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Prevalence and Risk Factors of Anaemia during HIV Infection in Bangui

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Abstract

Background: Haematological manifestations during HIV infection in Bangui are common and poorly documented. The objective of our study was to evaluate the frequency of anaemia before and during antiretroviral treatment in people living with HIV (PLHIV) and to identify associated factors.

Methods: This was a retrospective analytical study covering the period from 1 January 2012 to 31 December 2016. PLHIV who were naive or had been treated with ARVs for more than six months and whose medical records included a blood count and a CD_4 T-cell count were included. Sociodemographic and clinicobiological characteristics were collected using an anonymous questionnaire. The prevalence of anaemia was measured before and at the sixth month of antiretroviral treatment. Multiple logistic regressions were used to identify associated factors.

Results: We included 532 patients of whom 149 were men (28%). The average age was 37.5 ± 9.4 years. The patients were seen in stages 3 and 4 of the WHO classification of HIV infection in 70.81% of cases. The mean CD_4 T cell count increased from 201 ± 175/mm^3 before antiretroviral therapy (ART) to 361 ± 182/mm^3 after six months of ART. Risk factors for anaemia in PLHIV before ART were CD_4 200/mm^3 (p=0.0391) and thrombocytosis (p=0.0083); on ART, anaemia was associated with cotrimoxazole use (p=0.0285) and thrombocytosis (p=0.0212).

Conclusion: Anemia in PLWH is common and has multiple risk factors, some of which are preventable, such as late treatment and tuberculosis. Better knowledge of risk factors, early detection and management could help reduce anaemia-related morbidity and mortality.

Keywords: HIV • Anaemia • Risk Factors • Anti-Retroviral • Bangui

Introduction

According to the UNAIDS 2018 report, the prevalence of HIV infection among people aged 15-49 years was estimated at 3.6% in 2016 in the Central African Republic; during the same year, there were 8700 new HIV infections and 7300 AIDS-related deaths. Of 130,000 people living with HIV (PLHIV) in 2016, 24% had access to antiretroviral treatment [1]. This makes AIDS one of the leading causes of morbidity and mortality in adults. Human Immunodeficiency Virus (HIV) infection affects various body systems including the blood and blood-forming systems. The pathophysiological mechanisms are multiple and make the differential diagnosis complex; It may be inflammation secondary to an opportunistic infection, bone marrow toxicity due to anti-infective treatment, particularly antiretroviral treatment, martial or vitamin deficiency, bone marrow infiltration due to cancer or haematological disease, or erythroblastopenia secondary to reactivation of a parvovirus B_{19} infection or directly related to HIV infection [2,3].

During HIV infection, haematological abnormalities are common; the occurrence of clinical manifestations is directly related to the

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decrease in CD_4 T-cell counts. After infection, HIV in the blood is primarily targeted at CD_4 T cells. Lymphopenia is one of the main haematological manifestations of HIV infection [4]. Anemia is defined as a decrease in haemoglobin below its physiological value; in adult males anemia occurs when the haemoglobin level falls below 13 g/dl and in females below 12 g/dl [5]; anemia can lead to poor quality of life, compromise treatment efficacy through poor adherence, and shorten survival due to the associated morbidity. In sub-Saharan Africa, anaemia remains a common haematological abnormality during HIV infection [6]. According to the results of a study conducted in Bangui in 2016, the prevalence of anaemia observed before and at the twelfth month of Antiretroviral Therapy (ART), was 71.65% and 35.56% respectively; however, the risk factors are not documented [7]. A better understanding of these factors could help to strengthen HIV management strategies in a resource-limited setting such as the Central African Republic. The aim of our study is to contribute to the reduction of mortality related to anaemia during HIV infection.

Materials and Methods

Study design

The study was carried out in the infectious diseases department of the Friendship University Hospital in Bangui, Central African Republic. It was a cross-sectional analytical study covering the period from 1 January 2013 to 31 December 2017. The study population was people living with HIV who were hospitalized or followed up as outpatients during the study period.

Inclusion and exclusion criteria: We included in the study, PLHIV aged at least 15 years whose medical records included a blood count and CD_4 count. Each patient included was ART-naive or had been on ART for more than six months. PLHIV whose medical records did not contain socio-demographic, clinical and biological data at ART initiation were not included in the study.

Variables and data collection: The variables studied included socio-demographic characteristics (sex, age, marital status, income), clinical and biological data. An anonymous survey form was used to collect data from individual medical records and the antiretroviral register. We considered severe anaemia when a haemoglobin value was less than 8 grams/decilitres (g/dl); it was moderate for a haemoglobin value between 8 and 10.9 g/dl. Anaemia was slight when the haemoglobin was between 11 and 11.9 g/dl in women and between 11 and 12.9 g/dl in men. Microcytosis was defined as a Mean Blood Volume (MBV) less than 80 femtolitres (fl) and macrocytosis as a MBV greater than 100 fl; hypochromia was defined as a mean corpuscular haemoglobin concentration (MCHC) <32 picograms (pg). Leukopenia was defined as a neutrophil count <4000/mm^3. Thrombocytosis was defined as a platelet count below 150,000/mm^3 and thrombocytosis as a platelet count above 500,000/mm^3.

Statistical analysis: Text and table entry was done on Word and Excel 2016 software and data analysis was done with EpiInfo 7.2 softwares. The socio-demographic, clinical and characteristics as well as the results of various tests were obtained by simple frequencies. Summary statistics such as mean and standard deviation were calculated for continuous variables. Bivariate methods were used to show the relationship between variables; contingency tables were used to describe relationship between categorical variables. Tabular methods of describing the relationship between two nominal variables by finding proportions were also employed.

A simple logistic regression was used to establish the relationship between anaemia and socio-demographic, clinical and biological characteristics of participants before and after ART. The *Chi-square* and Wald tests were used as well as the odds ratio with their 95% confidence interval at the 5% threshold. Multiple logistic regressions were used with backward elimination stepwise selection with $p < 0.20$ to identify baseline explication that predicts anaemia.

Ethical considerations: Ethical clearance and research authorization were obtained for this study. Informed consent was written and submitted to participants who have read before agreeing to participate in this study. The ethics committee of the Faculty of Health Sciences of Bangui University had approved the study, and the ethical clearance had as number N°189/UB/FACSS/D/SP/AS.017.

Results

General characteristics of the participants

We included a total of 532 patients with a mean age of 37.5 ± 9.4 years; the median was 37 years with extremes of 15 and 66 years. The patients were under 45 years of age in 77% of the cases. There were 383 women (71.99%), giving a sex ratio of 0.38. Patients had no financial income in 56.39% of cases (300/532). At initiation, 55% (263/484) of patients had less than 200 CD_4/mm^3 compared to 49% (151/304) after 6 months of ART. The mean CD_4 T cell count increased from 201 ± 175 cells/mm^3 at baseline to 361 ± 182 cells/mm^3 by the sixth week of ART. Before ART, 67% of men had fewer than 200 CD_4 T cells/mm^3 compared with 33.3% of women. This difference was statistically significant (p=0.004). Initial ART included zidovudine (AZT) in 50.54% and tenofovir (TDF) in 35.73%.

Frequency of anaemia in people living with HIV

During the first six months of antiretroviral treatment, the mean haemoglobin increased from 10.7 ± 219 g/dl to 11.8 ± 1.8 g/dl. During the same period, 95 patients (19.11%), 55 of whom were women, had slight anaemia. After six months of antiretroviral treatment, moderate anaemia was observed in 64 patients (20.65%), 34 of whom were women (Table 1).

Severity of anaemia (Haemoglobin (g/dl))	Before antiretroviral treatment (n=497)	After 6 months of antiretroviral treatment (n=390)
	Number (%)	Number (%)
Severe anaemia (<8)	45 (9.05)	11 (3.55)
Moderate anaemia (8–10.9)	226 (45.47)	84 (27.10)

Slight anaemia (11-12.9)	95 (19.11)	64 (20.65)
No anaemia (≥ 13)	131 (26.36)	151 (48.70)

Table 1. Distribution of patients according to the severity of anaemia at initiation and after six months of antiretroviral treatment.

Risk factors for anaemia

In untreated PLHIV, factors associated with anaemia were male sex, age greater than or equal to 35 years, stage 3 or 4 HIV infection, CD_4 T cell count less than 200/mm^3, thrombocytosis and TB/HIV co-infection. Under antiretroviral treatment, the factors associated with the occurrence of anaemia were male sex, age greater than or equal to 35 years, thrombocytosis and cotrimoxazole chemoprophylaxis.

The prevalence of anaemia was 73.65% before ART compared to 51.29% after six months of ART; this difference was statistically significant (OR=2.65 (1.96-3.57), p=0.000).

Before all ART, risk factors for anaemia were CD_4 count less than 200/mm^3, OR=1.85 (1.03 - 3.34), p=0.0391 and platelet count greater than 400,000/mm^3 (thrombocytosis), adjusted OR= 5.22 (1.53-17.81), p=0.0083. After six months of ART, the independent risk factors for anaemia were thrombocytosis OR=2.43 (1.14-5.20), p=0.0212 and cotrimoxazole chemoprophylaxis ORa=5.69 (1.2-26.96), p=0.0285 (Tables 2 and 3).

Characteristics	Anaemia		OR (95% CI)	p	ORa (95 % CI)	p
	Yes	No				
	Number (%)	Number (%)				
Sex						
Men	108 (76.06)	34 (23.94)	1.18 (0.75 – 1.86)	0.227		
Women	259 (72.75)	97 (27.25)	1			
Age (years)						
<35	59 (44.4)	74 (55.6)	1			
≥ 35	100 (56.5)	77 (43.0)	1.62 (1.03 – 2.56)	0.017		
WHO stage						
1	23 (51.1)	22 (48.9)	1			
2	63 (65.6)	33 (34.4)	1.82 (0.88 – 3.75)	0.053		
3	176 (75.9)	56 (24.1)	3.0 (1.55 – 5.80)	0.0007	1.51 (1.18 - 3.00)	0.033
4	92 (83.6)	18 (16.4)	4.88[2.25 – 10.58]	0	2.81 (1.07 - 3.28)	0.023
CD4 T cells (/mm^3)						
<50	84 (80.8)	20 (19.2)	3.5 (1.33 – 9.24)	0.007		
50 – 199	121 (76.1)	38 (23.9)	2.6 (1.06 – 6.62)	0.022	1.85 (1.03 – 3.34)	0.039
200 - 499	139 (69.9)	60 (30.1)	1.93 (0.79 – 4.71)	0.079		
≥ 500	12 (54.6)	10 (45.4)	1		1	
Leukocytes (/mm^3)						
<150 000	71 (75.5)	23 (24.5)	2.31 (0.72 – 7.37)	0.087		
150 000-400 000	131 (75.7)	42 (24.3)	2.33 (0.76 – 7.12)	0.076		
>400 000	8 (57.1)	6 (42.9)	1			
Thrombocytes						
<150 000	30 (81.0)	07 (19.0)	1.86 (0.77 – 4.45)	0.08		
150 000-400 000	143 (70.0)	62 (30.0)	1		1	
>400000	36 (90.0)	04 (10.0)	3.9 (1.33 – 11.4)	0.002	5.22 (1.53 – 17.81)	0.008

TB/HIV co-infection						
Yes	100 (81.0)	23 (19.0)	1.77 (1.07 – 2.940)	0.011	1.31 (0.91 - 2.28)	0.073
No	257 (71.0)	105 (29.0)	1			

Table 2. Socio-demographic and clinico-biological characteristics and anaemia in PLHIV not receiving ART.

Characteristics	**Anaemia**		**OR (95% CI)**	**p**	**ORa (95 % CI)**	**p**
	Yes	**No**				
	Number (%)	**Number (%)**				
Sex						
Men	48 (62.3)	29 (37.7)	1.81 (1.07 - 3.08)	0.013	1.11 (0.87 - 1.78)	0.059
Women	111 (47.6)	122 (52.4)	1			
Age (years)						
<35	59 (44.4)	74 (55.6)	1			
≥ 35	100 (56.5)	77 (43.5)	1.63 (1.03 – 2.56)	0.017	1.21 (0.97 - 2.08)	0.063
WHO stage						
1-2	48 (49.5)	49 (50,5)	1			
3-4	107 (51.7)	100 (48.3)	1.09 (0.67 – 1.76)	0.36		
CD4 T cells (/mm3)						
<50	32 (57.1)	24 (42.9)	0.56 (0.21 – 1.49)	0.129		
50 – 199	48 (50.5)	47 (49.5)	0.43 (0.17 – 1.07)	0.035		
200 - 499	51 (50.4)	69 (49.6)	0.31 (0.12 – 0.76)	0.004		
≥ 500	19 (42.9)	8 (57.1)	1			
Leukocytes (/mm3)						
<150 000	48 (52.2)	44 (47.8)	1.01 (0.61 - 1.68)	0.476		
150000-400 000	87 (51.8)	81 (48.2)	1			
> 400 000	3 (50.0)	3 (50.0)	0.93 (0.18 - 4.74)	0.467		
Thrombocytes						
<150 000	7 (50.0)	7 (50.0)	1.04 ([0.35 - 3.09)	0.466		
150 000-400 000	104 (48.8)	109 (51.2)	1		1	
>400 000	27 (71.1)	11 (28.9)	2.57 (1.21 - 5.45)	0.005	2.43 (1.14 – 5.20)	0.021
TB/HIV co-infection						
Yes	34 (47.9)	37 (52.1)	0.86 (0.50 - 1.46)	0.288		
No	122 (51.7)	114 (48.3)	1			
Cotrimoxazole chemoprophylaxis						
Yes	152 (52.8)	136 (47.2)	4.09 (1.12 - 14.99)	0.012	5.69 (1.20 – 26.96)	0.028
No	3 (21.4)	11 (78.6)	1			
ART						

AZT	73 (50.3)	72 (49.7)	1	
No AZT	70 (52.2)	64 (47.8)	1.08 (0.67 -1.73)	0.374

Table 3. Relationship between the occurrence of anaemia on ART and sociodemographic and clinico-biological factors.

Discussion

Study limitations

The accurate etiological diagnosis of anaemia in our context is difficult due to limited resources. The detection of anaemia is based on the study of the haemogram which is done systematically in all PLWHIV at the beginning and then every six months during antiretroviral treatment. This retrospective study allowed us to measure the prevalence of anaemia before and after six months of regular antiretroviral treatment. In addition, we were able to identify factors associated with the occurrence of anaemia before or during antiretroviral treatment.

Characteristics of the participants

The patients included in the study were adults, mostly young and predominantly female. This finding is in agreement with national data that the prevalence of HIV infection is higher among young people and females. Female predominance has been observed in several studies of anaemia in PLHIV in Africa; it was 66.20% in Conakry and 73.80% in Burkina Faso [9,10]. Generally referring to HIV infection, it is observed in adults. In our study, this translates into an average age of 37 years at ART initiation.

Prevalence of anaemia before ART

Among PLHIV not on ARVs, the prevalence of anaemia was very high; about three out of four (73.64%) patients were affected. In most cases the anaemia was moderate or slight. This high frequency of anaemia is reported in Bangui in 2016 and by several authors in Africa and worldwide who describe anaemia as the most common haematological abnormality during HIV infection [11-17]. Anemia can be observed in all phases of HIV infection with a prevalence that varies from 63-95%. The prevalence and severity of anaemia increased with the progression of HIV infection. There are several causes of anaemia; it may be the direct or indirect effect of HIV action with impairment of red blood cell production or destruction of these cells [18]. HIV can cause anaemia directly with disruption of erythropoiesis through infection of red cell precursors or through cytokines. These factors contribute to the development of anaemia in chronic diseases and are the main causes of anaemia in HIV infection. Anemia is a factor in morbidity and mortality and impaired quality of life in PLHIV [19-21]. This high frequency of anaemia in our study could be explained by a late referral to care, which results in a high proportion of patients in the advanced stage of the disease with deep immunodepression. At this stage of the disease, in the absence of antiretroviral treatment, the disease is characterized virologically by a high HIV viral load which can cause bone marrow damage and maintain immunodepression. This may favour the occurrence of opportunistic infections, which are favourable factors for anaemia. Promoting early detection of HIV infection, in conjunction with the initiation of antiretroviral therapy, is a strategy that could help reduce the extent of this haematological abnormality in order to reduce HIV-related morbidity and mortality.

Prevalence of anaemia after six months of ART

We observed a significant reduction in the prevalence of anaemia from 73.65% before ART to 51.29% after six months of ART. This reduction in the prevalence of anaemia occurred in both moderate and severe forms. This was reflected in a significant increase in mean haemoglobin during antiretroviral treatment. The reduction in the frequency of anaemia under antiretroviral therapy has been reported by several authors. Antiretroviral treatment leads to a suppression of the viral load, responsible for an immune restoration which contributes to reduce the frequency of opportunistic diseases. This would explain the decrease in the prevalence of anaemia observed in our study. During antiretroviral treatment, we have recorded an increase in the frequency of slight anaemia. This could be related to the toxicity of zidovudine contained in antiretroviral combinations or cotrimoxazole or to the effect of HIV as reported in the literature by several authors.

Risk factors for anaemia

In ARV-negative patients, the factors associated with the occurrence of anaemia were multiple in univariate analysis. These were socio-demographic (male sex and age greater than or equal to 35 years), clinical (advanced stage of HIV infection, TB/HIV co-infection), biological (CD_4<200/mm^3) and therapeutic (cotrimoxazole chemoprophylaxis) characteristics. However, we did not find an association between anaemia and zidovudine use as reported in the literature.

In multivariate analysis, the only risk factors identified were severe immunosuppression with a CD_4 count below 200/mm^3 and thrombocytosis in ART-negative PLHIV. A low CD_4 T-cell count has been identified as a risk factor for anaemia. With immune recovery on ART, we no longer observed an association between CD_4 count and anaemia. However, there was still a significant association between anaemia and thrombocytosis. This is thought to be a reactive thrombocytosis that accompanies opportunistic conditions that may be present before or after initiation of ART [22]. However, in multivariate analysis, in ART-naive PLHIV, anaemia was significantly associated with severe immunosuppression with CD_4 T cells <200/mm^3 and thrombocytosis. Deep immunosuppression is a frequent feature of PLHIV followed in Bangui [23,24]. It is thought to be linked to late detection or management of HIV infection and is often characterized by a high frequency of opportunistic infections, including tuberculosis, Kaposi's disease and cryptococcal meningitis, and anaemia is more frequently observed. Most of these opportunistic diseases may be accompanied by anaemia or thrombocytosis. The use of cotrimoxazole for the prevention of opportunistic infections increases the frequency of this anaemia due to its toxicity to bone marrow. The control of anaemia in PLWHIV should take into account the control of opportunistic infections, which can be facilitated by early diagnosis of the infection.

Conclusion

Anaemia is a common haematological abnormality in PLHIV. Its prevalence is reduced after initiation of antiretroviral therapy. The main risk factors are profound immunosuppression, the use of cotrimoxazole as chemoprophylaxis and thrombocytosis. The results of this study show that it is necessary to make an early diagnosis of HIV infection and to start antiretroviral treatment as soon as possible.

Conflict of Interest

None

Acknowledgements

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