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Galactomannan Antigenemia among People Living with HIV: An Observational Study in Taiwan, 2009–2019

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How To Cite: Yang, C.-J.; Kuo, Y.-W.; Tsai, M.-S.; et al. Galactomannan Antigenemia among People Living with HIV: An Observational Study in Taiwan, 2009–2019. *eMicrobe* **2025**, *1*(1), 4. https://doi.org/10.53941/emicrobe.2025.100004.

Received: 12 June 2025
Revised: 22 August 2025
Accepted: 25 August 2025
Published: 8 September 2025

Abstract: Objectives: The clinical impact of elevated serum galactomannan (GM) in HIV treatment-naïve patients is unclear. We evaluated the prevalence and significance of GM antigenemia in people with HIV (PLHIV) in a talaromycosis-endemic area. Methods: From January 2009 to August 2019, we tested GM levels within a week of HIV diagnosis and reviewed initial medical records. Using a 1:1 case-control method, we matched GM-positive patients with controls to explore risk factors. We monitored GM levels in 81 patients to assess seroconversion. Results: Among 929 HIV/AIDS patients, 72 (7.8%) had positive GM tests with a median CD4 count of 324 cells/μL. None developed aspergillosis or talaromycosis after three months, and no deaths occurred during a one-year follow-up. Positive HAV (p = 0.011) and HCV (p = 0.012) serology were significantly associated with antigenemia. Patients with CD4 counts < 50 cells/μL had higher GM levels. Of 81 patients monitored, only one remained GM-positive after 1701 days. None of the initially negative patients seroconverted. Conclusions: GM antigenemia is common in PLHIV in Taiwan, but did not lead to disease after antiretroviral therapy. Continuous monitoring is preferable to immediate antifungal treatment.

Keywords: galactomannan antigen test; human immunodeficiency virus; acquired immunodeficiency syndrome; talaromycosis

1. Introduction

Galactomannan (GM), a mannoprotein found in the cell walls of certain fungi, serves as a reliable diagnostic marker for invasive aspergillosis [1–3]. It has been extensively used for the detection and management of invasive aspergillosis because of its high sensitivity and specificity [1,4,5]. However, the reliability of the GM testing is occasionally threatened by factors that can precipitate false-positive results, such as the administration of particular antibiotics, blood products, intravenous immunoglobulin (IVIG), and potential cross-reactivity with other fungal infections [6–9]. These factors can compromise the accuracy of GM testing, requiring careful attention and scrutiny when interpreting GM test results.

In our previous studies, we showed that serum GM frequently rises in HIV-positive patients with talaromycosis and may persist for weeks [10,11]. We observed that a significant 73.3% of patients with culture-proven talaromycosis had considerably elevated GM optical density indices (GM ODI), compared to 13.6% with cryptococcosis and a mere 9% without any fungal infection [10]. Furthermore, we observed that GM antigenemia

persisted for an extended period in follow-up cases, even in the absence of clinical symptoms [11]. Persistent antigenemia has also been observed during follow-up despite clinical stability, suggesting delayed clearance and underscoring the need to clarify its clinical significance in people living with HIV (PLHIV).

In Taiwan, talaromycosis is uncommon among PLHIV (0.7–3.1%), lower than reported in southern China (12.5–26.5%), Vietnam (~6.9%), and Thailand (~3.9%) [12–15]. Because timely diagnosis is critical, the role of serum GM as a screening tool for early detection of talaromycosis in PLHIV remains uncertain. We therefore conducted a prospective study measuring baseline GM at initial evaluation and longitudinally following a subset of patients to assess persistence, symptoms, and outcomes. This allowed us to observe antigenemia persistence, symptom recording, and outcome tracking. We also performed a 1:1 case–control comparison of GM-positive and GM-negative patients to identify associated conditions. This study aims to explore the influence of GM antigenemia on the prognosis of PLWHIV, particularly in regions where talaromycosis is endemic. The findings could contribute significantly to identifying PLWHIV at a heightened risk of developing GM antigenemia, thereby enhancing their management.

2. Materials and Methods

2.1. Settings and Study Design

We prospectively measured serum GM levels in all adult PLWHIV admitted for initial HIV evaluation at Far Eastern Memorial Hospital, a 1200-bed tertiary hospital in New Taipei City, from January 2009 to August 2019. Inclusion criteria were patients aged ≥20 years with confirmed HIV, and we excluded those unable to provide consent. We collected demographic data, baseline lab results, co-infections, and one-year outcomes. To identify risks associated with GM antigenemia, we conducted a 1:1 case-control study, selecting a negative case randomly for each positive case within the same month. Follow-up GM testing was also conducted in willing patients during 2019–2020. We followed participants for one year, as immune function generally recovers within 12 months of combination antiretroviral therapy (cART) initiation, and most unmasking immune reconstitution inflammatory syndrome events occur during this interval.

Microbiologic studies of clinical specimens for bacteria, fungi, mycobacteria, and viruses, as dictated by clinical assessment, were routinely performed to identify the etiologies of the presenting symptoms and signs because opportunistic infections remain the leading cause for HIV care at this referral hospital. *Aspergillus* GM antigen levels were determined using Platelia ELISA (Bio-Rad, Marnes-la-Coquette, France) by following the instructions of the manufacturer. Other than GM, serum specimens were also routinely subjected to cryptococcal antigen assays, toxoplasma IgG, rapid plasma reagin screening for syphilis (RPR), hepatitis profiles including anti-HAV, anti-HBs, HBsAg, and anti-HCV testing. Image studies, including routine chest plain film or computed tomography as clinically indicated, were performed at enrollment. The Research Ethics Committee of FEMH approved the study design; informed consent from each patient was not required for the routine testing and case control study (IRB number 107118-F). For the follow-up GM testing study, informed consent was required (IRB number 109173-F).

2.2. Definitions

We applied an ODI ≥ 0.5, the FDA-recommended threshold validated for aspergillosis. *Talaromycosis* was diagnosed when *T. marneffei* was isolated from any specimen. Hepatitis A was identified by serum HAV IgG detection without prior vaccination or a positive IgM. Chronic hepatitis B was defined by seropositivity for HBsAg without acute infection. Hepatitis C was confirmed by seropositivity for HCV. Syphilis was diagnosed with consistent clinical symptoms, elevated RPR titer, and reactive TPPA assay. HIV viral load detection limit was 40 copies/mL using the Abbott m2000 RealTime System (Abbott Molecular, Des Plaines, IL, USA). Tuberculosis was diagnosed with positive culture results. Pneumocystosis was defined by clinical suspicion and response to PJP treatment. Cryptococcosis was diagnosed with positive cryptococcal antigen or culture of serum or cerebrospinal fluid. Toxoplasmosis was defined by positive serum toxoplasma IgG. Diabetes mellitus was defined by fasting glucose >126 mg/dL or HbA1C > 6.5%. Hyperlipidemia was defined by total cholesterol >200 mg/dL.

2.3. Statistics

All statistical analyses were conducted using the R statistics software (R Foundation for Statistical Computing, Version 4.0.1, Vienna, Austria), and a p value less than 0.05 was deemed statistically significant.

3. Results

We screened 929 patients during the study period, and 72 patients (7.8%) had positive (ODI ≥ 0.5) GM test results. Stratifying by different cutoff values, 45 patients (4.8%) were positive at a cutoff of 0.7, 22 patients (2.4%) at 1.0, and 11 patients (1.2%) at 1.5. Demographic information for both the 72 patients with positive GM results and the corresponding 72 control cases is detailed in Table 1. These patients were male-predominant (96.5%) with a mean age of 39.3 years (standard deviation: 11.2 years). Ten patients were enrolled at admission, and 134 were from our outpatient clinic for their first visit. Five of the 10 inpatients tested positive for GM. Metabolic comorbidities were uncommon; six patients had diabetes mellitus, all among the GM-positive group. The mean fasting blood glucose, total cholesterol, and high-sensitivity CRP for patients with positive GM tests were 97.2 mg/dL (S.D. 31.6 mg/dL), 146 mg/dL (S.D. 29.9 mg/dL), and 0.68 mg/dL (S.D. 1.1 mg/dL), respectively. For those with negative results, their baseline results were 91.2 mg/dL (S.D. 11.8 mg/dL), 156.5 mg/dL (S.D. 29.0 mg/dL), and 0.78 mg/dL (S.D. 2.6 mg/dL), respectively. Eleven GM-positive and seven GM-negative patients had undetectable plasma viral load. One patient in each group had PVL more than 10^7 copies/mL. The interquartile range of on-scale PVL for GM-positive and negative patients was 157,783.5 copies/mL (mean: 219,315.5 copies/mL, S.D. 663,865 copies/mL) and 143,830.5 copies/mL (mean: 184,678.6 copies/mL, S.D. 381,952.1 copies/mL), respectively. Syphilis was the most common co-infections (35.4%) among these patients followed by chronic HCV (16.2%), pneumocystosis (10.4%), chronic HBV (7.0%), toxoplasmosis (8.0%), cryptococcosis (2.1%), tuberculosis (2.1%), and nontuberculous mycobacterium infections (NTM, one *Mycobacterium xenopi*, one *M. avium* complex). (1.4%). There was no liver cirrhosis nor chronic renal insufficiency under dialysis in our patients. All 144 patients survived after one year of follow up.

Table 1. Demographic data of the 72 patients with positive GM test and their 72 controls.

	Total (N = 144)	GM Negative (N = 72)	GM Positive (N = 72)	*p*-Value
Age, years	39.0 (11.2)	37.7 (11.5)	40.4 (10.9)	0.14
Gender, male	139 (96.5%)	69 (95.8%)	70 (97.2%)	0.65
Acute HAV	1/122 (0.8%)	0 (0.0%)	1 (1.7%)	0.30
HAV Ab	44/140 (31.4%)	15 (21.4%)	29 (41.4%)	0.011
Chronic HBV	10/142 (7.0%)	3 (4.2%)	7 (9.9%)	0.19
Chronic HCV	23/142 (16.2%)	6 (8.5%)	17 (23.9%)	0.012
Tuberculosis	3 (2.1%)	3 (4.2%)	0 (0.0%)	0.08
Pneumocystosis	15 (10.4%)	7 (9.7%)	8 (11.1%)	0.79
Cryptococcosis	3/136 (2.1%)	1 (1.4%)	2 (3.0%)	0.54
Toxoplasmosis	9/113 (8.0%)	5 (8.8%)	4 (7.1%)	0.75
Syphilis	51 (35.4%)	29 (40.3%)	22 (30.6%)	0.22
Antifungal usage [1]	6 (4.2%)	3 (4.2%)	3 (4.2%)	1.00
Mean WBC (S.D.)	6005.0 (2499.5)	6187.6 (2527.3)	5822.4 (2475.5)	0.38
Mean CD4 cells (S.D.)	364.6 (281.3)	355.9 (250.0)	373.3 (310.9)	0.71
Mean CD8 cells (S.D.)	1045.6 (567.1)	1039.0 (531.4)	1052.2 (604.2)	0.89
T-bilirubin	0.6 (0.7)	0.5 (0.3)	0.7 (0.9)	0.19
AST	45.4 (147.2)	31.8 (28.8)	59.1 (206.0)	0.27
ALT	44.5 (121.6)	32.0 (42.3)	57.0 (166.4)	0.22
Cre	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.54

[1] Antifungal usage at enrollment (fluconazole only). Abbreviations: AST: Aspartate transaminase; ALT: Alanine transaminase; Cre: creatinine; GM: galactomannan, HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; I.Q.R: interquartile range; S.D.: standard deviation; WBC: white blood cell.

Antifungal agent with fluconazole was given to 6 patients for their oral candidiasis at enrollment, and the GM ODIs were as follows: 0.132, 0.286, 0.419, 0.515, 1.015, and 5.158. The mean GM ODI in patients with the positive GM test was 1.197 (S.D. 1.164, range: 0.504–5.882), and the median was 0.818 (IQR: 0.504). For those with a negative GM test, the mean ODI was 0.208 (S.D.: 0.100, range: 0.055–0.462) and the median was 0.180 (IQR: 0.151). Among patients with CD4 < 50 cells/μL (N = 22), mean and median GM ODI were 1.177 (SD: 0.526; range: 0.148–5.882) and 0.521 (IQR: 0.99), significantly higher than in those with CD4 ≥ 50 cells/μL (N = 122, mean: 0.617, SD: 0.442, range: 0.055–5.158, median: 0.442, IQR: 0.588) (p = 0.0114) (Figure 1). No statistically significant difference in GM ODI was observed among patients with higher CD4 counts (see Supplementary Figure). The results of the case-control study revealed that positive HAV antibody (p = 0.011) and chronic HCV infection (p = 0.012) were two significant factors associated with GM antigenemia in PLHIV.

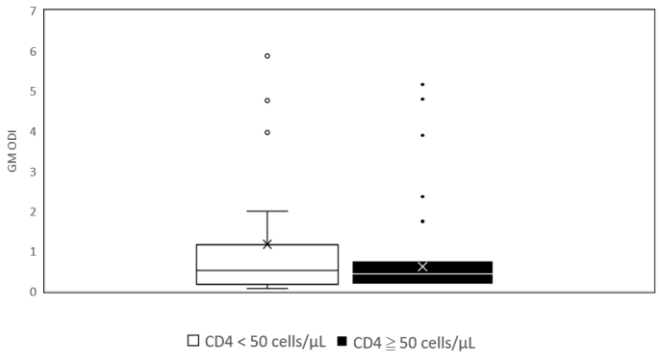

Figure 1. Galactomannan O.D. index distribution of patients with CD4 cell counts more or less than 50 cells/μL (p = 0.0114).

The demographic data of the 81 patients with follow-up GM test are shown in Table 2. The mean follow-up time was 1510 days (range: 241–3114 days). All 81 patients were receiving cART, and most of them (79.0%, N = 64) had undetectable HIV viral load when they participated in the follow-up GM test. The mean CD4 cell count at follow-up was 695.4 cells/μL (S.D.: 289.9 cells/μL), which was higher than their first visit (mean, 355.4 cells/μL and S.D. 264.8 cells/μL, respectively). Results of the GM test were shown in Figure 2. At enrollment, 49.4% (N = 40) of patients had positive GM results at their enrollment with a mean GM ODI of 0.69 (range: 0.07–4.76, median: 0.43, 25% and 75% quartiles were 0.18 and 0.84, respectively). The positive rates were 33.3%, 19.8% and 7.4% using different cutoff values (0.7, 1.0, and 1.5, respectively). The mean GM ODI at follow-up was 0.14 (range: 0.03–1.11, median: 0.12, 25% and 75% quartiles were 0.08 and 0.15, respectively), and there was only one patient who had a positive GM result (ODI: 1.11) (positive rate: 1.2%). The initial GM ODI of the patient was 0.92 and was 1701 days before his follow-up GM test. There was no clinical or microbiological evidence of aspergillosis or talaromycosis in this patient. All the 81 participants survived after a one-year follow up.

Table 2. Demographic data of the 81 patients enrolled for follow-up GM test.

	At Enrollment	On Follow-Up Examination
Age, years	35.9 (8.6)	
Gender, male	100.0%	
BMI (S.D)	20.7 (6.0)	23.2 (4.3)
Diabetes mellitus	7.4%	7.4%
Hyperlipidemia	16.0%	16.0%
HAV Ab	24.7%	79.0%
Chronic HBV	8.6%	8.6%
Chronic HCV	6.2%	12.3%
Syphilis	28.4%	19.8%
Toxoplasmosis	4.9%	6.2%
Tuberculosis	1.2%	0.0%
M. xenopi infection	1.2%	0.0%
Cryptococcosis	1.2%	2.5%
Mean WBC (S.D.)	5.83 (2.43)	6.68 (1.94)
Mean CD4 cells (I.Q.R, S.D.)	355.4 (347.0, 264.8)	695.35 (313.0, 289.9)
Viral load (I.Q.R, S.D.) [1]	190,966.6 (152,225.3, 580,168.9)	1466.3 (5, 5679.6)
T-bilirubin	0.66 (1.18)	0.48 (0.3)
AST (U/L)	53.8 (196.2)	28.9 (53.8)
ALT (U/L)	48.5 (156.1)	40.1 (128.4)
BUN (mg/dL)	12.2 (4.0)	13.5 (3.4)
Cre (mg/dL)	0.89 (0.17)	0.86 (0.17)
C-reactive protein (mg/dL)	0.44 (1.03)	0.36 (0.99)
AC sugar (mg/dL)	91.6 (16.8)	96.4 (13.4)
HbA1C (mg/dL)	5.5 (0.6)	5.3 (0.5)
Total cholesterol (mg/dL)	101 (89)	163.1 (36.3)

[1] There were 7 patients and 64 patients having undetectable viral load at enrollment and on follow-up examination, respectively. Abbreviations: AST: Aspartate transaminase; ALT: Alanine transaminase; AC sugar: Fasting plasma glucose; BMI: body mass index; Cre: creatinine; GM: galactomannan, HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; I.Q.R: interquartile range; *M. xenopi*: *Mycobacterium xenopi*; S.D.: standard deviation; WBC: white blood cell.

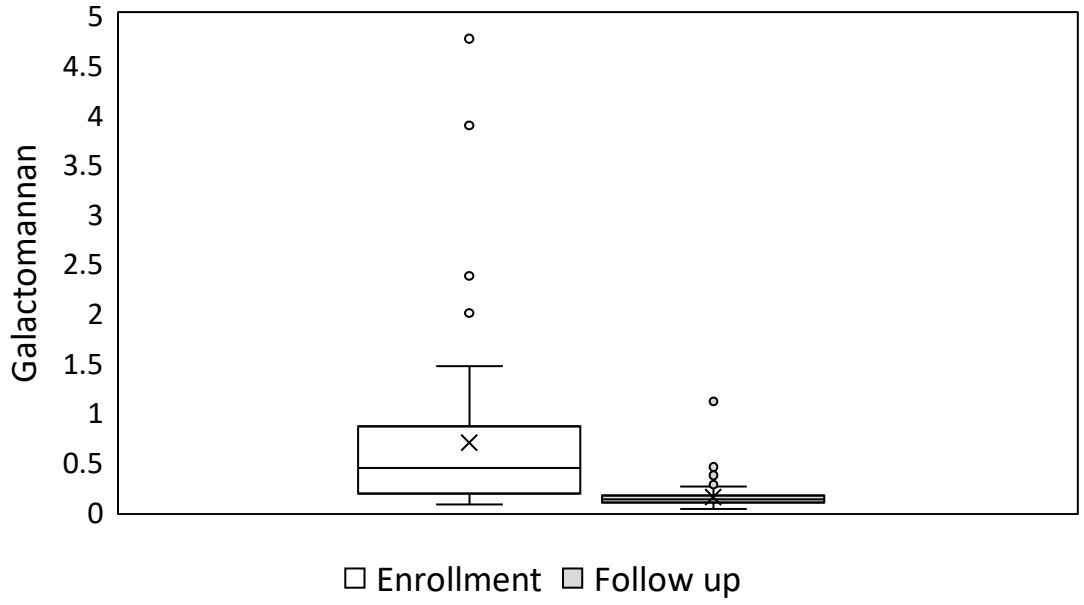

Figure 2. Follow-up of the galactomannan optic density index of the 81 PLHIV patients.

4. Discussions

Our surveillance in Taiwan found a significant prevalence (7.8%) of GM antigenemia among PLHIV, using a diagnostic cut-off value of ≥0.5 for aspergillosis. This suggests a higher-than-expected frequency, raising questions about the specificity and diagnostic utility of GM. Notably, none of the GM-positive patients developed aspergillosis or talaromycosis during the observation period, implying that antifungal treatments without clinical symptoms might be unnecessary. Unlike the screening for cryptococcal antigen in PLHIV to initiate preemptive treatment, our results suggest reevaluating routine GM screening, focusing on symptom monitoring rather than immediate antifungal treatments.

Talaromycosis is a neglected tropical disease among immunocompromised patients in Southeast Asia, causing significant mortality when diagnosis is delayed [16]. Traditional culture-based diagnostic methods have proven to be time-intensive and lack sensitivity. Non–culture-based diagnostics have become important complements, including immunoassays detecting the TM Mp1p mannoprotein or cytoplasmic yeast antigens with monoclonal antibody 4D1, TM-targeted nucleic acid–based assays (PCR and related methods), and metagenomic next-generation sequencing [17,18]. Many of these assays are not yet commercially available worldwide. Among them, enzyme immunoassays targeting Mp1p are the most extensively studied and are recommended in some endemic settings [16–19]. In the context of treatment, the initiation of therapy in patients who test positive for Mp1p following universal screening has been suggested, particularly for PLHIV in endemic areas [16]. A notable surveillance study by Wang et al., involving 2686 PLHIV patients in Guangzhou, China, revealed a serological prevalence of 9.4% for Mp1p among the population [20]. Additionally, a substantial correlation was observed between the Mp1p and the GM, with an 86.6% concurrence rate in the study. Similar to our results, they also identified the association of low CD4 counts, especially those below 50 cells/μL, with positive Mp1p results. In a recent study involving 784 Cantonese HIV-infected, HAART-naïve patients, the authors found an 11.4% prevalence of talaromycosis using the Mp1p test, with higher rates (32.2%) in patients having CD4+ counts ≤50 cells/μL [21]. In the study, of the 350 patients who received both fungal culture and Mp1p antigen detection, 27.1% patients were TM culture-positive, while 21.4% patients were Mp1p antigen-positive. There was no further discussion regarding the clinical presentations and outcomes of patients with discrepant results. The authors suggested that by screening for the Mp1p antigen, it is possible to motivate the diagnosis of talaromycosis in patients with low CD4 counts and the initiation of antifungal treatment. In our cohort, the prevalence of GM antigenemia was similar and also associated with low CD4 counts. However, as our findings indicate, GM testing should be interpreted cautiously and not as a stand-alone alternative for early diagnosis of TM.

In Taiwan, talaromycosis was a rare opportunistic infection among PLHIV, accounting for 0.7–3.1% and no aspergillosis have ever been diagnosed according to a longitudinal study from 2004–2015 [12]. The incidence density of talaromycosis was 1.5/1000 person-years according to the Taiwan Centers for Disease Control HIV Surveillance Database from 2000–2014, which was lower than pneumocystosis (21.63/1000 person-years), candidiasis (19.8/1000 person-years), and cryptococcal meningitis (1.77/1000 person-years) [13]. Over the past

decade in Taiwan, we observed no significant change in the interval of opportunistic infections (including talaromycosis) during our study period [16–18]. Our previous studies showed the cross-reactivity of GM and TM infection in addition to other fungi, including *Fusarium* spp., *Penicillium* spp., *Paecilomyces* spp., *Purpureocillium lilacinum*, and *Histoplasma* spp. [1,2,10,11]. We also noted the prolonged elevation of GM among TM-infected patients [11]. Other fungal infections, such as aspergillosis or fusariosis, were even less than talaromycosis among PLHIV in Taiwan [12–14]. We previously hypothesized the cross-reactivity that might enable the use of GM tests for talaromycosis early diagnosis. In the current study, we determined the prevalence of GM antigenemia among patients receiving HIV care, and none of the positive cases developed clinically significant talaromycosis the later during the follow-up period, and no mortality was observed for up to one year regardless of the GM status. Unlike the recommendation of early testing for cryptococcal antigen in this group, interpreting GM results should be approached with more caution [22]. Therefore, screening with GM and initiating pre-emptive or targeted therapy might not be essential in patients who do not exhibit clinical symptoms indicative of talaromycosis, according to our study.

The presence of GM in the bloodstream, given its inability to easily traverse biological barriers like the alveolar-capillary bilayer because of its molecular weight (35–200 kDa), typically indicates fungal angioinvasion rather than mere diffusion from adjacent infection sites [1,23,24]. The metabolism of GM in humans primarily involves hepatic and renal pathways with an estimated serum half-life of 2.4 days [23]. Studies show that uptake by hepatic Kupffer cells via macrophage mannose receptors, renal excretion, and neutrophils is involved in the elimination of serum GM [23–25]. Our study showed that positive anti-HAV and anti-HCV serologies, as well as CD4 counts below 50 cells/μL, were associated with GM antigenemia; however, none of our patients had liver cirrhosis, renal function impairment, or neutropenia. We observed that one of our patients regularly exhibited high GM levels in the follow-up testing, without any of the comorbidities previously mentioned. Further investigation is necessary to determine the causes behind the ongoing high GM levels in this patient, as the continuous elevation of GM could lead to incorrect conclusions in diagnosing fungal infections.

Our study has several limitations. First, no participant had culture-confirmed talaromycosis, and mycological cultures were not obtained systematically. Culture confirmation with clinical follow-up served as the sole reference standard, so subclinical or missed talaromycosis cannot be excluded. Second, the absence of a healthy control group limits inference about whether elevated serum GM levels are specific to PLHIV in Taiwan and precludes a robust assessment of assay specificity. Third, we did not collect dietary information, which may influence circulating GM levels and thus affect the interpretation and clinical relevance of the GM results. Fourth, some classifications relied on a single time-point GM measurement, and repeat testing was not universal, introducing potential misclassification. Finally, despite review for iatrogenic exposures and cross-reactive mycoses, residual confounding may persist.

In summary, serum GM should be used as an adjunct rather than a stand-alone screening test for early talaromycosis. In asymptomatic PLHIV with GM antigenemia, our findings support a management strategy of prompt cART initiation and close clinical follow-up, rather than routine empiric antifungal therapy. This approach may reduce unnecessary antifungal use while maintaining patient safety in endemic settings.

Supplementary Materials

The additional data and information can be downloaded at: https://media.sciltp.com/articles/others/2508251433220699/Supplementary-Materials.pdf. Figure S1: Galactomannan ODI distribution of patients with CD4 cell counts more or less than (A) 100 cells/μL ($p = 0.0503$) and (B) 200 cells/μL ($p = 0.1241$).

Author Contributions

Y.-T.H. and C.-J.Y.: concept and design of the study; M.-S.T., C.-H.L., and C.-Y.S.: acquisition of clinical data; Y.-T.H. and Y.-W.K.: data analysis and data interpretation; Y.-T.H., Y.-W.K., M.-S.T., C.-H.L., C.-Y.S. and C.-J.Y.: revising the manuscript critically for important intellectual content; Y.-T.H. and C.-J.Y.: drafting and revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding

This study was supported by the grant of Far Eastern Memorial Hospital (FEMH-2019-C-014).

Institutional Review Board Statement

This study was approved by the Research Ethics Committee of FEMH (107118-F and 109173-F); informed consent from each patient was not required for the routine test; and case-control study was approved (IRB number 107118-F). For the follow-up GM testing study, informed consent was required (IRB number 109173-F).

Conflicts of Interest

C.-J.Y. received speaker honoraria from Gilead Sciences, Merck, Pfizer and GSK/ViiV. M.-S.T. has received speaker honoraria from Gilead Sciences. C.-H.L. has received speaker honoraria from Pfizer. The other authors have no conflicts of interest.

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