VIEWPOINTS AND COUNTERPOINTS

Paracoccidioidomycosis: A Model for Evaluation of the Effects of Human Immunodeficiency Virus Infection on the Natural History of Endemic Tropical Diseases

Gil Benard[1,2] and Alberto J. S. Duarte[1]

[1]*Laboratory of Medical Investigation No. 56 and* [2]*Clinics of Infectious and Parasitic Diseases, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil*

The interaction of human immunodeficiency virus (HIV) infection with endemic tropical diseases has become a major concern, but its mechanisms are still poorly understood. Paracoccidioidomycosis (PCM), a South America endemic deep mycosis, may provide an interesting model to investigate this interaction, as clinical-epidemiological features of most HIV-PCM-coinfected patients are difficult to classify into the standard acute and chronic forms of PCM. Such patients have presented clinical features indicative of an uncontrolled infection with lymphohematogenous dissemination, similar to the more severe, acute form. However, this infection probably resulted from reactivated latent foci that, in nonimmunocompromised hosts, leads to the less severe chronic form, characterized by mucosal lesions. We propose that a new outcome of the *Paracoccidioides brasiliensis*–host interaction is induced by concomitant HIV infection. This outcome probably reflects an impaired anti–*P. brasiliensis* immune response during coinfection that is similar to that seen in the acute form, although the patients have a chronic *P. brasiliensis* infection.

An important issue raised by the AIDS epidemic is its influence on the natural history of endemic infectious diseases. Among endemic mycoses that reportedly cause opportunistic infections in HIV-infected patients, 2 in particular—histoplasmosis and coccidioidomycosis—have been investigated in terms of the impact of HIV coinfection on incidence and clinical manifestations [1–3]. These infections usually appear as severe, life-threatening, disseminated disease in patients whose $CD4^+$ cell counts are <200 cells/μL. These features are less frequently seen in immunocompetent hosts. However, neither the clinical features nor the information gathered in prospective studies of HIV-infected patients with these mycoses have helped to determine whether opportunistic infection by these fungi represents exogenous infection/reinfection or reactivation of a latent infection [4, 5].

In this regard, paracoccidioidomycosis (PCM) can provide an interesting model enabling a better understanding of the influence of HIV infection on the course of endemic deep fungal infections. This assumption is based on the fact that the natural history of PCM comprises different outcomes of the host-parasite interaction that clinically tend not to overlap [6].

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Reprints or correspondence: Dr. Gil Benard, Faculdade de Medicina da USP, Av. Dr. Arnaldo 455, sala 2345, CEP 01246-903, São Paulo, Brazil (mahong@usp.br).

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Clinical and Epidemiological Features of PCM in Nonimmunocompromised Hosts

PCM, the most important endemic deep mycosis in South America, is caused by the thermally dimorphic fungus *Paracoccidioides brasiliensis.* Its reservoir in nature is probably the soil, where it resides in the mycelial phase. It is generally accepted that the disease is acquired through the respiratory route by inhalation of airborne propagules (conidia) produced in the mycelial phase [7]. Subjects that have become infected with the fungus may subsequently fall into any of 4 categories [6]: (1) healthy carriers, comprising individuals who live or have lived in an area of endemicity and harbor the fungus in quiescent foci; (2) patients with the acute/subacute form of the disease, believed to develop weeks to months after inhalation of the fungus; (3) patients with the chronic form, which mostly results from reactivation of the quiescent foci in healthy persons; and (4) treated patients, with or without sequelae.

Clinically, the acute and chronic disease are clearly distinguishable, in that the former is characterized by involvement of the mononuclear-phagocytic system (lymph node enlargement, hepatosplenomegaly) and by osseous and cutaneous lesions, in individuals <30 years old in close contact with areas of endemicity. Chronic disease is characterized by mucosal in-

volvement (in the oral cavity and/or upper and lower respiratory tracts) in adults, usually during the fourth decade of age. Moreover, the chronic form of PCM predominantly affects men [8], whereas the acute form equally affects both sexes before puberty [9] but predominantly men after puberty [10, 11].

Estrogens are implicated in the relative protection of women against PCM, by blocking the conidia from yeast-cell transformation in the infected host, a crucial step for disease development [12]. The main defense mechanism against the fungus has been ascribed to cell-mediated immunity, which induces dense, compact granulomatous formations that are associated with low numbers of fungal cells in patients with less severe disease. On the other hand, histopathological examination of lesions from patients with severe disease frequently shows loose granulomata and high numbers of viable budding yeast cells [13]. In addition, immune evaluation of these patients reveals high levels of specific antibodies and polyclonal B cell activation.

Prototype Cases of PCM-HIV Coinfection with Distinct Features

Cases of PCM and HIV coinfection that presented with unusual clinical and epidemiological features were recently diagnosed at a reference infectious diseases hospital in São Paulo, Brazil. For example, a 32-year-old HIV-infected woman had disseminated disease (skin ulcers and fungal arthritis) resembling an acute form of PCM [14]. Nevertheless, her disease likely resulted from an endogenous reactivation, because she had been living for many years in urban areas; the single epidemiological risk factor for infection by *P. brasiliensis* was that, during her infancy, she had lived for 3 years in a rural area where PCM is endemic. Similarly, a report of the case of a 15-year-old HIV^+ boy with typical features of acute disease (which, as expected for his age, were lymph node and skin involvement) but with concomitant clinically and radiologically apparent lung disease, suggestive of the chronic form of PCM, was recently published [15]. Cases such as these prompted us to review the clinical and epidemiological features of all cases of PCM-HIV coinfection reported to date, to determine whether the cases fit into the conventional classification of acute or chronic forms of the disease.

Review of Case Reports of PCM-HIV Coinfection

We collected data from cases published in indexed journals as well as in proceedings from meetings on infectious diseases and medical mycology that were held in South America. We consulted the proceedings of virtually all meetings on these topics that occurred between 1989, when the first reports of HIV-PCM coinfection were published [16–18], and 1999.

We found 52 new cases since the last review, published in 1995 [19], which described 27 cases (total, 79 cases). In addition to 1 Equatorian [20], 1 Venezuelan [21], and 2 Colombian patients [22], the remaining 75 patients were Brazilian ([14–18, 23–53] and authors' unpublished observations). The increase in the number of cases may be attributed to several factors, including the progressive spread of the HIV epidemic in Brazil to small urban areas, which are close to rural areas where PCM is endemic.

Partial clinical and epidemiological data were available for 73 cases. The patients' ages ranged from 15 to 62 years (mean, 33.5 years). The risk factors for HIV transmission were reported in 45 cases and were sexual in 49%, hematologic in 35.5%, and both in 15.5%. The corresponding figures for the HIV-infected population in Brazil with known risk factors (for the period 1980–1999) are 64.5%, 15.0%, and 20.5%, respectively [54]. The high proportion of blood transmission in PCM-HIV–coinfected patients is probably related to the prevalence of intravenous drug addiction as a risk factor in communities where PCM is endemic.

A coexistent opportunistic infection other than PCM was noted in 37% of the patients; oral/esophageal moniliasis and pulmonary/extrapulmonary tuberculosis were the most frequent ones. These are also 2 of the most prevalent opportunistic infections in the Brazilian HIV-infected population [54].

With regard to the clinical presentation of PCM, 56 patients (77%) had disseminated disease with many characteristics of the acute form, such as lymph node enlargement of superficial chains, mainly cervical, in 41 (73%); hepatomegaly in 24 (43%); splenomegaly in 16 (29%); osteoarticular lesions in 10 (18%); and lymph-node enlargement of deep-seated chains, mainly intra-abdominal, in 9 (16%). This distribution is quite similar to that observed in HIV-negative patients with the acute form of PCM [10, 55].

Of note, however, was the striking incidence of paracoccidioidal skin involvement in HIV-infected patients (34 patients [61%]) in comparison with that in HIV-negative patients with the acute form of PCM (10%–15% [10, 55]) and in HIV-infected patients with histoplasmosis in Brazil (39%) [56]. In the majority of cases, these lesions were described as ulcerated papular lesions, occasionally with a necrotic center. Biopsies or smears of these lesions frequently revealed the typical *P. brasiliensis* yeast cells, reinforcing the hypothesis of hematogenous dissemination. Finally, the mean age of this subgroup of patients was 31 years, within a range of 15–62 years.

However, 31 of these 56 patients had concomitant clinically or radiologically apparent involvement of the upper or lower respiratory tract. Along with the findings suggestive of an acute form of the disease, these patients had mucosal lesions similar to those seen in the chronic form of the disease. Involvement of the lungs, usually with an interstitial infiltrate pattern, was most common (23 patients [74%]), followed by oral cavity lesions, usually with an ulcerated and granulomatous aspect (10 patients [32%]). Taken together, these findings suggest that these patients had an unusual mixed clinical form that has not been previously described.

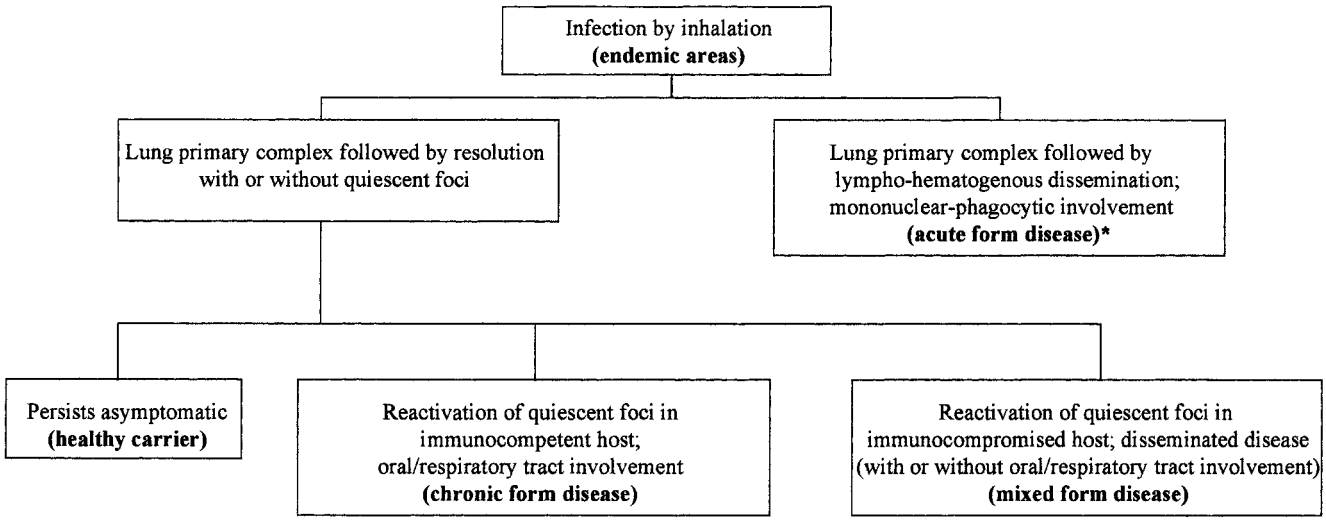

Figure 1. Different outcomes of the *P. brasiliensis*–host interaction in immunocompetent and immunocompromised individuals (*, the acute form of disease may also occur in HIV-infected patients).

The other 25 patients who had disseminated disease but no apparent mucosal involvement would be classified as having the standard acute form of PCM. However, among these 25 patients, a more detailed history was available for only 12, of whom 4 had performed activities in rural areas when the disease developed; the other 8 were residing in urban areas and had not performed any activities in rural areas at that time. In contrast, HIV-negative young adult patients with acute PCM often work in, reside in, and/or travel to rural areas in which PCM is endemic [57].

The remaining 17 patients (23%) could be accurately classified as having the chronic form of PCM; the organs most frequently involved were the lungs (interstitial infiltrates, 13 patients), followed by oral mucosa (6 patients), adrenal glands (2 patients), and nasopharynx (1 patient). The mean age of these patients was 39 years (range, 19–52 years).

Among HIV-infected patients, PCM was also more frequent in men (56 men vs. 17 women), with a male-to-female ratio of 3.3:1. Among the 56 patients with features resembling the acute form of disease, there were 44 men and 11 women (the sex of 1 patient was not noted). This predominance may support the theory that estrogen-mediated protection plays a role in HIV-infected patients, because most HIV-PCM–coinfected patients were at reproductive age. However, the observed ratio may more likely reflect the profile of HIV infection in Brazil, where the cumulative (1980–1999) male-to-female ratio is also 3.3:1 [54]. This observation also suggests that the determining factor for disease development in these *P. brasiliensis*–infected individuals was the immune imbalance caused by the HIV infection, as documented by the low $CD4^+$ cell count (see below). With regard to the cases of coccidioidomycosis, similarly, it was suggested that the immunodeficiency was the driving force behind the development of active coccidioidomycosis during HIV infection [5]. Therefore, these *P. brasiliensis*–infected individuals, if not HIV-coinfected, would probably remain asymptomatic throughout life or, rarely, develop a mild-to-moderate oral/pulmonary chronic form of PCM, the most common clinical presentation of the mycosis.

The basis of the diagnosis, when reported, was usually identification of the fungus in biological specimens (biopsy specimens or smears of superficial lesions or sputa). The value of serological diagnosis is controversial because negative results were reported in the previous reviews [17, 32]. B-cell dysfunction due to the HIV infection was the likely explanation. In this study, we found 47 cases in which serological tests were performed, with positive results in only 27 cases (57.6%), most commonly at low titers. The false-negativity rate was similar to that found with histoplasmosis (30%–50%) [58] but higher than that with coccidioidomycosis, for which serology is still very useful (diagnostic for ~80% of patients) [59]. Thus, the present data suggest that serology may be helpful but should not be used as the single method of diagnosis of PCM in HIV-infected patients.

Hypothesis

It is conceivable that, for a major proportion of the patients coinfected with PCM and HIV, the outcomes may be different from those seen in normal hosts (figure 1). Although the clinical presentation of many of these HIV-infected patients may suggest an acute form of PCM, the illness likely represents reactivation of a latent infection, making its classification as typical acute or chronic disease inappropriate. There are several reports of PCM in patients with other immunosuppressive conditions,

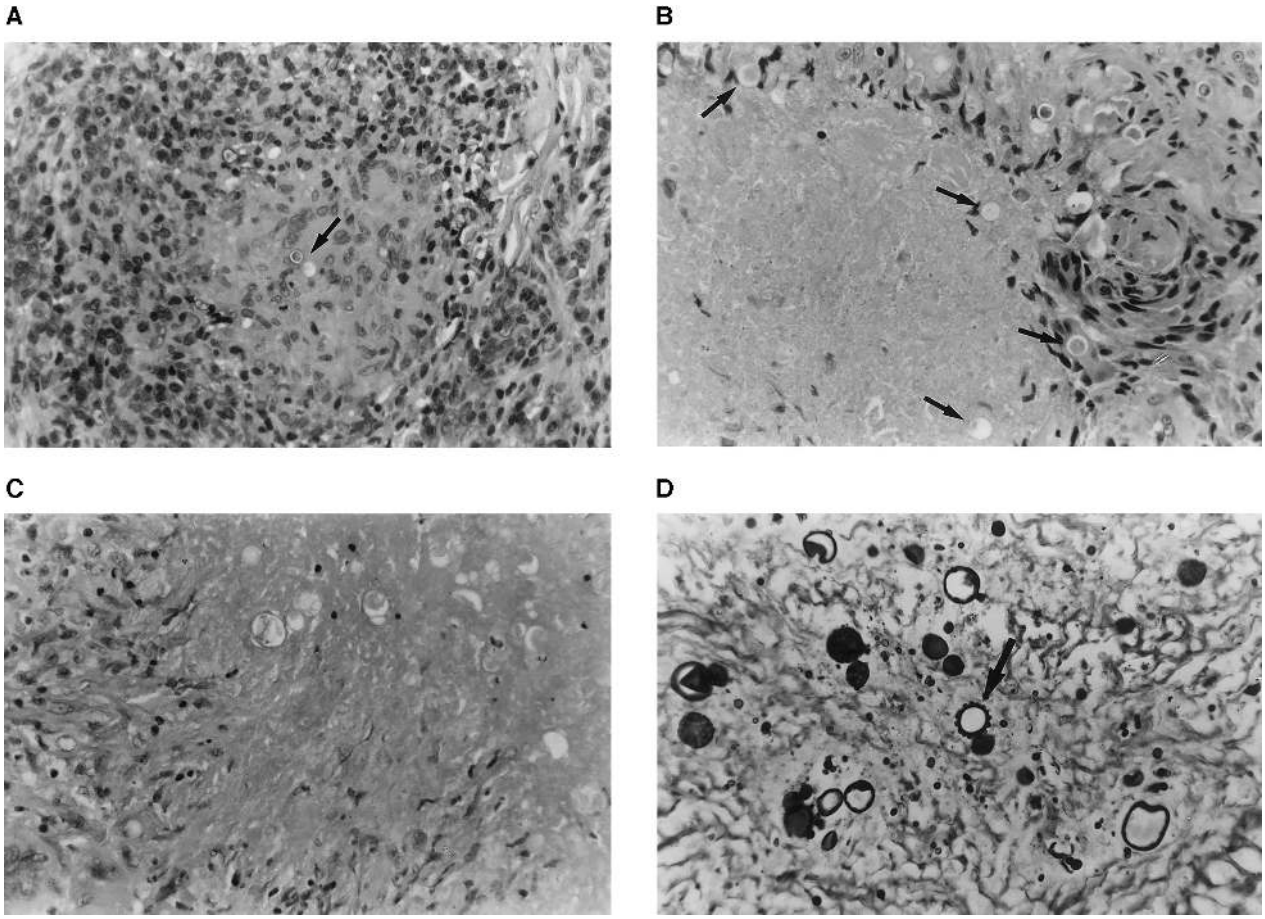

Figure 2. Illustrative histopathologic sections showing different patterns of response in lesions of patients with paracoccidioidomycosis (PCM) (hematoxylin and eosin; original magnifications, × 200 [except as stated otherwise]). *A,* Biopsy section of a mucosal lesion from a patient with the chronic form of PCM, showing a well-defined epithelioid granulomatous response and 2 yeast cells within a giant cell *(arrow). B,* Biopsy section of lymph node of a patient with the acute form of PCM, showing a poorly defined epithelioid response with an extensive necrotic area, where numerous yeast cells are seen *(arrows). C,* Biopsy section of a lymph node of a patient with PCM-HIV coinfection [24], showing (as in panel *B*) a poorly defined epithelioid granulomatous response and an extensive area of necrosis. *D,* Silver stain of the section in panel *C*, showing the high number of fungal cells, including a yeast cell with the typical "pilot wheel" shape *(arrow)* (magnification, × 400).

including hematologic malignancies, immunosuppressive therapy, transplantation, pregnancy, and idiopathic lymphopenia [32, 60–63]. When PCM is associated with these conditions, the clinical picture is not infrequently that of a disease affecting the mononuclear-phagocytic system (mimicking the acute form) but with a concomitant mucosal involvement typical of the chronic form [32, 63–67].

The acute form of the disease is considered to be the result of an even less effective immune response than the chronic form, because patients with chronic infection have been able to mount an immune response that restricts the fungal proliferation for years or decades in quiescent foci. Patients with the acute form of the disease have a more profound in vitro hyporesponsiveness to a cell-wall *P. brasiliensis* antigen, as well as decreased $CD4^+$ cell numbers [68–70]. In 5 patients ([14, 41, 52] and authors' unpublished observations), this hyporesponsiveness was demonstrated by the markedly depressed lymphocyte proliferative responses to *P. brasiliensis* antigens (data not shown).

These findings are comparable to those for HIV-infected patients with coccidioidomycosis, where in vitro anergy to coccidioidal antigens was dependent on both the general immune status and the coccidioidal skin test reactivity of the patients [5]. Of the HIV-PCM–coinfected patients described here, the $CD4^+$ cell count was noted for 29. Most of them (86%) had <200 $CD4^+$ cells/μL, similar to counts for HIV-infected patients with coccidioidomycosis or histoplasmosis [4, 71]. In fact, $CD4^+$ cells have an important role in the immune response against *P. brasiliensis.* They participate in the granulomatous reaction, forming a peripheral mantle surrounding macrophage aggregates, and are essential for in vitro antigen-specific T cell proliferative response and antibody production [72, 73].

Histopathologic data obtained from autopsies/biopsies of

Table 1. Induction treatment regimens for paracoccidioidomycosis (PCM) and outcomes for patients with PCM-HIV coinfection.

	Outcome of induction treatment regimen						
Clinical form of PCM	Amphotericin B[a] (n = 24)	Sulfonamides[b] (n = 11)	Ketoconazole (n = 4)	Itraconazole (n = 4)	Sulfadiazine/ ketoconazole (n = 1)	Sulfadiazine/ itraconazole (n = 1)	Total
Mixed[c]	19/2/1	1/3/0	1/1/1	3/0/0	1/0/0	—	33
Chronic	2/0/0	6/0/1	1/0/0	1/0/0	—	1/0/0	12
Total	21/2/1	7/3/1	2/1/1	4/0/0	1/0/0	1/0/0	45

NOTE. Data are no. of patients or no. with good/poor/undetermined response.

[a] Alone or in combination (usually with co-trimoxazole).

[b] Either sulfadiazine or trimethoprim-sulfamethoxazole (co-trimoxazole).

[c] Disseminated disease resembling the acute form but, in most cases, probably resulting from endogenous reactivation or with concomitant clinical features of the chronic form.

HIV-PCM–coinfected patients showed a poor granulomatous response [32] (figure 2), a frequently described finding in patients with the acute form of PCM [74]. Therefore, we believe that their impaired immunity may be similar to that seen with the acute form, resulting in a poorly controlled disease with lymphohematogenous dissemination. Studies have shown that HIV-infected patients with coccidioidomycosis also had a poor granulomatous response and a higher tissular fungal burden than did patients without AIDS [75].

As discussed elsewhere [76, 77], HIV can influence the natural history of endemic infections by facilitating the infection, increasing the ratio of disease to infection, changing the presentation of the disease, or exacerbating the course of the disease. With regard to PCM, we suggest that HIV infection alters the natural history of PCM by leading to a new outcome of the host-parasite interaction in a significant proportion of patients. This outcome would be characterized by the coexistence of clinical features of the acute and chronic forms of PCM, which otherwise rarely overlap in the immunocompetent patient. This outcome would probably reflect the uncontrolled proliferation of the fungus from reactivated quiescent foci rather than from an acute or subacute infection, as is usual in normal hosts with the acute form of the disease.

Implications for Current Prospects in Prophylaxis and Therapy

Currently, there is no recommendation for prophylaxis for PCM in HIV-infected patients. Initially, the lower-than-expected number of patients with HIV-PCM coinfection was attributed in part to the frequent use of drugs to treat or prevent other fungal diseases, especially oral/esophageal moniliasis and pneumocystosis [17]. These drugs, either imidazole derivatives or co-trimoxazole, probably keep the *P. brasiliensis* infection suppressed to a subclinical level. It is difficult to draw a conclusion about the value of these drugs in the prophylaxis of PCM from the cases presented here since prophylaxis was not described in the vast majority of the case reports, probably because either PCM and HIV infections were diagnosed simultaneously or the patients were not followed-up.

Among patients whose HIV status was known, many have never had previous opportunistic infections or had $CD4^+$ cell counts determined, which are the criteria for Brazilian health care institutions to provide these drugs. We also cannot rule out the possibility that the use of prophylaxis was in some degree underreported. The only 7 patients receiving "prophylaxis" when PCM was diagnosed were taking co-trimoxazole for ~1 month for cryptosporidiosis (1 patient [45]) or pneumocystosis (1 patient [16]); ketoconazole for moniliasis (2 patients [42]); itraconazole for maintenance treatment of histoplasmosis (1 patient [25]); or co-trimoxazole prophylactically for pneumocystosis (2 patients [28, 47]).

Although anecdotal, these cases may raise some concern about the efficacy of these drugs in an eventual anti–*P. brasiliensis* prophylactic regimen. This observation is in agreement with reports of treatment failure with these drugs when given to several patients with HIV with disease like the acute form of PCM, as shown in table 1. In fact, of all patients whose induction treatment was described (n = 45), 24 (53%) were treated with amphotericin B alone or in combination, an option usually reserved for more severe cases, whereas the remaining received sulfonamides (alone [sulfadiazine] or in combination [co-trimoxazole]), ketoconazole, or itraconazole. It is interesting that except for itraconazole, these last drugs appeared to be effective only for patients with the less severe chronic form. Thus, for patients with disease like the acute form of PCM, the use of amphotericin B seems obligatory, and an initial good response may generally be expected (table 1). Itraconazole may have an important role in the treatment of these patients, but its actual value remains to be determined.

Conclusion

In conclusion, there apparently has been an increase in PCM-HIV coinfections, in part because of changes in the epidemiology of the HIV epidemic in South America. This tendency, together with the indication that most cases are due to react-

ivation of latent infection, raises the possibility that patients with a history of exposure to *P. brasiliensis* and <200 $CD4^+$ cells/μL would benefit from anti–*P. brasiliensis* prophylaxis. This subject warrants further studies.

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