Clinical, biological, metabolic and immune changes associated with the use of Sodium-glucose cotransporter 2 inhibitors in people living with HIV

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Abstract:

Introduction: Positive cardiovascular and renal outcomes associated with the Sodium-Glucose cotransporter 2 inhibitor (SGLT2i) use are attributed to their anti-inflammatory properties. Persistent immune activation accounts for part of people living with HIV (PWH) elevated cardiovascular risk, but SGLT2i impact on this population has been poorly described.

Methods: All PWH with a history of SGLT2i treatment from May 2020 to April 2023 receiving care at Pitié-Salpêtrière Hospital (Paris, France) with pre- and post-treatment available blood samples were included. Clinical and biological data were extracted from medical records, metabolic and immune biomarkers from cryopreserved plasma samples.

Results: Most of the 20 patients with SGLT2i treatment were male (75%), with a median [IQR] age of 59 [55;68] years, receiving antiretroviral therapy for a median of 21.5 [15.3;26.5] years. Most had type 2 diabetes (95%), chronic kidney disease (90%), dyslipidemia (80%), and hypertension (75%). SGLT2i treatment was associated with a median of 3 kg weight loss, an increase in hematocrit and decreased AST levels. LDL, HDL, oxLDL and Lp-PLA2 levels were unaffected. SGLT2i was associated with inflammasome inhibition, with decreased circulating levels of IL-1β and IL-8. There was also a decrease in cytokines associated with the recruitment and activation of monocytes-macrophages MCP-1, MIP-1α, MIP-1β, Eotaxin, RANTES, IL-8, and their positive feedback, IL-13/IL-4. Decreased IL-6, CRP and sCD14 levels were non- significant.

Conclusion: on PWH, SGLT2i was associated with weight loss and a broad impact on innate immunity, with inhibition of inflammasome and monocyte-macrophage activation.

Keywords: dapagliflozin; empagliflozin; HIV; SGLT2; inflammation; metabolism

Highlights

- SGLT2i use was associated with a median weight loss in PWH of 3 kg
- SGLT2i use in PWH was linked to significant changes in surrogate markers associated with their clinical impact.
- SGLT2i may decrease IL-1 β and IL-8 levels, consistent with inflammasome inhibition
- SGLT2i may inhibit both monocyte-macrophage associated cytokines and their feedbacks

1. Introduction

Initially developed as glucose-lowering agents, sodium-glucose co-transporter 2 inhibitors (SGLT2i) have shown remarkable effects on improving cardiovascular and renal outcomes in patients with and without type 2 diabetes mellitus (DM) (1,2). Mechanisms underlying their characteristics are still unclear but seem to involve changes in body weight, blood pressure, diuresis, and cellular metabolism (1–4). This last property accounts for their significant anti-inflammatory effects, which manifest in both innate (mostly through inflammasome inhibition) and adaptive immunity (mostly through Th17 inhibition) (5–7).

Compared to the general population, people living with HIV (PWH) have an increased risk of cardiovascular disease (CVD), even after adjusting for traditional risk factors (8). This elevated risk is attributed, at least partially, to a residual immune activation that is not fully suppressed with antiretroviral therapy (ART) (9).

To date, however, potential effects of SGLT2i on HIV-associated inflammation remain to be studied. The aim of this study is to evaluate the impact of SGLT2i on clinical, biological and immunological parameters in PWH.

2. Methods

1. Patients and samples: All adult PWH patients with a history of SGLT2i treatment from May 2020 to May 2023, who routinely received care at Pitié-Salpêtrière Hospital (Paris, France), and had blood samples available both before and after treatment initiation, were included. If multiple post-treatment samples were available, the one closest to the 6-month post-treatment mark was selected to minimize potential biases. Patient with hematologic malignancies or with samples collected only under acute conditions were excluded. Finally, 10 healthy, non-SGLT2i treated patients routinely followed at Pitié Salpêtrière Hospital were selected to compare their cytokine levels with PWH before and after treatment initiation. Due

to legal constraints and sample availability, they were selected among pre-exposure prophylaxis (PrEP) users. Because the use of SGLT2i as a primary-prevention treatment would be to reduce the cardiovascular risk of PWH to the level of the general population, we selected PrEP users within the same age range as the SGLT2i patients with either no or limited co-existing diseases.

2. Data collection and sample processing: Patient's clinical and biological characteristics were retrospectively extracted from the medical records. Inflammatory and immune activation biomarkers were assessed in duplicate from -80°C stored plasma samples using the Bio-Plex Human Cytokine 27-Plex Panel (Bio-Rad, Hercules, CA, USA), Human C-Reactive Protein/CRP QuicKit ELISA (R&D Systems Inc, Minneapolis, MN, USA), and Human CD14 Quantikine ELISA Kit (R&D Systems Inc, Minneapolis, MN, USA) according to their respective manufacturer's recommendations on a Luminex 200 platform. The values below the detection limit were set to zero. Lipoprotein-associated phospholipase A2 (Lp-PLA2) activity was measured using the i-plaq Test (Techno-path Manufacturing Ltd., Ireland) on a Konelab 20i analyser (Thermo Fisher Diagnostics, France), and oxidized Low-Density Lipoprotein (oxLDL) using Mercodia oxidized LDL ELISA (Mercodia, Sweden). Quantification of total HIV-1 DNA was performed from frozen-stored cell pellets using the Generic HIV DNA Cell kit (Biocentric, Bandol, France) on a LightCycler480 (Roche) platform.

3. Statistical analysis: Statistical analyses were performed using R software. Categorical variables were expressed as numbers (percentages) and continuous variables as medians (interquartile ranges [IQR]). Univariate analyses were performed using Wilcoxon signed-rank test for continuous variables and McNemar test for categorical variables, with $p<0.05$ considered to be statistically significant.

4. Ethics: In accordance with French laws, patients were informed about the anonymous data collection and told that they could decline inclusion. Database is registered within the French National Information Technology and Civil Liberties Board (registration No. 770134, MR004 No 20231013131200). Patients were systematically notified of any supplementary biological analyses on frozen samples, initially collected as part of routine clinical practice.

3. Results

1. Baseline Characteristics

Among the 4323 PWH routinely followed in Pitié-Salpêtrière Hospital, 35 had an history of SGLT2i treatment, with biological data and frozen stored plasma samples available for 20 of them. One patient was excluded for no attending follow-up visit after treatment initiation, three for non-compliance with treatment, two because of acute hematological malignancies, and one because the only post-SGLT2i visit was because of a malaria episode. Eight were excluded due to lack of available samples. There were no significant differences between these eight patients and the included ones in term of age, BMI, CD4 nadir, time on ART, diabetes, dyslipidemia, statin use, hypertension, tobacco status and ARV or glucose-lowering therapies. Baseline characteristics of the study population is summarized in Table 1. Most patients were male (75%), with a median age of 59 years (IQR 55-68). The majority had chronic kidney disease (90%) and cardiovascular conditions, such as diabetes mellitus (95%), dyslipidemia (80%) and arterial hypertension (75%). They had been on ART for a median of 21.5 years (IQR 15.3-26.5). The most common current ART regimen was a combination of an integrase strand-transfer inhibitor (INSTI) with one or two nucleoside reverse transcriptase inhibitors. Eighty-eight percent of INSTI users were on second-generation INSTIs (dolutegravir, bictegravir, and elvitegravir), for a median of 3.7 (IQR [2.8-4.7]) years.

2. Changes in clinical and routine laboratory variables after SGLT2i treatment

Dapagliflozin was prescribed for all patients except one, who was prescribed Empagliflozin. After a median of treatment of 8.3 months (IQR [6.3-12.9]), there was no significant adverse event but significant clinical and laboratory changes. Weight decreased for a median of 3 kg ($p = 0.0018$), AST decreased for a median of 5 UI/L ($p=0.0224$), while hematocrit rose for a median 2% ($p=0.0094$) and creatinine 17.5 µmol/l ($p=0.029$). There was a trend for a diminution of uric acid level (median - 36.5 µmol/l compared to baseline), although it did not reach significance ($p=0.08$). Of note, there was a non-significant decrease in blood pressure and, while glycated hemoglobin (HbA1c) and lipid profiles, including oxLDL and Lp-PLA2 activity were unchanged. Finally, there was no change in HIV-related variables, with HIV viral load, HIV cell-associated DNA, CD4 level, CD8 levels and CD4/CD8 ratio roughly similar after treatment (Table 2).

3. Immunomodulatory Effects of SGLT2i on People Living with HIV

Introduction of SGLT2i was associated with a significant drop of inflammasome-related activity, with lower values of circulating IL-1β ($p=0.0026$) and IL-8 ($p=0.036$). Treatment was also associated with a decreased recruitment activity of macrophages and monocytes, as evidenced by a statistically significant reduction in MCP-1/CCL2 ($p=0.0042$), MIP-1α/CCL3 ($p=0.045$), MIP-1β/CCL4 ($p=0.012$), Eotaxin/CCL11 ($p=0.0027$), RANTES/CCL5 ($p=0.011$), IL-8 ($p=0.036$) and their positive feedback regulators IL-13 ($p=0.0009$), IL-4 ($p=0.029$) and GM-CSF ($p=0.035$). However, this reduced innate-immunity activity did not translated into significantly reduced levels of IL-6 ($p=0.13$), nor CRP ($p=0.21$). IL-15, a marker of atherosclerosis was also reduced after treatment ($p=0.016$). However, sCD14, a common marker of microbial translocation and mucosal integrity, was unaffected by treatment introduction ($p=0.43$). Changes in immunological markers after SGLT2i treatment are summarized in the Table 3 and Sup. Table 1.

Finally, we performed exploratory analyses to compare these immunological parameters with a control group composed of healthy subjects with similar age chosen among PrEP users (n=10). Because they were selected to have limited or no co-existing diseases, their clinical characteristics, as summarized in Sup. Table 2 are quite distinct from the SGLT2i group. For instance, there was no healthy subjects with a history of chronic kidney disease or any cardiovascular event, and none were on SGLT2i treatment. As expected, overall inflammation markers were numerically lower in the control group compared to PWH (Sup. Table 3). Interestingly, the use of SGLT2i was linked with a decrease in circulating IL-6, IL-13, IP-10, GM-CSF, MIP1β, and RANTES levels, which became similar to the control group. However, IL-5 level remained significantly higher in PWH compared to the control group, even after SGLT2i treatment.

4. Discussion

We present the first study addressing clinical, biological, metabolic and immunological parameters changes associated with SGLT2i treatment in PWH. Use of SGLT2i was associated with a median weight loss of 3 kg, an increase in hemoglobin / hematocrit and creatinine level, and a modest diminution of AST and uric acid levels compared to baseline. Immunological changes affected mainly inflammasome and monocyte-macrophage activation pathways, while CD4 level, CD8 level, CD4/CD8 ratio and HIV-associated cell DNA were unaffected. Of note, there was no significant change on lipid metabolism: total cholesterol, LDL-cholesterol, HDL-cholesterol and Triglycerides (TG) were roughly identical, as well as the more specialized parameters oxidized LDL and Lp-PLA2 activity.

Despite the limited number of patients included, changes in clinical and laboratory parameters remarkably aligned with data from previous cohort or randomized controlled trials performed on HIV-uninfected individuals. Weight has been reported to decrease from 1 to 3 kg, systolic

blood pressure around 1-5 mmHg and serum uric acid around 50-100 µmol/L, while hematocrit rose from 1 to 5 % (7,10–14). These last two points are especially of interest since they were repeatedly identified as the statistical determinants between SGLT2i use and their reduction in heart failure hospitalizations and major adverse renal events (3,15–17). Decrease in AST and ALT levels were inconsistently reported, and occurred mostly on patients with non-alcoholic fatty liver disease (NASH) (7,11,18,19) due to a broad impact on liver metabolism (20–22). Finally, we observed a significant increase in creatinine levels, a phenomenon attributed to the reduction in intraglomerular pressure and glomerular hyperfiltration (23,24). Importantly, this early decline is not associated with higher rates of kidney disease progression (24).

Inhibition of inflammasome activity by SGLT2i was expected, as it was a consistent finding from *in-vitro* and cohort studies (7,25,26). This point is of interest as inflammasome activation has been linked to higher coronary plaque and cardiovascular risk on PWH (27,28). Inhibition of IL-6 and CRP has also been steadily described (25,29), but did not reach statistical significance in the present study, owing probably to a lack of power and relatively low baseline levels due to long-term ARV. Inhibition of monocyte-macrophage activation by SGLT2i has been previously described in vitro or in animal studies (30–32), with conflicting in-vivo results (29,33). The relatively high impact of SGLT2i with both lower levels of cytokines associated with monocyte-macrophage inhibition MCP-1, MIP-1α, MIP-1β and RANTES (34,35) and cytokines associated with their positive feedbacks IL-13, IL-4 and GM-CSF (36,37) could be explained by the persisting upregulation of these cytokines in PWH despite effective ARV therapy (9,38), with this upregulation even more pronounced in the setting of CVD (39,40). In this setting, lower IL-15 levels post SGLT2i treatment is a compelling finding, as IL-15 levels have already been linked to cardiovascular risk in people with diabetes, regardless of HIV status (41,42).

Overall, SGLT2i concurrent impacts on innate immunity offers a promising therapy for the inflammatory part of HIV-associated cardiovascular risk.

This study has several limitations. First, we were able to include only 20 patients among the 4323 PWH routinely followed in this center. This finding is consistent with previous reports that highlighted that SGLT2i are substantially under-prescribed in this population (43,44). Second, due to its retrospective design SGLT2i duration length varied, although its impact on surrogate markers seems to be steady after 1 month treatment (11), and we could not prevent the introduction of other glucose-lowering agent. Fortunately, 90% of the patients studied had no introduction of other DM treatment, and opposed to GLP1 agonists SGLT2i does not seem to be associated with changes in food habits (45). Third, we presented a monocentric study from a high-income country. However, 70% of the patients included are non-native French, most of whom were born in Africa, reflecting the diversity of people followed-up in our center. Finally, choosing a limited number of healthy PrEP users as a control group to compare cytokines evolutions is another limitation. PrEP users are known to have slightly distinct inflammatory profiles from the general population (46), and intra-individual cytokine variabilities are not always non-negligible(47). These elements explained why these results can only be interpreted as exploratory, with further studies in larger groups needed to confirm these trends.

Conclusion

Overall, clinical, biological, metabolic and immunological parameters induced by SGLT2i treatment on PWH reflect the beneficial changes observed in previous clinical trials and cohort studies on HIV-negative people. SGLT2i may also have a broader influence on inflammation compared to the general population, presumably due to the increased basal levels present in PWH. As a consequence, SGLT2i offers a promising strategy for

cardiovascular risk reduction in PWH. Prospectives studies are needed to evaluate to what extent these changes might affect morbidity and mortality outcomes.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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411 Table 1: Baseline demographic and characteristics

Characteristic	SGLT2i patients (n=20)
Age, years, median (IQR)	59 (55-68)
Male sex at birth, n (%)	15 (75%)
BMI, kg/m², median (IQR)	26.7 (24.1-28.7)
Non-native French, n (%)	14 (70%)
Cardiovascular and metabolic	
Past tobacco smoker, n (%)	5 (25%)
Current tobacco smoker, n (%)	2 (10%)
Arterial hypertension, n (%)	15 (75%)
Dyslipidemia, n (%)	16 (80%)
Diabetes mellitus, n (%)	19 (95%)
Statin use, n (%)	14 (70%)
History of cardiovascular event, n (%)	5 (25%)
Chronic heart failure, n (%)	4 (20%)
Chronic kidney disease	
Stage 1, n (%)	2 (10%)
Stage 2, n (%)	7 (35%)
Stage 3A / 3B, n (%)	5 (25%) / 4 (20%)
Stage 4, n (%)	2 (10%)
HIV related health history	
Time since HIV diagnosis, years, median (IQR)	22.3 (16.3-25.9)
Total ART duration, years, median (IQR)	21.5 (15.3-26.5)
Nadir CD4 count, median (IQR)	166 (79-208)
Prior AIDS-defining event, n (%)	6 (30%)
Current ART regimen	
INSTI with NRTI, n (%)	14 (70%)
INSTI with NNRTI, n (%)	2 (10%)
NRTI with NNRTI, n (%)	1 (5%)
PI + INSTI + Maraviroc / PI alone, n (%)	2 (10%) / 1 (5%)
SGLT2i prescription	
Diabetologist	9 (45%)
Cardiologist	3 (15%)
Nephrologist	3 (15%)
General practitioner	2 (10%)
Infectious disease specialist	3 (15%)
Glucose lowering therapy co-medication	
Metformin	12 (60%)
sulfonylureas	6 (30%)
GLP-1 agonist	4 (20%)
DPP-4 inhibitor	1 (5%)
Insulin	6 (30%)

412

413

414 Table 2: Changes in clinical and biological variables after SGLT2i treatment.

Variables	Baseline	After iSGLT2 treatment	P value[a]
Clinical			
Weight (kg)	80.0 (74.0 - 89.5)	79.0 (68.0 - 85.8)	**<0.01**
BMI (kg/m²)	26.7 (24.1 - 28.7)	25.2 (22.9 - 28.2)	**<0.01**
SBP (mmHg)	137.5 (129.5 - 151.0)	135.0 (123.0 -149.5)	0.33
DBP (mmHg)	83.5 (80.0 - 90.3)	79.0 (71.5 - 86.0)	0.14
Laboratory			
Hemoglobin (g/dl)	13.0 (12.1 - 13.9)	14.2 (13.2 - 14.6)	**0.017**
Hematocrit (%)	38.2 (36.8 - 40.9)	41.5 (38.6 - 42.8)	**<0.01**
Leukocyte (cell/µL)	5.4 (4.8 - 6.0)	6.0 (4.6 - 6.5)	0.11
Creatinine (µmol/L)	113.5 (89.0 - 146.0)	122.5 (104.5 - 160.0)	**0.029**
Uric acid (µmol/L)	374.5 (320 - 432)	339 (266 - 382)	0.086
AST (UI/L)	29.0 (20.0 - 38.3)	26.0 (21.0 - 27.8)	**0.024**
ALT (UI/L)	26.5 (19.5 - 37.8)	23.5 (20.3 - 30.8)	0.16
Metabolic			
HbA1c (%)	7.1 (6.5 - 8.0)	6.7 (6.2 - 7.1)	0.29
TC (mg/dl)	1.56 (1.33 - 1.78)	1.39 (1.30 - 1.80)	0.64
LDL-C (mg/dL)	0.82 (0.65 - 1.09)	0.76 (0.65 - 0.86)	0.97
HDL-C (mg/dL)	0.46 (0.41 - 0.53)	0.48 (0.44 - 0.52)	0.23
TG (mg/dL)	0.86 (0.76 - 1.74)	0.96 (0.75 - 1.68)	0.79
oxLDL (mU/L)	31.6 (27.6 - 37.0)	31.3 (24.4 - 44.4)	0.76
LP-PLA2 (nmol/min/mL)	353.2 (311.2 - 451.9)	379.1 (275.6 - 483.8)	0.49
HIV-related variables			
Viral load below 20 cp/µL, n (%)	16 (80%)	17 (85%)	1[b]
CD4 (cell/µL)	586 (453 -744)	555 (468 - 724)	0.32
CD8 (cell/µL)	669 (545 - 816)	663 (587 - 840)	0.84
CD4/CD8 ratio	0.84 (0.68 - 1.05)	0.76 (0.61 - 1.04)	0.56
HIV-DNA (cp/10^6cells)	50.16 (5.02 - 76.92)	38.41 (4.83 - 86.25)	0.62

415 Results are expressed as medians and interquartile ranges (IQR).

416 [a] Wilcoxon signed-rank test unless otherwise specified.

417 [b] Using McNemar test.

418 SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; LP-PLA2, Lipoprotein-associated
419 phospholipase A2; ALT, alanine aminotransferase, AST, aspartate aminotransferase; HBA1C, glycated
420 haemoglobin, TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density
421 lipoprotein cholesterol, TG, Triglycerides

422

423 Table 3: Immunological changes associated with SGLT2i treatment.

Analyte	Before treatment	After treatment	P value*
Inflammatory markers performed in routine care			
IL-6	0.68 (0.27; 0.91)	0.55 (0.13; 0.72)	0.13
CRP (mg/l)	1.22 (0.68; 2.08)	0.83 (0.32; 1.97)	0.21
sCD14 (ng/mL)	1.27 (1.04; 1.48)	1.40 (1.10; 1.62)	0.43
Inflammasome-associated cytokines			
IL-1β	0.616 (0.506; 1.002)	0.517 (0.320; 0.532)	< 0.01
IL-8	4.91 (3.08; 6.43)	3.42 (2.73; 4.39)	0.036
Cytokines associated with monocyte-macrophage activation			
MIP-1α / CCL3	0.683 (0.605; 0.934)	0.673 (0.559; 0.866)	0.045
MIP-1β / CCL4	82.40 (76.11; 86.75)	77.49 (67.88; 81.92)	0.012
MCP-1 /CCL2	8.73 (7.49; 10.20)	7.14 (5.85; 8.33)	< 0.01
RANTES	724.2 (669.7; 773.6)	492.2 (426.5; 748.1)	0.011
Eotaxin / CCL11	36.79 (31.89; 48.18)	31.27 (21.90; 42.75)	< 0.01
Cytokines associated with positive feedback of monocyte-macrophage activation			
IL-4	1.60 (1.50; 2.19)	1.52 (1.24; 1.93)	0.029
IL-13	1.98 (1.26; 3.89)	1.34 (1.03 ;1.61)	< 0.01
GM-CSF	0.92 (0; 1.36)	0.19 (0; 0.65)	0.035
Cytokine associated with cardiovascular risk in people with diabetes			
IL-15	42.8 (0; 65.8)	0 (0; 0)	0.016

424 Concentrations are expressed in pg/mL Results are expressed as median (IQR) unless otherwise
425 specified.

426 * Wilcoxon signed-rank test

427

Supplementary Table 1: Cytokine quantification before and after SGLT2i treatment on PWH.

Analyte	Before treatment	After treatment	Difference (IQR)	P value*
CRP	1226.1 (678.9; 2076.1)	829.6 (317.1; 1971.0)	-453.6 (-1158; 150.6	0.21
IL-1β	0.616 (0.506; 1.002)	0.517 (0.320; 0.532)	**-0.200 (-0.399; -0.097)**	**2.6e-3**
IL-1RA	95.3 (81.6; 124.0)	80.3 (64.7; 98.4)	-19.37 (-58.7; 10.9)	0.080
IL-2	0.14 (0; 1.00)	0 (0; 0.24)	-0.03 (-0.79; 0)	0.093
IL-4	1.60 (1.50; 2.19)	1.52 (1.24; 1.93)	**-0.16 (-0.42; 0)**	**0.029**
IL-5	5.63 (2.62; 7.43)	5.64 (3.33; 10.46)	0.81 (-2.3; 4.7)	0.57
IL-6	0.68 (0.27; 0.91)	0.55 (0.13; 0.72)	-0.14 (-0.44; 0.13)	0.13
IL-7	5.27 (3.45; 6.73)	4.29 (3.80; 6.33)	-0.92 (-3.12; 1.11)	0.37
IL-8	4.91 (3.08; 6.43)	3.42 (2.73; 4.39)	**-1.06 (-2.98; 0.57)**	**0.036**
IL-9	148.2 (141.9; 169.9)	140.4 (120.2; 168.4)	-14.9 (-24. 8 ; 6.6)	0.22
IL-10	1.20 (0.74; 1.69)	0.64 (0.35; 1.33)	-0.27 (-0.86; 0.56)	0.33
IL-12	2.44 (2.31; 4.34)	2.43 (1.03; 3.60)	-1.05 (-1.72; 1.18)	0.43
IL-13	1.98 (1.26; 3.89)	1.34 (1.03 ;1.61)	**-0.54 (-2.18; -0.24)**	**9e-4**
IL-15	42.8 (0; 65.8)	0 (0; 0)	**-55.55 (-15.21; 0)**	**0.016**
IL-17A	2.98 (2.09; 4.00)	2.57 (2.00; 3.13)	-0.87 (-1.01; 0.33)	0.17
IP-10	151.8 (129.3; 195.3)	138.2 (101.9; 167.1)	-19.5 (-35.5; 12.4)	0.23
IFN-γ	2.46 (1.86; 3.66)	2.06 (1.55; 2.69)	-0.39 (-1.59; 0.29)	0.095
G-CSF	26.60 (16.85; 30.56)	19.64 (17.06; 24.77)	-7.47 (-10.42; -1.78)	0.076
GM-CSF	0.92 (0; 1.36)	0.19 (0; 0.65)	**-0.26 (-1.21; 0)**	**0.035**
FGF	5.08 (4.28; 6.14)	4.49 (4.18; 5.61)	-0.07 (-1.12; 0.67)	0.47
Eotaxin / CCL11	36.79 (31.89; 48.18)	31.27 (21.90; 42.75)	**-6.74 (-14.09; -0.74)**	**2.7e-3**
MIP-1α / CCL3	0.683 (0.605; 0.934)	0.673 (0.559; 0.866)	**-0.076 (-0.215; 0.004)**	**0.045**
MIP-1β / CCL4	82.40 (76.11; 86.75)	77.49 (67.88; 81.92)	**-8.25 (-10.6; 2.45)**	**0.012**
PDGF-BB	9.42 (0; 20.43)	0 (0; 8.49)	0 (-10.6; 0)	0.23
RANTES	724.2 (669.7; 773.6)	492.2 (426.5; 748.1)	**-269.0 (-354.3; 34.0)**	**0.011**
MCP-1 /CCL2	8.73 (7.49; 10.20)	7.14 (5.85; 8.33)	**-1.85 (-2.94; -0.27)**	**4.2e-3**
TNF-α	10.33 (8.69; 13.55)	9.52 (7.86; 12.15)	-1.22 (-4.03; 1.04)	0.16
VEGF	0 (0; 0)	0 (0; 0)	0 (0; 0)	0.28
sCD14	1268316 (1039405; 1478206)	1402230 (1097271; 1624068)	104589 (-220533; 383804)	0.43

Concentrations are expressed in pg/mL Results are expressed as median (IQR).

* Wilcoxon signed-rank test

Supplementary table 2: PrEP user demographic and characteristics

Characteristic	PrEP users (n=10)
Age, years, median (IQR)	61 (59–63.5)
Male sex at birth, n (%)	10 (100%)
BMI, kg/m², median (IQR)	29.6 (28.8-30.3)
Non-native French, n (%)	3 (30%)
Cardiovascular and metabolic	
Past tobacco smoker, n (%)	1 (10%)
Current tobacco smoker, n (%)	3 (30%)
Arterial hypertension, n (%)	2 (20%)
Dyslipidemia, n (%)	2 (20%)
Diabetes mellitus, n (%)	1 (10%)
Statin use, n (%)	2 (20%)
History of cardiovascular event, n (%)	0 (0%)
Chronic heart failure, n (%)	0 (0%)
Chronic kidney disease (any), n (%)	0 (0%)
Biological parameters	
Creatinine (µmol/L)	79 (72-83)
ASAT (UI/L)	29 (19-32)
ALAT (UI/L)	29 (27-34)

Supplementary table 3: Comparison of immunological parameters between PrEP users and PWH

Analyte	Before treatment	After treatment	PrEP users, n=10	P value PrEP users vs PWH before iSGLT2 treatment*	P value PrEP users vs PWH after iSGLT2 treatment*
CRP	1226.1 (678.9-2076.1)	829.6 (317.1-1971.0)	675.9 (608.6-1005.9)	0.42	0.64
IL-1β	0.616 (0.506-1.002)	0.517 (0.320-0.532)	0.42 (0.24-0.67)	0.067	0.76
IL-1RA	95.3 (81.6-124.0)	80.3 (64.7-98.4)	95.1 (73.41 - 109.17)	0.69	0.47
IL-2	0.14 (0-1.00)	0 (0-0.24)	0 (0-0.18	0.26	0.98
IL-4	1.60 (1.50-2.19)	1.52 (1.24-1.93)	1.58 (1.52-1.97)	0.71	0.61
IL-5	5.63 (2.62-7.43)	5.64 (3.33-10.46)	0.95 (0-3.33)	**0.017**	**6.8e-4**
IL-6	0.68 (0.27-0.91)	0.55 (0.13-0.72)	0.27 (0.034-0.41)	**0.035**	0.30
IL-7	5.27 (3.45-6.73)	4.29 (3.80-6.33)	4.79 (3.34-7.53)	0.76	0.70
IL-8	4.91 (3.08-6.43)	3.42 (2.73-4.39)	3.24 (2.76-4.04)	0.075	0.79
IL-9	148.2 (141.9-169.9)	140.4 (120.2-168.4)	133.6 (125.2-146.1)	0.065	0.40
IL-10	1.20 (0.74-1.69)	0.64 (0.35-1.33)	0.64 (0.35—1.59)	0.32	0.89
IL-12	2.44 (2.31-4.34)	2.43 (1.03-3.60)	1.68 (0.7-3.81)	0.23	0.74
IL-13	1.98 (1.26-3.89)	1.34 (1.03-1.61)	1.16 (0.93-1.56)	**0.023**	0.64
IL-15	42.8 (0-65.8)	0 (0-0)	0 (0-19.29)	0.23	0.31
IL-17A	2.98 (2.09-4.00)	2.57 (2.00-3.13)	2.50 (1.74-3.21)	0.47	0.98
IP-10	151.8 (129.3-195.3)	138.2 (101.9-167.1)	102.7 (97.4-112.5)	**0.0023**	0.059
IFN-γ	2.46 (1.86-3.66)	2.06 (1.55-2.69)	2.35 (1.18-2.75)	0.28	0.96
G-CSF	26.60 (16.85-30.56)	19.64 (17.06-24.77)	17.33 (14.70-29.42)	0.34	0.86
GM-CSF	0.92 (0-1.36)	0.19 (0-0.65)	0 (0-0)	**0.034**	0.27
FGF	5.08 (4.28-6.14)	4.49 (4.18-5.61)	5.00 (4.28-6.11)	0.98	0.66
Eotaxin	36.79 (31.89-48.18)	31.27 (21.90-42.75)	32.96 (24.15-43.22)	0.23	0.81
MIP-1α	0.683 (0.605-0.934)	0.673 (0.559-0.866)	0.544 (0.447-0.785)	0.0501	0.15
MIP-1β	82.40 (76.11-86.75)	77.49 (67.88-81.92)	73.43 (65.87-75.23)	**0.0062**	0.27
PDGF-BB	9.42 (0-20.43)	0 (0-8.49)	0 (0-1.44)	0.094	0.79
RANTES	724.2 (669.7-773.6)	492.2 (426.5-748.1)	541.2 (477.0-591.0)	**0.0045**	0.91
MCP-1	8.73 (7.49-10.20)	7.14 (5.85-8.33)	8.36 (6.78-10.20)	0.54	0.39
TNF-α	10.33 (8.69-13.55)	9.52 (7.86-12.15)	9.10 (7.75-11.39)	0.25	0.81
VEGF	0 (0-0)	0 (0-0)	0 (0-0)	0.47	0.68
sCD14	1268316 (1039405-1478206)	1402230 (1097271-1624068)	1265577 (1214559-1359647)	0.71	0.59

Concentrations are expressed in pg/mL.

Results are expressed as median (IQR).

* using Wilcoxon unpaired test.