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Haematological Perturbations in Human Immunodeficiency Virus (HIV) Positive Patients Receiving Antiretroviral Therapy in Edo State, Nigeria

K. Chikezie [a], C. L. Uche [b], N. C. Ekeleme [c], U. P. Okite [d], I. O. Abali [e], P. Jibiro [d] and A. I. Airaodion [f*]

[a] Department of Haematology, Federal Medical Centre, Umuahia, Abia State, Nigeria.
[b] Department of Community Medicine, Abia State University Teaching Hospital, Aba, Nigeria.
[c] Department of Haematology, Abia State University, Uturu, Nigeria.
[d] Department of Haematology and Blood Transfusion, University of Port Harcourt, Nigeria.
[e] Department of Surgery, Abia State University, Uturu, Nigeria.
[f] Department of Biochemistry, Federal University of Technology, Owerri, Imo State, Nigeria.

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

Aim: This study sought to investigate the haematological perturbations in HIV-positive patients undergoing antiretroviral therapy (ART) in Edo State, Nigeria.
Methodology: This cross-sectional case-controlled study was conducted at the HIV clinic of the University of Benin Teaching Hospital. The research enrolled 150 HIV-positive patients and an

**Corresponding author: Email: augustineairaodion@yahoo.com;*

equal number of sex and age-matched HIV-negative control subjects. Inclusion criteria encompassed individuals aged 18 years and older, confirmed HIV-positive, and receiving ART for at least six months. Exclusion criteria excluded those with sickle cell disorder, recent transfusions, or ongoing sepsis/malaria. Data collection involved self-administered questionnaires, HIV diagnosis via WHO-approved Nigerian National testing algorithms, and comprehensive haematological assessments. The obtained data were analysed using SPSS software, employing descriptive statistics and t-tests with a significance level of 0.05.

Results: Results revealed significant differences in demographic variables, duration of HIV infection, smoking history, and alcohol consumption between HIV-positive patients and control subjects. Furthermore, $CD4^+$ T lymphocyte counts showed substantial variations, indicating immunological differences. Haematological parameters such as haemoglobin levels, packed cell volume, white blood cell, platelet counts, and erythrocyte sedimentation rate exhibited statistically significant differences between the two groups. Additionally, a sub-analysis of HIV-positive patients based on $CD4^+$ T lymphocyte counts highlighted specific haematological changes associated with varying immunological statuses.

Conclusion: The findings underscore the impact of HIV and ART on haematological parameters, emphasizing the need for comprehensive monitoring and management strategies. This research contributes valuable insights into the context of HIV management in Nigeria, aiding healthcare professionals in optimizing patient care.

Keywords: Antiretroviral therapy; $CD4^+$ T lymphocyte counts; haematological perturbations; human immunodeficiency virus.

1. INTRODUCTION

Human immunodeficiency virus (HIV) infection causes acquired immune deficiency syndrome (AIDS) which is a late-stage disease [1]. HIV targets the immune system of the body, specifically the T lymphocytes, or $CD4^+$ T lymphocyte cells, which are part of the body's natural defence against infections [2]. The body becomes incapable of fighting off infections and illnesses as a result of HIV's gradual destruction of many of these T cells throughout infection. If HIV is left untreated, the body's T cell count decreases, which can lead to opportunistic infections or malignancies that prey on a weakened immune system, ultimately causing AIDS [2]. Nigeria's adult general population's HIV prevalence was 1.5%, according to UNAIDS data from 2018 [3]. This figure is on the increase. An estimated 1.9 million individuals in Nigeria are infected with the virus [4]. According to reports, Nigeria has one of the highest rates of new HIV infections in Sub-Saharan Africa and is the second-largest HIV epidemic worldwide [4].

Changes in the counts of peripheral blood cells in HIV infection cause haematological abnormalities, which are known to be highly reliable independent indicators of morbidity and death [5,6]. According to reports, these anomalies affect all three blood cell lineages and may result from both direct and indirect viral effects [7,8]. According to previous studies, as the disease progresses, haematological abnormalities in peripheral blood cell counts become more common and severe [5,8]. A variety of haematological disorders linked to HIV infection include impaired haematopoiesis, invasive bone marrow disease, splenomegaly-related peripheral blood cell destruction, cancers, immune-mediated cytopenias, and altered coagulation mechanisms [8]. According to literature, haematological abnormalities associated with HIV infection are among the most prevalent non-immunosuppressive side effects, and in patients who are new to therapy, they often manifest as cytopenias [9]. Anaemia is the most prevalent haematological perturbation in HIV infections and a significant predictor of the development of AIDS, according to research [10,11].

Leucopenia and neutropenia in HIV infection have been documented in earlier researches [10–13]. While neutropenia renders HIV patients more vulnerable to bacterial infections, leucopenia is known to raise the prevalence of opportunistic infections [8]. According to reports, lymphopenia and low total lymphocyte counts are frequent outcomes of HIV infection [13–15]. In HIV-positive individuals who do not exhibit any symptoms, thrombocytopenia is quite prevalent, according to previous studies [12,13]. Venous thromboembolism and thrombotic thrombocytopenic purpura are well-known haematological consequences of HIV infection

that have been observed in 1–5% and 2% of afflicted patients, respectively [16,17].

An established surrogate marker and screening tool, the Erythrocyte Sedimentation Rate (ESR) is frequently employed in clinical practice to assess inflammatory or acute response, infection, trauma, autoimmune, and malignant disorders [18]. The ESR has been shown in earlier research to be a significant predictor of the onset of AIDS [8,12].

An individual's total $CD4^+$ T cell count is quite valuable for assessing their immune system [19]. It is a crucial proxy sign for determining if an HIV-positive person is at risk of acquiring AIDS or contracting specific opportunistic illnesses [20]. HIV-positive patients have been found to have low $CD4^+$ T cell numbers in earlier studies [5,8].

It is known that HIV infection is associated with significant haematological alterations that make patient care and treatment more difficult. Thus, understanding the haematological peripheral blood cell alterations in this cohort in our setting is crucial to providing comprehensive care and therapy that improves the quality of life for HIV-positive patients. This proposed study aims to assess the changes in the peripheral blood cell counts and the absolute $CD4^+$ T cell levels among HIV-positive patients in Edo State, Nigeria.

2. METHODOLOGY

2.1 Study Design

This is a cross-sectional case-controlled study carried out at the HIV clinic of the University of Benin Teaching Hospital (UBTH), a tertiary and referral health care facility in Edo State, Nigeria. The study protocol was approved by the hospital research and ethics committee and informed consent was obtained from subjects. By systematic selection (simple random selection) of all the HIV-positive patients attending UBTH Clinics, subjects who were 18 years of age and older were enrolled over a 6-month period (from April to October 2023). Hospital employees, students, and traders were used as the control subjects.

2.2 Sample Size Determination

The sample size was calculated using Fisher's formula as stated in Ekeleme et al. [21]:

$$n = \frac{Z^2(Pq)}{e^2}$$

where

n = minimum sample size
Z = 1.96 at 95% confidence level,
P = known prevalence of HIV-positive patients in Nigeria
e = error margin tolerated at 5% = 0.05
q = 1 - p

According to Uduma et al. [22], the existing prevalence of HIV-positive patients in Nigeria is approximately 10%.

P = 10% = 0.1
q = 1 – p
= 1 – 0.1
= 0.9

$$n = \frac{(1.96)^2(0.1 \times 0.9)}{(0.05)^2}$$

$$n = \frac{0.345744}{0.0025} = 138.298$$

The minimum sample size was 138 and was adjusted to 150 to account for a non-response rate of 10%.
One hundred and fifty (150) HIV-positive patients receiving antiretroviral therapy (ART) were enrolled for the study. Also, one hundred and fifty (150) sex and age-matched HIV-negative control subjects were recruited.

2.3 Inclusion Criteria

Inclusion criteria of the patients for this study were age ≥ 18 years, confirmed for HIV infection, and receiving care at the ART clinic for at least 6 months were included in the study.

2.4 Exclusion Criteria

Adults with known or features of sickle-cell disorder, or who were newly transfused in the last one month as well as those with ongoing sepsis/malaria (febrile, icteric, etc.) were excluded from the study.

2.5 Data Collection

A self-administered questionnaire was used to gather sociodemographic and medical data from both HIV-positive patients and control respondents. After pretest counselling and post-testing, the diagnosis of HIV was established by testing the capillary blood of the patients and the

control subjects for antibodies to the virus. Rapid HIV testing was carried out using Determine TM HIV-1/2, Unigold, and Stat-Pak rapid kits following the WHO-approved Nigerian National Serial Testing Algorithm. HIV antibodies were tested for in the serial algorithm of serologic testing using two screening rapid test kits, Determine TM HIV-1/2 and Unigold, in that order. StatPack, a tiebreaker in inconclusive tests as described by Balogun et al. [23], and the Unigold fast kits were used to confirm a reactive sample to determine TM HIV-1/2.

Every HIV-positive patient was asked for their informed consent before 5 millilitres of whole venous blood were drawn from their cubital vein and placed into a vacutainer collecting tube containing potassium ethylenediamine tetraacetic acid (K-EDTA). A comparable volume of venous blood was drawn from HIV-negative, healthy control volunteers and placed into K-EDTA bottles. Every day, blood samples from the patients and the control subjects were analyzed using Cyflow R Counter for absolute $CD4^+$ T cell counts within six (6) hours of collection (Partec, Germany). Following the manufacturer's instructions, a Sysmex Kx-2IN Haematology autoanalyser (Sysmex Corporation, Japan) was used to perform complete blood cell counts on the same sample, including haemoglobin (Hb) levels, packed cell volume (PCV), total white blood cell (WBC), and platelet counts. As per the standard operating manual delineated by Balogun et al. [23], the erythrocyte sedimentation rate (ESR) of the samples was manually ascertained using the conventional Westergreen method.

2.6 Data Analysis

The statistical package for the social science was used to analyze the collected data (version 20.0; SPSS, Chicago, IL). The mean, median, mode, and t-test were the statistical tests employed in this investigation. Simple tables containing frequencies, percentages, and mean values were used to display the obtained results. The threshold of statistical significance for group comparisons was set at P-value ≤ 0.05.

3. RESULTS

The distribution of gender among HIV patients and control subjects shows no significant difference (p-value > 0.05). Significant differences in age distribution were observed among different age groups. The p-values for age groups "Less than 20" and "20 – 29" are less than 0.05, indicating a significant difference between HIV patients and control subjects in these age categories. Both smoking history and alcohol consumption show significant differences between HIV patients and control subjects (Table 1). $CD4^+$ T lymphocyte counts are significantly lower in HIV-positive patients compared to control subjects (p-value < 0.05) (Table 2). All the haematological parameters (haemoglobin, PCV, WBC, Platelet and ESR) show significant differences between HIV-positive patients and control subjects (Table 3). Table 4 categorizes patients based on $CD4^+$ T cell counts and shows the distribution of haematological changes within each category.

4. DISCUSSION

The observed differences in age distribution among HIV-positive patients and control subjects may be indicative of the changing demographics of HIV infection. A higher prevalence of HIV among younger individuals could be attributed to various factors such as risky behaviours, lack of awareness, or inadequate preventive measures.

The significant differences in smoking history and alcohol consumption patterns align with previous studies linking these lifestyle factors to HIV progression and treatment outcomes. Previous research has established a strong association between smoking and accelerated progression to AIDS, as well as increased mortality rates among HIV-positive individuals [24,25]. The higher prevalence of former smokers among HIV-positive patients in our study aligns with these findings, emphasizing the need for smoking cessation interventions in this population.

The association between alcohol consumption and compromised immune function in HIV-positive individuals has been well-established [26]. Our study corroborates these findings, showing a significant difference in the frequency of alcohol consumption between HIV-positive patients and control subjects. This underscores the importance of addressing alcohol use as part of comprehensive HIV care.

Consistent with the research by Cohen et al. [27] and Lundgren et al. [28], our study highlights the positive impact of early initiation of antiretroviral therapy on the duration of HIV infection. These findings emphasize the significance of early detection and treatment in improving clinical outcomes and reducing the burden of HIV-associated complications.

Table 1. Information of HIV-positive patients and control subjects

Variables	HIV Patients n (%)	Control Subjects n (%)	p-value
Gender			
Male	68 (45.33)	70 (46.67)	0.803
Female	82 (54.67)	80 (53.33)	0.769
Age (in Years)			
Less than 20	3 (2.00)	5 (3.33)	0.014*
20 – 29	46 (30.67)	33 (22.00)	0.005*
30 – 39	21 (14.00)	27 (17.00)	0.155
40 – 49	45 (30.00)	49 (32.67)	0.674
50 – 59	26 (17.33)	25 (16.67)	0.733
60 and above	9 (6.00)	11 (7.33)	0.069
Duration of HIV Infection			
Less than 1 year	34 (22.67)	00 (0.00)	
1-5 years	70 (46.67)	00 (0.00)	
6-10 years	34 (22.67)	00 (0.00)	
More than 10 years	22 (14.67)	00 (0.00)	
Smoking History			
Current smoker	3 (2.00)	41 (27.33)	0.000*
Former smoker	38 (25.33)	22 (14.67)	0.000*
Never smoked	109 (72.67)	87 (58.00)	0.001*
Frequency of alcohol consumption			
Never	80 (53.33)	64 (42.67)	0.027*
Stopped alcohol	67 (44.67)	23 (15.33)	0.000*
Occasionally	3 (2.00)	39 (26.00)	0.000*
Regularly	0 (0.00)	24 (16.00)	0.000*

p-value ≤ 0.05 are statistically significant

Table 2. $CD4^+$ T lymphocyte count of HIV positive patients and control subjects

$CD4_+$ T lymphocytes count/uL	HIV Patients	Control Subjects	p-value
Minimum	42	350	0.000*
Maximum	1082	1439	0.000*
Mean±Stanard Deviation	361±183	924±97	0.000*

p-value ≤ 0.05 are statistically significant

Table 3. Haematological variables of HIV-positive patients and control subjects

Variables with cut-off values	HIV Patients n (%)	Control Subjects n (%)	p-value
Haemoglobin			
<10 g/dL	51 (34.00)	00 (0.00)	0.000*
≥10 g/dL	99 (66.00)	150 (100.00)	0.000*
PCV			
<30%	48 (32.00)	00 (0.00)	0.000*
≥30%	102 (68.00)	150 (100.00)	0.000*
WBC			
<2/nL	14 (9.33)	00 (0.00)	0.000*
≥2/nL	136 (90.67)	150 (100.00)	0.000*
Platelet			
<100/nL	12 (8.00)	00 (0.00)	0.000*
≥100/nL	138 (92.00)	150 (100.00)	0.000*
ESR			
< 30 mm/hr	109 (72.67)	150 (100.00)	0.000*
≥ 30 mm/hr	41 (27.33)	00 (0.00)	0.000*

PCV = Packed Cell Volume, WBC = White Blood Cell, ESR = Erythrocyte Sedimentation Rate
p-value ≤ 0.05 are statistically significant

Table 4. $CD4^+$ T lymphocyte counts and haematological changes among HIV positive Patients

Haematological Parameters	$CD4^+$ T lymphocyte counts			Total
	<200 (n = 63)	200 – 499 (n = 59)	≥500 (n = 28)	
Haemoglobin (< 10 g/dL)	36 (57.14%)	10 (16.95%)	5 (17.86%)	51
PCV (<30%)	39 (61.90%)	6 (10.17%)	3 (10.71%)	48
WBC (<2/nL)	9 (14.29%)	4 (6.78%)	1 (3.57%)	14
Platelet (<100/nL)	7 (11.11%)	3 (5.08%)	2 (7.14%)	12
ESR (≥ 30 mm/hr)	30 (47.62%)	8 (13.56%)	3 (10.71%)	41

PCV = Packed Cell Volume, WBC = White Blood Cell, ESR = Erythrocyte Sedimentation Rate

The observed variations in the duration of HIV infection highlight the importance of early detection and initiation of antiretroviral therapy. Studies have consistently shown that early treatment leads to better clinical outcomes and lower rates of HIV-associated complications [27,28].

The findings of this study (Table 2) align with previous research highlighting the impact of HIV infection on $CD4^+$ T lymphocyte counts. Studies conducted in different regions have consistently shown lower $CD4^+$ T lymphocyte counts in HIV-positive individuals compared to uninfected controls [29,30]. The mean $CD4^+$ T lymphocyte count of 361 cells/uL in HIV-positive patients receiving ART in Edo State is in line with global trends [31].

Moreover, the significant difference in $CD4^+$ T lymphocyte counts between HIV-positive patients and control subjects (p-value = 0.000*) emphasizes the impact of HIV on the immune system, even with antiretroviral therapy. This underscores the importance of continuous monitoring and optimization of treatment regimens to ensure optimal immune reconstitution [32].

The results of this study (Table 3) align with previous research indicating that HIV infection and ART have profound effects on haematological parameters. The observed decrease in haemoglobin levels and packed cell volume (PCV) among HIV patients is consistent with findings from studies conducted in various regions [29,33]. These alterations may be attributed to factors such as chronic inflammation, nutritional deficiencies, or adverse effects of antiretroviral medications. This finding of the differences in the mean PCV values of the patients and controls also corroborates a previous report by De Carvalho et al. [7] in Pretoria, South Africa.

The present study's findings supported earlier observations [10,11] that anaemia is frequently associated with HIV infection. In this investigation, we discovered that patients with HIV who were extremely immunocompromised—that is, had an absolute CD4+ T cell count of less than 200 cells/µl—had the highest prevalence of anaemia. This result supports earlier observations [10,13,15,34] showing anaemia is more common in HIV-positive patients with $CD4^+$ T cell counts < 200 cells/µl. According to reports, anaemia is more common when the level of $CD4^+$ T cells is less than 200 cells/µl, and it is also independently linked to a higher risk of passing away [34,35]. It has been discovered that anaemia is the most frequent haematological perturbation in HIV infections and is a key sign that AIDS may eventually proceed [10,11,35].

HIV infection-related anaemia can be caused by a variety of factors, such as compromised haematopoiesis, immune-mediated processes, opportunistic infections, lymphoma, and the myelotoxic effects of antiretroviral medications [36,37]. Hypoplasia of the bone marrow happens in advanced HIV infection [38]. Parvovirus B19, CMV, and mycobacterium avium complex are among the known opportunistic infections that either produce cytopenias or cause anaemia by intercurrent bone marrow suppression [39]. According to reports, normochromic normocytic and hypochromic microcytic anaemias are the most common kinds in HIV-positive patients [5,8,12].

Results from related research [40,41] are corroborated by the decline in white blood cell count in HIV-positive people. Contributing factors to these alterations could be the immune dysregulation linked to HIV infection and the effect of ART on bone marrow function. Furthermore, research showing a connection between HIV and aberrant platelets and the thrombocytopenia seen in HIV patients is consistent with this observation [42].

Leucopenia (Total WBC of <2.0/nL) was shown to be more common in HIV positive patients

(9.33 percent) than in negative controls (0.00 percent) in this study. This result is similar to leucopenia prevalence estimates of 8 percent [23], 10 percent [12], but greater than 4.9 percent [5] and lower than 20.8 percent [13] among adult HIV-positive patients who have not started antiretroviral therapy. In a prior study, Chukwuezi et al. [43], similarly revealed that total white cell count was lower in HIV-positive persons than in seronegative individuals.

In our study, 14.29 percent of the severely immunocompromised ($CD4^+$ T cell < 200 cells) HIV-positive patients had leucopenia. This is extremely comparable to the 14.5 percent of antiretroviral therapy-naïve adult HIV-positive patients in Lagos, Nigeria, described by Balogun et al. [23]. Comparable values of leucopenia (16.8%) in severely immunocompromised ART-naive HIV-positive patients have been reported by Parinitha et al. [10] in India, but Munyazesa et al. [13] in Rwanda reported a lower value of 8.4% among women. Leucopenia has been identified as the second most prevalent haematological defect in HIV infection [8] and raises the incidence of opportunistic infections in infected individuals. The virus's suppression of leucopoiesis, pathogenic organisms infiltrating the bone marrow, neoplasia, side medication effects, autoimmune neutropenia, and hypersplenism are among the factors that contribute to leucopenia in HIV infection [16].

At a cut-off of 100/nL, the current study found that the proportion of thrombocytopenia in HIV patients was higher than in the control participants (8.00 percent vs. 0.00 percent, p = 0.000). The obtained prevalence value is consistent with other research findings [13]. We found a thrombocytopenia prevalence of 11.11 percent among critically immunocompromised individuals with a $CD4^+$ T cell count of fewer than 200 cells. In highly immunocompromised treatment-naïve HIV-positive individuals, a greater thrombocytopenia score of 21.7% was found in a prior Indian study [13]. Conversely, a lower thrombocytopenia value of 2.72 percent was found by Balogun et al. [23] among adult HIV-positive patients in Lagos, Nigeria. Thrombocytopenia can come from either a decrease in platelet formation or an increase in platelet breakdown, which can be immune-mediated [17,44]. It can also be an early sign of HIV infection.

The ESR was found to be much greater in the HIV-positive patients compared to the control subjects. This result supports other research findings that HIV-positive patients' mean ESRs are statistically considerably higher than those of negative controls [8,12,13]. The ESR has been shown in earlier research to be a significant predictor of the onset of AIDS [8,12]. The observed disparities could be explained by persistent inflammation, even in ART recipients [45]. The highest range of normal ESR in healthy adults, according to earlier research conducted in Nigeria, is 5.0 mm/hr for adult males and 12 mm/hr for adult females [46,47]. In an earlier Nigerian study, Abdulqadir et al. [48] found that compared to HIV-negative pregnant women, HIV-positive pregnant women had a higher ESR but a mean lower haematocrit and absolute white cell count.

The mean absolute $CD4^+$ T cell counts in patients and controls were also observed to differ statistically significantly (p = 0.000) at 361 and 924 cells/µL, respectively. These values matched published findings from earlier research [8,43]. The minimum $CD4^+$ T cell counts for the patients and controls in the current investigation were 42 and 350 cells/µL, respectively (p = 0.000). HIV-positive patients have also been shown to have reduced $CD4^+$ T cell values in earlier researches [5,8,34,43]. The most popular metric for assessing HIV progression, a patient's illness, and the ideal moment to start antiretroviral medication and preventive antibiotics is the absolute $CD4^+$ T cell count [20]. This antigen is also used in the laboratory staging of HIV infection. In a prior extensive nationwide investigation conducted in Nigeria, Oladepo et al. [49] showed that the typical reference range for absolute $CD4^+$ T cell counts in healthy persons was between 365 and 1571 cells/µL. For adult men and women in Nigeria, Aina et al. [50] similarly reported a reference range of 547–1327 cells/µL. Similar to these earlier studies, we found that normal, healthy control subjects had 350–1439 cells/µL of $CD4^+$ T cells in this study.

A prior study by Rahmana et al. [5] found a substantial correlation between declining $CD4^+$ T cell counts and an increase in anaemia, leucopenia, lymphopenia, and thrombocytopenia. Several other studies have reported a strong association between low $CD4^+$ T lymphocyte counts and an increased risk of haematological abnormalities among HIV-positive individuals undergoing antiretroviral therapy [29,30]. Anaemia, thrombocytopenia, and leucopenia have been consistently documented in individuals with advanced HIV disease,

emphasizing the importance of monitoring these parameters during treatment.

Furthermore, the prevalence rates of anaemia, low PCV, and altered white blood cell and platelet counts in this study are in line with global trends reported in diverse populations [51]. The similarity in findings across different regions suggests that certain haematological changes are inherent to the HIV infection itself, while others may be influenced by factors such as nutritional status, co-infections, and genetic predispositions.

5. CONCLUSION

This research provides valuable insights into the haematological changes observed in HIV-positive patients receiving antiretroviral therapy in Edo State, Nigeria. The findings, particularly the association between $CD4^+$ T lymphocyte counts and various haematological parameters, are consistent with existing literature, highlighting the importance of regular monitoring and comprehensive care for HIV-positive individuals. These findings underscore the importance of considering both immunological and haematological parameters in the management of HIV infection. Further research is warranted to explore the underlying mechanisms driving these observed differences and to develop targeted therapeutic strategies
.

6. LIMITATION OF STUDY

The findings of our study may not be universally applicable due to its single centre and hospital-based design among adults. It would be ideal to address the necessary gaps with a multicentre study and a significantly bigger sample size.

CONSENT AND ETHICAL APPROVAL

The study protocol was approved by the hospital research and ethics committee and informed consent was obtained from subjects.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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