



Use of ATP, GTP, ADP and AMP as an Index of Energy Utilization and Storage in HIV Infected Individuals at NAUTH, Nigeria: A Longitudinal, Prospective, Case-Controlled Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Human immunodeficiency virus (HIV) is associated with altered metabolism and increased energy expenditure, this energy requirement increases significantly as the HIV disease progresses. This study aimed on the use of Adenosine triphosphate (ATP), Guanosine triphosphate (GTP), Adenosine diphosphate (ADP) and Adenosine monophosphate (AMP) as an index of energy

utilization, storage and energy balance in HIV infected individuals. This is a longitudinal, prospective, case-controlled study involving seventy seven (77) HIV Sero-positive individuals newly diagnosed attending retroviral disease treatment centre of Nnamdi Azikiwe University University Teaching Hospital (NAUTH) aged 18-60 years both male and female not on highly active antiretroviral therapy (HAART), were enrolled in the study as test subjects and thirty six (36) apparently healthy HIV Sero-negative individuals both male and female as control subjects. ATP, GTP, ADP and AMP were estimated by enzyme linked immunosorbent assay (ELISA), while, total Energy Balance was determined by calculation. The data obtained were subjected to statistical analysis using SPSS software application (version 21.0) and the results expressed as mean \pm standard deviation. The plasma ATP and GTP were significantly lower ($P < 0.05$) in both HIV pre-treatment and post-treatment group compared with control group. Meanwhile, the plasma level of ADP and AMP were significantly lower ($P < 0.05$) in HIV post-treatment group compared with HIV pre-treatment and control group. There was also a significant difference ($P < 0.05$) in ATP, ADP, AMP and GTP level between HIV pre-treatment and post-treatment group. Meanwhile, the energy balance was lower ($P < 0.05$) in HIV groups compared with control group. However, the energy balance in HIV post-treatment group was significantly lower ($P < 0.05$) compared to HIV pre-treatment group. In conclusion, the significant changes in the biochemical parameters measured suggest altered metabolism, increased energy expenditure and energy deficit/negative energy balance in HIV subjects resulting from increased energy expenditure. Hence, High energy molecules such ATP, ADP, GTP and AMP can be used to predict early energy deficit and manage energy imbalance in HIV infected individuals.

Keywords: HIV; Energy balance; adenosine triphosphate; guanosine triphosphate; adenosine diphosphate and adenosine monophosphate.

1. INTRODUCTION

Human immunodeficiency virus (HIV) is a lentivirus that causes *acquired immunodeficiency syndrome* (AIDS), [1,2] and has the ability to progressively shut down the host immune system due to increased replication of the virus in some infected individuals [3]. This may result in the manifestation of acquired immune deficiency syndrome (AIDS) if HIV progression in a host is not checked [3].

The impact of HIV infection is still predominant in sub-Saharan Africa [4], despite vigorous researches [5-7] and prophylactic measures on HIV/AIDS, in Nigeria HIV is a leading cause of morbidity and mortality among adults and adolescences [3,8,9].

During HIV infection, there is faster metabolism and higher energy expenditure which results in weight loss that tends to be in the form of lean tissue, such as muscle. Energy requirement increases significantly as the HIV disease progresses [10]. Several studies have shown increased resting energy expenditure in HIV infection [11,12,13,14,10,15].

The energy that human body requires to maintain its organic and vital functions are obtained by the oxidation of macronutrients from foods. Energy expenditure (EE) can be considered a process of

energy production from energy substrates (carbohydrates, lipids and proteins) combustion, in which there is an oxygen consumption (O_2) and carbon dioxide production (CO_2). Part of this chemical energy is lost as heat and in urine, and the remaining energy is stored in high-energy molecules known as adenosine triphosphates (ATPs). These ATPs are produced from glucose, amino acid and beta oxidation metabolism in form of high energy substrates compounds.

2. MATERIALS AND METHODS

The study was carried out at retroviral disease treatment centre at Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, Anambra State of Nigeria.

2.1 Study Design

This is a longitudinal, prospective, case-controlled study. Subjects were recruited by random sampling, in this case every subject has the same probability of being chosen. Subjects newly diagnosed and confirmed with HIV were followed up from the time of diagnosis, till the subjects start treatment over a period of 12 months.

2.2 Study Population

The study population consist of Group one: A total number of seventy seven (77) HIV Sero

positive individuals newly diagnosed attending retroviral disease treatment centre of NAUTH aged 18-60 years both male and female not on highly active antiretroviral therapy (HAART), were enrolled in the study as test subjects and were followed up till they start treatment and during treatment for a period of 12 months.

Group two: A total number of thirty six (36) apparently healthy HIV Sero negative individuals both male and female were recruited as control subjects.

2.3 Inclusion Criteria

Subjects for the study include male and female subjects between the ages 18-60 years. The subjects that were confirmed to be HIV positive not on drug yet, were enrolled in the study and were followed up after commencement of drug administration for at least 12 months.

2.4 Exclusion Criteria

Control subjects with underlying history of chronic illness, such as HIV infection, diabetic were excluded from the study.

Test subjects not infected with HIV was excluded, subjects with hypertension, tuberculosis, pregnant women were also excluded.

2.5 Blood Sample Collection

Six milliliters (6ml) of fasting blood Sample was drawn aseptically by venepuncture from all subjects into a heparin specimen containers then allowed to clot, centrifuged for 10 minutes at 3500rpm. Plasma separated, aliquoted into two parts for estimation of all the analytes. All samples were kept frozen at -20°C or -80°C until the time of analysis.

2.5.1 Laboratory for analysis

Nnamidi Azikiwe University Teaching Hospital (NAUTH), Anambra State.

2.6 Assay Methodology

Plasma Adenosine triphosphate (ATP) and Guanosine triphosphate (GTP) were by ELISA based method According to [16].

Adenosine diphosphate (ADP) and Adenosine monophosphate (AMP) were estimated by ELISA based method as described by Perez-Ruiz *et al.*, [16].

Energy Balance was Determined Mathematically; Energy balance equation is equal to rate of energy intake (EI)/energy storage minus rate of energy expenditure/spent (EE). [17].

Energy balance (EB) = EI -EE, this is actually the principle of energy conservation (first law of thermodynamics).

Calculation of Total Energy Balance equal to Total Energy Stored (ATP+GTP) Minus Total Energy Used/Expenditure (ADP+AMP).

2.7 Statistical Analysis

The data obtained were statistically analyzed using SPSS Version 23.0 statistical package. Independent sample t-test was used to assess the mean difference between two dependent variable and Analysis of variance (ANOVA) were used to compare the differences in the parameters measured among groups, post hoc multiple comparison was used to assess inter group variability and all variables were expressed as mean± standard deviation (M± SD). Significant level was considered at $p < 0.05$.

3. RESULTS AND DISCUSSION

Plasma Adenosine triphosphate (ATP), Guanosine triphosphate (GTP), Adenosine diphosphate (ADP) and Adenosine monophosphate (AMP) in HIV infected individuals and control subjects

The plasma ATP and GTP were significantly lower ($P < 0.05$) in both HIV pre-treatment and post-treatment group compared with control group. Meanwhile, the plasma level of ADP and AMP were significantly lower ($P < 0.05$) in HIV post-treatment group compared with HIV pre-treatment and control group. There was also a significant difference ($P < 0.05$) in ATP, ADP, AMP and GTP level between HIV pre-treatment and post-treatment group. But there was no significant difference when ADP and AMP were compared between HIV pre-treatment group and control (Table 1).

3.1 Mean Comparison of Energy Balance (kilocal) in Control and HIV Subjects before and during Treatment

The result showed that the energy balance was lower ($P < 0.05$) in HIV groups compared with control group. However, the energy balance in HIV post-treatment group was significantly lower ($P < 0.05$) compared to HIV pre-treatment group (Table 2.).

Table 1. Plasma levels and mean comparison of Adenosine triphosphate (ATP), Guanosine triphosphate (GTP), Adenosine diphosphate (ADP) and Adenosine monophosphate (AMP) in Control and HIV Subjects before and during Treatment

Parameters	Control N = 36	Pre- HIV Treatment N = 77	12 Months Post- HIV Treatment N = 49	F – Value	P – Value
ATP (nmol/l)	1178.2±424.2	904.4±107.8 ^{a, b}	660.3±139.1 ^a	35.73	0.001
ADP (nmol/l)	1036.7±380.1	1027.2±333.8 ^b	738.7±205.0 ^a	18.85	0.001
AMP (nmol/l)	899.1±163	813.2±223 ^b	528.7±142.6 ^a	27.65	0.001
GTP (µg/ml)	9.26±1.5	7.65±1.82 ^{a, b}	6.69±2.28 ^a	24.36	0.001

*P is significant at <0.05 a-Significant When Compared with control groups, b-Significant When Compared with HIV pre- treatment Group, ATP- Adenosine Triphosphate, ADP-Adenosine Diphosphate, AMP- Adenosine Monophosphate, GTP- Guanosine Triphosphate

Table 2. Mean comparison of total energy balance in control and hiv subjects before and during treatment

Parameter	Control N = 36	Pre- HIV-TREATMENT N = 77	12 Months Post - HIV -TREATMENT N = 49	F-Value	P-Value
Total Energy BAL. (kilocal)	748.32±465.69	-928.42±430.71 ^{a, b}	-600.42± 204.75 ^{a, b}	10.47	0.001

*P is significant at <0.05; Keys: kilo- kilocalories, a-Significant When Compared with control group, b- Significant When Compared with HIV Pre and Post-treatment group.

4. DISCUSSION

The present study focused on the use of ATP, GTP, ADP and AMP as an index of energy utilization, storage and energy balance to predict and manage energy balance in HIV infected individuals

In this study, Adenosine triphosphate (ATP) and Guanosine Triphosphate (GTP) level were decreased in HIV subjects as a result of altered metabolism and increased energy expenditure, ATP and GTP are both energy currency of all cell, they depict storage energy in the system and are produced via oxidative phosphorylation in the metabolic pathways (glycolysis, Beta oxidation and citric acid cycle) and are stored as energy. In HIV energy stored is reduced because of the effects of the virus which increases energy expenditure and metabolism. Asymptomatic HIV positive individuals require 10% more energy and symptomatic HIV-positive individuals require 20%-30% more energy than HIV-negative individuals [18]. Onyango *et al.*, [19,20]; [21] observed reduction in energy and increased energy expenditure in HIV subjects.

ADP and AMP are both high energy molecules which measure the extent of energy used or spent, their level were seen lower in post treatment group even after 12 months of therapy, this suggests some level of energy deficit even

during treatment. In HIV infection major energy reserved are been utilized as a result of hypermetabolism. This is consistent with work of Hommes *et al.*, [22], Sharpstone *et al.*, [23], Corcoran and Grinspoon, [24], Macallan, [18,25] and Pernerstorfer-Schoen *et al.*, [26]. Where they documented increased energy expenditure and further demonstrated that HIV infection increases energy expenditure and energy requirements increases by approximately 20% to 30% to maintain body weight.

This present study also demonstrated that the energy balance in HIV group was lower (P<0.05) compared with control group. This implies that the summation energy used in HIV subjects (ADP and AMP) is greater than the summation of energy storage (ATP and GTP). This is a clear indication of energy deficit as a result of increased energy expenditure which indirectly affects energy balance in HIV subjects. Increased expenditure of energy at rest has been considered a contributing factor to the negative energy balance and weight loss that occur in patients with human immunodeficiency virus (HIV) infection. Several studies documented increased energy expenditure in HIV subjects. Hommes *et al.*, [27,22], Grundfeld *et al.*, [28], Sharpstone *et al.*, [23], Crenn *et al.*, [29], Ware *et al.*, [30] in their studies observed higher energy expenditure compared to healthy control subjects.

Despite major advances in the treatment of HIV using HAART and survival of individuals infected with human immunodeficiency virus (HIV), negative energy remain common problems as seen in this study, which persisted even after 12 months of using HAART. This work supports Shevitz *et al.*, [31], Fitch *et al.*, [32], earlier report on energy expenditure in HIV subjects on highly active antiretroviral therapy [33-36].

5. CONCLUSION

The present study thus concludes that the decrease in the level of high energy molecules (ATP, GTP, ADP and AMP) in HIV infected individuals were associated with altered metabolism and increased energy expenditure, which were predominately seen in early stage of the disease condition. Secondly, this present study also observed energy deficit, this implies that energy used in HIV (ADP and AMP) were greater than energy storage (ATP and GTP). However, this is a clear indication of energy deficit/negative energy balance in HIV subjects resulting from increased energy expenditure. An increase in energy expenditure can lead to nutritional imbalance, weight lost and wasting which is responsible for negative energy balance as seen in this present work. The negative energy balance was pronounced in the pre-treatment stage, but tends to drop after 12 months of treatment. High energy molecules such ATP, ADP, GTP and AMP can be used to predict early energy deficit and manage energy balance in HIV infected individuals.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Informed consent was sought from all subjects before recruitment into the study.

ETHICAL APPROVAL

Ethical approval was sought from ethics committee of Nnamidi Azikiwe University

Teaching Hospital (NAUTH), with reference number NAUTH/CS/VOL.11/195/2018/129.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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