UC San Diego
UC San Diego Previously Published Works

Title

Plasma (1 → 3)-β-d-glucan and suPAR levels correlate with neurocognitive performance in people living with HIV on antiretroviral therapy: a CHARTER analysis

Permalink

https://escholarship.org/uc/item/79c5q1sq

Journal

Journal of NeuroVirology, 25(6)

ISSN

1355-0284

Authors

Gianella, Sara
Letendre, Scott L
Iudicello, Jennifer
et al.

Publication Date

2019-12-01

DOI

10.1007/s13365-019-00775-6

Peer reviewed

Plasma (1 → 3)-β-D-glucan and suPAR levels correlate with neurocognitive performance in people living with HIV on antiretroviral therapy: a CHARTER analysis

Sara Gianella[1] · Scott L. Letendre[1,2,3] · Jennifer Iudicello[3] · Donald Franklin[3] · Thaidra Gaufin[1] · Yonglong Zhang[4] · Magali Porrachia[1] · Milenka Vargas-Meneses[1] · Ronald J. Ellis[3,5] · Malcolm Finkelman[4] · Martin Hoenigl[1,6]

Abstract

Despite antiretroviral therapy (ART), people living with HIV (PLWH) have higher rates of non-AIDS disorders, such as neurocognitive (NC) impairment (NCI) than the general population. (1-3)-β-D-Glucan (BDG) is a fungal cell wall component which serves as a biomarker for gut barrier integrity failure and microbial and fungal translocation. The primary objective of this study was to determine whether higher plasma and cerebrospinal fluid (CSF) levels of BDG and suPAR were associated with NCI in PLWH. Paired blood and CSF samples were collected cross-sectionally from 61 male adult PLWH on ART (95% virally suppressed) who underwent a detailed NC assessment as part of the prospective CHARTER study between 2005 and 2015. BDG and soluble urokinase plasminogen activator receptor (suPAR) were measured in frozen blood and CSF samples while soluble CD14 (sCD14), intestinal fatty acid binding protein (IFABP), and CD4/CD8 ratio were measured in blood only. Spearman's rho correlation analysis assessed associations between BDG, other biomarkers, and NC performance. Median BDG levels were 18 pg/mL in plasma (range 2–60 pg/mL) and 20 pg/mL in CSF (range 0–830 pg/mL). Higher levels of plasma BDG were associated with worse NC performance (Spearman's rho = − 0.32; $p = 0.013$) and with the presence of NCI ($p = 0.027$). A plasma BDG cutoff of > 30 pg/mL was 30% sensitive and 100% specific for NCI. After adjusting for age, higher plasma suPAR levels were also associated with worse NC performance ($p < 0.01$). No significant associations were observed between the remaining biomarkers and the NC variables. Plasma levels of BDG and age-adjusted suPAR may be new biomarkers for the detection of NCI in PLWH on suppressive ART.

Keywords CSF · Plasma · Neurocognitive impairment · Microbial translocation · Virally suppressed · Non-AIDS events · suPAR · sCD14 · IFABP · BDG

✉ Sara Gianella
gianella@ucsd.edu

✉ Martin Hoenigl

1 Present address: Division of Infectious Diseases & Global Public Health, University of California San Diego, San Diego, CA, USA

2 Department of Medicine, University of California San Diego, San Diego, CA, USA

3 Department of Psychiatry, University of California San Diego, San Diego, CA, USA

4 Research Laboratory, Associates of Cape Cod, Inc., Falmouth, MA, USA

5 Department of Neurosciences, HIV Neurobehavioral Research Center, University of California, San Diego, CA, USA

6 Section of Infectious Diseases and Tropical Medicine, Medical University of Graz, Graz, Austria

Introduction

Although antiretroviral therapy (ART) has improved survival and morbidity, people living with HIV (PLWH) have higher rates of non-AIDS disorders, such as neurocognitive (NC) impairment (NCI), than the general population (Palella Jr et al. 2006; Hunt 2012; Heaton et al. 2010). While the occurrence of severe forms of HIV-associated dementia has decreased with ART, milder forms of NC disorders are still estimated to affect one-third to one-half of PLWH (Heaton et al. 2010). NCI has been associated with chronic immune dysfunction, which persists in some individuals despite long-term suppressive ART (Deeks et al. 2012). While the exact mechanism is incompletely understood and likely multifactorial, translocation of microbial and fungal products from the gastrointestinal tract into the systemic circulation is an important driver of

immune dysfunction and persistent inflammation during suppressive ART (Morris et al. 2012; Ancuta et al. 2008). Microbial and fungal translocation may therefore play a role in the pathogenesis of NCI during HIV infection (Morris et al. 2012; Ancuta et al. 2008), and previous studies reported associations between higher biomarkers of microbial translocations (e.g., sCD14, LPS) and worse NC performance (Ancuta et al. 2008; Kamat et al. 2012).

(1-3)-β-D-Glucan (BDG) is a cell wall component of most fungal species and is also a common component of food products (Heldt et al. 2018; Prattes et al. 2014). Among PLWH and without invasive fungal infection, higher levels of BDG in serum are associated with gut barrier integrity failure and luminal content translocation, including microbes and/or endogenous fungal flora from the gastrointestinal tract into the systemic circulation, and consequently with HIV-associated immunosuppression and inflammation (Ancuta et al. 2008; Hoenigl et al. 2016a; Farhour et al. 2018; Mehraj et al. 2019). In line with this theory, our study team reported that BDG exhibited a strong negative correlation with the proportion of gut *Lactobacillales* in the distal gut microbiome (low proportion of gut *Lactobacillales* is an indicator of microbial translocation), and positive correlation with sCD14, the soluble form of the receptor for lipopolysaccharide (LPS) (Hoenigl et al. 2016a). BDG levels in blood and cerebrospinal fluid (CSF) may have significant prognostic potential, predicting mortality in patients with various underlying diseases (Reischies et al. 2016). In fact, previous studies found that blood BDG levels correlated with cardiovascular non-AIDS comorbidities among individuals with chronic HIV infection (Ancuta et al. 2008; Hoenigl et al. 2018). In a previous pilot study, BDG levels also correlated with neurocognitive performance among 14 PLWH (Hoenigl et al. 2016b).

The soluble urokinase plasminogen activator receptor (suPAR) is another biomarker that has been correlated with inflammation, non-AIDS events, and AIDS-related mortality (Hoenigl et al. 2018; Lawn et al. 2007; Rasmussen et al. 2016; Oliveira et al. 2012). The urokinase-type plasminogen activator system consists of a proteinase (uPA), a receptor (uPAR), and inhibitors. suPAR is the soluble form of uPAR and positively correlates with the activation level of the immune system (Hodges et al. 2015; Raggam et al. 2014; Hoenigl et al. 2013). In blood, suPAR is a marker of monocyte activation and chronic inflammation (Hoenigl et al. 2018; Lawn et al. 2007; Rasmussen et al. 2016; Oliveira et al. 2012). Interestingly, CSF suPAR levels are higher in PLWH with AIDS dementia complex than in neurologically asymptomatic adults (Cinque et al. 2004; Sidenius et al. 2004).

The primary objective of this study was to determine whether higher plasma and CSF levels of BDG and suPAR were associated with NCI in PLWH on ART.

Methods

In this cross-sectional analysis, we included paired plasma and CSF samples from a cohort of 61 PLWH on ART (50% NCI and 50% no NCI) who underwent a NC assessment as part of the multi-site prospective CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study between 2005 and 2015 coordinated by University of California San Diego (UCSD). The CHARTER study was funded in 2002 to explore the changing presentation of HIV neurological complications in the context of ART (Heaton et al. 2010). The UCSD Human Research Protections Program approved the study protocol, consent, and all study-related procedures. All study participants provided voluntary, written informed consent before any study procedures were undertaken.

Neurocognitive assessment and comorbid conditions

The degree of NCI at the time of sample collection was measured using an established and sensitive method to determine neurocognitive functioning among PLWH (Gonzalez et al. 2003; Carey et al. 2004; Blackstone et al. 2012). Briefly, individuals completed a comprehensive neuropsychological test battery consistent with Frascati recommendations for NeuroAIDS research (Carey et al. 2004). Raw NC test scores were converted to demographically adjusted T scores and used to derive a global T score (higher scores = better performance). Individual T scores were also converted to deficit scores and averaged to derive a global deficit score (GDS) which was used to classify NCI (i.e., GDS ≥ 0.5). The GDS has been shown to detect mild, HIV-associated cognitive impairment based on the assessment of multiple cognitive domains (Carey et al. 2004). NCI in PLWH may not only be caused by HIV infection but also by comorbidities. Comorbidities in CHARTER participants were therefore classified with respect to whether they should be considered incidental, contributing, or confounding as causes of NCI, as described before (Heaton et al. 2010; Antinori et al. 2007).

Testing of BDG and suPAR and other biomarkers

As part of the CHARTER study, blood samples were prospectively tested for HIV RNA, CD4, and CD8 T cell counts. A subset of 31 CSF samples was also tested for uPAR levels (using the Quantikine Human uPAR ELISA, R&D Systems, Minneapolis, USA; assay marked for research use only). All samples analyzed as part of this study had been stored at − 80 °C within 90 min of collection.

Sixty-one paired plasma and CSF samples were retrospectively evaluated for BDG levels using the Fungitell® assay at the Associates of Cape Cod, Inc., research laboratories (Associates of Cape Cod, Inc., East Falmouth, USA) and for suPAR levels using suPARnostic assay (ViroGates,

Copenhagen, Denmark), a CE-marked in vitro diagnostic according to the manufacturer's instructions. Blood plasma samples were tested for soluble cluster of differentiation 14 (sCD14) levels (a marker of monocyte activation) using an enzyme-linked immunosorbent assay (ELISA; R&D Systems Inc., Minneapolis, MN, USA), and intestinal fatty acid binding protein (IFABP, marker of gut epithelial dysfunction; R&D Systems Inc., Minneapolis, MN, USA) according to the manufacturer's instructions.

Statistical analysis

For statistical analysis, SPSS 25 (SPSS Inc., Chicago, IL, USA) was used. BDG, suPAR, and other biomarkers as well as global T scores were used primarily as continuous variables. GDS was used as a binary (cutoff ≥ 0.5, which defines NCI), or continuous variable. When using GDS as a binary variable, biomarkers and biomarker combinations were evaluated using the Wilcoxon rank-sum test and receiver operating characteristic (ROC) curve analysis for the determination of area under the curve (AUC) values. Correlations between levels of BDG, other biomarkers, global T scores, and GDS were calculated using Spearman rho correlation analysis due to the non-normal distributions of GDS scores and other biomarkers. We further calculated the coefficient of variability between the suPAR and the uPAR assays. Power calculation revealed that a sample size of 61 plasma and CSF samples provides at least 80% power (alpha = 0.05) to detect an effect size 0.73 when comparing BDG or suPAR between those with NCI versus others. Univariate and multivariable binary logistic regression analyses assessed the predictors of NCI. Variables with a p value < 0.2 in univariate analysis were included in the multivariable model. Variables in the final model were selected with a stepwise forward procedure. Model discrimination was assessed by the goodness-of-fit Hosmer-Lemeshow statistics. Odds ratios (ORs) and adjusted odds ratios (aOR) including 95% confidence intervals (CIs) were calculated, and a p value of < 0.05 was considered statistically significant.

Results

The study cohort was comprised of 61 male and mostly white PLWH, with a median age of 48 years (range 27–63 years), that were without symptoms of opportunistic infections. Overall, 58/61 (95%) of participants had undetectable HIV RNA in blood plasma, and 59/61 (97%) had undetectable HIV RNA in CSF at the time of sampling. Median CD4$^+$ T cell count was 589 cells/μL (IQR 407–776, range 69–1587 cells/μL), median CD4$^+$/CD8$^+$ T cell ratio was 0.72 (IQR 0.44–1.01, range 0.11–2.00). Clinical characteristics are summarized in Table 1.

Table 1 Demographics and clinical metrics of study participants

Characteristics	Total subjects (N = 61)
Male sex, n (%)	61 (100)
Race, n (%)	
White	32 (52)
Black	20 (33)
Hispanics	9 (15)
Age, years, median (range)	48 (27–62)
Undetectable HIV RNA plasma, n (%)	58 (95)
Undetectable HIV RNA CSF, n (%)	59 (97)
CD4/CD8 ratio, median (range)	0.72 (range 0.11–2.00).
CD4+ cell count[1], cells/μL, median (range)	589 (69–1587)
Nadir CD4+ cell count[1], cells/μL, median (range)	212 (3–816)
Neurocognitive impairment (GDS > 0.5), n (%)	33 (54)
Smoking status, n (%)	48 (79)
Duration on current ART, years, median (range)	2 (0–9)
Duration on any ART, years, median (range)	5 (0–19)
ART regimens*	
NNRTI-based, n (%)	23 (43)
PI-based, n (%)	25 (46)
Other regimens, n (%)	6 (11)

CSF, cerebrospinal fluid; *ART regiments available for 54 study participants; *NNRTI*, non-nucleoside reverse transcriptase inhibitors; *PI*, protease inhibitors

Median BDG level was 18 pg/mL in plasma (range 2–60 pg/mL) and 20 pg/mL in CSF (range 0–830 pg/mL). Higher levels of plasma BDG were associated with lower global T scores (Spearman's rho = − 0.32; $p = 0.013$), and more severe cognitive impairment as measured by the GDS (Spearman $r = 0.35$; $p = 0.006$; Fig. 1). No other significant associations were observed between the remaining biomarkers and the NC variables: CSF BDG and GDS ($r = 0.23$), plasma suPAR and GDS ($r = 0.19$), CSF suPAR and
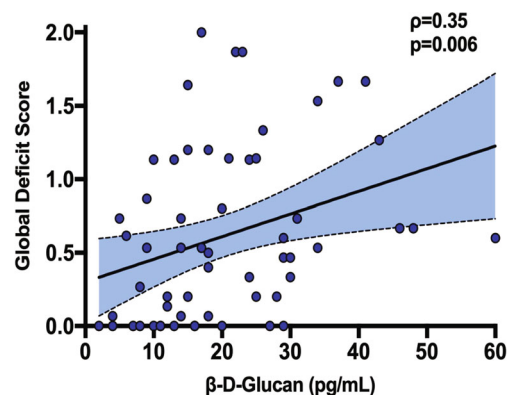

Fig. 1 Scatterplots of correlation of plasma beta-D-glucan levels with global deficit scores
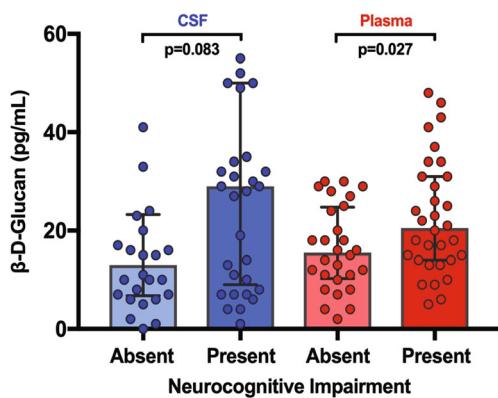
Fig. 2 Plasma and CSF beta-ᴅ-glucan levels in those with neurocognitive impairment (i.e., global deficit scores > 0.5) versus those without neurocognitive impairment

GDS ($r = -0.022$), sCD14 and GDS ($r = -0.033$), iFABP and GDS ($r = 0.057$), and CD4/CD8 ratio and GDS ($r = -0.028$). Interestingly, when plasma suPAR levels were adjusted for age, they were significantly associated with lower global T scores (beta -0.317; $p = 0.014$) and with higher GDS (beta 0.342; $p = 0.008$).

Comorbidities were classified as incidental in 32 participants, contributing to 19 participants, and confounding as causes of NCI in 10 participants. Correlation between plasma and CSF biomarkers and measures of NCI did not change after exclusion of participants with confounding comorbidities (plasma BDG level and global T scores $r = -0.33$; plasma BDG and GDS $r = 0.31$, other correlations not shown).

Individuals with NCI (i.e., GDS $\geq$ 0.5, $n = 33$) had higher plasma BDG levels compared to unimpaired individuals (median 21 pg/mL, range 5–60 versus median 16 pg/mL, range 2–30; $p = 0.027$; AUC = 0.666, 95%CI 0.530–0.801), and there was also a trend towards higher CSF BDG levels in impaired individuals ($p = 0.083$; AUC = 0.631, 95%CI 0.486–0.776;

Fig. 2). Plasma BDG levels > 30 pg/mL were observed in 30% of participants with NCI but not a single participant without NCI. No significant difference was observed for other biomarkers, including suPAR, sCD14, and IFABP.

In the univariate and multivariate model, only plasma BDG levels remained a predictor of NCI, while all other biomarkers and variables evaluated did not (Table 2; not displayed plasma IFABP, and plasma sCD14, both $p > 0.8$ in univariate analysis).

Plasma levels of BDG correlated significantly with plasma suPAR levels (rho = 0.31, $p = 0.016$), but not with other biomarkers.

CSF suPAR levels determined as part of this study correlated significantly with CSF uPAR levels determined at the time of sample collection as part of the CHARTER study with an assay marked for research use only (Spearman rho = 0.795; $p < 0.001$; $n = 31$). The coefficient of variation between the two assays (log_{10} values used for the research only assay) was mean 0.76, SD 0.23.

Discussion

Microbial imbalances in the gut likely play an important role in the pathogenesis of NCI (Dinan et al. 2015; Perez-Santiago et al. 2013; Petra et al. 2015). Translocation of bacterial and fungal products is one of many drivers of systemic inflammation and might contribute to HIV disease progression (Ramendra et al. 2019; Lozupone et al. 2013), as well as to NCI (Ancuta et al. 2008; McLaurin et al. 2019; Hoenigl 2019). As part of this study, we measured novel biomarkers of microbial translocation and immune activation in blood and CSF in a cohort of 61 PLWH on ART who underwent a detailed battery of NC assessments. We also compared

Table 2 Univariate and multivariable binary logistic regression models for predicting neurocognitive impairment

Variables for predicting neurocognitive impairment ($n = 61$)	OR	95% CI	p value	aOR	95% CI	p value
	Univariate Model			Multivariable Model		
Plasma BDG (per pg/mL)	1.066	1.010–1.124	0.020	1.066	1.010–1.124	0.020
CSF BDG (per pg/mL)	1.003	0.966–1.010	0.383			
Plasma suPAR	1.165	0.862–1.574	0.321			
Current CD4	0.999	0.997–1.001	0.290			
Current CD4/CD8 ratio	1.587	0.402–6.262	0.509			
Nadir CD4 count	0.997	0.994–1.000	0.083	–	–	n.s.
Months of ART exposure	1.004	0.995–1.013	0.341			
Age (per year)	1.041	0.977–1.110	0.213			
Higher education category	1.046	0.865–1.264	0.644			
Current smoker	0.627	0.195–2.019	0.434			

*Chi square 6.731; $p = 0.566$ Hosmer Lemeshow; Forward Wald binary logistic regression

OR, odds ratio; aOR, adjusted odds ratio; CSF, cerebrospinal fluid; n.s., not significant

performance for these novel biomarkers with established markers of monocyte activation (sCD14), immune dysfunction (CD4/CD8 ratio), and gut leakage (IFAB).

We found that in our cohort of chronically infected PLWH on suppressive ART, median levels of BDG in blood plasma (18 pg/mL) were similar to a previous study with a similar cohort of PLWH where the level of BDG was 15 pg/mL (Hoenigl et al. 2016b). Higher BDG levels (median 66 pg/mL) were reported from another study where PLWH began ART very early during infection and also had shorter follow-up times (Hoenigl et al. 2016a). Overall, the levels in our cohort were within the range of BDG levels previously reported for healthy subjects (Odabasi et al. 2004; Pruller et al. 2014), indicating that blood BDG levels may not consistently differentiate between those with and without HIV infection. Nevertheless, an increasing number of studies support BDG as a biomarker for microbial translocation and immune activation among those with HIV infection (Ancuta et al. 2008; Hoenigl et al. 2016a, b, 2018; Farhour et al. 2018; Mehraj et al. 2019; Hoenigl 2019). By contrast, the levels of BDG in CSF in our cohort were higher as compared to the cohort that received early ART (20 pg/mL compared to 5 pg/mL) (Hoenigl et al. 2016a). Subsequently, we found that elevated levels of BDG in blood plasma (but not in CSF) were significantly associated with worse NC performance in chronically infected PLWH on suppressive ART. This is in line with a previous smaller study from our group, showing a similar association in a group of 14 PLWH who started ART during early HIV infection (Hoenigl et al. 2016b). Also, higher plasma suPAR levels were significantly associated with worse NC performance, but only after adjusting for age. Interestingly, in our cohort, none of the other measured biomarkers (i.e., sCD14, IFABP, and CD4/CD8 ratio) were associated with NCI, which is in contrast to other studies (Lyons et al. 2011). These discrepancies might be because of differences in study populations, stage of HIV disease, and treatment status. Other limitations in our current study include the limited sample size and the cross-sectional design which may have biased our analysis and limited our ability to detect associations between NC performance and some of our other measured biomarkers.

Despite the mentioned limitations, our study confirms previous findings that elevated plasma levels of BDG may be an indicator of gut barrier integrity failure and an independent biomarker associated with NC performance in PLWH on suppressive ART. The same may be true for plasma suPAR levels, once adjusted for age.

Identification of biomarkers (or combination of biomarkers) that are sensitive to HIV-associated NC performance is essential to avenues of future research. While our findings might have clinical implications, future research is needed to validate our findings in an independent cohort. Incorporation of independent measurements of HIV-associated brain dysfunction (e.g., neuroimaging or neuropathological data) may provide further support of associations between BDG, suPAR, and NC performance. Future research is also needed to determine associations between biomarkers and the profile and pattern of neurocognitive performance, which is not feasible using dichotomous impairment outcome variables. Finally, longitudinal studies are needed to determine the prognostic and clinical utility of biomarkers such as BDG and suPAR in identifying those who may be at risk for subsequent neurocognitive decline.

Compliance with ethical standards

The UCSD Human Research Protections Program approved the study protocol, consent, and all study-related procedures. All study participants provided voluntary, written informed consent before any study procedures were undertaken.

Conflict of interest MH received grant funding from Gilead. YZ and MF are employees of Associates of Cape Cod. All other authors declare no conflict of interest.

Off-label use Fungitell®, the FDA-cleared IVD kit used for the measurement of $(1 \rightarrow 3)$-β-glucan in serum, does not have an indication for the diagnostic use of BG titers in CSF. The data presented here represents the research use only.

References

Ancuta P, Kamat A, Kunstman KJ, Kim EY, Autissier P, Wurcel A, Zaman T, Stone D, Mefford M, Morgello S, Singer EJ, Wolinsky SM, Gabuzda D (2008) Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. PLoS One 3:e2516

Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE (2007) Updated research nosology for HIV-associated neurocognitive disorders. Neurology 69(18):1789–1799

Blackstone K, Moore DJ, Franklin DR, Clifford DB, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, Ellis RJ, Atkinson JH, Grant I, Heaton RK (2012) Defining neurocognitive impairment in HIV: deficit scores versus clinical ratings. Clin Neuropsychol 26(6):894–908

Carey CL, Woods SP, Gonzalez R, Conover E, Marcotte TD, Grant I, Heaton RK, HNRC Group (2004) Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. J Clin Exp Neuropsychol 26:307–319

Cinque P, Nebuloni M, Santovito ML, Price RW, Gisslen M, Hagberg L, Bestetti A, Vago G, Lazzarin A, Blasi F, Sidenius N (2004) The

urokinase receptor is overexpressed in the AIDS dementia complex and other neurological manifestations. Ann Neurol 55(5):687–694

Deeks SG, Verdin E, McCune JM (2012) Immunosenescence and HIV. Curr Opin Immunol 24(4):501–506

Dinan TG, Stilling RM, Stanton C, Cryan JF (2015) Collective unconscious: how gut microbes shape human behavior. J Psychiatr Res 63:1–9

Farhour Z, Mehraj V, Chen J, Ramendra R, Lu H, Routy JP (2018) Use of (1–>3)-beta-d-glucan for diagnosis and management of invasive mycoses in HIV-infected patients. Mycoses 61:718–722

Gonzalez R, Heaton RK, Moore DJ, Letendre S, Ellis RJ, Wolfson T et al (2003) Computerized reaction time battery versus a traditional neuropsychological battery: detecting HIV-related impairments. J Int Neuropsychol Soc 9(1):64–71

Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F et al (2010) HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study. Neurology 75(23): 2087–2096

Heldt S, Prattes J, Eigl S, Spiess B, Flick H, Rabensteiner J et al (2018) Diagnosis of invasive aspergillosis in hematological malignancy patients: performance of cytokines, Asp LFD, and Aspergillus PCR in same day blood and bronchoalveolar lavage samples. J Infect 77(3):235–241

Hodges GW, Bang CN, Wachtell K, Eugen-Olsen J, Jeppesen JL (2015) suPAR: a new biomarker for cardiovascular disease? Can J Cardiol 31(10):1293–1302

Hoenigl M (2019) Fungal translocation: a driving force behind the occurrence of non-AIDS events? Clin Infect Dis. https://doi.org/10.1093/cid/ciz215

Hoenigl M, Raggam RB, Wagner J, Valentin T, Leitner E, Seeber K, Zollner-Schwetz I, Krammer W, Prüller F, Grisold AJ, Krause R (2013) Diagnostic accuracy of soluble urokinase plasminogen activator receptor (suPAR) for prediction of bacteremia in patients with systemic inflammatory response syndrome. Clin Biochem 46(3): 225–229

Hoenigl M, Perez-Santiago J, Nakazawa M, Faria de Oliveira M, Zhang Y, Finkelman M et al (2016a) (1 → 3)-β-glucan: a biomarker for microbial translocation in individuals with acute or early HIV infection? Front Immunol 7:404

Hoenigl M, de Oliveira MF, Perez-Santiago J, Zhang Y, Morris S, McCutchan AJ et al (2016b) (1 → 3)-beta-D-Glucan levels correlate with neurocognitive functioning in HIV-infected persons on suppressive antiretroviral therapy: a cohort study. Medicine (Baltimore) 95(11):e3162

Hoenigl M, Moser C, Funderburg N, Bosch R, Kantor A, Zhang Y et al (2018) Soluble urokinase plasminogen activator receptor (suPAR) is predictive of non-AIDS events during antiretroviral therapy-mediated viral suppression. Clin Infect Dis. https://doi.org/10.1093/cid/ciy966

Hunt PW (2012) HIV and inflammation: mechanisms and consequences. Curr HIV/AIDS Rep 9(2):139–147

Kamat A, Lyons JL, Misra V, Uno H, Morgello S, Singer EJ, Gabuzda D (2012) Monocyte activation markers in cerebrospinal fluid associated with impaired neurocognitive testing in advanced HIV infection. J Acquir Immune Defic Syndr 60:234–243

Lawn SD, Myer L, Bangani N, Vogt M, Wood R (2007) Plasma levels of soluble urokinase-type plasminogen activator receptor (suPAR) and early mortality risk among patients enrolling for antiretroviral treatment in South Africa. BMC Infect Dis 7:41

Lozupone CA, Li M, Campbell TB, Flores SC, Linderman D, Gebert MJ, Knight R, Fontenot AP, Palmer BE (2013) Alterations in the gut microbiota associated with HIV-1 infection. Cell Host Microbe 14(3):329–339

Lyons JL, Uno H, Ancuta P, Kamat A, Moore DJ, Singer EJ, Morgello S, Gabuzda D (2011) Plasma sCD14 is a biomarker associated with impaired neurocognitive test performance in attention and learning

domains in HIV infection. J Acquir Immune Defic Syndr 57(5):371–379

McLaurin KA, Booze RM, Mactutus CF (2019) Diagnostic and prognostic biomarkers for HAND. J Neurovirol

Mehraj V, Ramendra R, Isnard S, Dupuy FP, Ponte R, Chen J, Kema I, Jenabian MA, Costinuik CT, Lebouché B, Thomas R, Coté P, Leblanc R, Baril JG, Durand M, Chartrand-Lefebvre C, Tremblay C, Ancuta P, Bernard NF, Sheppard DC, Routy JP, Montreal Primary HIV Infection Study and Canadian HIV and Aging Cohort Study Groups, Milne C, Lavoie S, Friedman J, Duchastel M, Villielm F, Asselin F, Boissonnault M, Maziade PJ, Lavoie S, Milne M, Miaki NZ, Thériault ME, Lessard B, Charron MA, Dufresne S, Turgeon ME, Vézina S, Huchet E, Kerba JP, Poliquin M, Poulin S, Rochette P, Junod P, Longpré D, Pilarski R, Sasseville E, Charest L, Hamel A, Cloutier-Blais A, Massoud S, Chano F, Trottier B, Labrecque L, Fortin C, Hal-Gagne V, Munoz M, Deligne B, Martel-Laferrière V, Trottier B, Goyer ME, Teltscher M, de Pokomandy A, Cox J, Beauchamp E, Haraoui LP (2019) Circulating (1–>3)-beta-D-Glucan is associated with immune activation during HIV infection. Clin Infect Dis

Morris A, Hillenbrand M, Finkelman M, George MP, Singh V, Kessinger C, Lucht L, Busch M, McMahon D, Weinman R, Steele C, Norris KA, Gingo MR (2012) Serum (1–>3)-beta-D-glucan levels in HIV-infected individuals are associated with immunosuppression, inflammation, and cardiopulmonary function. J Acquir Immune Defic Syndr 61(4):462–468

Odabasi Z, Mattiuzzi G, Estey E, Kantarjian H, Saeki F, Ridge RJ, Ketchum PA, Finkelman MA, Rex JH, Ostrosky-Zeichner L (2004) Beta-D-glucan as a diagnostic adjunct for invasive fungal infections: validation, cutoff development, and performance in patients with acute myelogenous leukemia and myelodysplastic syndrome. Clin Infect Dis 39(2):199–205

Oliveira I, Andersen A, Furtado A, Medina C, da Silva D, da Silva ZJ, et al (2012) Assessment of simple risk markers for early mortality among HIV-infected patients in Guinea-Bissau: a cohort study. BMJ Open 2(6).https://doi.org/10.1136/bmjopen-2012-001587. Print 2012

Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT et al (2006) Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 43(1):27–34

Perez-Santiago J, Gianella S, Massanella M, Spina CA, Karris MY, Var SR et al (2013) Gut Lactobacillales are associated with higher CD4 and less microbial translocation during HIV infection. AIDS 27(12): 1921–1931

Petra AI, Panagiotidou S, Hatziagelaki E, Stewart JM, Conti P, Theoharides TC (2015) Gut-microbiota-brain axis and its effect on neuropsychiatric disorders with suspected immune dysregulation. Clin Ther 37(5):984–995

Prattes J, Hoenigl M, Rabensteiner J, Raggam RB, Prueller F, Zollner-Schwetz I, Valentin T, Hönigl K, Fruhwald S, Krause R (2014) Serum 1,3-beta-d-glucan for antifungal treatment stratification at the intensive care unit and the influence of surgery. Mycoses 57(11):679–686

Pruller F, Wagner J, Raggam RB, Hoenigl M, Kessler HH, Truschnig-Wilders M, Krause R (2014) Automation of serum (1–>3)-beta-D-glucan testing allows reliable and rapid discrimination of patients with and without candidemia. Med Mycol 52(5):455–461

Raggam RB, Wagner J, Pruller F, Grisold A, Leitner E, Zollner-Schwetz I et al (2014) Soluble urokinase plasminogen activator receptor predicts mortality in patients with systemic inflammatory response syndrome. J Intern Med 276:651–658

Ramendra R, Isnard S, Mehraj V, Chen J, Zhang Y, Finkelman M, Routy JP (2019) Circulating LPS and (1–>3)-beta-D-glucan: a Folie a Deux contributing to HIV-associated immune activation. Front Immunol 10:465

Rasmussen LJ, Knudsen A, Katzenstein TL, Gerstoft J, Obel N, Jorgensen NR et al (2016) Soluble urokinase plasminogen activator receptor (suPAR) is a novel, independent predictive marker of myocardial infarction in HIV-1-infected patients: a nested case-control study. HIV Med 17(5):350–357

Reischies FM, Prattes J, Pruller F, Eigl S, List A, Wolfler A et al (2016) Prognostic potential of 1,3-beta-d-glucan levels in bronchoalveolar lavage fluid samples. J Infect 72(1):29–35

Sidenius N, Nebuloni M, Sala S, Zerbi P, Price RW, Gisslen M, Hagberg L, Vago L, Lazzarin A, Blasi F, Cinque P (2004) Expression of the urokinase plasminogen activator and its receptor in HIV-1-associated central nervous system disease. J Neuroimmunol 157(1–2):133–139