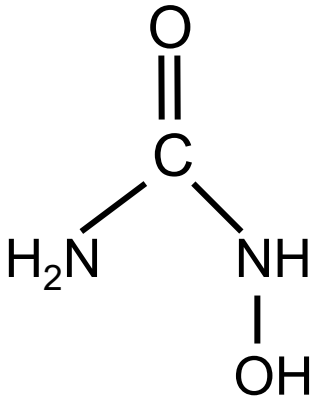
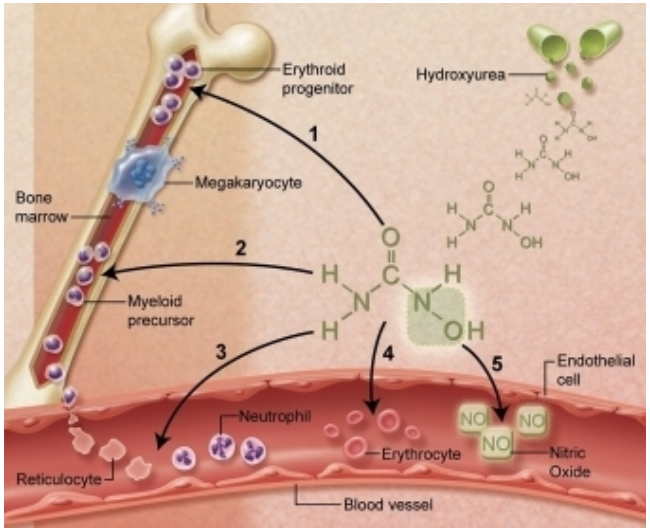


Hydroxyurea Trials in Africa

Russell E. Ware MD PhD
Cincinnati Children's Hospital

Hydroxyurea: Multiple Mechanisms of Action



Ware, Blood 2010

HbF induction

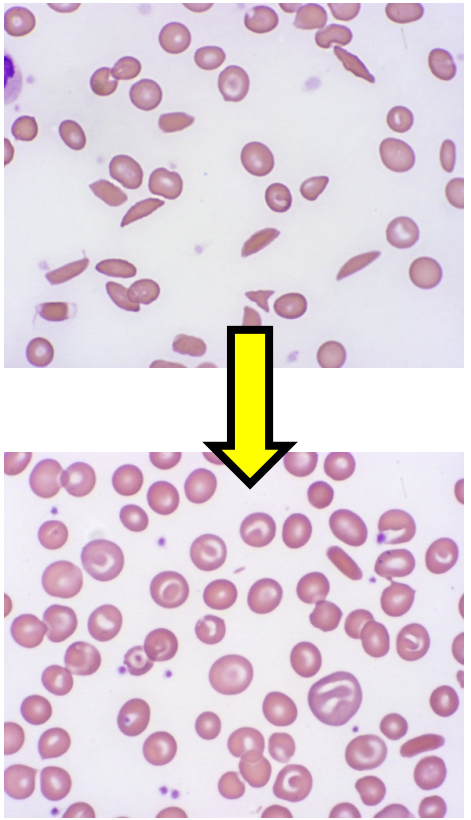
Myelosuppression

Less adhesion

Better rheology

Nitric Oxide

Endothelial effects



Sickle Cell Disease in Africa

WHO Reports: 2006 and 2010

World Health Organization
REGIONAL OFFICE FOR Africa

AFR/RC60/8
22 June 2010

SICKLE-CELL DISEASE: A STRATEGY FOR THE WHO AFRICAN REGION

Report of the Regional Director

current national policies and plans are inadequate;

Deaths from SCD complications occur mostly in children under five years.

Sickle Cell Disease in Africa
WHO Directives (2010)

Targets

Surveillance, healthcare management, national strategic plans

Guiding Principles

Country ownership, fairness, partnership, evidence-based interventions, cost-effectiveness, capacity building

Priority Interventions

Early identification/screening, affordable medications, research promotion

Sickle Cell Disease in Africa
WHO Directives (2010)

Targets

Surveillance, healthcare management, national strategic plans

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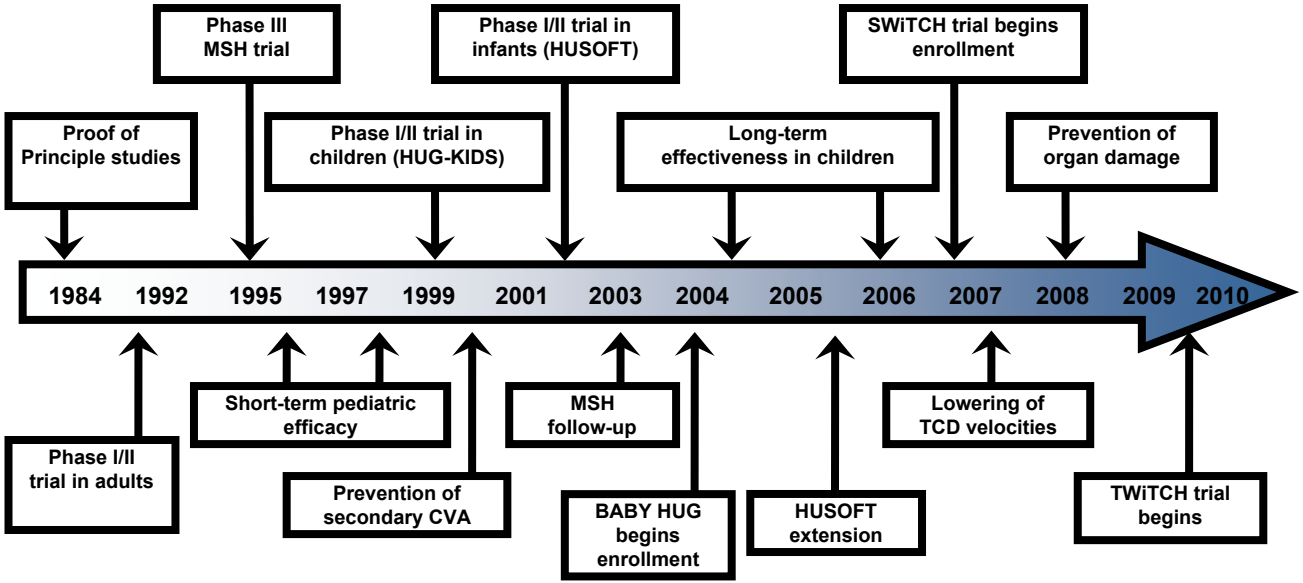
Country ownership, **fairness**, **partnership**, evidence-based interventions, cost-effectiveness, **capacity building**

Priority Interventions

Early identification/screening, affordable medications, **research promotion**

Hydroxyurea Research Trials



WHO Model List of Essential Medicines for Children

http://www.who.int/medicines/publications/essentialmedicines/en/index.html

3rd list
(March 2011)

10.3 Other medicines for haemoglobinopathies

hydroxycarbamide	*Solid oral dosage form: 200 mg; 500 mg; 1 g.*

Sickle Cell Research Efforts in Africa

Diagnosis

Surveillance

Treatment

7 countries

NOHARM

Novel use Of Hydroxyurea in an African Region with Malaria

Novel use Of Hydroxyurea in an African Region With Malaria

(NOHARM, ClinicalTrials.Gov NCT01976416)

DORIS DUKE CHARITABLE FOUNDATION

addmedica

Cincinnati Children's
changing the outcome together

Study Overview

Opoka et al, Blood 2017; 130:2585-93

Phase III double-blinded placebo-controlled RCT

Primary Endpoint: Malaria events

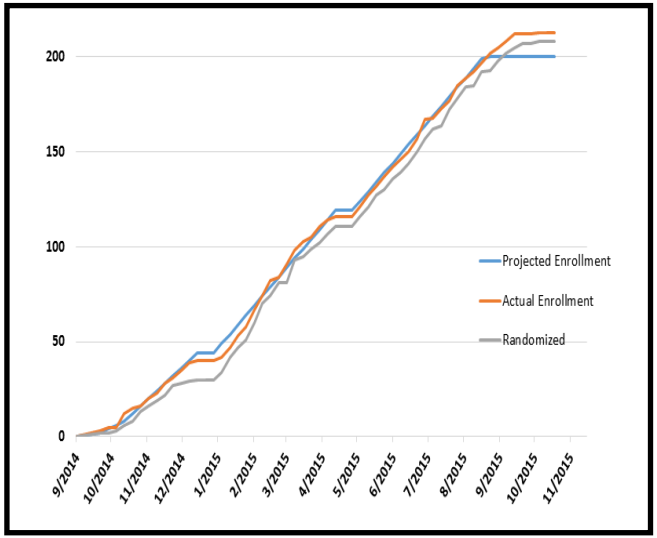
Enrollment: 200 children, age 1-4 years

Fixed hydroxyurea dose (20 mg/kg/day)

No increased risk of malaria

Expected treatment benefits

Equivalent dose-limiting toxicities

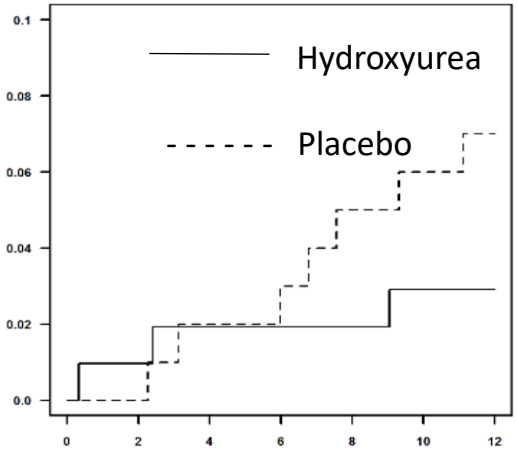


Hematological Effects at Month 12

Laboratory Parameters	Hydroxyurea (N=99)	Placebo (N=99)	p-value*
Hemoglobin (g/dL)	8.7 ± 1.3	7.4 ± 1.0	<0.001
Mean corpuscular volume (fL)	88 ± 9	81 ± 8	<0.001
Fetal hemoglobin (%)	22.9 ± 8.6	10.4 ± 4.8	<0.001
Enrollment age below median	24.1 ± 8.5	12.1 ± 4.8	<0.001
Enrollment age above median	21.4 ± 8.7	8.8 ± 4.2	<0.001
Absolute reticulocyte count (10^9/L)	247 ± 107	391 ± 122	<0.001
White blood cell count (10^9/L)	13.7 ± 5.1	18.0 ± 5.1	<0.001
Absolute neutrophil count (10^9/L)	5.2 ± 2.5	6.6 ± 2.6	<0.001
Platelets (10^9/L)	371 ± 166	446 ± 143	<0.001
Alanine transferase (ALT, U/L)	19 ± 8	18 ± 8	0.59
Creatinine (mg/dL)	0.32 ± 0.11	0.31 ± 0.08	0.64

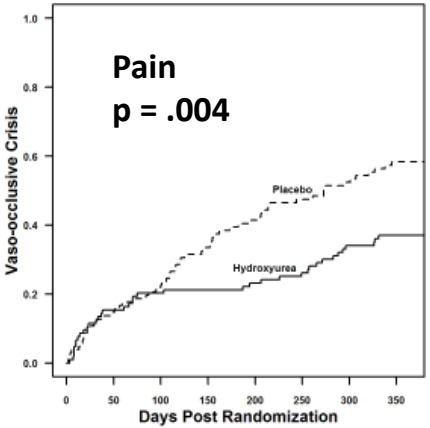
Dose-limiting toxicities: 21 on hydroxyurea and 17 on placebo

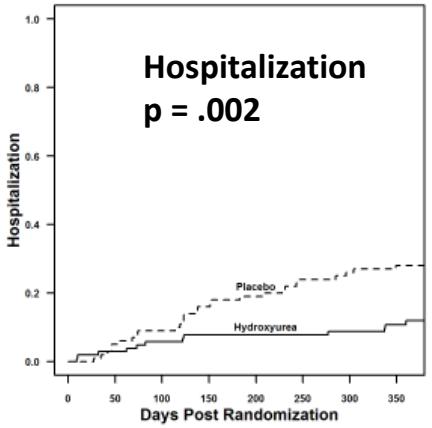
Clinical Safety and Benefits

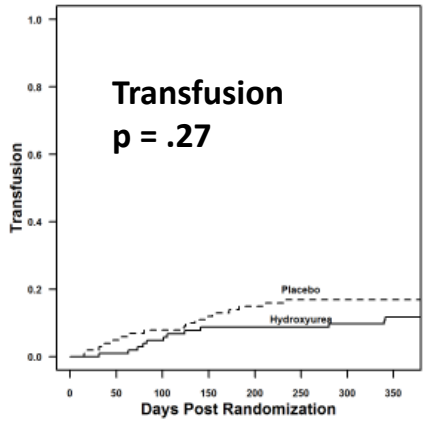


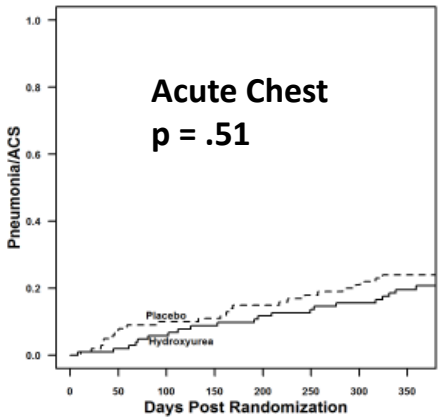
No increased risk of malaria

Expected clinical benefits









Realizing Effectiveness Across Continents with Hydroxyurea (REACH)

Phase I/II open-label hydroxyurea trial

- Feasibility, Safety, Benefits
- Fixed dose x 6 months, then dose escalation
- Drug donation from BMS

Enrollment: 600 children across 4 sites, age 1-10 years

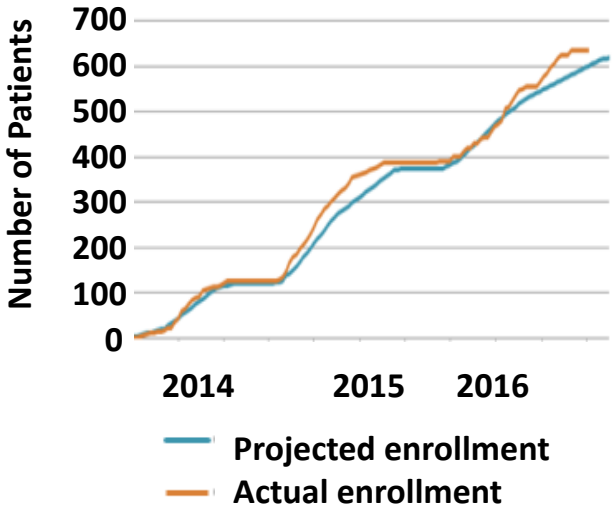
Cincinnati Children's
changing the outcome together

Bristol-Myers Squibb Company

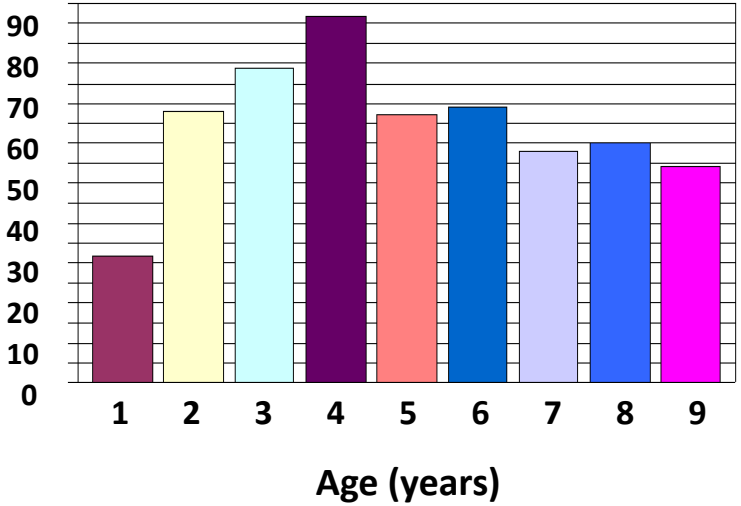
NIH National Heart, Lung, and Blood Institute

REACH, NCT01966731

606 treated children



1 – 10 years of age

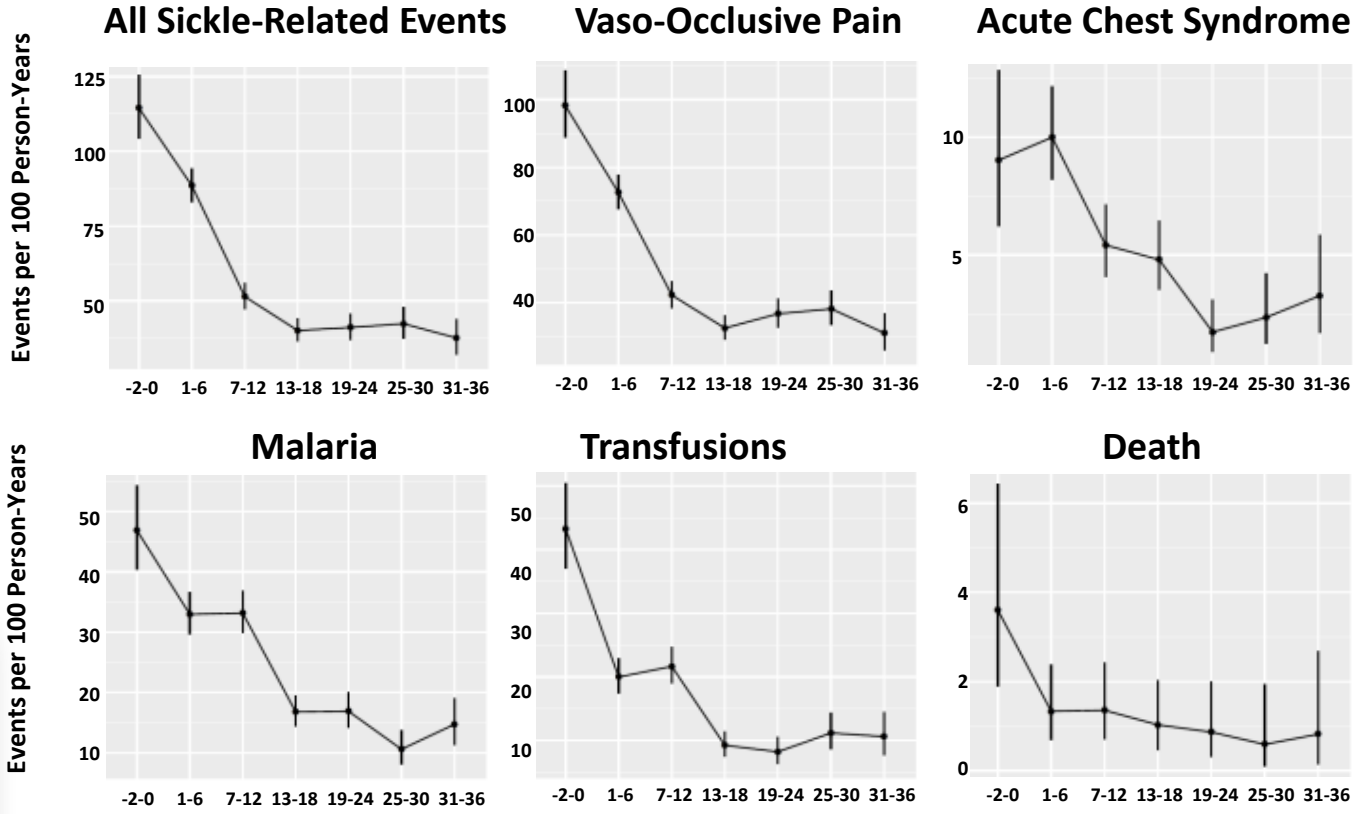


The NEW ENGLAND JOURNAL of MEDICINE

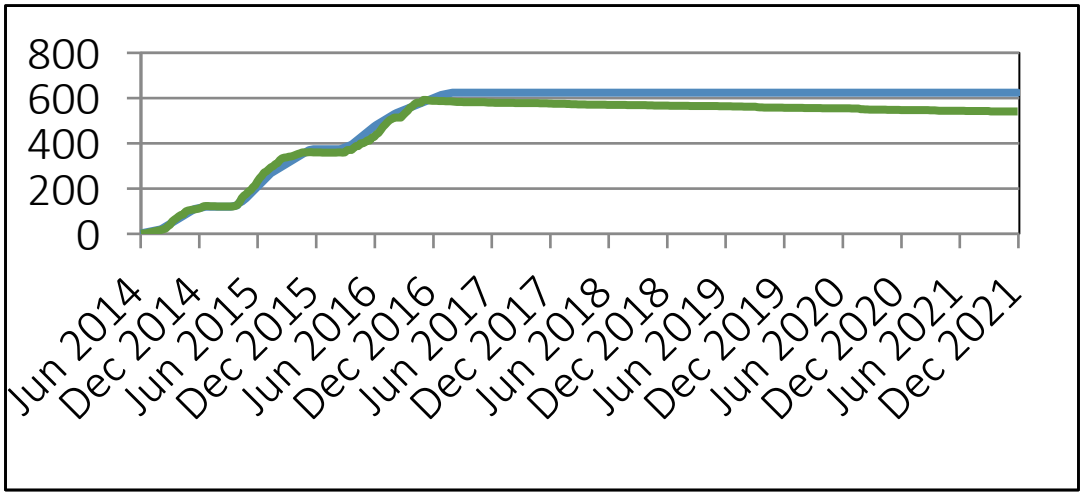
ORIGINAL ARTICLE

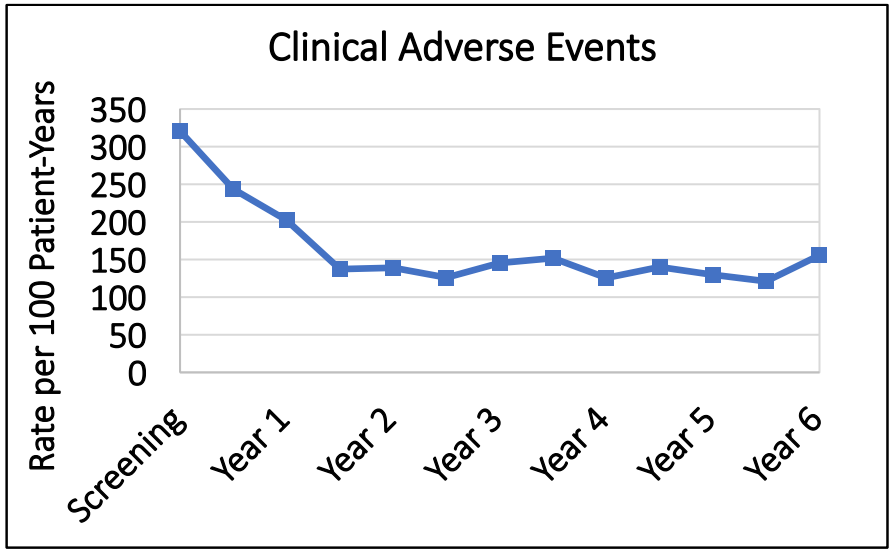
Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa

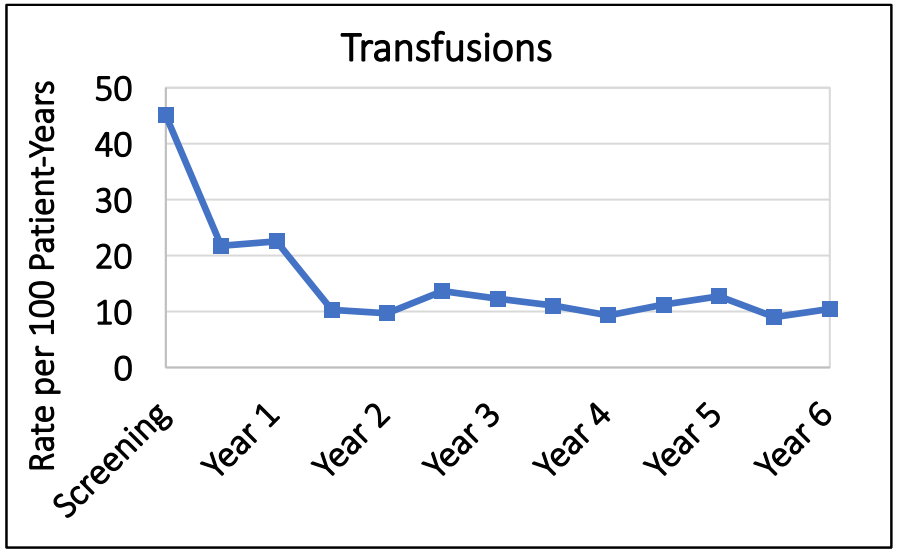
Léon Tshilolo, M.D., Ph.D., George Tomlinson, Ph.D., Thomas N. Williams, M.D., Ph.D., Brígida Santos, M.D., Peter Olupot-Olupot, M.D., Ph.D., Adam Lane, Ph.D., Banu Aygun, M.D., Susan E. Stuber, M.A., Teresa S. Latham, M.A., Patrick T. McGann, M.D., and Russell E. Ware, M.D., Ph.D., for the REACH Investigators*



Now at 7 years!

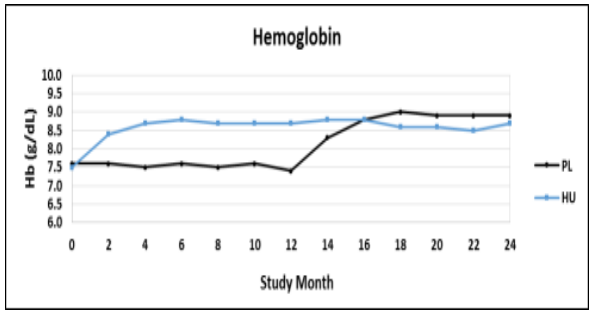






NOHARM MTD Trial

Year 1 randomized → Year 2 open-label

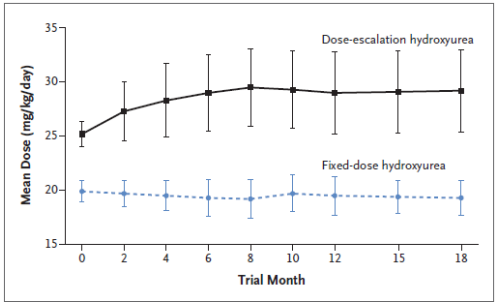


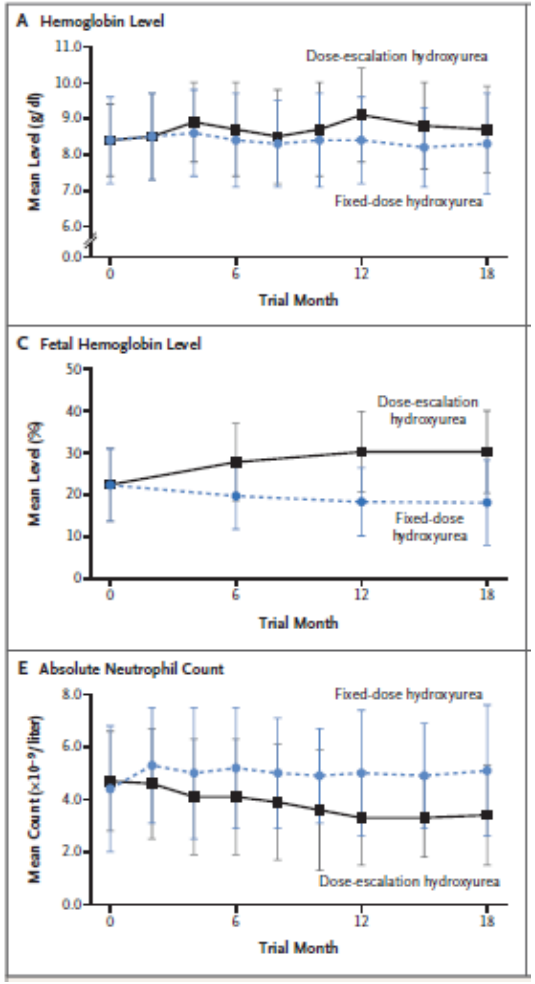
Fixed-Dose versus Escalation Dose to MTD

- 20 mg/kg/day versus 30 mg/kg/day
- Risks and benefits of higher dosing

Primary Outcome: Hb ≥ 9.0 g/dL or HbF ≥ 20%

Prediction: More benefits at MTD but more toxicities too





Sickle-related events	↓ 57%
Vaso-occlusive pain	↓ 57%
Pneumonia	↓ 77%
Transfusions	↓ 70%
Hospitalizations	↓ 79%
Dose-limiting toxicities	EQUAL

Primary Study Endpoint

86% vs 37%, p<0.001

STUDY HALTED EARLY

BY THE DSMB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyurea Dose Escalation for Sickle Cell Anemia in Sub-Saharan Africa

Chandy C. John, M.D., Robert O. Opoka, M.Med., Teresa S. Latham, M.A., Heather A. Hume, M.D., Catherine Nabaggala, M.B., B.S., Phillip Kasirye, M.Med., Christopher M. Ndugwa, M.Med., Adam Lane, Ph.D., and Russell E. Ware, M.D., Ph.D.

NEJM 2020; 382:2524-2533

SPHERE

Primary stroke prevention trial

TCD screening of 200 children in northwest Tanzania

Hydroxyurea with dose escalation

Endpoints: Stroke, TCD velocities

Emmanuela Ambrose MMED – local PI, ASH Global Research Award

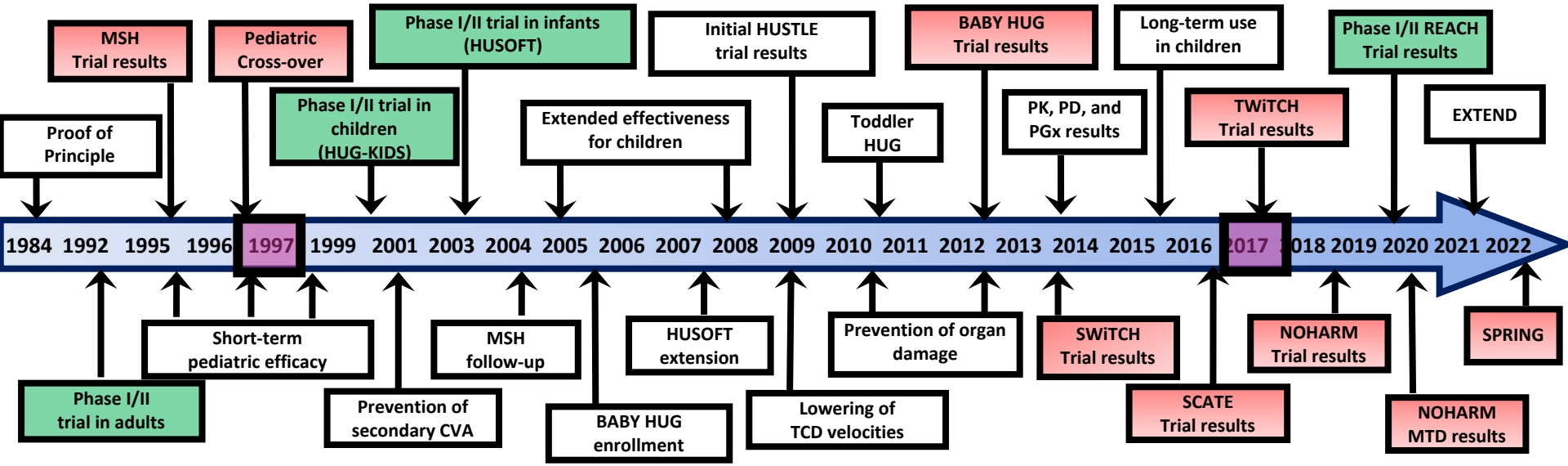
Luke Smart, MD

SPRING Results

Abdullahi et al, Lancet Haematology 2022;9;26-37

	Low-Dose Hydroxyurea	Moderate-Dose Hydroxyurea	IRR	p
Dose (mg/kg/day)	10.8	20.6	-	
Stroke (%)	2.75	4.50	0.62	0.77
Death (per 100 pt-years)	3.98	1.92	2.08	0.19
Hospitalization (per 100 pt-years)	27.43	16.08	1.77	0.007 1
Vaso-occlusive pain	15.51	9.19	1.69	0.055
Acute Chest Syndrome	3.18	0.77	4.15	0.097
Malaria	19.89	16.08	1.62	0.065
Normalized TCD Velocity (%)	29	40		
Hb ≥ 9.0 g/dL or HbF ≥ 20% (%)	29	67		
Median HbF increase (%)	1.9	10.0		

Hydroxyurea for SCA: ~40 Years of Experience



Safe and Effective in all Ages

Sickle Cell Disease in Africa

WHO Progress Report: 2020

World Health Organization
REGIONAL OFFICE FOR Africa

AFR/RC70/INF.DOC/3
30 July 2020

REGIONAL COMMITTEE FOR AFRICA

ORIGINAL: ENGLISH

Member States should: (a) Allocate to the SCD programme a budget that is commensurate with the national burden for screening, diagnosis, treatment, surveillance, and research; (b) Include hydroxyurea in the National Essential Medicine List and ensure its availability

WHO and partners should: (a) Engage with partners and national programmes to investigate the barriers to accessing hydroxyurea with a view to negotiating a reduced and affordable price; (b) Ensure that SCD remains high on national, regional and global health agendas through fostering collaborations and partnerships on SCD

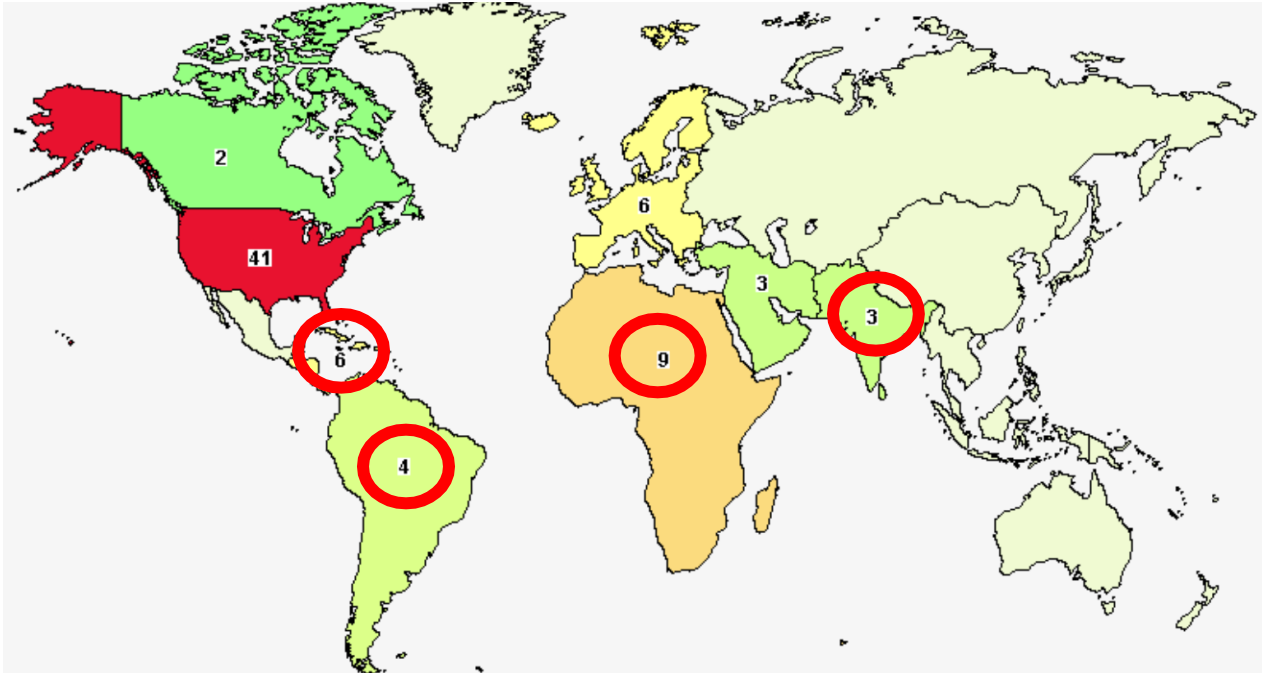
Current Global Hydroxyurea Research

CT.gov, PANCTR, WHO

409,120 in 220 countries

51 SCD and hydroxyurea

Only 9 in Africa



What are some remaining questions?

Safety and Efficacy → Implementation

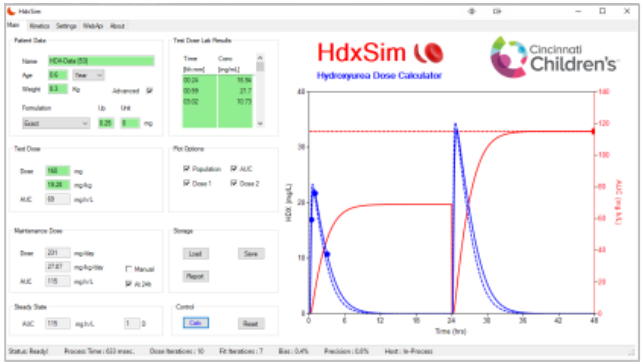
Dosing and Monitoring

- Low-dose, Fixed-dose, Optimal dose
- PK-guided individualized dosing → Smart at 1700

Future Directions

- Reduction in Malaria
- Reduction in Transfusions → ADAPT, Opoka, Power-Hays
- HbSC disease → PIVOT: Segbefia, Dei-Adomakah, Smart

Long-term effects



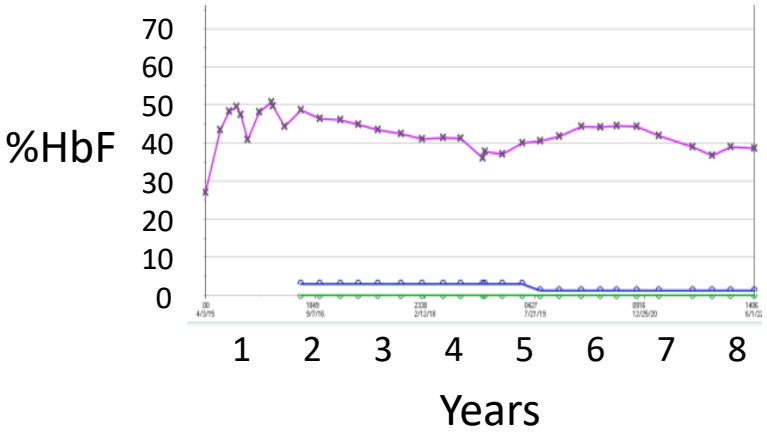
Long-Term Use: Safe & Effective

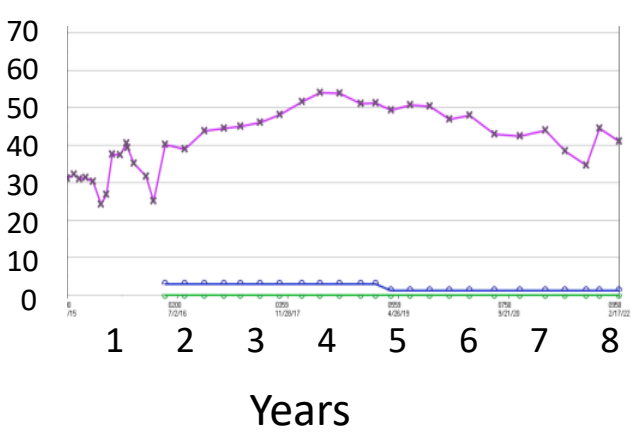
Can hydroxyurea achieve ‘curative’ levels of HbF?

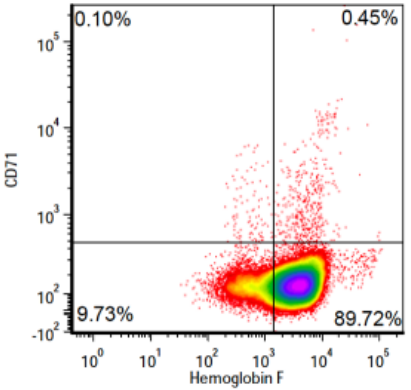
The 30% HbF target is often called ‘curative’

Pharmacokinetic-guided hydroxyurea dosing

Start at 6-12 months of age and use optimal dosing







Research in Africa: Avoiding Exploitation

Luzzatto Challenge

Global Tithe

Acknowledgments

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Katie McElhinney
Teresa Latham
Arielle Hernandez

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Chandy John
Patrick McGann
Heather Hume
Banu Aygun
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Léon Tshilolo
Tom Williams
Peter Olupot-Olupot
Emmanuela Ambrose
Cathy Segbefia
Yvonne Dei-Adomokah

Caribbean Co-Investigators

Marvin Reid
Angela Rankine-Mullings
Rosa Nieves
Rafael Mena

Funding Sources

Cincinnati Children's Research Foundation

Cincinnati Children's
changing the outcome together

NIH National Heart, Lung, and Blood Institute

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Bristol-Myers Squibb Company