

ORIGINAL ARTICLE

Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa

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ABSTRACT

BACKGROUND

Hydroxyurea is an effective treatment for sickle cell anemia, but few studies have been conducted in sub-Saharan Africa, where the burden is greatest. Coexisting conditions such as malnutrition and malaria may affect the feasibility, safety, and benefits of hydroxyurea in low-resource settings.

METHODS

We enrolled children 1 to 10 years of age with sickle cell anemia in four sub-Saharan countries. Children received hydroxyurea at a dose of 15 to 20 mg per kilogram of body weight per day for 6 months, followed by dose escalation. The end points assessed feasibility (enrollment, retention, and adherence), safety (dose levels, toxic effects, and malaria), and benefits (laboratory variables, sickle cell–related events, transfusions, and survival).

RESULTS

A total of 635 children were fully enrolled; 606 children completed screening and began receiving hydroxyurea at a mean ($\pm$ SD) dose of 17.5 ± 1.8 mg per kilogram per day. The retention rate was 94.2% at 3 years of treatment. Hydroxyurea therapy led to significant increases in both the hemoglobin and fetal hemoglobin levels. Dose-limiting toxic events regarding laboratory variables occurred in 5.1% of the participants, which was below the protocol-specified threshold for safety. During the treatment phase, 20.6 dose-limiting toxic effects per 100 patient-years occurred, as compared with 20.7 events per 100 patient-years before treatment. As compared with the pretreatment period, the rates of clinical adverse events decreased with hydroxyurea use, including rates of vaso-occlusive pain (98.3 vs. 44.6 events per 100 patient-years; incidence rate ratio, 0.45; 95% confidence interval [CI], 0.37 to 0.56), non-malaria infection (142.5 vs. 90.0 events per 100 patient-years; incidence rate ratio, 0.62; 95% CI, 0.53 to 0.72), malaria (46.9 vs. 22.9 events per 100 patient-years; incidence rate ratio, 0.49; 95% CI, 0.37 to 0.66), transfusion (43.3 vs. 14.2 events per 100 patient-years; incidence rate ratio, 0.33; 95% CI, 0.23 to 0.47), and death (3.6 vs. 1.1 deaths per 100 patient-years; incidence rate ratio, 0.30; 95% CI, 0.10 to 0.88).

CONCLUSIONS

Hydroxyurea treatment was feasible and safe in children with sickle cell anemia living in sub-Saharan Africa. Hydroxyurea use reduced the incidence of vaso-occlusive events, infections, malaria, transfusions, and death, which supports the need for wider access to treatment. (Funded by the National Heart, Lung, and Blood Institute and others; REACH ClinicalTrials.gov number, NCT01966731.)

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SICKLE HEMOGLOBINOPATHIES ARE COMMON and life-threatening genetic disorders. Homozygous hemoglobin S (HbSS) is the most severe genotype, and together with hemoglobin S β^0 thalassemia, is called sickle cell anemia.¹ On deoxygenation, erythrocytes become sickle-shaped, rigid, adhesive, and prone to lysis; blood flow is blocked within small vessels, leading to ischemic tissue injury.¹ In the United States, approximately 100,000 persons are affected,² most of whom have numerous acute and chronic medical complications that lead to poor quality of life and early death.^{1,3} On a global scale, the incidence of sickle hemoglobinopathies is greatest in sub-Saharan Africa, with more than 300,000 babies with sickle cell disease born annually, representing approximately 1% of births in the region.⁴

In high-resource settings such as the United States and Europe, as well as Jamaica and other Caribbean settings, the early identification of children with sickle cell anemia by means of neonatal screening allows for comprehensive care that includes simple, effective, and lifesaving interventions with penicillin prophylaxis, pneumococcal immunizations, and caregiver education.⁵⁻⁷ The advent of routine transcranial Doppler screening to identify children at risk for stroke, along with access to safe erythrocyte transfusions, has further contributed to marked decreases in morbidity.⁸ To date, however, very few settings in sub-Saharan Africa have established screening programs for sickle cell anemia, and specialized treatment is available at only a few large, urban centers.

Hydroxyurea was first shown to induce fetal hemoglobin production more than 30 years ago⁹ and is now a Food and Drug Administration–approved treatment for sickle cell anemia in both children (Siklos, Addmedica) and adults (Hydrea and Droxia, Bristol-Myers Squibb). By means of the induction of fetal hemoglobin and other beneficial changes, including mild myelosuppression, hydroxyurea therapy has been shown to have clinical efficacy in reducing the incidence of acute vaso-occlusive events,^{10,11} ameliorating chronic organ damage,¹² and prolonging survival.^{13,14} Evidence-based guidelines from the National Heart, Lung, and Blood Institute recommend offering hydroxyurea treatment to persons with sickle cell anemia as early as 9 months of age.¹⁵

Whether hydroxyurea will be safe and effective in Africa is unclear. Coexisting conditions such as malaria, other infectious diseases that are endemic to the area, and malnutrition may

increase the incidence of toxic effects and limit treatment responses. We conducted an international trial, Realizing Effectiveness across Continents with Hydroxyurea (REACH), to investigate the feasibility, safety, and benefits of hydroxyurea treatment for children with sickle cell anemia living in sub-Saharan Africa.

METHODS

TRIAL DESIGN

We designed this phase 1–2, open-label, international trial to assess the feasibility, safety, and benefits of hydroxyurea treatment in young children with sickle cell anemia living in sub-Saharan Africa. The two-stage trial design has been described previously¹⁶ and included a built-in pause in enrollment to ensure the safety of the initial dose level (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Children 1 to 10 years of age were recruited at four clinical trial sites in sub-Saharan Africa (Hospital Pediátrico David Bernardino in Luanda, Angola; Centre Hospitalier Monkole in Kinshasa, Democratic Republic of Congo; Kilifi District Hospital in Kilifi, Kenya; and Mbale Regional Referral Hospital in Mbale, Uganda), with a goal of treating 150 participants per site with once-daily oral hydroxyurea. At each site, enrollment was paused to allow for the evaluation of the 3-month incidence of hematologic toxic effects among the first 53 participants enrolled.¹⁶

The protocol (available at NEJM.org) was designed by the authors and approved by all appropriate institutional review boards or ethics committees, as well as by national regulatory groups. A parent or legal guardian provided written informed consent for each participant to enroll and begin the screening process. A full list of the investigative teams, including the physicians, nurses, pharmacists, and laboratory and data personnel who received specific protocol training, is provided in the Supplementary Appendix. Local trial teams collected the data, which were monitored and analyzed by the data management center. The first draft of the manuscript was written by the first and last authors, with contributions by all the authors. All the authors made the decision to submit the manuscript for publication. The sponsors had no oversight or involvement in data collection and analysis or in the writing and submission of the manuscript. The last author vouches for the accuracy and com-

pleteness of the data and for the fidelity of the trial to the protocol.

DRUG TREATMENT AND DOSE ESCALATION

Hydroxyurea capsules were donated by Bristol-Myers Squibb, which had no role in the trial design or conduct, the data collection or analysis, or the manuscript preparation or review. After a 2-month screening period that was used to collect pretreatment clinical and laboratory data, the starting dose of hydroxyurea was 15 to 20 mg per kilogram of body weight per day. After 6 months of treatment, the hydroxyurea dose was escalated by 2.5 to 5.0 mg per kilogram per day every 2 months on the basis of peripheral-blood counts to determine a maximum tolerated dose, which was defined as a stable daily dose that caused mild bone marrow suppression without toxic effects — typically, an absolute neutrophil count of less than 4000 per cubic millimeter. To ensure the safety of the participants, the dose level was monitored at each visit by trial staff, who entered the results of the complete blood count and reticulocyte count into an interactive online calculator tool before the drug was dispensed.

END POINTS

The primary safety end point was hematologic dose-limiting toxic effects in the first 3 months of hydroxyurea treatment in the first 133 children enrolled at each clinical trial site; the expected and allowable rates of this end point were 20% and 30%, respectively, on the basis of published toxicity data, with type I and II error rates of 10%.¹⁶ Protocol-specified thresholds for toxic effects involving laboratory variables included a hemoglobin level of less than 4.0 g per deciliter, an absolute neutrophil count of less than 1000 per cubic millimeter, an absolute reticulocyte count of less than 80,000 per cubic millimeter unless the hemoglobin level was more than 7.0 g per deciliter, and a platelet count of less than 80,000 per cubic millimeter. Additional trial end points included assessments of feasibility (enrollment, retention, and adherence), safety (dose levels, toxic effects, and malaria), and benefits (laboratory variables, sickle cell–related events, transfusions, and survival).

DATA COLLECTION AND STORAGE

All the trial data were collected and entered into a REDCap Internet-based data-capture system. Separate REDCap environments were developed in English, Portuguese, and French, which were

the official languages at each clinical site.¹⁶ Data on clinical adverse events of grade 2 or higher were collected during both the screening (pretreatment) phase and the treatment phase. Trial monitoring used a remote system and on-site evaluations. Data on adverse events were collected and curated, with review of source documentation whenever available. Deaths were further evaluated with the use of the World Health Organization (WHO) verbal autopsy form that has previously been validated for children with sickle cell anemia.¹⁷

STATISTICAL ANALYSIS

The Simon two-stage design for the primary safety end point (hematologic dose-limiting toxic effects in the first 3 months of hydroxyurea treatment) has been described previously.¹⁶ Secondary end points regarding feasibility, safety, and benefits were summarized with means and standard deviations or percentages, as appropriate. We used a competing-risk approach to estimate the cumulative incidence of death or withdrawal. Laboratory values at baseline and at 12 months were compared by Student's *t*-test. Rates of clinical adverse events during the pretreatment phase and during the treatment phase were presented as the number of events per 100 patient-years and compared by the incidence rate ratio with 95% confidence intervals, all of which were calculated from Poisson regression with the use of generalized estimating equations to account for clustering and overdispersion. A similar approach was used to show the effect of increasing treatment duration, with events and time at risk during treatment divided into consecutive 6-month intervals. There were no adjustments for multiple comparisons. All the statistical analyses were performed with the use of R software, version 3.4.4.

RESULTS

ENROLLMENT AND RETENTION

All four trial sites proceeded to the second stage of the trial and met their enrollment goals. A total of 635 children had consent provided by a parent or guardian and entered screening, 606 children completed screening and began receiving hydroxyurea treatment, and 600 children (99.0%) completed 3 months of the trial treatment (Fig. 1). The overall retention rate in the trial was 94.2% at 3 years of treatment (Fig. 2). A total of 33 children (5.4%) withdrew from the trial after treatment initiation. More than 98% of the trial visits were

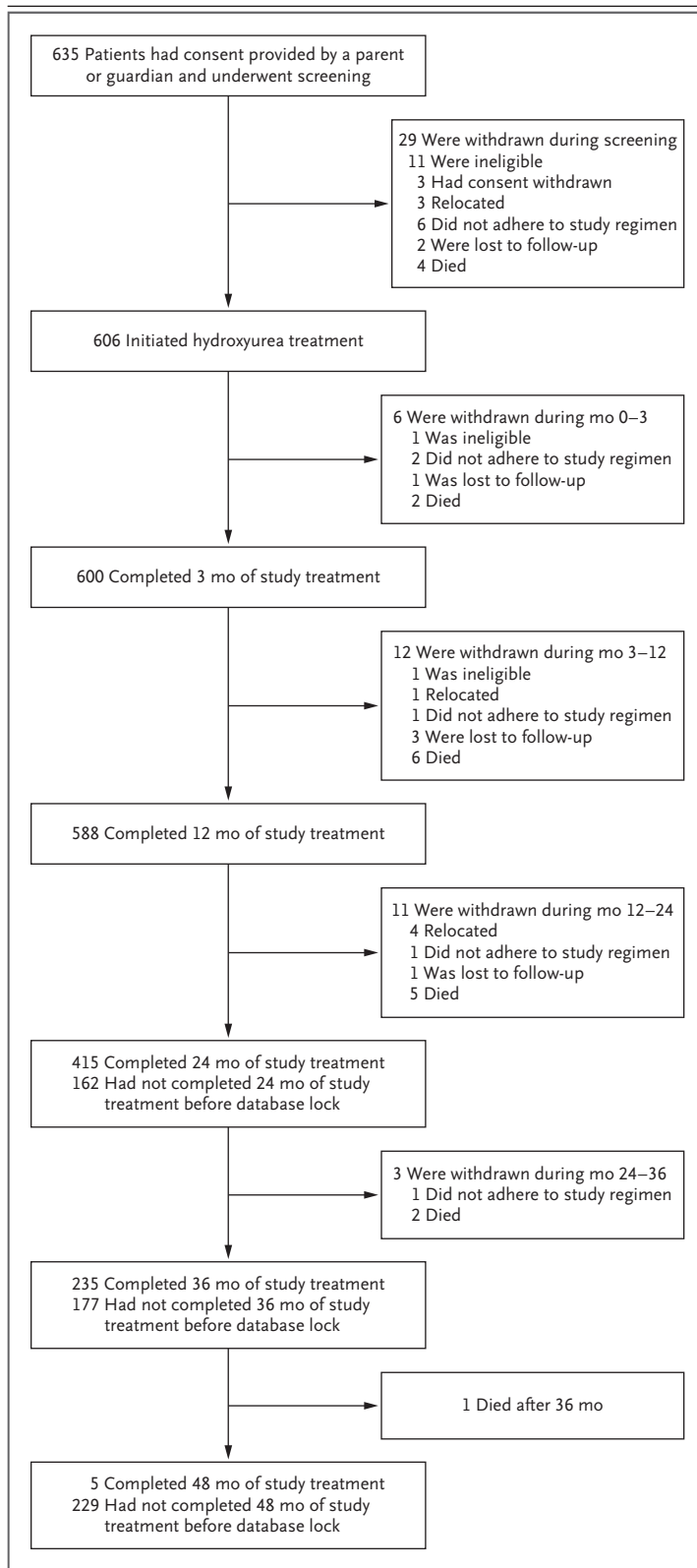


Figure 1. Screening, Enrollment, and Follow-up of the Participants.

The numbers of patients who withdrew from the trial or died are from the group of patients who completed treatment up to the respective time point.

completed, including 91% within the scheduled visit window.

HYDROXYUREA DOSE

The initial mean ($\pm$ SD) dose of hydroxyurea that was administered was 17.5 ± 1.8 mg per kilogram per day, which was within the protocol-directed starting dose range of 15 to 20 mg per kilogram per day. The initial dose was fixed for 6 months in all the participants to allow for the assessment of laboratory and clinical adverse events. Dose escalation began at month 6, and to date, 515 children (85.0%) have reached a mean maximum tolerated dose of 22.5 ± 4.9 mg per kilogram per day, with the dose ranging from 18.9 ± 4.2 mg per kilogram per day in Angola to 25.3 ± 4.8 mg per kilogram per day in Uganda. The mean time to reaching the maximum tolerated dose was 11 ± 4 months, and the mean overall treatment duration was 29 ± 9 months. The rate of adherence to medication was assessed at each scheduled visit, and more than 90% of assessments documented no missed doses. A brief drug shortage between February and April 2016 affected the administration of the medication at three sites but had no influence on the primary end point (Table S1 in the Supplementary Appendix).

ADVERSE EVENTS

Laboratory monitoring at scheduled visits and at unscheduled visits for illness identified dose-limiting toxic effects during the screening phase (a total of 2012 complete blood counts were performed over a period of 111 patient-years) and during the treatment phase (a total of 13,589 complete blood counts were performed over a period of 1469 patient-years). Hematologic dose-limiting toxic effects during the first 3 months (the primary safety end point) occurred in 5.1% of the participants overall, with the rate at each site being well below the protocol-specified thresholds for toxic events regarding laboratory variables. The rates of these safety events differed across sites, ranging from

0.8% to 8.3% ($P=0.01$ by Fisher's exact test) (Table S2 in the Supplementary Appendix), and the random-effects pooled estimate was 4.5% (95% confidence interval [CI], 2.3 to 8.8). No significant differences between the screening and treatment phases were found with regard to the individual laboratory toxic-effect variables (Table 1), but slight differences were noted between sites (data not shown).

LABORATORY BENEFITS

Laboratory variables at baseline revealed anemia with expected leukocytosis and reticulocytosis (Table 2). After 1 year of hydroxyurea treatment, the participants had significant increases in the hemoglobin level (increase of 1.0 g per deciliter; 95% CI, 0.8 to 1.0), the mean corpuscular volume (increase of 13 fL; 95% CI, 12 to 13), and the fetal hemoglobin level (increase of 12.5%; 95% CI, 11.8 to 13.1). During hydroxyurea treatment, the white-cell count, absolute neutrophil count, and absolute reticulocyte count significantly decreased, reflecting the intended mild bone marrow suppression, and these effects were sustained over time (Table 2). Similar results were recorded at each individual clinical trial site (data not shown).

CLINICAL BENEFITS

Comparison of event rates between the screening and treatment phases revealed significant reductions in the incidence of all clinical adverse events (308.4 vs. 170.7 events per 100 patient-years; incidence rate ratio, 0.54; 95% CI, 0.48 to 0.62) and serious adverse events (10.8 vs. 4.4 events per 100 patient-years; incidence rate ratio, 0.47; 95% CI, 0.25 to 0.90) during hydroxyurea treatment. The investigators did not consider any of the adverse events or serious adverse events to be related to hydroxyurea treatment.

The overall rate of sickle cell–related events was significantly reduced (114.5 vs. 53.0 events per 100 patient-years; incidence rate ratio, 0.47; 95% CI, 0.38 to 0.57), and the rates of vaso-occlusive pain and the acute chest syndrome were both reduced (Table 1). The rates of infection also declined, including rates of nonmalaria infection (142.5 vs. 90.0 events per 100 patient-years; incidence rate ratio, 0.62; 95% CI, 0.53 to 0.72) and severe infection of grade 3 or higher (28.9 vs. 8.0 events per 100 patient-years; incidence rate ratio, 0.28; 95% CI, 0.19 to 0.42).

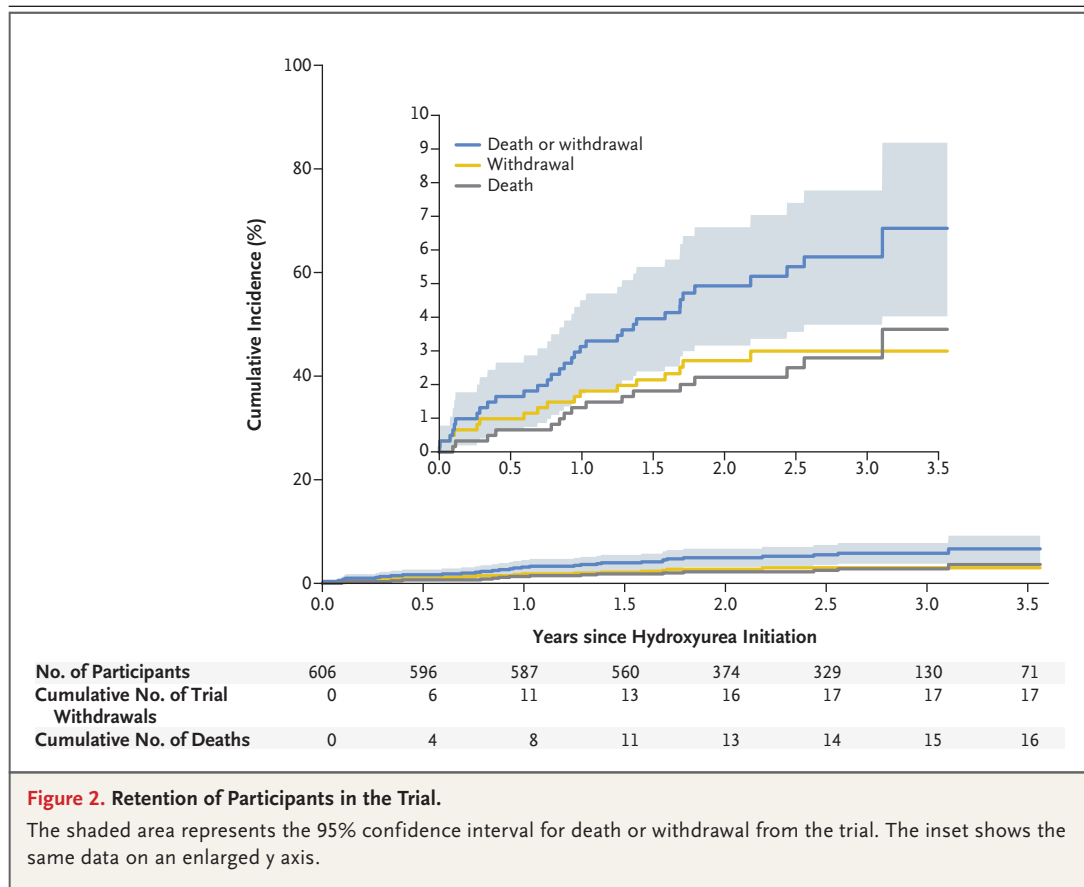
EFFECTS ON SURVIVAL

Analyses of additional key clinical events revealed significant reductions during hydroxyurea treatment in the rate of malaria infections (46.9 vs. 22.9 events per 100 patient-years; incidence rate ratio, 0.49; 95% CI, 0.37 to 0.66), blood transfusion (43.3 vs. 14.2 events per 100 patient-years; incidence rate ratio, 0.33; 95% CI, 0.23 to 0.47), and death (3.6 vs. 1.1 events per 100 patient-years; incidence rate ratio, 0.30; 95% CI, 0.10 to 0.88). When grouped into 6-month time intervals, the rates of multiple life-threatening clinical events declined rapidly after the initiation of hydroxyurea therapy and dose escalation, with a sustained or improved benefit. Reductions in event rates over time were noted for all sickle cell–related clinical events, malaria, vaso-occlusive pain, transfusion, the acute chest syndrome, and death from any cause (Fig. 3).

DISCUSSION

In this trial involving children with sickle cell anemia living in sub-Saharan Africa, we found that hydroxyurea treatment was feasible, reasonably safe, and had both laboratory and clinical benefits. Specifically, as compared with pretreatment rates, the rates of clinical events, including vaso-occlusive pain, infection, malaria, transfusion, and death, declined after 1 year of hydroxyurea treatment.

Enrollment was robust at all the clinical trial sites, with enthusiasm and support from local clinical research teams and populations of patients, which showed the feasibility of conducting a large-scale clinical trial in sub-Saharan Africa. Hematologic dose-limiting toxic effects during the first 3 months of treatment (the primary safety end point) occurred in only a small number of participants, and the hydroxyurea dose was then safely escalated toward a maximum tolerated dose, similar to treatment protocols in the United States.¹⁵ Expected hematologic benefits occurred, with significant increases in the hemoglobin and fetal hemoglobin levels. Significant reductions were observed in the incidence rates of sickle cell–related clinical events, including vaso-occlusive pain, and major clinical events including infection, malaria, transfusion, and death. No serious adverse events or deaths were considered by the investigators to be related to hydroxyurea treatment (Tables S3 and S4 in the Supplementary Appendix).



In the United States and Europe, hydroxyurea has emerged as a potent, disease-modifying therapy with regulatory approvals for use in both children and adults. Although the primary mode of action of hydroxyurea is through the induction of fetal hemoglobin, this drug has multiple salutary effects on erythrocytes, leukocytes, and even endothelium that make it a beneficial oral treatment for this life-threatening disease, especially at the maximum tolerated dose.¹⁸ The WHO includes hydroxyurea on its Model Lists of Essential Medicines for children and adults for the treatment of sickle hemoglobinopathies,^{19,20} which provides an impetus for widespread use on a global scale. To date, however, few studies have been completed in sub-Saharan Africa or other low-income settings where the burden of sickle cell disease is greatest.²¹ In addition to several small studies of hydroxyurea conducted in Nigeria,²²⁻²⁴ the Novel Use of Hydroxyurea in an African Region with Malaria (NOHARM) trial was a randomized, double-blinded, placebo-controlled trial that was conducted at a single, large, urban site in Uganda,

which showed that the rates of malaria were not higher with hydroxyurea than with placebo.²⁵ However, the overall incidence of malaria in the NOHARM trial was very low, whereas the participants in the REACH trial lived in urban and rural areas of Africa that have a much higher incidence of malaria than Kampala, Uganda, where the NOHARM trial was conducted.

With full enrollment, high rates of adherence to trial visits and medication use, and a retention rate of nearly 95% in the trial over a period of 3 years, our trial showed that hydroxyurea treatment was both feasible and safe in sub-Saharan Africa. Despite frequent laboratory monitoring, dose-limiting toxic effects were uncommon in the first 3 months of treatment, and then the incidence did not increase further (Table 1). After 6 months of fixed-dose hydroxyurea therapy, dose escalation was not associated with unacceptable side effects or with toxic effects regarding laboratory variables and reached daily doses that were similar to those reported in the United States.^{26,27} Our results indicate that a daily dose of approximately

Table 1. Laboratory and Clinical Adverse Events.*

Event	Screening Phase			Treatment Phase			Incidence Rate Ratio (95% CI)
	No. of Events	No. of Participants	Rate <i>no. of events per 100 patient-yr</i>	No. of Events	No. of Participants	Rate <i>no. of events per 100 patient-yr</i>	
Dose-limiting toxic effect	23	20	20.7	302	159	20.6	1.00 (0.62–1.61)
Anemia	8	8	7.2	86	61	5.9	0.82 (0.40–1.71)
Reticulocytopenia	3	3	2.7	72	61	4.9	1.82 (0.58–5.68)
Neutropenia	1	1	0.9	48	40	3.3	3.59 (0.50–25.71)
Thrombocytopenia	11	11	9.9	96	61	6.5	0.66 (0.34–1.25)
Clinical adverse event	342	234	308.4	2507	527	170.7	0.54 (0.48–0.62)
Grade 2	293	212	264.2	2354	513	160.2	0.60 (0.52–0.68)
Grade 3	48	43	43.3	150	112	10.2	0.24 (0.17–0.33)
Grade 4	1	1	0.9	3	3	0.2	0.23 (0.02–2.18)
Serious adverse event	12	12	10.8	65	58	4.4	0.47 (0.25–0.90)
Grade 3	8	8	7.2	24	23	1.6	0.23 (0.10–0.51)
Grade 4	0	0	0.0	25	21	1.7	NA
Grade 5 (death)	4	4	3.6	16	16	1.1	0.30 (0.10–0.88)
Clinical sickle cell–related event	127	107	114.5	779	359	53.0	0.47 (0.38–0.57)
Vaso-occlusive pain or dactylitis	109	92	98.3	655	323	44.6	0.45 (0.37–0.56)
Acute chest syndrome or pneumonia	10	10	9.0	73	56	5.0	0.55 (0.28–1.05)
Acute splenic sequestration	2	2	1.8	16	12	1.1	0.60 (0.13–2.75)
Stroke	2	2	1.8	11	10	0.7	0.42 (0.10–1.67)
Other sickle cell–related event	3	3	2.7	15	13	1.0	0.38 (0.11–1.34)
Any event of grade ≥3	26	23	23.4	104	85	7.1	0.30 (0.19–0.48)
Additional clinical events							
Malaria	52	50	46.9	336	200	22.9	0.49 (0.37–0.66)
Nonmalaria infection	158	138	142.5	1322	429	90.0	0.62 (0.53–0.72)
Any infection of grade ≥3	32	31	28.9	118	96	8.0	0.28 (0.19–0.42)
Septicemia	16	15	14.4	37	34	2.5	0.18 (0.09–0.32)
Transfusion	48	43	43.3	209	149	14.2	0.33 (0.23–0.47)

* The screening phase included 111 patient-years, and the treatment phase 1469 patient-years. The confidence intervals were not adjusted for multiple comparisons. NA denotes not applicable.

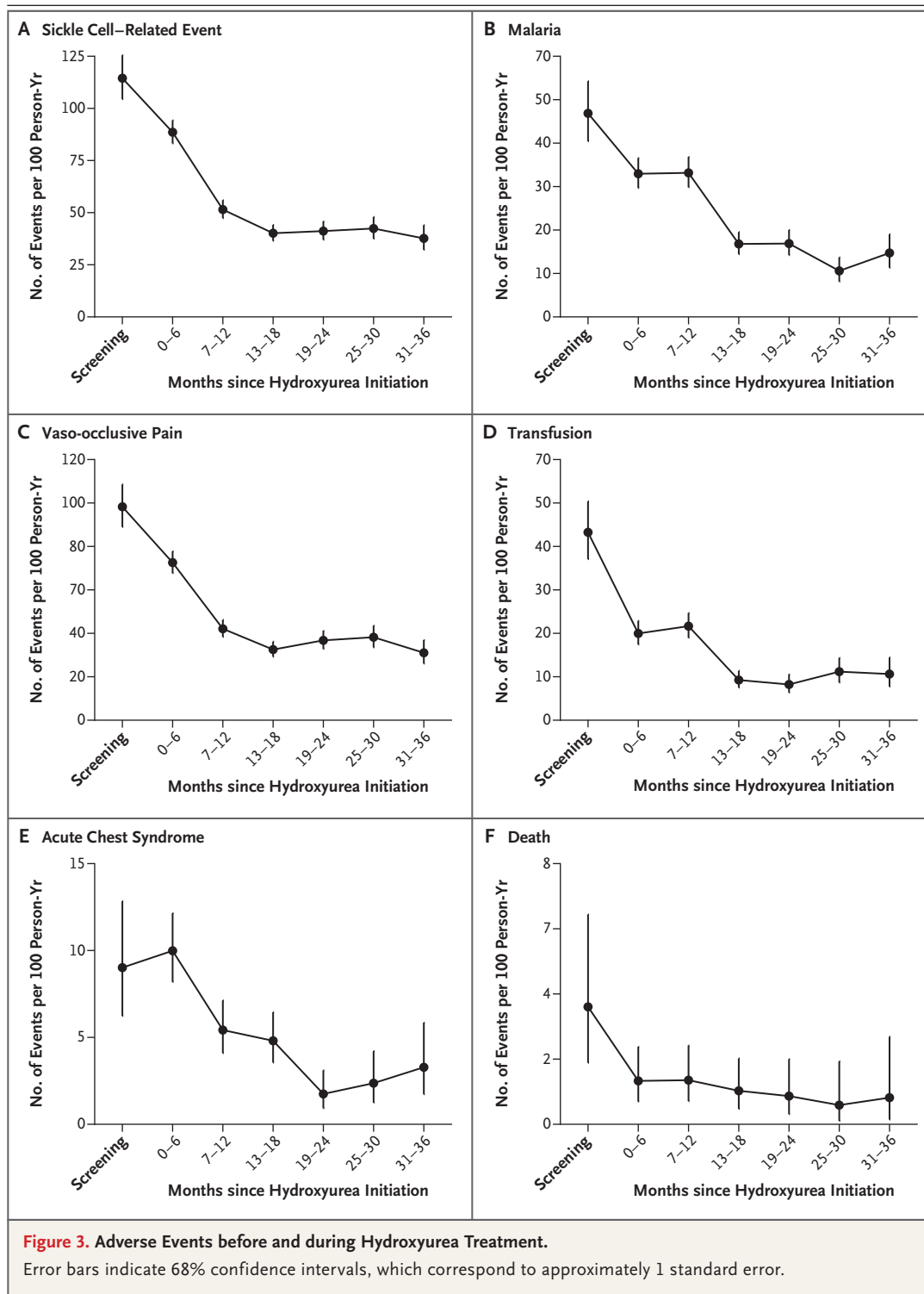
Table 2. Laboratory Effects of Hydroxyurea Treatment during the Trial.*

Variable	Month 0	Month 3	Month 6	Month 12	Month 24	Month 36	Change from Month 0 to 12 (95% CI)†
Hemoglobin (g/dl)	7.3±1.1	8.0±1.2	8.1±1.3	8.3±1.4	8.3±1.3	8.3±1.3	1.0 (0.8 to 1.0)
Mean corpuscular volume (fl)	77±9	84±10	85±10	89±12	91±13	91±13	13 (12 to 13)
Fetal hemoglobin (%)‡	10.9±6.8	17.3±8.2	19.3±8.7	23.4±9.1	23.4±9.6	21.2±8.8	12.5 (11.8 to 13.1)
White cells per mm ³	16,500±8000	12,700±5300	12,500±5000	10,100±4200	9400±3700	9400±3400	-6300 (-6900 to -5600)
Absolute neutrophil count per mm ³	6800±3000	5200±2700	5300±2700	4200±2200	4100±2100	4300±2300	-2500 (-2700 to -2200)
Platelets per mm ³	411,000±171,000	372,000±173,000	381,000±174,000	343,000±174,000	353,000±166,000	365,000±193,000	-67,000 (-82,000 to -52,000)
Absolute reticulocyte count per mm ³	344,000±147,000	233,000±104,000	220,000±85,000	187,000±77,000	180,000±77,000	176,000±65,000	-157,000 (-169,000 to -145,000)
Alanine aminotransferase (U/liter)	24±33	24±34	23±14	23±15	25±28	21±11	-1 (-4 to 2)
Creatinine (mg/dl)	0.41±0.15	0.40±0.13	0.43±0.20	0.42±0.16	0.43±0.14	0.44±0.14	0.02 (0.00 to 0.03)

* Plus-minus values are means ±SD. Time points refer to the duration since treatment initiation (month 0).

† The 95% confidence interval is for the difference between month 0 and month 12. Confidence intervals were not adjusted for multiple comparisons.

‡ The fetal hemoglobin level was calculated as follows: fetal hemoglobin ÷ (fetal hemoglobin + sickle hemoglobin).



20 mg per kilogram per day was reasonably effective and not associated with dose-limiting toxic effects. The trial was not designed to determine

the appropriate amount or frequency of laboratory monitoring.

The laboratory benefits of hydroxyurea treat-

ment were evident, despite relative malnutrition in the REACH cohort, as compared with WHO child-growth standards and with populations of patients with sickle cell disease in the United States and Europe. Expected significant increases were observed in both the hemoglobin and fetal hemoglobin levels, along with significant decreases in the absolute neutrophil and reticulocyte counts, and these changes were sustained over time (Table 2). The mean increase in the hemoglobin level of 1 g per deciliter, despite suboptimal nutrition and ongoing risks of malaria and other infections, is important because the hemoglobin level is a well-established predictor of adverse outcomes in children with sickle cell anemia.²⁸ Within 6 months after the start of treatment, expected clinical benefits were also observed with regard to sickle cell-related events such as pain and the acute chest syndrome, as well as all severe (grade ≥ 3) adverse events.

The benefits of hydroxyurea therapy with regard to malaria infections were significant — with a rate reduction of more than 50% — and were not predicted before the trial (Table 1), despite the lack of malaria chemoprophylaxis programs at all the clinical sites. This benefit was especially notable after 12 months of treatment, so it may reflect known inhibitory effects of fetal hemoglobin,²⁹ more than direct effects by hydroxyurea,³⁰ on parasite growth. The importance of this effect should be evident for sub-Saharan Africa, where *Plasmodium falciparum* malaria is a major killer of children and is especially lethal in those with sickle cell anemia.³¹ In a finding that perhaps reflects the decrease in the incidence of malaria, there was a significant reduction in the incidence of transfusions (Table 1), which is important because of the general lack of safe blood supply across Africa.³²

This trial showed a significant reduction in all-cause mortality in this young cohort (Table 1). This effect reflects the combined effect of fewer severe sickle cell–related clinical complications, infections, malaria, and possibly transfusions. However, because the REACH trial did not include a placebo control, the survival benefit could be due to hydroxyurea use but also to better overall care, since the participants had frequent visits while they were receiving treatment. However, these findings are similar to those of previous reports that have shown an effect of hydroxyurea therapy on survival.^{13,14,33,34}

A limitation of this trial was the open-label treatment design without randomization or a placebo control, which was a decision that was based on strong opinions from the local ethics boards. However, the design fully addressed the key end points of feasibility and safety, showing that hydroxyurea could be administered in low-resource settings. All the participants received good care with close monitoring, which probably contributed to better outcomes that were unrelated to hydroxyurea treatment; additional studies will be needed to confirm sustained benefits with less monitoring. Strengths of this trial included the following: the international design; the dosing algorithm of a fixed dose followed by escalation to the maximum tolerated dose; the use of an electronic-capture system for data entry; and the availability of an online dose calculator to help ensure the safety of the participants. Long-term follow-up of this African cohort is ongoing for the investigation of growth and development and possible effects on organ function and fertility.

In conclusion, our results show that daily hydroxyurea treatment was feasible and safe for children with sickle cell anemia in sub-Saharan Africa. Moreover, hydroxyurea treatment reduced the rates of painful events, infection, malaria, transfusion, and death. Despite the recognition that 50 to 90% of affected children in Africa die before the age of 5 years,³⁵ sickle cell anemia remains a neglected disease for which safe and effective treatment options are needed.³⁶ As countries in sub-Saharan Africa begin newborn screening programs to identify children with sickle cell anemia,³⁷⁻³⁹ wider access to hydroxyurea may provide a simple and inexpensive oral medication that can alter the disease course and prolong survival.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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