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Losartan to reduce inflammation and fibrosis endpoints in HIV disease

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Abstract

Background: Persistent inflammation and incomplete immune recovery among persons with HIV (PHIV) are associated with increased disease risk. We hypothesized that the angiotensin receptor blocker (ARB) losartan would reduce inflammation by mitigating nuclear factor (NF)κB responses and promote T-cell recovery via inhibition of transforming growth factor-beta (TGFβ)-mediated fibrosis.

Methods: Losartan (100 mg) versus placebo over 12 months was investigated in a randomized (1 : 1) placebo-controlled trial, among PHIV age at least 50 years, receiving antiretroviral therapy (ART), with HIV RNA less than 200 copies/ml and $CD4^+$ cell count 600 cells/μl or less. Inflammation, fibrosis and myocardial biomarkers were measured in blood using ELISA, electrochemiluminescence and immunoturbidimetric methods, and T-cell and monocyte phenotypes were assessed with flow cytometry among a subset of participants. Changes over follow-up in (log-2 transformed) biomarkers and cell phenotypes (untransformed) were compared between losartan and placebo arms using linear mixed models.

Results: Among 108 PHIV ($n = 52$ to losartan; $n = 56$ to placebo), 97% had a month 12 visit. Median age was 57 years and baseline $CD4^+$ cell count was 408 cells/μl. Losartan treatment was not associated with an improvement in interleukin-6 levels, or other blood measures of inflammation, immune activation, fibrosis activity or myocardial function. $CD4^+$ and $CD8^+$ T cells also did not differ by treatment group. Losartan reduced SBP and DBP by 6 and 5mmHg, respectively.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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Conclusion: Among older PHIV with viral suppression, losartan did not improve blood measures of inflammation nor T-cell immune recovery. Losartan treatment is unlikely to reduce inflammation associated comorbidities to a clinically meaningful degree, beyond the benefits from lowering blood pressure.

Keywords

ageing; comorbidities; fibrosis; HIV; immune recovery; inflammation

Introduction

Persons with HIV (PHIV) who are living to older ages with antiretroviral therapy (ART) are at an increased risk for comorbidities such as cardiovascular disease (CVD) and other non-AIDS defining end-organ diseases [1,2]. This increased clinical risk is due, in part, to persistent inflammation and incomplete immune recovery [3,4]. Despite suppression of plasma viremia with ART, ongoing immune activation during HIV disease results in chronic exposure to higher levels of inflammatory cytokines [e.g. interleukin-6 (IL-6)] that contributes to a wide spectrum of disease risk [4–6]. In addition, lower $CD4^+$ cell counts during ART treatment have been associated with an increased risk for comorbid conditions such as CVD, cancer, liver disease, osteoporosis and fractures [3,7].

Although immune recovery after ART initiation is substantial among most PHIV, $CD4^+$ cell count levels often remain lower than for uninfected persons. Approximately 15–20% of PHIV who start ART during advanced disease (e.g. $CD4^+$ cell count <200 cells/μl) will have persistent immune depletion (e.g. $CD4^+$ cell count <500 cells/μl) [8,9]. The pathogenesis of impaired immune recovery despite suppression of plasma viremia involves fibrosis within lymphatic tissues [10]. Collagen deposition within the parafollicular T-cell zone in lymph nodes disrupts the homeostasis of naive and central memory T cells and impairs immune recovery [11]. This pathologic collagen deposition within lymphatic tissues is mediate by transforming growth factor beta (TGFβ1) pathways as a consequence of ongoing immune activation in the context of HIV disease [12].

Losartan, an angiotensin receptor blocker (ARB), has several well established treatment effects beyond blood pressure (BP) lowering that make it a potentially useful candidate treatment to reduce inflammation and improve immune recovery among PHIV. Angiotensin receptor 1 (AT1) activates pro-inflammatory [through nuclear factor-kappa B (NF-κB) pathways] and pro-fibrotic (via TGFβ pathways) [13–15]. ARBs selectively block AT1 with resulting treatment effects that are both anti-inflammatory and antifibrotic [16–18]. For example, ARBs treatment has been shown to reduce inflammatory markers (e.g. IL-6 and C-reactive protein) [17,19]. In the context of HIV disease, ARBs also have potential to reverse tissue fibrosis through a well characterized mechanism of decreasing TGF-ß activity and thereby improve T-cell homeostasis [16,20–22]. In animal models of renal, vascular and cardiac fibrosis, losartan therapy inhibits TGF-ß activity and improves histologic fibrosis [23–25].

We studied the potential benefits of losartan as disease modifying treatment among PHIV, by conducting a randomized placebo-controlled trial of losartan dosed at 100 mg daily. The

target population was PHIV at older ages (i.e. age ≥50 years old) given that absolute disease rates of the comorbid conditions that are of primary interest (e.g. CVD) increase with advancing age [26]. In addition, losartan has an excellent safety profile and may also reduce risk for CVD and other comorbidities through its effects on lowering BP [27]. The study hypothesis was that losartan would reduce levels of IL-6 and improve $CD4^+$ T-cell counts among older PHIV taking ART.

Materials and methods

Research setting and target population

Participants were recruited at six HIV clinics within the following healthcare systems: Hennepin Healthcare (Minneapolis, Minnesota, USA); Allina Healthcare (Minneapolis, Minnesota, USA); Mayo Clinic (Rochester, Minnesota, USA); University of California San Francisco (San Francisco, California, USA); Washington DC VAMC (Washington, District of Columbia, USA); NIH Clinical Center (Bethesda, Maryland, USA). The trial protocol was approved by each site's institutional review board for conduct of human's research and was registered on ClinicalTrials.gov (NCT02049307). All study participants underwent a verbal and written informed consent process.

Eligibility criteria consisted of PHIV of age at least 50 years who were receiving continuous ART for at least 2 years and had maintained HIV RNA levels less than 200 copies/ml for at least 1 year. Participants also had a $CD4^+$ cell count of 600 cells/μl or less within blood, a SBP at least 110 mmHg and no clinical indication or contraindication to taking an ARB. Participants were also excluded if they had cirrhosis, a rheumatologic disease, invasive cancer within the prior year or had been treated with immune therapy or for hepatitis C within the last six months.

Randomization and study design

We investigated the treatment effects of oral losartan (100 mg once daily) versus placebo in a randomized (1 : 1 allocation) double-blind clinical trial. Study drug (losartan and matched placebo) was provided in tablet form by Merck & Co., Inc. (Kenilworth, New Jersey, USA). After oral and written informed consent and baseline visit procedures, participants were randomized to receive active or placebo study drug. Follow-up visits occurred at months 1, 3, 6, 9 and 12. The dose of 100 mg was chosen to maximize treatment effects, and because it was not different for adverse events when compared with 50 mg in data from 20 clinical trials [27]. If participants had low BP (e.g. systolic <100 mgHg) or side effects attributed to study drug or potentially triggered by low BP, then the study drug was stopped until symptom resolution. Participants were then offered a lower dose of 50 mg once daily for the duration of the study.

The primary outcome was plasma levels of IL-6, with the main secondary outcome of $CD4^+$ cell count in blood. Additional secondary outcomes included blood biomarkers of inflammation, immune activation, coagulation, fibrosis and myocardial function. T-cell homeostasis and recovery among memory subsets were also explored among a subset with peripheral blood mononuclear cells collection at baseline and month 6 and 12. Power for n =

100 participants was 80%, at an alpha = 0.05 and 5% missing data, to detect a 27% relative reduction in IL-6 levels; cohort data suggest this degree of IL-6 reduction would be associated with a 30% lower risk of non-AIDS conditions or death [4]. For the key secondary outcome of $CD4^+$ cell count, power was 80% to detect a 12% difference, which corresponds to an approximate average annual increase of 30–50 cells per year in our target population. Adherence was assessed both subjectively and objectively via pill count among participants who returned study drug. Safety was evaluated through ascertainment of any adverse events of grade 3 or higher, or if it resulted in stopping study drug.

Clinical assessments

$CD4^+$ and $CD8^+$ cell counts, HIV RNA level, metabolic panel, complete blood count and liver enzyme levels were measured at the individual site clinical laboratory. The fibrosis-4 (FIB-4) index was calculated from inputs of age, aspartate aminotransferase (AST), platelet count, alanine aminotransferase (ALT), as a clinically available tool reflecting liver fibrosis (with a lower cutoff <1.45 indicating low risk). Frailty phenotype was also characterized at entry using a validated approach devised by Fried et al. [28]. Nonfrailty, prefrailty and frailty were defined, respectively, by the presence of 0, 1–2 and at least three of the following five frailty criteria: unintentional weight loss, physical inactivity, exhaustion/fatigue, weak grip strength and slow walk. Differential treatment effects from losartan were explored by subgroups defined by FIB-4 and frailty phenotype status at entry.

Research laboratory methods

Participants were fasting for all blood draws. Soluble (s) biomarker levels were measured from batched cryopreserved samples, blinded to treatment group. Inflammation was assessed via levels of high sensitivity IL-6 (electrochemiluminescence; Meso Scale Discovery, Rockville, Maryland, USA) and tumour necrosis factor receptor-1 (TNFr-1; ELISA; R&D Systems, Minneapolis, Minnesota, USA). Monocyte activation was estimated via measures of sCD14 (ELISA; R&D Systems), sCD163 (ELISA; R&D Systems) and neopterin (ELISA; Brahms, Oklahoma City, Oklahoma, USA). Coagulation activity assessed via D-dimer (Sta-R analyser, Liatest D-DI; Diagnostic Stago, Parsippany, New Jersey, USA). Potential tissue fibrosis was indirectly assessed via circulating levels of hyaluronic acid (ELISA; Corgenix, Broomfield, Colorado, USA), which is a main component of the extracellular matrix, beta-crosslaps (electrochemiluminescence, Roche Cobas e411; Roche Diagnostics, Indianapolis, Indiana, USA), a specific marker for the degradation of type 1 collagen and Galectin-3 (ELISA; R&D Systems), a marker of fibrogenesis and tissue repair that also has prognostic value in heart failure [29]. Finally, given the potential cardioprotective effects of losartan, myocardial function and stress was explored via levels of N-terminal pro b-type natriuretic peptide (NTproBNP; electrochemiluminescence; Roche Cobas e411) and ST2 (receptor for interleukin-33; ELISA; Critical Diagnostics Presage, San Diego, California, USA).

Immunophenotyping to identify T-cell memory populations and monocyte subsets was performed for a subset of participants ($n = 33$), for whom viable peripheral blood mononuclear cells (PBMCs) were cryopreserved at baseline as well as follow-up. Dead cells were identified and excluded from further analysis with LIVE/DEAD Fixable Aqua Dead Cell Stain kit (Invitrogen, Carlsbad, California, USA). PBMCs were stained using

fluorescent labelled mAbs against extracellular and intracellular antigens. Samples were acquired on an LSRFortessa cytometer (BD Biosciences, San Jose, California, USA) and analysed with FlowJo 10.4.2 (BD Biosciences).

Statistical methods

Participant characteristics and laboratory measures were summarized by mean (SD) or median [IQR] for continuous variables and proportion (count) for categorical variables. Primary analyses for the treatment effect was intent-to-treat using generalized linear mixed models with log-2 transformed biomarker values as outcomes, adjusted for pretreatment biomarker level. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) with a two-sided Type I error probability.

Results

Study participants

Figure 1 presents the study design and flow diagram for all screened participants through randomization and follow-up visits. One hundred and fifty-one participants were screened, of which 108 were randomized into the study. The most common reason for exclusion included a screening $CD4^+$ cell count more than 600 cells/μl ($n = 17$), an HIV RNA level more than 200 copies/ml ($n = 5$) and SBP less than 110 mmHg ($n = 4$). All randomized participants completed at least one follow-up study visit on study drug, and 105 (97%) completed a month 12 visit.

Table 1 presents participant characteristics. Median age was 56 years, with 96% being male sex at birth, 57% white non-Hispanic and 34% African–American. Prevalence of CVD risk factors included 20% current smokers, 20% with hypertension and 26% prescribed lipid lowering therapy. Median (IQR) $CD4^+$ cell count was 439 cells/μl (304–498), and 70% had prior AIDS. Median time since HIV diagnosis was 20 years (12–26), and 76% had viral suppression more than 5 years at study entry. The ART regimen consisted of an integrase strand transfer inhibitor (INSTI) in 49%, a nonnucleoside reverse transcriptase inhibitor (NNRTI) in 39% and a protease inhibitor in 35%. Finally, only four (4%) participants met criteria for frailty phenotype, with 41 (38%) classified as prefrail.

Inflammation and other blood biomarkers

Median [IQR] IL-6 levels at entry were 1.1 pg/ml [0.7–1.4]. Median levels of all blood biomarkers in losartan and placebo groups separately are reported in Supplemental Table A, http://links.lww.com/QAD/B905. Figure 2 presents the primary intention-to-treat comparisons showing that losartan did not reduce IL-6 levels, nor any of the other plasma biomarkers of inflammation, monocyte activation, fibrosis activity and myocardial function. The effect estimate for losartan versus placebo on IL-6 was 0.6%, with 95% confidence interval (95% CI) of −14.7 to 18.7, and a 99% CI of −19.0 to 25. Sensitivity analyses were conducted restricted to those that maintained HIV viral suppression throughout follow-up or those indicating 100% adherence to study medication at all visits, and results were similar with no treatment effect on any of the blood biomarkers. Finally, approximately one-third ($n = 33$) study participants had monocyte activation phenotypes characterized, and there was no

evidence of a treatment effect on monocyte activation (Supplemental Figure A, http://links.lww.com/QAD/B905).

Subgroup analyses are shown for IL-6 in Fig. 3, and there was no significant treatment effect within subgroups or evidence of a treatment-subgroup interaction in these factors; similarly, null results were present for subgroups defined by race/ethnicity, duration of HIV diagnosis and ART class (data not shown). Subgroup analyses for the secondary outcome biomarkers reported in Fig. 1 also did not reveal evidence for treatment interactions (data not shown).

Immune recovery

Median levels of clinical T-cell measures at the baseline are reported in Table 1. Losartan treatment did not improve levels of peripheral blood $CD4^+$ or $CD8^+$ T cells, or the CD4:CD8 ratio. Null findings persisted for key subgroups (as studied in Fig. 3), and when restricted to those that maintained viral suppression or 100% adherence. Among the subset of $n = 33$ with immunophenotyping, losartan treatment did not change the percentage of $CD4^+$ or $CD8^+$ T-cell memory subsets (i.e. naive, central memory or effector memory; Supplemental Figure B, http://links.lww.com/QAD/B905).

Adherence and adverse events

Among 12 occurrences wherein participants stopped study drug due to possible side effects, one resumed study drug at 100 mg dose, five resumed at lower dose of 50 mg daily and six did not restart study medication. Among the 12 who stopped, two had an indication of low BP and both were in the active losartan group, and one was able to resume study medication at 50 mg daily. Among the participants expected to be taking study drug, the percentage that reported adherence on every study day was 93% during the first 3 months, but then decreased to 66% between months 9 and 12 of follow up (see supplemental Figure C, http://links.lww.com/QAD/B905). Eighty-one percent of dispensed bottles were returned facilitating objective estimate of adherence by pill count. Among this subset, the mean adherence was 97% of days during the first 3 months, decreasing to 87% of study days between months 9 and 12. There were no differences between treatment groups in study drug discontinuation, dose adjustment or subjective or objective adherence assessments. When restricting to those with high adherence (i.e. daily by subjective or >90% by objective measures), there remained no evidence of a treatment effect on IL-6 or any of the outcomes in Fig. 2.

Table 2 presents a summary adverse events and clinical assessments between losartan and placebo groups. Losartan treatment was associated with a small decline in BP and clinically insignificant change in serum creatinine and eGFR. There were more adverse events reported overall in the losartan versus placebo group, with differences not reaching statistical significance. The most frequent types of adverse events were fatigue ($n = 5$), dizziness ($n = 4$) and malaise ($n = 3$).

Discussion

In this randomized placebo-controlled trial, we tested the hypothesis that losartan given at 100 mg daily in addition to ART would reduce systemic inflammation and improve immune

recovery. In our study population, losartan treatment was not associated with reductions in blood measures of IL-6 or other measures of inflammation, immune activation and fibrotic activity. There was also no evidence of a treatment effect on immune recovery either by total $CD4^+$ cell count or within memory subsets. Losartan was well tolerated overall, but potentially associated with more adverse events in this study population that were attributable to low BPs.

Treatment with angiotensin-converting enzyme inhibition (ACE) or ARB has demonstrated anti-inflammatory effects via mechanisms both dependent and independent from mitigating angiotensin-2 effects on AT1 [19,30]. Additional mechanisms specific to ARB that may be unrelated to AT1 receptor blockade, include the unopposed stimulation of AT2 receptor activity and/or by reducing innate immune responses in circulating monocytes more broadly [e.g. as a response to bacterial lipopolysaccharide (LPS)] [19,30]. Numerous studies from the general population have demonstrated reductions in circulating cytokines and inflammatory mediators (e.g. CRP, IL-6, TNF-α) with ACE or ARB treatments, though many of these were among patients with additional risk factors or comorbidities (e.g. hypertension, metabolic syndrome, coronary artery disease, heart failure and so on). In a proof-of-concept trial of $n = 34$ PHIV, we previously showed a reduction in CRP and TNF-α levels from lisinopril versus placebo treatment [31].

Our current findings failed to demonstrate an anti-inflammatory effect of losartan in the setting of treated HIV disease. Recently, another well powered placebo-controlled randomized trial of losartan among older persons (age ≥70 years) in the general population also failed to demonstrate reductions in IL-6 levels [32]. Reasons for inconsistent findings when compared with prior studies may be related to differences between individual medications (i.e. lack of consistent ‘class effect’), and/or, importantly, to differences between the target populations being studied. Drivers of inflammation among persons with hypertension or cardiometabolic risk factors may be more directly related to pathways modulated by angiotensin-2, and thus, more responsive to ARB treatment. Whereas, losartan treatment effects may not sufficiently mitigate mechanisms driving persistent inflammation during ART-treated HIV disease, such as the persistence of HIV-specific immune responses, injury to mucosal effector sites with associated increase in microbial translocation and/or loss of immunologic control over other chronic copathogens (e.g. cytomegalovirus) [5,33–35]. Finally, IL-6 levels among PHIV in our study were low or modest overall, which likely diminishes the potential for detecting a meaningful effect.

The potential for losartan and other ARB to reduce fibrosis within tissues has been described in multiple end-organ diseases, such as renal interstitial fibrosis, myocardial fibrosis and aortic root dilation in Marfan’s syndrome [36,37]. The mechanism of fibrosis attenuation or reversal in these settings is largely attributed to losartan mitigating TGF-β signalling. However, two recently conducted trials among PHIV have failed to demonstrate an antifibrotic effect of ARB or ACE treatment within lymphatic tissues [38,39]. In a randomized trial of telmisartan versus placebo among PHIV with viral suppression ($n = 44$), there was no difference between groups in lymph node (LN) or adipose tissue collagen deposition over 1 year [38]. Similarly, lisinopril failed to demonstrate a reduction within gut associated lymphatic tissue (via rectal biopsy; $n = 30$), when compared with placebo [39]. In

contrast, using an SIV nonhuman primate model, the potent antifibrotic drug pirfenidone was shown to mitigate LN fibrosis and improved recovery of $CD4^+$ T-cell populations in blood [40]. Potential reasons for the lack of antifibrotic effects of ARB/ACE within lymphatic tissues in HIV studies, in part, may relate to mechanisms that are independent of TGF-β signalling and/or the degree of AT-1 blockade may be insufficient to overcome HIV-specific drivers of fibrosis. Finally, it is also worth emphasizing the inherent limitations related to the smaller samples sizes of studies evaluating fibrosis at the level of end-organ tissues. An earlier study of losartan in $n = 20$ patients with nonobstructive hypertrophic cardiomyopathy suggested an attenuation in myocardial fibrosis and hypertrophy by cardiac magnetic resonance, but a larger follow-up study of $n = 318$ patients with hypertrophic cardiomyopathy then failed to demonstrate these same effects [41,42].

This study has several limitations. The sample size remains modest for detecting smaller treatment effects, and results may also not be generalizable across sex given the very small number of women. In addition, losartan could have inflammation and immune effects on pathways not assessed, or that are only present among those with higher levels of ongoing inflammation. Specifically, treatment effects within tissues may not be detected in blood but could have important long-term implications. Evaluation of fibrosis and T-cell homeostasis with lymphatic tissues are planned among a subset of participants that underwent lymph node biopsies in this trial, and will provide additional context for these findings. Despite these limitations, our findings suggest that losartan is unlikely to have a meaningful impact on inflammatory markers among PHIV. The 95% CI of our estimated treatment difference for losartan versus placebo supports that we can rule out an effect of lowering IL-6 by at least 15% in this population. We have previously shown that an IL-6 decline less than 15% among PHIV would predict a modest reduction in risk (i.e. <17%) for serious non-AIDS events or mortality [4].

In summary, losartan treatment given in addition to ART among older persons with longstanding HIV disease did not improve blood measures of inflammation, fibrotic activity or T-cell immune recovery. These results suggest that losartan is unlikely to reduce inflammation associated end-organ complications among PHIV, beyond the established CVD risk reduction associated with lowering BP. Additional strategies to reduce inflammation and improve T-cell recovery are needed to improve the health of people living with HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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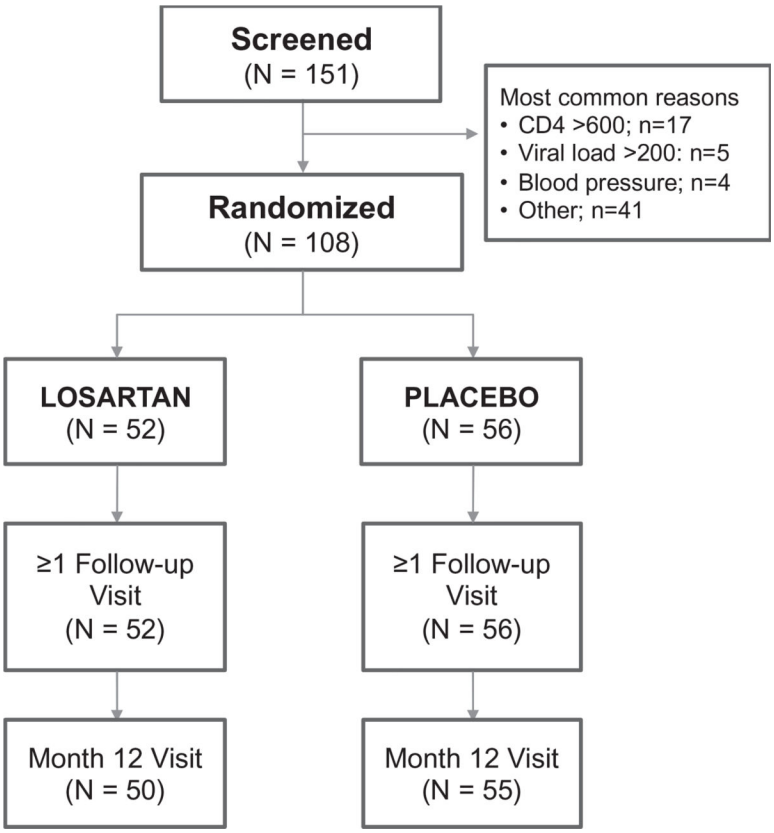

Fig. 1.
Study design and participant retention through follow-up.

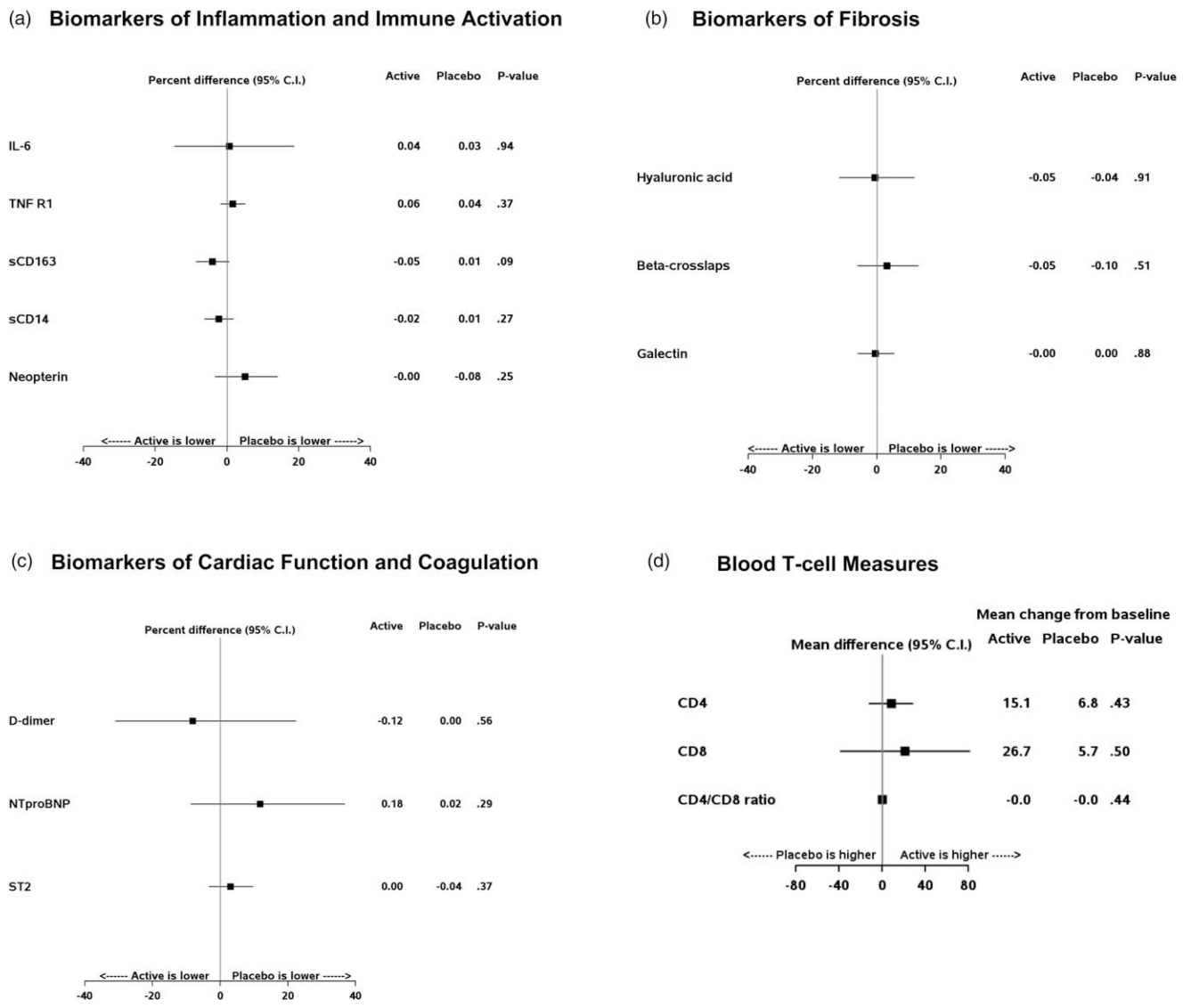

Fig. 2. Treatment effect of losartan versus placebo over 12 months.

Point estimates reflect the treatment effect over follow-up of losartan versus placebo, with 95% confidence intervals. Plasma biomarkers (a–c) plot a percentage difference for the corresponding marker, whereas T-cell measures (d) plot the absolute mean difference between groups. The mean change from baseline is shown to the right, with plasma biomarkers represented on log-2 scale (a–c) and T-cell measures on the corresponding absolute scale.

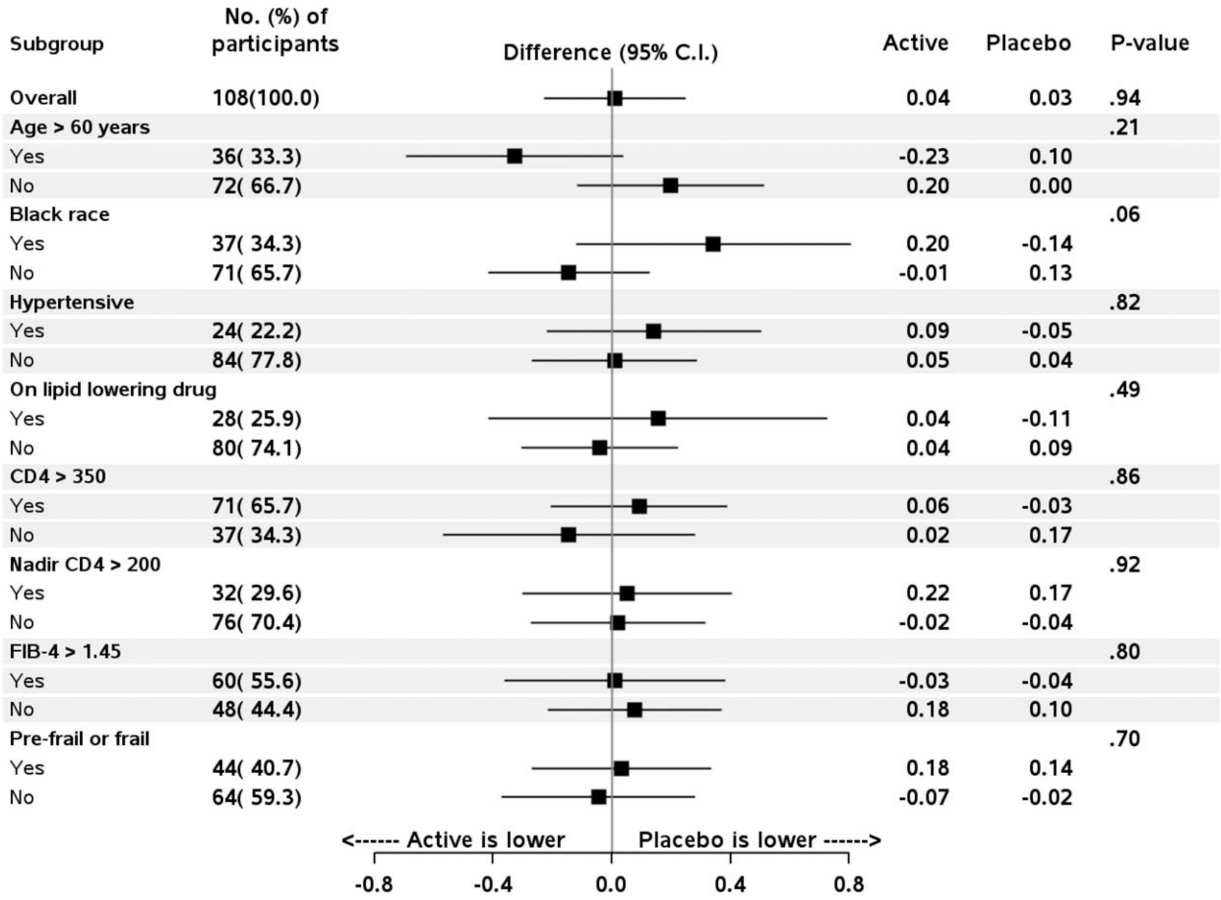

Fig. 3. Treatment effect of losartan on IL-6 levels among key subgroups.

Forrest plots include point estimates reflecting the treatment effect over follow-up of losartan versus placebo, with error bars reflecting 95% confidence intervals. The treatment effect reflects the percentage difference for the study population overall (top), and then for each of the subsequent subgroups defined at study entry. The mean change from baseline over follow-up within active-losartan and placebo groups is shown to the right of the graphs for each of the corresponding measures represented on log-2 scale.

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Table 1.

Baseline participant characteristics (n = 108).

	Median [IQR] or % (n)		
	Losartan (n = 52)	**Placebo (n = 56)**	**Overall (n = 108)**
Demographic characteristics			
Age (years)	56 [53, 62]	56 [53, 61]	56 [53, 61]
Male sex at birth	96% (50)	96% (54)	96% (104)
Race/ethnicity	–	–	–
White	62% (32)	52% (29)	57% (61)
Black	29% (15)	39% (22)	34% (37)
Hispanic or Latino	8% (4)	4% (2)	6% (6)
Clinical characteristics			
Smoking, current	15% (8)	25% (14)	20% (22)
Hypertension Diagnosis	23% (12)	18% (10)	20% (22)
Body mass index (kg/m^2)	26.6 [24.2, 29.7]	27.2 [23.0, 31.8]	26.8 [23.6, 30.7]
Hepatitis C antibody positive	16% (8)	11% (6)	13% (14)
SBP (mmHg)	126 [122, 136]	130 [121, 136]	129 [122, 136]
DBP (mmHg)	82 [73, 86]	81 [75, 86]	81 [74, 86]
Prescribed lipid lowering therapy	23% (12)	29% (16)	26% (28)
Total cholesterol (mg/dl)	173 [162, 195]	184 [165, 200]	182 [163, 198]
LDL cholesterol (mg/dl)	100 [80, 123]	103 [87, 123]	102 [84, 123]
HDL cholesterol (mg/dl)	44 [35, 60]	46 [39, 56]	45 [37, 57]
Serum creatinine (mg/dl)	1.1 [0.9, 1.2]	1.1 [1.0, 1.2]	1.1 [1.0, 1.2]
Fibrosis-4 index ≥1.45	64% (33)	48% (27)	56% (60)
Frail phenotype (at least three criteria)	2% (1)	6% (3)	4% (4)
Prefrail phenotype (one or two criteria)	44% (23)	32% (18)	38% (41)
HIV disease characteristics			
CD4$^+$cell count, nadir (cells/μl)	121 [46, 226]	119 [37, 240]	120 [37, 240]
CD4$^+$cell count current (cells/μl)	451 [300, 496]	430 [321, 516]	439 [304, 498]
CD8$^+$cell count, current (cells/μl)	698 [491, 879]	683 [450, 948]	683 [472, 906]
CD4:CD8	0.53 [0.40, 0.91]	0.65 [0.36, 0.95]	0.57 [0.39, 0.94]

	Median [IQR] or % (*n*)		
	Losartan (*n* = 52)	**Placebo (*n* = 56)**	**Overall (*n* = 108)**
Duration of HIV diagnosis (years)	20 [7, 25]	18 [12, 26]	20 [12, 26]
Time since first ART (years)	16 [7, 21]	17 [10, 22]	17 [8, 22]
ART includes NNRTI	35% (18)	43% (24)	39% (42)
ART includes PI	31% (16)	39% (22)	35% (38)
ART includes INSTI	50% (26)	48% (27)	49% (53)
Prior AIDS	71% (37)	70% (39)	70% (76)
Opportunistic illness	8% (4)	20% (11)	14% (15)
$CD4^+$cell count <200 cells/μl	64% (33)	50% (28)	57% (61)

ART, antiretroviral therapy; HDL, high-density lipoprotein; INSTI, integrase strand transfer inhibitor; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2.

Clinical monitoring and adverse events.

Clinical measures	Losartan Mean (SE) overall change	Placebo Mean (SD) overall change	*P* for diff.
SBP (mmHg)	−7.9 (1.0)	−1.7 (1.0)	<0.001
DBP (mmHg)	−4.8 (0.8)	0.4 (0.7)	<0.001
Serum creatinine (mg/dl)	0.05 (0.01)	0.00 (0.01)	0.002
Serum potassium (mmol/l)	0.04 (0.02)	−0.03 (0.02)	0.03
eGFR (ml/min per 1.73 m^2)	−3.03 (0.88)	0.02 (0.84)	0.01
Adverse events (AE)	#	#	
AE resulting in drug discontinuation	3	4	0.82
AE, grade 3 or 4	9	5	0.11
SAE	6	4	0.52
Death	0	0	–
Any above AE	18	9	0.06

AE, adverse event; BP, blood pressure; eGFR, estimated glomerular filtration rate; SAE, serious adverse event.