



# Effect of Sickle Cell Trait on the Treatment Response of Individuals Infected with Human Immune-Deficiency Virus (HIV)

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. Author NNO conceived and designed the paper, interpretation of data and revising the manuscript. Author JOO also contributed to the design of the paper, acquisition of data and interpretation of data, drafting the article. Author AZM analysed the data. Author PCAA contributed to data acquisition and analysis. Author ARA revised the manuscript. Author BLS revised the manuscript and approved. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Background:** Sickle cell disease is of public health importance and comes with systemic organ complications that can cause long-term disabilities and early death.

**Aim:** This study was to determine the effect of co-existence between sickle cell gene (HbS) and HIV infection in a Lagos population.

**Methods:** The study was conducted at the anti-retroviral (ARV) outpatient clinic of the Nigerian Institute of Medical Research (NIMR), Yaba, Lagos. It is a cross-sectional cohort study of 292 adult

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HIV- positive patients who were enrolled for treatment and support in the centre between the year 2004-2015. A review of case notes and database was done to extract haematologic, immunologic, virologic and clinical information of the patients. The enrolled participants were invited for additional clinical and socio-demographic information using a structured questionnaire. Blood samples were collected and reanalysed to confirm the haemoglobin genotype. Data analysis was performed using SPSS software.

**Results:** Out of 292 recruited patients, 274 participants had complete data of which 74.1%, 22.9% and 2.9% were HbAA, HbAS and HbAC respectively. Sick cell trait (SCT) was found in 25.9% of the participants and there was no record of sickle cell disease (SCD). HbAA participants were found to have a higher viral load (87.5%) at baseline ( $P < 0.001$ ). For HbAA and SCT groups, treatment response over the years was similar with lower figures seen in SCT.

**Conclusion:** It was concluded that lower HIV viraemia in SCT might mean a delay in HIV-1 disease progression and subsequently better quality of life for such patients.

*Keywords: Sickle cell disease; human immune-deficiency virus; disease progression; sickle cell trait.*

## 1. INTRODUCTION

Sickle cell disease (SCD) is an inherited red blood cell (RBC) disorder resulting from the structurally abnormal haemoglobin S (HbS) gene [1]. The disease is heralded by painful episodes which include pain in the back, chest, abdomen and extremities. SCD is a vaso-occlusive disease and haemolytic crisis is the clinical hallmark of this disease, which results in painful episodes, known as sickle cell crisis. The swelling of hands, and feet, enlargement of the spleen, heart as well as jaundice and several systemic organ complications can cause long-term disabilities and early death. The abnormal haemoglobin S in the low-oxygen environment assumes a sickle shape instead of the normal disk shape. These sickled cells obstruct the small blood vessels resulting in less oxygen delivery to the tissues leading to organ damage and death [2]. This haemoglobin abnormality results from a single amino acid substitution in the haemoglobin molecule of sickle cells (HbS). [3] There is increased rigidity of the sickle red cell with deoxygenation, which impairs the passage of the individual sickled red cell through the microcirculation. The ensuing reduction in blood flow may lead to regional infarction (vaso-occlusive crisis). Early symptoms appear at about five to six months of age when concentrations of foetal haemoglobin (HbF) have expectedly reduced [4]. These sickled cells show the abnormal electrophoretic mobility of haemoglobin in an affected individual

The Haemoglobin S gene is particularly common in people of West African descent. High haemoglobin S gene frequencies are found in African and Mediterranean populations, and populations arising from the slave trade or voluntary emigration from Africa and the

Mediterranean [1]. Sickle cell trait (SCT) (the carrier state of SCD) has a prevalence of 25%–30% in many countries in tropical Africa [5]. Worldwide, there were about 78 million carriers of sickle cell trait in 1992, with most of them (65 million) living in sub-Saharan Africa [5]. The WHO states that three-quarters of 200,000 infants born with Sickle Cells in Africa annually are Nigerians [6].

Geographic overlap exists between Human Immunodeficiency Virus (HIV) and sickle cell disease (SCD). The spread of the HIV virus has been particularly very high in developing countries, especially sub-Saharan Africa where most patients with SCD live. An estimated 3.1 million Nigerians are living with HIV and over 56,000 positive births annually [7]. It is expected that some degree of interaction may exist between the two diseases with the HbS gene influencing the course of HIV infection/progression.

Immunosuppression from HIV may affect the natural history of infection with other pathogens by expediting infection and modifying the course of the disease, or its manifestations [8]. Again, the pathogen and pathogen-derived products may result in increased HIV replication, which can alter the progression of HIV [8]. The commonest is malaria resulting from infection with *Plasmodium* species, which is a major cause of sickle cell crisis in SCD patients. Drakesmith et al. suggested that iron overload promoted viral replication. That means if an SCD HIV-positive patient has a malaria infection that precipitates a haemolytic crisis with a subsequent iron increase in circulation from the haemolysis of red cells, it may result in high HIV replication [8]. Therefore, the hypothesis is that HIV may exacerbate the SCD crisis, while SCD

haemolytic crisis speeds up the progression of HIV to AIDS. However, available evidence on SCD in HIV-infected patients, limited as it is, contradicts this hypothesis and suggests that despite frequent blood transfusion, SCD patients have a lower risk for HIV-1 infection [9], higher frequency of HIV-1 long-term non-progressors compared with the general HIV-positive population; 44% in SCD patients vs. 13.9% in Normal controls [10]. Analysis of national hospital discharge surveys; from 1997–2009 shows that SCD is associated with a lower frequency of HIV-1 diagnosis; with an odds ratio of 0.33, as compared with HBV and HCV [11].

Iron metabolism is inherently connected to HIV-1 infection and disease progression. The progression of AIDS is conveyed by an increased iron accumulation in macrophages, microglia, endothelial cells, myocytes, bone marrow, brain white matter, muscle and liver [12,13]. Increased iron stores are associated with rapid HIV-1 progression in AIDS patients. This was reported in iron-loaded thalassemia major patients, in HIV-positive patients managed with oral iron, and in those with the haptoglobin 2–2 polymorphism [14]. A retrospective study demonstrated the lower survival of HIV-1-infected individuals is inversely correlated to higher iron stores [14]. In addition, non-anaemic HIV-1-positive women in Zimbabwe with high serum ferritin concentration are reported to exhibit increased viral load, which provides further evidence for the association of increased iron stores with more severe HIV-1 infection [15]. The elevated iron level has been suggested as a potential predictive marker for higher mortality in HIV-1-infected Gambian adults [16]. In other words, in SCD patients with decreased iron stores, there might be a decrease in HIV-1 viral replication.

The aim of the present study was to establish the relationships between the sickle cell gene and the clinical, immunologic, biochemical and haematologic parameters of HIV patients. It is expected that the outcome of this study will positively influence the management of those with co-morbidity (HIV /HbS gene).

## 2. MATERIALS AND METHODS

### 2.1 Study Centre

This study was conducted at the anti-retroviral (ARV) outpatient clinic of the Nigerian Institute of Medical Research (NIMR), Yaba, Lagos; a large HIV care and treatment centre in Lagos, Nigeria

established in 2002. Over 25,000 HIV-positive adults and children are receiving care, treatment and support at the centre. Patients are referred from clinics and hospitals within and outside Lagos State to this centre.

### 2.2 Study Design

The study was a cross-sectional cohort study of purposively selected HIV-positive adults, who were enrolled for treatment and support in the centre between the year 2004 - 2015. They were HAART experienced, for at least 5 years.

A review of case notes and database was done to extract haematologic, immunologic, virologic and clinical information of the patients.

Additional clinical and socio-demographic information was obtained using a questionnaire, and blood samples were also collected to ascertain the genotype of these individuals through laboratory assay.

### 2.3 Sample Size Determination

Two hundred and ninety-two (292) purposively selected adult HIV-positive individuals who were enrolled for HAART treatment within the stated study period were recruited for this study. This sample size was calculated based on the WHO cross-sectional sample size formula

$$n = \frac{Z^2 [P(1-P)]}{D^2} [17]$$

$$P = 25\% [5]. Z = 1.96 \quad D = 5\% (0.05)$$

where P is the expected prevalence, and Z is the value of the reference normal distribution for the desired confidence level (1.96) for a 95% confidence level. D is the highest acceptable error in the estimate [17].

### 2.4 Study Population

The population studied included adult HIV-1 positive individuals that are HAART-experienced, and have been on treatment for at least 5 years.

### 2.5 Inclusion Criteria

Consented confirmed HIV-positive adults, 18 years and above at the time of enrolment, and were under HIV treatments and support for not less than 5 years.

## 2.6 Exclusion Criteria

Individuals who were pregnant or with any other co-morbidity (Tb, Hep B, Hep C, diabetes) were excluded from this study.

**Data Collection:** Data was extracted from the database. Clinical history, laboratory and socio-demographic information of the patients were obtained from the database. The clinical history includes history at presentation, presence of opportunistic infections, and other non-HIV-related history. The laboratory information obtained were CD4 cell counts, viral load, Full blood counts, liver function tests, and renal function tests.

A semi-structured questionnaire was used to obtain additional clinical and socio-demographic information- weight/ height (Body Mass Index), level of income etc.

**Sample Collection:** 2mls of blood was collected from each participant by venepuncture using vacutainers for genotype analysis.

## 2.7 Laboratory Procedures

The sickling status of each sample was determined by using the cellulose acetate electrophoresis method. The machine was set at 250V and the separation was read after 20 minutes.

Following electrophoretic migration, visualization of haemoglobin bands was accomplished and compared with known standards. This method yields rapid and reproducible separation of HbA, HbF, HbS and HbC as well as other variant haemoglobins with minimal preparation time.

## 2.8 Data Analysis

Data was collected, collated, entered and analysed using statistical package for social sciences (SPSS) version 20. Descriptive statistics were performed on the socio-demographic data (age, sex, occupation, ethnic group, religion, income). Data were summarized using frequency tables and bar charts. Chi-square was used to test the association between categorical variables. P value < 0.05 was considered to be statistically significant. For multivariate analysis, factors that were found by summary statistics to have a significant ( $P \leq 0.05$ ) association with SCD were entered into logistic regression.

## 3. RESULTS

### 3.1 Socio-Demographic Characteristics of Respondent

Two hundred and ninety-two patients were recruited for this study. The females were higher (73.8%) than males. The preponderance age group was 41-50, (46%), with majority being married (61.9%) and have secondary education (47.1%). The majority of the participants belong to the low-income class (43.8%) with Trading (49.3%) as the major occupation practised.

Table 1 shows the baseline clinical and laboratory characteristics of the participants. The distribution of Hb genotypes among study participants is as described. Out of the two hundred and ninety-two (292) participants that were sampled, two hundred and seventy-four (274) had results for Hb genotype, 74.1%, 22.9 and 2.9% were HbAA, HbAS and HbAC respectively. Sick cell trait (SCT-HbAS + HbAC) was found in 25.9% of the participants and no HbSS was recorded.

Table 2 compares the baseline laboratory parameters of HbAA and sickle cell trait (SCT). There was no significant difference in the baseline CD4, WBC, CRT and Hb of HbAA and SCT participants. However, high baseline VL was significantly associated with HbAA genotype.

There was no significant difference in age between SCT and HbAA study participants. The predominant age range in both groups was 41-50. There was no significant difference in sex (females were higher than males at a 1:3 ratio), level of education, occupation, marital status and level of income (Table 3).

No significant difference was observed in the mean BMI between HbAA ( $-1.31 \pm 2.6$ ) and SCT ( $2.07 \pm 0.9$ ),  $P > 0.05$ ; ART regimen ( $P = 0.431$ ), Duration of ART treatment, and presence of opportunistic infections at diagnosis ( $P = 0.221$ ). The mean WHO clinical stage (HbAA:  $1.04 \pm 0.07$ ; SCT:  $1.06 \pm 0.03$ ;  $P = 0.033$ ) was significantly different in the two groups. History of blood transfusion (10.8%,  $P = 0.046$ ) and presence of anaemia at diagnosis (14.8%;  $P = 0.006$ ) was significantly more common in HbAA genotype (Table 4).

**Table 1. Baseline Clinical and Laboratory Characteristics of Participants**

| Characteristic                         | Mean ± SD       |
|--|-----------------|
| Age at HIV Diagnosis (years):          | 44.20 ± 9.02    |
| Baseline HIV Viral Load (copies/ml)    | 4.518 ± 0.075   |
| Baseline CD4 Count (cells/μL):         | 241.54 ± 198.50 |
| Baseline Haemoglobin (Hb) level (g/L): | 122.3 ± 8. 5    |
| WHO Clinical Stage at Diagnosis        | 1.04 ± 0.29     |
| Baseline creatinine (CRT) level        | 98.68 ± 48.10   |
| Baseline white blood cell count (WBC)  | 4.59 ± 1.60     |

**Table 2. Baseline laboratory parameters among participants (SCT and HbAA)**

| Characteristics     | SCT                 | HbAA                 | P-value |
|---------------------|---------------------|----------------------|---------|
| <b>CD4_baseline</b> | <b>SCT (n = 59)</b> | <b>HbAA (n =185)</b> |         |
| < 100               | 13(22.0)            | 47(25.4)             | 0.576   |
| 101-200             | 13(22.0)            | 49(26.5)             |         |
| > 200               | 33(55.9)            | 89(48.1)*            |         |
| <b>WBC Baseline</b> | <b>SCT (n = 60)</b> | <b>HbAA (n =179)</b> |         |
| < 4.5               | 31(51.7)            | 102(57.0)            | 0.632   |
| 4.5-11              | 29(48.3)            | 76(42.5)             |         |
| >11                 | 0(0)                | 1(0.6)               |         |
| <b>CRT_Baseline</b> | <b>SCT (n = 61)</b> | <b>HbAA (n =173)</b> |         |
| < 44                | 1(1.7)              | 2(1.2)               | 0.912   |
| 44-115              | 50(83.3)            | 142(82.1)            |         |
| >115                | 9(15.0)             | 29(16.8)             |         |
| <b>VL_Baseline</b>  | <b>SCT (n = 61)</b> | <b>HbAA (n =160)</b> |         |
| < 2.0               | 11(19.0)            | 2(1.3)               | <0.001  |
| 2.0-3.1             | 47(81.0)            | 18(11.3)             |         |
| >3.1                | 0(0.0)              | 140(87.5)            |         |
| <b>HB Baseline</b>  | <b>SCT (n = 61)</b> | <b>HbAA (n =179)</b> |         |
| <135                | 61(100)             | 171(99.4)            | 0.551   |
| 135-175             | 0(0)                | 1(0.6)               |         |

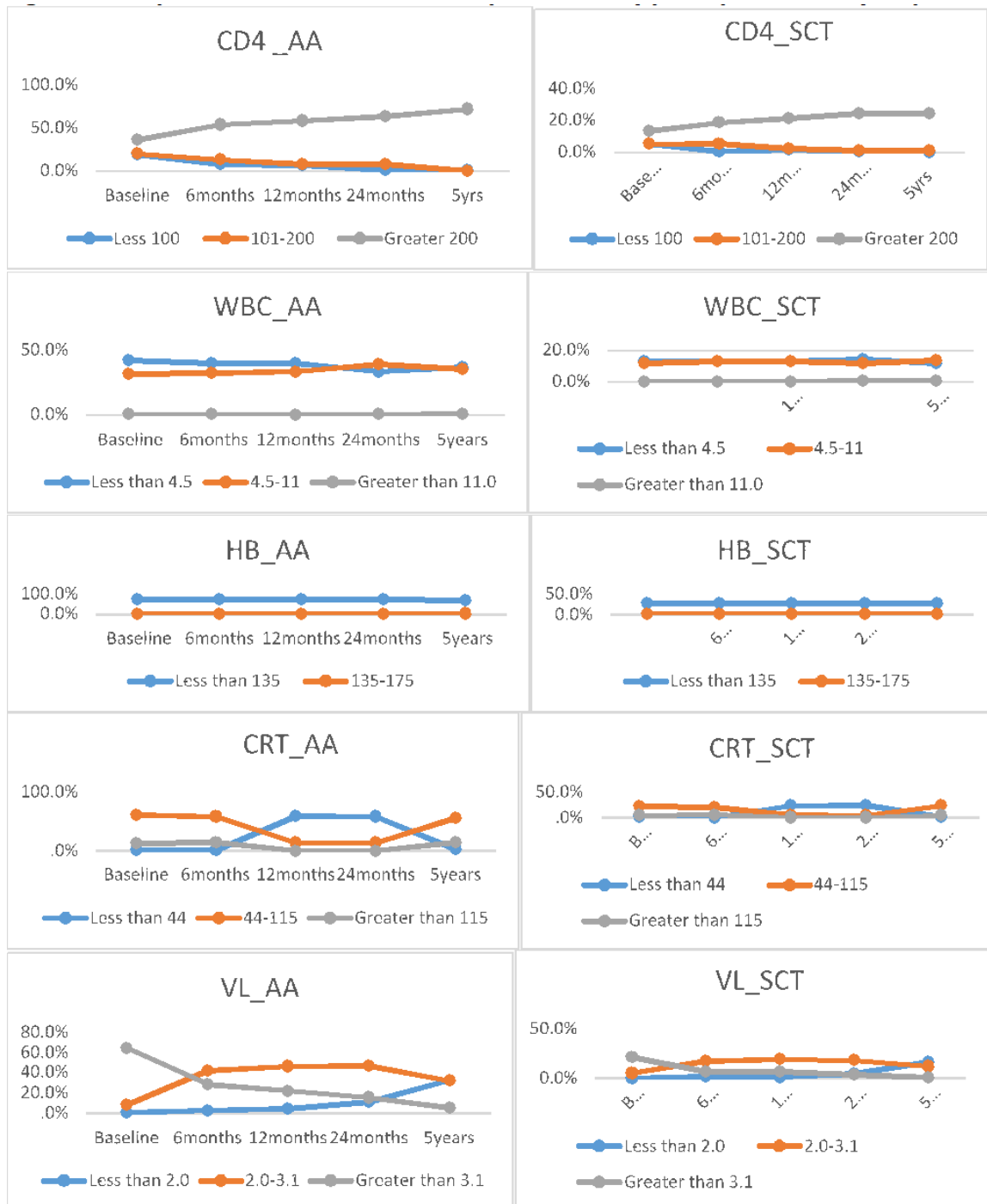
**Table 3. Relationship between Socio-demographics and HbAA and SCT**

| Characteristic            | No of participants (%) n = 292 | SCT (n = 71) | HbAA (n =203) | OR (95% CI)      | P value |
|---------------------------|--------------------------------|--------------|---------------|------------------|---------|
| <b>Age (years)</b>        |                                |              |               |                  |         |
| < 31                      | 13(4.5)                        | 4(5.6)       | 8(3.9)        |                  |         |
| 31-40                     | 86(29.8)                       | 18(25.4)     | 64(31.5)      |                  | 0.555   |
| 41-50                     | 133(46.0)                      | 37(52.1)     | 89(43.8)      |                  |         |
| 51 & above                | 57(19.7)                       | 12(16.9)     | 41(20.2)      |                  |         |
| <b>Sex</b>                |                                |              |               |                  |         |
| Male                      | 76(26.2)                       | 15(21.1)     | 55(27.1)      | 0.72 (0.37-1.37) | 0.311   |
| Female                    | 214(73.8)                      | 56(78.9)     | 147(72.4)     | 1.0              |         |
| <b>Level of Education</b> |                                |              |               |                  |         |
| None                      | 10(3.6)                        | 3(4.2)       | 6(2.9)        |                  |         |
| Primary                   | 40(14.6)                       | 9(12.7)      | 29(14.3)      |                  |         |
| secondary                 | 129(47.1)                      | 35(49.3)     | 93(45.8)      |                  | 0.419   |
| Tertiary                  | 88(32.1)                       | 21(29.6)     | 59(29.1)      |                  |         |
| Others                    | 7(2.6)                         | 4(5.6)       | 3(1.5)        |                  |         |

| <b>Occupation</b>      |           |          |           |       |
|------------------------|-----------|----------|-----------|-------|
| Unemployed             | 37(13.4)  | 9(12.7)  | 26(12.8)  |       |
| Artisan                | 14(5.1)   | 6(8.5)   | 7(3.4)    |       |
| Trader                 | 136(49.3) | 35(49.3) | 97(47.8)  |       |
| Civil Servant          | 35(12.7)  | 6(8.5)   | 27(13.3)  | 0.697 |
| Professional           | 33(12.0)  | 12(16.9) | 20(9.9)   |       |
| Others                 | 21(7.6)   | 3(4.2)   | 15(7.4)   |       |
| <b>Marital Status</b>  |           |          |           |       |
| Married                | 169(61.9) | 41(57.7) | 117(57.6) |       |
| Single                 | 40(14.7)  | 8(11.3)  | 31(15.3)  |       |
| Divorced               | 16(5.9)   | 5(7.0)   | 11(5.4)   | 0.238 |
| Separated              | 15(5.5)   | 3(4.2)   | 11(5.4)   |       |
| Widowed                | 33(12.1)  | 14(19.7) | 19(9.4)   |       |
| <b>Level of Income</b> |           |          |           |       |
| <20,000                | 99(43.8)  | 32(45.1) | 89(43.8)  | 0.098 |
| 20,000-50,000          | 64(28.3)  | 19(26.8) | 55(27.1)  |       |
| 51,000-100,000         | 29(12.8)  | 11(15.5) | 32(15.8)  |       |
| >100,000               | 34(15.0)  | 9(12.7)  | 27(13.3)  |       |

**Table 4. Association between HIV Characteristics and HbAA and SCT**

| <b>Characteristic</b>  | <b>SCT<br/>(n = 71)</b> | <b>HbAA<br/>(n =203)</b> | <b>OR<br/>(95% CI)</b> | <b>P value</b> |
|--|-------------------------|--------------------------|------------------------|----------------|
| <b>BMI/Weight for Age Z Score<br/>Mean (± SD)</b>            | -2.07(1.9)              | -1.31(2.6)               |                        | 0.245          |
| <b>WHO Clinical Stage: Mean (±<br/>SD)</b>                   | 1.06(0.03)              | 1.04(0.07)               |                        | 0.033          |
| <b>ART</b>   |                         |                          |                        |                |
| 1 <sup>st</sup> Line   | 54(76.1)                | 123(60.6)                | 1.29<br>(0.68-2.44)    | 0.431          |
| 2 <sup>nd</sup> Line   | 17(23.9)                | 50(24.6)                 | 1.0                    |                |
| <b>ART Duration (years): (Mean ±<br/>SD)</b>                 | 50(70.4)                | 147(72.4)                |                        |                |
| <b>History of Blood Transfusion</b>                          | 71                      | 183                      |                        |                |
| Yes  | 6(8.5)                  | 22(10.8)                 | 0.13<br>(0.02-0.96)    | 0.046          |
| No   | 65(91.5)                | 161(79.3)                | 1.0                    |                |
| <b>Presence of Opportunistic<br/>Infections at Diagnosis</b> | 71                      | 153                      |                        |                |
| Yes  | 8(11.3)                 | 27(13.3)                 | 0.59<br>(0.25-1.37)    | 0.221          |
| No   | 63(88.7)                | 126(62.1)                | 1.0                    |                |
| <b>Diagnosed with<br/>Anaemia/Shortage of Blood</b>          |                         |                          |                        |                |
| Yes  | 5(7.0)                  | 30(14.8)                 | 0.39<br>(0.15-1.05)    | 0.006          |
| No   | 66(93.0)                | 155(76.4)                | 1.0                    |                |



**Fig. 1. Comparative trend in treatment response of study participants over 5 year period**

The CD4 cells rise over the years was slow in SCT compared to HbAA. There was a higher number of HbAA participants with normal WBC counts over 5 years period than SCT and the rise peaks at 2 years and 5 years in HbAA and SCT respectively with a drop at 2 years in SCT. Most of the participants are anaemic in both HbAA and SCT with the majority having normal CRT level at baseline which drops gradually from 6 months to

12 months; plateaus from 12 months to 24 months and rises again from 24 months. Lower CRT level was high between 12 months to 24 months of treatment (Fig. 1). In general, both groups' response over the years was similar with lower figures in SCT. Very high viral load was seen at baseline in both groups which gradually drops in 5 years. However, the majority of HbAA had a higher viral load than SCT.

#### 4. DISCUSSION

The prevalence of HbAA and Sickle cell trait (SCT) among HIV-infected adults from this study is 74.1% and 25.9% respectively. There is no record of Sickle cell disease (SCD) among the study population. The zero prevalence of SCD could either be due to early death, as about 3% of births in Africa accounts for SCD, which is believed to be associated with high child mortality [18] or due to low susceptibility of SCD to HIV virus infection. However, available evidence suggests that SCD has a lower risk for HIV-1 infection [9] and this might explain the zero prevalence in this study. The SCT prevalence recorded in this study agrees with some earlier studies [8] that reported prevalence of 25-30% in Nigeria and sub-Saharan African countries.

There was no significant difference in the baseline CD4, WBC, CRT and Hb of HbAA and SCT participants. High baseline VL was significantly associated with HbAA genotype. The lower HIV viraemia in SCT could be due to lower iron metabolism as demonstrated by Namita Kumari, et, al. [19]; it could be inhibition of HIV-1 replication in vitro under low intracellular iron or heme treatment. This may suggest a potential restriction of HIV-1 infection in SCD. Iron metabolism is intrinsically connected to HIV-1 infection and disease progression. The development of AIDS is accompanied by an increased iron accumulation in macrophages, microglia, endothelial cells, myocytes, bone marrow, brain white matter, muscle and liver [12,13]. Increased iron stores correlate with rapid HIV-1 progression in AIDS patients. This is evidenced by a retrospective study demonstrating the lower survival of HIV-1-infected individuals is inversely correlated to higher iron stores [14]. The raised iron level has been proposed as a potential prognostic marker for higher mortality in HIV-1-infected Gambian adults [16]. In other words, SCT patients with lower iron stores are evidenced by a decrease in HIV-1 replication. Another possible reason for lower HIV viraemia in SCT participants could be because, the sickle red cell with deoxygenation, may not support HIV replication. Xiaodong Zhuang et. al. reported that low oxygen reduces HIV-1 replication [20].

Most of the participants were diagnosed with stage 1 of HIV disease and this could be due to provider-initiated counselling and testing and referral to care, put in place to diagnose apparently healthy individuals with little or no

symptoms of HIV. Anaemia and history of blood transfusion were recorded in most of the participants with a higher significant difference in the HbAA group. Anaemia has been implicated in HIV infected population and it is predictive of the disease progression [21].

All the study participants after recruitment were exposed to HIV treatment, and most of them had very high viral load at baseline before the commencement of treatment. Over the years, Highly Active Antiretroviral Therapy (HAART) had reduced the HIV disease to a chronic condition with clinical improvement demonstrated in both groups. However, treatment response was better in the SCT group than in HbAA group with respect to their viral load (Fig. 1), although CD4 response in SCT was slow.

#### 5. CONCLUSION

High baseline VL was significantly associated with HbAA genotype. Treatment response over the years was similar in both groups. It appears that the sickle cell gene contributes to delays in HIV disease progression. It was concluded that the lower HIV viraemia in SCT might mean a delay in HIV-1 disease progression and subsequently better quality of life for such patients.

#### CONSENT AND ETHICAL APPROVAL

This study was approved by NIMR institutional review board (IRB). Willingness to participate was solely the patients' decision and the participants could decide to withdraw at any time. Hence, withdrawal and refusal to participate did not attract any penalty whatsoever. In other words, only individuals who consented to be part of this study were recruited.

**What is already known on this topic:** there is paucity of data on this topic but available evidence suggests that individuals with high iron load exhibit an increase in HIV viral load.

**What this study adds:** sickle cell trait contributes to delay in HIV disease progression.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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