100,101] Seventy-five percent of patients with mild or moderately severe disease initially responded to fluconazole (800 mg/day), but nearly one-third relapsed within 6 months while receiving 400 mg/day as "step-down" maintenance therapy, causing closure of the study.[100] Overall 50% of treatment failure or relapse isolates developed resistance to fluconazole.[99]

Voriconazole MICs[96] are higher than those of itraconazole,[93] posaconazole[96] and isavuconazole.[102] Furthermore, resistance may develop to voriconazole.[96] Prospective trials using it for treatment of histoplasmosis have not been reported. The single published study evaluated 7 patients who had responded to treatment with other antifungal medications and were enrolled in a voriconazole trial because of toxicity. One patient received 147 days of voriconazole primary therapy but relapsed 36 days after stopping voriconazole. This study does not establish voriconazole's efficacy for the treatment of histoplasmosis.

Isavuconazole may be the best alternative to posaconazole because of excellent sensitivity (MICs ≤0.007 mcg/mL) including isolates resistant to fluconazole or voriconazole.[102] However, clinical experience of isavuconazole is limited: 3 of 7 patients failed treatment with isavuconazole.[103] and in animal models comparing isavuconazole with other azoles have not been reported. Despite these limitations, isavuconazole should be an effective alternative to posaconazole.

The total duration of treatment for disseminated histoplasmosis and disseminated or pulmonary histoplasmosis in patients with AIDS is at least one year. Discontinuation of therapy was safe in patients who completed at least 1 year of itraconazole treatment, were adherent treatment, lacked CNS involvement, had CD4 counts >150 cells/mL, HIV RNA <400 c/mL,

Histoplasma antigenuria <2 ng/mL.[104] Relapse was 13 times more likely in patients with antigenuria ≥2.0 ng/mL at the time of stopping antifungal therapy.[58]

Lifelong suppressive therapy with itraconazole 200 mg/day was recommended if immunosuppression could not be reversed or if histoplasmosis relapsed despite an appropriate treatment.[86] Fluconazole is less effective than itraconazole for this purpose but has some efficacy at 400 mg daily.[88,100] Although studies have not been conducted, posaconazole appeared to be the best alternative if itraconazole cannot be used.

Representatives from most of Latin America made an announcement in March, 2019, The Manaus Declaration on Histoplasmosis in the Americas and Caribbean, "By 2025, every country should have availability of itraconazole and both standard and lipid formulation of amphotericin B in the public sector."[83] This should be extended to other hyperendemic areas.

Treatment of Meningitis

Meningitis poses additional challenges in treatment. Liposomal amphotericin B for 4–6 weeks followed by itraconazole for at least one year is recommended. Evidence suggests selection of agents that penetrate the CSF is unnecessary.[84] An experimental model of *Histoplasma* meningitis in mice showed that fluconazole, which penetrates CSF well, was less effective than itraconazole or amphotericin B, drugs that do not penetrate CSF.[105] Penetration of brain and meninges may be more important than penetration of CSF.

Liposomal amphotericin B is preferred because of the higher risk for toxicity with deoxycholate amphotericin B at these dosages administered in for 4–6 weeks followed by itraconazole. Itraconazole (200 mg orally twice daily, adjusted not to exceed 10 mcg/mL) should be given for at least one year and may then be discontinued in patients receiving effective antiretroviral treatment to achieve immune reconstitution and suppression of HIV viral load. Posaconazole is preferred if itraconazole cannot be administered.

To determine if treatment should be stopped after one year, CSF should be evaluated including large-volume culture and *Histoplasma* antigen determination at the time of discontinuation. CSF cell profile and chemistry should be within normal limits and antigen and culture should be negative. Urine and serum antigen, if positive initially, should be repeated at 3–6-month intervals, if clinical findings are concerning for recurrence, or HIV viremia and CD4 counts suggest antiretroviral therapy is no longer effective.

Monitoring Treatment Response

Monitoring antigen levels during treatment is recommended.[86] Antigen levels declined within 2 weeks in serum and more slowly in urine.[76] Antigen cleared more rapidly in patients treated with amphotericin B than with itraconazole.[106] Antigen levels should be measured at initiation of treatment, at the end of the amphotericin phase, at 3, 6 and 12 months, and when discontinuation of therapy is considered.[86,107] Antigen testing should be repeated at 6–12-month intervals and if antiretroviral therapy is no longer working or clinical findings suggest recurrence.

Any increase in antigen or clinical worsening during or after treatment should be investigated by evaluating itraconazole blood concentration, adherence to treatment, CD4 count and HIV viral load. Nonadherence to therapy was the main predictor for relapse of histoplasmosis.[58] Clinical worsening during therapy may represent treatment failure, immune reconstitution inflammatory syndrome (IRIS) or a different opportunistic infection.

Special Considerations About When to Start Antiretroviral Therapy

Antiretroviral treatment must be introduced as soon as possible following the initiation of the antifungal treatment.[108] However, immune reconstitution in response to effective antiretroviral therapy may cause inflammation in tissues involved in the infection (pulmonary, lymphadenopathy in a variety of tissues, skin lesions, and CNS sites) and worsening of the clinical findings, some of which may be severe.

Management of Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is uncommon in AIDS patients with histoplasmosis.[41,109] The incidence rate was 0.74 cases per 1000 HIV-infected person-years in one study[110] and 0.5% in another.[111] But those studies were limited by the retrospective design and incomplete information. Also, the definition for IRIS is not universally accepted. The rate may be higher.

Most or all of the following features should be present: (1) AIDS with a low pretreatment CD4 count (often less than 100 cells/microL)[112,113] (2) a positive virologic and immunological response to antiretroviral therapy[114] (3) absence of evidence of antiretroviral resistance, a concomitant non-fungal infection, drug allergy or other adverse drug reactions, patient noncompliance, or reduced drug levels due to drug–drug interactions or malabsorption after evaluation for other causes for worsening (4) clinical manifestations consistent with an inflammatory condition[115] (5) a temporal association between ART initiation and the onset of clinical features of illness.[111]

A study of 22 cases reported that IRIS was four times more frequent in females than males, median time to IRIS was 11 days after antiretroviral therapy initiation.[110] The main clinical presentation was fever and disseminated disease.

Patients who manifest findings of IRIS while receiving effective antiretroviral therapy at the time of diagnosis should continue it and begin treatment for histoplasmosis. A two-week delay is recommended in patients who are not receiving antiretroviral treatment.[86] The role of corticosteroids is unclear[110] but may be appropriate in patients with more severe manifestations[116] if they are receiving amphotericin B or itraconazole, which should prevent progression of histoplasmosis.

Preventing Exposure

AIDS patients who live in or visit areas in which histoplasmosis is endemic cannot completely avoid exposure to it, but those with CD4 counts <150 cells/mm3 should avoid activities known to be associated with increased risk. These include creating dust when working with surface soil; cleaning chicken coops that are contaminated with droppings; disturbing areas contaminated with bird or bat droppings; cleaning, remodeling, or demolishing old buildings; and exploring caves.

Preventing Disease

Prophylaxis with itraconazole (200 mg daily) was effective in patients with CD4 cell counts <150 cells/mm3 in areas where the incidence of histoplasmosis is >10 cases per 100 patient-years.[104] Itraconazole can reduce the frequency of histoplasmosis, although not mortality, in patients who have advanced HIV infection and who live in areas where histoplasmosis is highly endemic.[117] However, incidence >10 cases/100 only occurs during outbreaks in the United States.[117] The incidence may be above 10% in some Latin American countries, but cost may be prohibitive. If prophylaxis is implemented, it can be discontinued in patients on antiretroviral treatment once CD4 counts are ≥150 cells/mm^3 for 6 months. Prophylaxis should be restarted if the CD4 count falls to <150 cells/mm^3.

Disclosure

Dr L Joseph Wheat is the president and medical director of MirVista Diagnostics, Fungal Diagnostic Laboratory and R & D lab. The authors report no other conflicts of interest in this work.

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