Antifungal Susceptibilities of *Cryptococcus Neoformans* Cerebrospinal Fluid Isolates and Clinical Outcomes of Cryptococcal Meningitis in HIV-Infected Patients with/without Fluconazole Prophylaxis

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Objectives: *To compare the MICs of FLUconazole (FLU) and amphotericin B against isolates of Cryptococcus neoformans (C. neoformans) obtained from the CerebroSpinal Fluid (CSF); and clinical outcomes of HIV-infected patients diagnosed with cryptococcal meningitis.*
Material and Method: *There were two groups including those who did not receive FLU (group A) and those who did receive either FLU 400 mg/week for primary prophylaxis cryptococosis or 200 mg/day for secondary prophylaxis cryptococosis (group B). CSF isolates of C. neoformans from group A and group B between January 2003 and October 2004 were retrospectively studied. The MICs were determined by using the standard NCCLS broth microdilution methods (M27-A). The MICs of FLU and amphotericin B, and clinical outcomes after 10 weeks of cryptococcal meningitis treatment were determined.*
Results: *There were 98 isolates; 80 in group A and 18 in group B. The patients in group B had a higher proportion of previous opportunistic infections (p = 0.008). The other baseline characteristics between the two groups were not different. The median (range) MIC of FLU was 8.0 (0.5-32) μg/ml in group A, and 6.0 (0.5-32) μg/ml in group B (p = 0.926). The median (range) MIC of amphotericin B was 0.25 (0.03-1.0) μg/ml in group A, and 0.25 (0.12-1.0) μg/ml in group B (p = 0.384). Sixty patients from group A and 14 from group B received standard treatment and continued to follow-up. After the 10-week treatment, 39/60 (65%) patients in group A and 7/14 (50%) in group B had complete recovery (p = 0.364; RR = 0.538, 95%CI = 0.166-1.742). The overall mortality rate was 14/60 (23.3%) in group A and 7/14 (50.0%) in group B (p = 0.096; RR = 3.286, 95%CI = 0.983-10.979).*
Conclusion: *The MICs of FLU and amphotericin B against CSF isolates of C. neoformans and clinical outcomes between HIV-infected patients who receive or did not receive FLU prophylaxis are not different.*

Keywords: *Fluconazole, Amphotericin B, Susceptibility, C. neoformans, HIV*

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Cryptococcal meningitis has been a leading cause of mortality and morbidity among patients with AIDS particularly in developing countries[1]. Before the Highly Active AntiRetroviral Therapy (HAART) era, approximately 5%-8% of HIV-infected patients in developed countries acquired disseminated cryptococcosis[2]. Cryptococcal meningitis is the major opportunistic infection in HIV-infected patients in

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Thailand, especially those who had a CD4 count of less than 50 cells/mm[3-5]. Fluconazole (FLU) 200 mg/day has been used for standard secondary prophylaxis after completion of induction treatment until immune reconstitution occurs as a consequence of HAART[6]. There have been some reported cases of recurrent cryptococcal meningitis during long-term secondary prophylaxis with FLU[7-9].

A previous study of multicentre, randomized, double-blind, placebo-controlled trial of primary cryptococcal meningitis prophylaxis in HIV-infected patients with severe immune deficiency has shown the survival benefit of primary prophylaxis for cryptococcal meningitis. Thus, FLU 400 mg/week is recommended for primary prophylaxis in these patients in Thailand[10]. Meanwhile, the use of primary cryptococcal meningitis prophylaxis is not routinely recommended in the United States because of a lack of survival benefit and cost effectiveness[11,12]. There also have been some evidences of breakthrough cryptococcal meningitis during primary prophylaxis[10]. The long-term use of FLU as maintenance therapy and primary prophylaxis in HIV-infected patients has generated concern about less susceptible strains that might begin to emerge in Thailand.

The primary objective of the present study was to compare the MICs of FLU against isolates of *Cryptococcus neoformans (C. neoformans)* obtained from the Cerebro Spinal Fluid CSF between HIV-infected patients diagnosed cryptococcal meningitis who did not receive FLU and the patients who received either FLU 400 mg/week for primary prophylaxis cryptococosisor FLU 200 mg/day for secondary prophylaxis cryptococosis. The secondary objective was to compare the lowest concentration of amphotericin B that prevents any discernable growth of *C. neoformans*, and the clinical outcomes of patients after 10 weeks of standard treatment between these 2 groups.

Material and Method

Clinical isolates and reference strains

98 CSF isolates of *C. neoformans* obtained from HIV-infected patients diagnosed with cryptococcal meningitis who were admitted to Bamrasnaradura Institute, Nonthaburi, Thailand between January 2003 and October 2004 were retrospectively studied. The CSF specimens for cultivation of *C. neoformans* were centrifuged; the sediments were inoculated onto Sabouraud's Dextrose agar and incubated at 30 C for 14 days. The suspected colonies were stained and identified by biochemical testing.

Antifungal drugs susceptibility testing

Tests were performed to amphotericin B and FLU by the broth microdilution method as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) M27-A document[13]. The testing medium was RPMI (Roswell Park Memorial Institute) 1640 with L-glutamine broth buffered pH 7.0 with morpholinepropanesulfonic acid (MOPS) buffer (0.165 M). The quality control was performed by testing *Candida parapsilosis* ATCC 22019 as the reference strain with each batch of clinical isolates. The microdilution plate tests were incubated at 35 C for 70-74 h in ambient air, and observed for the presence or absence of visible growth. For amphotericin B, the MIC was defined as the lowest concentration that prevents any discernible growth. For FLU, the MIC was defined as the lowest concentration that reduces growth by 50% relative to that of the growth control. The 50% reduction of turbidity was determined by the naked eye through comparing with 1:1 diluted growth control. All of the isolates in the present study were subcultured twice prior to FLU susceptibility testing.

Clinical data

The primary cryptococcal meningitis prophylaxis was defined as administration of FLU 400 mg/week orally at least six weeks to prevent the first episode of cryptococcal meningitis. The secondary cryptococcal meningitis prophylaxis was defined as administration of FLU 200 mg/day orally at least six weeks to prevent the second episode of cryptococcal meningitis. The medical records were retrieved and reviewed to study the demographic variables of the patients during the time of diagnosed cryptococcal meningitis including gender, age, previous opportunistic infections, baseline CD4 cell count, and %CD4. Clinical outcomes of the patients who continued to follow-up after 10 weeks of standard treatment including complete recovery, death, and relapse were studied. The standard 10-week treatment was defined as administration of amphotericin B for two weeks and followed by FLU 400 mg/day orally for an additional eight weeks. The patients were considered to have completely recovery when they were free of meningitis symptoms. A relapse was defined when the patients had recurrent meningitis after initial clinical response and/or positive CSF culture after ten weeks of treatment. The CSF isolates recovered from the patients who did not receive fluconazole prophylaxis were defined as group A. The isolates from the patients who received either primary or secondary FLU prophylaxis

were defined as group B. All patients in group B had breakthrough cryptococcal meningitis while taking FLU prophylaxis.

Statistical methods

The medians (range) and frequencies (%) were used to describe the patient characteristics in both treatment groups. The comparisons were performed using the Mann-Whitney U test for the continuous data, and the Chi-square test of Fishers' exact test where appropriate for the categorical data. The comparisons of the MICs were performed using the Mann-Whitney U test. The relative risk and its 95% confidence interval (CI) for the clinical outcomes between the two groups were determined. A P-value of less than 0.05 was considered statistically significant.

Results

98 clinical *C. neoformans* isolates were obtained from the CSF specimens, 80 (82%) isolates were recovered from the CSF of HIV-infected patients who did not receive fluconazole prophylaxis (group A) and 18 (18%) isolates were recovered from the CSF of HIV-infected patients who received either primary or secondary FLU prophylaxis (group B). The median (range) time of FLU prophylaxis was 217 (42-537) days in group B. Among 18 isolates in group B, nine isolates were recovered from HIV-infected patients who received primary and secondary prophylaxis equally. The baseline characteristics described between the two groups are shown in Table 1. The patients in group B had a higher proportion of previous opportunistic infections (p = 0.008). The MIC distribution of FLU and amphotericin B between the two groups is shown in Fig. 1 and Fig. 2, respectively. The median (range) MIC of FLU was 8.0 (0.5-32) g/ml in group A and 6.0 (0.5-32) g/ml in group B (p = 0.926). The median (range) MIC of amphotericin B was 0.25 (0.03-1.0) g/ml in group A and 0.25 (0.12-1.0) g/ml in group B (p = 0.384). For the MIC of FLU in group B, there was no difference between nine isolates from the patients who received primary and secondary prophylaxis (The median (range) MIC of 4.0 (0.5-32) g/ml in primary prophylaxis group and 8.0 (1-32) g/ml in secondary fluconazole prophylaxis group). The distributions of the number of patients in different MIC levels of FLU are shown in Fig. 3. Twenty-six (32.5%) isolates in group A and six (33.3%) isolates in group B had MIC of FLU equal or greater than 16 g/ml. There was no significant difference between the two groups (p = 0.946).

Twenty-four patients were referred or lost to follow-up during ten weeks of standard treatment. Sixty patients in group A, and fourteen patients in group B had continued to follow-up until ten weeks of treatment. The clinical outcomes after ten weeks of treatment are shown in Table 2. Overall, 39 (65%) patients in group A, and seven (50%) patients in group B had complete recovery (p = 0.364; RR = 0.538, 95%CI =

Table 1. Baseline characteristics of 98 study patients

Characteristics	Fluconazole prophylaxis		*p* value
	Group A (n = 80)	Group B (n = 18)	
Sex			0.604
Male	54 (67.5%)	11 (61.1%)	
Female	26 (32.5%)	7 (38.9%)	
Median age, years (range)	34.0 (22-63)	34.0 (24-47)	0.566
Median CD4 count, cells/mm^3 (range)	14.5 (3-71)	9.0 (1-137)	0.506
Median % CD4 (range)	2.0 (1-9)	1.0 (0-6)	0.091
Previous opportunistic infections			0.008
PCP	4 (5.0%)	2 (11.1%)	
TB	13 (16.3%)	9 (50.0%)	
CMV retitnitis	1 (1.3%)	0 (0%)	
PCP and CMV infection	1 (1.3%)	0 (0%)	
TB and CMV infection	1 (1.3%)	0 (0%)	
TB and toxoplasmosis	0 (0%)	1 (5.6%)	

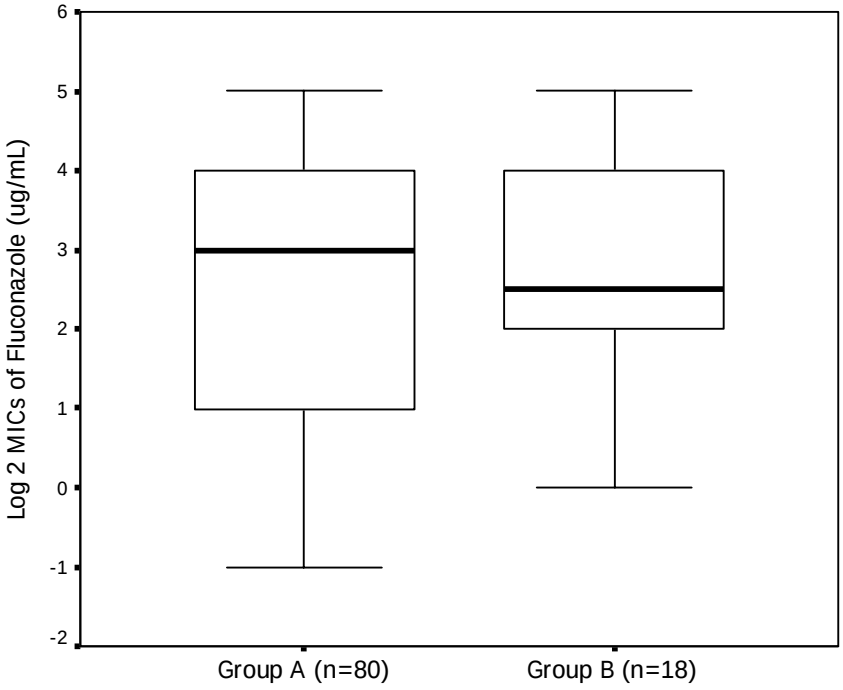

Fig. 1 Distribution of MICs of fluconazole between the two groups

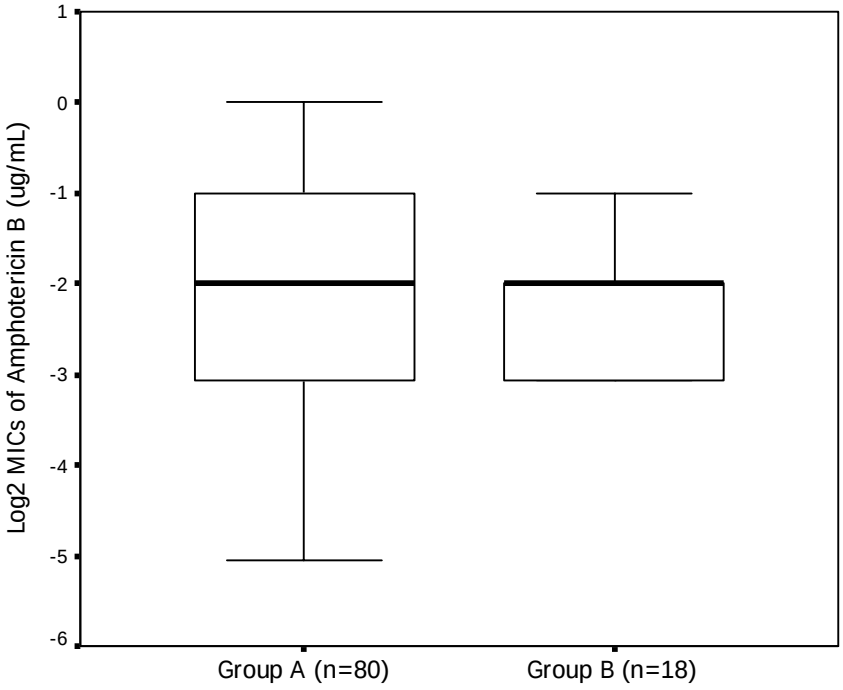

Fig. 2 Distribution of MICs of amphotericin B between the two groups

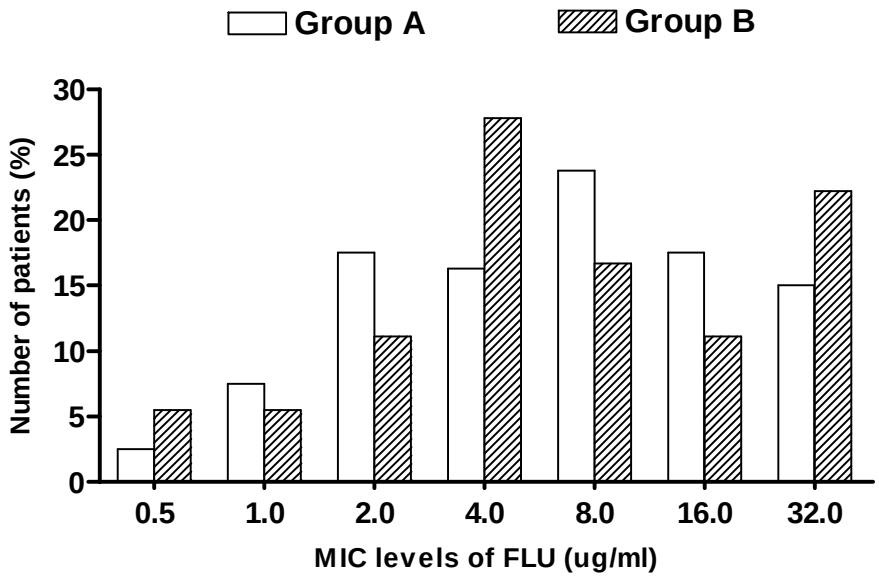

Fig 3. Distributions of number of patients in different MIC levels of FLU

Table 2. Clinical outcomes after ten weeks of standard treatment in 74 patients

Clinical outcomes	Fluconazole prophylaxis		*p* value	Relative risk, 95% confidence interval
	Group A (n = 60)	Group B (n = 14)		
Complete recovery				
Yes	39 (65.0%)	7 (50.0%)	0.364	0.538, 0.166-1.742
No	21 (35.0%)	7 (50.0%)		
Recurrent meningitis				
Yes	7 (11.7%)	0 (0%)*	1.000	0.582, 0.066-5.159
No	53 (88.3%)	14 (100%)		
Death				
Yes	14 (23.3%)	7 (50.0%)	0.096	3.286, 0.983-10.979
No	46 (76.7%)	7 (50.0%)		

* Substitute calculate 0 as 1

0.166-1.742). The overall mortality rate was fourteen (23%) in group A and seven (50%) in group B, (p = 0.096; RR = 3.286, 95%CI = 0.983-10.979).

Discussion

The authors conducted a retrospective cohort study to compare the MIC of FLU and amphotericin B among the CSF *C. neoformans* isolates of HIV-infected patients diagnosed with cryptococcal meningitis and clinical outcomes between those who did or did not receive FLU prophylaxis. The authors found that both median MIC of FLU and amphotericin B were not different between the two groups. The present results are consistent with the trends of FLU susceptibility that were isolated in the United States[14] and some countries in Asia[15]. In the present study, approximate 30% of patients in both groups had MICs of FLU equal or greater than 16 μg/ml. To date, the absolute MIC break point of FLU for *C. neoformans* is not determined.

Although it is clear that relapses of cryptococcosis in HIV-infected patients are often associated to a deterioration of the host immune status rather than

to changes in the FLU MICs[16], some published case reports demonstrate the potential for variation in the FLU MICs and indicate that FLU resistance can develop during treatment in some patients[16-18]. As shown in the baseline characteristics, the patients in the present study had a very severe immunosuppressed condition due to very low CD4 cell count and previous major opportunistic infections. To date, there have been a handful of published reports of the emergence of resistance to FLU during secondary prophylaxis[7,19,20]. Some evidence demonstrated that the high or rising MICs of FLU is sometimes associated with treatment failure in HIV-infected persons with cryptococcosis[7,19,20]. In the present study, the majority of cryptococcal isolates from the patients who had a history of FLU prophylaxis remain susceptible in vitro to FLU, nevertheless, continue surveillance for emerging resistance may be warranted.

Regarding the clinical outcomes at ten weeks of treatment; complete recovery, mortality rate, and recurrent meningitis were not different between both study groups. The reasons that might explain these results are that the cryptococcal isolates from those who had FLU prophylaxis are still susceptible to amphotericin B that were used to salvage therapy and these strains also had sustained susceptibility to fluconazole. However, there is a tendency of a higher mortality rate in the patients who received FLU prophylaxis. This may be explained by the patients in the FLU prophylaxis group having a tendency of more immunosuppressive status than patients without FLU prophylaxis.

The limitations of the present study are too small a number of patients in the FLU prophylaxis group. However, the study of a larger number of patients in this group is prohibitive due to the effectiveness of both primary and secondary prophylaxis. All of the isolates in the present study were subcultured twice prior to FLU susceptibility testing. This may influence the MICs level. A number of isolates from the patients without FLU prophylaxis has high MIC of FLU (16 and 32 g/ml). The previous history of FLU treatment of these patients could not be reviewed precisely due to limitation of retrospective study. Lastly, the serotypes of *C. neoformans* were not identified. However, there has been no significant difference in drug susceptibility among the various serotypes of *C. neoformans*[21].

In conclusion, the present results indicate that the median MICs of FLU and amphotericin B against isolates of *C. neoformans* obtained from the CSF and clinical outcomes between the HIV-infected patients who did or did not receive FLU prophylaxis were comparable. Further study with a larger number of patients and longer use of prophylaxis is needed to confirm the authors' findings. Before being available, continued surveillance for emerging resistance in this population is still needed.

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ความไวต่อยาต้านเชื้อราของเชื้อคริบโตคอคคัสนีโอฟอร์แมนที่แยกเชื้อจากน้ำไขสันหลังและการตอบสนองทางคลินิกในผู้ป่วยติดเชื้อเอชไอวีที่เป็นเยื่อหุ้มสมองอักเสบจากเชื้อคริบโตคอคคัสที่ได้รับการป้องกันและไม่ได้รับการป้องกันการติดเชื้อด้วยยาฟลูโคนาโซล

วีรวัฒน์ มโนสุทธิ, สมนึก สังฆานุภาพ, ศุภิดา ทองเย็น, นพนัฐ จำปาเทศ, บุญช่วย เอี่ยมโภคลาภ, อัญชนา ถาวรวรรณ, สุพร ฟุ้งลัดดา

วัตถุประสงค์: *เพื่อเปรียบเทียบความเข้มข้นยาฟลูโคนาโซลและยาแอมโฟเทอริซินบี การเจริญเติบโตของเชื้อราคริบโตคอคคัสนีโอฟอร์แมนที่แยกเชื้อได้จากน้ำไขสันหลังและการตอบสนองทางคลินิกของผู้ป่วยเอชไอวีที่ได้รับการวินิจฉัยว่าเป็นเยื่อหุ้มสมองอักเสบจากเชื้อราคริบโตคอคคัส*

วัสดุและวิธีการ: *ทำการศึกษาแบบย้อนหลังโดยนำเชื้อราคริบโตคอคคัสที่แยกจากน้ำไขสันหลังของผู้ป่วยกลุ่มเอและบีระหว่างเดือนมกราคม พ.ศ. 2546 ถึง ตุลาคม พ.ศ. 2547 โดยแบ่งผู้ป่วยเป็น 2 กลุ่มคือ กลุ่มที่ไม่เคยได้รับยาฟลูโคนาโซล (กลุ่มเอ) และกลุ่มที่เคยได้รับยาฟลูโคนาโซลขนาด 400 มก./สัปดาห์ เพื่อการป้องกันแบบปฐมภูมิ หรือ 200 มก./วัน เพื่อการป้องกันแบบทุติยภูมิ (กลุ่มบี)*

ผลการศึกษา: *สามารถทำการแยกเชื้อได้ 98 ตัวอย่าง แบ่งเป็นกลุ่มเอจำนวน 80 ตัวอย่าง และกลุ่มบีจำนวน 18 ตัวอย่าง ลักษณะพื้นฐานทางคลินิกของผู้ป่วยทั้ง 2 กลุ่มไม่มีความแตกต่างกัน ผู้ป่วยกลุ่มบีมีสัดส่วนของการติดเชื้อฉวยโอกาสก่อนหน้ามากกว่า (ค่าพี = 0.008) ค่าพิสัย (ค่าต่ำสุด-ค่าสูงสุด) ของความเข้มข้นของยาฟลูโคนาโซลต่ำสุดที่สามารถยับยั้งการเจริญของเชื้อได้ในกลุ่มเอมีค่าเท่ากับ 8.0 (0.5-32.0) ไมโครกรัม/มล. และในกลุ่มบีมีค่าเท่ากับ 6.0 (0.5-32.0) ไมโครกรัม/มล. (ค่าพี = 0.926) ค่าพิสัย (ค่าต่ำสุด-ค่าสูงสุด) ของความเข้มข้นของยาแอมโฟเทอริซินบีต่ำสุด ที่สามารถยับยั้งเชื้อได้ในกลุ่มเอมีค่าเท่ากับ 0.25 (0.03-1.0) ไมโครกรัม/มล. และกลุ่มบีมีค่าเท่ากับ 0.25 (0.12-1.0) ไมโครกรัม/มล. (ค่าพี = 0.384) มีผู้ป่วยกลุ่มเอจำนวน 60 ราย และกลุ่มบีจำนวน 14 ราย ได้รับการรักษาและติดตามการรักษาต่อเนื่อง ภายหลังการรักษา 10 สัปดาห์พบว่า ผู้ป่วยกลุ่มเอ 39 ราย จาก 60 ราย (65%) และผู้ป่วยกลุ่มบี 7 ราย จาก 14 ราย (50%) หายขาด (ค่าพี = 0.364, RR = 0.538, 95%CI = 0.166-1.742) ผู้ป่วยกลุ่มเอและกลุ่มบีมีการเสียชีวิตคิดเป็น 14 รายจาก 60 ราย (23.3%) และ 7 ราย จาก 14 ราย (50%) ตามลำดับ (ค่าพี = 0.096; RR = 3.286, 95%CI = 0.983-10.979)*

สรุป: *ไม่พบความแตกต่างของความเข้มข้นต่ำสุดของยาฟลูโคนาโซลและยาแอมโฟเทอริซินบีที่สามารถยับยั้งการเจริญของเชื้อราคริบโตคอคคัสนีโอฟอร์แมนที่เพาะได้จากน้ำไขสันหลังและผลการตอบสนองทางคลินิกระหว่างผู้ป่วยเอชไอวีที่ได้รับและไม่ได้รับยาฟลูโคนาโซลเพื่อการป้องกันการติดเชื้อรา*