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Amphotericin B Colloidal Dispersion is Efficacious and Safe for the Management of Talaromycosis in HIV-Infected Patients: Results of a Retrospective Cohort Study in China

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Background: Amphotericin B deoxycholate (AmB-D) have potential toxic effects in the treatment of talaromycosis, and high-quality, non-generic liposomal AmB (L-AMB) is still inaccessible in many regions of China. As such, the efficacy and safety of alternative drugs warrant further investigation for the management of talaromycosis. This study aimed to compare the efficacy and safety of Amphotericin B Colloidal Dispersion (ABCD) and AmB-D for the treatment of talaromycosis in a retrospective cohort of HIV-infected patients.

Methods: This was a retrospective study and the data of HIV-infected patients with talaromycosis who received ABCD or AmB-D from January 2018 to December 2022, were retrospectively collected and analyzed. We compared the efficacy and safety of the two antifungal drugs.

Results: Overall, 38 patients receiving ABCD and 33 patients receiving AmB-D were included. The conversion rates to fungal negativity at one week post-treatment were 86.84% (33/38) in the ABCD group and 90.09% (30/33) in the AmB-D group, which reached 100.00% in both groups at two weeks post-treatment. A higher symptom remission rate was observed at two weeks in the ABCD group compared with the AmB-D group (94.74% vs 75.76%; p=0.003). Additionally, the serum creatinine level significantly increased from baseline in the AmB-D group, whereas it did not increase significantly in the ABCD group. Furthermore, significantly fewer patients discontinued antifungal treatment due to drug intolerance in the ABCD group, and the incidences of leukopenia and elevated creatinine levels were lower in the ABCD group compared with the AmB-D group.

Conclusion: ABCD has a clinical efficacy comparable to AmB-D, with higher symptom remission rate, lower nephrotoxicity, and lower bone marrow suppression, indicating that ABCD may be an appropriate alternative option for the clinical management of talaromycosis.

Keywords: talaromycosis, human immunodeficiency virus, amphotericin B deoxycholate, amphotericin B colloidal dispersion, efficacy, safety

Introduction

Talaromycosis (formerly known as penicilliosis) is an invasive fungal disease caused by the dimorphic *Talaromyces marneffei* (TM) (formerly *Penicillium marneffei*) fungal organism. Talaromycosis is endemic in northern Thailand, Vietnam, Myanmar, and southern China including Hong Kong and Taiwan, and northeastern India.[1] The disease mainly affects people living with HIV (PLWH), especially those with advanced HIV disease or those with a $CD4^+$ T-lymphocyte cell count of <100 cells/μL.[2–4] The common clinical presentations of patients with advanced HIV disease include fever, weight loss, hepatosplenomegaly, lymphadenopathy, respiratory, and gastrointestinal symptoms.[5] However, the preceding manifestations are non-specific, and are indistinguishable from the clinical features of disseminated tuberculosis,

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systemic mycoses, or infections caused by intracellular pathogens such as *Salmonella* species. Recently, talaromycosis has been listed as the third most common HIV-associated opportunistic infection, after tuberculosis and cryptococcal meningitis.[6] Without timely diagnosis and effective antifungal therapy, the risk of mortality from talaromycosis is up to 50%,[7] and can be reduced to approximately 10–20% if appropriate antifungal drugs are prescribed timeously.[8]

Currently, amphotericin B deoxycholate (AmB-D) is recommended as the initial antifungal treatment for TM infection, and is generally an effective therapeutic option.[9] However, the clinical applications of AmB-D are greatly limited due to its high toxicity and the occurrence of frequent adverse effects. Botero Aguirre JP et al, reported that over 80% of patients developed varying degrees of renal impairment during AmB-D treatment.[10] Additionally, kidney disease is a common complication in PLWH,[11] and administering AmB-D to individuals with renal compromise may further damage the kidney, leading to irreversible renal damage and renal failure.[12,13] Therefore, the application of AmB-D as induction therapy is limited by the risk of renal injury and other safety concerns in PLWH with talaromycosis. Although liposomal amphotericin B (L-AmB) is as effective as AmB-D for fungal infections and is associated with less infusion-related toxicity and less nephrotoxicity,[14,15] only generic, locally-manufactured L-AmB is available in most part of China, especially under developed regions. Past evidence has shown that generic L-AmB made in China is not advantageous over AmB-D in terms of nephrotoxicity.[16] Given the toxic effects of AmB-D and the overall unavailability of original L-AmB in China, it is necessary to investigate whether other amphotericin B formulations are effective and safe for this fatal disease.

Amphotericin B Colloidal Dispersion (ABCD) is a disk-shaped nanoparticle colloidal dispersion formed by amphotericin B and sodium cholesteryl sulfate at a molecular molar ratio of 1:1. Sodium cholesteryl sulfate binds to amphotericin B, thereby reducing the binding of amphotericin B to cholesterol in human cell membranes.[17] Additionally, ABCD is rapidly absorbed by the liver, spleen, lungs, and other organs of the reticuloendothelial system after entering the blood, resulting in diminished kidney distribution and thus a lower likelihood of renal tubular damage.[18] Evidence has shown that ABCD is effective and safe for patients who experienced renal insufficiency or nephrotoxicity during previous AmB-D treatment.[19] In 2021, ABCD was approved as an antifungal medicine for patients with invasive fungal infections in China, and is particularly suitable for those who fail to tolerate or respond to AmB-D. Our previous study demonstrated that AmB-D had similar efficacy to voriconazole in HIV-infected patients with talaromycosis, and contributed to earlier fungal clearance and earlier clinical resolution of symptoms.[20] However, there is a scarcity of data with regards to the efficacy and safety of ABCD use in patients with talaromycosis. In the present study, we retrospectively compared the efficacy and safety of ABCD and AmB-D when used in the treatment of advanced HIV-infected patients with talaromycosis, aiming to provide valid evidence for the clinical application of ABCD.

Patients and Methods

Study Design

This is a retrospective cohort study. We retrospectively collected data of HIV-infected patients with talaromycosis seen at Chongqing Public Health Medical Center, China, from January 2018 to December 2022. We then analyzed the differences in efficacy and safety between patients receiving ABCD and those receiving AmB-D for induction antifungal therapy. This study was approved by the Ethics Committee of Chongqing Public Health Medical Center (2022-043-01-KY) and informed consent was waived owing to the retrospective nature of this investigation. Written informed consent was obtained from the patient for publication of the Figure 1.

Eligibility for Patient Inclusion

Data of all HIV-positive patients diagnosed with talaromycosis and who received ABCD or AmB-D treatment were screened. The diagnosis of talaromycosis was based on the culture-proven of the TM from blood, bone marrow, or other supposedly sterile body fluid samples. The identification of TM was established on the basis of the observation of the morphological characteristics of the mycelia and spores of the culture colony.[21] Patients who had at least one body fluid sample culture result after antifungal treatment was initiated and who completed at least one two-week follow up were

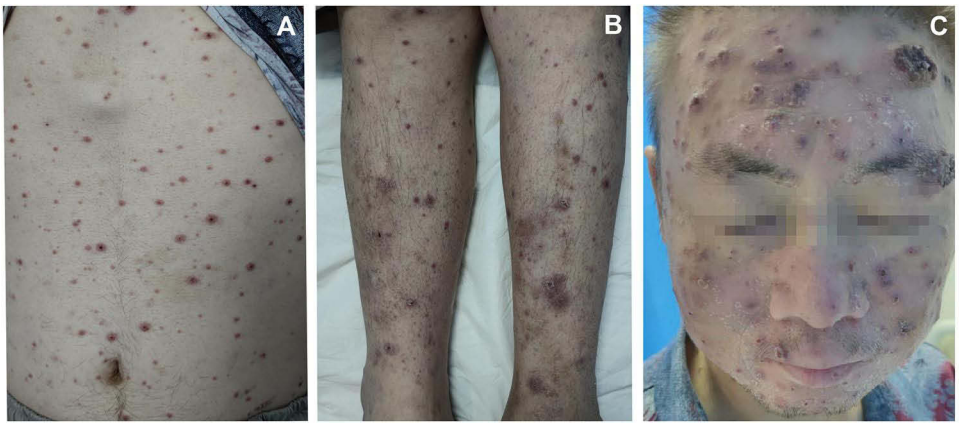

Figure 1 Typical skin lesions caused by *Talaromyces marneffei*, distributed on the abdomen (**A**), extremities (**B**), and face (**C**).

included for analysis. The data of those individuals who did not have fungal culture results prior to antifungal treatment and those who did not have fungal culture results after antifungal treatment was initiated were excluded from the analysis.

Antifungal Treatment Regimens

ABCD (CSPC Ouyi Pharmaceutical Group Co., Ltd., Hebei Province, China) was administered intravenously at an initial dosage of 1.0 mg/kg/d on day 1, 2.0 mg/kg/d on day 2, and 3.0 mg/kg/d for the remaining 12 days, with the total administered dose not exceeding 200 mg/d. AmB-D (North China Pharmaceutical Co., Ltd., Hebei Province, China) was administered intravenously at a dose of 0.1 mg/kg/d on day 1, 0.2 mg/kg/d on day 2, and 0.5 to 0.7 mg/kg/d for the remaining 12 days of induction therapy. All patients received oral itraconazole (200 mg twice daily for 10 weeks) as consolidation therapy following induction therapy with either ABCD or AmB-D. The dosage and duration of ABCD or AmB-D were allowed to be adjusted according to each patient's tolerance to either drug and/or on the severity of disease manifestations present in each patient.[22–24] Additionally, all patients were routinely administered oral potassium supplements (3 g/d) to prevent the occurrence of hypokalemia, and saline hydration solution to prevent nephrotoxicity.

Efficacy and Safety Assessment

Efficacy of ABCD or AmB-D was assessed by negative fungal conversion rates and symptom remission rates. Safety of the two antifungal drugs was assessed via changes in hematological laboratory results, discontinuations, and incidence of adverse events. Adverse events (AEs) caused by ABCD or AmB-D were recorded in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0), and included laboratory test results that changed from normal to abnormal during the induction antifungal treatment period, or values that deviated from baseline values.

Statistical Analysis

All data analyses were performed using SPSS software (IBM Corp, Version 25.0. Armonk, NY, USA: IBM Corp). Continuous data were tested for normality of distribution via the Shapiro–Wilk method. If data was normally distributed, the data is described as mean ± standard deviation (SD) and the comparison was analyzed using Student's *t*-test. Otherwise, medians and interquartile ranges (IQR) are used for description of data, and the Kruskal–Wallis non-parametric test was used for comparison of differences. Categorical data are expressed as percentages (%) and frequencies, and were compared via Pearson's Chi-Squared test or Fisher's exact test. Effect sizes are reported with 95% confidence intervals. Statistical significance was defined as $p < 0.05$ for all analyses.

Results

Baseline Characteristics of Patients

A total of 71 eligible patients were included in this study, among whom 38 received ABCD and 33 received AmB-D for induction antifungal therapy. All the 71 patients were confirmatively HIV-positive and tested positive for TM culture. Patient ages ranged from 19 years to 71 years, with a median age of 45.0 years in the ABCD group and 41.0 years in the AmB-D group, respectively. No differences were observed between the two groups in incident rates of bacterial pneumonia, tuberculosis, cytomegalovirus infection, and pneumocystis pneumonia, as well as in rates of physical TM infection-related disease manifestations, including fever, skin lesions (Figure 1) splenomegaly, deep lymph node enlargement, abdominal distension, and diarrhea (Figure 2). The median $CD4^+$ cell counts of the two groups of patients were 18.00 and 12.00, respectively, with no statistically significant difference between the two groups. Baseline levels of CD4/CD8, neutrophil counts, haemoglobin, platelets, creatinine, alanine transaminase (ALT) and aspartate transaminase (AST) were found to be comparable between the two groups. The blood fungal cultures were performed at baseline for all patients included in the study. The blood culture results demonstrated an organism that produced red pigment on a microbiological culture plate containing Sabouraud dextrose agar after four days of incubation at 25°C. Furthermore, the organism exhibited binary fission yeast form at 37°C. Microscopic examination of the organism confirmed the presence of *Talaromyces marneffei* infection. (Figure 3). There were no significant differences between the two groups with respect to other parameters measured. Detailed information is shown in Table 1.

Efficacy Assessment: Negative Fungal Conversion Rates and Symptom Remission Rates

The negative fungal conversion rates at one week post-treatment were 86.84% (33/38) and 90.09% (30/33) in the ABCD group and the AmB-D group, respectively, and reached 100.00% in both groups (38/38 vs 33/33) at two weeks post-treatment (Table 2). There was no significant difference in negative fungal conversion rates between the two groups at one week or at two weeks of antifungal treatment. With respect to physical TM infection-related manifestations, we observed comparable symptom remission rates at one week post-treatment in both groups (81.58% vs 78.72%; 31/38 vs

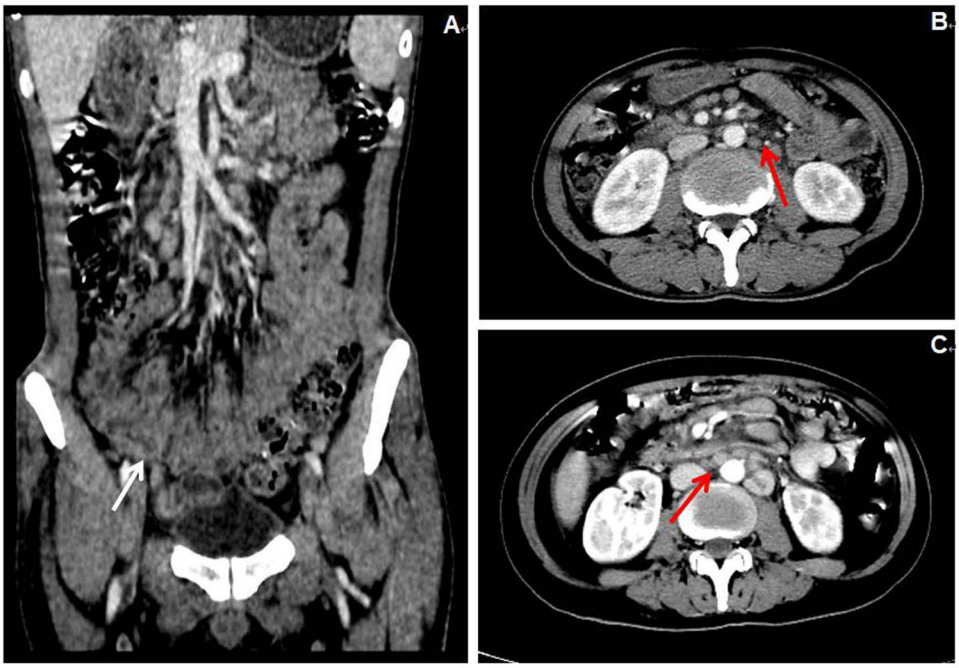

Figure 2 Enhanced abdominal CT (**A**–**C**) showing significant lymph node enlargement (red arrows) and multiple areas of thickening of the intestinal wall (white arrow).

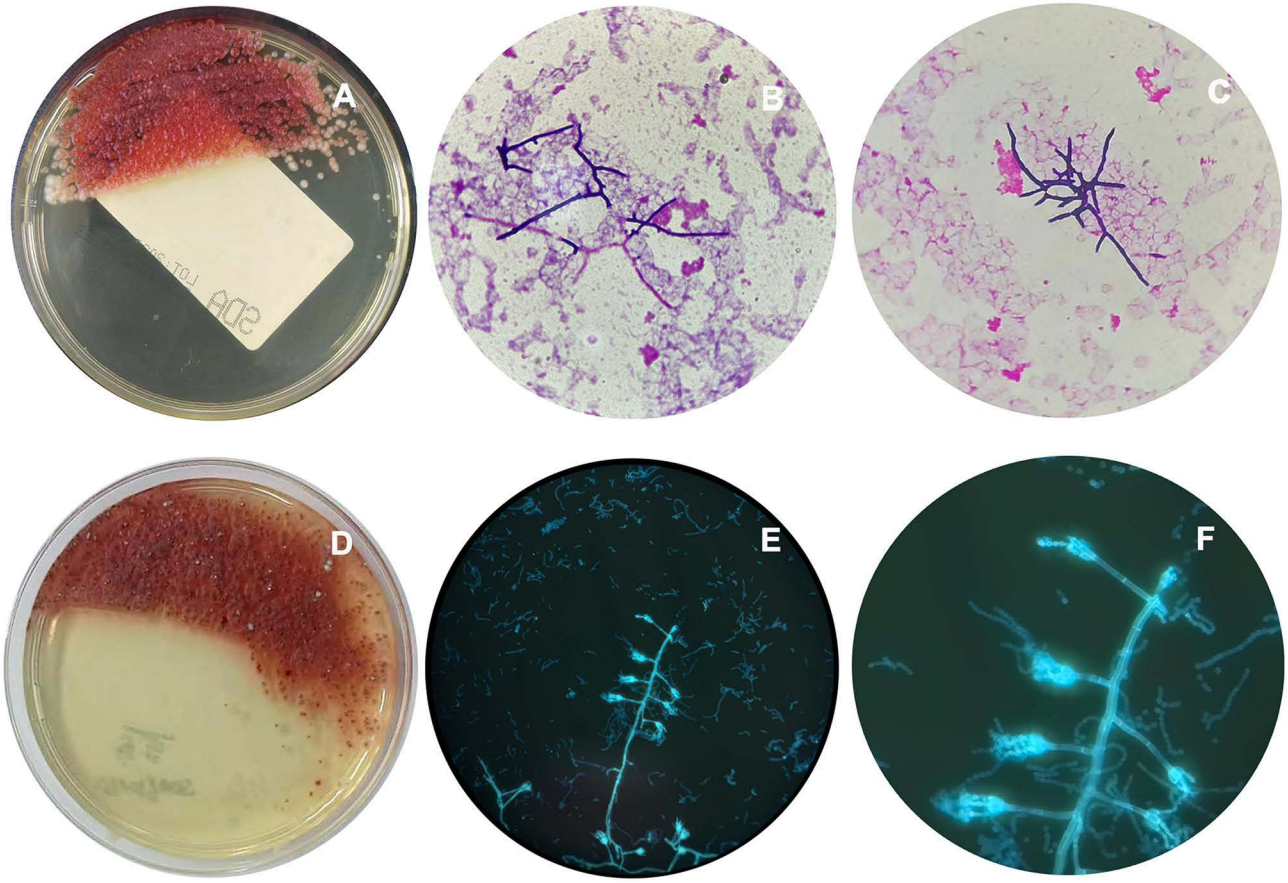

Figure 3 Colony appearance and microscopic morphology of *Talaromyces marneffei*. Blood culture results (incubated for four days at 25°C) indicated the growth of an organism that produced a red pigment on a microbiological culture plate containing sabouraud dextrose agar (**A**), and microscopic examination of the organism revealed the presence of broom-shaped *Talaromyces marneffei* strains (**B** and **C**). Magnification, ×1000. The organism exhibited a binary fission yeast form at 37°C (**D**), and microscopic examination revealed that the organism was arranged in a sausage-like pattern, mixed with hyphal-like structures (**E** and **F**). Magnification: ×1000.

26/33; p=0.775) and a higher symptom remission rate at two weeks post-treatment in the ABCD group, compared with the AmB-D group (94.74% vs 75.76%; 36/38 vs 25/33; p=0.003; Table 2).

Safety Assessment: Changes in Laboratory Parameters During Treatment

Table 3 and 4 show the hematological test results of patients in the two groups at baseline and at different time points after treatment. Median platelet levels in the ABCD group significantly decreased after one week of antifungal treatment compared to pre-treatment levels (67.00 vs 99.00, p=0.026), but improved in the ABCD group after another week of treatment (107.00 vs 99.00, p=0.380). No decrease in median platelet levels was observed in the AmB-D group. Both red

Table 1 Baseline Characteristics of Included Patients

Variables	ABCD Group (n=38)	AmB-D Group (n=33)	*p*-Value
Age (years), Median (IQR)	45.00 (35.00, 52.25)	41.00 (29.00, 49.50)	0.068
Gender, no. (%)			0.782
Male	30.00 (78.95)	25.00 (75.76)	
Female	8.00 (21.05)	8.00 (24.24)	
Body weight (kg), Median (IQR)	50.00 (45.00, 559.50)	49.00 (45.00, 57.25)	0.706
Body temperature (°C), Median (IQR)	38.5 (36.80, 39.15)	37.80 (36.80, 39.10)	0.711

(*Continued*)

Table 1 (Continued).

Variables	ABCD Group (n=38)	AmB-D Group (n=33)	*p*-Value
Complications*, no. (%)			0.360
No	8.00 (21.05)	4.00 (12.12)	
Yes	30.00 (78.95)	29.00 (87.88)	
Bacterial pneumonia	20.00 (52.63)	15.00 (45.45)	0.637
Tuberculosis	4.00 (10.53)	3.00 (9.09)	>0.999
Cytomegalovirus viremia	8.00 (21.05)	3.00 (9.09)	0.202
Pneumocystis pneumonia	4.00 (10.53)	1.00 (3.03)	0.363
Symptoms*, no. (%)			
Fever	28.00 (73.68)	23.00 (69.70)	0.794
Skin lesions	4.00 (10.53)	2.00 (6.06)	0.679
Splenomegaly	21.00 (55.26)	14.00 (42.42)	0.344
Deep lymph node enlargement	26.00 (68.42)	17.00 (51.52)	0.223
Abdominal bloating	12.00 (31.58)	5.00 (15.15)	0.163
Diarrhea	5.00 (13.16)	4.00 (12.12)	>0.999
Laboratory data, Median (IQR)			
$CD4^+$ cell count (cells/μL)	18.00 (10.50, 29.00)	12.00 (8.00, 24.00)	0.253
CD4/CD8	0.10 (0.06, 0.19)	0.08 (0.05, 0.16)	0.399
Neutrophil count, (10^9/L)	2.64 (1.56, 3.51)	1.91 (1.47, 3.16)	0.289
Hemoglobin, (g/L)	83.50 (70.75, 98.00)	81.00 (71.25, 94.50)	0.709
Platelets, (10^9/L)	99.00 (43.50, 145.00)	106.50 (48.25, 168.75)	0.572
Creatinine, (μmol/L)	63.10 (47.28, 79.52)	55.65 (47.82, 67.20)	0.197
ALT, (IU/L)	41.00 (22.75, 74.50)	49.00 (30.25, 73.25)	0.633
AST, (IU/L)	108.00 (52.25, 193.25)	101.00 (58.50, 187.25)	0.988
Serum Mp1p antigen detection, no. (%)			0.136
Not detected	2.00 (5.26)	3.00 (9.09)	
Positive	31.00 (81.58)	20.00 (60.61)	
Negative	5.00 (13.16)	10.00 (30.30)	

Note: *An individual patient may have multiple complications and symptoms.
Abbreviations: ABCD, Amphotericin B Colloidal Dispersion; AmB-D, Amphotericin B deoxycholate; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

Table 2 Negative Fungal Conversion Rates and Symptom Remission Rates in Both Groups

Variables, No. (%)	ABCD Group (n=38)	AmB-D Group (n=33)	*p*-Value
Negative fungal conversion rate (1 week)	33/38 (86.84)	30/33 (90.09)	>0.999
Negative fungal conversion rate (2 weeks)	38/38 (100.00)	33/33 (100.00)	-
Symptom remission rate (1 week)	31/38 (81.58)	26/33 (78.72)	0.775
Symptom remission rate (2 weeks)	36/38 (94.74)	25/33 (75.76)	0.003

Abbreviations: ABCD, Amphotericin B Colloidal Dispersion; AmB-D, Amphotericin B deoxycholate.

blood cell counts and hemoglobin levels decreased significantly in both groups after one week and two weeks of antifungal treatment, compared to pre-treatment levels ($p<0.001$).

No increase in liver function indices was observed in either of the two groups. Indeed, AST levels, ALT levels, and total bilirubin levels were observed to be lower both at week one and week two compared to baseline levels. Additionally, none of the differences in the changes in liver function test results (compared with baseline levels) were observed to be statistically significantly different between the two groups.

The median serum creatinine levels in the ABCD group was significantly lower after one week of treatment compared to baseline levels (52.80 μmol/L vs 63.10 μmol/L, $p<0.001$), and there was no significant change in serum creatinine levels at week one in the AmB-D group compared to baseline levels. However, serum creatinine levels in the AmB-D

Table 3 Results of Laboratory Parameters in Both Groups at Baseline, Week 1, and Week 2

Variables	Baseline (n_{ABCD}=38, $n_{AmB\text{-}D}$=33)	Week 1 (n_{ABCD}=35, $n_{AmB\text{-}D}$=33)	p_1-Value*	Week 2 (n_{ABCD}=32, $n_{AmB\text{-}D}$=23)	p_2-Value#
Red blood cells (10^12/L), Median (IQR)					
ABCD	2.98 (2.74, 3.51)	2.49 (2.22, 3.13)	<0.001	2.53 (2.11, 2.75)	<0.001
AmB-D	2.83 (2.61, 3.47)	2.45 (2.17, 3.02)	<0.001	2.22 (2.02, 2.81)	<0.001
Hemoglobin (g/L), Median (IQR)					
ABCD	83.50 (70.75, 98.00)	70.00 (60.00, 83.00)	<0.001	67.00 (61.25, 76.00)	<0.001
AmB-D	81.00 (71.25, 94.50)	70.00 (63.00, 82.50)	<0.001	69.00 (58.00, 76.00)	<0.001
Platelets (10^9/L), Median (IQR)					
ABCD	99.00 (43.50, 145.00)	67.00 (48.00, 105.50)	0.026	107.00 (80.50, 138.00)	0.380
AmB-D	106.50 (48.25, 168.75)	116.00 (68.00, 187.50)	0.123	120.00 (85.00, 151.00)	0.142
ALT (IU/L), Median (IQR)					
ABCD	41.00 (22.75, 74.50)	41.00 (27.00, 87.00)	0.156	25.50 (20.08, 78.50)	0.761
AmB-D	49.00 (30.25, 73.25)	42.00 (22.50, 64.50)	0.362	37.50 (16.00, 62.75)	0.008
AST (IU/L), Median (IQR)					
ABCD	108.00 (52.25, 193.25)	58.00 (42.00, 118.00)	0.001	47.50 (23.13, 74.50)	<0.001
AmB-D	101.00 (58.50, 187.25)	48.00 (35.00, 88.00)	<0.001	38.50 (24.00, 56.00)	<0.001
Total bilirubin (μmol/L), Median (IQR)					
ABCD	13.35 (9.25, 20.30)	8.20 (6.40, 11.40)	<0.001	8.05 (6.30, 11.10)	<0.001
AmB-D	13.10 (9.40, 19.90)	8.70 (6.00, 13.65)	<0.001	8.55 (6.45, 17.30)	0.006
Serum creatinine (μmol/L), Median (IQR)					
ABCD	63.10 (47.28, 79.53)	52.80 (45.10, 65.00)	<0.001	57.00 (46.20, 67.70)	0.354
AmB-D	55.65 (47.83, 67.20)	54.10 (45.80, 67.65)	0.485	69.10 (53.25, 101.35)	0.007
Potassium (mmol/L), Median (IQR)					
ABCD	3.76 (3.33, 4.03)	3.73 (3.33, 4.18)	0.477	3.75 (3.20, 4.26)	0.522
AmB-D	3.76 (3.33, 4.03)	3.71 (3.43, 4.21)	0.117	3.85 (3.22, 4.13)	0.810

Notes: *p_1 represents the intra-group comparison of laboratory indicators with baseline indicators at 1 week of treatment; #p_2 represents the intra-group comparison of laboratory indicators with baseline indicators at 2 weeks of treatment.

Abbreviations: ABCD, Amphotericin B Colloidal Dispersion; AmB-D, Amphotericin B Deoxycholate; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

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Table 4 Changes in Laboratory Parameters from Baseline at Week 1 and Week 2 in Both Groups

Variables	Week 1 (n_{ABCD}=35, $n_{AmB\text{-}D}$=32)		Week 2 (n_{ABCD}=31, $n_{AmB\text{-}D}$=23)	
	Change From baseline (Δ)	p_1-Value*	Change From baseline (Δ)	p_2-Value#
Red blood cells (10^12/L), Median (IQR)		0.335		0.196
ABCD	−0.50 (−0.71, −0.22)		−0.62 (−0.93, −0.37)	
AmB-D	−0.45 (−0.62, −0.14)		−0.60 (−0.79, −0.04)	
Hemoglobin (g/L), Median (IQR)		0.376		0.948
ABCD	−13.00 (−24.00, −6.00)		−4.00 (−9.00, 3.00)	
AmB-D	−12.00 (−16.75, −4.00)		−1.00 (−10.00, 3.00)	
Platelets (10^9/L), Median (IQR)		0.002		0.243
ABCD	−30.50 (−64.25, 7.00)		32.50 (−4.00, 47.00)	
AmB-D	13.50 (−18.75, 36.25)		10.00 (−27.00, 52.00)	
ALT (IU/L), Median (IQR)		0.167		0.778
ABCD	0.00 (−22.00, 53.00)		−14.00 (−35.00, 2.00)	
AmB-D	0.00 (−28.50, 8.25)		−15.00 (−34.25, −0.75)	
AST (IU/L), Median (IQR)		0.344		0.883
ABCD	−33.00 (−92.00, 0.00)		−19.00 (−55.00, −1.00)	
AmB-D	−49.50 (−111.00, −7.50)		−22.00 (−49.50, −5.00)	
Total bilirubin (μmol/L), Median (IQR)		0.826		0.757
ABCD	−3.70 (−8.10, −1.10)		0.00 (−1.90, 1.30)	
AmB-D	−4.40 (−7.10, −1.00)		−0.90 (−3.48, 2.20)	
Serum creatinine (μmol/L), Median (IQR)		0.002		0.013
ABCD	−6.70 (−17.20, −1.80)		1.25 (−6.70, 9.23)	
AmB-D	1.00 (−5.13, 8.18)		9.60 (1.88, 21.73)	
Potassium (mmol/L), Median (IQR)		0.087		0.250
ABCD	0.05 (−0.51, 0.36)		−0.16 (−0.45, 0.47)	
AmB-D	0.26 (−0.30, 0.79)		−0.32 (−0.84, 0.42)	

Notes: *p_1 represents the inter-group comparison of laboratory indicators with baseline indicators at 1 week of treatment; #p_2 represents the inter-group comparison of laboratory indicators with baseline indicators at 2 weeks of treatment.

Abbreviations: ABCD, Amphotericin B Colloidal Dispersion; AmB-D, Amphotericin B Deoxycholate; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

group was significantly higher at week two compared to baseline levels (69.10 μmol/L vs 55.65 μmol/L, p=0.007), whereas serum creatinine levels in the ABCD group did not increase in a statistically significant manner, even after two weeks of antifungal treatment. Additionally, the increase in serum creatinine levels from baseline was significantly lower at week two in the ABCD group than in the AmB-D group (1.25 μmol/L vs 9.60 μmol/L, p=0.013, Table 4). No significant decrease in serum potassium levels was observed in both groups when compared to baseline, and there was no significant statistical difference in changes in potassium levels during the two week treatment period between the two groups (Table 4).

Safety Assessment: Discontinuations

When considering reasons for premature treatment discontinuation, we observed that significantly fewer patients in the ABCD group discontinued antifungal treatment due to drug intolerance, compared to patients in the AmB-D group (5.26% vs 27.27%, 2/38 vs 9/33, p=0.019). Four cases in the AmB-D group discontinued antifungal treatment because of renal impairment whereas no patients discontinued treatment in the ABCD group secondary to renal impairment. Two cases in the AmB-D group switched to ABCD due to renal impairment, and renal function parameters gradually normalized after the drug regimen switch. In the AmB-D group, six patients discontinued antifungal treatment due to myelosuppression; however, no cases discontinued antifungal treatment in the ABCD group because of bone marrow suppression. Of the two discontinuations occurred in the ABCD group, one discontinuation was due to myelosuppression and the other was associated with refractory hypokalemia.

Table 5 Adverse Events in Both Groups

Adverse Events, no. (%)	ABCD Group			AmB Group			p_1-Value*	p_2-Value*
	G1-2	G3-4	Total	G1-2	G3-4	Total	Total	G3-4
Anemia	5/38 (13.16)	16/38 (42.11)	21/38 (55.26)	4/33 (12.12)	19/33 (57.58)	23/33 (69.70)	0.211	0.193
Leukopenia	9/38 (23.68)	7/38 (18.42)	16/38 (42.11)	6/33 (18.18)	18/33 (54.55)	24/33 (72.73)	0.009	0.001
Thrombocytopenia	9/38 (23.68)	9/38 (23.68)	18/38 (47.37)	6/33 (18.18)	4/33 (12.12)	10/33 (30.30)	0.142	0.209
Neutropenia	8/38 (21.05)	2/38 (5.26)	10/38 (26.32)	5/33 (15.15)	10/33 (30.30)	15/33 (45.45)	0.092	0.005
Increased alkaline phosphatase	4/38 (10.53)	0/38 (0.00)	4/38 (10.53)	6/33 (18.18)	1/33 (3.03)	7/33 (21.21)	0.215	0.465
Hypoalbuminemia	15/38 (39.47)	0/38 (0.00)	15/38 (39.47)	7/33 (21.21)	2/33 (6.06)	9/33 (27.27)	0.278	0.212
Abnormal liver function	8/38 (21.05)	1/38 (2.63)	9/38 (23.68)	6/33 (18.18)	1/33 (3.03)	7/33 (21.21)	0.804	>0.999
Elevated creatinine	0/38 (0.00)	0/38 (0.00)	0/38 (0.00)	6/33 (18.18)	0/33 (0.00)	6/33 (18.18)	0.008	-
Infusion reactions[#]	12/38 (31.58)	0/38 (0.00)	12/38 (31.58)	4/33 (12.12)	0/33 (0.00)	4/33 (12.12)	0.05	-
Nausea	1/38 (2.63)	0/38 (0.00)	1/38 (2.63)	5/33 (15.15)	0/33 (0.00)	5/33 (15.15)	0.090	-
Hypomagnesemia	3/38 (7.89)	0/38 (0.00)	3/38 (7.89)	0/33 (0.00)	1/33 (3.03)	1/33 (3.03)	0.459	-
Hypocalcemia	0/38 (0.00)	0/38 (0.00)	0/38 (0.00)	0/33 (0.00)	1/33 (3.03)	1/33 (3.03)	0.465	0.465

Notes: *p_1 and p_2 represent the inter-group comparison of the total adverse events and G3-4 adverse events, respectively. [#]The infusion reactions was defined as presence of a fever and/or chills during antifungal drug infusion.
Abbreviations: ABCD, Amphotericin B Colloidal Dispersion; AmB-D, Amphotericin B deoxycholate.

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Safety Assessment: Adverse Events Analysis

Adverse events (AEs) observed during AmB-D or ABCD treatment are summarized in Table 5. The incidence of AEs associated with leukopenia (42.11% vs 72.73%, 16/38 vs 24/33, p=0.009), and elevated creatinine levels (0.00% vs 18.18%, 0/38 vs 6/33, p=0.008) were significantly lower in the ABCD group than in the AmB-D group, respectively. In particular, among grade 3 or grade 4 AEs, the incidence of leukopenia (18.42% vs 54.55%, 7/38 vs 18/33, p=0.001) and neutropenia (5.26% vs 30.3%, 2/38 vs 10/33, p=0.005) was also significantly lower in the ABCD group than in the AmB group, respectively. However, the incidence of infusion reactions, which was defined as presence of a fever and/or chills during antifungal drug infusion, was observed to be significantly higher in the ABCD group than in the AmB-D group (31.58% vs 12.12%, 12/38 vs 4/33, p=0.05).

Discussion

The incidence of talaromyosis is closely correlated with that of HIV infection. For instance, 87.72% of talaromyosis cases occur in patients infected with HIV in mainland China.[6] It is widely acknowledged that HIV infection contributes to the development of a number of common diseases, including those affecting the bones, kidneys and liver.[25] Similarly, talaromyosis has the potential to disseminate to the liver, spleen and bone marrow.[26] This is precisely why severe leukopenia, anemia, thrombocytopenia,[27,28] and hepatic dysfunction often occur in HIV-infected patients with talaromycosis. In accordance with the established guidelines, AmB is the recommended pharmaceutical agent for the treatment of talaromyosis.[22] However, prolonged administration of AmB has been linked to the occurrence of adverse reactions, including anaemia, renal dysfunction and hypokalaemia.[29] It is therefore necessary to optimize the treatment regimens and explore the potential of new antifungal drugs. This study represents the first retrospective evaluation of the efficacy and safety of ABCD and AmB in the treatment of talaromyosis infection in HIV-positive patients.

In our retrospective cohort study, we observed that the overall efficacy of ABCD is comparable to AmB-D at one week and at two weeks post-treatment, with fungal clearance rates reaching 86.84% in the ABCD group and 90.09% in the AmB-D group after one week of treatment, and fungal clearance rates reaching 100% in both groups after two weeks of treatment. Similar to our results, Thuy Le, M.D. found that the proportion of fungemia clearance by day 8 in the formulation of AmB was more than 90%.[30] Additionally, we observed that symptom remission in the ABCD group was superior to that in the AmB-D group, particularly after two weeks of treatment. These results imply that ABCD has comparable fungicidal activity and clinical efficacy to AmB-D when used to treat talaromycosis in HIV-infected patients.

We also observed that ABCD seemed to have a superior safety profile and exhibit a lower incidence of nephrotoxicity. The results of observational studies among acquired immune deficiency syndrome patients with cryptococcal meningitis or talaromycosis who treated with AmB formulations indicate that the incidence of ABCD-related nephrotoxicity was lower than that of AmB, which is consistent with the results of our research.[31] Unsurprisingly, our results indicated that serum creatinine levels in the AmB-D group was significantly higher at week two compared to baseline levels (69.10 μmol/L vs 55.65 μmol/L, p=0.007), whereas serum creatinine levels in the ABCD group did not increase significantly even after two weeks of antifungal treatment. We also observed that the increase in serum creatinine levels from baseline was significantly lower at week two in the ABCD group than in the AmB-D group. Further, we observed that four patients in the AmB-D group discontinued antifungal treatment secondary to renal impairment, whereas no patients in the ABCD group discontinued treatment due to renal impairment, and that two patients in the AmB-D group switched to ABCD due to renal impairment. Renal functional parameters in the two patients gradually reverted to normal after regimen switch. This finding suggests that deterioration in renal function is generally a dose limiting factor for AmB,[32] thus ABCD may be useful in these settings owing to its superior safety profile.

Notably, ABCD was observed to have a less severe impact on bone marrow functional parameters. We observed that the incidence of leukopenia was significantly lower in the ABCD group compared to the AmB-D group, and this was especially true for grade 3 or grade 4 leukopenia and neutropenia. Six cases in the AmB-D group discontinued antifungal treatment due to myelosuppression, whereas no patients in the ABCD group discontinued antifungal treatment due to myelosuppression. These results suggest that for patients with underlying bone marrow dysfunction, ABCD may be a better choice to decrease adverse effects and improve outcomes. One patient discontinued the treatment due to

refractory hypokalaemia, which highlights the necessity for immediate supplementation with electrolytic potassium upon the commencement of an AmB and its derivatives.

We observed that ABCD was more likely to result in infusion-associated reactions, such as fever and chills, which is consistent with the results of other studies.[30,31] The observed increase in infusion-related toxic adverse reactions in patients treated with ABCD may be attributed to the upregulation of IL-1β protein synthesis and the concomitant decrease in IL-1ra levels.[33] Additionally, such reactions were mostly mild or moderate, and fever and/or chills resolved quickly after a single dose of dexamethasone. None of the patients in either treatment group discontinued treatment as a consequence of fever or chills.

We acknowledge that our study has limitations. Our study was a retrospective study, and consequently, some data was incomplete, and evaluation of clinical symptom remission relied on past medical records, which may have introduced a degree of bias into the assessment results. Another limitation is that our sample size was relatively small. However, our results provide useful data for the therapeutic use of ABCD in the clinical management of HIV-associated talaromycosis. A multicentre prospective study will be conducted in the future to further validate the findings of this study.

Conclusion

In summary, we compared the efficacy and safety of ABCD and AmB-D in a cohort of HIV-infected patients with talaromycosis and found that ABCD had comparable clinical efficacy, a higher symptom remission rate, lower nephrotoxicity, and lower bone marrow suppression compared to AmB-D, indicating that ABCD is an appropriate alternative induction option for the clinical management of talaromycosis.

Abbreviations

AmB-D, Amphotericin B deoxycholate; L-AMB, liposomal AmB; ABCD, Amphotericin B Colloidal Dispersion; TM, Talaromyces marneffei; AEs, Adverse events; SD, standard deviation; IQR, interquartile ranges; ALT, alanine transaminase; AST, aspartate transaminase.

Data Sharing Statement

All data generated or analyzed is included in this published article.

Institutional Review Board Statement

This study was approved by the Ethics Committee of Chongqing Public Health Medical Center.

Informed Consent Statement

Patient consent was waived due to the retrospective nature of the study. Written informed consent was obtained from the patient for publication of the Figure 1.

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Disclosure

The authors declare no conflict of interest.

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