



Histoplasmosis or Tuberculosis in HIV-Infected Patients in the Amazon: What Should Be Treated First?

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Histoplasmosis and tuberculosis are probably among the most frequent AIDS-defining illnesses in the Amazon region and beyond [1]. Whereas tuberculosis is a well-known disease present in clinical algorithms and in specific public health programs, disseminated histoplasmosis is relatively neglected in South and Central America [2,3]. Histoplasmosis and tuberculosis are often presented as clinically and paraclinically similar [4]. Recently, we showed that disseminated histoplasmosis, while having some similarities with tuberculosis, had some marked differences with more pulmonary signs and inflammation in tuberculosis whereas histoplasmosis was more likely to be associated with cytopenia, liver enzyme abnormalities, or symptoms from the abdominal sphere [5].

Histoplasmosis and tuberculosis in HIV patients often are disseminated infections with a fatal evolution in the absence of treatment. For both infections, diagnosis is often slow with cultures that may take weeks to isolate the pathogen [6]. Patients with severe disseminated histoplasmosis are at risk of early death within days of their admission, notably if there is treatment delay. For tuberculosis, early mortality in severely immunocompromised patients is also a problem and has led to promote early rather than late initiation of antiretroviral therapy [7].

In practice, once other common opportunistic infections have been excluded, clinicians facing a severely immunocompromised HIV patient will need to conduct investigations and start a presumptive treatment, which often includes antituberculosis drugs but not antifungal drugs. This heuristic of HIV care does not rely on precise epidemiologic data and should be adapted to the local epidemiology.

In French Guiana, HIV is a major public health problem [8]. Histoplasmosis and tuberculosis incidences in

HIV-infected patients are high [1,9,10]. Therefore, clinicians facing a severely immunocompromised patient often need to consider both alternatives and make a decision.

Since what treatment to start and when to start it may lead to different survival chances in this very common differential diagnosis situation, we aimed to gather additional evidence to guide clinicians.

Longitudinal data from the French Hospital Database on HIV infection (FHDH) in French Guiana between 1996–2008, described in [11], allowed us to collect incidence and mortality rates. The diagnosis of histoplasmosis was performed according to the European Organisation for Research and Treatment of Cancer (EORTC) criteria [12]. The diagnosis of tuberculosis relied on confirmed tuberculosis (culture and identification of *Mycobacterium tuberculosis*). All HIV patients in French Guiana can receive free antiretroviral treatments (including the most recent drugs) regardless of their origin or socioeconomic level.

A total of 2,323 patients were included. This amounted to 40,443 records and

9,608 years at risk. There were 141 first episodes of disseminated histoplasmosis observed and 119 cases of confirmed tuberculosis. Figure 1 shows the incidence rates of first episodes of disseminated histoplasmosis and of tuberculosis for different CD4 strata, and the gradual increase of the incidence rate ratio of histoplasmosis/tuberculosis as immunosuppression increases.

Figure 2 shows the respective Kaplan Meier curves for survival for histoplasmosis and tuberculosis in patients with CD4 counts below 200 cells per mm³ within the first 12 months after the opportunistic infection. Histoplasmosis seemed to lead to more deaths than tuberculosis; however, this difference was not statistically significant. For the 141 patients with a first episode of histoplasmosis, there were 13.5% of deaths at one month, 17.5% at three months, and 22.5% at six months after the date of diagnosis of histoplasmosis. Among 119 first episodes of confirmed tuberculosis, 68 were in patients with CD4 counts less than 200 cells per mm³. For patients with CD4 counts below 200 cells per mm³, there was 10% mortality at one

Citation: Nacher M, Adenis A, Sambourg E, Huber F, Abboud P, et al. (2014) Histoplasmosis or Tuberculosis in HIV-Infected Patients in the Amazon: What Should Be Treated First? *PLoS Negl Trop Dis* 8(12): e3290. doi:10.1371/journal.pntd.0003290

Editor: Gary L. Simon, George Washington University, United States of America

Published: December 4, 2014

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Data Availability: The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. The data concerns computerized patient records of HIV patients. All elements allowing patient recognition cannot be shared. Our ethical point of contact is Commission Nationale de l'Informatique et des Libertés at the phone number 0153732222.

Funding: This work has benefited from an "Investissement d'Avenir" grant managed by Agence Nationale de la Recherche (CEBA, ref. ANR-10-LABX-25-01). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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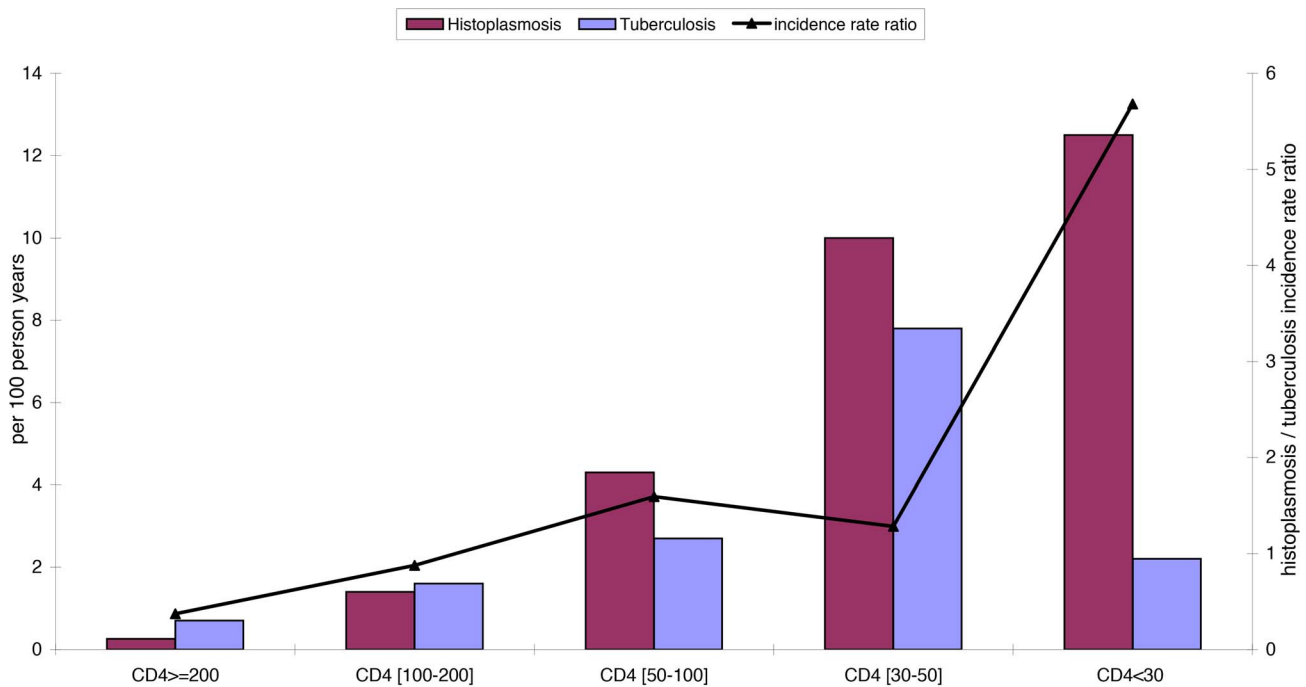


Figure 1. Shows the incidence rate for tuberculosis and histoplasmosis for different CD4 strata.
doi:10.1371/journal.pntd.0003290.g001

month, 19% at three months, and 31% at six months.

For clinicians, the situation where a severely immunocompromized HIV-infected patient is admitted for a “tuberculosis-like” illness is common and requires prompt identification and treatment of

both the opportunistic agent and the underlying immunosuppression. Ideally, treatments should be administered once the opportunistic agent has been identified. However, in the Amazon region, invasive diagnostic procedures are often not performed or available, and laboratory

facilities are lacking. Thus, empirical treatment remains an important strategy. Despite the potential adverse events or drug interactions, it is common to simultaneously treat different confirmed or suspected opportunistic infections. However, when possible, it is preferable to

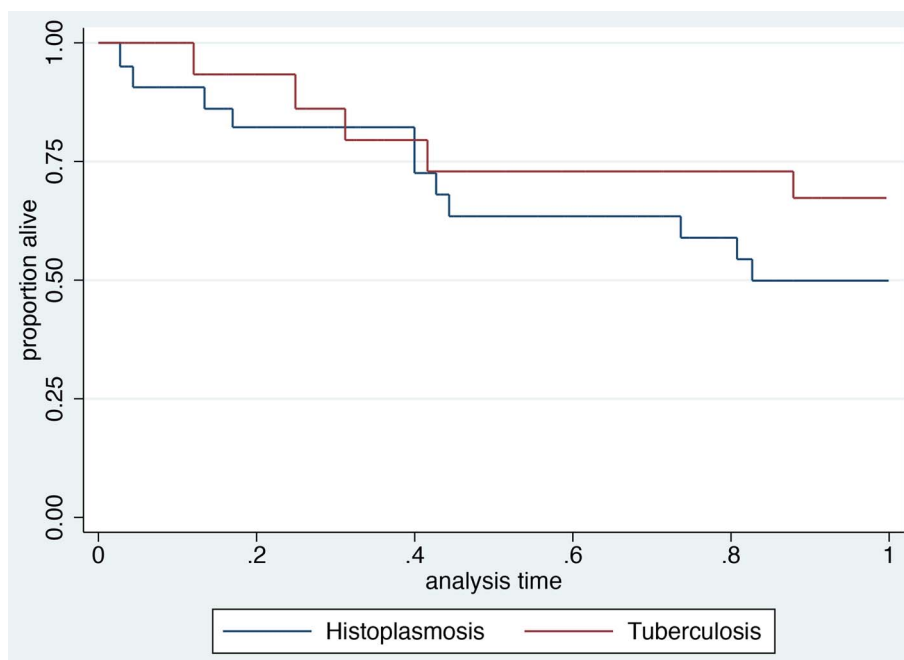


Figure 2. Shows the incidence of death during the first year after histoplasmosis or tuberculosis among patients with CD4 counts less than 200.
doi:10.1371/journal.pntd.0003290.g002

target the most likely agent than to give numerous drugs, which makes it difficult to know what leads to improvement or what drug leads to adverse events [13].

In an Amazonian context, among immunosuppressed patients, the incidence of histoplasmosis was higher than that of tuberculosis. Despite comparable overall mortality in terms of proportion of patients with histoplasmosis and tuberculosis dying,

the number of histoplasmosis-related deaths was higher. Thus, for HIV patients with CD4 counts below 200 with a tuberculosis-like syndrome (histoplasmosis-like may be a more appropriate heuristic in our epidemiological context), clinicians with poor diagnostic facilities may be better inspired, given the differences in incidence rates, to start with amphotericin B (ideally in its liposomal formulation) than

antituberculosis drugs and reevaluate the situation 3–7 days later in view of the treatment response [6,14]. As shown elsewhere [15], the data also suggests antiretrovirals should be started without delay in order to minimize the duration of the severe immunosuppression that puts the patient at great risk of dying from other opportunistic agents.

References

1. Nacher M, Adenis A, Adriouch L, Dufour J, Papot E, et al. (2011) What is AIDS in the Amazon and the Guianas? Establishing the burden of disseminated histoplasmosis. *Am J Trop Med Hyg* 84: 239–240.
2. Nacher M, Adenis A, Aznar C, Blanchet D, Vantilcke V, et al. (2014) How Many Have Died from Undiagnosed Human Immunodeficiency Virus-Associated Histoplasmosis, A Treatable Disease? Time to Act. *Am J Trop Med Hyg*.
3. Nacher M, Adenis A, Mc Donald S, Do Socorro Mendonca Gomes M, Singh S, et al. (2013) Disseminated histoplasmosis in HIV-infected patients in South America: a neglected killer continues on its rampage. *PLoS Negl Trop Dis* 7: e2319.
4. Krug ES, Glenn HR (1948) Comparative studies in tuberculosis and histoplasmosis among 2000 students entering Pennsylvania State College, September, 1947. *J Lancet* 68: 206–208.
5. Adenis A, Nacher M, Hanf M, Basurko C, Dufour J, et al. (2014) Tuberculosis and histoplasmosis among human immunodeficiency virus-infected patients: a comparative study. *Am J Trop Med Hyg* 90: 216–223.
6. Huber F, Nacher M, Aznar C, Pierre-Demar M, El Guedj M, et al. (2008) AIDS-related *Histoplasma capsulatum* var. *capsulatum* infection: 25 years experience of French Guiana. *AIDS* 22: 1047–1053.
7. Blanc FX, Sok T, Laureillard D, Borand L, Rekacewicz C, et al. (2011) Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 365: 1471–1481.
8. Nacher M, Vantilcke V, Parriault MC, Van Melle A, Hanf M, et al. (2010) What is driving the HIV epidemic in French Guiana? *Int J STD AIDS* 21: 359–361.
9. Nacher M, Aznar C, Blanchet D, Demar M, El Guedj M, et al. (2006) AIDS-related disseminated histoplasmosis in the greater Caribbean: how frequent is it? *AIDS* 20: 951–952.
10. Guernier V, Guegan JF, Deparis X (2006) An evaluation of the actual incidence of tuberculosis in French Guiana using a capture-recapture model. *Microbes Infect* 8: 721–727.
11. Nacher M, Adenis A, Blanchet D, Vantilcke V, Demar M, et al. (2014) Risk factors for disseminated histoplasmosis in a cohort of HIV-infected patients in French Guiana. *PLoS Negl Trop Dis* 8: e2638.
12. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, et al. (2008) Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 46: 1813–1821.
13. Couppie P, Sobesky M, Aznar C, Bichat S, Clyti E, et al. (2004) Histoplasmosis and acquired immunodeficiency syndrome: a study of prognostic factors. *Clin Infect Dis* 38: 134–138.
14. Couppie P, Aznar C, Carme B, Nacher M (2006) American histoplasmosis in developing countries with a special focus on patients with HIV: diagnosis, treatment, and prognosis. *Curr Opin Infect Dis* 19: 443–449.
15. Lawn SD, Little F, Bekker LG, Kaplan R, Campbell E, et al. (2009) Changing mortality risk associated with CD4 cell response to antiretroviral therapy in South Africa. *AIDS* 23: 335–342.