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Efficacy and Tolerance of Hydroxycarbamide with Adult Sickle Cell Patients in Mali: A Cohort of 157 Patients Followed for 60 Months

Boubacari Ali Touré[1,2], Mahamoud Mahamadou Koureichi[1], Diakalia Siaka Berthé[1,2], Moussa Coulibaly[1], Aissata Traoré[1], Mariam Kanta[1], Sekou Kéné[1], Yeya dit Sadio Sarro[1,3], Aldiouma Guindo[1,3]*

[1]Centre de Recherche et de Lutte contre la Drépanocytose (CRLD), Bamako, Mali
[2]Faculty of Medicine and d'Odontostomatology, USTTB, Bamako, Mali
[3]Faculty of Pharmacy, USTTB, Bamako, Mali
Email: *aldguindo@icermali.org

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Abstract

Introduction: Hydroxycarbamide or Hydroxyurea (HU) remains the only treatment considered as a modifier of the course of sickle cell disease, although it does not cure the disease. Its efficacy has been established through randomized, blinded clinical trials. The objective of this study was to describe the evolution of hematological parameters and the frequency of vaso-occlusive crisis. **Method:** This was a single-center retrospective cohort study of 157 adult patients aged 18 years and older who received HU treatment between January 2010 and December 2020. Hematological parameters and the annual number of vaso-occlusive crises were recorded at baseline and then at 6, 12, 24, and 60 months. At each time point, the analysis was restricted to patients who actually reached this period of follow-up. Paired comparisons were performed using the Wilcoxon signed-rank test. Changes at 60 months are reported on the matched subgroup of patients contributing a value both at baseline and at 60 months, with 95% confidence intervals. **Results:** The median age at initiation was 29 years (IQR 23-37), and 89 patients (56.7%) were female. The SS phenotype represented 68.2% of the cohort. Eighty-four patients (53.5%) had completed at least 60 months of treatment at the time of data extraction. In this matched subgroup, fetal hemoglobin increased from 4.8 ± 2.5% to 14.4 ± 5.4% (n = 36; mean change +9.6 points, 95% CI 8.0 to 11.2), hemoglobin from 8.8 ± 2.4 to 10.5 ± 1.4 g/dL (n = 79; +1.6 g/dL, 95% CI 1.2 to 2.1) and Mean Corpuscular Volume (MCV) from 82.2 ± 7.4 to 102.8 ± 8.6 fL (n = 79; +20.6 fL, 95% CI 18.5 to 22.7). The leukocyte count decreased from 9995 ± 3240 to 7544 ± 2082/µL (n = 79). In the same 84 patients, the annual number of vaso-occlusive crises fell from 3.80 ± 3.00 before treatment to 0.44 ± 0.95, a reduction of

88.4% (95% CI 83.5 to 92.9), and the proportion of patients without any crisis rose from 22.6% to 75.0%. Thrombocytopenia was recorded in 9 patients (5.7%). Cutaneous manifestations were frequent (29.3%) and benign. **Conclusion:** In this Malian adult cohort, HU treatment was associated with a sustained improvement in most hematological parameters and with a substantial reduction in the number of vaso-occlusive crises. Total hemoglobin was the exception, remaining statistically unchanged in the SC/Sβ^+ group. Tolerance was dominated by benign cutaneous effects and by mild to moderate thrombocytopenia.

Keywords

Sickle Cell Disease, Hydroxycarbamide, Adult, Fetal Hemoglobin, Vaso-Occlusive Crises, Mali, Sub-Saharan Africa

1. Introduction

Sickle cell disease (SCD) is the most common inherited hemoglobinopathy worldwide. Each year, more than 300,000 children are born with SCD, and more than 3/4 of these births occur in sub-Saharan Africa [1] [2]. In Mali, the prevalence of the sickle cell trait is estimated at between 12% and 15% of the general population, placing the country among the most affected in the world [3] [4]. Without systematic neonatal screening and preventive care, an important proportion of these children do not reach adulthood.

From a pathophysiological standpoint, the polymerization of hemoglobin S under deoxygenated conditions leads to irreversible shape change of red blood cells (RBC), chronic hemolysis, and increased adhesion to the vascular endothelium. This leads to recurrent vaso-occlusive crises, the main cause of hospitalization, and progressive damage of organs, including the retina, kidneys, lungs, and central nervous system [5]. In adults, these chronic complications become predominant and determine long-term survival [6].

Hydroxycarbamide or Hydroxyurea (HU), a cytoreductive agent that induces the re-expression of fetal hemoglobin, remains the only drug whose efficacy has been demonstrated in randomized clinical trials for SCD. The Multicenter Study of HU in SCD published in 1995 established a 44% reduction in the frequency of painful crises in adults with the SS genotype [7]. Subsequently 17 year follow-up of this cohort showed a reduction in mortality among patients exposed to this treatment [8]. These results led to the inclusion of HU on the World Health Organization's list of essential medicines and its recommendation as first-line therapy in most of the guidelines implemented for SCD care in the world [9] [10].

African data have increased considerably over the last decade, but they concern almost exclusively children. The REACH trial, conducted in 635 children in four sub-Saharan African countries, confirmed the feasibility and the safety of the treatment, with a reduction of the number of vaso-occlusive crises, infections,

transfusion, and mortality [11]. The NOHARM trial showed no increase in malaria risk [12], and the NOHARM MTD trial subsequently established the superiority of dose escalation to the maximum tolerated dose [13]. Extended follow-up of REACH at eight years confirmed this benefit without an increase in toxicity [14]. In contrast, few studies describe the outcomes of this treatment with African adult cohorts followed for several years under HU, even though this population has a high burden of chronic complications and limited access to treatment [15] [16].

Several specific characteristics of the African context warrant a tailored assessment. The diversity of hemoglobin phenotypes is high in this area compared to North America or Europe, with a significant proportion of SC and Sβ-thalassemia phenotypes, whose response to treatment is not well documented. Infections, comorbidities, irregular drug availability, and economic constraints impacting adherence are all factors likely to alter the benefit-risk ratio observed in clinical trials.

The Centre de Recherche et de Lutte contre la Drepanocytose (CRLD) of Bamako is the reference center for SCD management in Mali. HU has been prescribed there for adults with severe forms of the disease expression since 2010. The objective of this study was to describe, in adult patients followed in this center, the evolution of hematological parameters and the frequency of vaso-occlusive crises under HU treatment over a follow-up period, as well as the tolerance of the treatment and its outcomes.

2. Methodology

2.1. Study Design and Site

This was a single-center retrospective cohort study conducted at the Sickle Cell Disease Center in Bamako, a reference center providing diagnosis, monitoring, and therapeutic management of sickle cell patients in Mali. The study report was aligned with STROBE's recommendations framework applied to cohort studies [17].

2.2. Study Population

All sickle cell patients aged 18 years or older who initiated HU treatment at the center between 2010 and 2020 were included. The diagnosis of SCD was based on hemoglobin electrophoresis performed by High-Performance Liquid Chromatography (HPLC) at the center's laboratory. Patients whose records lack usable baseline laboratory data were excluded. No exclusion criteria based on hemoglobin phenotype or the presence of chronic complications were applied, so the cohort reflects the center's current practice.

2.3. Treatment Protocol and Follow-Up Procedures

HU was initiated after informing the patient and verifying the absence of contraindications, particularly severe cytopenia, pregnancy, or a desire for pregnancy in the near future. The initial dose was 15 mg/kg/day for the majority of our patients and 20 mg/kg/day in those with a particular severe form of disease expression. Indications included recurrent vaso-occlusive crises, acute chest syndrome, reti-

nopathy, nephropathy, severe anemia, recurrent priapism, stroke, heart disease, and leg ulcers.

Follow-up was conducted on a quarterly basis, and medical consultations and laboratory tests were done during the first year, and then twice a year. Dose adjustments were determined based on hematological tolerance and clinical response. Treatment was discontinued in cases of severe hematological toxicity or pregnancy.

2.4. Data Management

Data were extracted from the center's medical records and database by a single investigator. Parameters were recorded at baseline and then at 6, 12, 24, and 60 months of treatment.

Hematological parameters included fetal hemoglobin in percentage, hemoglobin level in g/dL, mean corpuscular volume (MCV) in fL, white blood cell count, and platelet in count per µL. The primary clinical parameter was the number of vaso-occlusive crises recorded over the observation interval preceding each assessment, a crisis being defined as an acute painful episode requiring emergency care, hospitalization, or the use of a level-2 analgesic. The baseline count covers the twelve months preceding HU initiation. The counts at 12, 24 and 60 months each cover the twelve months preceding that assessment, an interval that lies entirely after initiation. At the 6-month assessment, only six months of treatment had elapsed, so the count covers that six-month post-initiation interval alone and is reported as a six-month count.

The sociodemographic data collected included age at HU initiation, gender, profession, and residence. Therapeutic data included the initial doses, total duration of treatment, treatment status at the end of follow-up, adverse events, concomitant treatments, dosage modifications, and transfusion occurrence. Documented chronic complications included retinopathy, nephropathy, aseptic osteonecrosis, cerebral vasculopathy, leg ulcers, and hypertension.

Definition of hematological toxicity: hematological toxicity was defined a priori by the monitoring thresholds applied at the center, namely a platelet count below 150×10^9/L, an absolute neutrophil count below 1.5×10^9/L, or a fall in hemoglobin of more than 20% below the individual baseline value. An abnormal value had to be confirmed on a repeat count before being recorded as an adverse event, so that isolated unconfirmed values were not counted. Severity of thrombocytopenia was graded as mild (platelets 100 - 149 $\times 10^9$/L), moderate (50 - 99 $\times 10^9$/L) or severe (below 50×10^9/L). For the present report, all platelet counts available at the scheduled time points were in addition reviewed systematically, independently of the adverse events recorded by the treating physician.

2.5. Monitoring Plan and Definitions and Missing Data Management

Horizon or Time point: This represented the planned time point for the evalua-

tion with the patient. The time points (horizons) selected for this study were the 6-month, 12-month, 24-month, and 60-month after HU initiation.

Treatment duration: This is an open cohort, and treatment initiation is not done at the same time for all participants. This is why, when we are writing this paper, all the participant did not reach the 60th month of follow-up, but the benefit was clearly shown. For this reason, the analysis at each time point was restricted to only patients whose treatment duration was at least equal to that time point. Specifically, the 60th month assessment covers the 84 patients. This precaution is necessary because the variable describing vaso-occlusive crises was recorded for all patients at all time points, including those whose treatment was more recent. Counting these patients as crisis-free at 60 months would have led to an overestimation of the observed crisis reduction. No imputation of missing data was performed. The analyzed sample sizes are reported for each parameter and each time point.

Participant retention and its assessment: the number of patients contributing to each time point was determined by treatment duration, as defined above. The flow of participants across the four time points, the reasons why patients did not contribute to the 60-month analysis (five years of treatment not yet reached at the time of data extraction, treatment discontinuation, death), and the number of available measurements for each parameter are reported in the Results. No imputation was performed. The possibility that retention was selective was examined in two ways: by comparing the baseline characteristics of the patients who reached 60 months with those of the patients who did not, and, within the patients who reached 60 months, by comparing those with and without a fetal hemoglobin measurement at that time point. These comparisons used the Mann-Whitney U test for quantitative variables and the chi-square or Fisher exact test for qualitative variables.

2.6. Determination of the Treatment Response Status

The hematological response was assessed based on the fetal hemoglobin level measured at the twelfth month of treatment. This timeframe was chosen because it corresponds to the point at which the increase of this parameter can be better evaluated.

The relationship between fetal hemoglobin levels and disease severity is continuous and does not break down naturally. Data from the Cooperative Study of Sickle Cell Disease showed that low fetal hemoglobin levels are associated with a higher frequency of painful crises [18] and an increased risk of early death [19], although no clinical benefit threshold has been formally established. Therapeutic trials conducted with dose escalation, however, use a target of 20% or more as responder to treatment [13]. In the absence of a consensus threshold, response patterns have been defined pragmatically. They therefore do not delineate prognostic categories.

Type of Responder to treatment: Three categories were defined a priori based

on the level achieved at twelve months. Patients with a fetal hemoglobin level greater than or equal to 10% were classified as good responders, this threshold corresponding to twice the average level observed before treatment (*i.e.*, 4.9%). Those with a level between 5% (included) and 10% (excluded) were classified as intermediate responders. Those whose level remained below 5% were classified as poor responders.

Non-response to treatment: Non-response was defined separately, not by the level achieved but by its evolution, as the absence of any increase in fetal hemoglobin between baseline and the 12th month. This distinction is necessary because a patient with a very low initial level may experience significant relative improvement while remaining below the 5% threshold, and would then be classified as a poor responder even though they responded to treatment. Patients without a fetal hemoglobin measurement at baseline or at the twelfth month were not classified, and no imputation was performed.

2.7. Statistical Analysis

Quantitative variables were analyzed using the mean and standard deviation, as well as the median and interquartile range. Qualitative variables were expressed as counts and percentages. The normality of the distributions was examined using the Shapiro-Wilk test and graphical inspection.

Longitudinal comparisons between baseline and each follow-up time point were based on the Wilcoxon signed-rank test for paired data. Comparisons between independent groups, particularly between initial doses, used the Mann-Whitney U test for quantitative variables. The chi-square test or Fisher's exact test was used for qualitative variables, depending on the expected sample sizes. For the phenotype analysis, patients were grouped into two classes based on having the same pattern of disease expression: Group-1: SS and Sβ^0-thalassemia and Group-2: SC and Sβ^+-thalassemia. The overall effect of time was tested using a linear mixed model with a random intercept per patient (a Poisson mixed model for the number of crises), with a likelihood ratio test. This model used all available measurements. Each follow-up time point was then compared to inclusion data by the paired Wilcoxon signed-rank test when at least ten pairs of measurements were available. For the 60-month assessment, the change from baseline was in addition computed on the matched subgroup of patients contributing a value at both time points. Mean changes are reported with their 95% confidence interval derived from the student t distribution, and the relative reduction in the annual number of crises with a 95% confidence interval.

The threshold for statistical significance was set at 0.05 in the two-sided design. Given the descriptive and exploratory nature of this work, no correction for multiple tests was applied, and p-values should be interpreted as indicators of internal consistency rather than as confirmatory tests. Analyses were performed using R software version 4.6.0.

2.8. Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol received approval from the institutional ethics committee of the hospital in Mali. Data were extracted anonymously, and no patient-identifying information was retained in the analysis file.

3. Results

3.1. Cohort Characteristics and Participant Flow

One hundred and fifty-seven adult patients with sickle cell disease were included. The median age at treatment initiation was 29 years, with 25th and 75th percentiles of 23 and 37 years and extremes ranging from 18 to 63 years. The cohort comprised 89 women (56.7%). The vast majority of patients resided in Bamako (82.8%). The SS phenotype was predominant, with 107 patients (68.2%), followed by the SC phenotype with 41 patients (26.1%). In terms of occupation, housewives (32.5%), students (20.4%), and the unemployed (14.0%) were the most represented categories.

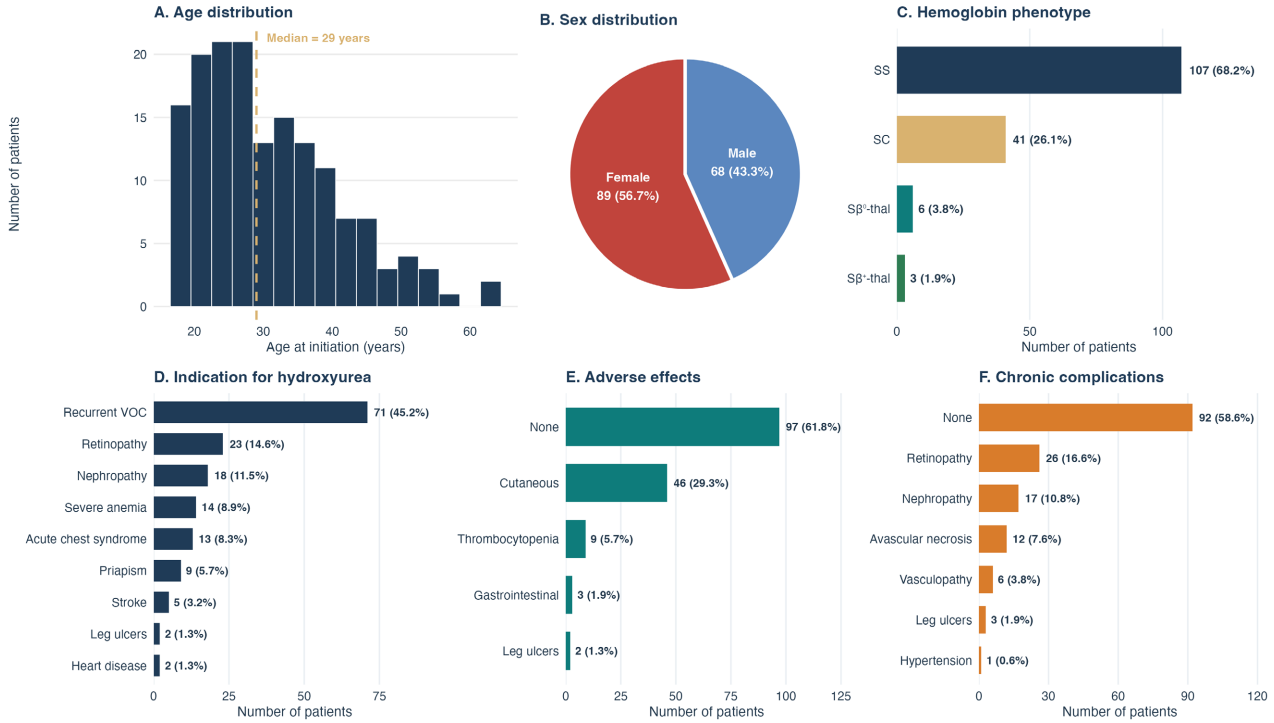


Figure 1. Sociodemographic, clinical, and therapeutic characteristics of the cohort at inclusion (n = 157). A, age distribution at treatment initiation, with the dotted line marking the median. B, sex distribution. C, hemoglobin phenotype. D, indication for hydroxyurea. E, adverse events observed during follow-up. F, chronic complications. Numbers and percentages are reported on each bar.

The primary indication for treatment was recurrent vaso-occlusive crises in 71 patients (45.2%), followed by retinopathy in 23 patients (14.6%), nephropathy in 18 patients (11.5%), severe anemia in 14 patients (8.9%), and acute chest

syndrome in 13 patients (8.3%). Priapism, stroke, heart disease, and leg ulcers were the remaining indications. The initial dose was 15 mg/kg/day in 135 patients (86.0%) and 20 mg/kg/day in 22 patients (14.0%). The median duration of hydroxyurea treatment was 5 years, with 2 and 6 years as 25th and 75th percentiles and a maximum of 14 years. Detailed characteristics are illustrated in Figure 1.

All 157 patients reached the 6-month assessment, 155 reached 12 months, 127 reached 24 months and 84 reached 60 months of treatment. The 73 patients who do not contribute to the 60-month analysis had not completed five years of treatment at the time of data extraction: 60 were still on treatment with a shorter exposure, 7 had stopped treatment before five years and 6 had died before five years. Among the 84 patients who reached 60 months, 63 were still on treatment at the end of follow-up, 8 had stopped treatment thereafter and 13 died after that time point. At 60 months, the crisis count was available for all 84 patients, hemoglobin and leukocyte count for 79, mean corpuscular volume and platelet count for 80, but fetal hemoglobin for only 36, because HPLC quantification was not performed at every visit and depended on reagent availability.

The patients who reached 60 months did not differ from the other 73 at baseline in age (median 28 vs 30 years, $p = 0.632$), annual number of crises (median 3.5 vs 5, $p = 0.538$), hemoglobin ($p = 0.487$), fetal hemoglobin ($p = 0.953$), mean corpuscular volume ($p = 0.500$), leukocyte count ($p = 0.268$), sex ($p = 1.000$), phenotype ($p = 0.216$) or initial dose ($p = 1.000$), which argues against retention of the patients with the mildest disease. Within the 84, however, fetal hemoglobin at 60 months was measured preferentially in the more severely affected patients: those with a 60-month value had a lower baseline hemoglobin (median 7.7 vs 9.4 g/dL, $p = 0.002$) and more crises in the year before treatment (median 5.5 vs 2, $p = 0.024$) than those without, and 32 of the 36 belonged to the SS phenotype. The 60-month fetal hemoglobin value therefore reflects mainly the SS subgroup and must not be read as a cohort-wide figure.

3.2. Evolution of Hematological Parameters

3.2.1. Fetal Hemoglobin

Fetal hemoglobin levels increased progressively and steadily throughout the follow-up period. From 4.9 ± 2.9% at baseline (n = 149), it increased to 7.9 ± 2.2% at 6 months (n = 96), then to 10.3 ± 2.2% at 12 months (n = 95), to 12.0 ± 2.9% at 24 months (n = 59), and to 14.4 ± 5.4% at 60 months (n = 36). All comparisons with baseline were significant ($p < 0.001$). The increase was double the baseline level at 12 months and almost triple at 60 months.

At 12 months, 52 of 95 patients (54.7%) were classified as good responders, 42 patients (44.2%) as intermediate responders, and only one patient (1.1%) as a poor responder. This poor responder's level improved from 1.4% to 4.1%. Only one patient (1.1%) showed no increase in fetal hemoglobin between enrollment and 12 months (Figure 2(A)).

3.2.2. Hemoglobin Levels

Hemoglobin levels increased from 8.7 ± 2.2 g/dL at baseline (n = 157) to 9.4 ± 1.7 g/dL at 6 months (n = 156), 10.0 ± 1.4 g/dL at 12 months (n = 154), 10.3 ± 1.4 g/dL at 24 months (n = 126), and 10.5 ± 1.4 g/dL at 60 months (n = 79). The mean gain of Hemoglobin level from baseline to 60 months was 1.8 g/dL, representing a relative increase of 21.0%. An important part of this gain occurred during the first 12 months, with an increase of 1.4 g/dL, followed by a plateau. All comparisons with baseline were significant ($p < 0.001$) (**Figure 2(B)**).

3.2.3. Mean Corpuscular Volume

The mean corpuscular volume increased from 82.9 ± 7.7 fL at baseline (n = 157) to 95.6 ± 8.2 fL at 6 months (n = 156), 99.5 ± 7.4 fL at 12 months (n = 154), 101.6 ± 7.2 fL at 24 months (n = 126), and 102.8 ± 8.6 fL at 60 months (n = 79), representing a mean gain of 19.9 fL, corresponding to a 24.1% increase ($p < 0.001$ in each comparison). The mean value was still just below the 100 fL threshold at twelve months (99.5 fL) and first exceeded it at 24 months (101.6 fL), in agreement with **Figure 2(C)**.

3.2.4. Leukocytes and Platelets



Figure 2. Evolution of hematological parameters and the frequency of vaso-occlusive crises under hydroxyurea, from baseline to 60 months. A: fetal hemoglobin. B: total hemoglobin. C: mean corpuscular volume. D: leukocytes. E: platelets. F: vaso-occlusive crises. At each time point, the analysis focuses on patients who actually completed this treatment duration, the number of whom is indicated next to each mean value. Shaded areas represent the interquartile range. Asterisks placed below the x-axis correspond to paired comparisons with the baseline value (***$p < 0.001$, Wilcoxon signed-rank test).

The white blood cell count decreased from 10,397 ± 3252/µL at baseline (n = 157) to 9435 ± 2727/µL at 6 months (n = 156), 8591 ± 2457/µL at 12 months (n =

150), 8171 ± 2273/µL at 24 months (n = 124) and 7544 ± 2082/µL at 60 months (n = 79), representing a reduction of 27.4% ($p < 0.001$). The platelet count decreased from 335,820 ± 141,325/µL to 287,708 ± 135,335/µL, representing a 14.3% decrease ($p < 0.001$). A detailed overview of all parameters is shown in **Figure 2**.

Matched changes at 60 months. Because the composition of the sample changes with the horizon, the change from baseline to 60 months was also computed on the patients contributing a value at both time points. The mean changes were: fetal hemoglobin +9.6 points (95% CI 8.0 to 11.2; from 4.8 ± 2.5 to 14.4 ± 5.4%; n = 36; $p < 0.001$), hemoglobin +1.6 g/dL (95% CI 1.2 to 2.1; from 8.8 ± 2.4 to 10.5 ± 1.4 g/dL; n = 79; $p < 0.001$), mean corpuscular volume +20.6 fL (95% CI 18.5 to 22.7; from 82.2 ± 7.4 to 102.8 ± 8.6 fL; n = 79; $p < 0.001$), leukocyte count −2452/µL (95% CI −3014 to −1889; from 9995 ± 3240 to 7544 ± 2082/µL; n = 79; $p < 0.001$) and platelet count −45,400/µL (95% CI −82,750 to −8042; from 333,100 ± 145,000 to 287,700 ± 135,300/µL; n = 79; $p < 0.001$). These matched estimates are close to the unmatched values reported above; the only appreciable difference concerns the relative gain in hemoglobin, which is 18.6% rather than 21.0%.

3.3. Frequency of Vaso-Occlusive Crisis

The number of vaso-occlusive crises fell steadily throughout follow-up. Over the twelve months preceding treatment, the mean was 3.9 ± 2.8 crises (n = 157). Over the first six months of treatment, an interval lying entirely after initiation, patients experienced 1.8 ± 1.7 crises (n = 157), which corresponds to an annualized rate of 3.7 crises per year. The mean annual number was then 0.9 ± 1.1 at 12 months (n = 155), 0.7 ± 1.0 at 24 months (n = 127) and 0.4 ± 0.9 at 60 months (n = 84), with $p < 0.001$ for each comparison with baseline. The six-month figure is a six-month count and is not directly comparable with the annual counts of the later time points; most of the measurable benefit appears from the twelfth month onwards.

The proportion of patients who had not experienced any crisis during the previous twelve months increased in parallel, rising from 18.5% at baseline to 34.4% at 6 months, 45.8% at 12 months, 60.6% at 24 months, and 75.0% at 60 months. In other words, three out of four patients among those treated for at least five years have no longer experienced any vaso-occlusive crisis.

Matched estimates of the reduction. Computed on paired data from the same patients, the mean annual count fell from 3.97 to 0.90 in the 155 patients assessed at 12 months, a reduction of 77.4% (95% CI 74.4 to 80.4), and from 3.80 ± 3.00 to 0.44 ± 0.95 in the 84 patients assessed at 60 months, a reduction of 88.4% (95% CI 83.5 to 92.9; $p < 0.001$). In these same 84 patients, the proportion free of any crisis rose from 22.6% before treatment to 75.0% at 60 months. The figure of 88.9%, which compares the 60-month mean with the baseline mean of the whole cohort, is therefore marginally optimistic, and the matched estimate of 88.4% is the one retained throughout this paper.

It should be noted that these observations are based solely on patients who actually reached each time point. If the entire cohort had been considered at 60

months, including patients with more recent treatment who were free of crises, the apparent reduction would have been 93.2% instead of the matched estimate of 88.4%. The restricted analysis was chosen because it more accurately reflects the observed trend.

3.4. Treatment Efficacy within Phenotypic Group

Table 1. Evolution of hematological parameters and frequency of vaso-occlusive crises within each phenotypic group, from inclusion to 60 months.

Settings	Inclusion[1]	6 months[1]	12 months[1]	24 months[1]	60 months[1]	p (time)2
SS/Sβ^0-thalassemia group (n = 113)						
Fetal hemoglobin (%)	5.1 (3.0)	8.0 (2.1)	10.4 (2.0)	12.3 (2.6)	15.0 (5.1)	**0.001**
p vs inclusion [n]	—	0.001 [90]	0.001 [89]	0.001 [55]	0.001 [33]	
Hemoglobin (g/dL)	7.5 (1.1)	8.6 (1.1)	9.4 (0.9)	9.7 (1.1)	9.9 (1.2)	**0.001**
p vs inclusion [n]	—	0.001 [112]	0.001 [112]	0.001 [90]	0.001 [54]	
VGM (fL)	86.1 (6.4)	98.7 (7.2)	102.1 (6.3)	103.7 (6.0)	105.6 (8.8)	**0.001**
p vs inclusion [n]	—	0.001 [112]	0.001 [112]	0.001 [90]	0.001 [54]	
Leukocytes (10^3/µL)	11.5 (2.8)	10.3 (2.5)	9.2 (2.2)	8.4 (2.4)	8.2 (1.8)	**0.001**
p vs inclusion [n]	—	0.001 [112]	0.001 [112]	0.001 [88]	0.001 [54]	
Platelets (10^3/µL)	357.8 (152.6)	324.9 (129.2)	287.7 (104.1)	301.6 (115.1)	317.7 (146.8)	**0.001**
p vs inclusion [n]	—	0.001 [112]	0.001 [112]	0.001 [90]	0.045 [54]	
Vaso-occlusive crises (n/year)	4.7 (2.4)	2.2 (1.7)	1.1 (1.2)	0.7 (1.1)	0.6 (1.1)	**0.001**
p vs inclusion [n]	—	0.001 [113]	0.001 [113]	0.001 [91]	0.001 [59]	
SC/Sβ^+ thalassemia group (n = 44)						
Fetal hemoglobin (%)	4.5 (2.6)	6.9 (3.9)	8.2 (3.9)	8.5 (4.1)	7.6 (3.8)	
p vs inclusion [n]	—	— [6]	— [6]	— [4]	— [3]	
Hemoglobin (g/dL)	11.8 (1.0)	11.6 (0.9)	11.8 (1.0)	11.7 (1.0)	11.9 (0.8)	0.544
p vs inclusion [n]	—	0.249 [44]	0.983 [42]	0.978 [36]	0.462 [25]	
VGM (fL)	74.4 (3.0)	87.8 (4.8)	92.4 (4.8)	96.4 (7.3)	96.9 (4.2)	**0.001**
p vs inclusion [n]	—	0.001 [44]	0.001 [42]	0.001 [36]	0.001 [25]	
Leukocytes (10^3/µL)	7.5 (2.4)	7.3 (2.1)	6.9 (2.3)	7.6 (1.7)	6.1 (2.0)	**0.001**
p vs inclusion [n]	—	0.147 [44]	0.001 [38]	0.547 [36]	0.001 [25]	
Platelets (10^3/µL)	279.3 (85.3)	236.0 (91.7)	245.7 (83.5)	211.7 (85.1)	222.9 (74.4)	**0.001**
p vs inclusion [n]	—	0.002 [44]	0.007 [42]	0.001 [36]	0.001 [25]	
Vaso-occlusive crises (n/year)	2.0 (2.9)	1.0 (1.6)	0.5 (0.8)	0.4 (0.6)	0.0 (0.2)	**0.001**
p vs inclusion [n]	—	0.001 [44]	0.001 [42]	0.001 [36]	0.008 [25]	

Note: [1]: Mean (standard deviation) of patients who reached the time horizon; [2]: Overall effect of time: mixed model with random intercept (linear; Poisson for CVOs), likelihood ratio test. "p vs inclusion" line: paired Wilcoxon signed-rank test [n = number of pairs]; —: fewer than 10 pairs, test not performed.

Patients were grouped into two phenotypic classes: SS and Sβ^0-thalassemia (n = 113) on the one hand, and SC and Sβ^+-thalassemia (n = 44) on the other. Since these two groups inherently have different hematological profiles, the evolution of each parameter was analyzed within each group, without direct comparison between them (Table 1).

In the SS/Sβ^0 group, all parameters changed significantly during follow-up ($p < 0.001$). Fetal hemoglobin increased from 5.1 ± 3.0% at inclusion to 10.4 ± 2.0% at 12 months and 15.0 ± 5.1% at 60 months, hemoglobin level from 7.5 ± 1.1 to 9.9 ± 1.2 g/dL and mean corpuscular volume from 86.1 ± 6.4 to 105.6 ± 8.8 fL. The white blood cell count decreased from 11.5 ± 2.8 to 8.2 ± 1.8 × 10^3/µL and the annual number of crises from 4.7 ± 2.4 to 0.6 ± 1.1. All comparisons with inclusion were significant at each horizon ($p < 0.001$), with the exception of the platelet count at 60 months ($p = 0.045$), which rose again after a maximum decrease at 12 months.

In the SC/Sβ^+ group, hemoglobin levels remained stable throughout the follow-up (11.8 ± 1.0 g/dL at baseline and 11.9 ± 0.8 g/dL at 60 months; $p = 0.544$ for the effect of time, no comparison with baseline being significant). The treatment nevertheless resulted in a marked macrocytosis (from 74.4 ± 3.0 to 96.9 ± 4.2 fL, $p < 0.001$ at each horizon), a decrease in platelet count (from 279.3 to 222.9 × 10^3/µL, $p \leq 0.007$ at each horizon) and a reduction in vaso-occlusive crises from 2.0 ± 2.9 per year at inclusion to 0.5 ± 0.8 at 12 months and then 0.0 ± 0.2 at 60 months ($p < 0.001$ up to 24 months and $p = 0.008$ at 60 months). The white blood cell count decreased less steadily ($p < 0.001$ at 12 and 60 months, non-significant difference at 6 and 24 months). Fetal hemoglobin was measured during follow-up in only six patients at most in this group, which does not allow for assessment of its evolution.

3.5. Impact of the Initial Dose

Comparison between patients starting at 15 mg/kg/day and those starting at 20 mg/kg/day revealed no significant difference at 12 months for fetal hemoglobin (medians 10.1% vs. 11.1%, $p = 0.118$), total hemoglobin ($p = 0.856$), or mean corpuscular volume ($p = 0.594$). However, the number of crisis at 12 months was higher in the 20 mg/kg/day group ($p = 0.007$). This difference reflects a bias in treatment indication, with the higher dose being reserved for patients with the most severe initial disease, rather than a lower efficacy of this dose. The frequency of adverse events did not differ between the two groups.

3.6. Tolerance

Of the 157 patients, 97 (61.8%) experienced no adverse events during follow-up. Skin manifestations were the most frequent, affecting 46 patients (29.3%), and included dry skin, nail hyperpigmentation, and xerosis. Thrombocytopenia was recorded as an adverse event by the treating physician in 9 patients (5.7%) and gastrointestinal disturbances in 3 patients (1.9%). Systematic review of all platelet

counts available at the scheduled time points showed that 17 patients (10.8%) had at least one value below 150×10^9/L and 11 (7.0%) at least one value below 100×10^9/L; no value fell below 50×10^9/L, the lowest count recorded being 59×10^9/L. Thrombocytopenia was therefore mild or moderate in every case and never reached the severe grade. Among the nine patients with a recorded event, the dose was reduced in seven and treatment was permanently discontinued in three; a fourth patient died later during follow-up from an undocumented cause. No severe neutropenia, renal or hepatic toxicity attributable to treatment, or secondary neoplasia were documented. No serious adverse reaction attributable to the treatment was therefore identified, which is a statement about attribution and not about the absence of serious events: the 19 deaths recorded during follow-up are serious events, and their causes were not documented (section 3.8).

3.7. Frequency Chronic Complications

In our study population 65 patients (41.4%) had at least one chronic complication. Retinopathy was the most frequent, affecting 26 patients (16.6%), followed by nephropathy (17 patients, 10.8%), avascular necrosis of the hip (12 patients, 7.6%), cerebral vasculopathy (6 patients, 3.8%), leg ulcers (3 patients, 1.9%), and hypertension (1 patient, 0.6%). This high prevalence highlights the fact that the cohort consisted of adult patients who already had advanced disease at the time treatment was initiated. These chronic complication can be the indication for HU initiation.

3.8. Mortality in This Cohort

In total, 19 patients (12.1%) died. The deceased patients did not differ from the survivors in age at initiation (median 26 vs. 29 years, $p = 0.581$), sex (death in 15.7% of women vs. 7.4% of men, $p = 0.141$), phenotypic group (11.5% in SS/Sβ^0 patients vs. 13.6% in SC/Sβ^+ patients, $p = 0.786$), or initial dose ($p = 0.478$). They had been treated for a long time before their death, with a median treatment duration of 6 years (IQR 2-7) versus 5 years (IQR 2-6) in survivors ($p = 0.070$), and 14 of the 19 deaths occurred after at least four years of treatment. Their disease was, however, more severe because they experienced more vaso-occlusive crises during the year preceding treatment (median 6 vs 4, $p = 0.031$), and mortality was higher in patients with a chronic complication (18.5% vs 7.6%, $p = 0.049$) and in those who had transfusions (23.4% vs 7.3%, $p = 0.007$). The medical records did not document the cause of death for any of the 19 patients, so no cause-specific analysis of mortality was possible and no death could be formally attributed either to the disease or to the treatment.

4. Discussion

This cohort of 157 adult sickle cell patients followed for up to sixty months constitutes one of the largest African series dedicated to HU treatment with adults. HU treatment was associated with a marked and sustained improvement in most

of the hematological parameters assessed, with a major reduction in the annual number of vaso-occlusive crises, and with an acceptable tolerability profile. Total hemoglobin was the exception, remaining statistically unchanged in the SC/Sβ^+ group. Because the study is observational and has no control group, these relationships are associative and no causal effect can be claimed.

4.1. Hematological Response

The near-tripling of fetal hemoglobin levels, from 4.9% to 14.4%, falls within the upper range of values reported in the literature. The Multicenter Study of HU observed a progression of 5.0% to 9.0% in North American SS patients [7]. The long-term follow-up of the REACH trial, conducted in pediatrics with dose escalation up to the maximum tolerated dose, reported an average of 23.3% at a mean dose of 28.2 mg/kg/day [14]. Our cohort therefore falls between these two reference values, which is consistent with initial dosages of 15 to 20 mg/kg/day without systematic escalation. The proportion of good responders, exceeding half of the patients in the first year, nevertheless demonstrates a satisfactory pharmacological response under the center's prescribing conditions. This long-term value must nevertheless be read with the composition of the measured sample in mind: fetal hemoglobin was available for only 36 of the 84 patients assessed at 60 months, and 32 of these 36 had the SS phenotype, with a lower baseline hemoglobin and more crises before treatment than the patients left unmeasured. The 14.4% figure therefore describes the SS subgroup rather than the cohort as a whole.

The increase in hemoglobin level of 1.8 g/dL and the increase in mean corpuscular volume of nearly 20 fL confirm this response. The observed kinetics, with the majority of the benefit occurring during the first year followed by a plateau, corresponds to what is described in longitudinal studies and allows for guidance on the frequency of biological monitoring.

4.2. Reduction of the Number of Vaso-Occlusive Crisis

The 88.4% reduction (95% CI 83.5 to 92.9) in the annual number of vaso-occlusive crises between baseline and month 60, computed on the 84 patients assessed at both time points, represents the most significant clinical outcome of this study. This far exceeds the 44% reduction reported by the Multicenter Study of HU [7]. Several factors explain this difference. The follow-up period is considerably longer here, five years compared to two years in the American trial. The comparison is based on intra-patient evolution without a control group, whereas the trial compared two randomized arms. Finally, regression to the mean necessarily plays a role, as the patients were started on treatment when their disease was particularly active.

The proportion of patients completely free of crisis, which rose from 22.6% to 75.0% in the 84 patients assessed at both time points, is an important clinical indicator. It reflects a transformation in the disease trajectory for a majority of patients.

4.3. Benefit beyond the SS Phenotype

The reduction in vaso-occusive crisis was comparable in SS and SC patients, ranging from 77% to 78% in one year. This observation is noteworthy because HU remains less frequently prescribed in SC phenotype group due to a lack of robust data. A recent randomized trial conducted in Ghana with SC patients showed hemoglobinosis, a clinical benefit of treatment, at the cost of an increased frequency of dose-limiting hematological toxicities [20]. Our results, although observational, support this finding and suggest that the indication should be discussed on a case-by-case basis in these patients. However, the trends observed in the SC/Sβ^+ group warrant some qualification. Hemoglobin levels did not increase, which is expected in patients with moderate hemolysis and a baseline level close to normal. The significant macrocytosis observed in this group nevertheless attests to the pharmacological effect of the treatment and satisfactory adherence in this group.

4.4. Macrocytosis and Compliance

The increase in mean corpuscular volume (MCV) is a reliable and readily available pharmacodynamic marker. In a setting where plasma drug level monitoring is unavailable, it represents, in practice, the best indirect indicator of adherence. The negative correlation between MCV and hemoglobin at 12 months is mainly explained by the phenotypic composition of the cohort, with SS patients exhibiting the lowest hemoglobin levels and the most pronounced macrocytic response.

4.5. Tolerance

The observed tolerability profile is reasonnable, with nearly two-thirds of patients free from any adverse effects. Cutaneous manifestations, which are largely predominant, are benign and rarely lead to treatment discontinuation. The frequency of thrombocytopenia, at 5.7%, corresponds to the expected myelosuppressive effect and remains lower than the dose-limiting toxicity rates reported in dose-escalation trials [13] [14]. The absence of severe neutropenia is particularly important in a context of high infectious and malaria endemicity and is consistent with the findings of the NOHARM trial [12].

4.6. Mortality

The 12.1% mortality rate observed during follow-up must be considered within the context of this cohort, composed of adults whose disease was already advanced at the time of HU initiation, as it is reserved for severe forms. The dead patients did not differ from the survivors in age, sex, or phenotype, but rather in markers of severity such as a higher frequency of attacks before treatment, a greater proportion of chronic complications, and more frequent transfusion requirements. Because the cause of death was not documented in any case, no cause-specific interpretation is possible: these deaths can neither be attributed to pre-existing organ damage nor excluded as treatment-related. What the data support is only an association between death and baseline markers of severity. It remains plausi-

ble, and is consistent with data from North American adult cohorts in which chronic complications are the main determinant of survival [6], that established organ damage drives this mortality, but the present study cannot establish it.

Fourteen of the 19 deaths occurred after at least four years of treatment, and the median treatment duration of the deceased patients was at least as long as that of the survivors. Treatment duration is not informative about the cause of death, however: it measures the length of exposure to both the disease and the drug, and it cannot be used to argue either for or against an effect of treatment on mortality. Prospective documentation of causes of death is a priority for future work in this setting. These observations nonetheless underscore the importance of initiating HU earlier, before irreversible damage of organs.

4.7. Strengths of the Study

The sample size, the follow-up period of up to five years, the diversity of hemoglobin phenotypes represented, and the standardized follow-up protocol within a reference center are the main strengths of this study. The decision to restrict each analysis to patients who actually reached the considered time points, rather than using default values, strengthens the credibility of the reported estimates. The sample sizes analyzed are specified for each parameter and each time point, allowing for an assessment of the robustness of each comparison.

4.8. Limitations of the Study

This study has several limitations that must be considered in its interpretation. Its retrospective and single-center nature exposes it to biases inherent in data collection from medical records, particularly for counting vaso-occlusive crises, which relies in part on patient self-reporting. The absence of an untreated control group prevents definitively attributing the observed changes to the treatment. Finally, adherence to treatment was not directly measured. Three further limitations should be stated. First, the number of patients contributing to each time point decreases with time, and fetal hemoglobin was available for only 36 of the 84 patients at 60 months, preferentially in the more severely affected SS patients; the long-term fetal hemoglobin estimate is therefore not representative of the whole cohort, even though the patients who reached 60 months did not differ from the others at baseline. Second, hematological toxicity was ascertained from adverse events recorded by the treating physician, so mild transient cytopenias may be under-recorded; the systematic review of platelet counts presented here mitigates but does not remove this limitation. Third, the causes of the 19 deaths were not documented, which precludes any analysis of cause-specific mortality and any attribution of these deaths to the disease or to the treatment.

4.9. Practical Implications and Perspectives

These results reinforce the value of hydroxcarbamide in adults with sickle cell disease in sub-Saharan Africa and argue for expanding access to treatment, which is

currently limited by the availability and cost of the drug. Three key areas emerge. The first concerns early initiation, as established chronic complications appear to be the main determinant of prognosis. The second focuses on dosage optimization, with comparisons to cohorts conducted using dose escalation up to the maximum tolerated dose suggesting potential for improvement in fetal hemoglobin response. The third concerns expanding the indication to non-SS phenotypes, for which our data show a comparable benefit. Prospective multicenter studies, including systematic recording of dosages, objective assessment of adherence, and monitoring of organ damage, would help to clarify these areas and refine management strategies for adults with sickle cell disease in the region.

5. Conclusions

In this cohort of 157 adult sickle cell patients followed at the Bamako Sickle Cell Disease Research and Care Center, hydroxycarbamide was associated with a significant and sustained improvement in most hematological parameters, with a near tripling of fetal hemoglobin, an increase in total hemoglobin of 1.6 g/dL in the patients assessed at both time points, and marked pharmacological macrocytosis; total hemoglobin was the exception, remaining statistically unchanged in the SC/Sβ^+ group. In the 84 patients assessed at 60 months, the annual number of vaso-occlusive crises was 88.4% lower than before treatment (95% CI 83.5 to 92.9) and three out of four patients were free of any crisis. The tolerability profile remained satisfactory, with no severe neutropenia and no severe thrombocytopenia, while 19 deaths occurred during follow-up and their causes could not be documented.

These observations, from the routine practice of an African reference center, are associative and not causal, but they reinforce the place of hydroxyurea in the management of adult sickle cell disease and justify a sustained effort to broaden access to it in sub-Saharan Africa, where the disease remains responsible for considerable morbidity and mortality.

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Author Contributions

BAT and MMK designed the study protocol. MK, DSB, MC, AT and SK managed the patients and assisted with data collection. MMK conducted the statistical analyses and assisted with manuscript preparation. AG and YS critically reviewed the document. All authors read and approved the final document.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

[1] Piel, F.B., Steinberg, M.H. and Rees, D.C. (2017) Sickle Cell Disease. *New England Journal of Medicine*, **376**, 1561-1573. https://doi.org/10.1056/nejmra1510865

[2] Mburu, J. and Odame, I. (2019) Sickle Cell Disease: Reducing the Global Disease Burden. *International Journal of Laboratory Hematology*, **41**, 82-88. https://doi.org/10.1111/ijlh.13023

[3] Diallo, D.A. and Guindo, A. (2014) Sickle Cell Disease in Sub-Saharan Africa: Stakes and Strategies for Control of the Disease. *Current Opinion in Hematology*, **21**, 210-214. https://doi.org/10.1097/moh.0000000000000038

[4] Diallo, D.A. (2008) Sickle Cell Disease and Public Health in Mali. *Mali Médical*, **23**, 1-5.

[5] Ware, R.E., de Montalembert, M., Tshilolo, L. and Abboud, M.R. (2017) Sickle Cell Disease. *The Lancet*, **390**, 311-323. https://doi.org/10.1016/s0140-6736(17)30193-9

[6] Elmariah, H., Garrett, M.E., De Castro, L.M., Jonassaint, J.C., Ataga, K.I., Eckman, J.R., *et al.* (2014) Factors Associated with Survival in a Contemporary Adult Sickle Cell Disease Cohort. *American Journal of Hematology*, **89**, 530-535. https://doi.org/10.1002/ajh.23683

[7] Charache, S., Terrin, M.L., Moore, R.D., Dover, G.J., Barton, F.B., Eckert, S.V., *et al.* (1995) Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia. *New England Journal of Medicine*, **332**, 1317-1322. https://doi.org/10.1056/nejm199505183322001

[8] Steinberg, M.H., McCarthy, W.F., Castro, O., Ballas, S.K., Armstrong, F.D., Smith, W., *et al.* (2010) The Risks and Benefits of Long-Term Use of Hydroxyurea in Sickle Cell Anemia: A 17.5 Year Follow-Up. *American Journal of Hematology*, **85**, 403-408. https://doi.org/10.1002/ajh.21699

[9] Lanzkron, S., Strouse, J.J., Wilson, R., Beach, M.C., Haywood, C., Park, H., *et al.* (2008) Systematic Review: Hydroxyurea for the Treatment of Adults with Sickle Cell Disease. *Annals of Internal Medicine*, **148**, 939-955. https://doi.org/10.7326/0003-4819-148-12-200806170-00221

[10] McGann, P.T. and Ware, R.E. (2015) Hydroxyurea Therapy for Sickle Cell Anemia. *Expert Opinion on Drug Safety*, **14**, 1749-1758. https://doi.org/10.1517/14740338.2015.1088827

[11] Tshilolo, L., Tomlinson, G., Williams, T.N., Santos, B., Olupot-Olupot, P., Lane, A.,

et al. (2019) Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa. *New England Journal of Medicine*, **380**, 121-131. https://doi.org/10.1056/nejmoa1813598

[12] Opoka, R.O., Ndugwa, C.M., Latham, T.S., Lane, A., Hume, H.A., Kasirye, P., *et al.* (2017) Novel Use of Hydroxyurea in an African Region with Malaria (NOHARM): A Trial for Children with Sickle Cell Anemia. *Blood*, **130**, 2585-2593. https://doi.org/10.1182/blood-2017-06-788935

[13] John, C.C., Opoka, R.O., Latham, T.S., Hume, H.A., Nabaggala, C., Kasirye, P., *et al.* (2020) Hydroxyurea Dose Escalation for Sickle Cell Anemia in Sub-Saharan Africa. *New England Journal of Medicine*, **382**, 2524-2533. https://doi.org/10.1056/nejmoa2000146

[14] Aygun, B., Lane, A., Smart, L.R., Santos, B., Tshilolo, L., Williams, T.N., *et al.* (2024) Hydroxyurea Dose Optimisation for Children with Sickle Cell Anaemia in Sub-Saharan Africa (REACH): Extended Follow-Up of a Multicentre, Open-Label, Phase 1/2 Trial. *The Lancet Haematology*, **11**, e425-e435. https://doi.org/10.1016/s2352-3026(24)00078-4

[15] Power-Hays, A. and Ware, R.E. (2020) Effective Use of Hydroxyurea for Sickle Cell Anemia in Low-Resource Countries. *Current Opinion in Hematology*, **27**, 172-180. https://doi.org/10.1097/moh.0000000000000582

[16] Kavanagh, P.L., Fasipe, T.A. and Wun, T. (2022) Sickle Cell Disease: A Review. *JAMA*, **328**, 57-68. https://doi.org/10.1001/jama.2022.10233

[17] von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C. and Vandenbroucke, J.P. (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *The Lancet*, **370**, 1453-1457. https://doi.org/10.1016/s0140-6736(07)61602-x

[18] Platt, O.S., Thorington, B.D., Brambilla, D.J., Milner, P.F., Rosse, W.F., Vichinsky, E., *et al.* (1991) Pain in Sickle Cell Disease. Rates and Risk Factors. *New England Journal of Medicine*, **325**, 11-16. https://doi.org/10.1056/nejm199107043250103

[19] Platt, O.S., Brambilla, D.J., Rosse, W.F., Milner, P.F., Castro, O., Steinberg, M.H., *et al.* (1994) Mortality in Sickle Cell Disease—Life Expectancy and Risk Factors for Early Death. *New England Journal of Medicine*, **330**, 1639-1644. https://doi.org/10.1056/nejm199406093302303

[20] Dei-Adomakoh, Y.A., Segbefia, C.I., Latham, T.S., Lane, A.C., Dzefi-Tettey, K., Amissah-Arthur, K., *et al.* (2025) Hydroxyurea for Children and Adults with Hemoglobin SC Disease. *NEJM Evidence*, **4**, EVIDoa2400402. https://doi.org/10.1056/evidoa2400402