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Hydroxycarbamide and Sickle Cell Disease in a Context of Malaria Endemicity in Sub-Saharan Africa: Experience of the Sickle Cell Disease Center in Bamako, Mali

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Abstract

Introduction: Sickle cell disease and malaria represent both major health problems in sub-Saharan Africa. This study aims to evaluate the impact of hydroxycarbamide or hydroxyurea treatment on the incidence and time to onset of malaria in children with sickle cell disease in Mali. **Methodology:** This was a retrospective cohort study conducted at the Research and Control Center for Sickle Cell Disease (CRLD) in Bamako. It included 100 children with sickle cell disease (aged 1 to 17 years) and compared data between those treated with hydroxyurea (n = 52) and those not treated (n = 48). Follow-up started at the date of registration at the center; the event of interest was the first episode of malaria, and children without malaria were censored at their last recorded event. Log-rank tests were used for comparisons, and a Cox model was used to identify factors associated with the occurrence of malaria. **Results:** All children who did not develop malaria (31/31) were receiving hydroxyurea, while only 30% (21/69) of those who did ($p < 0.001$) were. The time to malaria onset was longer in children treated with hydroxyurea (mean: 6.9 vs. 5.0 years, $p = 0.005$). Survival analysis showed a significantly higher probability of remaining malaria-free while receiving hydroxyurea (log-rank $p < 0.0001$). Treatment reduced the instantaneous risk of malaria by 77% (adjusted HR = 0.23, 95% CI: 0.13 - 0.42). The incidence of malaria was nearly four times lower with hydroxyurea (5.2 vs. 20.1 cases/100 patient-years, a 74% reduction). A longer

duration of treatment was associated with a lower estimated risk, but no dose-effect relationship could be established, as neither the dose nor adherence was recorded. **Conclusion:** In this cohort, hydroxyurea was associated with a lower incidence of malaria and a longer time to its onset in children with sickle cell disease. Because of the observational design and the residual biases described in the manuscript, these results do not establish a causal relationship, but they support wider access to this treatment and its prospective evaluation in malaria-endemic areas.

Keywords

CRLD, Sickle Cell Disease, Hydroxyurea, Malaria

1. Introduction

Sickle cell disease, the most widespread genetic disease in the world, and malaria, a vector-borne parasitic disease, constitute a major health challenge in sub-Saharan Africa [1]. Sickle cell disease results from a mutation in the hemoglobin gene, leading to the production of abnormal hemoglobin (HbS) and red blood cell fragility, causing painful vaso-occlusive crises and chronic anemia [2]. Malaria, caused primarily by *Plasmodium falciparum*, causes cyclic fevers and can progress to severe complications. Hydroxyurea, a cytoreductive agent, is thought to increase fetal hemoglobin (HbF) levels, thereby improving hematological parameters and reducing the frequency of crises in individuals with sickle cell disease [3] [4].

From an epidemiological standpoint, the burden of these two diseases is considerable and geographically overlapping [1] [5] [6]. By 2050, the annual incidence of major sickle cell syndromes could exceed 400,000 cases, according to a 2017 study [2]. According to the World Health Organization, malaria remains a leading cause of morbidity and mortality, with an estimated 247 million cases and 619,000 deaths in 2021, nearly 96% of which occurred in Africa [7]. In Mali, the prevalence of sickle cell trait ranges from 6% to 16% depending on the region, with 10,000 to 12,000 births with sickle cell disease each year [8].

This co-occurrence generates a particularly heavy clinical burden. Children with sickle cell disease are at increased risk of developing severe forms of malaria [6] [9]. These are characterized by anemia and visceral complications, contributing to high mortality in this vulnerable population [6]. Faced with this challenge, malaria prevention strategies rely primarily on insecticide-treated bed nets and intermittent chemoprophylaxis [10]. However, the emergence of resistance and adherence problems limit their effectiveness. Hydroxyurea, by reducing the overall number of sickle cell crises and transfusion requirements, improves the general health of patients [11]-[13]. Recent data suggest that it may also exert a direct protective effect against malaria [11], thus offering an additional benefit. However, its use in Africa remains limited by constraints of access, monitoring and a lack of robust local data on its long-term effects, particularly in the context

of high malaria transmission.

These factors justify the need to evaluate the impact of hydroxyurea on malaria in real-world healthcare settings in Africa. In malaria-endemic areas like Mali, where sickle cell disease is highly morbid, it is crucial to determine whether this treatment, beyond its recognized hematological benefits, substantially modifies the risk and time to onset of malaria episodes. Such an evaluation would strengthen the arguments for wider access to this medication and guide integrated care policies for this doubly vulnerable population. This study therefore aims to analyze the association between hydroxyurea treatment and the incidence and time to onset of malaria in children with sickle cell disease followed at the Sickle Cell Disease Research and Treatment Center.

2. Methodology

2.1. Study Framework

This study was conducted at the Day Hospital of the Research and Treatment Center for Sickle Cell Disease (CRLD), a Public Scientific and Technological Establishment (EPST) located in Bamako (Point G, Commune III). The CRLD is a regional referral center that treats sickle cell disease patients not only from Mali but also from neighboring countries such as Niger, Guinea, and Mauritania. In accordance with its core missions, the center promotes scientific research, provides specialized continuing education, and ensures comprehensive care for sickle cell patients.

2.2. Type of Study and Period of Study

This was a cohort study. This approach was motivated by the need to highlight the effect of hydroxyurea treatment on the occurrence of malaria. This study focused on events (malaria, vaso-occlusive crisis) that occurred between 2019 and 2025 in patients registered between 2012 and 2024.

2.3. Study Procedure

This study took place in three phases:

Preparation phase: This step included pre-testing the questionnaire and setting up the data collection tools on REDCap.

Data collection phase: At the CRLD (Center for Research and Development in Sickle Cell Disease), patients with sickle cell disease experiencing a crisis were seen, registered, and examined through the administration of a basic questionnaire, clinical examinations, and paraclinical tests. The current study aimed to collect sociodemographic data, characteristics related to the malaria episode, follow-up time, and hydroxyurea treatment intake.

Data management phase: The collected data were recorded in REDCap to review and correct outliers. It was then exported in CSV format for transfer to the R software for analysis.

2.4. Study Population

Patients with sickle cell disease seen at the CRLD and admitted for hospitalization complaining of sickle cell pain represented our study population. Eligible children were aged 1 to 17 years, registered in the center's REDCap database and hospitalized during the study period.

2.5. Selection of the 100 Eligible Children

All children with sickle cell disease hospitalized at the day hospital during the study period for an acute event (vaso-occlusive crisis and/or clinical suspicion of malaria) were screened in the center's records. A child was eligible when the record contained, on the one hand, the result of the parasitological investigation performed for the suspected malaria episode, whether this result was positive or negative, and, on the other hand, the hydroxyurea status. The date of initiation of hydroxyurea, and therefore the duration of treatment, was documented for 38 of the 52 treated children. Children whose record contained no parasitological result, or whose hydroxyurea status was not documented, were not eligible. This procedure yielded the 100 children analyzed, including the 31 children for whom no malaria episode was confirmed during follow-up. Because eligibility required a documented parasitological result, which in practice was obtained during a hospitalization for symptoms suggestive of malaria, children followed without any hospitalization for a febrile episode were under-represented.

2.6. Inclusion Criteria

The patients included in this study were those who had been admitted for clinical symptoms suggestive of malaria.

2.7. Exclusion Criteria

Children whose medical record did not contain the result of the parasitological investigation for the suspected malaria episode, and those whose hydroxyurea status was not documented, were not included. As the study relied exclusively on the retrospective review of existing records, no eligibility criterion was based on the patient's consent.

2.8. Sampling

The sampling method was non-probability based on purposive selection. It consisted of including all hospitalized patients for whom a diagnosis of malaria was or was not confirmed, and for whom information regarding hydroxyurea treatment and its duration was known.

2.9. Variables under Study

The main variable of interest in this study was the use of hydroxyurea treatment. The independent variables considered were sociodemographic characteristics such as patient age and sex, occurrence of malaria, phenotype, number of years of

follow-up, number of years on hydroxyurea, hemoglobin and white blood cell counts.

2.10. Operational Definitions

The following variables were defined as follows within the framework of this study:

Number of years of follow-up: This variable is defined as the time elapsed between the patient's registration in the center's REDCap system and the occurrence of the last event considered by the study. This last event was malaria or vaso-occlusive crisis.

Number of years on hydroxyurea: This variable represents the duration of taking the first dose of hydroxyurea and the occurrence of the last event considered by the study.

Malaria: This referred to the diagnosis of malaria established by healthcare personnel based on a set of clinical and/or paraclinical evidence.

2.11. Origin of Follow-Up, Endpoint and Censoring

For each child, follow-up started at the date of registration at the CRLD, the date from which events are recorded in the center's REDCap database and therefore the date from which a malaria episode became observable. The event of interest was the first episode of malaria meeting the diagnostic criteria defined above. Recurrent episodes were not modelized. Children with no confirmed malaria episode were censored at the date of their last event recorded in the database, which marks the end of the period during which they were actively observed at the center. The occurrence of a vaso-occlusive crisis did not in itself terminate follow-up. It served as a marker of the last contact only for children without malaria, and only when it was the last recorded event.

2.12. Alignment between Registration and the Observation Window

Registrations extend from 2012 to 2024, whereas events were extracted for the period 2019 to 2025. For children registered before 2019, the first part of the follow-up time therefore precedes the window in which events were systematically recorded. Episodes occurring during that interval could not be identified, which may underestimate early episodes and lengthen the apparent time to the first malaria episode in these children.

2.13. Diagnostic Criteria for Malaria

To confirm malaria diagnoses in patients using their medical records, this study considered all those who presented with signs and symptoms such as fever, headache, or pallor, accompanied by positive blood smears or thick blood films. In some cases, results from malaria rapid diagnostic tests (RDTs) were also accepted for those who began their care at a community health center or local clinic.

2.14. Data Management and Analysis

After data collection, the data were transferred to RStudio (V_2026.01.2 + 392; R console V_4.5.2) for processing and analysis [14]. This involved consistency checks and age categorization. Descriptive statistics included the mean (with its standard deviation) and proportions (expressed as percentages). For inferential statistics, Pearson's chi-squared test or Fisher's exact test was used to compare proportions, and Welch's t-test was used to compare means. The Kaplan-Meier curve was used to illustrate the time to follow-up until the onset of malaria. The log-rank test was used to compare the median follow-up time between patients receiving hydroxyurea treatment and those not receiving it. The results of the multivariate analysis were presented as Hazard Ratios (HR) with their 95% confidence intervals. The significance level was set at less than 5% for the p-value. Analyses were performed on the available data, without imputation: the hemoglobin level and the white blood cell count were documented for 88 of the 100 children, and the date of initiation of hydroxyurea for 38 of the 52 treated children. The adjusted Cox model was therefore fitted on 88 children and 57 events.

Handling of exposure to hydroxyurea: in the Cox model, hydroxyurea was analyzed as a fixed covariate corresponding to the treatment status documented in the medical record. As hydroxyurea was generally started after registration at the center, the person-time accumulated before the first dose was attributed to the treated state. This allocation exposes the estimate to immortal-time bias, since a treated child must have survived and remained in follow-up until treatment was initiated. The resulting overestimation of the protective effect, and its consequences for the interpretation of the duration of treatment, are set out in the Limitations section. An analysis treating hydroxyurea as a time-dependent exposure, with the pre-treatment person-time assigned to the untreated state, is the appropriate approach for quantifying this bias.

Covariate selection and confounding: the covariates retained in the adjusted model (age group, sex, hemoglobin phenotype, hemoglobin level) were chosen a priori on the basis of their documented association with the risk and the severity of malaria in sickle cell disease and of their availability in the records. The hemoglobin level used was the steady-state value closest to and preceding the index event. In treated children, it was therefore measured while hydroxyurea was already being taken, and must be regarded as a marker partly modified by the treatment rather than as a strictly baseline covariate. The white blood cell count, which is also directly modified by hydroxyurea, was examined in the crude analysis only and was not retained in the adjusted model.

2.15. Ethical Considerations

This study was approved by the ethics committee of the CRLD and complied with the ethical standards in force. As the CRLD is a research center, patients are informed, from their first admission, that the data collected during their care may be used for research purposes; no specific approval number is issued for the ret-

rospective analysis of these anonymized routine-care data. No individual consent was sought for the present study, which relied exclusively on the review of existing records, with no contact with the patients and no additional procedure. Data confidentiality was strictly maintained through the anonymization of all personal information during analysis.

3. Results

Table 1. Description of the study population according to hydroxyurea treatment.

Features	Hydroxyurea Treatment			p
	Total	No	Yes	
	100	48	52	
Malaria	**n**	**n (%)**	**n (%)**	**<0.001**
No	31	0 (0)	31 (100)	
Yes	69	48 (70)	21 (30)	
Age groups				0.701
Under 9 years old	48	24 (50)	24 (50)	
Ages 9 and up	52	24 (46)	28 (54)	
Sex				0.573
Male	55	25 (45)	30 (55)	
Female	45	23 (51)	22 (49)	
Phenotype				**0.012**
SB°	10	5 (50)	5 (50)	
SC	13	11 (85)	2 (15)	
SS	77	32 (42)	45 (58)	
Number of years of follow-up	100	5.0 (3.1)	7.7 (2.8)	**<0.001**
Number of years of treatment with hydroxyurea	38	–	7.2 (3.0)	
Hemoglobin level (g/dl)	88	9.1 (2.1)	8.0 (1.3)	**0.008**
White blood cell count (10^3/µL)	88	12.3 (5.2)	11.1 (3.9)	0.215

Note: Continuous variables: Mean (Standard deviation); g/dL: grams per deciliter; µL: microliter. Comparisons: Pearson's chi-squared test or Fisher's exact test for proportions, Welch's t-test for means. The hemoglobin level and the white blood cell count were available for 88 of the 100 children, and the date of initiation of hydroxyurea for 38 of the 52 treated children.

The study included 100 children with sickle cell disease aged 1 to 17 years. The population was predominantly of the SS phenotype (77%), male (55%), and aged 9 years or older (52%). Malaria was documented in 69 children (69%). A difference was observed according to hydroxyurea treatment status, as all children who did not develop malaria (31/31, 100%) were receiving hydroxyurea, while only

30% (21/69) of those who experienced a malaria episode had received treatment ($p < 0.001$). The mean follow-up duration was longer in the treated group (7.7 years [SD: 2.8]) than in the untreated group (5 years [SD: 3.1], $p < 0.001$) (Table 1).

Survival analysis (Kaplan-Meier method) showed a significantly higher probability of remaining malaria-free in the hydroxyurea group (log-rank test, $p < 0.0001$). The divergence between the survival curves of the two groups appeared early and persisted throughout the follow-up (Figure 1).

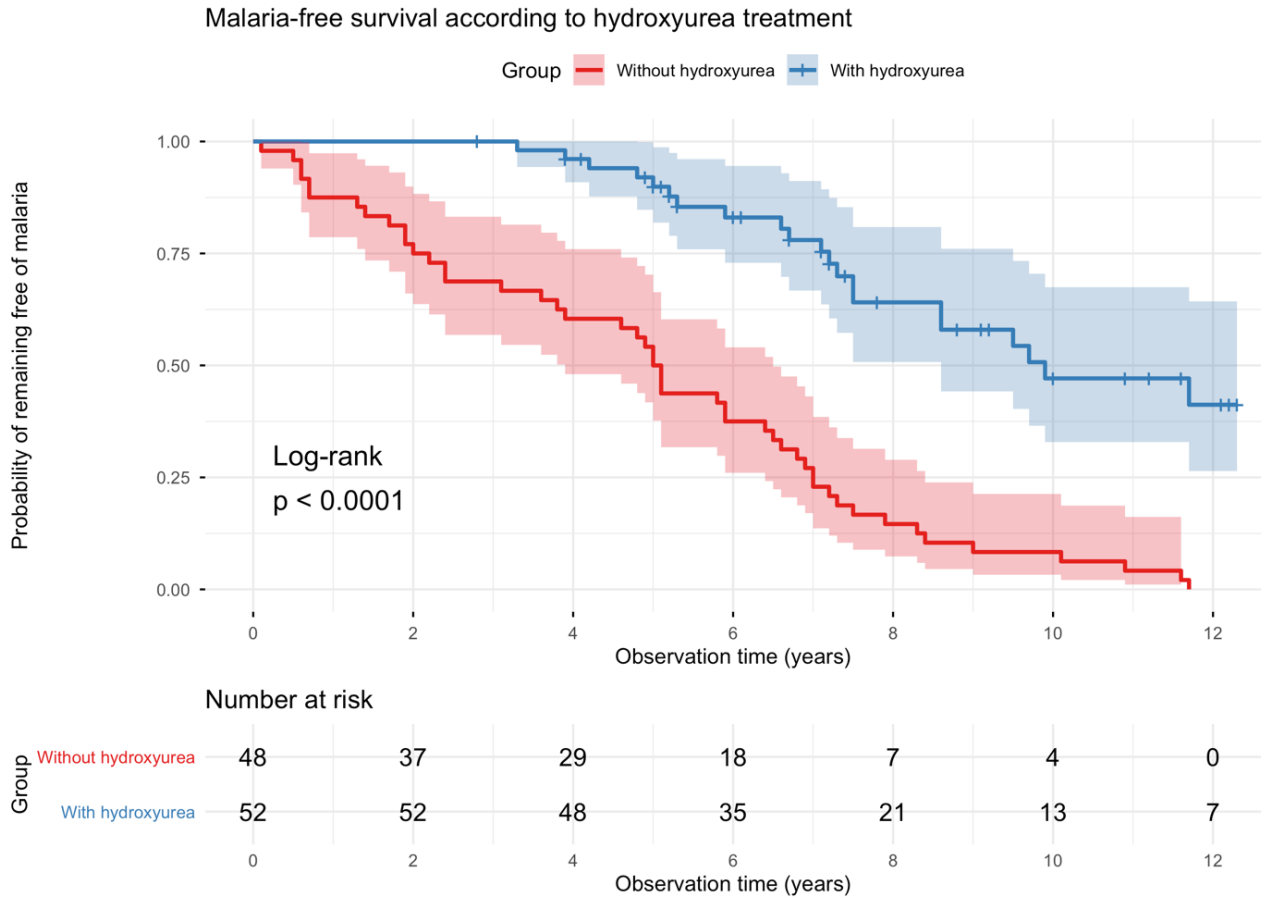


Figure 1. Variation in the probability of not contracting malaria over time.

In the crude Cox model, hydroxyurea treatment was associated with an 80% reduction in the instantaneous risk of malaria (HR = 0.20; 95% CI: 0.12 - 0.34, $p < 0.001$). This significant protective effect persisted after adjusting the model for age, sex, phenotype, and hemoglobin level (adjusted HR = 0.23; 95% CI: 0.13 - 0.42, $p < 0.001$) (Table 2). The malaria incidence rate was nearly four times lower with hydroxyurea, at 5.2 cases per 100 patient-years compared to 20.1 cases per 100 patient-years without treatment (Figure 2(A)). An inverse relationship was observed between the duration of treatment and the estimated risk of malaria, with the latter decreasing from nearly 80% to less than 20% after 10 years with hydroxyurea (Figure 2(B)).

Table 2. Factors associated with the instantaneous risk of malaria occurrence.

Factors	N = 100	Crude model			Adjusted model		
	%	HR	95% CI	p	HR	95% CI	p
Hydroxyurea							
No	48	Ref	—		Ref	—	
Yes	52	0.20	0.12 - 0.34	**<0.001**	0.23	0.13 - 0.42	**<0.001**
Sex							
Male	55	Ref	—		Ref	—	
Female	45	1.39	0.86 - 2.25	0.183	1.37	0.69 - 2.73	0.368
Age groups							
Under 9 years old	48	Ref	—		Ref	—	
Ages 9 and up	52	0.69	0.43 - 1.11	0.124	0.89	0.50 - 1.59	0.692
Phenotype							
SB°	10	Ref	—		Ref	—	
SC	13	1.54	0.62 - 3.86	0.353	0.62	0.19 - 2.05	0.431
SS	77	0.51	0.24 - 1.08	0.079	0.67	0.25 - 1.79	0.419
Hemoglobin level	8	1.40	1.17 - 1.66	**<0.001**	1.19	0.95 - 1.49	0.121
White blood cell	12	1.02	0.97 - 1.08	0.356			

Note: Abbreviations: HR = hazard ratio, CI = confidence interval. The crude models were fitted on the 100 children; the adjusted model was fitted on the 88 children with an available hemoglobin value (57 events).

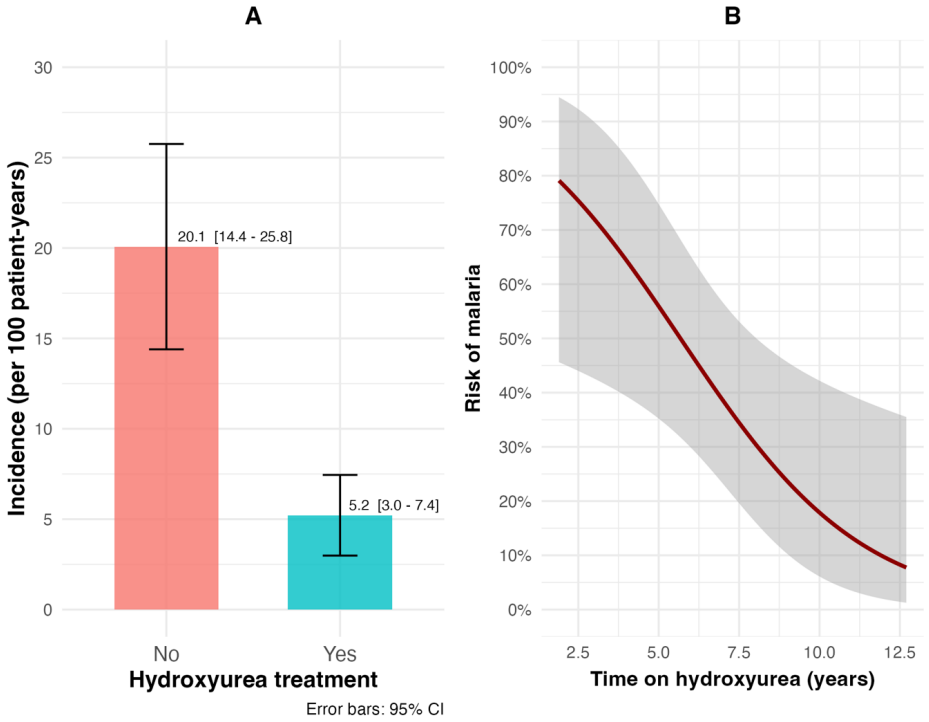


Figure 2. Malaria incidence rate according to treatment (A) and evolution of the risk of developing malaria over time (B).

Among treated children, the duration of hydroxyurea treatment was longer for those who did not develop malaria (mean: 8.2 years) than for those who did (mean: 5.6 years, p = 0.009) (Figure 3(A)). Among children who experienced an episode of malaria, the time to onset was significantly longer for those receiving hydroxyurea (mean: 6.9 years) than for those not receiving treatment (mean: 5.0 years, p = 0.005) (Figure 3(B)).

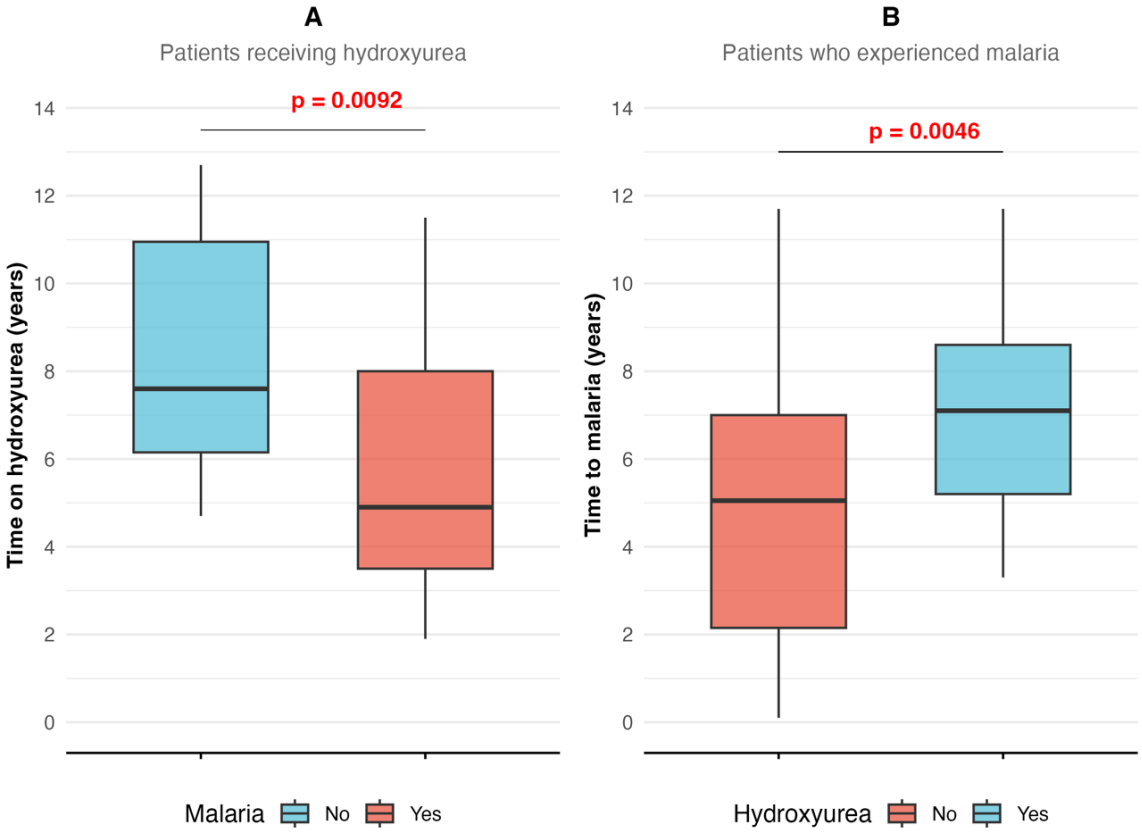


Figure 3. Duration of treatment according to malaria status (A) and Time to malaria according to treatment (B).

4. Discussion

4.1. Potential Level of Protection from Hydroxyurea Treatment

The protective effect observed in this study (77% reduction in adjusted risk, HR = 0.23) exceeds that reported in the NOHARM trial in Uganda, which documented a non-significant reduction of approximately 30% [12]. This difference may be related to the longer duration of exposure in our cohort (mean 7.2 years of treatment) and to the observational design, which, unlike a randomized trial, does not allow the effect of the treatment to be separated from the characteristics of the children who receive it. As neither the dose actually taken nor adherence was recorded, our data cannot establish a dose-effect relationship: the decrease in the estimated risk with the duration of exposure (Figure 2(B)) is descriptive and is also compatible with the fact that the children treated for the longest time are those followed most regularly. This aligns with the findings of the REACH study, which

identified a protective threshold linked to mild myelosuppression (neutrophils < 3.0×10^9/L) induced by the maximum tolerated dose [11]. As neutrophils were not measured systematically, we cannot determine whether such a degree of myelosuppression was reached in our cohort, and this mechanistic hypothesis remains untested here.

The significantly longer time to malaria onset in children treated with hydroxyurea (6.9 vs. 5.0 years) is a novel finding that goes beyond simply reducing incidence. It suggests that hydroxyurea not only creates a less conducive environment for infection but could also modify exposure dynamics or the host immune response over the long term [15]. This additional time without malaria could contribute to preserving physical and cognitive development during childhood, an outcome that was not measured in this study. This result corroborates and extends the observations of the REACH study on the durability of protection over six years [13].

Among treated children, those who did not experience malaria had been receiving hydroxyurea for longer (8.2 vs. 5.6 years). This difference in duration cannot be interpreted as a dose-effect relationship, as neither the dose nor adherence was systematically recorded and as the duration of treatment itself depends on the duration of follow-up and on the regularity of attendance at the center. It remains compatible with the hypothesis of a benefit of early initiation and of sustained treatment, which only a prospective study could confirm.

4.2. Early and Widespread Initiation of Hydroxyurea

The 74% reduction in incidence observed (5.2 vs. 20.1 cases/100 patient-years) is of a magnitude that could modify the benefit-risk balance of the treatment in malaria-endemic areas. Hydroxyurea should no longer be considered solely as a preventive treatment for vaso-occlusive complications, but also as a treatment whose possible contribution to reducing the burden of malaria deserves to be evaluated in its own right, this observational study not being sufficient to establish it as a chemoprevention strategy [4]. Our data support recent recommendations advocating its initiation at a very young age, as soon as a diagnosis of sickle cell disease (SS) is confirmed [11] [12]. Treatment of children with hydroxyurea should be integrated into standard care packages for sickle cell disease, alongside antibiotic prophylaxis and vaccination. The longer time to onset of malaria observed in this cohort could, if confirmed, make it possible to postpone exposure until an age at which children are less vulnerable.

4.3. Hypotheses Regarding Mortality and Development

Neither mortality nor cognitive development was assessed in this study, and our results allow no conclusion to be drawn on these outcomes. By reducing the frequency of malaria episodes and of the associated acute anemia, hydroxyurea could nevertheless contribute to reducing infant mortality related to sickle cell disease in Africa, as suggested by the REACH data on overall mortality [9] [11]. A pro-

tective effect against repeated infections could likewise benefit academic and cognitive development. These two hypotheses require specific evaluation and were not tested here.

4.4. Limitations of the Study and Future Directions

The observational design of this study does not allow for the establishment of a causal relationship. Several limitations must be taken into account when interpreting the magnitude of the association. Eligibility required a documented parasitological result, which in practice was obtained during a hospitalization for symptoms suggestive of malaria. Untreated children who were not hospitalized for a febrile episode were therefore less likely to be included, which may have accentuated the contrast between the two groups and inflated the estimated effect. Hydroxyurea was also analyzed as a fixed exposure, with the person-time preceding the first dose attributed to the treated state, which exposes the estimate to immortal-time bias and calls for caution in interpreting the relationship between the duration of treatment and the risk of malaria. Follow-up time was counted from registration at the center, whereas events were extracted only from 2019 onwards, so that episodes occurring before that date in children registered earlier could not be identified. Finally, several factors that were not documented in the records (adherence to intermittent preventive treatment and to insecticide-treated nets, intensity of local transmission, severity of the disease before the initiation of treatment, socio-economic level and access to care) leave residual confounding possible, and the hemoglobin level used for adjustment was measured under treatment in treated children. The lack of systematic data on treatment adherence, the exact dose of hydroxyurea, and biological parameters such as neutrophil count or fetal hemoglobin levels limits the analysis of the underlying mechanisms. The single-center design may limit the extrapolation of the results, even though the study population came from several countries.

Multicenter trials, including regular laboratory measurements, would be necessary to confirm these results and elucidate the precise mechanisms (immunomodulation, effect on iron, alteration of the erythrocyte cycle). Cost-effectiveness trials evaluating the impact of expanded access to hydroxyurea on malaria-related mortality in this population would also be warranted. An analysis treating hydroxyurea as a time-dependent exposure, together with the prospective recording of the dose, adherence and markers of myelosuppression, would also make it possible to separate more clearly the effect of the treatment from that of the characteristics of the children who receive it.

5. Conclusion

In conclusion, our study shows an association between hydroxyurea treatment and both a lower incidence of malaria and a longer time to its onset in children with sickle cell disease. Given its observational design and the limitations described above, this study does not establish a causal relationship and does not al-

low a benefit in terms of mortality or of neurocognitive development to be attributed to hydroxyurea. These results nevertheless support improving access to hydroxyurea for children with sickle cell disease living in malaria-endemic areas and justify a prospective evaluation of the extent of the protection observed.

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Author Contributions

AG, YSS and MMK designed the study protocol. MK, BAT, DSB, SK, EHSD, DD, MO, YF and MC managed the patients and assisted with data collection. MMK conducted the statistical analyses and assisted with manuscript preparation. AG and YSS 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] Williams, T.N. and Obaro, S.K. (2011) Sickle Cell Disease and Malaria Morbidity: A Tale with Two Tails. *Trends in Parasitology*, **27**, 315-320. https://doi.org/10.1016/j.pt.2011.02.004

[2] 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

[3] Ware, R.E. (2010) How I Use Hydroxyurea to Treat Young Patients with Sickle Cell Anemia. *Blood*, **115**, 5300-5311. https://doi.org/10.1182/blood-2009-04-146852

[4] Pasvol, G., Weatherall, D.J. and Wilson, R.J.M. (1977) Effects of Foetal Haemoglobin on Susceptibility of Red Cells to Plasmodium Falciparum. *Nature*, **270**, 171-173. https://doi.org/10.1038/270171a0

[5] Uyoga, S., Macharia, A.W., Mochamah, G., Ndila, C.M., Nyutu, G., Makale, J., *et al.* (2019) The Epidemiology of Sickle Cell Disease in Children Recruited in Infancy in Kilifi, Kenya: A Prospective Cohort Study. *The Lancet Global Health*, **7**, e1458-e1466. https://doi.org/10.1016/s2214-109x(19)30328-6

[6] McAuley, C.F., Webb, C., Makani, J., Macharia, A., Uyoga, S., Opi, D.H., *et al.* (2010)

High Mortality from Plasmodium Falciparum Malaria in Children Living with Sickle Cell Anemia on the Coast of Kenya. *Blood*, **116**, 1663-1668. https://doi.org/10.1182/blood-2010-01-265249

[7] World Health Organization (2022) World Malaria Report. 372 p. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022

[8] Guindo, A., Cisse, Z., Keita, I., Desmonde, S., Sarro, Y.D.S., Touré, B.A., *et al.* (2024) Potential for a Large-Scale Newborn Screening Strategy for Sickle Cell Disease in Mali: A Comparative Diagnostic Performance Study of Two Rapid Diagnostic Tests (Sicklescan® and Hemotypesc®) on Cord Blood. *British Journal of Haematology*, **204**, 337-345. https://doi.org/10.1111/bjh.19108

[9] Ranque, B., Kitenge, R., Ndiaye, D.D., Ba, M.D., Adjoumani, L., Traore, H., *et al.* (2022) Estimating the Risk of Child Mortality Attributable to Sickle Cell Anaemia in Sub-Saharan Africa: A Retrospective, Multicentre, Case-Control Study. *The Lancet Haematology*, **9**, e208-e216. https://doi.org/10.1016/s2352-3026(22)00004-7

[10] Kajubi, R., Ochieng, T., Kakuru, A., Jagannathan, P., Nakalembe, M., Ruel, T., *et al.* (2019) Monthly Sulfadoxine-Pyrimethamine versus Dihydroartemisinin-Piperaquine for Intermittent Preventive Treatment of Malaria in Pregnancy: A Double-Blind, Randomised, Controlled, Superiority Trial. *The Lancet*, **393**, 1428-1439. https://doi.org/10.1016/s0140-6736(18)32224-4

[11] Olupot-Olupot, P., Tomlinson, G., Williams, T.N., Tshilolo, L., Santos, B., Smart, L.R., *et al.* (2023) Hydroxyurea Treatment Is Associated with Lower Malaria Incidence in Children with Sickle Cell Anemia in Sub-Saharan Africa. *Blood*, **141**, 1402-1410. https://doi.org/10.1182/blood.2022017051

[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] McGann, P.T., Williams, T.N., Olupot-Olupot, P., Tomlinson, G.A., Lane, A., Luís Reis da Fonseca, J., *et al.* (2018) Realizing Effectiveness across Continents with Hydroxyurea: Enrollment and Baseline Characteristics of the Multicenter REACH Study in Sub-Saharan Africa. *American Journal of Hematology*, **93**, 537-545. https://doi.org/10.1002/ajh.25034

[14] R Core Team (n.d.) The R Project for Statistical Computing. https://www.R-project.org/

[15] Pino, P., Taoufiq, Z., Brun, M., Tefit, M., Franetich, J.F., Ciceron, L., *et al.* (2006) Effects of Hydroxyurea on Malaria, Parasite Growth and Adhesion in Experimental Models. *Parasite Immunology*, **28**, 675-680. https://doi.org/10.1111/j.1365-3024.2006.00907.x