Fungal Translocation: A Driving Force Behind the Occurrence of Non-AIDS Events?

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(See the Major Article by Mehraj et al on pages 232–41.)

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In this world, nothing is certain except death and taxes, declared Benjamin Franklin in his bon mot. Unfortunately, despite effective antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection remains associated with morbidity and mortality due to non-AIDS-defining events, best predicted by markers of immune activation [1]. Microbial translocation, driven by epithelial gut damage caused by depletion of intestinal CD4 T cells during early stages of HIV infection, has been identified as a driver of immune activation in HIV infection. However, a reliable gold standard biomarker for measuring microbial translocation is lacking [2, 3]. Bacteria and fungi are the 2 most abundant populations of the gut microbiome [4]. The gut mycobiome consists primarily of ascomycete fungi including *Candida albicans* as well as other yeast, but *Aspergillus* spp., *Penicillium* spp., and *Fusarium* spp. also have been commonly detected within the gut of healthy individuals [4,

5]. What most of these fungal species have in common is that they produce the fungal polysaccharide (1→3)- β -D-glucan (β DG), which serves as a component of their cell wall. Clinicians utilize β DG as a blood and cerebrospinal fluid (CSF) biomarker for early diagnosis of invasive fungal infections [6, 7]. In the absence of invasive fungal infections, elevated blood β DG levels have been reported not only after open or laparoscopic intestinal surgery [8] but also during hemodialysis [9], most likely explained by transient reduced blood flow within the splanchnic region, potentially resulting in ischemia and transient barrier damage in the gut.

Despite the abundance of fungi in the gut microbiome, research on the causes of immune activation and associated non-AIDS morbidity and mortality has, to date, focused mostly on bacterial translocation and markers thereof [10]. In contrast, fungal translocation has only very recently come into focus as a potential contributor to immune activation and driver of non-AIDS events in HIV infection.

In this issue of *Clinical Infectious Diseases*, Mehraj and colleagues provide important new insights into the role of fungal translocation as a potential cause of immune activation. They investigated blood levels of β DG in people living with HIV (PLWH) [11] and found that plasma β DG levels were elevated during early and

chronic HIV infection when compared to HIV-uninfected controls. β DG levels in PLWH correlated negatively with CD4 T-cell count and positively with viral load and markers of gut damage, bacterial translocation, and inflammation. Further, they demonstrated that early ART initiation prevents further β DG increase, while β DG increased significantly over 24 months in those without ART.

In this cross-sectional cohort study, Mehraj et al investigated β DG for the first time longitudinally in PLWH with early and chronic HIV infection and on or off ART. While they evaluated correlations between β DG and a comprehensive bundle of other more established markers of immune activation, the study design did not allow for correlation of β DG levels with clinical outcomes, namely, non-AIDS events. Therefore, the researchers could not confirm results of a very recent, rigorous, case-control study in which it was found that circulating β DG levels were an independent predictor of non-AIDS events in PLWH virally suppressed on ART, with odds ratios between 1.4 and 1.5 per 1 interquartile range increase of β DG levels. In that study, non-AIDS events were defined as myocardial infarction or a stroke, a non-AIDS-defining malignancy, serious bacterial infection, or death from a nonaccidental non-AIDS-related event [12]. The results reported by Mehraj et al complement the findings

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of that case-control study by identifying early ART as an effective intervention to cease the increase of β DG levels. The findings by Mehraj et al can be also seen as being in line with findings from other recent studies in which it was found that circulating β DG levels in PLWH on ART correlated with other markers of immune activation [12, 13], systemic inflammation [13, 14], and microbial translocation, including *Lactobacillales* proportions in the gut microbiome [6], and that elevated β DG levels were associated with neurocognitive and cardiovascular non-AIDS events [15, 16].

While there is overwhelming evidence that β DG levels are associated with immune activation in PLWH, the role of fungal translocation in the pathogenesis of non-AIDS events needs to be further investigated. While it seems logical to assume that translocated fungal components would be a mediator of chronic inflammation and immune activation, the extent to which fungal translocation contributes to the development of non-AIDS events remains unknown. Data that show a potential link between fungal translocation and non-AIDS events currently exist mostly for neurocognitive impairment. Very recently, it was shown in a mouse model that chronic transient candidemia, while being cleared quickly from the circulation, led to highly localized cerebritis that, in the long term, could lead to substantial neuronal loss and progressive cognitive impairment [17]. There is also emerging but still limited evidence that the gut mycobiome is intricately involved in neurological disease and that fungal components may play a role in Alzheimer disease and multiple sclerosis [18–20]. For PLWH on suppressive ART, it has been shown that β DG was detectable in CSF, with a trend toward higher CSF β DG levels in individuals with neurocognitive impairment [21].

Mehraj et al's findings that early ART, rather than duration of ART, prevents an increase in β DG levels in PLWH highlights the importance of early diagnosis and treatment to limit gut damage and immune

activation. This is true particularly because the β DG increase does not seem to be reversible under ART, as even 24 months of suppressive ART failed to reduce β DG levels. While ART and viral suppression seem to have a limited effect on decreasing β DG levels, systemic antifungals have been shown to effectively decrease β DG levels in patients with invasive fungal infections [22]. Interestingly, not only paroxetine, a selective serotonin reuptake inhibitor, but also an antifungal agent, fluconazole, protected hippocampal neurons in an in vitro model of mixed rat neuronal cultures that screened more than 2000 compounds, half of which were US Food and Drug Administration approved drugs for putative neuroprotective effects against oxidative stress-mediated neuronal injury [23]. In another study, the combination of paroxetine and fluconazole protected macaques from simian immunodeficiency virus-associated neurodegeneration [24]. However, a phase 1/2, randomized, double-blind, placebo-controlled study for the treatment of HIV-associated neurocognitive impairment did not show an improvement of neurocognitive outcomes among the 9 participants randomized to fluconazole treatment alone [25].

When interpreted in conjunction with previous findings, the study by Mehraj et al may open the door to novel therapeutic strategies that involve systemic antifungals in PLWH who have high β DG levels. The systemic antifungal drugs used in such trials would ideally be well tolerated, have a broad spectrum of activity (ie, ideally covering the whole spectrum of β DG-producing fungi that are commensals in the human gut, including *Aspergillus* spp., *Penicillium* spp., and *Fusarium* spp.), and be easy to use in terms of frequency and application. While broad-spectrum triazoles seem to be an obvious choice for such a trial, there are a number of new antifungal drugs currently in phase 2 or phase 3 studies that may fit those requirements even better as they promise to be better tolerated and/or allow for once-weekly administration.

In conclusion, the fungal antigen β DG contributes to immune activation and represents a potential therapeutic target to prevent non-AIDS events. Gaining a comprehensive understanding of the origin and consequences of this circulating fungal polysaccharide is of critical importance to finding therapeutic strategies to decrease immune activation and prevent non-AIDS events in PLWH.

Notes

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