

Use of (1→3)-β-D-glucan for diagnosis and management of invasive mycoses in HIV-infected patients

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Summary

People living with HIV (PLHIV) are highly vulnerable to invasive fungal infections (IFIs) due to their immune dysfunction. Diagnosis and treatment of IFIs remain challenging due to the requirement of deep tissue sampling to visualise and culture fungi before initiating treatment. Such techniques are less practical in resource-limited settings due to their cost and requirement of relatively invasive procedures. Hence, identification of surrogate markers for the early diagnosis and therapeutic monitoring of IFIs is required. Recent studies have shown that (1→3)-β-D-glucan (BDG), a major fungal cell wall antigen, represents a promising soluble marker for the presumptive diagnosis and therapeutic monitoring of IFIs in HIV-infected patients. Herein, we review findings on the merits of BDG assays in the diagnosis of IFIs and monitoring of antifungal therapies for PLHIV. Conversely to other types of immunocompromised patients, HIV infection is associated with gut damage and subsequent bacterial and fungal translocation leading to elevated BDG plasma levels.

KEYWORDS

(1→3)-β-D-glucan, diagnosis of mycoses, gut microbial translocation, HIV, invasive fungal infections

1 | INTRODUCTION

Invasive fungal infections (IFIs) are a leading cause of morbidity in immunocompromised people, including those living with HIV (PLHIV).^{1,2} Pathogenic fungi are responsible for a variety of syndromes in PLHIV, such infections can develop into life-threatening

conditions.³ *Pneumocystis jirovecii* is the most common cause of respiratory infection while *Cryptococcus neoformans* is a frequently isolated pathogen from central nervous system (CNS) of PLHIV worldwide.⁴ Prevalence of other IFIs depends largely on geographic localisation as *Histoplasma capsulatum* is more frequent in Americas, whereas *Talaromyces marneffeii* (formerly *Penicillium marneffeii*) is common in South and Southeast Asia. Other common IFIs in PLHIV include aspergillosis and candidiasis. Early diagnosis and appropriate antifungal therapy could play a significant role in improving management of patients with IFIs.⁵ Encouragingly, early diagnosis and prompt antiretroviral therapy (ART) initiation among PLHIV have significantly decreased the incidence of IFIs. However,

Abbreviations: BALF, bronchoalveolar lavage fluid; BDG, (1→3)-β-D-glucan; CM, cryptococcal meningitis; CNS, central nervous system; CSF, cerebrospinal fluid; IFIs, invasive fungal infections; IL, interleukin; LBP, lipopolysaccharide binding protein; LPS, lipopolysaccharide; PJP, *Pneumocystis jirovecii* pneumonia; sCD14, soluble CD14; TNFα, tumour necrosis factor-α.

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in many regions with high prevalence of HIV, particularly in sub-Saharan Africa and in Southern Asia, IFIs remain a clinical challenge. In these regions, many PLHIV still present with advanced stage disease and low CD4 counts.⁶ Therefore, new scalable tools for early diagnosis and access to antifungal drugs are needed to improve the life of PLHIV.

2 | (1→3)-B-D-GLUCAN AS AN EMERGING DIAGNOSTIC TOOL

Fungal infections can be asymptomatic or subtle in early stages; this makes diagnosis of IFIs a major concern in clinical practice. Most IFIs are currently diagnosed by histopathological methods or by culturing the organism from deep tissue.¹ These methods are often invasive with possible complications to the patients. Therefore, recent studies have focused on finding non-invasive methods to improve the early diagnosis and therapeutic monitoring of IFIs.⁷ Fungal nucleic acids, antigens and cell wall components are potential surrogates. Examples of which include the use of galactomannan in the diagnosis of invasive aspergillosis and cryptococcal antigen for diagnosis of cryptococcosis. (1→3)- β -D-glucan (BDG), a component of several fungal cell walls, provides another surrogate marker for the diagnosis of IFIs.⁸⁻¹⁰ Since its first assay developed in Japan in 1985,¹¹ BDG has been recommended to diagnose probable IFIs by the European Organization for Research and Treatment of Cancer, the Mycoses Study Group, the European Society of Clinical Microbiology and Infectious Diseases, the Infectious Diseases Society of America and the American Society for Microbiology.^{12,13}

Currently, commercial BDG assay kits are available from several countries including USA, Japan and China.¹⁴ These kits apply different detecting methods and cut-off values to diagnose IFIs which lead to variable accuracy. Of the available kits only the Fungitell assay (Associates of Cape Cod, USA) is FDA approved and widely used in the United States, Canada and Europe.^{15,16} The Fungitell assay measures plasma concentrations of BDG using a kinetic protocol which involves the binding of BDG to a horseshoe crab coagulate. This triggers a coagulation cascade which can be used to subsequently quantify BDG concentrations using colorimetric methods similar to that of an enzyme-linked immunosorbent assay.¹⁷

The utility of the BDG assay in diagnosis of IFIs has been extensively reviewed in general populations with a pooled sensitivity of 76.8% and specificity of 85.3%.⁷ However, its use for diagnosis of IFIs in PLHIV remains to be established. In this paper, we review relevant studies which investigated the clinical implications of BDG assays to diagnose IFIs and monitor therapeutic responses to antifungal therapy in both the blood and cerebrospinal fluid (CSF) of PLHIV. Herein, we searched literature in English language using PubMed and Google scholar to select publications reported on the merits of BDG in the diagnosis of IFIs in the general population and PLHIV. We limited the search to publications with a sample size of more than 10 PLHIV and for which we could have sensitivity and/or specificity of BDG for the diagnosis of IFIs.

3 | APPLICATION OF BDG AS A DIAGNOSTIC AND MONITORING TOOL FOR IFIS IN PLHIV

(1→3)- β -D-glucan has been used for the diagnosis of IFIs including *P. jirovecii* pneumonia (PJP), Cryptococcosis and others in PLHIV, as summarised in Table 1. PJP is a common HIV-infected opportunistic infection caused by *P. jirovecii*.¹⁸ The standard method to diagnose PJP requires visualisation of *P. jirovecii* cysts in microscopic examination of respiratory secretions such as bronchoalveolar lavage fluid or lung biopsy samples. Both of these techniques require severely invasive procedures for definitive diagnosis.¹⁹ We describe studies reporting BDG as a diagnostic tool for PJP in PLHIV.

The first reporting of serum BDG sensitivity for PJP diagnosis was in 2007 by Fujii et al²⁰, which showed a sensitivity of 97% using kits from Japan. Later studies using Fungitell test with different cut-off values showed a sensitivity ranging from 90% to 100% and specificity ranging from 65% to 96.4%^{21,22} (Table 1). In addition, the study suggested that increasing the cut-off value for the diagnosis of PJP as compared to the diagnosis of invasive aspergillosis or invasive candidiasis could improve the specificity of the test. Similarly, using the cut-off value of 23.2 pg/mL, Watanabe et al²³ from Japan reported sensitivity of 96.4% and specificity of 87.8% using the Fungitec G MK test for the diagnosis of PJP. Desmet et al²¹ showed the potential of BDG assay as a diagnostic tool of PJP in PLHIV with a cut-off value of 100 pg/mL, sensitivity of 100% and specificity of 96%. Comprehensively, these studies consistently suggest that BDG could be used as an adjunct tool in the diagnosis of PJP in PLHIV. However, this requires varying cut-offs dependent upon the geographic locations and degree of immunodeficiency. The diagnostic utility of BDG is less studied in other conditions due to their reduced burden.

Although the FDA approved assay is not recommended for the presumptive diagnosis of cryptococcosis, a few studies investigated the utility of BDG assay in diagnosing cryptococcal meningitis (CM) in PLHIV. Rhein et al²⁴ evaluated CSF BDG levels in 117 adult PLHIV in Uganda and South Africa with CM compared to those without meningitis. They reported a sensitivity of 89% and a specificity of 85%. In a related study from the United States, Lyons et al²⁵ investigated the utility of CSF and serum BDG in diagnosis of CNS infection in 92 immunocompromised patients, out of which 32% were HIV-infected. This study showed that CSF BDG assay could be useful for the diagnosis or exclusion of fungal CNS infection.

Although infections caused by other invasive fungi including *Candida albicans*, *Aspergillus fumigatus*, *H. capsulatum* and *T. marneffei* are common in PLHIV, very few small-scale studies have shown potential utility of BDG in diagnosis of these IFIs.^{5,26,27} Thus, further studies on a larger scale are required to explore the merits of BDG in these less frequent IFIs.

Few studies had evaluated the value of BDG in monitoring treatment response of IFIs in PLHIV.^{23,24} A study using Fungitec G MK test failed to find any correlation between disease severity and BDG levels. This indicates that the assay may not be useful for therapeutic monitoring of PJP.²³ Another study showed that positive BDG result is probable

TABLE 1 Deployment of BDG as a diagnosis tool of IFIs in HIV-infected patients

Reference	BDG assay	Name of commercial kits	IFIs	Study design	Study population/sample size (N)	Countries of the study	Major findings
Fujii 2007	Plasma	β -glucan Wako test	PJP	Retrospective	32 HIV patients had PCP	Japan	Sensitivity 97% for PJP diagnosis. Specificity not applicable due to all study group being positive for PJP
Desmet 2009	Serum	Fungitell® assay	PJP	Case-control study	16/32 HIV patients had PCP	Belgium	Sensitivity 100% and specificity 96.4%.
Watanabe 2009	Serum	Fungitec G MK test	PJP	Case-control study	111/536 HIV-infected patients had PCP	Japan	Sensitivity 96.4% and specificity 87.8%
Sax 2011	Plasma	Fungitell® assay	PJP	Retrospective	173/252 HIV-infected patients had PCP	USA	Sensitivity: 92% and specificity 65%
Esteves 2014	Serum	Fungitell® assay	PJP	Case-control study	69/100 HIV-infected patients had PCP	Portugal	Sensitivity: 91.3% and specificity 61.3%
Passos 2017	Serum	Fungitell® assay	PJP	Cross-sectional prospective	19/60 patients had PCP	Brazil	Sensitivity: 90% and specificity: 80%
Rhein 2014	CSF, serum	Fungitell® assay	Cryptococcosis	Retrospective	CSF: 78/117 HIV-infected patients had cryptococcal meningitis Serum: 47/109 HIV-infected patients had cryptococcal meningitis	Uganda and South Africa	In CSF: 89% sensitivity and 85% specificity In serum: 79% sensitivity and 61% specificity
Lyons 2015	CSF	Fungitell® assay	IFIs	Retrospective	27/92 were infected with HIV	USA	CSF BDG could be useful for diagnosing or excluding fungal CNS infections. Additionally, it may be an important determinant of fungal disease well before organism growth in culture

CNS, central nervous system; PJP, *Pneumocystis jirovecii* pneumonia; CSF, cerebrospinal fluid; IFIs, invasive fungal infections; BDG, (1 \rightarrow 3)- β -D-glucan.

in any given patient with CM, particularly amongst those with severe conditions.²⁴ Therefore, CSF BDG assay could be used as a monitoring tool for the response to antifungal therapy among patients with CM.

4 | BDG AS A PLASMA LEVEL BIOMARKER OF MICROBIAL TRANSLOCATION

In HIV-negative people, the specificity of BDG test is compromised in the presence of factors that could increase BDG levels for reasons other than IFI. This includes haemodialysis with cellulose membranes, administration of human blood products (immunoglobulins or albumin), use of antibiotics such as amoxicillin-clavulanate or piperacillin-tazobactam, presence of serious bacterial infections, use of surgical gauzes containing glucan, or severe mucositis.⁷ In PLHIV, it may be further limited as recent evidences showed BDG may be also a surrogate marker of microbial translocation in asymptomatic people.

From the early phase of HIV infection to a chronic state, substantial immunological and structural disruption occurs in the gastrointestinal tract. This leads to microbial translocation and subsequently contributes to systematic immune activation.²⁸⁻³⁰ Gut "microbial translocation" is defined as the non-physiological passage of the gastrointestinal microflora or their products through the intestinal epithelial barrier into circulating blood.³¹ Markers of bacterial translocation such as lipopolysaccharide (LPS), a major cell wall component of gram-negative bacteria found in the gut microbiome, have been associated with systemic immune activation.³¹ However, a marker to assess microbial translocation of products of the gut mycobiome has not yet been established. In a cohort of PLHIV free of IFIs and colitis, Hoenigl et al³² reported elevated BDG levels which correlated with soluble markers of gut integrity. This elicits the question of whether PLHIV experience microbial translocation of fungal cell products. They were able to show that the level of plasma BDG correlated with soluble CD14 (sCD14), marker of monocyte activation and lower proportions of gut *Lactobacilli* in PLHIV not having IFIs.^{32,33}

Furthermore, elevated levels of plasma BDG was recently reported as a potential marker contributing to systemic immune activation likely via microbial translocation in PLHIV not suffering from IFIs.³³⁻³⁵ Maurice et al³⁴ reported that elevated levels of BDG in serum correlate with advanced HIV-associated immunosuppression, inflammation and cardiopulmonary comorbidity. Consistent with these findings, Hoenigl et al³⁶ reported in 2016 that BDG may also represent a biomarker for neurocognitive impairment in PLHIV receiving ART. We confirmed and expanded these finding by showing in 131 patients that plasma BDG elevation was present at the very onset of HIV infection and further increased during chronic infection.³⁷ Such elevated BDG plasma levels positively correlated with plasma HIV viral load, whereas a negative correlation of BDG was observed with CD4 T cell count and CD4/CD8 ratio. Importantly, elevation of BDG was significantly associated with markers of microbial translocation (LPS, LBP and sCD14) and inflammation (IL-6 and IL-8). We also observed a positive correlation of elevated BDG levels with tryptophan catabolising interferon gamma-inducible indoleamine 2,3-dioxygenase enzyme activity.³⁷ Dysregulations in

tryptophan catabolism have been linked with gut mucosal dysfunction and immune activation during chronic viral infections including HIV.^{28,38} Globally, BDG represents a new marker of microbial translocation in PLHIV regardless of IFIs and may directly contribute to immune activation.

Therefore, to differentiate from microbial translocation, a higher cut-off value is required to improve the specificity of IFIs in PLHIV, which warrants further investigation. Meanwhile, it is critical to take other laboratory tests (e.g. microbial results and radiology profiles) into consideration to rule in IFIs in asymptomatic PLHIV with elevated BDG level. In some cases, monitoring the dynamic of BDG may also be necessary.²⁴

5 | CONCLUSION AND FUTURE DIRECTIONS

(1→3)-β-D-glucan assays represent a promising tool for the early diagnosis of PJP while its role in other IFIs including invasive aspergillosis and invasive candidiasis still needs to be established in PLHIV. Its diagnostic cut-off may also depend on BDG originating from microbial translocation that should be taken into consideration for diagnosis of patients with advanced AIDS and opportunistic fungal infections. Recent studies show the usefulness of BDG as a biomarker of gut microbial translocation and immune activation in PLHIV. A collaborative effort between mycologists, immunologists, clinicians and epidemiologists will be needed for the optimal diagnosis and management of patients suffering from IFIs.

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