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Association of periodontitis with markers of immunologic and haemostatic state in people living with HIV. Letter to the Editor

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Sir,

In this journal, we previously reported that the prevalence and severity of periodontitis is higher in people living with HIV (PLWH) compared to controls, particularly in older males¹. Therefore, we now assessed whether the inflammatory burden of periodontitis, as quantified by the periodontal inflammation area (PISA)² is associated with immune senescence and a hypercoagulable state in PLWH.

Despite using combination antiretroviral therapy (cART), PLWH have an increased prevalence of non-AIDS, age-related co-morbidities, such as atherosclerosis, cardiovascular diseases, malignancies, and liver disease compared to HIV uninfected people.³ Chronic inflammation, persistent immune activation and accelerated immune ageing, also referred to as immunosenescence, are considered to underlie accelerated ageing in PLWH, despite a near-complete suppression of viral replication.⁴ The source of the persistent immunosenescence in PLWH is still not completely understood. Damage to the mucosa of the gastrointestinal tract by massive HIV-induced local CD4+ T-cell depletion, resulting in translocation of microbial products into the peripheral blood and consecutive immune activation, has been presumed to be a mechanism behind the ongoing immune activation in spite of undetectable HIV virus particles in the plasma.⁵ The gastrointestinal tract is considered to be the most apparent source of microbial products. Another major source might be the oral cavity, because microbial translocation and inflammation have been shown to be elevated in people with periodontitis.⁶ Periodontitis is a chronic inflammatory disease of the tissues supporting the teeth, caused by specific microorganisms or groups of specific microorganisms. Periodontitis has shown to be a risk factor for a broad range of age-related diseases, such as cardiovascular disease.⁷ There is a higher prevalence of periodontitis in PLWH compared to controls,¹ but its role in HIV-related immune activation has been scarcely studied. Furthermore, inflammation not only affects the immune system, but also drives hypercoagulability, i.e., the increased tendency of blood clotting (coagulation). There is some evidence of a hypercoagulable state in PLWH, which only reverses partially after initiation of antiretroviral therapy.⁸ As periodontitis is frequently found in PLWH, the systemic effect raised by the periodontal inflammation might also be a driver for the hypercoagulability, which might also be an explanation for, e.g., the elevated risk of cardiovascular disease in PLWH.

Of the 258 PLWH included in the previous study¹, 125 people accepted the invitation for a follow-up study. The participation inclusion criteria were: presence of ≥ 6 teeth, use of cART for ≥ 6 months, and the last two viral load measurements showing < 40 copies/ml or undetectable virus. Forty-five people had to be excluded, resulting in 80 eligible people for our study. These 80 dentate PLWH were subjected to full-mouth probing pocket depth and bleeding on probing assessments, from which PISA was calculated.² In addition, to find out whether immune function can be affected by periodontitis, we assessed markers for: 1) microbial translocation (lipopolysaccharides (LPS)), 2) inflammation (IL-6, CXCL-10), 3) activation of innate immunity (monocyte and macrophage activation markers, i.e., soluble CD14 and CD63), and 4) activation of adaptive immunity (CD4+ and CD8+ T-cells, naïve and memory T-cells, 'senescent' T-cells, activated T-cells, PD-1 level). Furthermore, haemostatic parameters associated with inflammation and periodontitis were collected, i.e., factor VIII, von-Willebrand-Factor Antigen (VWF:Ag) and activity, d-dimer, thrombin generation and clot lysis time. Correlations between PISA and immunological and haemostatic parameters were assessed using Pearson's rho (ρ), and multiple linear regression analyses controlling for factors that might

influence PISA. The institutional review board of the University Medical Center Groningen (METc number 2014/128) approved the study. All PLWH provided written informed consent .

The study population consisted mainly of males (86.3%) with a mean age of 50.8 years (SD 11.4), The PLWH had received cART for a mean duration of 9.5 years (SD 6.1). mean PISA was 968.9 mm² (SD 561.2 mm², Table 1). Clinical and virologic characteristics as well as type of cART were also not associated with the PLWHs' PISA ($r < 0.3$ and $p > 0.05$, Table 2). After adjusting for sex, body mass index and age, a trend was found towards an association between periodontitis severity and factor VIII ($p = 0.06$) and von Willebrand factor antigen (VWF:Ag)($p = 0.05$, Table 2). This association might be explained by the fact that both factor VIII and VWF:Ag are acute phase reactants, heavily influenced by both acute and chronic inflammation,⁹ such as severe periodontitis. Although we assume that the association between factor VIII /VWF:Ag and severe periodontitis is causal, it is currently unknown what the potential impact of reducing periodontal burden might be on PLWH's risk for cardiovascular disease.

We found no association between PISA and immune senescence in PLWH. PISA was not significantly correlated with measured levels of microbial translocation, inflammation and immune senescence (Table 2). These findings suggest that the periodontal inflamed surface is not a significant source of microbial translocation within PLWH. This is in contrast to the gastrointestinal tract which probably plays a greater role in HIV-related systemic immune activation. It is known that increased gastrointestinal tract translocation contributes directly to systemic immune activation in the chronic phase of HIV infection and may ultimately determine the rate of progression to AIDS.¹⁰ Thus, it can be presumed from our results that microbial translocation occurring in the gastrointestinal tract has a greater impact than microbial translocation from a periodontal inflamed surface in the oral cavity.

On basis of our analyses, we like to conclude that severity of periodontal decay is not an important large contributing factor in immune senescence of PLWH who are virologically suppressed, but the observed association between periodontitis and the hypercoagulable state might partially explain why the risk of cardiovascular disease is elevated in PLWH.

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Table1: Clinic and virological characteristics of the 80 studied PLWH.

Male N (%)		69 (86.3)
Mean Age in years (SD)		51(11.4)
Mean BMI (kg/m ²) (SD)		24 (3.0)
Ethnicity N (%)	African	7 (8.8)
	European	69 (86.3)
	North American	3 (3.8)
	South American	1 (1.3)
Tobacco use N (%)	Current smokers	22 (27.5)
	Never smoked	32 (40)
	Former smokers	26 (32.5)
History of cardiovascular disease N (%)	Absent	55 (68.8)
	Present	17 (21.3)
	Unknown	8 (10)
Person with diabetes mellitus N (%)		6 (7.5)
Visit the dentist N (%)	No	5 (6.3)
	Yes, regularly	66 (82.5)
	Only with complaints	9 (11.3)
Dentist is not aware of the HIV/AIDS infection#N (%)		25 (33.3)
Mean PISA, mm ² (SD)		969 (561)
Mean Number of elements present (SD)		25 (4.6)
Median VAS regarding importance of dental health (IQR)		9 (1.3)
Mode of HIV transmission N (%)	MSM	59 (73.8)
	Heterosexual	17 (21.3)
	Blood and otherwise	4 (5.0)
Type of cART N (%)	PI-based	19 (23.8)
	NNRTI-based	42 (52.5)
	INI-based	12 (15.0)
	Other	7 (8.8)
CD4+ nadir*(109/L) N (%)	Stage 1	28 (35.0)
	Stage 2	41 (51.3)
	Stage 3	7 (8.8)
sexually transmitted diseases N (%)	Syphilis	9 (11.3)
	Gonorrhoea	36 (45.0)
	Chlamydia	35 (43.8)
CMV IgG* N (%)		74 (92.5)
Median CD4 ⁺ /CD8 ⁺ (10 ³ /L cells/mm ³) (IQR)		0.94 (0.61-1.31)
Median CD4 ⁺ nadir (cells/mm ³)* (IQR)		225.0[122.5-340.0]
Mean Duration of infection (years) (SD)		11.2 (6.8)
Mean Period using cART (years)(SD)		9.5 (6.1)

a subset of 75 people who reported visiting a dentist regularly

*CD4+ nadir and CMV IgG was not known for 4 PLWH, due to incomplete patient files

Table 2: Immunology and haemostasis parameters of the 80 studied PLWH.

Immunology & Haemostasis parameters	Mean	SD	Pearson's rho correlation	p	Adjusted Beta (/100 mm2 PISA increment) #	p
CD3 ⁺ T-cells (10 ⁹ /L)	1519.0	549.7	0.10	0.39	---	---
CD4 ⁺ T-cells (10 ⁹ /L)	670.3	273.7	-0.06	0.61	---	---
Naive CD4 ⁺ T-cells (% of CD4 ⁺ T-cells)	26.8	14.3	-0.15	0.19	-0.44	0.07
CD4 ⁺ HLA-DR ⁺ T-cells (% of CD4 ⁺ T-cells)*	20.0	14.3	0.08	0.48	---	---
CD4 ⁺ CD38 ⁺ T-cells (% of CD4 ⁺ T-cells)	45.1	15.2	-0.20	0.08	-0.61	0.02
CD4 ⁺ HLA-DR ⁺ +CD38 ⁺ T-cells (% of CD4 ⁺ T-cells)*	6.5	5.2	0.04	0.75	---	---
CD4 ⁺ CD28 ⁺ CD57 ⁺ T-cells (% of CD4 ⁺ T-cells)	6.6	6.1	0.18	0.12	0.22	0.07
CD8 ⁺ T-cells (10 ⁹ /L)	754.8	363.5	0.17	0.13	10.7	0.16
Naive CD8 ⁺ T-cells (% of CD8 ⁺ T-cells)	13.2	10.7	-0.03	0.81	---	---
CD8 ⁺ HLA-DR ⁺ T-cells (% of CD8 ⁺ T-cells)*	28.6	16.7	0.05	0.67	---	---
CD8 ⁺ CD38 ⁺ T-cells (% of CD8 ⁺ T-cells)	30.2	14.8	-0.15	0.19	-0.38	0.22
CD8 ⁺ HLA-DR ⁺ +CD38 ⁺ T-cells (% of CD8 ⁺ T-cells)*	11.0	9.9	-0.01	0.94	---	---
CD8 ⁺ CD28 ⁺ CD57 ⁺ T-cells (% of CD8 ⁺ T-cells)	16.9	14.0	0.04	0.75	---	---
CD4:CD8 ratio(10 ⁹ /L)	1.1	0.7	-0.18	0.11	-0.02	0.20
IL-6 R&D (pg/ml)	1.3	1.9	0.17	0.14	0.06	0.16
sCD14 (µg/ml)	3.9	1.3	0.17	0.13	7.6	0.16
PD-1 (pg/ml)	335.7	738.7	0.08	0.49	---	---
CXCL10* (pg/ml)	160.4	63.1	0.03	0.80	---	---
sCD163 (ng/ml)	44.4	36.9	0.04	0.73	---	---
LPS/DPLG70 (ng/ml)	136.0	46.3	-0.16	0.15	-0.06	0.20
Fragment 1+2 (pmol/l)	162.6	80.5				
von Willebrand factor antigen (%)	163.8	67.1	0.21	0.07	2.6	0.05
Fibrinogen (g/l)	2.9	0.7	0.09	0.41	---	---
Factor VIII (%)	146.1	41.3	0.20	0.08	1.5	0.06
D Dimer (ng/ml)	293.2	282.3	-0.12	0.28	---	---
Velocity index (nm/min)	88.6	29.9	0.16	0.16	0.62	0.28
Thrombin generation: peak thrombin (nm)	217.0	44.5	0.13	0.27	---	---
Thrombin generation: ETP TM (nm/min)	465.4	153.5	-0.01	0.96	---	---
Thrombin generation: Velocity index TM (nm/min)	67.2	26.7	0.09	0.43	---	---
Thrombin generation: Lagtime TM (min)	1.8	0.4	0.02	0.89	---	---
Thrombin generation: Peak TM (nm)	133.0	45.6	0.05	0.68	---	---
Clot lysis time* (min)	74.3	19.2	0.15	0.17	0.40	0.32

Adjusted for age, sex and BMI

* data available for 79 PLWH

** data was not known for 4 PLWH due to incomplete patient files