Relationship between plasma L-lysine concentrations and levels of HIV-1 RNA

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Introduction

The HIV/AIDS pandemic continues to be a major health problem with an estimated 34 million people living with human immunodeficiency virus, with 2.5 million new infections in 2011 and an estimated 1.7 million deaths from HIV-related illnesses in the same year.1,2 The development of an effective vaccine, new drugs, methods and approaches in the treatment of HIV-infection remains an urgent and pressing need. Conquering this enormous challenge demands further understanding of the biology of the virus, and its interaction not only with infected cells and the immune system, but also its negative impact on the development of metabolic disturbances.

The significant changes of the host protein and lipid metabolism, catabolic effect and the negative nitrogen equilibrium in HIV progression are widely appreciated,3-7 but there are few data in the literature about infection-related amino acid imbalance in HIV infected patients.8-13 At the same time, metabolic changes in patients with various pathological conditions14-25 lead to alterations in their amino-acid profiles and the concentrations of amino acids in the extracellular medium was found to be critical in the life cycle of some viruses.26-35 Observational studies indicate that amino acid imbalances are related to increased risk of rapidly progressing virus infections through changes of the protein homeostasis. Thus, amino acid profiles may be useful as early biomarkers of the physiological disturbances and disease progression.36,37

Since it is likely that the virus so formed arises from free amino acids of the cell, knowledge of the changes of free amino acids in the host cell and tissue, and its modification by infection, should be of interest. In virus infection, the protein metabolism of the host cell is shifted from the synthesis of cellular protein to the synthesis of virus protein of a different character with significant variations in amino acids concentrations.38-41 Amino acids are not only useful for protein synthesis but also act as regulators of gene expression via the mechanism of amino acid-regulated transcription factors.12-44

The presence or absence of amino acids in the extracellular medium and its concentrations in the cell modulate specific transcription factors so as to promote or repress the synthesis of multiple genes.45-47 The same mechanism is well known in HIV pathogenesis. The conversion of the single-stranded RNA genome into double-stranded DNA by virus-coded reverse transcriptase (RT) is an essential step in the retrovirus life cycle. Human immunodeficiency virus requires a cellular tRNA Lys as a primer for initiation of reverse transcription and HIV is not infectious unless the cellular tRNA Lys interacts directly on the specific region of the viral RNA genome.48-50 But only the presence of a sufficient concentration of the essential L-lysine in HIV-infected cells activates the cellular tRNA Lys.49

To date, there are no direct clinical trial data on the effect of changes in L-lysine concentrations on HIV-1 viral load, and plasma amino acid profiles in HIV-infected patients are not adequately documented. The purpose of this study was to detect a possible relationship between levels of L-lysine and HIV-1 RNA. We hypothesized that the more rapid progression of HIV-infection is associated with the level of excess supply of this essential amino acid. To test these hypotheses, we measured levels of L-lysine, HIV-1 RNA and markers of immunological status, not only in clinical stages of the disease, but in the groups of the elite controllers, slow-progressors, and progressors among HIV-infected individuals. And our current findings do support this hypothesis.

Results

Clinical characteristics of HIV-infected patients. After the screening measurement of plasma L-lysine concentrations, HIV-1 RNA levels and CD4 count lymphocytes, 100 patients had to be excluded from the study: 32 patients had amino acid concentrations above the reference range of 80–470 μmol/l, 38 patients with HIV viral load above 1000000 copies/ml and 30 patients with severely immunodepressed (A3, B3, and C3 stages of HIV-infection).

As potential explanatory variables for plasma L-lysine concentration, organ failures (hepatic and renal failure) or biochemical markers of hepatic (AST, ALT, bilirubin, alkaline phosphatase, and lactate dehydrogenase) and renal (creatinine, γ-glutamyltransferase, and urea) function were entered in the analysis.

Clinical data, stages, immunological, and virological status of the HIV-infected patients are summarized in Table 1.

Our data revealed the differences between some hematological parameters in HIV-infected patients in CDC stages of HIV infection. The survey shows a significant decrease in the levels of CD4...
The concentrations of t-lysine were evaluated between CDC groups of HIV-infected individuals and with our reference values. No previous studies are available for comparison. The levels of the amino acid in asymptomatic stage A (58%, in the following the percentage denotes the mean of the patients in relation to the mean of healthy controls), stage B (66%), and stage C (67%) were significantly reduced in the HIV patients compared with controls.

Plasma t-lysine concentrations markedly decreased with the progression of HIV-infection. The mean amino acid levels were significantly lower in advanced stage B and C; 233.3 ± 135.0 and 149.1 ± 110.9 HIV-infected patients compared with healthy subjects (275.8 ± 120.3, P < 0.005 and P < 0.001, respectively; the Student t test) and with the level in asymptomatic stage (A) patients (263.1 ± 144.9, P < 0.01 and P < 0.001, respectively). No difference was observed between plasma t-lysine concentrations in asymptomatic stage (A1) HIV-infected patients and controls (P = 0.50).

At the same time, after initiation of HAART, the levels of t-lysine significantly increased in 80/100 (80%) of our HIV-infected individuals. As regards antiretroviral therapy, plasma amino acid concentrations (322.0 ± 115.9) were significantly higher compared with HIV-infected patients in stage A, B, and C without treatment (P < 0.0001, P < 0.0001, and P < 0.0001, respectively). We examined the difference in plasma t-lysine concentrations between HIV-infected subjects after introduction of HAART and healthy controls (P < 0.001).

Among the study patients, low levels of amino acid were found in HIV individuals with recurrent herpes infection (170.1 ± 144.5) which is different from values of controls (P < 0.01). The plasma t-lysine concentrations are given in Table 2.

Plasma t-lysine concentrations and CD4 count lymphocytes in HIV-infected patients. CD4 count lymphocytes markedly decreased with the progression of HIV-infection. The mean of these immunological parameters in clinical stage B was 345.6 (SD = 240.3) and in stage C, 245.5 (SD = 171.1). We found significant differences in CD4 count lymphocytes between advanced stage (B, C) HIV-infection compared with our reference values (1253 ± 230.3, P < 0.0001 and P < 0.0001, respectively).

A mild positive correlation was observed between plasma t-lysine concentrations and CD4 count lymphocytes in HIV-infected patients. CD4 count lymphocytes markedly decreased with the progression of HIV-infection. The mean of these immunological parameters in clinical stage B was 345.6 (SD = 240.3) and in stage C, 245.5 (SD = 171.1). We found significant differences in CD4 count lymphocytes between advanced stage (B, C) HIV-infection compared with our reference values (1253 ± 230.3, P < 0.0001 and P < 0.0001, respectively).

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between plasma L-lysine levels and CD4 count lymphocytes in entire cohort HIV-infected patients ($r = 0.19$, $P < 0.008$; Pearson correlation coefficient) and in groups I and III ($P < 0.04$ and $P < 0.03$, respectively).

The lowest levels of amino acid and CD4 count lymphocytes were found in HIV patients with recurrent herpes infection and patients with AIDS (284.2 ± 173.1 and 245.5 ± 171.1, respectively) (Table 3).

**Table 2.** Plasma L-lysine concentrations in HIV-infected patients and healthy subjects

| HIV patients                                      | L-lysine (µmol/l) | Controls (µmol/l) | Student t test |
|---------------------------------------------------|-------------------|-------------------|----------------|
| The entire cohort $n = 450$                        | 253.4 ± 152.8     | 275.8 ± 120.3     | $P < 0.041$ (S) |
| Group I ($A_1$, $A_2$) $n = 290$                  | 263.1 ± 144.9     | 275.8 ± 120.3     | $P = 0.50$ (NS) |
| Group II ($B_1$, $B_2$) $n = 110$                 | 232.3 ± 135.0     | 275.8 ± 120.3     | $P < 0.005$ (S) |
| Group III ($C_1$, $C_3$) $n = 50$                 | 149.1 ± 110.5     | 275.8 ± 120.3     | $P < 0.001$ (S) |
| HIV-infected patients with recurrent herpes infection $n = 12$ | 170.1 ± 144.5     | 275.8 ± 120.3     | $P < 0.01$ (S) |
| HIV infected patients on HAART ($B_1$, $B_2$, $C_1$, $C_2$) $n = 100$ | 322.0 ± 115.9     | 275.8 ± 120.3     | $P < 0.001$ (S) |

(S). Differences were considered significant when $P < 0.05$; (NS), not significant. Values are given as mean ± SD (range).

We observed the mild significant negative correlation between plasma L-lysine levels and viral load in clinical stage A and B HIV-infected patients ($r = -0.18$, $P < 0.006$ and $r = -0.23$, $P < 0.03$, respectively; Pearson correlation coefficient) and strong negative correlation in stage C ($r = -0.48$, $P < 0.006$). The relation between amino acid concentrations and HIV-1 RNA levels was not significant in patients on HAART ($P = 0.83$) and HIV-infected subjects with acute herpes infection ($P = 0.86$) (Table 4).

The absence of significance in HIV infected patients with recurrent herpes infection and group III may be due to the small number of subjects ($n = 12$). Our analysis was limited by a cohort size that may have been too small to allow detection of statistical associations when limited to subgroups.

In study, we observed the most significant negative correlation between plasma L-lysine levels and HIV viral load in patients with a range of viremia from 5000 to 50000 copies/ml ($r = -0.42$, $P < 0.0001$; Pearson correlation coefficient). The mild negative correlation was found in subjects with viral load from 5000 to 75000 copies/ml and from 5000 to 100000 copies/ml ($r = -0.29$, $P < 0.002$ and $r = -0.24$, $P < 0.007$, respectively). The weak negative correlation was also found in HIV-infected patients with viral load from 5000 to 50000 copies/ml and from 5000 to 100000 copies/ml ($r = -0.15$, $P < 0.03$ and $r = -0.12$, $P < 0.04$, respectively) (Table 5; Fig. 1).

The results of our study suggest that there is evidence for an association between the triad of plasma L-lysine and HIV-1 RNA levels and CD4 count lymphocytes in clinical A, B, and C stages HIV infected patients (Fig. 2).

**Plasma L-lysine concentrations and clinical data of HIV-controllers and progressors.** From all patients observed in the our center we identified 13 HIV individuals as long-term non-progressors (elite controllers) whose viremia remained controlled for more than 10 years after HIV-infection, with the constant level of HIV-1 RNA less than 500 copies/ml and CD4 count lymphocytes more than 500 cells/µl; and 25 slow-progressors whose viral load remained low for more than 7 years, with the constant level of HIV-1 RNA less than 10000 copies/ml and CD4 count lymphocytes more than 400 cells/µl. We selected 100 patients infected during the 5 years in comparison groups. The levels of plasma L-lysine, HIV-1 RNA, and CD4 count lymphocytes were evaluated between groups of HIV-1 elite controllers, slow-progressors and progressors (A2, B1, B2 stages of CDC classification). No previous studies are available for comparison.

The mean of viral load in HIV elite controllers was 550.1 (SD = 135.7), in slow-progressors 2631 (SD = 2606), and in HIV progressors 186500 (SD = 150100). The mean of CD4 count lymphocytes in HIV elite controllers was 549.6 (SD = 123.8), in slow-progressors 476.7 (SD = 326.3) and in HIV progressors 352.0 (SD = 199.9). Low levels of plasma L-lysine were observed in 9/13 (75%) of HIV elite controllers, 15/25 (60%) slow-progressors and 66/100 (66%) in HIV progressors compared with controls. The mean amino acid levels were significantly reduced in HIV elite controllers and non-progressors compared with HIV progressors ($P < 0.0001$ and $P < 0.007$, respectively;
lower in advanced CDC stage (B and C) HIV-infected patients than in asymptomatic stage (A) and patients on HAART. We examined that plasma \( l \)-lysine concentrations were negatively correlated with HIV-1 RNA levels and inversely with CD4 count lymphocytes. The mean plasma \( l \)-lysine concentrations were significantly lower in HIV-1 elite controllers and slow-progressors compared with healthy individuals and HIV-progressors. And the levels of amino acid increased in HIV-infected subjects after introduction of HAART. It sounds paradoxical, accordingly, the highest viral load was detected in progressors.

Conclusions

In this study, we clearly demonstrated serious changes plasma concentrations of \( l \)-lysine in HIV-infected patients. We formerly hypothesized that the amino acid levels were related to increased viral load and to the clinical stages of HIV-infection; and, our current findings support this hypothesis. The mean plasma \( l \)-lysine concentrations were significantly lower in advanced CDC stage (B and C) HIV-infected patients than in asymptomatic stage (A) and patients on HAART. We examined that plasma \( l \)-lysine concentrations were negatively correlated with HIV-1 RNA levels and inversely with CD4 count lymphocytes. The mean plasma \( l \)-lysine concentrations were significantly lower in HIV-1 elite controllers and slow-progressors compared with healthy individuals and HIV-progressors. And the levels of amino acid increased in HIV-infected subjects after introduction of HAART. It sounds paradoxical,

### Table 3. Comparison plasma \( l \)-lysine concentrations and CD4 count lymphocytes in HIV-infected patients

| HIV patients | CD4 lymphocytes (cells/\( \mu l \)) | \( l \)-lysine (\( \mu \)mol/l) | Pearson correlation coefficient |
|--------------|-----------------------------------|-------------------------------|-------------------------------|
| The entire cohort  
\( n = 450 \)       | 448.5 ± 247.5                     | 253.4 ± 152.8                 | \( r = 0.19, P < 0.008 \) (S) |
| Group I  
(A1, A2)  
\( n = 290 \) | 496.3 ± 236.9                     | 263.1 ± 144.9                 | \( r = 0.14, P < 0.049 \) (S) |
| Group II  
(B1, B2)  
\( n = 110 \) | 345.6 ± 240.3                     | 232.3 ± 135.0                 | \( r = 0.21, P = 0.04 \) (S) |
| Group III  
(C1, C3)  
\( n = 50 \) | 245.5 ± 171.1                     | 149.1 ± 110.5                 | \( r = 0.70, P < 0.03 \) (S) |
| HIV infected patients with recurrent herpes infection  
\( n = 12 \) | 284.2 ± 173.1                     | 170.1 ± 144.5                 | \( r = 0.57, P = 0.10 \) (NS) |
| HIV-infected patients on HAART  
(B1, B2, C1, C2)  
\( n = 100 \) | 449.6 ± 214.3                     | 322.0 ± 115.9                 | \( r = 0.02, P = 0.90 \) (NS) |

(S), Differences were considered significant when \( P < 0.05 \); (NS), not significant. Values are given as mean ± SD (range).

### Table 4. Comparison plasma \( l \)-lysine concentrations and HIV-1 RNA levels in HIV-infected patients

| HIV patients | HIV-1 RNA (copies/ml) ± s.e. | \( l \)-lysine (\( \mu \)mol/l) | Pearson correlation coefficient |
|--------------|-------------------------------|-------------------------------|-------------------------------|
| The entire cohort  
\( n = 450 \)       | 170 300 ± 15 640               | 253.4 ± 152.8                 | \( r = −0.14, P < 0.023 \) (S) |
| Group I  
(A1, A2)  
\( n = 290 \) | 107 600 ± 10 100               | 263.1 ± 144.9                 | \( r = −0.18, P < 0.006 \) (S) |
| Group II  
(B1, B2)  
\( n = 110 \) | 188 600 ± 22 050               | 232.3 ± 135.0                 | \( r = −0.23, P < 0.031 \) (S) |
| Group III  
(C1, C3)  
\( n = 50 \) | 327 200 ± 46 990               | 149.1 ± 110.5                 | \( r = −0.48, P = 0.006 \) (S) |
| HIV-infected patients with recurrent herpes infection  
\( n = 12 \) | 1 071 100 ± 647.6              | 170.1 ± 144.5                 | \( r = −0.05, P = 0.86 \) (NS) |
| HIV infected patients on HAART  
(B1, B2, C1, C2)  
\( n = 100 \) | 630.7 ± 95.4                   | 322.0 ± 115.9                 | \( r = −0.02, P = 0.83 \) (NS) |

(S), Differences were considered significant when \( P < 0.05 \); (NS), not significant. Values are given as mean ± SD (range).
but can be explained by the influence of amino acid deficiency on HIV reproduction. Excess of l-lysine concentration leads to active HIV replication and reduce the concentration of plasma amino acid.

We hypothesized that the disease progresses more rapidly among patients with the level of excess supply of this essential amino acid. We now intended that the excess of l-lysine leads to active HIV replication and reduce the concentration of plasma amino acid. To test these hypotheses, we measured levels of this essential amino acid, HIV-1 RNA and markers of immunological status in the groups of the elite controllers, slow-progressors and progressors among HIV-infected individuals. The lowest concentrations of essential amino acid were found in HIV elite controllers and slow-progressors. From these findings it may be assumed that if the infected cells contain a limited amount of l-lysine, synthesis of HIV virions could probably have been prevented or reduced to the level of latent infection. It is possible that this mechanism is used in HIV controllers.

In summary, our study seems to support the hypothesis that changes in plasma l-lysine play a key role in the synthesis of the virus proteins and in transcription initiation of the retrovirus life cycle. It sounds paradoxical, but excessive intake of this essential amino acid may increase the risk of high HIV-1 RNA levels, subsequent acceleration of immunosuppression and HIV progression, and further research is needed to understand the impact of l-lysine amino acid on HIV infection pathogenesis.

**Material and Methods**

**Patients.** We included 550 HIV-1-infected males (age range: 20–38 y; mean ± SD: 34 ± 5.9 y), who were periodically monitored in the Municipal Center of HIV/AIDS prophylaxis. We ascertained patients’ general attributes (age, sex), medical history, and stage of HIV infection, co-infections and the simultaneous survey period, without antiretroviral therapy. Blood samples for this study were collected during routine clinical control and analytical monitoring, which included hematological, immunological and virological evaluation. Clinical stages of the disease were based on the 1993 revised guidelines for HIV-1 infection (Centers for Disease Control and Prevention). All patients, 550 HIV-1-infected males without highly active antiretroviral therapy (HAART), were classified into groups I (asymptomatic; A1, A2), II (symptomatic, non AIDS; B1, B2) and III (AIDS; C1, C2). Patients who were severely immunodepressed (A3, B3, and C3) were excluded from the study.

Group I: 290 patients were asymptomatic or had slight symptoms, non- and moderately immunodepressed (A1, A2).

Group II: 110 patients were moderately symptomatic and immunodepressed (B1, B2).

Group III: 50 patients were severely symptomatic and moderately immunodepressed (C1, C2).

**Comparison groups:** 100 subjects after introduction of HAART for more than two years, 25% HIV patients on nucleoside analog reverse-transcriptase inhibitors (NARTIs) and non-nucleoside reverse-transcriptase inhibitors (NNRTIs) therapy, 5% only on NARTIs and 70% HIV patients on NNRTIs and protease inhibitors (PIs) therapy (age range: 25–45 y, mean ± SD: 36 ± 5.1 y).

Reference values were established in healthy regional donors (age range: 23–45 y, mean ± SD: 34 ± 4.4 y) by measurement of plasma l-lysine concentrations (n = 120). Blood samples were obtained after informed consent from the patients.

**Laboratory studies.** Fasting venous blood samples for measurement of hematological and immunological parameters, HIV-1 RNA levels and amino-acid

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**Table 5. Comparison of plasma l-lysine concentrations in HIV-infected patients ranged by HIV-1 RNA levels**

| HIV-infected patients with HIV-1 RNA levels | HIV-1 RNA (copies/ml) | µ-mol/l | Pearson correlation coefficient |
|-------------------------------------------|-----------------------|---------|--------------------------------|
| 5000-20000                                 | 12400 ± 4432          | 313.2 ± 150.4 | r = −0.35, P < 0.028 (S) |
| n = 39                                    |                       |         |                                |
| 5000-30000                                 | 15990 ± 7155          | 296.3 ± 151.5 | r = −0.32, P < 0.018 (S) |
| n = 54                                    |                       |         |                                |
| 5000-40000                                 | 21190 ± 11960         | 283.1 ± 154.0 | r = −0.35, P < 0.003 (S) |
| n = 69                                    |                       |         |                                |
| 5000-50000                                 | 24900 ± 14870         | 261.9 ± 134.8 | r = −0.43, P < 0.0001 (S) |
| n = 74                                    |                       |         |                                |
| 5000-75000                                 | 32480 ± 23070         | 265.9 ± 156.1 | r = −0.29, P < 0.002 (S) |
| n = 105                                   |                       |         |                                |
| 5000-100000                                | 41790 ± 35000         | 261.6 ± 154.7 | r = −0.24, P < 0.007 (S) |
| n = 120                                   |                       |         |                                |
| 5000-250000                                | 78490 ± 76600         | 256.0 ± 151.2 | r = −0.16, P < 0.048 (S) |
| n = 160                                   |                       |         |                                |
| 5000-500000                                | 122100 ± 133500       | 250.6 ± 150.7 | r = −0.15, P < 0.035 (S) |
| n = 186                                   |                       |         |                                |
| 5000-1000000                               | 180900 ± 263600       | 247.4 ± 142.4 | r = −0.12, P < 0.040 (S) |
| n = 255                                   |                       |         |                                |

(S), Differences were considered significant when P < 0.05. Values are given as mean ± SD (range).
In plasma amino acid concentrations were observed in repeat samples obtained from any given patient. The overall reproducibility of results was consistent to within ± 5%.

Body mass index (BMI) at baseline was calculated using the formula weight (kg)/ (height[m])² and categorized as underweight (< 18.5 kg/m²), normal (18.5−24.9 kg/m²), overweight (25−29.9 kg/m²).

Statistical analysis. Plasma l-lysine values follow a Gaussian distribution (Kolmogorov–Smirnov), so the Student t test was applied to compare patients’ concentrations to reference values, as well as those found in patients in comparison groups, with a 95% confidence interval.

The correlation between HIV-1 RNA and amino-acid concentrations was estimated by a Pearson correlation coefficient. Data are reported as mean ± SD (standard deviation), and P values below 0.05 were considered to indicate statistical significance. Statistical analyses were performed using the statistical software package Biostat®.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.
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Table 6. Compared plasma l-lysine concentrations, HIV-1 RNA levels and CD4 count lymphocytes in HIV-1 elite controllers, slow-progressors, and progressors

|                          | HIV-1 elite controllers | HIV-1 slow-progressors | HIV progressors | Controls         |
|--------------------------|-------------------------|------------------------|----------------|-----------------|
| l-lysine (µmol/l)        | 162.5 ± 116.4*†         | 221.1 ± 130.8*†        | 239.9 ± 148.9  | 275.8 ± 120.3   |
| HIV-1 RNA levels (copies/ml) | 550.1 ± 135.7*          | 2631.0 ± 2606*         | 186 500.0 ± 150 100.0 | -               |
| CD4 lymphocytes (cells/mm³) | 549.6 ± 123.8*†         | 476.7 ± 326.3*†        | 320.2 ± 199.9* | 1253.2 ± 230.3  |

*Patients vs. controls, P < 0.01; †Patients vs. HIV progressors, P < 0.01. Values are given as mean ± SD (range).

Figure 2. Correlation between the plasma l-lysine, HIV-1 RNA levels, and CD4 count lymphocytes in clinical A, B, and C stages HIV-infected patients.
