Risk factors for chronic kidney disease do not influence the serum levels of asymmetric dimethylarginine in HIV-1-infected patients without significant renal disease

Article ID: doi:10.20452/pamw.3508

ISSN: 1897-9483

Authors: Anna Szymanek-Pasternak, Aleksandra Szymczak, Małgorzata Zalewska, Krzysztof Małyszczak, Brygida Knysz

Article type: Original article

Received: April 25, 2016.

Revision accepted: July 18, 2016.

Published online: August 18, 2016.

This article has been peer reviewed and published immediately upon acceptance. It is an open access article, which means that it can be downloaded, printed, and distributed freely, provided the work is properly cited. Articles in Polish Archives of Internal Medicine are listed in PubMed.
Risk factors for chronic kidney disease do not influence the serum levels of asymmetric dimethylarginine in HIV-1-infected patients without significant renal disease

Short title: ADMA level in HIV-1-infected patients without chronic kidney disease

Anna Szymanek-Pasternak¹, Aleksandra Szymczak², Małgorzata Zalewska², Krzysztof Małyszczak³, Brygida Knysz²

¹ 1st Department of Infectious Diseases, J. Gromkowski Specialist Regional Hospital, Wrocław, Poland
² Department of Infectious Diseases, Hepatology and Acquired Immune Deficiencies Wroclaw Medical University, Wrocław, Poland
³ Department of Psychiatry, Division of Psychotherapy and Psychosomatic Medicine, Wroclaw Medical University, Wrocław, Poland

Correspondence to: Aleksandra Szymczak, MD, PhD, Katedra i Klinika Chorób Zakaźnych, Chorób Wątroby i Nabytych Niedoborów Odpornościowych Uniwersytetu Medycznego we Wrocławiu, ul. Koszarowa 5, 52-314 Wrocław, Poland, phone: +48 71 395 75 49, e-mail: aleksandra.szymczak@umed.wroc.pl

Received: April 25, 2016.

Revision accepted: July 18, 2016.

Published online: August 18, 2016.

Conflict of interest: none declared.

Abstract

Introduction Chronic kidney disease (CKD) is one of the consequences of human immunodeficiency virus-1 (HIV-1) infection. It increases the risk of progression to acquired immunodeficiency syndrome and death and complicates antiretroviral therapy. The prevalence of CKD in HIV-1-infected patients is difficult to estimate and depends on the diagnostic criteria for CKD.

Objectives The aim of the study was to evaluate the usefulness of a single measurement of serum asymmetric dimethylarginine (ADMA) levels in the diagnosis of kidney damage in patients infected with HIV-1.

Patients and methods The study included 119 HIV-1-infected individuals (88 males [74%]), both on antiretroviral treatment and treatment-naive, with a negative history of kidney disease, and 31 healthy volunteers. We analyzed demographic characteristics as well as data on concomitant diseases, antiretroviral regimen, serum ADMA concentrations, parameters of renal function, CD4+ cell count, and HIV-1 viral load. In a statistical analysis, a P value of less than 0.05 was considered significant.

Results No significant impairment of renal function was observed. Mean serum ADMA levels in HIV-1-infected patients, HIV-1-infected treatment-naive patients, and HIV-1-infected treated patients were significantly higher ($P < 0.001; P = 0.0001; P < 0.0001$, respectively) compared with those in the control group. The difference between naive and treated HIV-1-infected patients was nonsignificant. ADMA levels were not correlated with the mean duration of antiretroviral therapy, antiretroviral drugs used, or other risk factors for CKD.
Conclusions  A single measurement of ADMA levels is not useful for the diagnosis of CKD in patients without significant renal pathology or as an indicator of kidney damage related to antiretroviral therapy. The significance of repeated measurements of ADMA levels in renal function assessment needs further research.

Key words
antiretroviral therapy, asymmetric dimethylarginine, chronic kidney disease, HIV-1 infection

Introduction  Wide access to effective combined antiretroviral therapy (cART) and increasingly better virological and immunological control of human immunodeficiency virus 1 (HIV-1) infection results in constant improvement of the prognosis for survival of HIV-1-infected persons. Therefore, increasing attention is directed towards prevention and treatment of comorbidities and minimizing the side effects of antiretroviral drugs.

The first reports of kidney disease in patients with acquired immunodeficiency syndrome caused by HIV-1 date back to the mid-1980s [1-3]. It was proved then for the first time that HIV-1 can infect epithelial cells of the kidney [4]. Later, it was shown that there are many other infectious agents that can affect the course of renal disease, also in patients infected with HIV-1. These are hepatitis C and B viruses (HCV, HBV), parvovirus B19, cytomegalovirus, Ebstein-Barr virus, BK virus, Cryptococcus neoformans, Mycobacterium tuberculosis, and other opportunistic infections, as well as nephrotoxic drugs [5,6]. The risk of chronic kidney disease (CKD) is associated with age, hypertension, diabetes, lower T CD4+ cell count, higher HIV viral load, and proteinuria [7-10]. CKD increases the risk of progression to acquired immunodeficiency syndrome (AIDS) and death as well as the risk of side effects of antiretroviral therapy with protease inhibitors (PI) [11]. The prevalence of renal disease in HIV-1-infected patients is difficult to estimate and depends on the diagnostic criteria for CKD. Moreover, the diagnosis of CKD, particularly at its early
stages, has still unclear clinical importance [12]. Therefore, data on CKD from various studies are not uniform. The differences may result from the use of different formulas for glomerular filtration rate (GFR) estimation or from including or not proteinuria and albuminuria into diagnostic criteria.

The most commonly used method of the assessment of renal function by measuring serum creatinine is not sufficiently sensitive and specific. GFR estimation can be affected by numerous factors that influence plasma levels of creatinine and its synthesis, tubular secretion, as well as by the various factors affecting the course of laboratory testing [13]. The aim is to select the best formula that would most accurately estimate GFR for all stages of CKD, in acute kidney injury and healthy kidney, in all groups of patients, regardless of the type of kidney problem and associated diseases. In everyday practice, the most common formulas used for GFR estimation are those based on endogenous substances: creatinine and recently also on cystatin C. Experts of Kidney Disease: Improving Global Outcomes recommend the measurement of cystatin C and determination of estimated GFR (eGFR) on its basis in patients whose GFR calculated on the basis of creatinine is in the limit range for the diagnosis of CKD (45–59 ml/min/1.73 m²) [13].

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide (NO) synthesis. NO is the most potent endogenous vasodilator and, due to its anti-inflammatory and antithrombotic potential, also endogenous antiatherogenic factor [14]. Elevated levels of ADMA were observed in numerous studies in patients with CKD, even at stage 1 of the disease [15-19]. In contrast, there have been no studies on the use of ADMA in the diagnosis of CKD in HIV-1-infected patients. This marker has been studied in HIV-1-infected patients mainly in terms of diagnosis of cardiovascular disease [20-26]. Due to the complex pathology of HIV-1 infection, associated with a number of kidney-damaging agents, that occur more frequently in people living with HIV-1 than in the general
population, it is important to determine the scale of the problem in this population, living in a given region, as well as the most optimal early diagnosis of the renal changes. It could have a positive impact on early intervention, closer monitoring of renal function, and adjusting antiretroviral therapy and treatment of comorbidities to kidney function.

The aim of this study was to evaluate the prevalence of the abnormalities of kidney function in patients infected with HIV-1 in the population of Lower Silesia, an administrative region of Poland, as well as to evaluate the usefulness of ADMA in the diagnosis of kidney damage in patients infected with HIV-1. We also studied the effect of some antiretroviral drugs on the parameters of renal function.

**Patients and methods**

The study was approved by the Bioethical Committee of the Medical University in Wroclaw (no. of consent: KB-237/2011). All study participants gave written informed consent for the participation in the study.

The study group consisted of 119 people infected with HIV-1, both on antiretroviral treatment and treatment-naive, with a negative history of kidney disease. The control group included 31 HIV-negative volunteers, from the Lower Silesia region, Poland, matched for age and sex. All participants were Caucasians, older than 18 years of age. The study group consisted of 88 men (74%) and 31 women (26%), aged from 23 to 68 years (mean age, 40 ±9.5 years), while the control group consisted of 21 men (68%) and 10 women (32%), aged from 23 to 58 years (mean age, 40.1 ±8.9 years). All HIV-1-infected patients belonged to the clinical category A of the Center for Disease Control and Prevention criteria from 1993.

The exclusion criteria were as follows: diabetes, uncontrolled hypertension, thyroid disease, rheumatoid arthritis treated with corticosteroids, malignancy, fever, acute bacterial, viral, or fungal infection, currently with AIDS-defining disease, infected with HBV (patients with detectable HBs antigen in the serum), any other known inflammatory states potentially
influencing ADMA levels, as well as the episode of acute renal failure in the past, and use of active intravenous and other illicit drugs.

Data concerning the course of HIV infection, smoking status, and concomitant diseases (HCV infections, hypertension, hyperlipidemia, hyperuricemia, and nephrolithiasis) were collected. Hypertension was defined as previous diagnosis and use of antihypertensive medications, as uncontrolled hypertension was the exclusion criterion. Dyslipidemia was defined as any of the following: total cholesterol and low-density lipoprotein (LDL) cholesterol levels above the upper normal range, triglyceride level above the upper normal range, and high-density lipoprotein (HDL) cholesterol below the lower normal range.

The serum ADMA concentration was measured using an enzyme-linked immunosorbent assay (DLD Diagnostics GMBH). The sensitivity of the method was 0.05 mmol/l. HIV-1 viral load was determined by real-time polymerase chain reaction assay (COBAS TaqMan HIV-1 Test v. 2.0). The isolation of HIV-RNA was performed using System Viral Nucleic Acid Kit from Roche Diagnostics. The CD4⁺ T cell count was determined by flow cytometry using FacsCount Becton Dickinson system. Other tests were performed with standard methods used in routine diagnostics.

**Statistical analysis** The groups were tested for normal distribution. Mean values were compared by analysis of variance with the t test and post-hoc Newman–Keuls test. For nonnormal distribution, nonparametric Kruskal–Wallis test, Mann–Whitney test, and χ² test were used. For the analysis of ADMA levels, Mann–Whitney test with Bonferroni correction was used. The dependence of the variables was assessed using the Pearson correlation coefficient r. The P values of less than 0.05 were considered statistically significant. Calculations were performed using Statistica 10.0 for Windows (StatSoft Inc., Tulsa, Oklahoma, United States).
Results  The characteristics of the study and control group are presented in TABLE 1. Among HIV-1-infected patients, 98 were treated with standard cART. The schedules were as follows: 65 patients were treated with 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and ritonavir-boosted PI (PI/r); 25 patients, with 2 NRTI and non-nucleoside reverse transcriptase inhibitor (NNRTI); 3 individuals, with 2 NRTI and integrase inhibitor; 3 patients, with PI/r and integrase inhibitor; and 2 persons, with PI/r only.

All patients with diagnosed hypertension from the study and control groups were successfully treated with antihypertensive medications. No individual was treated with potentially anti-inflammatory medications, including acetylsalicylic acid, other nonsteroid anti-inflammatory drugs, or statins.

Values of eGFR calculated according to the CKD-EPIcreat in the study and control groups are presented in Table 2. The highest values of GFR were observed in cART-naive patients and the lowest values—in the control group. Significant differences were observed between the treatment-naive group and patients on cART \((P = 0.003)\) and between the treatment-naive patients and controls \((P = 0.001)\). After adjustment for age, the differences of eGFR between the naive and treated groups were on the border of significance \((P = 0.051)\). The difference in eGFR between all HIV-1-infected patients and controls was not significant \((P = 0.21)\).

Impaired renal function (eGFR below 60 ml/min/1.73 m²) was observed only in 1 HIV-infected patient and in no control individuals. The levels of ADMA in the study group are presented in TABLE 3. HIV-1-infected patients were divided according to the cART status. Additionally, the treated patients were divided into subgroups according to the use of potentially nephrotoxic antiretroviral drugs (tenofovir [TDF], PI/r, with, separately, atazanavir and lopinavir [LPV]).
Serum ADMA levels in HIV-1-infected patients were significantly higher than those in the control group ($P < 0.0001$). The significant differences were also noted between treatment-naive HIV-1-infected patients and controls ($P < 0.0001$) and between treated individuals and controls ($P < 0.0001$). Among HIV-1-infected individuals, ADMA levels were higher in treatment-naive patients than in patients on cART; however, the difference was not significant ($P = 0.14$). Adjustment for significantly different variables: age, smoking status, HCV infection, and intravenous drug use did not influence the results.

We observed significant effects of potentially nephrotoxic antiretroviral drugs on higher ADMA levels compared with controls: TDF, $P = 0.0001$; any PI/r, $P < 0.0001$; TDF with PI/r, $P = 0.0002$; ATV/r, $P = 0.005$; LPV/r, $P < 0.0001$ (FIGURES 1-5). There were no significant differences in ADMA levels between patients treated with different potentially nephrotoxic drugs and in comparison with the cART regimens without the use of these drugs. ADMA levels and eGFR values were not correlated with the antiretroviral drug used (TDF, PI/r, TDF + PI/r). Serum ADMA levels were also not correlated with the mean duration of cART.

In 8 HIV-1-infected individuals, proteinuria was observed. Mean serum ADMA levels were higher in the group with proteinuria compared with individuals with normal urinalysis (0.708 vs 0.601). This difference was on the border of statistical significance ($P = 0.054$).

The effect of HIV infection-related factors on ADMA level was analyzed. No significant differences in ADMA levels were noted according to either current CD4$^+$ T cell count, CD4$^+$ nadir, or HIV-1 viral load in treatment-naive and suboptimally treated patients. Coinfection with HCV also did not affect ADMA levels. There were no significant differences related to HIV-1 transmission route. The highest ADMA levels were observed in current smokers, and the lowest levels were noted in never-smokers; however, this difference was not significant. Other nonsignificant parameters included sex, age, body mass index.
(BMI), concomitant conditions (arterial hypertension and nephrolithiasis), white blood cell count, and C-reactive protein level.

**Discussion** CKD is currently one of the most important causes of morbidity and mortality among so-called non-AIDS diseases in HIV-infected patients [27,28], ranking the fourth place after malignancies, cardiovascular diseases, and liver diseases, according to the EuroSIDA study [28]. The scale of the problem is not fully understood in the population of Polish HIV-1-infected patients. Among patients infected with HIV-1 in Poland, there is still a large group of drug users (many currently inactive) [29]. The drugs used by them were prepared by themselves with poppy and contained various contaminations, whose type and amount could not be determined. A large percentage of HIV-positive patients in Poland is coinfect ed with HCV or HBV (or both). The socioeconomic status of these patients is often low, which affects their lifestyle, diet, and treatment, similarly as in the report of Ganesan el al [30] in different populations.

The age of patients included in our study ranged from 23 to 68 years. This is the typical age of the population of people infected with HIV-1 in Poland [29]. Immunological results and HIV-1 viral loads did not differ from the data presented by authors from other Polish centers treating people with HIV infection.

ADMA plays an important role in the pathogenesis and progression of CKD and cardiovascular diseases, and this role is related to endothelial function. ADMA works by inhibiting the synthesis of NO. As an inhibitor of NO, ADMA impairs vasodilatation of capillaries. Impaired blood flow through the renal tubular capillaries causes hypoxia within the tubules and renal parenchyma [31], which results in renal fibrosis [32,33]. ADMA is a marker of renal impairment, independent from GFR, proteinuria, hemoglobin, and homocysteine levels [34]. Thus, ADMA allows objective assessment of renal function. Research on ADMA is conducted in 2 directions: to assess its usefulness as a diagnostic tool
and to develop drugs lowering its concentration, thereby inhibiting its pathogenic effect on endothelial function [31]. Given the numerous publications on the diagnostic role of ADMA in renal diseases, we studied it in patients infected with HIV-1, who have multiple risk factors of impaired kidney function. We did not demonstrate any significant relationship between ADMA levels and age, BMI, history of intravenous drug use, smoking, or hypertension, although other authors demonstrated a correlation between ADMA levels and hypertension [24,32-35]. HCV coinfection was noted in 39.5% of patients in the study group. This coinfection was acquired primarily by intravenous drug use. The proportion of HCV-positive patients also did not differ from data obtained in other regions of Poland. Our data showed no effect of HCV coinfection on ADMA levels.

In our study, we did not find any correlation between serum ADMA levels and eGFR in patients on cART and treatment-naive patients. We did not find differences in the concentration of ADMA in patients with eGFR values above and below 90 ml/min/1.73m². As for these latter results, we did not find literature any similar analysis in the available. We did not observe a relationship between the concentration of ADMA and severity of albuminuria. In contrast, there were significantly higher levels of ADMA among persons infected with HIV-1, treated and untreated with cART, compared with the control group, regardless of the type of antiretroviral therapy. It seems that not the antiretroviral drugs but the presence of HIV-1 infection itself affects the concentration of ADMA. Hudson et al [36] and Jang et al [24] showed that people infected with HIV had significantly higher levels of ADMA compared with uninfected individuals. On the other hand, Kurz et al [23,37] and Baker et al [20] proved that the concentration of ADMA decreased on cART and correlated with a decrease in levels of immune activation markers. In most publications concerning ADMA and HIV infection, the impairment of endothelial function, as a result of chronic inflammation, is underlined. This impairment results in the development of subclinical
atherosclerosis [24] and primary pulmonary hypertension [21]. It is believed that accumulation of ADMA as a result of chronic immune activation is associated with a predisposition to atherosclerosis [22].

It is known that antiretroviral drugs, mainly PIs, are responsible for the development of lipodystrophy syndrome [5]. In this syndrome, body fat distribution disorders, metabolic disorders such as hyperlipidemia, insulin resistance, and glucose intolerance are present and can lead to the development of accelerated atherosclerosis [5,38,39]. On the other hand, ADMA is involved in the pathogenesis of atherosclerosis [20,22-24]. In the literature, there are few reports on ADMA in patients infected with HIV-1 treated with PIs or other antiretroviral drugs. The development of atherosclerosis in people infected with HIV-1 is a complex process. The primary consideration is the virus that causes chronic inflammation, in which ADMA is also involved. On the other hand, antiretroviral drugs cause metabolic abnormalities associated with lipodystrophy syndrome. Our results point out on the chronic inflammation, independently from suppression of HIV-1 replication, as the etiological factor of atherosclerosis. We should also keep in mind the microreplication of HIV-1, undetectable with routine molecular tests, which could have an impact on the higher levels of ADMA in patients on effective cART. Perhaps the determination of ADMA levels in HIV-infected patients could have prognostic value in the assessment of atherosclerosis and its consequences, including for the kidneys.

As mentioned above, Kurtz et al [23] and Baker et al [20] showed a decrease in the concentration of ADMA as a result of antiretroviral treatment, explaining this phenomenon with the reduction of chronic immune activation and inflammation. However, they did not analyze ADMA levels in relation to the different classes of antiretroviral drugs, including PIs. It would be interesting to compare ADMA concentrations before treatment and during antiretroviral therapy with the use of certain classes of drugs. It might enable to determine the
practical value of this marker in the decision making process on changing the antiretroviral
drug for the drug that efficiently inhibits immune activation. Such studies, however, as well as
those examining the significance of ADMA as a marker of various degrees of renal
dysfunction, require a large cohort of patients and the involvement of many HIV and AIDS
centers.

Summarizing, ADMA is useful in the assessment of chronic inflammation (in HIV-1-infected
patients on cART and treatment-naive patients) and indirectly in the renal capillaries
circulation. A single measurement of ADMA levels does not have the diagnostic value for
identifying certain risk factors for CKD in patients without advanced renal pathology or an
indicator of cART-related kidney damage. The diagnostic value of repeated measurements of
ADMA needs further research.

**Study limitations** Our study has several limitations. The study group was relatively small.
We did not include the parameters of chronic immune activation and microinflammation to
the analysis. Data were obtained at 1 timepoint, without follow-up, so we could not show the
dynamics of ADMA levels.

**Contribution statement** BK conceived the idea for the study. AS-P and BK contributed
to the design of the research. AS-P, AS, MZ, and BK were involved in data collection. AS-P,
AS, KM, and BK analyzed and interpreted the data. All authors edited and approved the final
version of the manuscript.

**Acknowledgements** This work was supported by Wroclaw Medical University (grant No.
ST-586, to BK).

**References**


<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIV-1 infected individuals</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>untreated with cART (n = 21)</td>
<td>Control (n = 31)</td>
</tr>
<tr>
<td>total (n = 119)</td>
<td>119 (100)</td>
<td>21 (17.6 of HIV-1 infected)</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>119 (100)</td>
<td>21 (100)</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>----------</td>
</tr>
<tr>
<td>males, n (%)</td>
<td>88 (74)</td>
<td>18 (85.7)</td>
</tr>
<tr>
<td>age, y, mean ± SD (range)</td>
<td>40 ± 9.5 (23–68)</td>
<td>35.5 ± 8 (26–56)</td>
</tr>
<tr>
<td>CD4⁺ count, cells/μl, mean ± SD</td>
<td>545 ± 243</td>
<td>476 ± 206</td>
</tr>
<tr>
<td>CDC category of HIV infection, n (%)</td>
<td>1</td>
<td>64 (54.7)</td>
</tr>
<tr>
<td>HIV-1 viral load</td>
<td>undetectable (&lt;34 copies/mL)</td>
<td>77 (64.7)</td>
</tr>
<tr>
<td>IVDU</td>
<td>47 (40.9)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>BMI, kg/m², mean ± SD</td>
<td>23.76 ± 0.32</td>
<td>23.52 ± 0.78</td>
</tr>
<tr>
<td>smoking status, n</td>
<td>never smoking</td>
<td>19 (16.8)</td>
</tr>
</tbody>
</table>

**Notes:**
- NS: Not significant
- a: Statistical significance
- b: Significant difference
- c: Significant difference with previous category
<table>
<thead>
<tr>
<th>(%)</th>
<th>past smokers</th>
<th>current smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 (22.1)</td>
<td>69 (61.1)</td>
</tr>
<tr>
<td></td>
<td>1 (0.05)</td>
<td>14 (70)</td>
</tr>
<tr>
<td></td>
<td>24 (25.8)</td>
<td>55 (59.1)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Concurrent diseases

<table>
<thead>
<tr>
<th></th>
<th>hypertension, n (%)</th>
<th>dyslipidemia, n (%)</th>
<th>hyperuricemia, n (%)</th>
<th>HCV infection, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13 (11)</td>
<td>89 (74.8)</td>
<td>11 (9.2)</td>
<td>47 (39.5)</td>
</tr>
<tr>
<td></td>
<td>1 (4.8)</td>
<td>16 (90.4)</td>
<td>3 (14.3)</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td></td>
<td>12 (12.2)</td>
<td>73 (74.5)</td>
<td>9 (9.2)</td>
<td>45 (45.9)</td>
</tr>
<tr>
<td></td>
<td>1 (3.2)</td>
<td>24 (77.4)</td>
<td>6 (19.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.002^a</td>
</tr>
</tbody>
</table>

Basic markers of inflammation

<table>
<thead>
<tr>
<th></th>
<th>CRP, mg/dl, median (IQR)</th>
<th>WBC, 10^9/l, mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>1.1 (0.0–2.1)</td>
<td>5.57 ±0.15</td>
</tr>
<tr>
<td></td>
<td>1.3 (1.0–2.3)</td>
<td>5.00 ±0.7</td>
</tr>
<tr>
<td></td>
<td>0.5 (0.0–1.9)</td>
<td>5.69 ±0.17</td>
</tr>
<tr>
<td></td>
<td>1.0 (1.0–1.5)</td>
<td>5.94 ±0.3</td>
</tr>
<tr>
<td></td>
<td>NS^d</td>
<td>NS^b</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>NS^e</td>
<td></td>
</tr>
</tbody>
</table>

a χ² test, b Newman-Keuls test, c t test, d Kruskal-Wallis test, e Mann-Whitney test

Abbreviations: cART, combined antiretroviral therapy; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CRP, C-reactive protein; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus 1; IQR, interquartile range; IVDU, intravenous drug user; N/A, not applicable; NS, not significant; WBC, white blood cell count
Table 2 Mean values of estimated glomerular filtration rate (according to the CKD-EPI<sub>creat</sub> formula)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIV-1 infected individuals</th>
<th>Controls (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total (n = 119)</td>
<td>total</td>
<td>HIV-1 infected group vs controls</td>
</tr>
<tr>
<td></td>
<td>untreated with cART (n = 21)</td>
<td>untreated vs treated group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>treated with cART (n = 98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m², mean ±SD</td>
<td>105.0847 ±15.64941</td>
<td>114.53 ±9.42</td>
<td>103.014 ±16.2</td>
</tr>
</tbody>
</table>

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; others, see TABLE 1

Table 3 ADMA levels according to the antiretroviral treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIV-1 infected individuals (n = 119)</th>
<th>Controls (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total (n = 21)</td>
<td>total (n = 98)²</td>
</tr>
<tr>
<td></td>
<td>untreated with cART (n = 21)</td>
<td>TDF (n = 53)</td>
</tr>
<tr>
<td></td>
<td>treated with cART (n = 98)</td>
<td>PI/r (n = 70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF+PI/r (n = 37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATV/r (n = 21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LPV/r (n = 26)</td>
</tr>
<tr>
<td>ADMA, μmol/l, median</td>
<td>0.6 (0.5–0.7)</td>
<td>0.59 (0.5–0.7)</td>
</tr>
</tbody>
</table>
The total number of the patients treated with listed drugs is larger than that of the total group because the subgroups of patients were partially overlapping.

Abbreviations: ADMA, asymmetric dimethylarginine; ATV/r, ritonavir-boosted atazanavir; LPV/r, ritonavir-boosted lopinavir; PI/r, ritonavir-boosted protease inhibitor; TDF, tenofovir; others, see TABLE 1

FIGURE 1 Serum asymmetric dimethylarginine levels in patients treated with ritonavir-boosted protease inhibitors, treated with other drugs, not treated individuals, and controls ($P < 0.0001$)

FIGURE 2 Serum asymmetric dimethylarginine levels in patients treated with tenofovir, treated with other drugs, not treated individuals, and controls ($P = 0.0001$)
FIGURE 3 Serum asymmetric dimethylarginine levels in patients treated with tenofovir and ritonavir-boosted protease inhibitor, treated with other drugs, not treated individuals, and controls ($P = 0.0002$)
FIGURE 4 Serum asymmetric dimethylarginine levels in patients treated with ritonavir-boosted atazanavir, treated with other drugs, not treated individuals, and controls \((P = 0.005)\)

FIGURE 5 Serum asymmetric dimethylarginine levels in patients treated with ritonavir-boosted lopinavir, treated with other drugs, not treated individuals, and controls \((P < 0.0001)\)