A Randomized, Double-blinded, Placebo-controlled Trial of Sitagliptin for Reducing Inflammation and Immune Activation in Treated and Suppressed Human Immunodeficiency Virus Infection

Michael P. Dubé,¹ Ellen S. Chan,² Jordan E. Lake,³ Brett Williams,⁴ Jennifer Kinslow,⁴ Alan Landay,⁴ Robert W. Coombs,⁵ Michelle Floris-Moore,⁶ Heather J. Ribaud,² and Kevin E. Yarasheski⁷; for the AIDS Clinical Trials Group 5346 Team

¹Keck School of Medicine, University of Southern California, Los Angeles; ²Harvard T. H. Chan School of Public Health, Boston, Massachusetts; ³University of Texas Health Science Center, Houston; ⁴Rush University Medical Center, Chicago, Illinois; ⁵University of Washington, Seattle; ⁶University of North Carolina, Chapel Hill; and ⁷Washington University, St. Louis, Missouri

Background. Dipeptidyl peptidase-4 (DPP-4) inhibitors have pleotropic anti-inflammatory and immune regulatory effects in addition to glucoregulation. We evaluated inflammation and immune markers in suppressed human immunodeficiency virus (HIV) infection during treatment with the DPP-4 inhibitor sitagliptin.

Methods. Virologically suppressed adults with HIV without diabetes on stable antiretroviral therapy (ART) with $\geq 100/\mu\text{L}$ CD4 cells were randomized to 16 weeks of sitagliptin 100 mg/day vs placebo in a multicenter trial. The primary endpoint was the change in plasma soluble CD14 (sCD14) from baseline to week 15–16.

Results. Ninety participants were randomized, and 42 from each arm were included in per-protocol analyses. Participants were 45% non-Hispanic white, 38% non-Hispanic black, and 15% Hispanic, with a median age of 51 years; 83% were male; and the median CD4 count was 602 cells/ μL . At week 15–16, there was no difference in sCD14 change between the 2 arms ($P = .69$). Relative to placebo, the sitagliptin arm had 47% greater decline in CXCL10 (95% confidence interval, –57% to –35%) at week 15 ($P < .001$). There were no significant between-arm differences in other soluble biomarkers, total CD4 and CD8 counts, or markers of lymphocyte or monocyte activation. Sitagliptin was well tolerated.

Conclusions. Sixteen weeks of sitagliptin had no effect on sCD14 levels in virologically suppressed participants with HIV. CXCL10, a chemokine involved in atherogenesis that predicts non-AIDS events during ART, declined markedly with sitagliptin. This suggests that DPP-4 inhibition has the potential to reduce cardiovascular morbidity in treated HIV infection.

Clinical Trials Registration. NCT01426438.

Keywords. HIV; inflammation; soluble CD14; CXCL10; dipeptidyl peptidase-4 inhibitor.

Chronic inflammation and immune activation contribute to the higher risk for type 2 diabetes (T2D), cardiovascular disease, and other comorbid complications as well as mortality in people living with human immunodeficiency virus type 1 (HIV-1) infection (PLWH). Although the exact proinflammatory mechanisms are unclear, interventions that reduce inflammation and immune activation are believed to reduce morbidity and mortality and may also reduce cardiometabolic complications and cardiovascular disease risk in PLWH.

Dipeptidyl peptidase-4 inhibitors (DPP4i; eg, sitagliptin, alogliptin, saxagliptin, linagliptin) are a relatively new class of

oral antidiabetes medications. In animal models and clinical studies of T2D, DPP4i appear to have many beneficial cardiometabolic, anti-inflammatory, immunoregulatory, and hematopoietic effects [1–8] in addition to their glucoregulatory actions.

In single-center pilot studies that enrolled a relatively small number of participants with controlled HIV infection but without T2D, sitagliptin did not adversely affect plasma HIV RNA or CD4 T-cell counts [9], and it improved select soluble inflammatory biomarkers [10]. These pilot studies did not select for participants with low baseline CD4⁺ T-cell counts (<350 cells/ μL), or elevated levels of proinflammatory biomarkers, that is, those that could benefit most from the potential immunoregulatory or anti-inflammatory actions of DPP4i. Also, the pilot studies did not control for the use of lipid-lowering medications (eg, statins) that are reported to have anti-inflammatory properties in PLWH. To overcome these limitations, the current randomized, double-blinded, placebo-controlled multicenter trial tested whether 16 weeks

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Correspondence: M. P. Dubé, Keck School of Medicine, University of Southern California, 1300 N Mission Rd, Rm 349, Los Angeles, CA 90033 (mdube@usc.edu).

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of sitagliptin (100 mg/day; Januvia) reduces inflammatory biomarkers and immune cell surface activation markers in PLWH on antiretroviral therapy (ART) who were stratified by baseline CD4⁺ T-cell count and statin use. The primary hypothesis was that sitagliptin will reduce soluble CD14 concentrations (sCD14; a marker of monocyte activation). Secondary hypotheses were that sitagliptin will (1) reduce circulating levels of other soluble markers of inflammation; (2) reduce T-cell and monocyte immune activation markers and increase the CD4⁺/CD8⁺ ratio; and (3) not be associated with significantly more grade 3 or 4 events than placebo.

MATERIALS AND METHODS

Participants

PLWH aged 18 years or older with a CD4⁺ count ≥ 100 cells/ μ L were eligible if they had ≥ 48 weeks of continuous ART with HIV viral suppression prior to study entry, no ART regimen changes within the prior 12 weeks, and HIV-1 RNA below the limit of detection. ART interruption of ≤ 7 consecutive days during that period was allowed. Single HIV-1 RNA measurements between the assay quantification limit and 500 copies/mL were allowed if the preceding and subsequent determinations were below the level of quantification. Entry laboratory criteria included hemoglobin A1C $\leq 6.5\%$, platelets $\geq 50\,000/\mu$ L, absolute neutrophil count $\geq 750/\mu$ L, hemoglobin ≥ 8.0 g/dL, liver aminotransferases ≤ 5 times the upper limit of normal, and estimated creatinine clearance ≥ 60 mL/minute (Cockcroft-Gault formula). Participants on statin therapy were required to be taking the same dose for at least the prior 12 weeks with no anticipated change in statin or dose during the study. Exclusion criteria included a diagnosis of T2D or congestive heart failure, a history of pancreatitis, current hepatitis C virus infection with detectable hepatitis C RNA, current hepatitis B virus infection with detectable hepatitis B DNA or surface antigen, known intolerance of the study medication, severe substance abuse, active opportunistic infection, or other acute illness. Institutional review boards at each site approved the study. All participants provided written informed consent.

Randomization and Drug Treatment

Participants were randomized at a 1:1 ratio (sitagliptin:placebo) using permuted blocks without institutional balancing with stratification by statin use and screening CD4⁺ T-cell count (100–350 vs >350 cells/ μ L). Sitagliptin (Januvia) 100 mg tablets and matching placebo were supplied by Merck Pharmaceuticals. Study drug was taken as 1 tablet daily for 16 weeks.

Evaluations

At a preentry visit, plasma samples were obtained for sCD14, ≤ 7 days prior to the entry visit. At study entry and at weeks

8 and 15, samples were obtained for sCD14 and other soluble markers of activation and inflammation, along with safety laboratory tests, and peripheral blood mononuclear cells (PBMCs) for lymphocyte and monocyte phenotyping. At week 16, repeat samples were obtained for sCD14. Samples were obtained for fasting metabolic testing and CD4/CD8 counts at entry and week 15. Sample collection was delayed by at least 7 days after any acute inflammatory condition, severe illness, or vaccination, or if a participant had a temperature $>38^{\circ}\text{C}$ at the research visit.

Primary adverse events for this study included events that meet the International Council for Harmonisation definitions for a serious adverse event; postentry, new signs/symptoms and laboratory abnormalities of grade ≥ 2 or that lead to a change in treatment, regardless of grade; and any diagnoses.

Assays

Centrally performed assays used specimens stored at -70°C and shipped on dry ice. Plasma glucose, liver aminotransferase, and hemoglobin A1C concentrations were measured locally at sites. Serum insulin concentration was measured in batch by an enzyme-labeled immunometric assay (DPC Immulite 2000, Quest Diagnostics, Baltimore, Maryland). Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured enzymatically. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation when triglycerides were <400 mg/dL. Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. Soluble CD14, high-sensitivity C-reactive protein, CXCL10 (also known as interferon gamma-inducible protein 10 [IP-10]), soluble CD163, soluble tumor necrosis factor receptors 1 and 2, and soluble CD26 protein were measured in batch analysis by enzyme-linked immunosorbent assay (R&D Systems) at Rush University.

Lymphocyte and monocyte activation markers were quantified by flow cytometry on PBMCs that were processed and frozen at sites using a standard protocol [11, 12] at Rush University. The percentage of CD4⁺ and CD8⁺ lymphocytes expressing both activation markers CD38 and HLA-DR were reported. The percentage of CD14⁺CD16[−] (classical), CD14⁺CD16⁺ (intermediate), and CD14^{dim}CD16⁺⁺ (nonclassical) monocyte subpopulations were quantified.

Statistical Analysis

The primary hypothesis was that treatment of PLWH with suppressed HIV infection with the DPP-4 inhibitor sitagliptin will result in an anti-inflammatory effect, as assessed by reduction in circulating concentration in the monocyte activation marker sCD14 over 16 weeks, as compared to placebo. The primary outcome measure was change in sCD14 from baseline to week 16. To reduce variability, the sCD14 results from the preentry

and entry visits were averaged for the baseline value, and the week 15 and 16 sCD14 results were averaged for the week 16 outcome. The target of 72 evaluable participants (36 per arm) was chosen to provide 90% power to detect a clinically relevant difference of 0.07 $\log_{10}$ (15%) in the change in sCD14 levels between arms. The preplanned primary analysis and secondary analyses for immunology outcomes were per-protocol and limited to participants who completed study treatment and had complete data. A per-protocol analysis was chosen to best confirm a positive biologic effect of the intervention and thus potentially justify more advanced-phase studies of sitagliptin in this clinical setting. The primary analysis used linear regression models to evaluate the treatment effect, adjusted for the stratification factors screening CD4⁺ T-cell count (100–350 vs >350 cells/ μ L) and statin use (yes/no). Stratified Wilcoxon rank-sum exact tests were used to evaluate treatment group differences in primary and secondary outcomes, also stratified by screening CD4⁺ T-cell count (100–350 vs >350 cells/ μ L) and statin use. Spearman correlations evaluated the associations between pairs of continuous variables. All statistical tests are 2-sided with a nominal α level of .05. No adjustment for multiple testing was performed.

RESULTS

Participant flow through the study is shown in [Figure 1](#). One hundred thirty individuals were screened for participation. The most common reason for not enrolling was a laboratory value that did not meet entry criteria. Ninety participants were randomized (45 sitagliptin, 45 placebo). Only 3 participants from each group were not included in the per-protocol analysis.

Demographics and baseline characteristics of the per-protocol, primary analysis population (42 sitagliptin, 42 placebo) are shown in [Table 1](#). The majority were men (82%) and either non-Hispanic white (45%) or non-Hispanic black (38%). The treatment groups were evenly distributed with respect to ART duration, type, and abacavir use. Statin use at baseline (a stratification factor) was 33% in the sitagliptin group and 31% in the placebo group. Median CD4 cells counts tended to be high overall (641 cells/ μ L sitagliptin, 551 cells/ μ L placebo), but 10 (24%) in the sitagliptin group and 13 (31%) in the placebo group had a CD4 count between 100 and 350 cells/ μ L.

Results for soluble markers of inflammation and activation are shown in [Figure 2](#). For the primary endpoint sCD14 ([Figure 2A](#)), there was no significant difference in the change from baseline to week 15–16, with an estimated sitagliptin treatment effect

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) participant flowchart. Abbreviation: HIV, human immunodeficiency virus.

Table 1. Demographics and Baseline Characteristics: per-protocol, Primary Analysis Population

Characteristic	Sitagliptin (n = 42)	Placebo (n = 42)
Age, y, median (IQR)	52 (40–55)	51 (45–56)
Male sex	37 (88)	33 (79)
Race/ethnicity		
Hispanic (regardless of race)	6 (14)	7 (17)
White non-Hispanic	22 (52)	16 (38)
Black non-Hispanic	14 (33)	18 (43)
>1 race	0 (0)	1 (2)
BMI, kg/m ² , median (IQR)	27.7 (25.4–30.8)	27.7 (23.6–30.6)
Months on current ART, median (IQR)	37 (18–94)	27 (12–79)
ART		
Integrase inhibitor	16 (38)	17 (40)
Protease inhibitor	15 (36)	12 (29)
NNRTI	17 (40)	19 (45)
NRTI	41 (98)	40 (95)
Abacavir	7 (17)	7 (17)
Statin use	14 (33)	13 (31)
CD4 ⁺ count, cells/μL, median (IQR)	641 (351–806)	551 (317–816)
CD4 ⁺ count ≤350 cells/μL	10 (24)	13 (31)
Hemoglobin, g/dL, median (IQR)	14.5 (13.2–15.3)	14.4 (13.1–15.1)
Hemoglobin A1C, %	5.5 (5.3–5.7)	5.5 (5.1–5.7)
Total cholesterol, mg/dL, median (IQR)	180 (157–208)	172 (157–201)
Fasting insulin, μIU/mL, median (IQR)	8.5 (5.1–12.1)	8.0 (5.2–13.0)

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

of 2% (95% confidence interval [CI], –7% to 12%; $P = .69$ from regression model comparing week 16 changes between arms, adjusting for screening CD4 stratum and statin use). There was also no difference in the estimated treatment effect by tertiles of baseline sCD14. Of the remaining soluble markers tested, a significant difference between the 2 treatment groups in changes from baseline to week 15 was detected only for CXCL10 (Figure 2B). With sitagliptin, CXCL10 levels fell by a median of 50.5% from baseline to week 15 (interquartile range [IQR], –60.1 to –28.9) and increased by a median of 70.6% during the post-treatment phase (IQR, 48.0–149.5). Relative to placebo, the sitagliptin arm had an estimated effect of 47% greater decline in CXCL10 (95% CI, –57 to –35) at week 15 (between-arm $P < .001$, regression model adjusting for screening CD4 stratum and statin use). At week 20, 4 weeks after cessation of sitagliptin, levels of CXCL10 returned to near-baseline levels and were not significantly different than placebo. There were no significant correlations between the week 15–16 changes in the levels of CXCL10 and the week 15 changes of any other soluble biomarker (data not shown).

Results for lymphocyte and monocyte activation markers are shown in Table 2. Lymphocyte activation tended to be low at baseline for this group of individuals with suppressed HIV infection. There were no differences in change from baseline to week 15 between the 2 treatment arms in any of the cellular

markers (all $P > .30$), nor were there any significant within-arm changes.

Metabolic, renal, and hepatic variables are listed in Table 3. There were no differences in change from baseline to week 15 between the 2 treatment arms in any of these measures ($P > .40$).

Sitagliptin was generally well tolerated. Of 90 enrolled participants in the safety analysis, 42 (47%) reported at least 1 primary adverse event, 22 (49%) from the sitagliptin arm and 20 (44%) from the placebo arm. The proportion of participants with grade 3 or grade 4 primary adverse events was 11% for the sitagliptin arm compared to 16% for the placebo arm. Only 1 participant (in the sitagliptin arm) reported a grade 4 primary adverse event. This participant had a grade 4 myocardial infarction at week 11 that was assessed as not related to the study treatment by the site investigator. Study treatment was completed, and this participant was included in the per-protocol analysis. Because this event occurred 4–5 weeks prior to the primary endpoint evaluations, it is unlikely that it influenced the results. There were 3 participants whose primary adverse events were determined by the site investigators as possibly related to study treatment, all from the sitagliptin arm: 1 had a grade 3 low creatinine clearance at week 8, 1 had grade 3 elevated triglycerides at week 15, and 1 had a grade 2 rash at week 15. There were no grade 2 or higher low blood glucose values reported during the course of this study. No deaths were reported.

DISCUSSION

Sixteen weeks of the DPP-4 inhibitor sitagliptin had no effect on the primary endpoint measure sCD14, a soluble marker of monocyte activation, when administered to participants with treated and suppressed HIV infection. There was a large and statistically significant fall in CXCL10 with sitagliptin, a chemokine that is implicated in cardiovascular disease and atherogenesis [13] and distal sensorimotor polyneuropathy [14], and predicts non-AIDS events in participants on ART [12]. However, no significant changes in other soluble or cellular markers of inflammation and activation were detected.

The primary endpoint of changes in sCD14 was chosen because levels of this circulating marker of monocyte activation have shown strong association with mortality and morbidity in cohort studies during ART [12, 15, 16] as well as with key HIV comorbidities [17–23]. Longitudinal data from the Multicenter AIDS Cohort Study [24] suggest that, among multiple inflammatory biomarkers measured (including CXCL10, interleukin 6, and C-reactive protein), sCD14 fulfills multiple criteria for a highly relevant soluble biomarker. Specifically, sCD14 was higher in both untreated and virologically suppressed HIV infection compared with controls, did not normalize with effective ART, and predicted mortality across the range of untreated to long-term treated HIV infection; in addition, changes in sCD14 after ART initiation predicted mortality. To date,

Figure 2. Soluble biomarkers over time. *A*, sCD14. *B*, CXCL10. *C*, sCD163. *D*, IL-6. *E*, sCD26. *F*, hsCRP. *G*, sTNF-RI. *H*, sTNF-RII. Abbreviations: BL, baseline; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; sCD14, soluble CD14; sCD26, soluble CD26; sCD163, soluble CD163; sTNF-RI, soluble tumor necrosis factor receptor I; sTNF-RII, soluble tumor necrosis factor receptor II.

no anti-inflammatory intervention tested in individuals with treated HIV has been shown to favorably affect sCD14 concentrations, with the notable exceptions of rosuvastatin [25] and pitavastatin [26]. Despite being well powered, we found no signal for improvement in the biomarker with 16 weeks of sitagliptin. It is possible that our participants, who were largely well with good immune reconstitution (median CD4 count,

586 cells/ μ L), had limited room for improvement in sCD14. However, there was no suggestion of any differential treatment effects by entry sCD14 tertile in secondary analyses. Similarly, compared to other populations of treated and suppressed HIV infection [25, 27, 28], our participants had relatively lower levels of lymphocyte activation, likely limiting the ability to detect changes in this outcome.

Table 2. Lymphocyte and Monocyte Activation Markers

Marker	Baseline	Week 15	Absolute Change	PValue ^a
% CD4 ⁺ CD38 ⁺ /HLA-DR ⁺				
Sitagliptin	2.60 (2.02–3.62)	2.75 (2.11–4.05)	0.12 (–0.15 to 0.52)	.77
Placebo	2.48 (2.00–3.68)	2.46 (1.99–4.19)	0.08 (–0.41 to 0.43)	
% CD8 ⁺ CD38 ⁺ /HLA-DR ⁺				
Sitagliptin	5.16 (3.89–7.70)	6.63 (4.08–8.62)	0.03 (–0.90 to 1.83)	.67
Placebo	6.59 (4.56–8.99)	6.65 (4.13–10.30)	–0.27 (–1.11 to 1.33)	
% CD3 ⁺ CD14 ⁺ /CD16 ⁺				
Sitagliptin	80.60 (76.00–83.40)	79.30 (72.00–82.90)	–2.30 (–6.20 to 3.20)	.51
Placebo	80.55 (72.10–86.60)	79.95 (72.10–85.80)	–0.80 (–4.75 to 2.75)	
% CD3 ⁺ CD14 ⁺ /CD16 ⁺				
Sitagliptin	4.49 (3.00–7.39)	5.25 (3.22–9.19)	0.87 (–1.32 to 3.08)	.46
Placebo	5.94 (3.00–9.01)	4.55 (2.89–7.65)	–0.12 (–2.33 to 1.97)	
% CD3 ⁺ CD14 _{dim} ⁺ /CD16 ⁺⁺				
Sitagliptin	5.84 (4.01–9.89)	6.18 (4.70–9.61)	0.31 (–1.02 to 2.05)	.36
Placebo	5.32 (3.26–8.17)	6.00 (2.94–9.18)	–0.03 (–2.08 to 2.31)	

All values are presented as median (interquartile range).

^aStratified Wilcoxon rank-sum *P* value evaluating the difference in absolute changes between the 2 treatment groups, stratified by screening CD4 count (100–350 or >350 cells/μL) and statin use.

Table 3. Fasting Metabolic, Liver, and Renal Variables

Variable	Baseline	Absolute Change at Week 15	PValue ^a
Total cholesterol, mg/dL			
Sitagliptin	180 (157–208)	1 (–14 to 14)	.842
Placebo	172 (157–201)	6 (–11 to 11)	
HDL cholesterol, mg/dL			
Sitagliptin	46 (38–57)	–1 (–3 to 3)	.915
Placebo	50 (43–58)	0 (–6 to 5)	
LDL cholesterol–calculated, mg/dL			
Sitagliptin	108 (88–121)	–4 (–14 to 10)	.495
Placebo	94 (78–118)	2 (–15 to 12)	
Triglycerides, mg/dL			
Sitagliptin	109 (75–178)	5 (–20 to 20)	.416
Placebo	104 (76–156)	–4 (–18 to 18)	
Non-HDL cholesterol, mg/dL			
Sitagliptin	124 (108–167)	0 (–12 to 12)	.895
Placebo	128 (93–141)	2 (–16 to 9)	
Serum insulin, μIU/mL			
Sitagliptin	8.5 (5.1–12.1)	0.2 (–1.8 to 1.9)	.868
Placebo	8.0 (5.2–13.0)	0.0 (–2.5 to 2.5)	
AST, × ULN			
Sitagliptin	0.60 (0.51–0.80)	–0.05 (–0.13 to 0.06)	.816
Placebo	0.62 (0.52–0.73)	–0.04 (–0.11 to 0.01)	
ALT, × ULN			
Sitagliptin	0.58 (0.33–0.75)	0.00 (–0.11 to 0.06)	.818
Placebo	0.53 (0.43–0.70)	–0.04 (–0.10 to 0.05)	
Calculated CrCl ^b , mL/min			
Sitagliptin	106 (92–122)	–3 (–7 to 7)	0.506
Placebo	105 (79–124)	–3 (–10 to 4)	

All values are presented as median (interquartile range).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ULN, upper limit of normal.

^aStratified Wilcoxon rank-sum *P* value evaluating the difference in absolute changes between the 2 treatment groups, stratified by screening CD4 count (100–350 or >350 cells/μL) and statin use.

^bCockcroft-Gault estimation.

There was a marked effect of sitagliptin treatment on the inflammatory chemokine CXCL10, which decreased by a median of approximately 50% in the sitagliptin arm and promptly returned to baseline levels 4 weeks after drug discontinuation. Smaller, but nonetheless significant decreases in CXCL10 levels were seen in a smaller study of 8 weeks of sitagliptin in participants with HIV and impaired glucose tolerance [10]. CXCL10 was increased in untreated HIV infection, and its levels correlated with viral replication and more rapid CD4 cell decline [29]. CXCL10 levels remained significantly elevated even after successful ART [29], and on-treatment levels predicted non-AIDS events on ART [12]. CXCL10 levels decreased with rosuvastatin therapy in treated HIV infection [25]. Moreover, CXCL10 is a ligand for CXCR3, which is expressed in immune cells of atherosclerotic plaque [30] and is involved in atherogenesis [13]. CXCL10 promotes T-cell adhesion to endothelial cells during atheroma formation [31]. Thus, it is plausible that reduced CXCR3 signaling mediated by a sizable drug-induced decrease in CXCL10 levels may have beneficial cardiovascular and virologic effects in treated HIV infection. With the prompt return to baseline levels after discontinuation of sitagliptin, it would be expected that this intervention would require long-term use to maintain a benefit. Further study is needed to explore this hypothesis.

CXCL10 is a substrate for DPP-4, and DPP-4 inhibition with sitagliptin is known to affect the relative levels of different CXCL10 isoforms [32] with minimal impact on total levels of the chemokine in healthy participants. Moreover, the biology of CXCR3-induced signaling is complex, with multiple ligands and CXCR3 isoforms [33]. More work is needed to evaluate the functional implications at the cellular level of sitagliptin-induced reductions in CXCL10 levels.

Our study has several limitations. Mostly men were enrolled, limiting generalizability of our results to women. Participants were largely well, with good immune reconstitution and low levels of lymphocyte activation. It is possible that individuals with lower CD4 counts may benefit more from sitagliptin, but we found no evidence for this in our secondary analyses. Similarly, no evidence was found for a differential effect with higher baseline levels of sCD14. Due to the number of variables examined, it is possible that the CXCL10 results were due to chance. However, this seems very unlikely for multiple reasons. First, the magnitude of the difference was large, approximately 50%, and highly statistically significant. Although we did not perform statistical comparisons for the week 8 changes, there was a very similar fall in CXCL10 at week 8 (Figure 2B). Last, there was a prompt and clear return to near-baseline levels of CXCL10 4 weeks after sitagliptin discontinuation.

In conclusion, in treated and suppressed HIV infection, 16 weeks of sitagliptin was well tolerated and had a major impact on the proinflammatory chemokine CXCL10, but no effect on

other soluble and cellular markers thought to contribute to HIV-related comorbidities and mortality including the primary endpoint sCD14. More work is needed to determine the implications of these findings.

Notes

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References

1. Makdissi A, Ghanim H, Vora M, et al. Sitagliptin exerts an antiinflammatory action. *J Clin Endocrinol Metab* 2012; 97:3333–41.
2. Chaudhuri A, Ghanim H, Vora M, et al. Exenatide exerts a potent antiinflammatory effect. *J Clin Endocrinol Metab* 2012; 97:198–207.

3. Broxmeyer HE, Hoggatt J, O'Leary HA, et al. Dipeptidylpeptidase 4 negatively regulates colony-stimulating factor activity and stress hematopoiesis. *Nat Med* **2012**; 18:1786–96.
4. Drucker DJ. Incretin action in the pancreas: potential promise, possible perils, and pathological pitfalls. *Diabetes* **2013**; 62:3316–23.
5. Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev* **2012**; 33:187–215.
6. Ishikawa S, Shimano M, Watarai M, et al. Impact of sitagliptin on carotid intima-media thickness in patients with coronary artery disease and impaired glucose tolerance or mild diabetes mellitus. *Am J Cardiol* **2014**; 114:384–8.
7. Mulvihill EE, Drucker DJ. Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. *Endocr Rev* **2014**; 35:992–1019.
8. Tremblay AJ, Lamarche B, Deacon CF, Weisnagel SJ, Couture P. Effects of sitagliptin therapy on markers of low-grade inflammation and cell adhesion molecules in patients with type 2 diabetes. *Metabolism* **2014**; 63:1141–8.
9. Goodwin SR, Reeds DN, Royal M, Struthers H, Laciny E, Yarasheski KE. Dipeptidyl peptidase IV inhibition does not adversely affect immune or virological status in HIV infected men and women: a pilot safety study. *J Clin Endocrinol Metab* **2013**; 98:743–51.
10. Best C, Struthers H, Laciny E, Royal M, Reeds DN, Yarasheski KE. Sitagliptin reduces inflammation and chronic immune cell activation in HIV⁺ adults with impaired glucose tolerance. *J Clin Endocrinol Metab* **2015**; 100:2621–9.
11. Hearps AC, Martin GE, Angelovich TA, et al. Aging is associated with chronic innate immune activation and dysregulation of monocyte phenotype and function. *Aging Cell* **2012**; 11:867–75.
12. Tenorio AR, Zheng Y, Bosch RJ, et al. Soluble markers of inflammation and coagulation but not T-cell activation predict non-AIDS-defining morbid events during suppressive antiretroviral treatment. *J Infect Dis* **2014**; 210:1248–59.
13. Altara R, Mallat Z, Booz GW, Zouein FA. The CXCL10/CXCR3 axis and cardiac inflammation: implications for immunotherapy to treat infectious and noninfectious diseases of the heart. *J Immunol Res* **2016**; 2016:4396368.
14. Herder C, Kannenberg JM, Carstensen-Kirberg M, et al. A systemic inflammatory signature reflecting cross talk between innate and adaptive immunity is associated with incident polyneuropathy: KORA F4/FF4 study. *Diabetes* **2018**; 67:2434–42.
15. Hunt PW, Sinclair E, Rodriguez B, et al. Gut epithelial barrier dysfunction and innate immune activation predict mortality in treated HIV infection. *J Infect Dis* **2014**; 210:1228–38.
16. Sandler NG, Wand H, Roque A, et al; INSIGHT SMART Study Group. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis* **2011**; 203:780–90.
17. Kelesidis T, Kendall MA, Yang OO, Hodis HN, Currier JS. Biomarkers of microbial translocation and macrophage activation: association with progression of subclinical atherosclerosis in HIV-1 infection. *J Infect Dis* **2012**; 206:1558–67.
18. Lyons JL, Uno H, Ancuta P, et al. Plasma sCD14 is a biomarker associated with impaired neurocognitive test performance in attention and learning domains in HIV infection. *J Acquir Immune Defic Syndr* **2011**; 57:371–9.
19. Imp BM, Rubin LH, Tien PC, et al. Monocyte activation is associated with worse cognitive performance in HIV-infected women with virologic suppression. *J Infect Dis* **2017**; 215:114–21.
20. Abraham AG, Darilay A, McKay H, et al. Kidney dysfunction and markers of inflammation in the Multicenter AIDS Cohort Study. *J Infect Dis* **2015**; 212:1100–10.
21. Anderson AM, Harezlak J, Bharti A, et al; HIV Neuroimaging Consortium. Plasma and cerebrospinal fluid biomarkers predict cerebral injury in HIV-infected individuals on stable combination antiretroviral therapy. *J Acquir Immune Defic Syndr* **2015**; 69:29–35.
22. McKibben RA, Margolick JB, Grinspoon S, et al. Elevated levels of monocyte activation markers are associated with subclinical atherosclerosis in men with and those without HIV infection. *J Infect Dis* **2015**; 211:1219–28.
23. Sunil M, Nigalye M, Somasunderam A, et al. Unchanged levels of soluble CD14 and IL-6 over time predict serious non-AIDS events in HIV-1-infected people. *AIDS Res Hum Retroviruses* **2016**; 32:1205–9.
24. Wada NI, Jacobson LP, Margolick JB, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. *AIDS* **2015**; 29:463–71.
25. Funderburg NT, Jiang Y, Debanne SM, et al. Rosuvastatin reduces vascular inflammation and T-cell and monocyte activation in HIV-infected subjects on antiretroviral therapy. *J Acquir Immune Defic Syndr* **2015**; 68:396–404.
26. Toribio M, Fitch KV, Sanchez L, et al. Effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in INTREPID: a randomized trial in HIV. *AIDS* **2017**; 31:797–806.
27. Kelesidis T, Tran TT, Stein JH, et al. Changes in inflammation and immune activation with atazanavir-, raltegravir-, darunavir-based initial antiviral therapy: ACTG 5260s. *Clin Infect Dis* **2015**; 61:651–60.
28. O'Brien MP, Hunt PW, Kitch DW, et al. A randomized placebo controlled trial of aspirin effects on immune activation in chronically human immunodeficiency virus-infected adults on virologically suppressive antiretroviral therapy. *Open Forum Infect Dis* **2017**; 4:ofw278.
29. Ploquin MJ, Madec Y, Casrouge A, et al. Elevated basal pre-infection CXCL10 in plasma and in the small intestine after infection are associated with more rapid HIV/SIV disease onset. *PLoS Pathog* **2016**; 12:e1005774.
30. Tavakolian Ferdousie V, Mohammadi M, Hassanshahi G, et al. Serum CXCL10 and CXCL12 chemokine levels are associated with the severity of coronary artery disease and coronary artery occlusion. *Int J Cardiol* **2017**; 233:23–8.
31. Mach F, Sauty A, Iarossi AS, et al. Differential expression of three T lymphocyte-activating CXC chemokines by human atheroma-associated cells. *J Clin Invest* **1999**; 104:1041–50.
32. Decalf J, Tarbell KV, Casrouge A, et al. Inhibition of DPP4 activity in humans establishes its in vivo role in CXCL10 post-translational modification: prospective placebo-controlled clinical studies. *EMBO Mol Med* **2016**; 8:679–83.
33. Metzmaekers M, Vanheule V, Janssens R, Struyf S, Proost P. Overview of the mechanisms that may contribute to the non-redundant activities of interferon-inducible CXC chemokine receptor 3 ligands. *Front Immunol* **2017**; 8:1970.