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Non-substitutive strategies to improve hemophilia care in developing countries. Experience in Côte d'Ivoire.

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Thesis submitted in fulfilment of the
requirements for the degree of
"Docteur en sciences médicales"

March 2020
Brussels

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ACKNOWLEDGEMENTS

The moment of acknowledgements is a challenging task as it will be difficult to express my gratitude to all the people who contributed in any way to my thesis work. May those who I have not mentioned apologize and accept my gratitude.

First of all, I would like to thank my thesis promoter and mentor, Professor Cedric HERMANS, who trusted me from the beginning of my career in hematology. He made me grow, accompanied and supervised me throughout my thesis. His scientific ambition and creativity are a permanent source of inspiration for me. Thank you, Chief, for your availability and the many encouragements.

I am delighted to have worked with my co-promoter, Professor Philippe De MOERLOOSE for his scientific support. With his experience in developing countries, he provided me wise advice during the elaboration of this project.

I would like to thank all the members of my supervising committee who took the time to listen and discuss with me. Their comments allowed me to approach my work from a different perspective and to develop it further.

I would particularly like to thank Dr. Sébastien LOBET for not only agreeing to participate in my thesis jury, but especially for his personal investment in the on-site missions, for his participation in the elaboration of the scientific projects as well as the time he devoted to my research. Sébastien, thank you for your friendship and for having been my companion at every step of my journey even to the remote areas of Côte d'Ivoire...

I warmly thank Professor Jean-Cyr YOMBI for his unfailing support, our discussions and his guidance, which have been of great help to me in managing the missions in Côte d'Ivoire.

I would like to express my gratitude to Professor Séverine HENRARD for her support and contribution in the statistical interpretation of my data.

It is impossible for me not to thank Professor Stéphane EECKHOUDT who joined me on several occasions in Abidjan to train the team of the Yopougon's laboratory and to supervise the collection of the biological data which were crucial in my work.

Thanks to Dr. Nathalie LANNOY for coaching me in the analysis of molecular data which is a complex field.

Many thanks to Miko and Antoine for taking up the challenge and participating successfully in the implementation of the self-physiotherapy program for the Ivorian people with hemophilia. I wish both you a fulfilling career.

I thank my colleagues, Sarah BAILLY, Violaine HAVELANGE, Nicole STRAETMANS, Marie-Christiane VEKEMANS, Xavier POIRE and Eric VAN DEN NESTE for their support throughout these 3 years.

The team of hematology secretaries and Dominique POTHEN provided me with a serious logistical help to organize my missions. I thank them warmly.

I would also like to thank the hematology team of the Yopougon's University Hospital, Professor Ibrahima SANOGO, Dr. N'Dogomo MEITE and Mr. Mama KAMAGATE, who regularly hosted me at the hemophilia treatment centre in Abidjan. This thesis is the outcome of more than five years of collaboration and I am proud to have contributed together with you to the improvement of the condition of the Ivorian hemophilia community.

Thank you to Dr. Alidou TRAORE, our guardian angel during our stays in Abidjan.

Thanks to Bayer, CSL Behring, Pfizer, Sanofi and Sobi for their financial support.

I wish to underline the major role that the World Federation of Hemophilia played in the undertaking of this thesis. The twinning program between the Belgian-Ivorian hemophilia treatment centers was the trigger for me to initiate this original and ambitious project. Thank you to the members of the Belgian (AHVH) and Ivorian (IHMS) hemophilia patient associations who will now take over for 3 years to further extend the action.

With all my heart, I would like to thank the Ivoirian patients and their families, who agreed to participate in my research and who answered the questions I was asking, with calm and patience. Your courage and determination to move forward despite the daily difficulties added a unique dimension, full of humanism and hope, to this thesis.

Many thanks to all my dear friends who have supported me. Your messages, and your encouragement have been precious to bring this thesis to a successful completion. A special thanks to Jean-Christophe, my IT support.

My last thanks go to my family who always supported me in what I undertook. To my parents who guided me in my education and taught me the rigor and passion of work well accomplished.

To my sons, Jonathan and Joaquim, thanks from a mother who had not always enough time for you these last years.

Finally, Sam, thank you for your patience...

SUMMARY

Hemophilia care relies on multidisciplinary management and expensive replacement therapy, two requirements rarely met in less developed countries. Local lack of knowledge, underdiagnosis of the disease and very limited or no access to treatment have a major impact on the mortality and morbidity associated with hemophilia. This work, carried out in Côte d'Ivoire as part of the World Federation of Hemophilia (WFH) twinning program, aims to evaluate the impact of various so-called non-substitutive strategies (not based on concentrates of missing clotting factors) on the management of hemophilia. The establishment of a detailed and global register characterizing all the patients with hemophilia (PWH) as well as the female carriers made it possible to identify the main challenges and needs in Côte d'Ivoire. The originality of this work is also based on the elaboration and validation of several specific tools to promote a better knowledge and understanding of hemophilia and its implications in the community. To relief the common musculoskeletal complications in the Ivoirian PWHs, a locally tailored program of self-physiotherapy was developed, implemented and validated. Finally, cross-cultural adaptation and validation of instruments to assess the quality of life of adults and children with hemophilia was another major step of this project. The initiatives described above were the starting point of setting hemophilia care in Côte d'Ivoire, using inexpensive measures and creating an environment favorable for the use of substitutive treatment gradually available through WFH's donation programs.

BIOGRAPHY OF CATHERINE LAMBERT, MD

Catherine LAMBERT was born in 1974 in Brussels, Belgium. She completed her medical education in 1999 at the University Catholic of Louvain (UCLouvain). After a fellowship in internal medicine, she obtained the degree of specialist in adult hematology in 2006. Since then, she has been affiliated to the Hemostasis and Thrombosis unit, Division of Hematology of the Cliniques Universitaires Saint-Luc in Brussels. She is responsible for the Apheresis Unit and has a broad clinical expertise in the management of patients with bleeding and thrombotic diseases. She is involved in several education programs of the UCLouvain and takes part in the post-graduate teaching in hematology of the Belgian Hematology Society.

Catherine Lambert is actively involved in the comprehensive hemophilia treatment center (HTC) of the Cliniques universitaires Saint-Luc. She regularly collaborates with the World Federation of Hemophilia in the setting of international hemophilia trainings, HTC twinning programs, and workshops (mainly in African countries). She participated in a first HTC twinning with Bucarest, Romania from 2007 to 2011 and played a major role in setting a second twinning with the HTC of Yopougon, Abidjan, Côte d'Ivoire in 2014.

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INDEX OF ABBREVIATIONS

2MWT	2-Minute Walking Test
ABR	Annual Bleeding Rate
AJBR	Annual Joint Bleeding Rate
BMI	Body Mass Index
BU	Bethesda Unit
BWH	Boy with hemophilia
CBR	Community-Based Rehabilitation
CFC	Clotting Factor Concentrate
CHU	Centre Hospitalier Universitaire
CHO-KLAT	Canadian Haemophilia Outcomes-Kids' Life Assessment Tool
DDAVP	Synthetic Analogue Desmopressin Acetate
ED	Exposure Day
EQ-5D-5L	EuroQoL-Five Dimensional with 5 Levels
EQ VAS	EuroQoL Visual Analog Scale
ES	Effect Size
FVIII	Factor VIII
FIX	Factor IX
HA/HB	Hemophilia A/ Hemophilia B

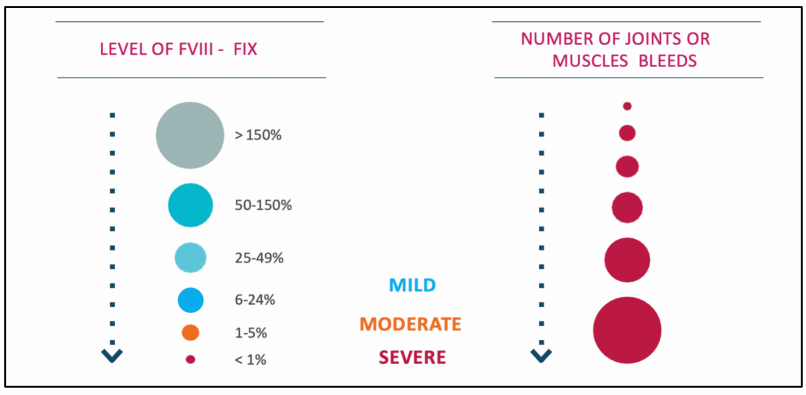
Haem-A-QoL	Haemophilia-Specific Quality of Life Questionnaire for Adults
HJHS	Hemophilia Joint Health Score
HRQoL	Health-Related Quality of Life
HTC	Hemophilia Treatment Centre
ICC	Intraclass Correlation Coefficient
IU	International Unit
MSK	Musculoskeletal
N	Newton
NMO	National Member Organization
OA	Osteoarthritis
PEDsQL	Pediatric Inventory of Quality of Life
PWH	Person/Patient/People with Hemophilia
RAGS	Report on the Annual Global Survey
RICE	Rest-Ice-Compression-Elevation
ROM	Range of Motion
TPE	Therapeutic Patient Education
TUG	Timed Up and Go
WFH	World Federation of Hemophilia
WHO	World Health Organization

INTRODUCTION

1. Definition of hemophilia

Hemophilia is a congenital, X-linked recessive bleeding disorder resulting in partial or complete deficiency of either factor VIII (FVIII, hemophilia A [HA]) or factor IX (FIX, hemophilia B [HB]). It occurs in approximately 1 in 5.000 (HA) and 1 in 20.000-30.000 (HB) live male births [1], with a similar incidence across ethnic populations [2]. The disease is classified according to the residual circulating FVIII or FIX activity as severe (<0.01 IU/mL), moderate (0.01-0.05 IU/mL) and mild (0.05-04 IU/mL) [3]. Depending on the severity of the disease, people with hemophilia (PWH) experience various degrees of bleeding, primarily affecting joints (mainly the knees, the ankles and the elbows), muscles, and soft tissues [3], but also prolonged bleeding in case of trauma or surgery and life-threatening bleeds including intra-cranial hemorrhage. The frequency of bleeding complications is inversely correlated with the level of FVIII or FIX (Fig. 1). Recurrent joint bleeds cause long-term complications encompassing acute and chronic pain, arthropathy, and disability [4] resulting in a reduced health-related quality of life (HRQoL) [5]. The condition affects men while their female relatives are likely to be hemophilia carriers. Carriers are at risk of having sons with hemophilia but may also have an increased bleeding risk [6].

Figure 1. Correlation between the bleeding frequency and the severity of hemophilia



Illustrative figure developed by the author

2. Hemophilia care

Hemophilia treatment is complex, comprises multiple approaches and mainly, but not only, relies on hemostatic substitutive and non-substitutive therapies to prevent and treat bleedings and their musculoskeletal complications.

Replacement of the missing coagulation factor to achieve adequate hemostasis is the cornerstone of hemophilia care. The major goal of substitutive therapy is to treat bleeds (on-demand therapy) or to prevent and reduce the frequency of bleeds and consequently joint damage and life-threatening bleeds (prophylactic therapy). In developed countries with no or limited economical restrictions, prophylaxis initiated in early childhood is actually the standard of care in severe hemophilia [7]. In those countries, PWH have a life expectancy close to the general population [8] and do less frequently develop arthropathy.

Major advances have been achieved in replacement therapy over the last decades after the discovery of the cryoprecipitate fraction of plasma [9]. Since then, tremendous biotechnological progress made it possible to provide PWH with self-administered home therapy with safe, available, and various types of clotting factor concentrates (CFC) and by-passing agents (in case of inhibitors). Bio-engineered products were developed to extend CFC half-life (by fusion or by PEGylation techniques) or to reduce their immunogenicity [10].

Over the last few years, the concept of disruptive technologies barged into hemophilia therapy. Emicizumab, a bispecific antibody directed against factors IX, IXa, X, and Xa, which can mimic the function of FVIIIa, dramatically decreases bleeding in PWH with and without neutralizing antibodies against factor VIII. Therapies that target the coagulation inhibitors including a small interfering RNA reducing the synthesis of anti-thrombin and monoclonal antibodies directed against tissue factor pathway inhibitor are currently being validated. Finally, gene therapy with AAV vectors in hemophilia A and

B, to restore the production of FVIII or IX by the liver appears to be promising [11-12].

Treatment of hemophilia relies on the access and availability of concentrates. The minimum number of units per capita of FVIII to target was established at 1 in 2002 by the WFH to achieve survival of PWH [13] and at 4 in Europe in 2016 by the European Directorate for the Quality of Medicines and HealthCare [14]. In its 2017 Annual Global Survey, the World Federation of Hemophilia (WFH) reports great disparities in the amount of CFC consumption around the world [15] (Fig. 2), following the 20-80 rule with 80% of the global hemophilia expenditures incurred by 20% of PWH living in developed countries [16]. In high income countries, prophylaxis is the standard of care in children and even in adults [17]. Severe hemophilia treatment is associated with a major economic burden for the health care system. The study 'Cost of Haemophilia in Europe: A Socioeconomic Survey' estimated the total annual cost of severe hemophilia across five European countries in 2014 at EUR 1.4 billion, i.e. approximately EUR 200.000 per patient, while CFC representing 99% of the costs [18].

Non-substitutive hemostatic drugs can be very useful (alone or in combination with CFC) to prevent or treat bleeds in PWH and symptomatic hemophilia carriers. For example, antifibrinolytic drugs (tranexamic acid and epsilon amino caproic acid) are low-cost hemostatic therapies that are taken orally or intravenously but can also be used in local application or diluted in a mouthwash. They are indicated to control mucocutaneous bleeds and or are used after dental procedures. The synthetic analogue desmopressin acetate (DDAVP) is a widely used hemostatic agent since the mid 1970's. DDAVP increases FVIII and von Willebrand factor plasma concentrations through endothelial release. It can be administered intravenously, by nasal spray or subcutaneously, it is inexpensive, safe and available in many countries. Finally, fibrin glue improves local hemostasis during surgery [7].

As approximately 80% of hemorrhages occur in the musculoskeletal system, about two-thirds of people with severe hemophilia suffer from chronic arthropathy, resulting in long-term restricted range of motion, stiffness, pain, deformity and disability. Therefore, hemophilia care requires a close collaboration between the hematologist, the physiotherapist and the orthopedic surgeon. This multidisciplinary approach aims at preventing hemarthrosis, managing acute joint bleeds, assessing joint function, and treating chronic arthropathy [19].

Pain represents a major problem in PWH leading to a reduced HRQoL [20]. Usually, joint distension and tissue injury provoked by an hemarthrosis is associated with acute pain while synovitis and arthropathy account for chronic pain, sometimes associated with flair-up episodes. According to the HERO study, 50% of adult PWH report pain and in 89% of them, pain interferes with their daily life [20]. The pain alleviation in PWH is based on a tailored and multidisciplinary approach integrating replacement therapy, pharmacological treatment, physiotherapy [21], orthopedic procedures [22], psychosocial support, behavioral therapy, [23-24], …

As the management of hemophilia is complex and represents much more than just prescribing replacement therapy with CFC, Hemophilia Treatment Centres (HTC) should rely on a highly coordinated team to provide comprehensive care in PWH and hemophilia carriers. The setting up of HTCs and the centralization of hemophilia care are clearly beneficial to treat hemophilia and its complications and is strongly endorsed by the WFH [25] and the European Association for Haemophilia and associated disorders (EAHAD) [26]. The European principles of comprehensive care of hemophilia are summarized in Table 1.

Table 1. The European principles of comprehensive care of hemophilia [26]

1. A central hemophilia organization with supporting local groups
2. National hemophilia patient registries
3. Comprehensive care centres and hemophilia treatment centres
4. Partnership in the delivery of hemophilia care
5. Safe and effective concentrates at optimum treatment levels
6. Home treatment and delivery
7. Prophylaxis treatment
8. Specialist services and emergency care
9. Management of inhibitors
10. Education and research

3. Hemophilia in the developing world

Developing countries face several major issues in hemophilia care. Besides poor awareness of the disease among affected people and their families, as well as healthcare givers and government decision makers, there are issues with disease recognition, lack of access to biological accurate diagnosis, no or very limited access to hemostatic treatment with CFC and comprehensive hemophilia care [27]. Data collected by the WFH indicate that among the estimated 400.000 PWH living worldwide, 70% of them are not identified and only 25-30% of the diagnosed patients have access to adequate treatment [28-30]. As approximately 70% of the world population lives in the developing world, it is logical to admit that 70% of PWH should be there.

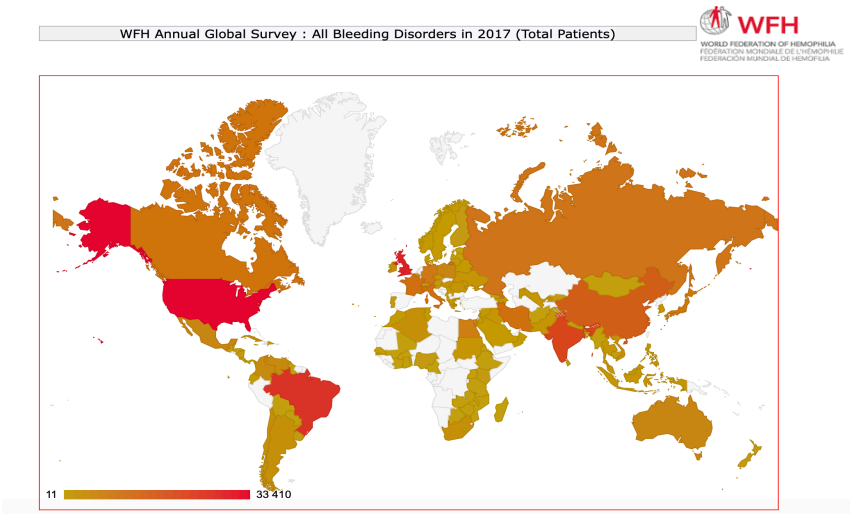
Despite a similar incidence in all ethnic populations, hemophilia prevalence widely varies among countries (Fig.2) and is closely related to their economic status because of the effect of premature deaths and shortened life span in low-income countries [31]. Indeed, in low gross national income countries, less than 10% of PWH are identified and only 30% of those who are diagnosed have access to hemophilia care and clotting concentrates (Fig.3)

[32]. Without early diagnosis and appropriate treatment, patients with severe hemophilia often die in childhood [33], thereby resulting in a decreased prevalence relative to the number of cases born. Those who survive experience recurrent bleeds in the musculoskeletal system and intracranial hemorrhages, that account for a high rate of morbidity, pain and disability.

Expenses dedicated to hemophilia care are scarce in resource-constrained countries. As it is a rare, chronic, and cost-intensive condition, hemophilia is not a priority in countries where governments focus their limited resources on public health issues, such as nutrition, immunization, sanitation, and treatment of infectious diseases [28;34]. In the poorest countries, the greater part of the population has no medical insurance and must pay their own health expenses and access to CFC is often exclusively supplied by humanitarian aid.

Besides the non-availability of CFC, basic pillars of hemophilia management are frequently lacking in developing countries: organized HTCs providing comprehensive hemophilia care - a national registry of hemophilia and other bleeding disorders - access to laboratory facilities enabling accurate diagnosis - access and adequate use of adjuvant non-substitutive therapies (*i.e.* physiotherapy, DDAVP, antifibrinolytics, dental care, pain relief …) - detection and care of carriers - antenatal diagnosis - outreach programs - training of care providers - education of PWH, carriers and their families - research publications relevant to the country - awareness of hemophilia among the general population, the healthcare givers, and the policy makers [16]. Despite a growing number of WFH National Member Organizations (NMO) all over the world, several countries, mainly in Africa, have no NMO [15]. Visibility of the disease, data collection, active NMO's, are however, the cornerstones for advocacy and initiating negotiations between the stakeholders to set up proper health care infrastructure for hemophilia.

Figure 2. Number of hemophilia and other rare bleeding disorders cases reported per country over the world [15]



Where there is no color on the map, no data were reported by the country for that year

Figure 3. Mean factor VIII use per capita over the world [15]

Where there is no color on the map, no data were reported by the country for that year.

4. The WFH twinning program

Since its founding in 1963, the WFH has been committed to improving care for patients with inherited bleeding disorders regardless of where they live and is achieving its goals to develop sustainable care through many programs [30]. The WFH twinning program is designed to raise hemophilia care at a global level by promoting collaborative networking between emerging HTCs and well-established and experienced HTCs. The twinning activities mainly (but not only) aim at: providing medical advice, passing on knowledge and skills, donation of equipment, laboratory reagents and CFC, conducting research, developing local patients' registry, advocacy with the authorities of the country of the emergent partner… [35]. The HTC twinning concept was proposed in 1993 by Guglielmo Mariani [36] and since then, 153 HTC, 86 Hemophilia Organization and 4 Youth Group Twinnings were already conducted.

5. Twinning in Côte d'Ivoire

The Republic of Côte d'Ivoire is a Western African country with a population of 24 million and is classified by the World Bank as a lower middle-income country [37]. In Côte d'Ivoire, the 2014 WFH Annual Global Survey reported on 73 PWH, of whom 0% were on prophylaxis, and a mean per capita FVIII and FIX use of 0.015 IU and 0.001 IU, respectively. CFC were supplied by humanitarian aid exclusively. No data were available on inhibitors and no carriers were reported [38]. The Ivoirian NMO was established in 2008 and the only HTC of the country was located in Abidjan.

The very low prevalence of hemophilia was mainly due to the lack of awareness and the underdiagnosis of the disease, and premature death namely related to circumcision. Published scientific data on hemophilia in Côte d'Ivoire were extremely limited with the last publication dating from 1990 [39]. As already reported in South Africa, the unawareness of the hemophilia carriers about their condition and the risk of transmission to

their offspring was high [40]. This is crucial as gender plays an important role in shaping hemophilia care and education in the African context with women being more likely than men to take on caregiving activities. As in many other African countries, the burden and the psychosocial impact on the carriers was important and should not be underestimated [41]. Circumcision is the most prevalent surgical procedure carried out in boys in Côte d'Ivoire and is performed by medical or paramedical staff but quite often by traditional practitioners. It is considered as a benign surgery but its complications such as hemorrhage are frequent and sometimes severe [42]. This is common in Africa where circumcision is mainly supported by religious, cultural, and social reasons [43].

A WFH twinning partnership between the HTC of the Centre Hospitalier Universitaire (CHU) of Yopougon in Abidjan, Côte d'Ivoire and the international HTC of the Cliniques universitaires Saint-Luc in Brussels, Belgium was formally recognized and approved by the WFH HTC Twinning Committee in October 2014. A multidisciplinary Belgian team (2 hematologists, one physiotherapist, and a member of the hemostasis laboratory) was set up and the first visit at the HTC of Yopougon took place in February 2016

6. The humanitarian aid program of the World Federation of Hemophilia

Since 1996, CFC are distributed by the WFH in countries with a FVIII use of less than 1 IU per capita. The humanitarian aid has evolved from sporadic donations to a sustainable program. Although crucial, the impact of this program remains limited in countries lacking in medical hemophilia expertise, resulting in only a few PWH benefiting from the donated products, inadequate use of the limited amount of CFC, unawareness of complementary non- substitutive hemophilia treatment and unavailability of home therapy [32]. In 2015, Côte d'Ivoire was provided with 320.000 IU of FVIII and 26.100 IU of FIX from the humanitarian aid program. Those products were for mostly used at the HTC of Yopougon, solely to treat acute

bleeding episodes. No surgeries were performed and no PWH were on prophylaxis.

7. Initiation of a research project in the frame of the WFH twinning

At the end of the first on-site twinning mission, the magnitude of the challenge appeared more evident. Hemophilia care in Côte d'Ivoire, as in most developing countries, was almost non-existent. Several critical issues (besides the very limited access to CFC - see above) were identified and are listed below:

1. Major underdiagnosis of hemophilia regarding the low number of identified PWH.
2. Absence of national registry of patients affected with hemophilia or other bleeding disorders.
3. Unawareness of the hallmarks of the disease, its mode of transmission, its treatment and complications among the PWH, their families and health care givers.
4. Restricted access to laboratory facilities offering accurate diagnosis capacities.
5. A high number of deaths early in life related to circumcision due to the unawareness of the mode of transmission of hemophilia and the absence of systematic familial screening.
6. The insufficient use of physiotherapy and measures alleviating pain.
7. The burden of the disease for the hemophilia community was compound by constrained financial resources as medical care is entirely at the patient's expense.
8. The lack of knowledge and use of adjuvant non-substitutive therapies.
9. Absence of outreach and prevention programs.
10. No identification and assessment of carriers.
11. Absence of hemophilia recognition by the government and the policy makers and no economic resources dedicated to hemophilia.
12. No recent research publications relevant to the country.

Taking the above-mentioned observations into account, it clearly appeared that the initial twinning action plans had to be refined and should concentrate on locally-adapted, affordable and complementary non-substitutive strategies that could in a second phase contribute to set up a favorable environment for optimizing the use of the limited available CFC resources and preparing the landscape for the use of novel therapies. More time and resources were also needed to elaborate and implement those strategies. In this frame, while continuing the twinning process, a research project was therefore undertaken to further explore pathways to improve hemophilia care in Côte d'Ivoire.

8.Outlines of the thesis

Without questioning the essential role of the CFC, given their very limited availability and considering the local major lacks in hemophilia management in Côte d'Ivoire, we hypothesized that it was possible to improve hemophilia care in the country, and by extension to other developing countries, by using different and complementary non-substitutive (not based on replacement therapy) strategies. This project aimed at performing an initial in-depth analysis of the condition of Ivoirian PWH and carriers and, in a second step, at developing, implementing and evaluating the impact of interventions appropriate to the local needs and the economic and socio-cultural context. In parallel, we sought to provide adapted tools to assess the outcomes of the actions and enable the participation in future international studies.

Section 1: Baseline situation of hemophilia in Côte d'Ivoire.

In the first section, results of detailed and accurate information collected on the baseline condition of hemophilia in Côte d'Ivoire to better identify the local challenges and needs are presented and discussed. The first two chapters summarize the extensive data on demographics, clinical and biological characteristics of Ivoirian PWH and carriers that were obtained through standardized, systematic and multidisciplinary assessments held by

both Belgian and Ivoirian hematologists, physiotherapists and hemostasis laboratory members.

Chapter 1 focused on PWH and comprised a careful clinical, musculoskeletal and biological evaluation of the participants. A significant part of the work also investigated the gaps in hemophilia management and the dramatic consequences of the unawareness of the disease in Côte d'Ivoire. The purpose of **Chapter 2** was to identify, on basis of pedigrees, obligate and potential Ivoirian hemophilia carriers among PWH's families, to assess their bleeding phenotype and risk, and to provide them with appropriate hemostatic treatment plans and recommendations to screen properly their offspring. The two first chapters, report findings that were instrumental to establish the groundwork for a national register and to identify a large portion of the targeted population for education programs described below.

In the context of an attempt to set the stage for an adequate use and follow-up of the donated CFC, we prospectively collected data on inhibitor epidemiology and genetic-related risk factors for inhibitor development in PWH from Côte d'Ivoire, as described in **Chapter 3.** The main goals of this research project was to obtain data on inhibitor prevalence, create a database of hemophilia genotypes, establish correlations between inhibitor presence and genetic variants identified amongst Ivoirian PWH, and evaluate exposure to CFC through the systematic review of a two-year period of logbooks implemented in the frame of the twinning program activities.

Section 2: Interventions with non-substitutive locally adapted strategies

The second part of this thesis describes the elaboration and implementation of locally adapted, low cost and non-substitutive measures to improve management of hemophilia, prevent complications, relieve pain and musculoskeletal consequences and improve awareness and the recognition of the condition among the Ivoirian hemophilia community. In the light of the situation observed in Chapters 1 and 2, it appeared that the lack of

knowledge on the disease, its mode of transmission and its treatments represented a critical issue in hemophilia care in Côte d'Ivoire.

As a consequence, we undertook the development and evaluation of the impact of appropriate, culturally adapted educational tools on hemophilia for Ivoirian PWH, carriers, and their families to enable them to gain a better disease understanding, to acquire self-management skills, promote the use of non-substitutive hemostatic drugs to treat and prevent bleeding complications, introduce disease screening and prevention, and to improve hemophilia-related health outcomes in Côte d'Ivoire. **Chapter 4** presents the short- and long-term effects of the educational materials.

Chapter 5 examined the feasibility of implementation and the impact of a self-based and community-based physiotherapy program on the joint and functional status of Ivoirian PWH. This inexpensive project was initiated to answer specific needs in developing countries: the cost of rehabilitation session is entirely at the patient's expense and is challenging in a country with a very low average income, the lack of experienced physiotherapists and the large distance between the HTC and the place of residence of some PWH.

Section 3: Cross-cultural adaptation and validation of hemophilia specific HRQoL tools

In the last part of the thesis, we investigated on the cross-cultural adaptation and the validation of HRQoL measure tools in Ivoirian pediatrics and adult PWH. This work had the ambition to allow enable the outcome assessment of future interventions in this population. It also intended to study the appropriateness of some domains of the international HRQOL assessment instruments and the need to identify measures to ensure their optimal understanding as those have been developed in culturally distinct countries and with unlimited access to treatment. **Chapter 6** reports on the trans-cultural adaptation and validation process of the Canadian Haemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT) in boys with hemophilia in

Côte d'Ivoire and **Chapter 7** describes the cross-cultural adaptation and validation of the adult version of the Haemophilia-Specific Quality of Life Questionnaire (Haem-A-QoL) in adult Ivoirian PWH.

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SECTION 1

Baseline situation of hemophilia in Côte d'Ivoire

Chapter 1

Hemophilia in Côte d'Ivoire in 2017: extensive data collection as part of the World Federation of Hemophilia's twinning program.

Haemophilia. 2019 Mar;25: 236-243.

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SUMMARY

Introduction: In Sub-Saharan African countries, research on hemophilia is limited. Since 2015, a partnership has been established through the World Federation of Hemophilia (WFH) between the hemophilia treatment center (HTC) of the Centre Hospitalier universitaire of Yopougon in Abidjan, Côte d'Ivoire, and the Cliniques universitaires Saint-Luc of Brussels, Belgium.

Aim: This study sought to collect accurate, and detailed demographic, clinical, and laboratory data on the whole identified Ivoirian hemophilia population.

Methods: A prospective study was conducted in 2017 in Yopougon's HTC. Participants were assessed through multidisciplinary workups including interviews, logbook review, pedigree establishment, clinical examination, and laboratory testing.

Results: Data on 81 persons with hemophilia (PWH) (78 severe and moderate) were collected. Post-circumcision bleeding was the most common diagnosis reason (32%). Mouth bleeds and skin wounds accounted for 55.2% of bleeds. Pedigrees revealed 63 deaths in affected relatives among 33 families. Most PWHs (76.5%) were treated on demand, and 21% had never been exposed to clotting factor. Non-substitutive therapies (tranexamic acid [43%], physiotherapy [11%] and DDAVP [0%]) were underused. Overweight was uncommon. Knees were the most clinically affected joints at the Hemophilia Joint Health Score. Inhibitors were present in 7.8% of previously treated PWHs.

Conclusions: This study highlights the value of simple, feasible, and inexpensive tools to collect data in the Ivoirian hemophilia population and provides the basis for developing and implementing locally appropriate strategies to improve screening, diagnosis, preventive care, treatment, and education. It demonstrated the WFH twinning program's benefits for hemophilia care in the developing world.

INTRODUCTION

Hemophilia is a congenital, X-linked recessive bleeding disorder resulting in low levels of either factor VIII (FVIII, hemophilia A [HA]) or factor IX (FIX, hemophilia B [HB]). It occurs in approximately 1 in 5.000 (HA) and 1 in 20.000-30.000 (HB) live male births [1]. Despite a similar hemophilia incidence for all ethnic populations, hemophilia prevalence varies among countries [2;3] in general and developing countries as well; in the latter, prevalence is lower than expected from the international average [4]. Several reasons have been raised to explain this lower prevalence, namely the lack of diagnosis capacities, no access to care, very limited access to clotting factor concentrates (CFC), and the lack of economic resources dedicated to hemophilia [5]. Without adequate treatment, patients with severe hemophilia often die early in life [6], thereby resulting in a decreased prevalence relative to the number of cases born. The World Federation of Hemophilia (WFH) Report on the Annual Global Survey (RAGS) actually revealed significant differences in the reported hemophilia prevalence between countries with low and high gross national income [7].

The WFH estimated the total number of patients with hemophilia (PWH) at approximately 400.000, among whom 70-75% remain undiagnosed or untreated, mostly in developing countries [8-9]. As a rare, chronic, and cost-intensive condition, hemophilia is obviously not a priority in developing countries where governments focus their limited resources on public health issues, such as nutrition, immunization, sanitation, and treatment of infectious diseases [2;8;10]. In Sub-Saharan African countries, research on hemophilia is limited, with data mainly coming from South Africa [11], Senegal [10], Zimbabwe [12], Nigeria [13] and Cameroon [14]. Epidemiological data on hemophilia in Côte d'Ivoire are scarce [15]. Precise hemophilia data are, however, critical to enable government agencies to develop a national hemophilia care program.

Since 1993, The WFH Hemophilia Treatment Centre (HTC) twinning program has promoted the development of a collaborative network of HTC's around the world in order to help emerging centers to improve care for PWHs [16]. A twinning partnership was established in 2015 between the Ivoirian HTC of the Centre hospitalier universitaire of Yopougon in Abidjan and the international HTC of the Cliniques universitaires Saint-Luc in Brussels, Belgium. Côte d'Ivoire had a population of over 23 million inhabitants in 2017 [17]. In this country, the 2016 WFH RAGS reported 81 PWHs, of whom 0% on prophylaxis, and a mean per capita FVIII and FIX use of 0.032 and 0.005, respectively [7]. CFCs are supplied by humanitarian aid.

STUDY OBJECTIVES

This study was aimed at collecting accurate, systematic, and detailed demographic, clinical, and laboratory data on the whole identified Ivoirian hemophilia population. This ultimate goal was to better define the local needs, challenges, and pathways in order to improve hemophilia care, develop an appropriate landscape for future research, and provide healthcare planners with data so that sustainable resources can be allocated to hemophilia management.

PATIENTS AND METHODS

Patients

Between January and December 2017, we called all the Ivoirian PWHs to invite them to participate in this study that took place at the HTC of Yopougon in Abidjan, where most of them had previously been diagnosed. Candidates were identified either in the HTC's database or through family trees of PWHs followed at the Yopougon HTC. The patients, their parents, or legal guardians gave written informed consent for participating in the study. In total, 81 PWHs were included in the study. Only five PWHs who were lost to follow-up did not accept the invitation. The full protocol was approved by

the Ivoirian Ethics Committee (*Comité National d'Ethique de la Recherche*) and is registered on ClinicalTrials.gov (NCT03054662).

Methods

We conducted a cross-sectional descriptive study in the Ivoirian hemophilic population from January to December 2017. Data were prospectively collected during multidisciplinary standardized consultations held by both Belgian and Ivoirian teams comprising a hematologist, a physiotherapist, and a hemostasis laboratory member.

For each patient, we performed an in-depth face-to-face interview providing data on demographics, educational or professional activity, medical and surgical history, bleeding symptoms and circumstances, and age at diagnosis. A detailed pedigree was drawn to identify affected males in each family, list the causes of hemophilia-related deaths and age at death, and identify the obligate and possible carriers.

In 2016, a locally adapted logbook [18] was provided to each PWH (or parents) in order to record data about all bleeding episodes, annual bleeding rate (ABR), annual joint bleeding rate (AJBR), exposure days (ED), CFC consumption, use of non-substitutive treatments, and number of school or work days missed.

Regarding treatment, information was collected on blood and fresh frozen plasma transfusion history, CFC consumption (based on self-reports and logbook), co-medications including desmopressin (DDAVP), antifibrinolytic agents (tranexamic acid), iron supplementation, painkillers, anti-inflammatory drugs, traditional medicines, RICE (Rest-Ice-Compression-Elevation) protocol in case of hemarthrosis [19], physiotherapy and dental care.

Participants underwent a clinical examination comprising body mass index (BMI) calculation and a musculoskeletal assessment by an experimented

physiotherapist using the Hemophilia Joint Health Score (HJHS) 2.1 [20]. The HJHS 2.1 is an 11-item tool for assessing impairment of the six key index joints (elbows, knees, and ankles) in children aged 4-18 years [20]. Recent studies also demonstrated the HJHS reliability and validity in adult PWHs [21;22], and the HJHS 2.1 has been validated worldwide [23].

The biological workup included a complete blood count (Cell-Dyn Ruby, Abbott, IL, USA), and screening for HIV (Determine HIV-1/2 Combo, Alere, IL, USA), HCV (by detection of HCV antibodies) and HBV (by detection of HBsAg and anti-HBcore in first intention and if indicated anti-HBs antibodies) (ARCHITECT Combo, Abbott).

FVIII and FIX activities were measured by one-stage assay method on a semi-automated coagulometer (Option 4 Plus, Biomerieux, ME, France) using human plasma immunodepleted of FVIII and FIX (HemosIL, Werfen, Barcelona, Spain). A systematic inhibitor screening was performed on site, with oversight from the Belgian partner, by mixing studies (at two different occasions) and, if appropriate, with an inhibitor titration by the Nijmegen-Bethesda method [24]. In case of inhibitor suspicion after the first mixing study, PWHs were advised to avoid CFC for non-severe bleeding until inhibitor confirmation.

Statistical analysis

All data were entered into a structured electronic medical record and analyzed using SIGMASTAT and SIGMAPLOT (Systat Software Inc, San Jose, USA).

RESULTS

We collected data from 81 PWHs, with 85.1% of total participants and 88.4% of severe cases being <30 years (Table 1). The median (range) age at evaluation was 12 (1-64) years.

Table 1. Distribution of age and severity in the 81 Ivoirian patients with hemophilia.

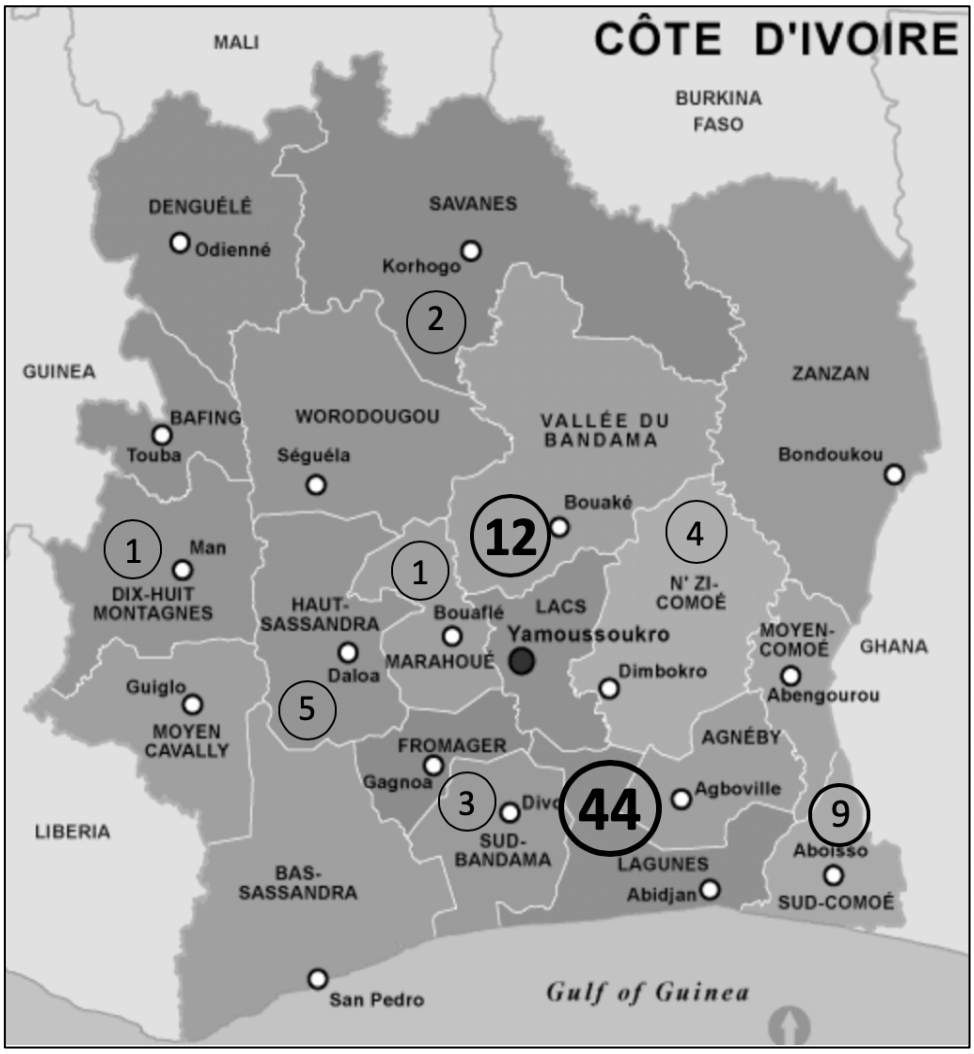
Type and severity of Hemophilia							
	Hemophilia A			Hemophilia B			
Age category, y*	Severe	Moderate	Mild	Severe	Moderate	Mild	% per age group
0-4	11	2	0	1	0	0	17,3
5-13	23	2	0	4	0	0	35,8
14-18	10	1	1	1	0	0	16,1
19-44	17	2	1	2	0	0	27,1
> 45	0	1	1	1	0	0	3,7
Total (n)	61	8	3	9	0	0	n = 81

**Age categories according to the distribution proposed in the World Federation Hemophilia Annual Global Survey*[7]

Socio-demographics and medical history

Regarding ethnicity, PWHs were classified as Akan (42%), Krou (23.4%), Mandé (21%), Gour (7.4%) and others (6.2%), which is consistent with the Ivoirian ethnic distribution [25]. A population-based spot map was drawn based on the PWHs' place of residence (Fig. 1). Patients were geographically clustered (54.3%) around Abidjan, where the HTC is located, and in the central-southern part of the country, with large regions of the country showing no cases. School attendance among children was 86%. Fifty-six % of adults had a professional activity and 39% were unemployed because of hemophilia condition.

Figure 1: Population-based spot map of hemophilia cases in Côte d'Ivoire (adapted from a map bought on eMapsWorld.com).



Malaria was the most frequent medical condition, and no orthopedic surgical procedure was reported, except a pelvic pseudotumor resection (performed in Morocco). The other medical and surgical histories are listed in Table 2

Table 2. Medical and surgical history in Ivoirian patients with hemophilia

Medical event	**n = 20**	**Surgical procedure**	**n = 18**
Malaria	12	Subcutaneous hematoma evacuation	5
Asthma	2	Tooth extraction	4
Fracture with conservative treatment	2	Appendicitis	3
Seizures (*)	1	Joint biopsy for hemarthrosis	3
Mental retardation (*)	1	Inguinal hernia repair	1
HIV infection (on retroviral therapy)	1	Pelvic pseudotumor resection	1
Hemorrhoids	1	Eyelid surgery	1
Total	20		18

**Intra-cranial bleeding complications*

Diagnostic circumstances and bleeding symptoms

For severe and moderate forms, the median age at diagnosis was 3 years (range: 7 days-34 years). The most frequent diagnostic circumstance was circumcision (32%) followed by spontaneous (23,5%) and traumatic (23,5%) bleeds, family screening (16%) and other surgery (5%). Despite a family history of hemophilia with, in some cases hemophilic relatives who died after circumcision (34.3%), 32 PWHs were circumcised without any hemostatic measure and 97% had postoperative bleeding, requiring blood transfusion in 56.2% of cases. At the time of diagnosis, blood exteriorization (mouth bleeds [44.7%] and skin wounds [10.5%]) accounted for 55.2% of spontaneous or traumatic bleeds; and hemarthrosis or hematomas accounted for 28.9%.

Pedigrees

In total, 57 families were included in our study. Sporadic cases, defined as cases with no other PWH (alive or deceased) within the family, were reported in 29.6% of patients. Pedigree analysis revealed a family history of

hemophilia in 57 PWHs (70.4%) belonging to 33 families, with a ratio of 1.68 PWH/family. In familial forms, the median (range) number of affected relatives for a PWH was 2 (1-11). Among these 33 families, we identified 63 deaths in affected relatives (ratio of 1.91 death/family) due to the following reasons: circumcision (33.3%), intracranial hemorrhage (14.2%), oral bleeding (12.7%), other bleeding (23.8%), and unknown causes (16%). Median (range) age of death in hemophilic relatives was 3 years (0-49). Among the 57 families in our study, we identified 83 obligate carriers (12 for HB and 71 for HA) and 248 possible carriers (30 for HB and 218 for HA). Pedigrees also made it possible to screen five PWH relatives, with hemophilia status being confirmed in three of them.

Treatments

Most PWHs (76.5%) were treated on demand: 21% had never been treated with CFC, cryoprecipitate, or plasma (13 severe, 2 moderate, and 2 mild forms; median age: 12 years, range: 1-39 years), and 2.5% were treated with CFC every 1-2 weeks. The type of product was distributed as follows: recombinant (20%), plasma-derived (14%), both (20%), and unknown (46%). Extended half-life products were used in 10.9% of patients, with two additionally treated with cryoprecipitate. Self-infusion was performed by 4.7% of adult PWHs. It took several months before all the 81 PWHs or parents started to complete the logbooks and at the time of writing this paper, no reliable data were available regarding the ABR, AJBR, EDs, CFC consumption and the number of school or working days missed during the study period.

Whole blood transfusion was reported after 23 circumcisions, five other surgical procedures, and 32 spontaneous or non-surgical traumatic bleeds. Pre-surgery CFC prophylaxis was reported in a single procedure (appendicectomy). Tranexamic acid was used by 43% of PWHs in case of bleeding symptoms. None had been evaluated for or treated with DDAVP.

Bypassing agents and immune tolerance therapy are currently unavailable in Côte d'Ivoire.

Other reported treatments included iron supplementation in 34.5% of patients and painkillers consisting in paracetamol in 63%, non-steroidal anti-inflammatory drugs in 12.3%, Cox-2 inhibitors in 11.1%, and traditional herbal medicine in 7.4%. Regular physiotherapy had been initiated in 11.1%. In case of joint bleeds, the RICE protocol [19] was not systematically applied or was sometimes inappropriate (application of hot water, vigorous massage, etc.). Most patients (82.7%) had never had dental care despite 50.6% of them experiencing regular dental or gingival bleeds. The main indication for dental intervention was tooth extraction. Preventive dental care remained exceptional.

Clinical characteristics

BMI was calculated using the kg/m^2 formula in adults and the BMI-for-age formula [26] in children (0-19 years). In adults, the median BMI (range) was $20.7kg/m^2$ (16.5-32.0), with 32% underweight (BMI <18.5), 56% normal-weight (BMI 18.5-24.9), and 12% overweight/obese (BMI $\geq$25) patients. In children, the median BMI was $15.9kg/m^2$, with 16.1% underweight (percentile (P) $\leq$5), 80.3% normal-weight (P 5-84.9), 3.6% overweight/obese (P $\geq$85) patients.

After excluding children aged <4 years (n=8) [20] and minor forms of hemophilia (n=3), participants were divided into following age categories: 4-11 years (n=25), 12-18 years (n=19), and >18 years (n=26). The HJHS was calculated on 410 joints, with the exclusion of 10 joints (one recent femoral fracture, two elbow and one ankle hemarthrosis, and one knee arthrodesis). Joint impairment was observed in 91.4% of patients. The knees were the most affected joints, followed by elbows and ankles, with the worst scores observed in adults (Table 3)

Table 3. Hemophilia Joint Health Score of ankles, knees and elbows in Ivorian patients with hemophilia

Age Category	Joint by Age Category	Median score (range)
4-11 years	Elbow L + R score (max=20)	0 (0-12)
12-18 years		0 (0-8)
> 18 years		4,5 (0-15)
4-11 years	Knee L + R score (max=20)	0 (0-14)
12-18 years		5 (0-17)
> 18 years		8 (0-16)
4-11 years	Ankle L + R score (max=20)	0 (0-9)
12-18 years		0.5 (0-10)
> 18 years		2.5 (0-13)

R, Right; L, Left

Laboratory results

Anti-FVIII antibodies were found in five severe HA patients (Table 4) and one patient (whose brother has a persistent inhibitor) had a transient inhibitor, which corresponds to an inhibitor prevalence of 7.8% among the 64 PWHs previously exposed to CFC. For the above-mentioned reasons, no accurate data about cumulative EDs was available, and exposure could only roughly be evaluated based on patients' or parents' reports. Molecular analysis (Laboratory of Genetic and Molecular Biology, Cochin Hospital, Paris, France) was obtained for these five patients with inhibitors.

The median (range) hemoglobin level was 11.2 g/dl (6.53-16.7), with a <10g/dl level found in 26% of PWHs from Côte d'Ivoire where malaria is endemic [17]. The median (range) platelet count was 307 x 10^9/L (121-768). One adult was HIV-positive and another HCV-positive. Data were missing for two viral serologies and four hemograms.

Table 4. Characteristics of the 5 Ivoirian patients with hemophilia with inhibitors

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Type of hemophilia	A	A	A	A	A
Severity of hemophilia*	Severe	Severe	Moderate	Severe	Severe
Age of hemophilia diagnosis	4 years	2 years	1 week	18 months	18 months
Familial hemophilia	Yes	Yes	Yes	Yes	Yes
Age at time of inhibitor detection	23 years	18 years	22 years	14 years	7 years
Inhibitor titre**	1,4 BU	2,2 BU	2,2 BU	0,7 BU	6,8 BU
Inhibitor history in the family	No	Yes	No	No	No
Factor*8* gene mutation	Inversion intron 22	Del exon 7	Substitution C5587-2A>G	Inversion intron 22	Inversion intron 22
Estimated age of first exposure	Childhood Not more specified	3 years	1 week	8 years	4 years
Estimated cumulative ED	20-30	30-40	100	20-25	30-40
Treatment regimen	On demand	On demand	On demand	On demand	On demand

**Based on molecular analysis; **Measured at distance of FVIII exposure; ED: Exposure day*

DISCUSSION

Epidemiological data on hemophilia in Côte d'Ivoire are scarce, and this is the first study on hemophilia since the publication by Sangare *et al.* in 1990 [15]. Our work provides a robust and valuable local database that will enable the Ivoirian HTC to participate in registries, and international clinical trials. The accurate and detailed data obtained highlight the local needs of PWHs and are useful to propose adapted solutions and prompt government agencies to improve hemophilia care.

The prevalence, age, and severity distribution of hemophilia found in our study are consistent with those usually found in developing countries with low economic income and restricted access to CFC [3;5;6]. The PWH's geographical distribution emphasizes the very limited access to adequate diagnosis and appropriate care in some Ivoirian regions and the need to develop a close collaboration between proximity care centers and the Abidjan HTC.

Frequent surgeries included subcutaneous hematoma evacuation by incision and joint biopsy for hemarthrosis, which illustrates the insufficient diagnosis of hemophilia. The absence of orthopedic surgical procedure reflects the restricted access to CFC and lacking surgical experience in PWHs in the country. Treating orthopedic complications of hemophilia and performing surgery with lower doses of CFC are, however, feasible in developing countries [27-28] and should be developed.

PWHs and their families have insufficient knowledge about the clinical hallmarks of hemophilia and its mode of transmission, as illustrated by the delayed diagnosis, the bleeding pattern leading to diagnosis, the discrepancy between the number of PWHs with a family history and the number of systematic family screening, as well as the number and young age of hemophilia-related deaths among PWH relatives. Using pedigrees was of great value to identify potential PWHs and possible or obligate carriers

within families. Detection of hemophilia early in life is critical, as circumcision was major cause of bleeding, transfusion, and death in our population. This situation is common in Africa where circumcision is the first surgery in young boys, mainly supported by religious, cultural, and social reasons [29]. Thus, promoting adapted educational programs for PWHs, carriers, and health professionals is mandatory to improve awareness of hemophilia and take appropriate preventive and therapeutic measures so as to avoid hemorrhages and their complications. Adapted educational tools have been developed for PWHs and their families in Côte d'Ivoire [30] and their impact is under evaluation.

Logbook completion appeared more complex than expected, as participants needed some time to familiarize with systematic data recording. Furthermore, the barrier of literacy should not be underestimated. Instructions were given orally and in writing and repeated to PWHs in order to enhance the logbook completeness and obtain in a near future data regarding ABR, AJBR, and the number of school and working days missed. Recording all bleeds will help supporting improved access to CFC and prophylaxis in Côte d'Ivoire.

The data regarding substitutive treatments highlight the poor access to CFC in Côte d'Ivoire, with 21% of PWHs who had never been treated, and the absence of prophylaxis even in children. Non-substitutive hemostatic treatments, such as DDAVP and antifibrinolytics, are underused especially in the prevention and treatment of mucosal bleeds. Systematic and appropriate use of the RICE protocol, painkillers, and physiotherapy is lacking and should actively be promoted.

The prevalence of overweight and obese PWHs is similar to that in the United States, where 35% of the general population are obese [31]. The increasing overweight/obesity prevalence has been observed in developing countries [32]. In our study, overweight/obesity prevalence was low both in adults (12%) and children (3.6%).

Initiating prophylaxis is urgent, especially in young children, in order to preserve their joints, since the median HJHS score was 0 for the six index joints in children aged <12 years and significant damages were observed in the 12-18 years. Both in children and adults, the most clinically affected joints were the knees, followed by the elbows and ankles. This pattern was observed in developed countries until prophylaxis was introduced and nowadays, the ankle is the most common target joint [33]. Musculoskeletal health improvement and disability prevention will also require the implementation of regular physiotherapy, RICE measures, and rehabilitation medicine approaches [34].

The low inhibitor prevalence is probably related to the limited exposure to CFC and absence of prophylaxis in Côte d'Ivoire. The low titers in our population can be explained by CFC exposure avoidance during the months before inhibitor's confirmation by the Nijmegen-Bethesda method [24]. Since January 2018, low dose prophylaxis was initiated in 15 young boys with hemophilia at the HTC of Yopougon. A systematic inhibitor monitoring in this population and in PWHs who have now an improved access to on demand therapy will be carried out.

The HIV and HCV prevalence in PWHs was similar to that in 2016 in the Ivoirian general population, reflecting the safety of blood products and low exposure to CFC [17;35]. In 2016, the UNAIDS estimated the HIV prevalence in the country at 2.7% in adults aged 15-49 years [35]. The hepatitis C prevalence was estimated at 1%-3% in 2016 [17].

CONCLUSION

This study highlights the value of simple, feasible, and inexpensive tools, such as pedigrees and logbooks, to collect robust data about hemophilia in developing countries. Detailed characteristics of Ivoirian PWHs and their needs are the basis for developing and implementing locally appropriate strategies to improve screening, diagnosis, preventive care, treatment, and education. This work also demonstrated the benefits and the strengths of a

multidisciplinary and comprehensive approach in hemophilia care in the setting of the WFH twinning program.

ACKNOWLEDGEMENTS

The capacity-building component of this project in Côte d'Ivoire was funded by grants from the WFH twinning program, SOBI and SANOFI Belgium.

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Chapter 2

Hemophilia carrier's awareness, diagnosis, and management in emerging countries: a cross-sectional study in Côte d'Ivoire.

Orphanet Journal of Rare Disease. 2019 Feb 1;14(1):26.

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SUMMARY

Background: Little data is available on awareness of hemophilia carrier condition or associated bleeding risk and management in Sub-Saharan African countries. This study sought to identify hemophilia carriers in Côte d'Ivoire in order to collect data on demographics, bleeding phenotype, and laboratory results. Another purpose was to provide Ivoirian hemophilia carriers with counseling on their risk of bleeding and of having children with hemophilia. A 12-month prospective study was conducted involving Ivoirian hemophilia carriers recruited through pedigree analysis pertaining to 81 hemophilia patients followed-up at the Yopougon Hemophilia Treatment Center in Abidjan. They were assessed using in-depth interviews, pedigree analysis, and laboratory testing.

Results: Sixty-one subjects comprising 27 obligate and 34 possible carriers were recruited. None had previously been assessed, with 64% unaware of their carrier status despite a familial history of hemophilia in 69%. The most frequently reported bleeding symptom was menorrhagia (31%). Prolonged bleeding was reported after vaginal delivery in 19.6%, post-surgery in 4.9%, and post-dental extraction in 4.9%. Only one carrier was treated with tranexamic acid, with no other hemostatic therapy recorded. The median (range) clotting FVIII was 0.85 IU/mL (0.24-1.90 IU/mL) and FIX 0.60 IU/mL (0.42-1.76 IU/mL) in hemophilia A and B carriers, respectively. Hemophilia A carriers had a FVIII < 0.5 IU/mL in 12.5%.

Conclusions: This study highlights the need of implementing care for hemophilia carriers in developing countries, and the high value of pedigree analysis for carrier identification, along with the relevance of diagnosis, treatment, and education of carriers, families, and caregivers.

INTRODUCTION

Hemophilia is a congenital X-linked recessive bleeding disorder causing low levels of Factor VIII (FVIII, hemophilia A [HA]) or Factor IX (FIX, hemophilia B [HB]), occurring in approximately 1 in 5.000 for HA and 1 in 20.000-30.000 for HB) live male births [1], with a similar incidence across ethnic populations [2]. The condition affects men while their female relatives are likely to be hemophilia carriers. It has been estimated that for each male with hemophilia, there are five potential female carriers [3]. Carriers are at risk of having sons with hemophilia but may also carry a bleeding risk [4].

A wide range in clotting FVIII or FIX levels is observed in carriers, independently of hemophilia severity within the family [5], which is attributed to the lyonization phenomenon (random X-chromosome inactivation during embryonic life) [6]. In HA carriers, Factor VIII levels display a considerable variability, ranging from very low to the upper limit of normal [7]. Carriers in the mild hemophilia range are defined by factor levels <0.30 IU/mL, though there is no consensus about this threshold, and are labeled “symptomatic carriers” [8]. Carriers may show an increased bleeding tendency [5], even those with normal FVIII levels [9;10]. Assessing bleeding risk is therefore mandatory in all obligate or potential carriers [5].

Previously, pedigree analysis and clotting FVIII/IX levels were applied for diagnosing hemophilia carriership [11]. Since the 1980’s, DNA analysis has been available, which ascertains hemophilia carriership in most developing countries [12;13]. Currently, comprehensive care in hemophilia patients comprises carrier factor testing, genetic counseling, and prenatal diagnosis [5;8;14]. Detection of carriers is likewise relevant considering the 3.5-4% incidence of intracranial bleeding in affected male newborns [14].

In developing countries, carrier detection proves even more crucial for early hemophilia diagnosis in children, because they often die early in life due to the lack of diagnostic opportunities, absence of care facilities, and limited

access to clotting factor concentrates (CFC) [15]. As circumcision generally represents the first surgical intervention in African boys with hemophilia, it is a major cause of bleeding and death [16]. Unawareness of carrier condition and bleeding risk, as well as healthcare givers' ignorance concerning appropriate management modalities, are also major issues of concern in these countries [4;17]. In Sub-Saharan Africa, little is known about hemophilia carriers [3;4;18;19], with only very limited access to molecular testing [18;20], and pedigree and clotting FVIII and IX analyses being often the principal screening and assessment tools.

In 2015, a twinning partnership was established between the Ivoirian hemophilia treatment center (HTC) of the *Centre Hospitalier universitaire (*CHU) of Yopougon in Abidjan and the international HTC of the *Cliniques universitaires Saint-Luc* in Brussels, Belgium. This collaboration has provided the opportunity to identify and assess potential and obligate hemophilia carriers among families of patients with hemophilia (PWH) in this location.

STUDY OBJECTIVES

This study aimed to identify obligate and potential carriers of hemophilia in Côte d'Ivoire and collect detailed information on their demographics, pedigree, bleeding phenotypes, and laboratory results. Yet, its ultimate goal was to provide Ivoirian hemophilia carriers with appropriate counseling on the risk of bleeding and of having children with hemophilia.

PATIENTS AND METHODS

Patients

Between January and December 2017, we invited all the ≥12-year-old female Ivoirians, identified as HA or HB carriers, to participate in this study conducted at the Yopougon HTC. Candidates were recruited via detailed family trees of 81 PWHs followed-up at the HTC. The carriers, their parents,

or legal guardians provided written informed consent for participating in the study.

Methods

This was a single-center cross-sectional study conducted from January to December 2017 on the Ivoirian hemophilia carrier population. Data were prospectively collected during standardized consultations held by Belgian and Ivoirian teams including a hematologist and hemostasis laboratory member.

For each carrier, an in-depth face-to-face interview was performed gathering data on carrier status awareness, socio-demographics, educational activity, employment, medical, obstetrical, and surgical history, bleeding symptoms and circumstances, requirement and indication for whole blood transfusion, as well as co-medications including estroprogestative contraception, iron supplementation, and hemostatic and antifibrinolytic agents' usage. A specific attention was paid to menorrhagia assessed by the bleeding questionnaire described by *Tosetto et al*, 2006. Women who had one point or more for this item were considered as having menorrhagia.

To identify carriers in each family, a detailed pedigree was drawn. Efforts were made to investigate as many generations as possible. Of note is that the family trees were repeated at each evaluation of several different members of the same family, whether carriers or PWHs. This allowed us to establish exhaustive and validated trees, after merging, correcting and updating steps. Mendelian laws were applied to determine the probability of being a carrier. The carriers were categorized as obligate or possible/probable carrier, based on the pedigree, the level of FVIII or FIX and according to the WFH definitions [21].

The biological workup comprised a complete blood-count (Cell-Dyn Ruby, Abbott) and FVIII and FIX activity measurements by one-stage assay method

on a semi-automated coagulometer (Option 4 Plus, Biomerieux) using human plasma immunodepleted for FVIII and FIX (HemosIL, Werfen).

Statistical analysis

All data were entered into a structured electronic medical record and analyzed using SigmaStat and SigmaPlot (Systat Software Inc., USA). The pedigrees were drawn using the Progeny Free Online Pedigree Tool from Progeny Software (Progeny Software LLC, FL., USA).

RESULTS

Based on pedigree analysis of 81 Ivoirian PWHs, we identified 83 obligate carriers (12 for HB and 71 for HA) and 248 possible carriers (30 for HB and 218 for HA), resulting in an average of four carriers per PHW. A total of 61 carriers for severe and moderate hemophilia A and B were included with 27 obligate carriers (3 for HB and 24 for HA) and 34 possible carriers (2 for HB and 32 for HA) (Table 1). The median (range) age at evaluation was 34 (13-58) years. None had previously been assessed nor were clotting FVIII or IX levels measured prior to the WFH's twinning program, with 64% unaware of their carrier status.

Table 1. Distribution of hemophilia carriers in Côte d'Ivoire

Obligate carriers	***n* =**	**Possible carriers**	***n* =**
Obligate carriers for severe HA	23	Possible carriers for severe HA	29
Obligate carriers for moderate HA	1	Possible carriers for moderate HA	3
Obligate carriers for severe HB	3	Possible carriers for severe HB	2
Total	27		34

Obligate and possible carriers for hemophilia were determined by pedigree analysis
HA: Hemophilia A; HB: Hemophilia B

Socio-demographics and medical history

Regarding ethnicity, carriers were classified as Akan (36%), Krou (36%), Mandé (14,8%), Gour (10%), or other (3,2%). Most were living in or around Abidjan (54%), had a professional activity (47.6%), were homemakers (36%), with the remainder either students or in professional training (16.4%). Their marital status was as follows: married (44%), single (28%), in couple (15%), divorced (11%), or widowed (2%). Malaria, which is endemic in Côte d'Ivoire, was the most common medical condition [22]. The HIV prevalence in carriers (3,3%) was similar to that of the Ivorian general population [23]. Surgical histories were recorded in 19,7%, with cesarean and appendectomy as the most common procedures (Table 2).

Table 2. Medical and surgical history

Medical event	***n* = 26**	**Surgical procedure**	***n* = 14**
Malaria	6	Caesarian section	7
Peptic ulcer/gastritis	5	Appendicectomy	6
Hypertension	4	Inguinal hernia repair	1
HIV infection (On retroviral therapy)	2		
Ectopic pregnancy	2	Tooth extraction (non-surgical)	15
Uterine fibroid	2		
Asthma	1		
Allergies	1		
Arthrosis	1		
Glaucoma	1		
Bowel disease	1		

Pedigrees

Detailed pedigrees were obtained through 142 interviews with 61 carriers and 81 PWHs. The 61 carriers studied were issued from 32 families. A familial form of hemophilia was present in 20 families involving 42 carriers and a sporadic form, defined as cases with no other PWH – whether alive or deceased - within the family, in 12 families involving 19 carriers. In familial forms, the median number of affected relatives per carrier was 4 (range 2-11). The median (range) number of obligate carriers and possible carriers per family for familial forms was 2 (0-4) and 4 (1-14), respectively.

In sporadic forms, the median (range) number of possible carriers per family was 3 (1-6). Among these 20 families, 39 PWH's death cases were identified, 12 of whom were related to circumcision and 7 to intracranial hemorrhage. The median number of children per carrier was 2 (range 0-9) and that of sons affected with hemophilia per carrier was 1 (range 0-6).

Bleeding symptoms and circumstances

The most frequently spontaneous bleeding symptom was excessive or prolonged menstrual bleeding, with 31% prevalence among the whole carrier population and 26% prevalence in the obligate carrier group. Other unprovoked hemorrhagic symptoms, such as nose bleeds, cutaneous bruising, gum bleeding, or hemarthrosis, had <5 % prevalence (Table 3).

Prolonged bleeding after vaginal delivery or miscarriage was reported in 19.6% and 2.2% of the 46 carriers, respectively, during previous pregnancies involving 160 deliveries and 6 miscarriages. Postoperative bleeding was recorded in 4.9% of cases upon 2 caesarians and 1 episiotomy (stitches rupture). A prolonged bleeding after tooth extraction was mentioned in 4.9%. Of note, these tooth extractions were simple, non-surgical.

Table 3. Spontaneous bleedings in Ivoirian hemophilia carriers

Event	All carriers (n= 61) Event/total (%)	Obligate carriers (n= 27) Event/total (%)	Possible carriers n= 34) Event/total (%)
Heavy/prolonged periods	19 (31%)	7 (26%)	12 (35%)
Nose bleeding	3 (5%)	3 (11%)	2 (6%)
Gum bleeding	3 (5%)	1 (3,7%)	2 (6%)
Bruising	2 (3%)	1 (3,7%)	1 (3%)
Joint bleeds	0 (0%)	0 (0%)	0 (0%)

Treatments

No carrier had previously been treated with CFC, cryoprecipitates, or fresh frozen plasma. Whole blood transfusion was reported in 3 carriers (1 symptomatic obligate carrier for HB and 2 obligate carriers for HA), 1 after vaginal delivery, 1 after cesarean, and 1 after a complicated episiotomy. No transfusion was recorded after spontaneous bleeding. One carrier reported a blood transfusion for anemia in childhood. Tranexamic acid was used on-demand by only one symptomatic carrier for severe HA while experiencing menorrhagia, mucocutaneous bleeding, and postpartum hemorrhage. None of the HA carriers had previously been assessed nor treated with Desmopressin (DDAVP), or preventively treated with hemostatic therapies. Iron supplementation was recorded in 3.3%. Eighteen % were on hormonal therapy, using estroprogestative pills (9), implants (1), or subcutaneous injections (1). Other treatments comprised paracetamol in 14.8%, anti-malarial drugs in 4.9%, and antiretroviral therapy in 3.3 %. No one reported using anti-inflammatory drugs.

Laboratory results

In 38% of participants, clotting factor activity had previously been determined in the 2016 WFH's twinning program, with the lowest value considered for this study. The median (range) clotting FVIII level in the 56 HA carriers was 0.85 IU/mL (0.24-1.90 IU/mL). The median (range) clotting FVIII level in obligate and possible HA carriers were 0.75 IU/mL (0.24-1.90 IU/mL) and 0.92 IU/mL (0.60-1.57 IU/mL), respectively. Overall, 7 (12.5%) HA carriers had a FVIII < 0.50 IU/mL. In the 5 HB carriers, the median (range) FIX level was 0.60 IU/mL (0.42-1.76 IU/ml), with 2 (40%) displaying FIX <0.50 IU/mL. Bleedings in correlation with factor level decreases are listed in Table 4. Table 5 details FVIII and IX levels in carriers, along with the HA carrier percentages on hormonal therapy. The median (range) hemoglobin level was 11.9g/dL (8.81-14.8), with a level <10g/dL found in 8.8%. The median (range) platelet count was $243x10^9$/L (57-415). Blood counts were missing in 4.

Table 4. Spontaneous and post-operative bleedings according to FVIII and FIX levels

Bleeding event	**Clotting Factor VIII or IX level (IU/mL)**		
	> 0.60 IU/ml (%) (*n*= 46)	Between 0.41 and 0.60 IU/mL (%) (n= 10)	≤ 0.40 IU/ML (%) (n= 5)
Heavy/prolonged periods	16 (35%)	1 (10%)	2(40%)
Nose bleeding	2 (4%)	2(20%)	1(20%)
Gum bleeding	2 (4%)	0 (0%)	1(20%)
Bruising	1 (2%)	0 (0%)	1(20%)
Post-partum	6 (13%)	2(20%)	1(20%)
Post-abortum	1 (2%)	0 (0%)	0 (0%)
Post-operative	0 (0%)	2 (20%)	1(20%)

Table 5. Clotting FVIII and IX levels among Ivoirian hemophilia carriers

Factor VIII level	**> 0.60 IU/ml (%)**	**Between 0.41 and 0.60 IU/mL (%)**	**≤ 0.40 IU/ML (%)**
Carriers of HA (n=56)	78,6% [8]	12,5% [1]	8,9% [0]
Obligate (n=24)	30,4% [3]	3,6% [0]	8,9% [0]
Possible (n=32)	48,2% [5]	8,9% [1]	0% [0]
Factor IX level	**> 0.60 IU/ml (%)**	**Between 0.41 and 0.60 IU/mL (%)**	**≤ 0.40 IU/ML (%)**
Carriers of HB (n=5)	40%	60%	0%
Obligate (n=2)	0%	60%	0%
Possible (n=2)	40%	0%	0%

[] *Number of carriers on hormonal therapy*
HA: Hemophilia A; HB: Hemophilia B

DISCUSSION

Limited research has been conducted so far in Sub-Saharan countries on hemophilia carriers [3;4;18;19]. Accurate and detailed data in this population are highly relevant to prevent and treat bleedings appropriately, offer genetic counseling, and diagnose hemophilia early in life in boys, with the aim to avoid death and severe complications, mainly due to intracranial bleeding and circumcision. This is the first prospective study focused on detection and assessment of Ivoirian hemophilia carriers.

Pedigree analysis rendered it possible to identify 331 possible or obligate carriers, of which 61 were considered for analysis. Considering the theoretical 400 carriers linked to the 81 PHWs from the HTC of Yopougon, pedigree was of great value to target carriers within PWH's families. In the absence of molecular testing availability, pedigree is a cost-effective and useful tool for assessing the carrier status of females from PWH's families

and can be of a great help in providing genetic counselling [24]. Family trees were sometimes large and complex to build up. It was thus repeated through several family members, be merged, corrected, and updated in order to obtain quality data.

Despite numerous affected relatives or hemophilia-related deaths (31% after circumcision), at least in the familial forms, 64% of participants were unaware of their carrier status. None had ever been clinically assessed, nor had FVIII or IX level measurements been conducted prior to the twinning program. No carrier had ever had DDAVP testing, with only one carrier previously treated with tranexamic acid for bleeding. These data highlight the lack of the carriers' knowledge of hemophilia inheritance and their bleeding risks, along with the ignorance of healthcare providers concerning their increased bleeding risk and bleeding management. This highly relevant unawareness about carrier condition has already been reported in studies conducted in India and South Africa [4;16;25].

In our study, 44.3% of carriers reported spontaneous bleeding, with menorrhagia the most common symptom. This is in line with data from other studies focused on hemophilia carriers [9;10], several of which were conducted in African countries [3;4]. The rate of other unprovoked bleedings, such as epistaxis 5%, gingivorrhagia 5%, and bruising 3%, proved low in our cohort, in comparison with previous studies [4;10]. No hemarthrosis was reported. Postpartum bleeding frequency, reported to vary in the scientific literature [4;10;19], was estimated at 19.6% in our cohort. Postoperative hemorrhage was reported in 4.9% of cases and dental extraction hemorrhage in 20%. In published reports, there were higher postsurgical bleeding rates, occurring mainly after tonsillectomy [5] and tooth extraction [9;10]. Several studies conducted in Africa demonstrated lower tooth extraction bleeding rates [4;19]. In our study, however, the number of surgical procedures was limited, with only appendectomy, caesarian section, and non-surgical tooth extractions considered. Another hypothesis to account for the low frequency of hemorrhagic symptoms

could be the fact that it was the first time Ivoirian carriers were questioned about their bleeding symptoms, or due to their unawareness of increased bleeding risk.

Although most carriers exhibited normal-range factor levels, a significant proportion displayed decreased factor activity (between 0.40 and 0.60 IU/mL in 12.5 % of HA carriers and 60% of HB carriers and <0.40 IU/mL in 9 % of HA carriers and 0 % of HB carriers). Bleeding was recorded in the three factor level categories. Our findings are consistent with literature data indicating that carriers may exhibit variable factor levels [7], with an increased bleeding tendency for those with clotting factor levels at the distribution extremes (<0.40 IU/mL), with mildly-reduced clotting factor levels (0.41-0.60 IU/mL) [5] or even normal FVIII activity [9;10].

Our study displays several limitations: 1) molecular testing was unavailable to formally establish or confirm the carrier diagnosis; 2) factor levels were measured only once in 62% and twice in 38%, and this measurement could not be repeated at distance of hormonal therapy; 3) the factor activity testing was performed using only a one-stage coagulation assay; 4) we had no information on blood group and von Willebrand antigen/activity; 5) anemia interpretation proves difficult in Côte d'Ivoire where malaria is endemic [22].

Given our study data and within the frame of the WFH's twinning program, actions have been implemented at Yopougon's HTC designed to improve the care of hemophilia carriers. All the participants were personally informed, using either oral or written support, about their carrier status, bleeding risk, preventive and therapeutic hemostatic measures to apply if necessary, need for a medical follow-up especially during pregnancy and upon delivery, as well as the relevance to screen all male children for hemophilia early in life and at least before circumcision. The seven carriers with a FVIII level <0.50 IU/mL underwent DDAVP testing, and the use of tranexamic acid was encouraged as necessary. Educational booklets and workshops were

developed and provided, highlighting the need to actively screen carriers among PWH's families, and assess their bleeding risk by factor level measurements.

Possible and obligate carriers were provided with the same information, as there is actually no regular access to DNA analysis in Côte d'Ivoire. Mother education proves to be the cornerstone towards improving PWH's care, as gender plays a key role in shaping the burden of care in Africa, with women more likely than men to take on caregiving activities [3]. Moreover, these educational sessions offered the opportunity to address carriers' personal and familial psychosocial burden - not to be underestimated in developing countries [4]. This awareness campaign is scheduled to be repeated over time, with its outcome monitored through surveys and corresponding data published.

CONCLUSION

The current study illustrates the lacking awareness of the hemophilia carrier condition and its implications for carriers, PWH's families, and medical community in Côte d'Ivoire and by extension in other developing countries. The data highlight the need for implementing dedicated care and developing guidelines taking in account local conditions and priorities, enabling carriers to be identified, their factor levels to be assayed, and counseling on the possible chances of bleeding and having children with hemophilia.

This work underlines the significance of repeated and detailed pedigrees in carrier screening, especially in countries with limited molecular testing. Providing access to individual assessment, establishing appropriate hemostatic treatment plans, and using adjunctive hemostatic drugs (DDAVP, antifibrinolytics) should be actively promoted. Education and information of the carriers, their families, and healthcare givers form the basis enabling us to carry out this major project in Côte d'Ivoire.

This research demonstrates the benefits and strengths of a multidisciplinary and comprehensive approach in holistic hemophilia care involving all family members including females in the WFH twinning program setting.

ACKNOWLEDGEMENTS

The authors wish to thank the World Federation of Hemophilia for their support of this project through the twinning program.

FUNDING

This project in Côte d'Ivoire was funded by grants from the WFH's twinning program, SOBI and SANOFI Belgium.

ETHICS APPROVAL

The full protocol was approved by the Ivoirian Ethics Committee (Comité National d'Ethique de la Recherche number 002/MSHP/CNER-kp) and is registered on ClinicalTrials.gov (NCT03054662).

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Chapter 3

Inhibitor epidemiology and genetic-related risk factors in people with hemophilia from Côte d'Ivoire.

Haemophilia. 2019 Jan;26(1):79-85.

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SUMMARY

Introduction: In Sub-Saharan Africa, inhibitor prevalence data in people with hemophilia (PWH) are scarce, as are data on genetic or treatment-related risk factors.

Aims and Methods: We performed a prospective study on PWH from Côte d'Ivoire to collect data on inhibitor prevalence, create a database of hemophilia genotypes, establish correlations between inhibitor presence and genetic variants identified amongst Ivoirian PWH, and evaluate exposure to CFC.

Results: The study included 54 unrelated participants (43 severe, four moderate, two mild hemophilia A, and five severe hemophilia B). PWH were treated on-demand with various product types for short periods, non-intensively, and using low-dose regimens. We reported similar distributions of intron 22 inversions (39.5 %), point pathogenic variants (32.6 %), and rearrangements in Ivoirian severe hemophilia A patients versus non-African ethnic groups. The haplotypes H1 (29.6 %), H2 (36.3 %), and H3 (34.1%) frequencies in hemophilia A was consistent with results published on African populations. We identified eight new causal variants. An inhibitor was found in 12% of hemophilia A patients previously exposed to replacement therapies. Among PWH with inhibitors, 66.7% had a positive intron 22 inversion, and 50% the H1 haplotype.

Conclusion: This study provides original data on molecular diagnosis of hemophilia, inhibitor prevalence, and risk factors for inhibitor development previously associated with inhibitors in Côte d'Ivoire. The low inhibitor prevalence likely reflects the limited exposure to replacement therapy in Côte d'Ivoire. Further larger, multicentric and international studies are needed to gain more insight on inhibitor incidence and risk factors in African PWH.

INTRODUCTION

Despite tremendous improvements in hemophilia treatment over the last decades, the development of an inhibitor remains the greatest complication for people with hemophilia (PWH) [1] who are treated with clotting factor concentrates (CFC). The management of inhibitors is even more challenging in resources-constrained countries due to limited access to CFC, no regular access to prophylaxis treatment, immune tolerance therapy, or by-passing agents [2].

The onset of inhibitors remains complex, modulated by genetic and environmental factors that are not yet fully understood. This phenomenon has primarily been studied in Caucasian populations from developed countries. In hemophilia A [HA] patients, an important predictor of inhibitor development is the F*8* gene pathogenic variant, followed by disease severity and positive family history [1]. Intron 22 inversion, the most common F*8* variant, displays an inhibitor incidence of 21% in severe HA, while large deletions involving multiple domains shown to exhibit an 88% proportion of inhibitor formation [3].

PWH of African heritage in North America bear an increased risk of inhibitor development, up to twice that of Caucasians [4-6]. The mechanisms accounting for these ethnic differences remain unclear. As the hemophilia genetic causing variant spectrum does not differ among ethnic groups, other explanations for the higher incidence of inhibitors in black PWH may be related to genetic variations on immunoregulatory genes or environmental factor related to the modalities of replacement treatment [4;7]. Although Viel and colleagues found that differences in Factor VIII (FVIII) haplotype among black patients and recombinant FVIII products could explain this difference [5], findings from other large cohort studies did not supported this hypothesis [8;9].

Treatment-related risk factors for inhibitor development were extensively studied in previously untreated patients [10-12], and along with the number of exposure days (ED), the concept of danger days has recently been introduced in the pathophysiology of inhibitors [13]. Several environmental factors influence the risk of inhibitor development, such as age and reason for the first infusion, the treatment intensity (dose of FVIII), and the setting (bleeding, trauma, or surgery) [10;13]. As access to CFC widely varies worldwide with no or extremely limited access in most developing countries [2;14], the impact of treatment-related factors in resource-constraints countries could differ but this was not well studied so far.

In Sub-Saharan African countries, data on inhibitor prevalence and causal hemophilia variants are scarce [15-18]. In 2015, a World Federation of Hemophilia (WFH) twinning program was established between the Yopougon hemophilia treatment center (HTC) in Abidjan, Côte d'Ivoire, and the international HTC of the *Cliniques universitaires Saint-Luc* in Brussels, Belgium.

In this setting, we studied genotypes, inhibitor prevalence, genetic related risk factors and exposition to CFC among Ivoirian PWH. The study was conducted to determine the background inhibitor prevalence just prior to initiating a low-dose prophylaxis program in children with hemophilia, rendered possible by improved access to CFC through WFH donation programs.

STUDY OBJECTIVES

We initiated a prospective study in Ivoirian PWH designed to: (I) assess the inhibitor prevalence; (II) create a database (including haplotypes) of hemophilia genotypes; (III) examine the correlation between inhibitor prevalence and causal hemophilia variants/haplotypes; (IV) collect data on exposure to CFC.

PATIENTS AND METHODS

Patients

The study was conducted from January to December 2017 at the HTC of Yopougon, located in Abidjan. This is the unique HTC in Côte d'Ivoire, and the only place where PWHs are provided with CFC, exclusively issued from humanitarian aid. We invited all identified 81 PWH belonging to 57 different families, registered and regularly followed at the Yopougon HTC, to participate. It is worth noting that this cohort represents the entire Ivoirian hemophilia population identified and reported by the WFH at the time of the initiation of the study [14].

The study protocol was approved by the Ivoirian Ethics Committee (*Comité National d'Ethique de la Recherche)* and registered at ClinicalTrials.gov (NCT03054662). In accordance with the Declaration of Helsinki, written informed consent was obtained from all participants and their parents or legal guardians.

Data Collection

Of note is that prior to 2016, there were no data available on either inhibitors or ED in Ivoirian PWH. Since January 2016, a locally adapted logbook has been provided to each PWH (or their parents) to record data on annual bleeding rate including treated and untreated bleeds, ED, and CFC consumption [19]. Demographics on the Ivoirian PWH were collected for the first time in 2017, as reported elsewhere [20]. It was, thus, impossible to obtain data on cumulative life-long ED, with the collection of objective data on ED limited to the 2016-2017 evaluation period. CFC consumption and ED were calculated using systematic analysis, based on a combination of the data recorded in the PWH's logbooks, on regular follow-up consultations, and in CFC donation registry.

Methods

FVIII and FIX activities were measured on site with the one-stage assay method on a semi-automated coagulometer (Option 4 Plus, Biomerieux) using human plasma immunodepleted of FVIII and FIX (HemosIL, Werfen). A systematic inhibitor screening was performed on site with oversight from the Belgian partner by mixing studies (at two different occasions, within 3 months-during twinning visits) and, if appropriate, with an inhibitor titration through the Nijmegen-Bethesda method [21].

Genomic DNA extraction was performed using a QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany), following the manufacturer's instructions. Molecular analysis was performed in the Genetic and Molecular Biology Laboratory, Cochin Hospital, Paris, France. F*8* intron 22 inversion was detected by performing long-range polymerase chain reaction (PCR) in a two-tube PCR assay according to the Liu et al. method, along with some modifications such as optimized the PCR conditions (initial denaturing step at 95°C for 10 min followed by 30 cycles of denaturing at 95°C for 30 sec, annealing at 57°C for 1 min, extension at 72°C for1.5 min and a final extension step at 72°C for 10 min [22]. F*8* intron 1 was detected using a PCR protocol described by Bagnall et al [23]. All known functional *F8* and *F9* coding regions, including their immediate 5' and 3' flanking splice junctions, promotor, and 3'-genomic DNA sequences, were sequenced through next-generation sequencing (NGS) using an Ion PGM System (ThermoFisher Scientific). Two detection tools, a variant caller, Polydiag, and Nextgene were used to detect variants (point variants and copy number variations). The nomenclature of the *F8* and *F9* gene variants relied on cDNA reference sequences NM_000132.3 and NM_000133.3 and protein reference sequences NP_000123.1 and NP_000124.1, respectively, in accordance with the recommendations of the Human Genome Variation Society (http:// www.hgvs.org/mutnomen/). Variants were identified by searching against the Human Gene Mutation professional database and hemophilia A/B locus-specific variant databases (http://www.factorviii-db.org/, http://hemo-

base.com, and http://www.cdc.gov/ncbddd/hemophilia/champs.html). Structural impacts on protein function and potential splice effects of novel missense variants were evaluated by different bioinformatics tools (Table 1) [24]. Data from non-synonymous single nucleotide polymorphisms (SNPs)—rs35383156 (c.1508G>A; Arg503/484His) in exon 10, both rs2228152 (c.2383A>G; Arg795/776Gly) and rs1800291 (c.3780C>G; Asp1260/1241Glu) in exon 14, and rs1800297 (c.6769A>G; Met2257/2238Val) in exon 25—were collected during exon sequencing to draw F*8* haplotypes named H1 through H6, as described by Viel [5]. All variants were interpreted according to the consensus guidelines of both the American College of Medical Genetics and Genomics and the Association for Molecular Pathology [25].

Finally, we compared our results on prevalence of inhibitor and genetic-related risk factors for inhibitor development (if available–with those obtained from other sub-Saharan African countries (Cameroon [18], Senegal [5;17], and South Africa [16]) and reported in peer-reviewed journals.

RESULTS

Overall, 57 PWH were included in the study, though we analyzed complete data from only 54 unrelated PWH, as DNA could not be extracted from three samples. The cohort comprised 49 PWH with HA (43 severe, four moderate and two mild) and five PWH with severe hemophilia B [HB]. The median [range] age at evaluation was 12 [1–64] years. Spontaneous cases, defined as cases with no other PWH (alive or deceased) within the family, were reported in 33.3% (*n*=18) of participants. Participants were geographically clustered (50.0%) around Abidjan, where the HTC is located, but half of them were also living in remote areas of the country.

In severe HA patients, intron 22 inversion was the most recurrent variant (39.5%;*n*=17), followed by a single nucleotide variant (nonsense (16.2%;*n*=7), missense (14.0%;*n*=6), nonsense, and splicing variant (2.3%;*n*=1)) identified in 32.6% (*n*=14). Frameshift causal variants and large rearrangements (deletion/duplication) were found in 14.0% (*n*=6) and 7.0%

(*n*=3), respectively, while one 9pb in-frame deletion was identified in 2.3% (*n*=1) of the severe HA patients. SNPs analysis results (haplotype H1 to H6) were available in 44 HA PWHs, with a frequency of 36.3% (*n*=16) for H2, 34.1% (*n*=15) for H3, and 29.6% (*n*=13) for H1. No participant exhibited H4, H5, or H6 haplotypes. Results of the F*8* and F*9* genetic PWH analyses are summarized in Table 1. Of the 28 unique variants identified in our HA cohort, seven new variants were previously unreported. In the HB patients, only one variant was still unreported. According to both the guidelines and in silico pathogenicity prediction, these variants were predicted to affect FVIII and FIX protein function.

We obtained detailed data on self-reported CFC consumption and indication for infusion in 85% of PWH in 2016 and 98% of PWH in 2017, as logbook completion improved over time since its introduction. In 2016, 24% (*n*=13) of PWH, with a median [range] age of 10 [1–63] years, had never been exposed to CFC in their lifetime, and the rest were treated on-demand. At time of inclusion in 2017, 7.4% (*n*=4) of PWH had still never been treated with CFC (median [range] age of 5.5 [1–17] years). Of the PWH without exposure to CFCs, 53% were living in the Abidjan district. PWH were provided with CFC at the HTC and infused either at the HTC or in a clinic located close to their living area. The median [range] and mean± SD ED were 4 [0–35] days and 6.5±8.0 days in 2016, and 5 [0–27] days and 6.5±6.6 days in 2017, respectively. Indication for CFC administration was exclusively on-demand therapy, with one infusion per bleed on average in 84%. The CFC amount was usually low (10–20 IU/Kg^{-1}). No surgery was performed during the 2016–2017 period. Based on these findings, we considered our population as having a low rate of danger days. Substitutive hemostatic treatment included recombinant standard, extended half-life products, and plasma-derived concentrates from different manufacturers. The CFC were often used alternately, depending on the donations' availability and supply.

Table 1. Distribution of F*8* and F*9* hemophilia causing variants among the 54 Ivoirian people with hemophilia

HEMOPHILIA CAUSING VARIANT						
Phenotype	**Exon /intron**	**Observed cDNA change (HGVS notation)**	**Predicted protein change (HGVS notation)**	**Mutation Effect**	**Haplotype**	**Inhibitor**
HEMOPHILIA A						
Severe	2	c.209_212delTTGT	p.Phe70*	Frameshift	H2	
Severe	2 to 10	c.144-?_1537+?dup	**	Large duplication	UNK	
Severe	**3 to 26**	**c.266-?_*1788+?dup**	**	**Large duplication**	H2	
Severe	4	c.536C>T	p.Ser179Phe	Missense	H3	
Severe	7	c.788+?_1009-?del	**	Large deletion	H2	YES
Severe	8	c.1172G>A	p.Arg391His	Missense	H1	
Severe	9	c.1336C>T	p.Arg446*	Nonsense	H1	
Mild	13	c.1930T>G	p.Leu644Val	Missense	H2	
Severe	**13**	**c.1921T>G**	**p.Phe641Val**	**Missense**	H1	
Mild	**13**	**c.2027C>A**	**p.Thr676Asn**	**Missense**	UNK	
Severe	**14**	**c.[4738_4753del;4754_4771dup]**	**p.Leu158fs*41**	**Frameshift**	H1	
Severe	14	c.4825dup	p.Thr1609Asnfs*4	Frameshift	H3	
Severe	14	c.4382delA	p.Asn1461Thrfs*4	Frameshift	H2	
Severe	14	c.4379dupA	p.Asn1460Lysfs*2	Frameshift	H1	
Severe	14	c.2702C>G (*n*=2)	p.Ser901*	Nonsense	H2	
Severe	14	c.2933C>A	p.Ser978*	Nonsense	UNK	
Severe	**15**	**c.5322_5330del9**	**p.Leu1777_Gly1779del**	**In-Frame**	UNK	
Severe	16	c.5409_5412delCTTC	p.Phe1804Ilefs*66	Frameshift	H3	
Severe	16	c.5575G>C	p.Asp1859His	Missense	H3	
Moderate	Intron 16	c.5587-2A>G	**	Splicing	H1	YES
Severe	17	c.5766C>A	p.Cys1922*	Nonsense	H1	
Severe	18	c.5825G>T	p.Gly1942Val	Missense	H2	
Moderate	**18**	**c.5852T>C**	**p.Leu1951Ser**	**Missense**	UNK	
Severe	18	c.5953C>T	p.Arg1985*	Nonsense	H3	
Severe	**Intron 19**	**c.6115+2T>A**	**	**Splicing**	H2	
Severe	22	c.6403C>T	p.Arg2135*	Nonsense	H2	
Severe	Intron 22	Inv 22 (*n*=17)		Inversion	H2 (*n*=5) H3 (*n*=7) H1 (*n*=5)	YES (n=4)
Moderate	23	c.6506G>A	p.Arg2169His	Missense	H1	
Severe	23	c.6544C>T	p.Arg2182Cys	Missense	H3	
Moderate	26	c.7021G>A	p.Glu2341Lys	Missense	H3	
Severe	NO mutation	NA (*n*=2)	NA	NA	H3 (*n*=1) H2 (*n*=1)	
HEMOPHILIA B						
Severe	5	c.423C>A	p.Cys141*	Nonsense		
Severe	**7**	**c.779_780insTAGAG**	**p.Lys260Asnfs*6**	**Frameshift**		
Severe	8	c.1135C>G	p.Arg379Gly	Missense		
Severe	All exons	c.-29-?_*1437+?del	NA	Deletion		
Severe	NO material	NA	NA	NA		

***RNA supplementary analysis required, NA: not applicable, UNK: unknown, new mutations are in bold. HGVS: Human Genome Variation Society*

An inhibitor against FVIII was detected in 12% (*n*=6) of the 50 previously exposed PWH (five severe forms and one moderate). Their median age [range] was 16 years [7–23 years]; one patient exhibited a high-titer inhibitor (6.8 BU mL^{-1}) and another one a transient inhibitor, while another patient had a sibling with an inhibitor history. With regard to the genetics of the PWH with inhibitors, 66.7% (*n*=4) had a positive intron 22 inversion, with the following haplotype distribution: 50% (*n*=3) had H1, 33% (*n*=2) had H3, and 17% (*n*=1) had H2.

The prevalence result comparison with other Sub-Saharan African countries is detailed in Table 2. To better reflect the hemophilia context of each country, we added data from the 2016 WFH Report on Annual Hemophilia Survey (RAGS) indicating the number of PWH and the annual consumption of FVIII (IU per capita) among those countries.

Table 2. Comparison of results obtained from the literature on the prevalence of inhibitors and genetic-related risk-factors (if available) in other sub-Saharan countries

Country	Cameroon [14]	Côte d'Ivoire	Senegal [11]	Senegal [15]	South Africa [14]
Type of hemophilia	HA+HB	HA+HB	HA	HA	HA
Number of PWH	42	54	22	50	116 Black*
Number of severe HA	25	44	21	NR	108
Prevalence of inhibitors	19%	12%	22.7%	20%	18%
Identified variants	NR	51/54	21/22	NR	100%
Inversion intron22**	NR	38.6%	38%	NR	40%
New variants	NR	8	5	NR	UNK
Study of haplotypes available	NO	YES	NO	NO	YES
Number of PWH identified in the country***	176	81	193	193	2206
Mean use of FVIII in IU per capita***	0.052	0.032	0.118	0.118	1.049
Year of NMO creation	2008	2008	1996	1996	1970

PWH: people with Hemophilia; HA: Hemophilia A; HB: hemophilia B; UNK: Unknown; NR: Not reported

NMO: National Member Organization recognized by the World Federation of Hemophilia

**the study also included white PWH, with a prevalence of inhibitors of 13% among the total population, but we only considered the results of the black PWH*

***among severe HA patients*

**** Data from the 2016 World Federation of Hemophilia Report on Annual Global Survey [14].*

DISCUSSION

Data on inhibitors and molecular diagnosis in PWH are scarce in Sub-Saharan Africa [15;16]. This is the first prospective study in Côte d'Ivoire, providing data on inhibitor prevalence, molecular diagnosis (including haplotypes), and exposure to CFC. Despite a population of over 23 million inhabitants [26], only 81 PWH were reported in 2016 by the WFH RAGS in Côte d'Ivoire [14]. Although small in size, our cohort was thus representative, with data obtained from 95% of the 57 Ivoirian PWH families identified at time of the study and participants coming from various regions of the country. Age and severity distributions were in line with other African countries with low economic income and restricted access to hemophilia care [17;18].

We reported a similar distribution of intron 22 inversions, point variants, and rearrangements compared to non-African ethnic groups. This distribution had previously been reported in studies from Senegal and South Africa [15;16]. The frequency of H1–H3 haplotypes in our patients was consistent with data published from African populations [5;16]. We identified eight new variants, which were registered into the EAHAD Variant Database. No hemophilia causing variant was found in 3.7% (*n*=2) of participants. This is consistent with the 2–4% sensitivity in detecting causal variants, reported in the literature [27]. These results support the view that the molecular diagnostic algorithms applied in Europe and North America are applicable in Africa.

The prevalence of inhibitors in our study was slightly lower than that in studies performed in Senegal [15;17], Cameroon [18], and Black PWH from South Africa [16]. This difference should be interpreted with caution and take into account the small size of the study cohorts, the variable recruitment methodology and the limited number of publications. Little is actually known on inhibitors in Sub-Saharan Africa that represents 48 countries and with only 19 of those having established national member organizations reporting to the Annual Global WFH Survey in 2017. One could

assume that the difference in inhibitors prevalence is related to variations of CFC consumption. However, CFC consumption (IU per capita) in Cameroon and Senegal is very low and comparable to Côte d'Ivoire [14]. Another hypothesis could be a longer standing experience in hemophilia care in some of these countries resulting in a larger number of PWH identified and more PWH exposed to CFC [14].

We investigated the association between the causal variants, haplotypes, and presence of an inhibitor. According to published data, intron 22 inversion is an intermediate risk factor for inhibitor development [3]. In our population, intron 22 inversion was present in two-thirds of PWH, whereas only one participant had a high-risk inhibitor hemophilia causing variant (large deletion). Fifty percent (*n*=3) of PWH with an inhibitor displayed the H1 haplotype. While absent in Caucasian and Chinese populations, the H3 haplotype was initially suggested to be associated with a higher risk for inhibitor development [5]. This hypothesis has however not been confirmed in subsequent work performed in Afro-American PWH [8;9].

Lochan et al. examined F*8* gene haplotypes, ethnicity and inhibitor development in black and white intron22 positive PWH from South Africa. Although results suggested that the H3/H5 haplotype group had a higher inhibitor incidence than the H1/H2 haplotype group, the size sample was too small to reach statistical significance. On the other hand, the authors found a significant association between inhibitor development and ethnicity as well as with F*8* gene variant type [16]. The haplotype distribution among Ivoirian PWH with inhibitors was discrepant with the black South African PWH, but this cannot be interpreted because of the small number of inhibitors positive participants in both studies. Based on these data, ethnicity and F*8* pathogenic variant type actually emerge as the strongest genetic risk factor in the onset of inhibitors.

Regarding the environmental risk factors likely to impact inhibitor development, several aspects should be considered when interpreting our

findings. First, in Côte d'Ivoire, the 2016 WFH Global Survey reported a mean per capita FVIII and FIX use of 0.032 and 0.005, respectively [14], with CFC supplied exclusively by humanitarian aid since 2008. This accounts for the very low ED number in our population, with an important proportion of previously untreated patients (PUPs) having a "zero" risk of developing inhibitors, with the remaining majority composed of minimally treated patients (MTPs). Decrease in number and age of PUPs between 2016 and 2017 can be explained by the progressive increase in WFH donation programs. Secondly, we observed an extremely low rate of danger days that could trigger the inhibitor development (*e.g.,* neither surgery nor prolonged or intensive treatments), as well as the use of low-dose regimens of CFC. However, as CFC are supplied exclusively by humanitarian aid, a higher inhibitor level could have been expected, given the variations of product types and sources used, which are dependent on the availability and manufacturers' supply of the donation programs. From the Sippet study, little is known about the influence of the product source in African PWH, as only four participants from South Africa were randomized in this study [12].

Our study has several limitations. First, the number of PWH with inhibitors was very small. Secondly, there are only data on the inhibitor prevalence and exposure data over a limited period, with no point of comparison available in Côte d'Ivoire, and only little data from other African countries. We have no data on cumulative exposure since birth and on inhibitor incidence, as this was impossible to assess. However, with the systematic use of logbooks and regular screening for inhibitors, we plan to better assess inhibitor incidence and treatment-related risk factors in Ivoirian PWH in the future. Finally, information on the familial history of inhibitors is still lacking, as regular screening only started in 2016 in Côte d'Ivoire. Therefore, further larger studies and participation to international registries are needed in the upcoming years to confirm these data and improve knowledge on inhibitors in Côte d'Ivoire and by extension to other Sub-Saharan African countries.

CONCLUSION

Our study displays original data on molecular diagnosis of hemophilia, inhibitor prevalence, and prevalence of risk factors associated with inhibitors in Côte d'Ivoire. The background inhibitor prevalence in Côte d'Ivoire is still low, possibly but not only reflecting the limited exposure to available replacement therapies in PWH, who predominantly harbor the intron 22 inversion and H1 haplotype. Yet, these data are critical to evaluate the impact on inhibitor incidence/prevalence of improved replacement therapy access through donations in Ivoirian PWH. In the future, pooling data from other African countries and participation to large, multicentric and international studies would be of great value to gain more insight on inhibitor incidence and risk factor development in African PWH.

ACKNOWLEDGEMENTS

The molecular analysis work in people with hemophilia and carriers from Côte d'Ivoire was funded by a research grant from BAYER Belgium

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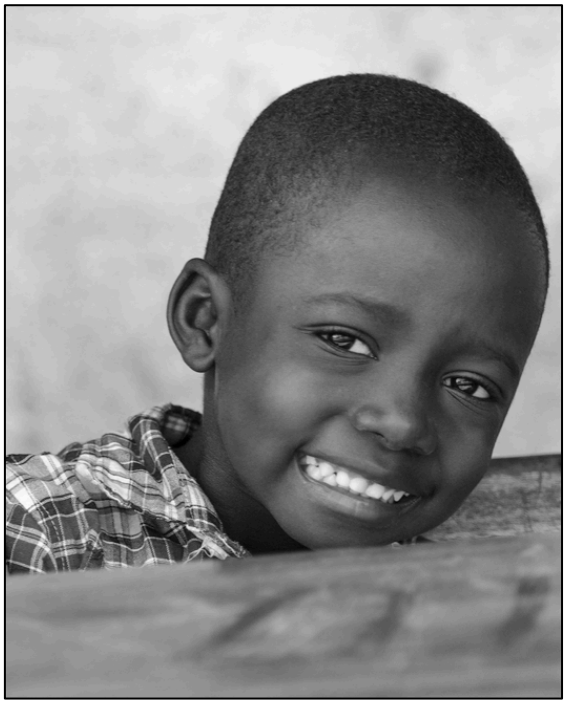
SECTION 2

Interventions with non-substitutive locally adapted strategies



Chapter 4

Development and evaluation of appropriate, culturally adapted educational tools for Ivoirian patients with hemophilia, hemophilia carriers, and their families.

Haemophilia. 2019 Sep;25(5):838-844.

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SUMMARY

Introduction: Patient education is the cornerstone in the management of chronic diseases, such as hemophilia. The education of patients with hemophilia, hemophilia carriers, and their families requires educational materials adapted to their socio-cultural situations for maximum effectiveness. These tools are currently lacking in developing countries, such as Côte d'Ivoire.

Aims: We sought to develop educational materials adapted to the Ivoirian context, assess its short- and long-term impacts on knowledge about hemophilia, and evaluate the participants' motivation and their satisfaction with the tools.

Methods: Following its elaboration, the material was administered to 71 participants (37 patients with hemophilia, 29 carriers, and 5 fathers). Their level of knowledge was assessed before (T0), just after (T1), and 1 year following the intervention (T2). We evaluated, analyzed, and compared the scores at T0, T1, and T2 and evaluated motivation at T0 and satisfaction at T1.

Results: All participants significantly improved their skills at T1 ($P<0.001$), maintaining a sustained and significant improvement at T2 in comparison with T0 ($P<0.001$). We observed a high degree of motivation towards improving their knowledge and high degree of satisfaction with the materials in all participants.

Conclusion: Appropriate, culturally adapted educational tools focused on hemophilia are now available in Côte d'Ivoire. These materials will likely contribute to improving hemophilia awareness, to implementing screening, prevention, and self-management of the disease, and to positively impacting the outcomes of Ivoirian people with hemophilia in the long-term.

INTRODUCTION

Hemophilia is a congenital, X-linked bleeding disorder resulting in low levels of either factor VIII (FVIII, hemophilia A [HA]) or factor IX (FIX, hemophilia B [HB]) [1]. Hemophilia requires adequate care throughout life and serious commitment from the patient and their family. Nowadays, therapeutic patient education is recognized by the World Health Organization (WHO) as a key component in improving chronic disease management strategies [2]. A good understanding of the mechanisms of hemophilia and its common clinical features, treatment options, and mode of transmission proves critical to improve awareness of the disease, promote adherence to treatment, prevent complications, raise the number of diagnosed cases, and improve the quality of care. Educational interventions are low-cost public health tools. Numerous educational tools focused on hemophilia have been developed, primarily in developed countries, and are widely used. However, in the developing world where a majority of people with hemophilia (PWH) live [3], there is a lack of contextualized, language and literacy adapted, and culturally sensitive educational material on hemophilia [4;5]. The topics addressed (*e.g.,* pre-implantation diagnosis; prophylaxis throughout life*)*, the wording and iconography used (*e.g.,* pictures of Caucasian PWH without any signs of arthropathy), and several recommendations extracted from the educational material primarily created for developed countries are generally not appropriate for the linguistic, conceptual, and cultural specificities of developing countries.

At present, there is growing evidence for the positive impact of culturally adapted interventions [6]. Educational tools tailored to ethnicity [7] and socio-cultural and religious contexts [8;9] have been proven beneficial in the treatment adherence of patients affected by chronic diseases. Several therapeutic patient education programs, primarily focused on HIV, have been successfully culturally adapted and administered in African countries [10-12]. In the setting of the WFH twinning program, a partnership was established in 2015 between the Ivoirian hemophilia treatment center (HTC)

of Yopougon in Abidjan and the international HTC of the Cliniques universitaires Saint-Luc in Brussels, Belgium. Regular on-site multidisciplinary visits enabled us to ascertain the unawareness of hemophilia among Ivoirian PWH, carriers, and their families [13;14]. Given this context, we undertook the development and evaluation of the impact of appropriate, culturally adapted educational tools on hemophilia for Ivoirian PWH, carriers, and their families to enable them to gain a better disease understanding, to acquire self-management skills, and to improve hemophilia-related health outcomes in Côte d'Ivoire.

STUDY OBJECTIVES

The current study had three complementary objectives: (i) to develop and provide PWH, as well as their parents and known or suspected carriers, with appropriate educational material on hemophilia adapted to the socio-cultural context and linguistic specificities of Côte d'Ivoire; (ii) to assess the impact of these educational tools, combined with teaching activities, on the level of disease knowledge and proper management in PWHs, their parents, and carriers in both the short- and long-term; (iii) to evaluate participants' motivation towards improving their knowledge on hemophilia, as well as their degree of satisfaction with the developed educational tools.

PATIENTS, MATERIAL, AND METHODS

Patients

This study was conducted from January 2018 until January 2019 at the HTC of Yopougon in Abidjan, the only HTC of Côte d'Ivoire. PWH aged 12 years or older, their parents, and potential and obligate carriers regularly followed-up at the Yopougon HTC were invited to take part in the study.

Ethics

The study protocol was approved by the Ivorian Ethics Committee (Comité National d'Ethique de la Recherche) and registered in ClinicalTrials.gov

(NCT03054662). In accordance with the Declaration of Helsinki, written informed consent was obtained from all participants and their parents or legal guardians. The project was conducted as part of the WFH twinning program established between the Yopougon and Brussels HTCs.

Methods

This was an interventional study assessing the impact of adapted educational tools on the level of hemophilia knowledge and self-management in Ivoirian PWH, their parents, and the carriers.

Data collection

Data were collected on site by the clinical team during multidisciplinary standardized consultations held at the Yopougon HTC. Socio-demographics data comprised age, gender, place of residence, type and severity of hemophilia, familial or sporadic form, education level, occupation, place of residence, number of relatives affected by hemophilia in the entire family, treatment regimen and inhibitor status for PWH and carriers, marital status, total number of children, as well as number of affected children. In addition, we recorded the duration of follow-up at the HTC (more or less than 12 months) since the twinning program initiation.

Development of educational material and assessment tools

The educational material was developed in 2017 by researchers in the aftermath of a survey, highlighting the tremendous lack of knowledge on hemophilia detected during the visits, as previously reported in several papers [13;14], in addition to a review of the related literature. The content and lay-out of the tools elaborated were aimed at providing basic, yet relevant, information on hemophilia to best meet local needs, while respecting the socio-cultural context and the country's economic constraints. The tools were developed in French, as this is the official language of Côte d'Ivoire. The material had specific pedagogical and

iconographic characteristics with concise explanations, using local terminology and wording (*e.g.*, swelling or bulging to designate a joint bleed), culturally sensitive examples and illustrations, as well as smart draws and pictures exclusively presenting African PWH.

A written questionnaire consisting of 20 true/false questions, scaled from 0 to 20, was developed in order to assess participants' knowledge of hemophilia. Each item was scored using either 0 or 1 [0 for incorrect or no answer; 1 for correct answer]. A higher score correlated with a higher knowledge level about hemophilia. The questions were grouped in five domains exploring the following skills: general knowledge of hemophilia, mode of transmission, diagnosis, general management of hemophilia, and treatment of hemarthrosis. A Likert scale was applied to assess the participants' motivation towards improving their knowledge of hemophilia (four items + one question evaluating the confidence level of knowledge) and satisfaction with the informational material provided (six items). The results were expressed on a scale ranging from 0 [strongly disagree] to 5 [strongly agree]. To ensure relevance, understanding, and appropriateness of the material, the latter was reviewed by clinicians from the Yopougon HTC and by members of the National Members' Organization. Adaptations and modifications were made, considering the various comments. The final version was approved in December 2017 via consensus of the research team.

Completion of the educational materials and intervention

The educational material comprised a booklet, PowerPoint slide kit (same information as the booklet), game illustrating hemophilia mode of inheritance, fact sheets on managing joint bleeds with prompt CFC injections, application of the RICE protocol (Rest-Ice-Compress-Elevate) [15], and emergency settings. The topics addressed were as follows: hemophilia pathophysiology, clinical features (including bleeding symptoms in carriers) and complications, mode of transmission, therapeutic options (replacement therapy), adjunctive therapies (RICE, antifibrinolytics), preventive care

(screening before circumcision and dental care), screening, and diagnosis. The tools were launched in January 2018 at the Yopougon HTC. The materials were distributed as printed booklets and orally explained to patients and families during interactive sessions, repeated on several occasions and delivered by two Belgian and Ivoirian twinning team hematologists. Teaching was provided as lectures lasting about 45 minutes with PowerPoint support, followed by interactive discussions. The participants were given the opportunity to play the didactic game on hemophilia transmission, with research team supervision to ensure understanding. Sessions were limited to small groups of about 20 people. The participants received the booklet and the two fact sheets at the oral education session's end. Outcome measures were assessed individually through the questionnaire and Likert scales. The questions were read aloud to overcome any reading difficulties.

Assessment of the educational material

We evaluated and compared the level of knowledge about hemophilia in the same population before (T0), just after (T1), and 1 year (T2) following the educational intervention. The participants' motivation and satisfaction levels were recorded at T0 and T1, respectively.

Statistical analysis

All data were analyzed using JMP® Pro 14.1.0 (SAS Institute Inc., USA) and IBM ® SPSS ® 25. Continuous variables were expressed as means and standard deviations (SD), with between- group comparisons made using the Student's t-test for independent variables or Wilcoxon rank-sum test, depending on normality distribution. The T0, T1, and T2 scores were tested using non-parametric repeated measures ANOVA (Friedman test) with Bonferroni correction for pairwise comparisons. Effect sizes were computed using Cohen's d, with P-values considered significant at <0.05.

RESULTS

Socio-demographic participant characteristics

The study included 71 participants consisting of 37 PWH, 29 obligate or potential carriers (21 PWH mothers, four sisters, and four aunts), and five fathers. The carriers' group comprised 17 obligate carriers (six symptomatic carriers) and 12 possible carriers. The carriership was based on family tree and factor VIII or IX activity. The mean age was 23.0±11.1 years (range: 12-64 years) for PWH and 33.9±9.4 years (range: 17-59 years) for carriers. The hemophilia type, severity, and forms of PWH or affected relatives of participating parents were as follows: 63 HA and 8 HB; 64 severe, four moderate, and three mild forms; 48 familial and 23 sporadic forms. In the familial forms, the mean PWH number per family was 4.8. All were treated on demand. Three PWH displayed an active inhibitor (two low and one high titers). The education levels and occupations of the participants are shown in Table 1. All fathers were professionally active, with a majority (62%) of PWH being students; 48% of carriers were housewives/homemakers. Regarding education, upper secondary certification and higher education levels were achieved by 27.5% of carriers, 32% of PWHs, and 60% of fathers. The mean age at study end was 18.6±3.6 years (range: 11-24 years) for PWH, 17.6±3.3 years (range: 11-23 years) for carriers, and 21.6 ± 2.9 years (range 18-24 years) for fathers. Concerning the geographical distribution, the participants mainly originated from the country's central and southern parts, with 36% living in the Abidjan area where the Yopougon HTC is located. The mean HTC follow-up period before inclusion was >12 months in 60% and 312 months in 40%.

Table 1. Participants' education level and occupation

	PWH (*n*=37) % (*n*)	CARRIERS (*n*=29) % (*n*)	FATHERS (*n*=5) % (*n*)
HIGHEST LEVEL OF EDUCATION AT INCLUSION			
Never went to school	0	10.3 (3)	0
Did not finish primary school	13.6 (5)	0	0
Primary school	32.4 (12)	20.6 (6)	0
Lower secondary education	21.6 (8)	41.5 (12)	40 (2)
Upper secondary education	32.4 (12)	10.3 (3)	0
Post-graduate	0	13.7 (4)	60 (3)
University	0	3.6 (1)	0
OCCUPATION			
School pupils	62.2 (23)	13.8 (4)	0
Active worker	21.6 (8)	37.9 (11)	100 (5)
Homemaker-housewives	0	48.3 (14)	0
Retired	2.7 (1)	0	0
Unemployed	13.5 (5)	0	0

PWH: patients with hemophilia

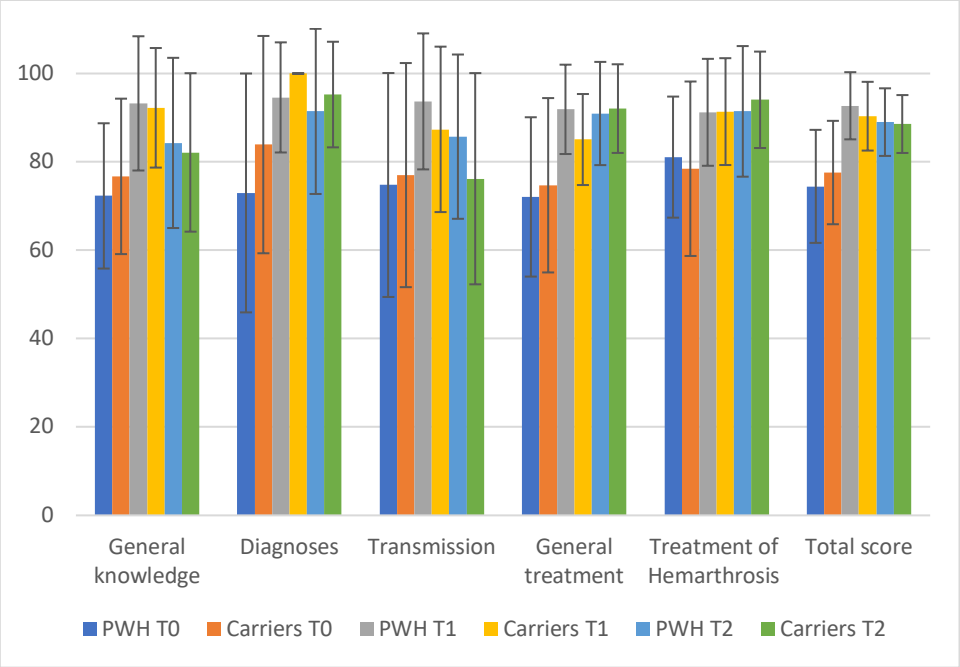
Intervention analysis and impact

The questionnaire and motivation evaluation were administered to 71 participants at T0, while the questionnaire and satisfaction test were administered at T1. Despite the invitation to attend the 1-year follow-up visit, 11 participants dropped out, thus not completing the T2 questionnaire.

The mean (%) population scores at T0, T1, and T2 were illustrated in Figure 1. At baseline, the best scores were observed in the carriers' group, though these results were not statistically significant (p=0.294). All participants significantly improved their skills in all the examined domains just after the intervention, with the mean total score increasing from 75.3%±12.1 (range:

45-95%) to 91.9%±7.6 (range: 65-100%) (P<0.001; 95%CI:13.8,19.4). Despite a discrete reduction in the scores (mainly concerning general knowledge and transmission sections), when comparing results between T1 and T2, there was a sustained and significant score improvement observed at one-year post-intervention compared to baseline (P<0.001) (Table 2). The best score progression and stability were recorded in the PWH group (Figure 1).

Figure 1. Mean knowledge scores (%) in Ivoirian PWH and carriers at T0, T1, and T2



For the sake of clarity of the graph, we have not indicated the significant results. These results are presented in Table 2.

Regarding evaluated skills, the highest increase (T1-T0) was reported in the basic knowledge (73.2% to 93.3%, p<0.001) and diagnosis (77.0% to 96.7%, p<0.001) sections; the best stability of the long-term gain (T2-T1) was observed in the general treatment (89.2% to 90.3%, p=0.672) and hemarthrosis treatment (91.9% to 92.1%, p=0.718) sections (Table 2).

Table 2. Comparison of knowledge scores (%) between T0, T1, and T2 in all participants

	Mean score±SD T0	Mean score±SD T1	Mean score±SD T2	Effect size T0-T1	Effect size T1-T2	Effect size T0-T2
	n=71	*n*=71	*n*=60	*n*=71	*n*=60	*n*=60
General knowledge	73.2±17.1	93.3±14.0	83.8±18.3	1.29***	0.59**	0.60*
Diagnosis	77.0±26.2	96.7±10.0	92.8±16.3	0.99**	0.30	0.71*
Transmission	74.2±25.3	90.6±1.1	82.2±21.7	0.76**	0.43	0.34
General treatment	73.2±18.1	89.2±10.6	90.3±11.6	1.07***	0.10	1.10***
Treatment of hemarthrosis	79.9±16.2	91.9±11.8	92.1±13.4	0.85*	0.01	0.81**
Total score	75.3±12.1	91.9±7.6	88.5±7.1	1.64***	0.46***	1.30

**** p<0.0001; ** p<0.01;*
** p<0.05 of pairwise comparison by non-parametric repeated measures ANOVA*

At T0, the most common wrong answers were related to the need for regular dental care, possibility of playing in the playground for boys with hemophilia, pertinence of regular HTC follow-up even outside of bleeding episodes and need for physiotherapy in case of joint bleeds. At T2, the questions the most often incorrectly answered were as follows: the possibility of playing in the playground for boys with hemophilia and need to screen PWHs' brothers. Concerning PWH, the need for physiotherapy in case of joint bleeds and relevance of HTC consultations outside bleeding episodes were proven problematic.

Overall, the participants' motivation to improve their knowledge about hemophilia was high, with a mean score of 18.4/20±2.5 (range: 8-20). The mean score of how well they rated their disease knowledge was 3.4/5±1.3 (range: 1-5). No significant difference in motivation was observed between PWH and carriers (18.4±2.6 for PWH; 18.7±2.5 for carriers, p=0.821).

In general, participants adequately assessed their knowledge level. In T0, participants who were positive about their knowledge (*i.e.,* answer 4 or 5 to Q3 in the motivation test) exhibited a better disease knowledge than participants who were less confident (83.8% vs 68.8%, p=0.011). Their satisfaction with the educational tools (booklet, game, and PowerPoint) was remarkably high, with a mean score of 27.7/30±2.6 (range: 21-30).

DISCUSSION

Empowering patients with appropriate and efficient educational tools are the cornerstone of a meaningful chronic disease management. The WHO recommends therapeutic patient education (TPE) and promotes education oriented to the health needs of the target population [2]. TPE is designed to train patients in the skills of self-managing or adapting treatment to their particular chronic disease and therefore appears to be an essential part of hemophilia managing [16]. Health literacy is defined as the capacity of individuals to obtain, process, and understand the basic health information and services needed to make appropriate health decisions [5]. It enables self-management support [17] and, low health literacy is often associated with poorer health outcomes and increased mortality [18]. Thus, education of PWH and their families helps reduce mortality and morbidity [5]. In the WFH twinning program setting, regular multidisciplinary consultations have highlighted the lack of knowledge and understanding of hemophilia, its management, its complications such as deaths related to circumcision, and bleeding risks for carriers [13;14].

By integrating the above recommendations, while considering the local and cultural contexts and specific unmet needs identified during the twinning activities, and by mixing experiences from developed and developing countries, we created educational tools that are appropriate, contextually adapted, relevant, and efficient to improve hemophilia management, rendering it applicable to the local realities of the Côte d'Ivoire hemophilia community. The participants were provided with a booklet and two fact

sheets at the educational lectures' end. In administering the same information orally and with written support, we sought to overcome potential literacy difficulties, maintaining knowledge in the long-term with the booklets. The participants demonstrated a strong motivation to learn more about hemophilia and reported a high degree of satisfaction with the educational material. Overall, we observed a significant improvement in their skills, with a sustained gain in the long-term. These results confirmed the efficacy of the developed tools.

It should be noted that the baseline knowledge level was quite high, primarily because adequate recommendations had been previously provided during the multidisciplinary consultations conducted prior to inclusion. Ideally, the good results obtained with this tool should also be assessed among PWH and their family at the first visit at the HTC as their baseline knowledge will be lower. It could be of interest to consider other validation methods that were used in Côte d'Ivoire to validate educational tools related to other diseases. Interestingly, several topics (*e.g.,* possibility of playing at the playground for boys with hemophilia) remained problematic, reflecting the limited access to CFC and basic care for PWH in Côte d'Ivoire. The tools highlighted the relevance of adjunctive therapies (RICE, physiotherapy, and antifibrinolytics) and preventive care (regular follow-up at the HTC and dental care), yet several recommendations remained difficult to implement for economic reasons.

We paid specific attention to the carriers because mothers' education has proven to be the cornerstone in improving PWH's care in Africa, as women are more likely than men to take on caregiving activities [19]. Additionally, mothers had shown insufficient knowledge about the risk of transmitting the disease to their offspring and of their own bleeding risk [2]. Indeed, the number of carries in our study was substantially higher than that of fathers.

This project was undertaken to develop appropriate educational tools and evaluate their impact on disease understanding and its management, using

questionnaires. The next step will be to evaluate these initiatives' impact on hemophilia care at an individual level. This educational program will assumedly impact the management of bleeds, adoption of precautionary measures before circumcision, recognition of hemophilia in families, and awareness of hemophilia in potential carriers. Considering the very limited resources in terms of replacement therapy, these measures will positively impact the consequences of hemophilia if they are well-integrated.

As low-dose prophylaxis was initiated in children in Côte d'Ivoire in January 2018, it proved essential to promote self-management skills, which will likely positively influence adherence [20], and will contribute to develop home therapy and self-infusion programs.

CONCLUSION

Appropriate, culturally adapted educational tools about hemophilia were originally developed and validated and are now available in Côte d'Ivoire. By improving knowledge on hemophilia and empowering patients, carriers, and their families, this material will likely contribute to better disease awareness, allowing for implementing disease screening, prevention, and self-management, and positively impact the outcomes of Ivoirian PWH in the long-term. In the future, the tool could be more widely used in other sub-Saharan, French-speaking African countries and be even adapted into other languages. Based on the assumption that these countries' patients will have increased access to replacement therapy and innovative treatments, this kind of educational program will have to be regularly adapted and updated.

ACKNOWLEDGEMENTS

This project in Côte d'Ivoire was funded by grants from the WFH twinning program and PFIZER Belgium.

This research has benefitted from the statistical consult with Statistical Methodology and Computing Service, technological platform at UCL-SMCS/IMMAQ UCL. The authors expressly thank C. Bugli for her input in the statistical analysis.

ADDENDUM

Questionnaire assessing the participants' knowledge on hemophilia

1. A coagulation factor (FVIII or IX) is missing in a person with hemophilia (PWH)

2. The daughter of a PWH is always a carrier

3. Hemophilia should be suspected in the brothers of a PWH

4. The son of a carrier has 50% of chance to have hemophilia

5. PWH do not have to go to the dentist

6. Physiotherapy can relief and make stronger the joints of a PWH

7. Some bleedings can be dangerous and cause the death of a PWH

8. It is necessary to wait until the age of 5 years before to test children for hemophilia

9. A blood test allows to diagnose of hemophilia

10. Screening for hemophilia should be done before circumcision

11. In case of pain, a PWH can take aspirin

12. Carriers of hemophilia can also have bleeding symptoms

13. A child with hemophilia should not be allowed to play in the playground

14. In case of a joint bleed, ice should be applied on the joint

15. In case of a joint bleed, physiotherapy should be initiated immediately

16. In case of a joint bleed, clotting factor concentrates should be infused immediately

17. In case of a joint bleed, rest is recommended a few days

18. In case of head injury, PWH should see a doctor urgently

19. Before any surgery, the hemophilia treatment center should be contacted

20. Visits to the hemophilia treatment center is necessary only in case of bleeding

☐ True ☐ False

Participants' motivation assessment (Likert scale)

1. To learn more about hemophilia is important to me
2. I want to learn more about hemophilia
3. My level of knowledge of hemophilia is already good
4. Learn more about hemophilia will be useful for me
5. Learn more about hemophilia will give me confidence

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

Participants' satisfaction assessment (Likert scale)

1. I learned more about hemophilia
2. The information will be useful for treating my hemophilia / my son's hemophilia
3. The game helped me understanding how hemophilia is transmitted
4. The training was easy to understand
5. I want to follow another training session

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

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Chapter 5

Implementation and assessment of a self- and community-based rehabilitation program in patients with hemophilia from Côte d'Ivoire.

Haemophilia. 2019 Sep;25(5):859-866.

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SUMMARY

Introduction: In resource-constrained countries, few patients with hemophilia have access to clotting factor concentrates (CFC), with increased musculoskeletal (MSK) complications. Physiotherapy actively contributes to preventing MSK complications, minimizing joint damage and reducing pain.

Aim: To assess the impact of a 20-week self- and community-based rehabilitation (CBR) program in Ivoirian people with hemophilia.

Methods: Fifty participants underwent a clinical and functional baseline assessment with identification of joints' functional defects and initiation of an individualized exercise program comprising exercises to improve strength, joint mobility, and proprioception. Hemophilia Joint Health Score (HJHS), 2-minute walking test (2MWT), timed up and go (TUG), goniometry, and maximal isometric voluntary contractions using the MicroFET2 were performed at baseline (T1) and at Week 20 (T2).

Results: At T2, there was a significant improvement in both the 2MWT and TUG tests. The HJHS-total score decreased significantly from 23.6±14.2 at T1 to 20.4±13 at T2. A significant improvement in joint health was found in the left elbow, right knee, and right ankle, with elements correlating with joint function responsible for these improvements. A strong program adherence was observed, with 94% of participants reporting regular exercise performance, and a high degree of satisfaction.

Conclusion: The program with its encouraging results is meant to be the first step towards a more ambitious project. Self-based and CBR programs are inexpensive and efficient treatment options designed to minimize the detrimental effects of joint and muscle bleedings, and to increase the functional independence and quality of life of people with hemophilia with limited access to CFC and physiotherapy.

INTRODUCTION

Hemophilia is a congenital X-linked recessive bleeding disorder resulting in low levels of either Factor VIII (FVIII, hemophilia A [HA]) or Factor IX (FIX, hemophilia B [HB]). Depending on residual coagulation factor activity, people with hemophilia (PWH) experience various degrees of bleeding, primarily affecting the joints, muscles, and soft tissues. Recurrent joint and deep muscle bleeds can lead to hemophilic arthropathy, nerve compression, or muscle fibrosis with adverse consequences, such as pain, limited range of motion (ROM), muscular atrophy, and disability [1].

Prevention of joint bleeds and subsequent arthropathy relies on regular prophylaxis with clotting factor concentrates (CFC) of FVIII or FIX, ideally initiated at a young age [2]. In resource-constrained countries, where 70% of PWH live, very few people have access to CFC, resulting in a high morbidity and mortality due to untreated bleedings and increased rates of musculoskeletal (MSK) complications [3]. Physiotherapy actively contributes to preventing MSK complications because it helps maintain good mobility and sufficient strength. Management early in life by a physiotherapist helps minimize joint damage and reduce pain in PWH. Moreover, physiotherapy is inexpensive and requires little infrastructure.

In the World Federation of Hemophilia (WFH) twinning program setting, a partnership was established between the Ivoirian hemophilia treatment center (HTC) of Yopougon in Abidjan and the international HTC of the *Cliniques universitaires Saint-Luc* in Brussels, Belgium. Regular on-site multidisciplinary visits enabled us to assess the MSK status of Ivoirian PWH and to ascertain either the lack of use or availability of physiotherapy in hemophilia care in Côte d'Ivoire [4]. An initial attempt to improve access to regular physiotherapy in PWH via training Ivoirian physiatrists across the country did not achieve the expected results for several reasons: (I) the cost of the sessions, which is entirely at the patient's expense and is challenging in a country with a very low average income (II) the lack of physiotherapists

in Côte d'Ivoire; (III) the unawareness of hemophilia and its management among PWH, their families, and caregivers; (IV) the large distance between the Abidjan HTC and the place of residence of certain PWH.

For the above reasons, we initiated a self- and community-based rehabilitation (CBR) program in Ivoirian PWH. CBR is "*a strategy for rehabilitation, equalization of opportunities, poverty reduction and social inclusion of people with disabilities"* [5]. CBR has already been applied in developing countries for other conditions [6;7]. The concept of CBR is relevant in countries, where institution-based rehabilitation facilities and comprehensive care hemophilia centers are scarce, communication is difficult, and distances between residence of PWH and such facilities are large.

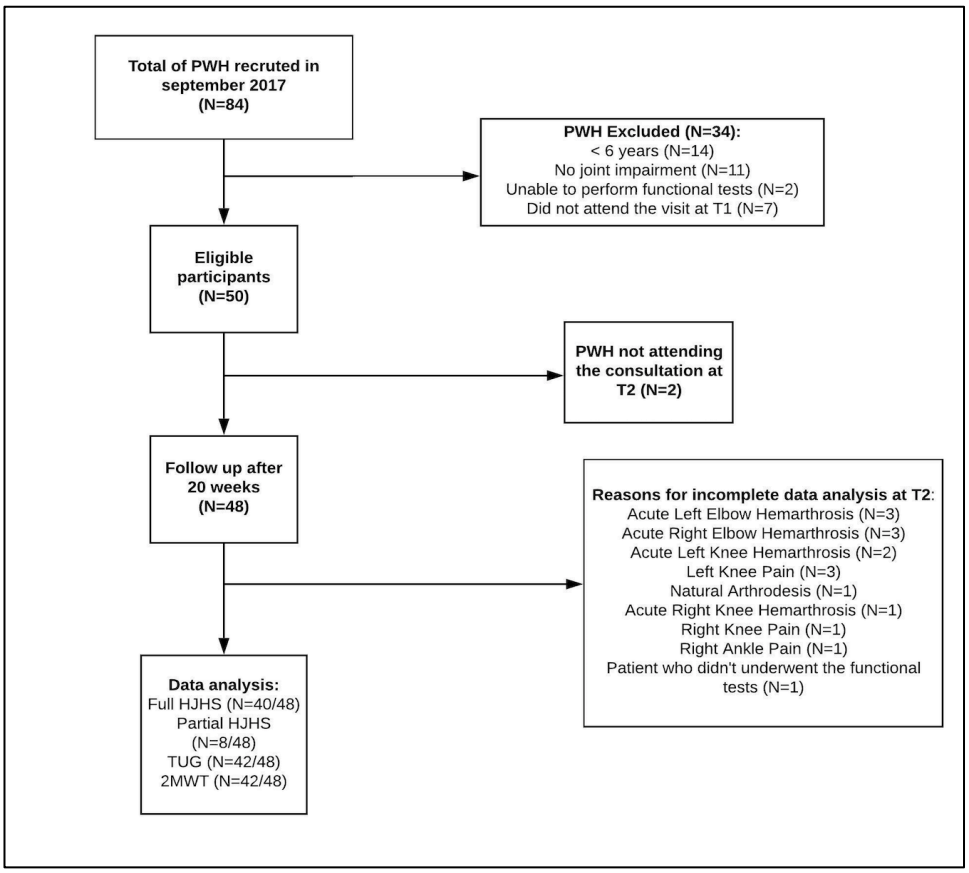
Our study sought to implement and assess the impact of a self-based and CBR program on the joint and functional status of Ivoirian PWH and to determine its feasibility in *Côte d'Ivoire*. To do this, we studied the 4-month interval evolution of the Hemophilia Joint Health Score (HJHS), maximal isometric voluntary contractions of knee, elbow, and ankle flexors and extensors, as well as general mobility and balance using simple performance-based tests: the 2-minute walking test (2MWT) and the timed up and go (TUG) test.

MATERIALS AND METHODS

Participants

The study was conducted from September 2018 to January 2019 at the HTC of Yopougon in Abidjan, the only HTC in *Côte d'Ivoire*. Eighty-four candidates were identified upon previous multidisciplinary consultations performed in the frame of the WFH twinning program (Fig 1). We included PWH with clinical evidence of MSK impairment and aged ≥ 6 years. Patients who were unable to undergo functional tests due to acute hemarthrosis were excluded. Overall, 50 PWH were included in the program.

Figure. 1 Flow of the participants



2MWT: 2-min walking test; HJHS: Hemophilia Health Joint Score
PWH: People with hemophilia; TUG: Timed Up and GO

The clinical characteristics and current treatment of the included patients are presented in Table 1. A majority (94%) exhibited severe forms of hemophilia. Almost all participants (98%) were treated on-demand. A minority (14%) of PWH was on regular physiotherapy at the time of inclusion. Overall, 10% were unable to work or attend school, owing to hemophilia complications. Half (52%) of the participants were geographically clustered around Abidjan, where the HTC is located, but 48% lived outside the district of Abidjan and at times in remote country areas.

TABLE 1. Characteristics of the 50 Ivoirian patients with hemophilia

PATIENTS CHARACTERISTICS	
Age (years)	14.0 (9.0;23.5)
BMI (Kg/m^2)	17.1 (15.3;19.6)
HEMOPHILIA CHARACTERISTICS	
HA	82% (N=41)
HB	18% (N=9)
Severe (<1%)	94% (N=47)
Moderate (1-5%)	6% (N=3)
Mild (>5%)	0%
Active inhibitor	6% (N=3)
History of inhibitor	2% (N=1)
TREATMENT	
On-demand therapy	98% (N=49)
Prophylaxis therapy	2% (N=1)
Self-Infusion	4% (N=2)
USE OF ANALGESICS	
Paracetamol	72% (N=36)
Anti-inflammatory drugs	16% (N=8)
Cox-2 inhibitors	10% (N=5)
PREVIOUSLY ON REGULAR PHYSIOTHERAPY	14% (N=7)
OCCUPATION	
Student	78% (N=39)
Active worker	12% (N=6)
Unemployed	8% (N=4)
Not attending school	2% (N=1)

Note: Values are expressed as median (P25; P75); BMI: Body mass index, HA: hemophilia A; HB: Hemophilia B

Clinical assessment of the participants

Participants underwent a MSK assessment using the HJHS 2.1, a disease-specific 9-item tool (swelling, duration of swelling, muscle atrophy, crepitus on motion, flexion loss, extension loss, joint pain, strength and gait) for assessing impairment of six joints (elbows, knees, and ankles) in children aged 4–18 years [8]. Recent studies have demonstrated HJHS reliability and validity in adult PWH [9;10]. At baseline, the HJHS was calculated on 295 joints, with the exclusion of five joints (four recent hemarthrosis and 1 natural arthrodesis). Joint impairment was observed in 182 joints (Table 2).

Table 2. Musculoskeletal status of the participants at baseline (N=50)

Clinical assessment		(N)	Data
HJHS left elbow	max 20 points	48	0.5 [0;5,75]
HJHS right elbow	max 20 points	50	1 [0;6.25]
HJHS left knee	max 20 points	49	5 [0;9,5]
HJHS right knee	max 20 points	48	7 [0.25;12.75]
HJHS left ankle	max 20 points	50	1 [0;3.25]
HJHS right ankle	max 20 points	50	1 [0;4.25]
HJHS total	max 120 points	45	23.6 ± 14.2

Values are expressed as mean ± SD (min.-max.) or median [P25; P75].
HJHS, hemophilia joint health score.

Methods

This is a prospective interventional study assessing the impact of a 20-week self-and community-based rehabilitation program on Ivoirian PWH. Participants underwent a clinical and functional baseline assessment that

allowed the identification of joints' functional defects. Based on these results, an individualized exercise program was provided to the participants and comprised exercises to improve strength of principal muscular groups, joint mobility, and proprioception. Most exercises were analytical in nature. Exercises were limited to spend a maximum of 30 minutes per day. In case of multiple joint arthropathy, exercises were selected so as to target the most affected joints. The exercises were provided with the support of fact sheets indicating how to correctly perform the movements, along with the number of repetitions and frequency per day.

Ethics

The study protocol was approved by the Ivorian Ethics Committee (*Comité National d'Ethique de la Recherche*) and registered at ClinicalTrials.gov (NCT03054662). In accordance with the Declaration of Helsinki, written informed consent was obtained from all participants their parents or legal guardians.

Educational materials

S.L. and C.L. developed the educational material (freely available at the following web link: http://www.davincihealth.be/haemophilia/). The content and layout of the material were developed in the French language, the official language of *Côte d'Ivoire*. The material had culturally sensitive pedagogical and iconographic characteristics with concise explanations and used local terminology and wording, and pictures exclusively presenting African subjects. The material was distributed in the form of printed fact sheets and was orally explained to the patients and their families during interactive sessions. To ensure they were well understood and executed, the exercises were systematically shown and repeated by participants under the oversight of the research team. Participants were also video recorded with their own cell phones to enable them to review their exercises. Another fact sheet informed the participants about the basic rules of joint bleed management namely the interruption of the physiotherapy program for a

few days. Patients were also advised not to continue the exercises in case of recurrent pain and to consult the local HTC. Most of the exercises could be performed with affordable material (light weight, towels) and elastic rubber bands of various resistance provided by the investigators. For the youngest participants, passive mobilization exercises were taught to parents, who then had the child do the exercises.

Functional assessment

In addition to the HJHS flexion and extension items, raw range of motion (ROM) scores were collected using a digital goniometer (Medigauge®, Taylor Toolworks LLC, Columbia, USA). For the elbow and knee, the same goniometry protocol from HJHS 2.1 was used [11]. Because ankle ROM measurement is subjective, we used the goniometry protocol developed by Thornton et al., owing to its excellent inter- and intra-rater reliability in patients with and without ankle arthritis [12].

Maximal isometric voluntary contractions of knee, elbow, and ankle flexors and extensors were measured using a MicroFET2® hand-held dynamometer (Hoggan Industries, Inc., West Jordan, UT, USA). The device is battery operated with a digital reading of peak force expressed in newtons (N). The measurement consisted of three consecutive maximal contractions for each muscle group, preceded by three warm-up sets. The three measures were performed with 30-s intervals between contractions, with the highest performance considered for analysis. Subjects were asked to gradually increase their muscle force to maximum effort, which had to be sustained for 6-s. Observers provided standardized encouragement.

To avoid inter- and intra-observer bias, the test sequences between the different muscle groups were randomly determined in the first assessment and the same observers and same order in the second assessment. The test was not performed in case of clinical acute hemarthrosis or severe pain.

Finally, participants were asked to walk with standardized flat sole shoes (Newfeel®, Decathlon, Villeneuve d'Ascq, France) to perform the 2MWT [13] and the TUG test [14]. These performance-based tests have been proven to be reliable and valid tests for quantifying functional mobility in many patient groups [15]. The 2MWT was employed instead of the 6MWT because many PWH showed severe lower limb arthropathy and were unable to ambulate for 6 minutes. The test was administered in a quiet room where PWH were asked to walk as far as they could in two minutes without any further encouragement between two cones that were 20 m apart. The TUG measures the time required for an individual to stand up from a standard chair, walk 3 m, turn around, walk back to the chair, and sit down again [14]. The starting position was standardized, including buttock placement, back support, use of hands, and foot placement.

Data collection

Participants were assessed in September 2018 (T1) and January 2019 (T2) by the same investigators. A logbook, under the form of a calendar, was provided at T1 to record the program adherence. The participants were asked to record daily the practice of the exercises and, in case of non-completion, to report the reason. At mid-term of the study period, the study team contacted by phone the patients or their parents to ensure the follow-up of the program. A Likert scale was applied to assess the participants' satisfaction with the program at T2 (five questions). The results were expressed on a scale ranging from 0 (strongly disagree) to 10 (strongly agree) or expressed with smiling emoji (meaning 10/10), neutral emoji (meaning 5/10), or unhappy emoji (meaning 1/10) in PWH < 12 years old.

Statistical analysis

All data were analyzed using Sigmastat and Sigmaplot (Systat Software Inc, San Jose, USA). To evaluate the program's impact over time, comparison of clinical and functional variables across the two-time intervals was performed using a paired t-test or Wilcoxon's signed-rank nonparametric test for paired

variable with a threshold α of 0.05. Effect size (ES) was calculated using Cohen's d: ES values of 0.00 to ≤0.49 indicated small effects, ES values of 0.50 to ≤0.79 indicated medium effects, and ES values ≥0.80 indicated large effects [16].

RESULTS

At T2, we observed a significant improvement in distance walked in 2 minutes in comparison with baseline (186.1 ± 31.0 m vs 174.7 ± 31.0 m; *P*<0.001; Table 3). In addition, the time of the TUG significantly decreased between T1 and T2 (9.2 ± 2.2 s vs 7.4 ± 1.8 s; *P*<0.001; Table 3). Evolution of the HJHS-total scores and HJHS-joint scores are shown in Tables 3 and 4. HJHS-total score decreased significantly from 23.6 ± 14.2 at T1 to 20.4 ± 13 at T2, *P*<0.001 (Table 3).The HJHS scores for the right elbow, left knee, and left ankle did not change significantly from T1 to T2 (Table 4). However, a significant moderate improvement in joint health was found in the left elbow, right knee, and right ankle.

Post-hoc analysis revealed that the items responsible for these improvements were ROM, joint pain, and strength (*P*<0.05), that is, the items correlated with joint function (Table 4). Improvement in joint pain was the most significant with an ES of 0.301. Items in relation to the structural aspect of the joints, such as swelling, muscle atrophy, and crepitus in motion remained unchanged. To assess the potential influence of adherence to the program on the improvement in the functional results, post-hoc correlation analysis was conducted between the number of days the exercises were performed and TUG, 2MWT, and HJHS total scores. No significant correlation was found (respectively, *P*= 0.996, 0.452, 0.343).

Table 3. Clinical and functional assessment before and after the self-rehabilitation program

Test	(unit)	(N)	T1	T2	*P*-value	Effect size
Timed up and go	(s)	42	**9.2 ± 2.2**	**7.4 ± 1.8**	**<0.001**	**0.890**
2-min walking test	(m)	42	**174.7 ± 31.0**	**186.1 ± 31.0**	**<0.001**	**0.370**
HJHS total (max. 120 points)		40	**23.6 ± 14.2**	**20.4 ± 13**	**<0.001**	**0.230**
Goniometry						
ROM left elbow	(°)	42	140 [115;146]	140 [122;145]	0.899	0.008
ROM right elbow	(°)	44	140 [119;148]	140 [125;147]	0.430	0.104
ROM left knee	(°)	40	135 [100;145]	135 [105;150]	0.338	0.108
ROM right knee	(°)	44	**130 [90;140]**	**130 [102;146]**	**0.009**	**0.141**
ROM left ankle	(°)	46	60 [51;65]	60 [52;65]	0.323	0.113
ROM right ankle	(°)	44	60 [50;65]	60 [50;65]	0.196	0.178
Isometric strength						
Flexion left elbow	(N)	12	150.6 ± 67.4	156.6 ± 60	0.151	0.090
Extension left elbow	(N)	12	**82.6 ± 29.1**	**106 ± 43.7**	**<0.001**	**0.640**
Flexion right elbow	(N)	9	145.4 [90.1;218.3]	117 [93.6;183.9]	0.164	0.222
Extension right elbow	(N)	9	**83.2 [63.5;105.5]**	**79.6 [73.1;128.1]**	**0.008**	**0.345**
Extension left knee	(N)	26	**144.5 [88;208.8]**	**150.8 [87.8;221.7]**	**0.009**	**0.134**
Flexion left knee	(N)	27	132.8 ± 49.4	120.9 ± 52.8	0.219	0.230
Extension right knee	(N)	32	**156.1 ± 90**	**180.9 ± 115.9**	**0.028**	**0.240**
Flexion right knee	(N)	31	**143.7 ± 54**	**130.9 ± 58.7**	**0.007**	**0.230**
Dorsiflexion left ankle	(N)	10	157.9 ± 39.1	188.5 ± 54	0.117	0.660
Plantar flexion left ankle	(N)	10	212.8 ± 83.2	224.5 ± 103.8	0.218	0.130
Dorsiflexion right ankle	(N)	13	**158.3 ± 49.3**	**182 ± 58.4**	**0.015**	**0.440**
Plantar Flexion right ankle	(N)	13	195 ± 61.4	212.1 ± 86.6	0.137	0.229

N: newton; HJHS: Hemophilia Joint Health Score; ROM: range of motion; s: seconds. Bold values with P<0.05

Table 4. Evolution of the HJHS per grouped items (mean score for elbows, knees, and ankles) and per joint before and after the self-rehabilitation program (paired comparison).

		N	T1	T2	*P*-value	Effect size
HJHS per grouped items						
Swelling (3 points) + duration (1 point)	Max 4 points	48	0.85 ± 0.46	0.79 ± 0.46	0.159	0.130
Muscle atrophy (2 points)	Max 2 points	48	0.41 ± 0.35	0.39 ± 0.33	0.255	0.059
Crepitus on motion (2 points)	Max 2 points	48	0.45 ± 0.38	0.42 ± 0.35	0.245	0.082
ROM in flexion (3 points) and extension (3 points)	Max 6 points	48	**1.49 ± 1.12**	**1.28 ± 1.09**	**<0.001**	**0.190**
Joint pain (2 points)	Max 2 points	48	**0.30 ± 0.28**	**0.22 ± 0.25**	**0.009**	**0.301**
Strength (4 points)	Max 4 points	48	**0.32 ± 0.33**	**0.26 ± 0.31**	**0.041**	**0.187**
HJHS per joint						
HJHS left elbow	Max 20 points	45	**0.5 [0;5.75]**	**0 [0;5]**	**0.043**	**0.084**
HJHS right elbow	Max 20 points	45	1 [0;6.25]	0 [0;3.5]	0.191	0.113
HJHS left knee	Max 20 points	45	5 [0;9.5]	6 [0;9]	0.281	0.042
HJHS right knee	Max 20 points	47	**7 [0.25;12.75]**	**6 [0;11]**	**0.009**	**0.148**
HJHS left ankle	Max 20 points	48	1 [0;3.25]	0.5 [0;4]	0.231	0.035
HJHS right ankle	Max 20 points	48	**1 [0;4.25]**	**0 [0;3]**	**0.004**	**0.282**

HJHS: Hemophilia Joint Health Score; ROM: range of motion
Values are expressed as mean ± SD or median [P25; P75].
Bold values are significant with P<0.05

After comparing the raw joint ROM recorded with the goniometer, subjects showed a discrete but significant improvement in the right knee (p=0.009). The other five joints did not improve following completion of the self-mobilization program. Strength measurements displayed significant changes between pre- and post-program levels in some muscular groups (Table 3). Significant differences in the strength of the extension of both elbows and knees, flexion of the right knee, and dorsiflexion of the right ankle were found. Among these, the extension of the right elbow and flexion of the right knee were the only muscular group to decrease. There were no significant changes for the other muscular groups.

We observed a strong adherence to the program, with 94% of the participants reporting regular exercise performance. A high degree of satisfaction was observed, with an overall score of 43/50.

DISCUSSION

The current study sought to implement and assess the feasibility and impact of a self- and CBR program on the clinical and functional status of PWH in Côte d'Ivoire. Initially, this initiative was set up to overcome the lack of physiotherapy access for Ivorian PWH. We selected exercises individualized to the participants based on their clinical MSK assessments. The exercises were intentionally basic and applicable to all ages, and they required no or only simple equipment to avoid any restriction in participation.

Our results showed significant improvement in the TUG and 2MWT with a large and small ES, respectively (Table 3). Previously, randomized control trials have compared the natural evolution of the 6MWT (more frequently studied than the 2MWT) and the TUG among control groups that did not receive intervention treatment. In patients with hip or knee osteoarthritis (OA) [17-21], subjects with chronic rheumatoid arthritis [22], healthy children [23], or children with hemophilia [24], similar [17-19], improved [20;22], or impaired [21;25], performances have been reported for the 6MWT[17-23;24] and the TUG [19-22]. Because our study did not include a

control group, we cannot attribute the functional improvement solely to the program, although the improvements reported in these former studies were much smaller than those recorded in ours.

We reported a mean three-point-decrease in the HJHS total score. When HJHS items were grouped per structural (swelling, atrophy, and crepitus) and functional (ROM, pain, and strength) categories, we were able to allocate this moderate clinical status improvement to an improvement in joint function and a greater ES for pain in comparison to ROM and strength (0.301, 0.190, and 0.187, respectively; Table 4). Hand-held isometric strength measurements displayed significant changes between pre- and post-program levels in some muscular groups. Increased strength in knee extensors could be explained by the high proportion of exercises aiming to specifically strengthen the quadriceps. However, we cannot explain the observed decrease in knee flexor strength and these results should be confirmed in further studies as the reliability of the microfet2 has shown contradictory results especially for assessing large muscle groups such as knee flexors and extensors [26] and monitoring changes at individual level [27].

The World Health Organization actively promotes self-rehabilitation [28] that has already demonstrated its effectiveness in increasing patients' treatment compliance [29;30]. According to Coudeyre et al., education with regular physical activity practice is a part of nonpharmacological treatment in patients with chronic arthropathic diseases. Empowerment of the patient as well as his or her family members in the learning process of the exercises can contribute to improving the efficacy of the program [31]. The involvement of the local community and the education of PWH and their families are the first steps toward comprehensive hemophilia care [32]. Only very few authors have studied the effectiveness of a self-rehabilitation program in patients with OA or hemophilic arthropathies. Based on a meta-analysis, Anwer et al. concluded that home exercise programs reduced knee pain and improved function in individuals with knee OA [33].

Cuesta-Barriuso et al. assessed for the first time the efficacy of a 15-week physiotherapy home exercise intervention in patients with hemophilic arthropathy [33]. The authors reported an improvement in pain perception following the program, particularly at the ankle joint.

In our study, the sample size was rather representative (n=48), as it should be taken into account that ours was a monocentric study and that hemophilia is a rare condition largely underdiagnosed in developing countries [35]. Of note, the participants demonstrated a strong motivation and adherence to the program, reporting a high degree of satisfaction with the self-rehabilitation exercises.

Our study exhibits some limitations. First, we had no control group because it was ethically difficult not to offer self-rehabilitation to PWH with advanced arthropathy and limited access to CFC. Second, participants and their parents were only trained once for the program at the time of inclusion, and we had no means to supervise them remotely or assess their compliance and adequacy to perform the exercises.

Our results are encouraging and open up a wide range of opportunities for improving the program through more individualized exercises and improved supervision. Family members should be actively involved because they can help, stimulate and, encourage PWH to carry out regular exercises. Achieving adequate education for both patients and their family members is of high relevance, especially so in developing countries [32]. Local physiotherapists should concurrently be actively involved to initiate and provide systematic and regular follow-up. In the future, telemedicine could also be used for the monitoring of such exercises program. The exercises were essentially analytical in the actual program. More functional and personalized exercises that can facilitate the accomplishment of daily life tasks should be proposed to render the program even more attractive. In addition to a self-rehabilitation program, MSK health improvement and disability prevention in Ivorian PWH will require a global approach that encompass better access to CFC, and rehabilitation medicine approaches [32].

CONCLUSION

We developed an effective and feasible self-rehabilitation program for Ivoirian PWH. Hemophilia care is building up in Côte d'Ivoire, and this project was the starting point for a more structured, supervised, individualized, and developed program that will require adjustment in the future. Our population showed excellent adherence, but a close follow-up and long-term assessment will be needed to implement this therapeutic approach to a larger population. This program revealed encouraging results and is meant to be the first step towards a more ambitious project that can be extended to other countries where there is an urgent need for appropriate solutions to relieve the burden of hemophilic arthropathy. Self-based and CBR programs are an inexpensive and remain efficient treatment option to minimize the detrimental effects of joint and muscle bleedings and to increase the functional independence and quality of life for PWH with limited access to CFC.

ACKNOWLEDGEMENTS

This project in Côte d'Ivoire was funded by grants from the WFH twinning program and PFIZER Belgium.

The authors expressly thank Professor Jean-Louis Croisier, department of motricity and rehabilitation sciences, University and CHU of Liège, Liège, Belgium for his assistance in the development of the isometric strength assessment protocol.

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SECTION 3

Cross-cultural adaptation and validation of hemophilia-specific health-related quality of life tools

Chapter 6

Cross-cultural adaptation and validation of the Canadian Haemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT) in Côte d'Ivoire.

Health and Quality of Life Outcomes. 2020 Mar 18;18(1):76

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SUMMARY

Introduction: Health-related quality evaluation is recognized as an important outcome in the assessment of boys with hemophilia. In fact, in developing countries, reliable health-related quality data is even more critical to advocate for government agencies to develop national hemophilia care programs. Validated tools are, however, not yet available in Sub-Saharan African countries.

Aims: The purpose of this study was to complete a cultural adaptation and validation of the CHO-KLAT version$_{2.0}$ in Côte d'Ivoire.

Methods: The process included four steps: a linguistic adaptation, cognitive debriefing interviews with children and their parents, a validity assessment with the PedsQL as comparator, and a test-retest reliability assessment.

Results: The initial Ivoirian version of CHO-KLAT$_{2.0}$ resulted from a linguistic adaptation performed in close collaboration with members of the local medical team and hemophilia community. Cognitive debriefings were completed with five boys and their parents, with the final Ivoirian version of CHO-KLAT$_{2.0}$ obtained in September 2017. The validation process included 37 boys with hemophilia (mean age: 11.4 years; 34 severe and three moderate forms, all treated on demand) with their parents. In the child-reported population (n=20), we observed a mean CHO-KLAT$_{2.0}$ score of 51.3±9.2; a moderate correlation with the PedsQL (r=0.581; p=0.007) and an inverse correlation between the CHO-KLAT$_{2.0}$ and PedsQL scores and the global rating of how much bother hemophilia caused. The mean CHO-KLAT$_{2.0}$ score for the proxy-parent (n=17) was 53.5±9.8. Among the parents, we found no significant correlation between the Ivoirian CHO-KLAT$_{2.0}$ and PedsQL, nor between the parent-reported scores and their global rating of bother. The test-retest intra-class correlation coefficient was 0.879 (95%CI: 0.673; 0.954) for the child-reported questionnaires and 0.880 (95%CI: 0.694; 0.955) for the proxy-respondents.

Conclusion: A cross-cultural adapted and validated version of CHO-KLAT$_{2.0}$ is now available in Côte d'Ivoire, enabling baseline values to be obtained, along with measurement of intervention outcomes (namely prophylaxis) in Ivoirian boys with hemophilia.

INTRODUCTION

Hemophilia is a congenital X-linked recessive bleeding disorder resulting in low levels of either Factor VIII (FVIII, hemophilia A [HA]) or Factor IX (FIX, hemophilia B [HB]). The condition occurs in approximately 1 in 5.000 (HA) and 1 in 20.000-30.000 (HB) live male births [1]. Depending on residual coagulation factor activity, people with hemophilia (PWH) experience various degrees of bleeding, primarily affecting the joints, muscles, and soft tissues [2]. Recurrent joint bleeds cause long-term complications including pain, arthropathy, and disability [3]. The major goal in treating PWH is to reduce the frequency of bleeds and consequently mortality and joint damage. Treatment is based on replacement of the missing clotting factor when the bleed occurs (on-demand) or preventively with regular prophylaxis. Hence hemophilia-related complications and treatment have a major impact on health-related quality of life (HRQoL) [4]. Consequently, HRQoL is considered a key clinical outcome in assessment of PWH [5;6]. Given that HRQoL is closely linked to people's culture, HRQoL tools developed in one context may not reflect the culture from another, and assessment tools often require cross-cultural adapting and validation [5-7]. The process of cross-cultural translation and adaptation of HRQoL measures is well-documented in the literature [8;9], including modified methods enabling limitations to be overcome, such as small sample sizes in children with rare disorders [10].

The Canadian Haemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT) is a disease- specific, child-centric, HRQoL measure for boys with hemophilia (BWH) that requires few resources [11]. There is only a version for children aged 4 to 18 years old, including both children's self-reported and parent-proxy reported questionnaires. The CHO-KLAT contains 35 items, is scaled from 0 to 100 [11], and has been validated against the Pediatric Inventory of Quality of Life (PedsQL), a generic HRQoL assessment tool [12]. It is valid, sensitive to significant clinical developments, and capable of assessing the impact of hemophilia-related interventions on HRQoL in a

target population [12]. The CHO-KLAT has strong psychometric properties, offering proven test-retest reliability [12], content validity [11], and high child-parent concordance [12]. It was initially developed in North American English, was updated to a version$_{2.0}$ [13] and was cross-culturally adapted and validated in several European countries [14], as well as China [15;16] and Brazil [17;18].

Only a few studies have fully evaluated HRQoL in developing countries, where most PWH are treated on-demand, resulting in repeated bleeding episodes with potentially negative impact on HRQoL. Accurate data on HRQoL are, however, critical for advocating government agencies to develop a national hemophilia care program. In Sub-Saharan African countries, research on hemophilia is limited [19] though, and the CHO-KLAT$_{2.0}$ was, until now only translated in South African languages [20]. No HRQoL measurements have yet been cross-culturally validated in the Ivoirian hemophilia population, although French versions do exist. In 2016, the World Federation of Hemophilia reported on 81 PWH in Côte d'Ivoire where there is, as in most developing African Sub-Saharan countries, no access to prophylaxis, and a mean per capita FVIII and FIX use of 0.032 and 0.005, respectively [21]. Clotting factor concentrates are supplied by humanitarian aid.

Our study sought to complete a cultural and linguistic adaptation of the CHO-KLAT version$_{2.0}$ and assess its validity and reliability in Côte d'Ivoire and by this obtain baseline values and enable measurement of intervention outcomes in BWH.

PARTICIPANTS AND METHODS

Participants

This study was conducted from January 2017 to January 2018 at the Hemophilia Treatment Center (HTC) of the Yopougon university hospital in Abidjan, Côte d'Ivoire's only HTC. At the occasion of multidisciplinary visits,

we screened all 43 BWH aged 4-18 years old followed at the Yopougon's HTC, and their parents.

The study was conducted as part of the World Federation of Hemophilia twinning program with a partnership established between the Ivoirian HTC of Yopougon and the international HTC of the Cliniques universitaires Saint-Luc in Brussels, Belgium.

Methods

The translation and validation process followed a modified approach of cross-cultural translation [10], comprising a cultural and linguistic adaptation, cognitive debriefing interviews, and validity test (including test-retest reliability) of the Ivoirian CHO-KLAT$_{2.0}$. To decide to use either proxy or self-reported assessment, literacy skills were evaluated in BWH 8 to 12 years of age whereas for children aged 4 to 8 years old, the questionnaires were completed by the parents.

Linguistic adaptation

The Ivoirian version was based on the French CHO-KLAT$_{2.0}$, as the official language in Côte d'Ivoire is French. The questionnaire was reviewed by two Ivoirian hematologists from the HTC, two members of the National Members' Organization, two adolescent BWH, and three BWH parents. All provided comments and proposed modifications that were reviewed by the Canadian CHO-KLAT development team and a Belgian physician experienced in treating hemophilia, fluent in both French and English, and involved in the twinning program. A back-translation was then performed by three native speakers of the target language with the following expertise: one orthopedic surgeon, one embassy official, and one former schoolteacher from Côte d'Ivoire currently living and working in Canada. The back-translation consisted in comparing the initial Ivoirian CHO-KLAT$_{2.0}$ to the original English Canadian version to ensure the meaning of the original questionnaire was preserved, and any discrepancies were adjudicated by the Canadian team

and Belgian-Ivorian partners. The final version was verified and approved by consensus of the team in August 2017. The resulting alignment created the initial child and parent Ivoirian CHO-KLAT$_{2.0}$.

Cognitive debriefing interviews

Cognitive debriefing (using Jobe's framework [22]) was conducted to ensure the initial Ivoirian version of the CHO-KLAT$_{2.0}$ was well understood by both children and parents in all linguistic, cultural, and clinical contexts.

Cognitive debriefings of the initial Ivoirian CHO-KLAT$_{2.0}$ were conducted at Yopougon HTC in September 2017. The following inclusion criteria were applied: boys aged 4-17.9 with hemophilia A or B, having inhibitors or not, native French speakers, without significant cognitive impairment, able to read French, and with a parent available for interviews. BWH and parents participated separately in face-to-face interviews conducted by two Ivoirian physicians, the hematologist from the Belgian HTC twin team and a member of the Canadian CHO-KLAT development team overseeing the interviews. Respondents completed the initial Ivoirian version of the CHO-KLAT$_{2.0}$ alongside a research team member and were asked to read the items out loud, verbalizing their thinking for each question and response. Any suggestions for improvements made by the respondents were recorded. Finally, participants were asked if they felt any items were missing. A research team member kept detailed notes. After completion of the 3rd pair's debriefing, the team reviewed the data to identify common problems, discussed solutions to enhance comprehension, and implemented the agreed revisions in the ensuing cognitive debriefings of two pairs. After cognitive debriefing with five pairs and a consensus group discussion, the team established the final Ivoirian CHO-KLAT$_{2.0}$ version.

Data collection

All data were collected on site by the same medical team. Demographics obtained for all participating BWH comprised: age, type and severity of

hemophilia, familial or sporadic form, treatment regimen, inhibitor status, place of residence, and education. In addition to this, in the sample of BWH aged 4-18 recruited for the validity testing, the body mass index (BMI) was calculated using the BMI-for-age formula [23] and a musculoskeletal assessment was performed by a trained physiotherapist using the hemophilia joint health score ($HJHS_{2.1}$), an 11-item scoring tool for assessing joint impairment in 4-18 year-olds [24]. Demographical data obtained from proxy-responders parents included: family relationship with the BWH, occupation and education. Participants were given the CHO-$KLAT_{2.0}$ and PedsQL at baseline (T1) during a clinical visit, then a second time (T2) using the Ivoirian version CHO-$KLAT_{2.0}$, 1-2 weeks after initial administration. Only clinically stable children, without active bleeds during this period were included in the test-retest analysis.

Statistical analysis

The final Ivoirian CHO-$KLAT_{2.0}$ version's validity was assessed against the PedsQL, a 23-item self-reporting generic measure of HRQoL [25], chosen as a comparator as it was used to validate the original CHO-KLAT in Canada [12] and as a modified version had already been widely administered in Côte d'Ivoire [26]. This step aimed to demonstrate if the previously established correlation between the CHO-KLAT and PedsQL [12] was maintained with the Ivoirian version. The CHO-$KLAT_{2.0}$ and PedsQL summary scores were calculated according to the questionnaires' manuals. Both CHO-$KLAT_{2.0}$ and PedsQL are scaled 0 to 100, 100 corresponding to the best HRQoL. The strength of correlation between the Ivoirian CHO-$KLAT_{2.0}$ and other instruments was calculated qualitatively using Pearson's correlation coefficient (r) as follows: very weak (|r|: 0.00-0.19), weak (|r|: 0.20-0.39), moderate (|r|: 0.40-0.59), strong (|r|: 0.60-0.79), very strong (|r|: 0.80-1.00).

Pearson's correlation was computed to assess the relationship between the two HRQoLs and a global rating of how much sufferers were bothered by

hemophilia. This was assessed by responses ranging from “not at all” to “very much”. The internal consistency of the Ivoirian CHO-KLAT$_{2.0}$ items was assessed using Cronbach’s alpha for the child self-report and parent proxy-reports. Note that, since the CHO-KLAT is a clinimetrically-derived tool, high internal consistency was not expected.

Test-retest reliability between the T1 and T2 CHO-KLAT$_{2.0}$ scores was assessed using an intraclass correlation coefficient (ICC) of absolute agreement based on a two-way mixed model [27]. An ICC over 0.70 indicated excellent test-retest reliability.

As joint impairment directly affects the HRQoL, and as muskulo-skeletal assessment was available from the multidisciplinary visits, a Pearson’s correlation between both HRQoLs measures and HJHS$_{2.1}$ score was also assessed.

All analyses were performed using R software Version 3.3.1. Continuous variables were presented as means and standard deviation (SD), compared between groups using Student’s t-test for independent variables, or as medians with interquartile ranges compared between groups using Wilcoxon rank-sum test, according to distribution normality. Categorical variables were presented as number of proportions, compared between groups using Pearson’s chi-squared test, Pearson’s chi-squared test with Yates continuity correction, or Fisher’s exact test, depending on the validity condition of each test.

RESULTS

Linguistic adaptation findings

In January 2017, the French CHO-KLAT$_{2.0}$ was reviewed by the Ivoirian team, and judged understandable based on patient feedback. However, some difficulties were signaled related to semantic, idiomatic (linguistic expression), and conceptual (disease-related) aspects of the CHO-KLAT$_{2.0}$

and minor changes (mainly to prepositions) were made by the local team to improve understanding. This step was reviewed by both Belgian and Canadian teams. After a backward translation and adjudication by the Canadian team and twin partners, 17 items were modified to improve linguistic accuracy and comprehension for children and parents. An important issue was the terminology used to describe joint bleeding. The word "swelling" was chosen ("*gonflement* or *enflement*") as this is used in Côte d'Ivoire. The sentence "These things did not happen to you in the past 4 weeks" was adapted to facilitate comprehension ("*Si ces choses ne sont pas arrivées dans ton cas, tu auras une autre réponse à choisir - If these things did not happen in your case, you will have another answer to pick* " and in the example: "*Je ne suis pas allé à l'école ces 4 dernières semaines et je n'ai donc pas écrit - I have not been to school in the past 4 weeks and so I have not written*"). One item of the overall evaluation (the activity "summer program") was removed. The same modifications were applied to self- and proxy-report versions. No new changes were made following backwards translation and changes were made to 48.6% of the CHO-KLAT$_{2.0}$ items in total, based on the clinical expert review. The harmonization step was completed end of August 2017.

Cognitive debriefing findings

Five children and parent pairs were interviewed. The mean BWH age was 13.9 years (SD 1.6; range: 11.7-15.3). They all had HA (three severe, two moderate), two familial and three sporadic. One had an active inhibitor. All were treated on-demand, no home therapy was available. Participating caregivers included three mothers, one father, and one brother considered a proxy-parent.

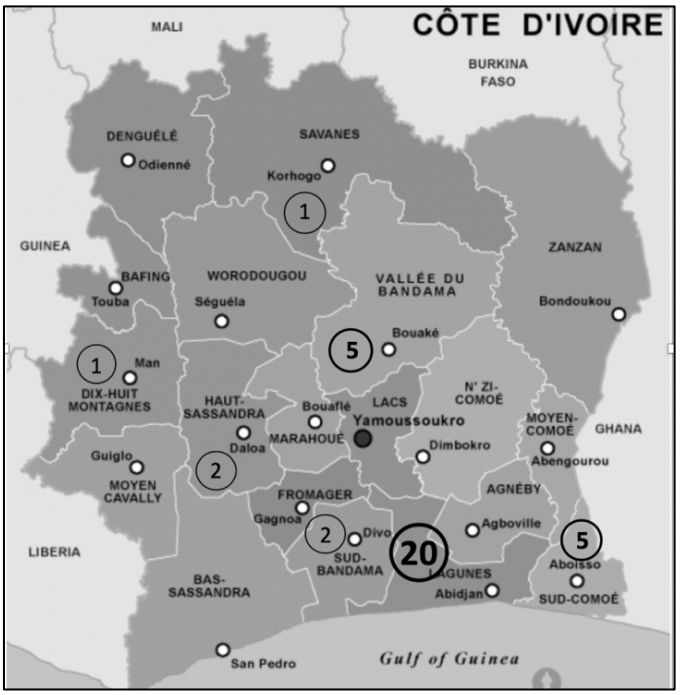
All CHO-KLAT$_{2.0}$ items were globally well understood by the five boys and their parents. However, similarly to the experience of the adaptation of CHO-KLAT$_{2.0}$ in Brazil [28], we observed significant variability in reading skills among BWH during the cognitive debriefing interviews. The team review

meeting after the 3rd and 5th cognitive debriefing interviews identified consistent concerns, instigating four minor modifications to the wording of five items (14.2% of the items modified). The same changes were applied to self-report and proxy-report versions. The mean CHO-KLAT$_{2.0}$ score was 56.7 (SD 6.1) for boys with hemophilia and 47.7 (SD 15.6) for parents. The Ivoirian CHO-KLAT$_{2.0}$ was finalized in September 2017.

Validation results

The validity assessment of the final Ivoirian CHO-KLAT$_{2.0}$ included 37 BWH. The clinical characteristics of the validity sample are shown in Table 1. The mean age was 11.4 years (range 4.7-17.5 years). A joint impairment was observed in 84.8% of cases and significant joint disease (HJHS >10) was found in 66.7%. A majority (54%) were living in the district of Abidjan where the Yopougon HTC is located. The geographical distribution of the study subjects is detailed in Figure 1.

Fig. 1. Geographical distribution of the Ivoirian study subjects



All children attended school regularly except one who left aged 10 due to severe arthropathy (this boy had the worst HJHS score [41] of the cohort). One 16-year old BWH was held back in primary school due cognitive impairment secondary to an intracranial bleed in infancy. To decide if BWHs aged 8-12 years old were able to complete self-assessment, they were asked to read two simple wording short stories and to respond to three questions with multiple-choice answers to evaluate their reading and understanding. All the 15 BHW aged 8-12 years were tested on their literacy prior to completing the self-report questionnaire. Seven were able to complete the Ivoirian CHO-KLAT$_{2.0}$ without assistance.

It should be pointed out that 2 BWH, 13 and 14 years old, experienced difficulties with the not applicable (NA) option (corresponding to "these things did not happen to you in the past 4 weeks"). We proposed therefore to practice the use of the NA option by including an example to illustrate and train boys how to answer the NA option.

In total, 20 BWH completed the self-questionnaire on their own; parents of BWH under 8 years, with cognitive impairment or that failed the literacy test completed the parent-proxy versions. The 17 proxy-responders included 11 mothers and five fathers. One mother was the proxy-parent for two sons with hemophilia. The details of the proxy participants are described in Table 1.

Distribution of CHO-KLAT$_{2.0}$ and PedsQL scores

BWH reported a mean CHO-KLAT$_{2.0}$ score of 51.3 (range: 35.5-71.7) and a mean PedsQL score of 58.9 (range: 37.0-92.4). The mean score for the proxy-parent was 53.5 for CHO-KLAT$_{2.0}$ (range: 36.7-64.4) and 59.6 for the PedsQL (range: 40.3-75.0). (Table 1). No outliers were observed in the data.

Table 1. Characteristics of the population participating to the validation of Ivoirian CHO-KLAT$_{2.0}$

	Total (N=37) Mean±SD or Median [P_{25}; P_{75}] or n (%)	Self-reported outcome (n=20) Mean±SD or Median [P_{25}; P_{75}] or n (%)	Proxy-reported outcome (n=17) Mean±SD or Median [P_{25}; P_{75}] or n (%)	p-value
Boy's age, years	11.4±3.6	13.6±2.1	8.8±3.1	<0.001
Type of hemophilia				0.609
Hemophilia A	33 (89.2)	17 (85.0)	16 (94.1)	
Hemophilia B	4 (10.8)	3 (15.0)	1 (5.9)	
Clinical severity				0.234
Mild hemophilia	0 (0.0)	0 (0.0)	0 (0.0)	
Moderate hemophilia	3 (8.1)	3 (15.0)	0 (0.0)	
Severe hemophilia	34 (91.9)	17 (85.0)	17 (100.0)	
Inhibitor status				0.999
Previous inhibitor	1 (2.7)	1 (5.0)	0 (0.0)	
Current inhibitor	2 (5.4)	1 (5.0)	1 (5.9)	
Never had an inhibitor	34 (91.9)	18 (90.0)	16 (94.1)	
Boy's age categories				<0.001
4-7.9 years	8 (21.6)	0 (0.0)	8 (47.1)	
8-11.9 years	10 (27.0)	4 (20.0)	6 (35.3)	
12-17.9 years	19 (51.4)	16 (80.0)	3 (17.6)	
Proxy-responder for the boy				
Mother		/	12 (70.6)	
Father		/	5 (29.4)	
Familial hemophilia				0.157
Yes	22 (59.5)	14 (70.0)	8 (47.1)	
No (sporadic)	15 (40.5)	6 (30.0)	9 (52.9)	
BMI percentile	24.1 [9.1; 38.9]	28.5 [8.2; 46.2]	23.2 [10.4; 35.1]	0.479
Underweight (<5th percentile)	7 (18.9)	4 (20.0)	3 (17.6)	
Normal weight (5th-84th percentile)	30 (81.1)	16 (80.0)	14 (82.4)	
Proxy's occupation				
Work at home			11 (64.7)	
Work outside home			6 (35.3)	
Proxy's highest diploma				
Never went to school			2 (11.8)	
Primary school			13 (76.5)	
Secondary school			1 (5.9)	
Graduate school			1 (5.9)	
PedsQL total score	59.2±13.2	58.9±16	59.6±9.5	0.858
CHO-KLAT total score	52.3±9.4	51.3±9.2	53.5±9.8	0.491
HJHS total score*	16.0 [6.0; 23.0]	18.5 [11.8; 22.8]	15.0 [1.0; 23.5]	0.425

**4 missing values (10.8%); SD: standard deviation*

BMI: body mass index; Pediatric Inventory of Quality of Life: PedsQL; CHO-KLAT: Canadian Haemophilia Outcome-Kid's Life Assessment Tool; HJHS: Health Joint Hemophilia Score 2.1.

Validity results

The correlation results between the Ivoirian CHO-KLAT$_{2.0}$ and PedsQL were expected to be similar to the original Canadian study (r=0.59)[12] and are described in Table 2. The Pearson's correlation between the child-reported Ivoirian CHO-KLAT$_{2.0}$ and PedsQL at baseline revealed a moderate correlation. This confirms the validity of the final Ivoirian CHO-KLAT$_{2.0}$ for self-reporting BWH. However, in the proxy-reporting population, we found no significant correlation between the Ivoirian CHO-KLAT$_{2.0}$ and PedsQL. We identified the questions producing significantly different answers for the self and proxy-questionnaires for both HRQoL measures. Differences were observed for answers regarding emotional, social, and educational dimensions, but not physical health.

The degree of correlation between the HRQoL scores and the degree the BWH are bothered by their hemophilia was assessed (Table 2). We observed an inverse relationship between the child-reported Ivoirian CHO-KLAT$_{2.0}$ scores and the global rating of bother and between the child-reported PedsQL and the degree of bother. No significant relationship was observed between the parent-report scores and the global rating of bother.

Table 2. Pearson's correlation between CHO-KLAT$_{2.0}$ and other instruments, in self-reported and proxy-reported outcomes

Instrument	**Total (N=37)**		**Self-reported outcome (n=20)**		**Proxy-reported outcome (n=17)**	
	R	p-value	R	p-value	R	p-value
CHO-KLAT$_{2.0}$ vs PedsQL	0.350	0.034	0.581	0.007	-0.050	0.850
CHO-KLAT$_{2.0}$ vs HJHS	-0.392	0.024	-0.339	0.169	-0.414	0.125
PedsQL vs HJHS	-0.537	0.001	-0.653	0.003	-0.490	0.064
CHO-KLAT$_{2.0}$ vs GQ1	-0.186	0.271	-0.367	0.111	-0.081	0.757
PedsQL vs GQ1	-0.341	0.039	-0.497	0.026	-0.164	0.529

R: Pearson's correlation coefficient; CHO-KLAT$_{2.0}$: total score of CHO-KLAT$_{2.0}$ questionnaire; PedsQL: total score of the PedsQL questionnaire; HJHS: haemophilia joint health score 2.1; GQ1: General question 1 of the CHO-KLAT$_{2.0}$ questionnaire "How much are you bothered by your haemophilia"

The internal consistency of the Ivoirian CHO-KLAT$_{2.0}$ items, as measured by Cronbach's alpha, was 0.58 (95%CI: 0.42; 0.78) for the self-reported questionnaire and 0.65 (95%CI: 0.43;0.88) for the proxy-reported questionnaire. This confirmed the internal consistency of the Ivoirian CHO-KLAT$_{2.0}$.

Reliability results

The ICC between T1 and T2 assessments was calculated for 19 BWH (one boy did not bring back the questionnaire at T2), who recorded their own answers. The delay between T1 and T2 was on average 8.16 days (range: 6-11 days, median: 8 days). The test-retest reliability was assessed in 17 proxy-parents. The proxy-respondents answered the surveys at a mean of 8.59 days' interval (range: 6-13 days, median of 8 days). We observed an excellent ICC in both self-and proxy-reported questionnaires. Detailed results are in Table 3.

Table 3. Reliability of CHO-KLAT$_{2.0}$ total score between the assessment at T1 and T2

	T1 Mean±SD	T2 Mean (SD)	ICC (95%CI)
Total (n=36)	52.8±9.1	50.8±9.0	0.877 (0.734; 0.941)*
Self-reported outcome (n=19)	52.2±8.7	50.1±8.8	0.879 (0.673; 0.954)*
Proxy-reported outcome (n=17)	53.5±9.8	51.6±9.4	0.880 (0.694; 0.955)*

*ICC: intraclass correlation coefficient; 95%CI: 95% confidence interval; *p-value <0.05 to test if the ICC was >0.70*

One on 37 patient was excluded due to not completing the second assessment

Relationship between the HRQoL and HJHS

The correlation between the HRQoL measures and $HJHS_{2.1}$ score was assessed. Joint damage evaluation presented a weak inverse correlation with the Ivoirian CHO-$KLAT_{2.0}$ (Pearson's r=-0.339; P=0.169) and strong inverse correlation with PedsQL (r=-0.653 and P=0.003) in the self-reported population. For the parents, Pearson's correlation between the HJHS score and CHO-$KLAT_{2.0}$ showed a weak correlation (r=-0.329; P=0.230) and a very weak correlation with PedsQL (r=-0.178; P=0.494).

Participants' experience with the CHO-$KLAT_{2.0}$

BWH gave an average rating of 8.9 for the test, while proxy-responders gave it an average rating of 9.4 (based on a scale of 0 [very bad] to 10 [very good]). The average time required to independently complete both CHO-$KLAT_{2.0}$ and PedsQL surveys was 25.6 min for BWH and 27.3 min for proxy respondents. Most participants (75.6%) did not say any items were missing, in their opinion.

One parent reported the need to tailor the questionnaire to different ages, another suggested adding the answer "I have no idea of the thoughts of the child" and another suggested an item about the financial considerations of hemophilia. Two parents commented on their motivation to learn how to infuse clotting factor concentrates.

The open-ended questions highlighted the hemophilia consequences that most affected boys and their parents. Swellings (joint and muscle bleedings) and limitations in sports were the most frequent concerns reported. Only 1 BWH complained about the burden of infusions.

DISCUSSION

This study was conducted to develop a cultural and linguistic adaptation of the CHO-KLAT$_{2.0}$ and complete its validity and reliability testing in Côte d'Ivoire. The process of cultural and linguistic adaptation and validation required few resources (no need for translators since we used the validated French CHO-KLAT$_{2.0}$ version for France and French is the official language in Côte d'Ivoire), thus accessible for countries with financial restrictions. However, we wish to acknowledge the major importance of input from clinical experts in the linguistic adaptation, validation, and cognitive debriefing step to obtain the final Ivoirian CHO-KLAT$_{2.0}$.

Although the sample size was small, most (86%) of the BWH diagnosed and monitored in 2018 in Côte d'Ivoire were included in the study. With 46% of the participants not living in the Abidjan area, we had a good representation of Ivoirian regions.

Unsurprisingly, the mean child-reported CHO-KLAT$_{2.0}$ (51.3) and PedSQL scores (58.9) in the Ivoirian BWH were lower than observed in Canada (CHO-KLAT$_{2.0}$ = 75.4 and PedSQL = 80.9) [13] and European countries (CHO-KLAT$_{2.0}$ = 77.0 and PedSQL = 83.8) [14] where there is regular access to prophylaxis. The same results were found for the proxy-respondents. The mean HJHS$_{2.1}$ score of the 33 Ivoirian BWH was clearly higher (indicating more joint damage) than those observed in BWH from Canada [29]. Similar findings were recently described in a study comparing the burden of hemophilia in children from Canada with that of Brazil sufferers [29]. This underlines the gap in HRQoL between BWH living in countries with economic resource limitations and those without, as well as the urgent need to improve prophylaxis access.

The Ivoirian CHO-KLAT$_{2.0}$ correlated moderately with the PedsQL for child reports (Pearson's r=0.581), with similar results to the Canadian study (r=0.59) [12] and when other transcultural validations of CHO-KLAT$_{2.0}$ were

performed (*e.g.* in Brazil (r=0.47) [16] and China (r=0.67) [18]). This confirms the validity of the final Ivoirian CHO-KLAT$_{2.0}$ in self-reporting BWH. We found an inverse correlation between the degree BWH were bothered, the child-reported Ivoirian CHO-KLAT$_{2.0}$ scores, and the PedsQL. The reason we obtained stronger correlation with the generic measure instead of the specific measure (more relevant to hemophilia issues) could be due to the small sample size.

For the proxy-reports, we found no correlation between the Ivoirian CHO-KLAT$_{2.0}$ and PedsQL. Nor was any significant relationship observed between the parent-reported scores and global bother. Discordances were observed between self-reported and proxy-questionnaires for both HRQoLs when concerning emotional, social, and educational aspects, though not for physical health. As there were no obvious differences (in terms of disease severity and treatment) between the self- or proxy-assessed BWH, we hypothesized that the perception or understanding of the Ivoirian CHO-KLAT$_{2.0}$ could have been problematic for some proxy respondents, potentially due to parents having greater difficulty estimating the social and emotional impact of hemophilia compared to the physical consequences for their child. This difficulty is well illustrated by one parent's suggestion to add an answer box "I have no idea of the thoughts of the child". This conceptual barrier could be related to the local culture or the parents' education level. We had carefully selected the children using the literacy test yet did not anticipate the possibility that some parents might also face literacy difficulties. It is important to note that schooling has been compulsory for ages 6 to 16 since 2015 in Côte d'Ivoire (legislative decree n° 2015-635 of September 17, 2015). We thus called the parents back and asked them about their education. A majority (76.5%) stopped after elementary school (Table 1). This is concordant with the data reported in 2018 by the United Nations Human Development Program (UNDP) (5.2 years on average of schooling reported in Côte d'Ivoire), while China and Brazil had 7.8 years of schooling on average [30] and an established correlation between the CHO-KLAT$_{2.0}$ and PedsQL among parents.

As previously reported during adaptation of CHO-KLAT$_{2.0}$ in Brazil [27], literacy assessment is of high importance considering the low number of BWH able to complete the questionnaires without assistance. The age limit to be set for children independently responding remains to be determined in Côte d'Ivoire in view of some difficulties observed even among older BWH in answering questions. Assessing literacy among proxy-responders should also be considered prior to administering the HRQoL questionnaire, and if required, assistance should be provided to parents to ensure their understanding and perception of the questions. Further work is thus needed to develop and validate appropriate tools for the literacy assessment tools in children and parents before administering CHO-KLAT$_{2.0}$ in Côte d'Ivoire.

The test-retest reliability of the Ivoirian CHO-KLAT$_{2.0}$ was high in both BWH and parents and it demonstrated good concordance over time. Finally, we identified interesting similarities (limitation in sports) and differences (only one boy complained about the burden of clotting factor infusions) between the concerns reported by Ivoirian participants and those from countries where prophylaxis is a standard of care [14].

CONCLUSION

Accurately assessing the hemophilia burden in Côte d'Ivoire is crucial when advocating for improved access to safe factor concentrates. The need for HRQoL outcome measures became urgent as low-dose prophylaxis with extended half-life products was initiated in 17 young BWH in January 2018. Now a cross-cultural adapted and validated Ivoirian version of the CHO-KLAT$_{2.0}$ is available, a baseline can be obtained, the impact of prophylaxis in Ivoirian BWH assessed, and the outcome of further interventions in this population measured.

The Ivoirian CHO-KLAT$_{2.0}$ will be administered 1 and 2 years after initiating low-dose prophylaxis. Finally, the ability to assess HRQoL should also enable the Ivoirian HTC to participate in multisite international hemophilia clinical trials. However, our experience from this study highlights that some

measures should be applied to ensure an optimal understanding of quality of life questionnaires that have been developed in culturally distinct countries and that could be used in clinical studies assessing different treatment regimens.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Helsinki Declaration. The full protocol was approved by the Ivoirian Ethics Committee (*Comité National d'Ethique de la Recherche*) and registered on ClinicalTrials.gov (NCT03054662). Written consent was obtained from adult participants and the parents or legal guardians of all the participating children, in both cognitive debriefing and validation process. In addition, assent was obtained from minor participants aged over 12-years old.

ACKNOWLEDGEMENTS

The authors wish to warmly thank Koyo Usuba, research analyst at the Laurentian University of Canada, for his advices and support in the statistical analysis.

All the participants are thanked for their active contribution to the study.

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Chapter 7

Cross-cultural adaptation and validation of Haem-A-QoL in Côte d'Ivoire

Haemophilia. 2020 May;26(3):459-466

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ABSTRACT

Introduction: Health-related quality (HRQoL) evaluations are considered essential outcomes in the assessment of people with hemophilia. In developing countries, reliable HRQoL data are even more critical whilst enabling government agencies to develop national hemophilia care programs. However, validated tools are not yet available in Sub-Saharan African countries.

Aims: This study sought to perform a cultural adaptation and validation of the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) in Côte d'Ivoire.

Methods: The process comprised several steps, such as linguistic adaptation, cognitive debriefing interviews with adult hemophilia patients and psychometric testing, including reliability (internal consistency, test-retest reliability) and validity assessments (convergent with EQ-5D-5L, criterion with HJHS 2.1, known-groups).

Results: The final Ivoirian Haem-A-QoL version was obtained in December 2017 following linguistic adaptation and cognitive debriefings with six participants. The validation process included 25 patients, mainly hemophilia A patients (88%) with severe forms (80%). All participants received on-demand treatment, with joint impairment observed in 92%. Internal consistency and test-retest reliability of the Ivoirian Haem-A-QoL were very good. A Pearson correlation analysis revealed a moderate negative correlation between EQ-VAS and total Haem-A-QoL scores and a moderate positive correlation between HJHS 2.1 and total Haem-A-QoL scores.

Conclusion: A cross-culturally adapted and validated Haem-A-QoL version in Côte d'Ivoire is now available, enabling measurement of intervention outcomes in the targeted population and Ivorian participation to multisite international trials. However, further work is needed to ensure optimal understanding of HRQoL questionnaires, previously developed in culturally distinct countries, with unlimited access to different treatment regimens.

INTRODUCTION

Hemophilia is a congenital X-linked recessive bleeding disorder resulting in low levels of either Factor VIII (FVIII, hemophilia A [HA]) or Factor IX (FIX, hemophilia B [HB]) [1]. Depending on residual coagulation factor activity, people with hemophilia (PWH) experience various degrees of bleeding, primarily affecting the joints, muscles, and soft tissues [2]. In PWH with a severe phenotype, repeated bleeding into joints cause long-term complications, including pain, arthropathy, and disability, which significantly impair their health-related quality of life (HRQoL) [3]. Treatment is based on either replacing the missing clotting factor when bleeding occurs (on-demand) or preventively using regular prophylaxis. Hemophilia-related complications and treatments significantly impact HRQoL and daily functioning, which encompasses physical, social, cognitive, and emotional aspects [4,5].

In hemophilia, HRQoL assessment plays a key role in providing a comprehensive perspective of health status and treatment outcomes [5,6]. To assess HRQoL, it is recommended to employ self-reported instruments, either generic or disease specific. While the former enable HRQoL assessments across various conditions, the latter are more sensitive to changes, and provide a more accurate assessment of the symptom patterns and probable difficulties associated with the specific disease [5,7]. Given that HRQoL is closely linked to people's culture, HRQoL tools developed in one context may not reflect the culture of another, and assessment tools require cross-cultural adaptation and validation which is needed to facilitate multisite studies required to ensure adequate sample sizes [5-8]. The process of translation and cross-cultural adaptation of HRQoL measures is well-documented in the literature [7,9,10,11].

The adult version of the Haemophilia-Specific Quality of Life Questionnaire (Haem-A-QoL) is a disease-specific HRQoL measure for adult PWH [12,13]. Initially developed in Italian [14], the questionnaire has been translated until

today into 71 languages, including French for France [15]. Haem-A-QoL has demonstrated internal consistency and reproducibility; it is valid, sensitive to relevant clinical changes, and capable of assessing the impact of hemophilia-related interventions on HRQoL within a target population [4].

Only very few studies have fully evaluated HRQoL in PWH from developing countries, wherein most patients receive on-demand treatments, resulting in repeated bleeding episodes with a potentially negative impact on HRQoL. Data on HRQoL are, however, critical for advocating governments to develop a national hemophilia care program. In Côte d'Ivoire, HRQoL measurements have been cross-culturally validated in children [16] but not in adult PWH. In 2018, the World Federation of Hemophilia (WFH) reported that in Côte d'Ivoire, like in most developing Sub-Saharan African countries, there is no access to prophylaxis [17].

Our study sought to conduct a cultural and linguistic adaptation of Haem-A-QoL and assess its validity and reliability in Ivoirian adult PWH. The study was part of the WFH twinning program between the Ivoirian Hemophilia Treatment Centre (HTC) of Yopougon and international HTC, Cliniques universitaires Saint-Luc, in Brussels, Belgium.

METHODS

Instruments

Outcome measures included the Haem-A-QoL [13,14], the EuroQoL Five-Dimension generic measure with five Levels (EQ-5D-5L) [18], and the Hemophilia Joint Health Score (HJHS) [19,20]. The Haem-A-QoL is a hemophilia-specific HRQoL measure comprising 46 items pertaining to the following 10 dimensions (no of items): 'Physical Health' (5), 'Feelings' (4), 'View of Self' (5), 'Sports & Leisure' (5), 'Work & School' (4), 'Dealing With Hemophilia' (3), 'Treatment' (8), 'Future' (5), 'Family Planning' (4) and 'Partnership & Sexuality' (3). A raw score for each domain is calculated by summing up all item values, some items need to be reversely coded,

provided that a minimum number of questions have been answered for the respective domains. Scoring is performed by transforming the raw score achieved in each dimension, as well as the total score, on a scale ranging from 0 to 100, with 0 representing the best and 100 the worst HRQoL [3].

The EQ-5D-5L, a standardized instrument measuring generic HRQoL in adults, consists of the EQ-5D descriptive system and EuroQoL visual analogue scale (EQ-VAS). The EQ-5D-5L comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension displays five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-VAS records the patients' self-rated health on a vertical visual analogue scale wherein the end points are labeled "the best health you can imagine (score=100)" and "the worst health you can imagine (score= 0)" [18]. The EQ-5D-5L is available in over 130 languages [21] and has been used in a wide range of conditions and populations, including Western Africa [22].

As the joint status directly affects HRQoL in PWH, we used the HJHS 2.1, an 11-item scoring tool for assessing joint impairment in 4-18-year-olds [23]. Recent studies have demonstrated the reliability and validity of the HJHS 2.1 in adult PWH [19,24], and it has been validated in many countries over the world [25,26,27]. It combines the scores of all six index joints and gait to provide a total score ranging from 0 to 148.

Cross-cultural adaptation and validation

The translation and validation process of the Haem-A-QoL in Côte d'Ivoire followed a modified approach of cross-cultural translation [11,28] comprising a cultural and linguistic adaptation, pilot-testing step in the target population (known as cognitive debriefing interviews), and psychometric testing of the revised questionnaire (including testing of validity and test-retest reliability).

Cultural and linguistic adaptation

The Ivoirian Haem-A-QoL was based on the Haem-A-QoL version for France, French being the official language in Côte d'Ivoire. Therefore, no forward translated step was needed, but the questionnaire was reviewed by a working group of native speakers of Ivory Coast and members of the Belgian twinning team, including physicians, physiotherapists, members of the Ivorian National Member Organization, and two adult PWH. This aimed to identify comprehension difficulties, on account of local vocabulary, idiomatic expressions, and cultural specificities. The group rephrased the items representing comprehension issues, provided comments, and proposed modifications.

A back-translation into English was then performed, that allowed the instrument developer to compare the new version with the original UK English version of the Haem-A-QoL and to review the done modifications. This was meant to ensure the original questionnaire's meaning was preserved. Any discrepancies were adjudicated, with the initial Ivoirian Haem-A-QoL approved by consensus.

Cognitive debriefing interviews

Cognitive debriefing interviews, using Jobe's framework [29], were conducted to ensure the initial Ivoirian Haem-A-QoL to be well understood by the targeted population. Interviews were conducted by two hematologists, one Ivoirian and one from the Belgian twinning team. Participants had to speak French as first language. Respondents completed the initial Ivoirian Haem-A-QoL version and were asked to verbalize their thinking concerning each question. Any suggestions for improvement were recorded and participants were asked if any items were missing. Following consensus group discussions, the team established the Ivoirian Haem-A-QoL.

Psychometric testing

The psychometric characteristics such as reliability (in terms of internal consistency and test-retest reliability) and validity (in terms of construct validity criterion and known group validity) of the Ivoirian Haem-A-QoL were examined. For the convergent validity, the domains of the Haem-A-QoL were compared with the EQ-5D-5L. As no EQ-5D index turned out to be available for Côte d'Ivoire, the Haem-A-QoL was solely validated against the EQ-VAS. For the criterion validity a comparison of the Haem-A-QoL with the HJHS 2.1 was performed.

Patients

The study was conducted from January 2017 to January 2018 at the Yopougon's HTC in Abidjan, the only HTC in Côte d'Ivoire. The following inclusion criteria were applied: adult PWH, fluent in speaking and reading French (at least for those participating in the cognitive debriefing), without significant cognitive impairment, provided signed informed consent. In case of reading difficulties, assistance was provided to answer the questionnaire.

Ethics approval and consent to participate

The study was performed in accordance with the Helsinki Declaration principles. The full protocol was approved by the Ivoirian Ethics Committee and registered on ClinicalTrials.gov (NCT03054662). Written consent was obtained from all participants in the pilot-testing group and validity assessment.

Data collection

All data were collected on site by the same medical team upon recruitment during multidisciplinary twinning visits. Demographics included age, type and severity of hemophilia, familial or sporadic form, treatment regimen, inhibitor status, residence, employment status, and education. Participants underwent a musculoskeletal assessment performed by a trained

physiotherapist and were given the Ivoirian Haem-A-QoL and EQ-5D-5L at baseline (T0) during a clinical visit. The Ivoirian Haem-A-Qol was administered a second time (T1), approximately two weeks after T0.

Statistical analysis

The psychometric analysis of the Ivoirian Haem-A-QoL was based on reliability and validity testing. Reliability was examined using the internal consistency, a Cronbach's alpha (α) was considered adequate if $\alpha > 0.70$. The test-retest reliability between T0 and T1 was assessed using an intraclass correlation coefficient (ICC) of absolute agreement based on a two-way mixed model [30]. An ICC exceeding 0.70 indicated excellent test-retest reliability. To test the convergent construct validity and the concurrent criterion validity, a Pearson correlation analysis was performed between Haem-A-QoL domain and total scores versus the EQ-5D-5L and HJHS 2.1 scores. The correlation strength was calculated using the Pearson correlation coefficient I, set up according to the von Mackensen's report [14]. Convergent and concurrent validity was supported when the Haem-A-QoL total and domain scores were $|r| \geq 0.3$ (indicating at least moderate correlation); a strong correlation was demonstrated when achieving a magnitude of $|r|: \geq 0.60$ [31]. A known-groups validity comparison was performed between the Haem-A-QoL domain and total scores for each EQ-5D-5L item dichotomized into "no problem" (level 1) and "problem" (levels 2–5). All analyses were performed based on JMP Pro software Version 14.1.0. Continuous variables were expressed either as means and standard deviation (SD), and compared between groups using the Student's t-test for independent variables, or as medians with interquartile ranges, and compared between groups using the Wilcoxon rank-sum test, according to distribution normality. Categorical variables were expressed as the number of proportions and compared between groups using Pearson's chi-squared test, Pearson's chi-squared test with Yates continuity correction, or Fisher's exact test, as appropriate. Statistical significance was set at $p < 0.05$.

RESULTS

Linguistic adaptation findings

The French Haem-A-QoL was deemed understandable by the working group, yet with some difficulties signaled concerning semantic, linguistic expression, and conceptual (disease-related) features. The main issue was the terminology used to describe joint bleeding. The word "swelling" ("*gonflement*") was chosen, as generally used in Côte d'Ivoire. Minor linguistic changes were proposed by the local team designed to improve understanding. Following the backward translation and adjudication process, the initial Ivoirian Haem-A-QoL was obtained.

Cognitive debriefing findings

Cognitive debriefing interviews were conducted at Yopougon's HTC in June 2017 with six adult PWH. Their mean age was 26 years (range: 20–33). Five had HA (four severe and one moderate) and one severe HB, involving four familial and two sporadic forms. One had an active inhibitor. All were treated on-demand, with no home therapy available. Fifty percent were still in high school (upper-grade level). All Haem-A-QoL items were globally well understood. The team review identified consistent concerns, instigating three minor modifications concerning the general instructions' wording *(eg: "certains domaines" (some domains) was changed in "certains aspects" (some aspects),* 13 minor modifications regarding the questionnaire's 46 items' wording *(eg: "je me suis senti exclu" (I felt excluded) was changed to "je me suis senti rejeté" (I felt rejected)* with in total 28% of the items that were modified, and one conceptual modification (the word "swelling" (*gonflement*) was chosen to designate a joint bleed as this is used in Côte d'Ivoire). The Ivoirian Haem-A-QoL final version was verified and approved by consensus in December 2017.

Validity findings

Demographics of the validity testing population

The psychometric testing of the final Ivoirian Haem-A-QoL was carried out on 25 adult PWH. The patients' socio-demographic and clinical characteristics are summarized in Table 1.

Their mean age was 31.28 years. The predominant form was severe HA. All were treated on-demand, with joint impairment observed in 92% of evaluated cases (*n*=24), and significant joint disease (HJHS >10) in 87.5%. The highest diploma obtained was primary school in 36%, secondary school in 32%, and graduate school in 24%.

Distribution of the EQ-5D-5L and Haem-A-QoL

A detailed percentage of each of the five items' level of the EQ-5D-5L is shown in Figure 1. Participants reported a mean EQ-VAS score 58.2 (range: 15-85). Data on the Haem-A-QoL central tendency, variability, and reliability (Cronbach's alpha) are depicted in Table 2. Participants reported a mean total Haem-A-QoL score of 43.16 (range: 8.9–65.6). Among the 10 domains, the 'Dealing with hemophilia' and 'Partnership & Sexuality' scored the best, and the 'Sports & leisure' and 'Future' domains scored the worst. There were no missing data.

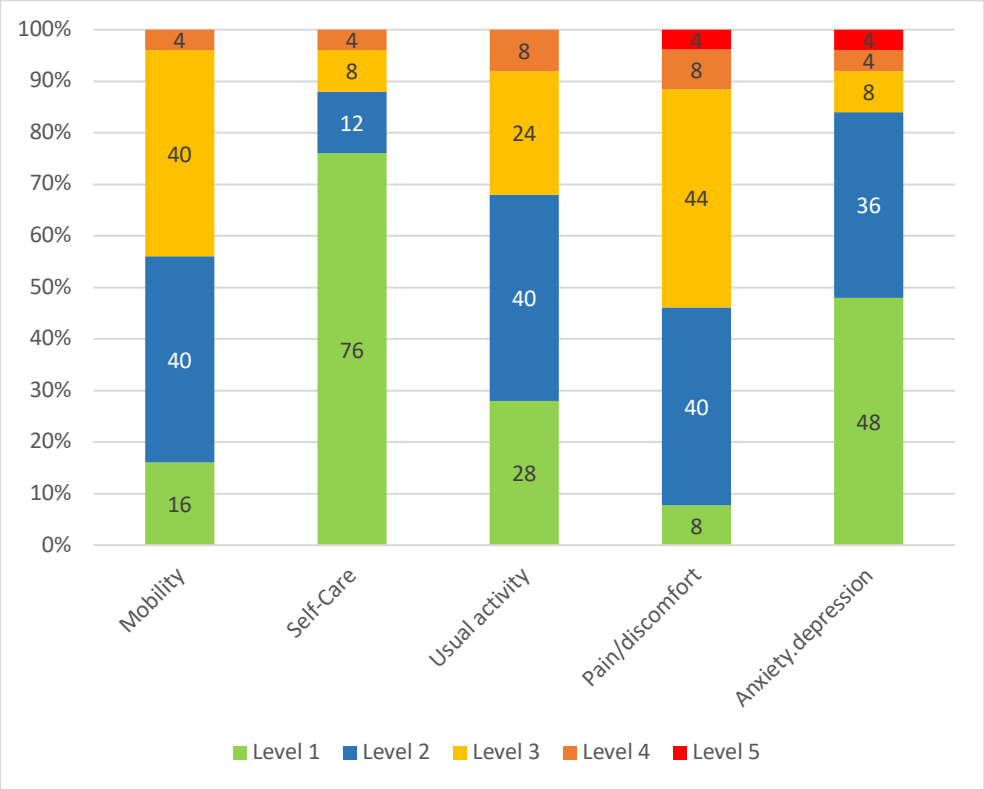
Reliability

Internal consistency reliability, assessed by Cronbach's alpha, was adequate ($\alpha > 0.70$) for all 10 Haem-A-QoL domains and the total score (ranging from α=0.74-0.85), thereby confirming the Ivoirian Haem-A-QoL's internal consistency. The median time between T0 and T1 was 13 days (range: 10–17). The test-retest reliability was assessed involving the 25 participants, with an excellent ICC observed (Table 3).

Table 1. Socio-demographic and clinical characteristics of the validity sample

Age, years	
Mean (SD)	31.28±12.86
Median (min-max)	28 [18-65]
Marital status, *n* (%)	
Married	6 (24.0%)
Single	15 (60%)
Divorced	4 (16.0%)
Occupation, *n* (%)	
Student	9 (36.0%)
Work	11 (44.0)
Retired	1 (4.0%)
Unemployed	4 (16%)
Highest diploma, *n* (%)	
Never went to school	2 (8.0%)
Primary school	9 (36.0%)
Secondary school	8 (32.0%)
Graduate school	6 (24.0%)
Offspring, *n* (%)	
Yes	11 (44.0%)
No	14 (56.0%)
Place of residence, *n* (%)	
Abidjan	14 (56.0%)
Outside of Abidjan	11 (44.0%)
Type of hemophilia, *n* (%)	
Hemophilia A	22 (88.0%)
Hemophilia B	3 (12.0%)
Clinical severity, *n* (%)	
Mild hemophilia	3 (12.0%)
Moderate hemophilia	2 (8.0%)
Severe hemophilia	20 (80.0%)
Inhibitor status, *n* (%)	
Active inhibitor	3 (12.0%)
Never had an inhibitor	22 (88.0%)
Familial hemophilia, *n* (%)	
Yes	19 (76.0%)
No (sporadic)	6 (24.0%)
Treatment on demand, *n* (%)	25 (100%)
HJHS total score (*n*=24)	
Mean ±SD	31.41±17.76
Median (min-max)	32.5 [0.0; 56.0]
HCV positive, *n* (%)	1 (4.0%)
HIV positive, *n* (%)	1 (4.0%)

Figure 1. EQ-5D-5L frequencies and proportions reported by dimension and level



EQ-5D-5L, EuroQoL- Five Dimension with Five Levels

Level 1: No Problem; Level 2: Slight Problems; Level 3: Moderate Problems; Level 4: Severe problems, Level 5: Extreme Problems

Table 2. Distribution characteristics and reliability of the Ivoirian Haem-A-QoL scores at T0

Haem-A-QoL domains	N	Mean	SD	Min	Max	Median	IQR	Cronbach's alpha
Physical Health (5 items)	25	52.2	21.2	0.0	100.0	55.0	22.5	0.76
Feeling (4 items)	25	46.8	28.4	0.0	93.8	43.8	43.8	0.74
View of yourself (5 items)	25	51.0	22.7	0.0	85.0	55.0	27.5	0.75
Sports & leisure (5 items)	22	76.2	20.3	15.0	100.0	80.0	12.5	0.77
Work & school (4 items)	23	44.0	23.0	0.0	93.8	43.8	31.3	0.78
Dealing (3 items)	25	19.0	21.3	0.0	100.0	25.0	25.0	0.85
Treatment (8 items)	25	31.4	15.4	0.0	56.3	31.3	23.4	0.79
Future (5 items)	25	58.4	23.3	0.0	95.0	55.0	27.5	0.77
Family planning (4 items)	19	31.5	31.8	0.0	100.0	25.0	56.3	0.77
Partnership & sexuality (3 items)	24	23.4	36.1	0.0	100.0	0.0	62.5	0.77
Total (46 items)	25	43.2	15.5	8.9	65.6	45.0	21.4	0.80

Haem-A-QoL, Haemophilia-specific Quality of Life Questionnaire for adults; SD, standard deviation; IQR, Interquartile Range

Table 3. Test-Retest reliability of the Ivoirian Haem-A-QoL scores between T0 and T1 assessments

		T0	T1	
Haem-A-QOL domains	**N**	**Mean±SD**	**Mean±SD**	**ICC (95%CI)**
Physical Health	25	52.2±21.2	53±21.9	0.95
Feeling	25	46.8±28.4	47±30.4	0.98
View of yourself	25	51±22.7	52±23.5	0.94
Sports & leisure	22	76.2±20.3	77.2±20.5	0.98
Work & school	23	44.0±23.0	46.2±24	0.94
Dealing	25	19±21.3	19.3±20.7	0.99
Treatment	25	31.4±15.6	30.5±14.2	0.96
Future	25	58.4±23.3	58.6±22.5	0.96
Family planning	19	31.5±31.8	30.5±31.5	0.99
Partnership & sexuality	24	25.4±36.1	24.7±36.5	0.99
Total Haem-A-QOL	25	43.2±15.5	43.5±15.9	0.99

*Haem-A-QoL, Haemophilia-specific Quality of Life Questionnaire for adults; ICC, intraclass correlation coefficient; 95%CI: 95%confidence interval; *p-value <0.05 to test if the ICC was > 0.70; SD, standard deviation.*

Construct and criterion validity

The convergent validity between the baseline correlation among the Ivoirian total scores of the Haem-A-QoL, EQ-VAS, and the concurrent criterion validity with the HJHS were examined. A Pearson correlation analysis revealed a moderate negative correlation between Haem-A-QoL and EQ-VAS (|r|: -0.38) and moderate positive correlation between Haem-A-QoL and HJHS (|r|: 0.38). The Pearson correlation analysis between the EQ-VAS scores and scores of each Ivoirian Haem-A-QoL's domain showed moderate negative relationships for 'Physical Health', 'Sports & leisure', 'Future', and 'Family planning' domains, yet weak correlations for the other domains (Table 4).

Table 4. Pearson correlation between the baseline scores of EQ VAS and Haem-A-QoL scores for each domain and total score

Haem-A-QoL	EQ-VAS
Physical Health	**-0.31**
Feeling	-0.1
View of yourself	-0.26
Sports & leisure	**-0.47**
Work &school	-0.11
Dealing	0.19
Treatment	-0.03
Future	**-0.57**
Family planning	**-0.50**
Partnership &sexuality	-0.21
Total Haem-A-QoL	-0.38

EQ-VAS, EuroQoL Visual Analog Scale; Haem-A-QoL, Haemophilia-specific Quality of Life Questionnaire for adults. Pearson correlation coefficient (r) was categorised as follows: weak $|r|<0.30$, moderate ($|r|\geq 0.30$-0.59, strong $|r|\geq 0$

Known-groups validity

The known-groups validity tests compared the mean Haem-A-QoL scores at baseline by response levels in the EQ-5D-5L domains (classified in two dichotomized groups: “no problems” (level 1) and “problems” (level $\geq$ 2). Significant differences between patients reporting “no problems” and those reporting “problems” in the pain and usual activities domain of the EQ-5D-5L were found for almost all domains of the Haem-A-QoL (Table 5).

No further known-groups validity testing could be performed due to the limited size and the uniform distribution of the population (a majority was affected with severe forms and were exhibiting significant arthropathy).

Table 5. Known-group validity. Comparison between the mean Haem-A-QoL scores at T0 with the response levels in EQ-5D-5L.

		Mobility Level			Self-care Level			Usual activities Level			Pain_Level			Anxiety_Level		
		No problem	Problems		No problem	Problems		No Problem	Problems		No problem	Problems		No problem	Problems	
	N	Mean±SD	Mean±SD	P-Val.	Mean±SD	Mean±SD	P-Val.	Mean±SD	Mean±SD	P-Val.	Mean±SD	Mean±SD	P-Val.	Mean±SD	Mean±SD	P-Val.
Physical Health	25	28.8±33.3	56.7±15.5	NS	49.2±23.2	61.7±8.2	NS	33.6±24.5	59.4±14.9	**	0	56.7±14.8	***	45.8±27.8	58.1±10.5	NS
Feeling	25	14±13.9	53±26.2	**	44.7±30.9	53.1±19.2	NS	18.8±17.3	57.6±24.2	***	3.1±4.4	50.5±26.3	*	38.5±33.8	54.3±21	NS
View of yourself	25	21.3±25	56.7±17.7	**	47.4±23.8	62.5±14.8	NS	28.6±24.8	59.7±14.9	*	2.5±3.5	55.2±18.1	***	38.8±24.4	62.3±13.9	**
Sports & leisure	22	46.6±32.2	82.9±8.3	NS	73.1±22.2	84.6±12	NS	55±34.1	82.4±8.4	NS	20±7.1	81.8±9.4	***	65.6±27	83.6±9.8	NS
Work & school	23	20.3±18.7	49±21	*	42±24.4	51.3±17.3	NS	21.9±15.2	51.8±20.2	**	6.3±8.8	47.6±20.6	*	31.3±15.8	55.7±22.8	**
Dealing	25	37.5±43.8	15.5±13.3	NS	19.7±23.6	16.7±12.9	NS	21.4±36.9	18.1±12.5	NS	66.7±47.1	14.9±13.1	NS	19.4±28.9	18.6±1.9	NS
Treatment	25	35.2±26.9	30.7±13.1	NS	31.4±16.4	31.3±13	NS	29±20.9	32.3±13.3	NS	14.1±19.9	32.9±14.5	NS	30±20.1	32.7±9.9	NS
Future	25	38.8±3.7	62.1±19.2	NS	56.8±25.2	63.3±16.9	NS	37.1±27.4	66.7±15.6	*	10±14.1	62.6±18.8	***	55.4±31.3	61.2±13.1	NS
Family planning	19	8.3±14.4	35.8±32.6	NS	31.1±31.3	32.5±37.1	NS	6.3±10.8	40.5±32.2	**	0	35.2±31.7	***	21.4±36.6	37.3±28.8	NS
Partnership & sexuality	24	12.5±25	27.9±37.9	NS	27.6±37.4	16.7±32.8	NS	7.1±18,9	32.8±39.1	*	0	27.7±36.9	**	19.4±36.8	31.3±35.9	NS
Total QOL T0	25	27.4±19.7	46.2±13.1	*	41.7±17.5	47.9±4.7	NS	25.7±14.7	50±9.4	***	12.3±4.8	45.9±12.9	**	36.2±18.5	49.6±8.7	*

NS: non significatif, P-Val : P-value,*: p <0.05, ** p <0.01, ***: p <0.001. Unequal variance.

DISCUSSION

This study primarily sought to perform a cultural and linguistic adaptation of the Haem-A-QoL, testing its validity and reliability within the Ivorian PWH population. This process required only few resources, being accessible to countries with limited financial resources.

Although the sample size was small, it turned out to be representative, as most (83%) of the adult PWH regularly followed-up in 2017 at the Yopougon's HTC, the only Ivoirian HTC, participated to the study. Furthermore, 44% of the participants were not living in the Abidjan district, with some coming from remote areas.

Unsurprisingly, the mean Ivoirian Haem-A-QoL (43.16) and EQ-5D-5L scores (58.2) depicted more impaired HRQoL and higher joint damage (mean HJHS scores 31.41), as compared to developing countries with regular access to prophylaxis [13]. Contrarily, the mean Ivoirian Haem-A-QoL score was quite close to that obtained in adults affected with severe hemophilia from Turkey in 2010 (mean Haem-A-QoL score 47.4) [32]. At that time, the WFH reported in Turkey, no regular access to prophylaxis, with a mean per capita FVIII and FIX use of 1.47 and 0.28, respectively [33]. This underlines the gap in HRQoL between PWH living in countries with economic resource limitations and those without, along with the urgent need to improve access to coagulation factor concentrates and prophylaxis. Interestingly, the Haem-A-QoL domains that yielded the best and worst scores were quite similar to published literature data in both developed [13,26] and emerging countries [27].

The final Ivoirian Haem-A-QoL questionnaire demonstrated excellent internal consistency in all domains and good concordance over time. Regarding the construct validity, the mean scores of the Ivoirian Haem-A-QoL correlated moderately negatively with the EQ-VAS (r=-0.38) and moderately positively with the HJHS (r= 0.38). Negligible correlation was observed for some domains ('Feeling', 'Work &school', 'Treatment',

'Dealing'). In a study involving over 200 adults with severe HA or HB, von Mackensen and colleagues demonstrated a similar correlation between the Haem-A-QoL and the modified HJHS (r= 0.38). A strong correlation was observed between the total Haem-A-QoL scores and EQ-5D index (r=-0.60 for UK index and r=-0.63 for US index), whereas moderate negative relationships were observed between the EQ-5D index and six of the 10 Haem-A-QoL domains [13].

Known-groups validity between patients reporting the "level 1" and "level $\geq$ 2" in the EQ-5D domains could be proven. Significant differences in the Haem-A-QoL were mainly observed between the groups reporting pain or no pain, whereas no significant differences were observed between the groups reporting no or problems with self-care. Of note that the population groups were small-sized and unbalanced. Further research will be needed in larger and more balanced groups in terms of hemophilia severity and arthropathy to gain more insight in known-groups validity.

Several elements must be considered when interpreting the validity results of the Haem-A-QoL in Côte d'Ivoire. First, this was the first transcultural adaptation of the Haem-A-QoL for Sub-Saharan African PWH rending it difficult to find psychometric data from a comparable country in terms of demographics, clinical characteristics, and restricted access to treatment. Second, the participants were not used to being questioned on their HRQoL and other patient-reported outcomes. Finally, the education level of the study population was quite low. Therefore, it cannot be ruled out that the perception or understanding of the Ivoirian Haem-A-QoL may have proven problematic for some respondents. Moreover, specific domains exhibited no correlation at all ('Feeling' and 'Treatment') or seemed difficult to evaluate, most likely due to the socio-cultural and restricted economic contexts. To illustrate, assessing the perception of treatment can prove challenging in populations wherein all undergo on-demand treatment, and many bleeds remain untreated due to the extremely limited access to coagulation factor concentrates. Finally, the size of the sample was small.

CONCLUSION

Assessing the hemophilia burden in Côte d'Ivoire proves crucial when advocating improved access to coagulation factor concentrates. Given that a cross-cultural adapted and validated Ivoirian version of the Haem-A-QoL is now available, baseline values can be obtained. Moreover, the outcome of further interventions in this population can be measured, and Ivoirian PWH can participate to multisite international hemophilia clinical trials. Of note, our experience based on this study has also highlighted that some specific measures must be applied to ensure an optimal understanding of quality of life questionnaires, previously developed in culturally distinct countries, with unlimited access to treatment.

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GENERAL DISCUSSION AND PERSPECTIVES

GENERAL DISCUSSION AND PERSPECTIVES

This research project was undertaken to explore and validate strategies that could improve hemophilia care in the developing world. In the frame of a WFH twinning program with Côte d'Ivoire, we aimed to provide scientific evidence that it is possible to set up hemophilia care in developing countries, by using different and complementary non-substitutive strategies (not based on replacement therapy). We summarize in Table 1 the key findings of this project, discuss the results, highlight the additional benefits already obtained and will end with perspectives and final conclusions.

Table 1. Key Findings of the PhD thesis project in Côte d'Ivoire

Landscape of hemophilia in Côte d'Ivoire: challenges and opportunities

- Unawareness of hemophilia in the community and among health care providers.
- Underdiagnosis of the disease
- Unawareness of the carriers' condition
- High morbidity and mortality of hemophilia related to a lack of knowledge
- Inadequate/non-use of non-substitutive therapies in PWH and carriers
- Low prevalence of inhibitor likely related to the limited exposure to clotting factors concentrates and lack of knowledge in risk factor development in this population
- Rigorous data collection is feasible with a systematic and multidisciplinary approach

Non-substitutive interventions: development, implementation and validation

- Low-cost, locally adapted, non-substitutive interventions (defined on basis of baseline observations) proved to be feasible and efficient to increase awareness on hemophilia (education) and improve joint health status in PWH (CBR) as demonstrated by prospective robust studies and statistical analysis.

Health Related-QoL outcomes assessment with culturally adapted and validated tools

- Cross-culturally adapted and validated hemophilia specific health-related quality of Life instruments are now available in Côte d'Ivoire
- Measures are needed to ensure literacy and appropriateness of some domains of these tools that were developed in culturally distinct countries with unlimited access to treatment.

Implementation and conduction of prospective high-quality standards studies is achievable

Landscape of hemophilia in Côte d'Ivoire: challenges and opportunities

In **Chapter 1**, we report systematically collected and detailed data on all Ivoirian PWH identified in 2017. This chapter confirms that hemophilia is largely underestimated in Côte d'Ivoire. Indeed, the very low prevalence rate in addition to demographic details (i.e. age, severity and geographical distribution) all suggest that the disease is underdiagnosed and that, comprehensive management of hemophilia is absent. Unawareness of the disease in the community and among healthcare providers appears obvious considering the delayed diagnosis, the reasons leading to diagnosis (mainly circumcision), the absence of preventive measures for hemostatic challenges, the high number of undiagnosed cases despite a positive family history, the inexistent screening and the dramatic number and young age of hemophilia-related deaths. Moreover, this study highlights the consequences of the very limited access to CFC and the inadequate and insufficient use of non-substitutive therapies to prevent or treat bleeds and to relief musculoskeletal complications and pain. The low inhibitor prevalence observed in this study was further explored in Chapter 3.

Another major objective of this work, as described in **Chapter 2** was to identify and assess, for the first time in Côte d'Ivoire and very originally in a developing country, the status of hemophilia carriers in order to collect data on their demographics, bleeding phenotype, and detect those with FVIII or FIX deficiencies. The results of this study underline the major unawareness of carriers' condition in several dimensions: knowledge on the mode of transmission, the need to screen offspring, the bleeding risk and hemostatic management was extremely scarce among the carriers and their care givers. The most common spontaneous bleeding reported in our population was expectedly menorrhagia and, a significant proportion displayed a decreased factor activity. Our findings are consistent with the literature indicating that carriers may exhibit variable factor levels [1], with an increased bleeding tendency even in those with normal FVIII activity [2;3].

A further purpose of this research project was to provide each carrier with individualized information about her carrier status, bleeding risk, appropriate hemostatic measures (including DDAVP and antifibrinolytics), the need to screen sons early in life and before any invasive procedure to avoid death and severe complications, mainly due circumcision. Deliberately, possible and obligate carriers were provided with the same instructions, as there is no regular access to DNA analysis in Côte d'Ivoire. This seems to be a strategy that should be promoted in developing countries and in geographical areas where carrier status cannot be formally established.

The two studies performed **in Chapters 1** and **2** relied on multidisciplinary, standardized and systematic assessments of in-depth demographics, clinical and biological characteristics of the Ivoirian PWH and carriers. They provide robust and highly detailed data enabling to identify the local challenges and needs of the hemophilia community. These studies emphasize the value of inexpensive tools and strategies, such as face-to-face interview, pedigrees (especially where there is no access to molecular analysis), clinical musculoskeletal evaluation and logbooks. Finally, they demonstrate the feasibility in a developing country of rigorous data collection allowing to set up a high-quality local database and to establish the first national registry on hemophilia.

In Chapter 3, we present the results of the first prospective study on inhibitors in Côte d'Ivoire. We aimed at determining the inhibitors' prevalence, creating a database of hemophilia genotypes of all identified PWH, attempted to draw correlations between inhibitor presence and genetic variants identified amongst Ivoirian PWH, and evaluated exposure to CFC.

Unsurprisingly, we observe in our population a similar distribution of hemophilia genetic causing variants compared to non-African groups [4;5]. The frequency of haplotypes was also consistent with data from African

populations [6;7]. The prevalence of inhibitors (12%) was lower than reported in the African literature [7-10]. However, considering the small size of the study cohorts, the variable recruitment methodology and the limited number of publications, final conclusions could not be drawn. Ivoirian PWH with inhibitors (*n*=6) predominantly harbored the intron 22 inversion and H1 haplotype. Based on the current literature, ethnicity and F*8* mutation actually emerge as the strongest genetic risk factor for the onset of inhibitors [7]. The very limited exposure and number of danger days were likely contributing to the low inhibitor prevalence in our study.

This work additionally highlights the lack of data on inhibitors' risk factors among African PWH as the great majority of studies on genetic factors for inhibitors development in black PWH were conducted in North America [4;6,11-13] and the number of African PWH included in the Sippet study was negligible [14]. Therefore, pooling data from African countries and participation to large multicentric studies and registries would be of great value to gain more insight on inhibitor prevalence, incidence and risk factor development in African PWH.

Non-substitutive interventions: development, implementation and validation

The challenges and needs of the Ivoirian hemophilia community identified in **Chapters 1 and 2** provided the groundwork for the elaboration of locally adapted, low cost and non-substitutive strategies to enhance awareness and management of hemophilia in the country.

In **Chapter 4**, we evaluate the efficacy of tailored educational tools to promote better knowledge about hemophilia among Ivoirian PWH, carriers and their families. Overall, we observed significant improvements in their skills, with a sustained gain in the long-term (after one year). Moreover, participants demonstrated a strong motivation to learn more about the disease and reported a high degree of satisfaction with the material.

With respect to the crucial role of physiotherapy to relief musculoskeletal complications and pain in PWH [34] and regarding its lack of use and availability of use in Côte d'Ivoire, we elaborated an original self-rehabilitation program aiming to overcome the local barriers to regular access to physiotherapy in PWH. **Chapter 5** depicts the results of the implementation and the impact of a 20-week self-based and community-based rehabilitation (CBR) program on the joint and functional status of 48 Ivoirian children and young adults with hemophilia.

Significant improvement the 2 minutes walking test, the Timed up and Go and in the HJHS-total score were observed between baseline and the end of the study period. Analysis of the data shows that items accounting for the HJHS-total score improvements were those correlated with the joint function (pain, range of motion and strength). As expected, items related to joint structure remained unchanged. The participants demonstrated a strong motivation, and a high degree of satisfaction and adherence to the program.

Our results are encouraging and are of high relevance in the context of developing countries as these inexpensive interventions proved to be effective and feasible in Ivoirian PWH. The efficiency of the educational tools and CBR program can be attributed to their particular content, layout and way of administration. They were developed according to the local needs, the socio-cultural context, the economic constraints, and the linguistic specificities. They had specific didactic and iconographic characteristics with concise explanations, using local terminology and wording, culturally sensitive examples and illustrations, as well as smart draws and pictures exclusively presenting African PWH. To overcome literacy barriers and ensure appropriate understanding, the educational information was first presented orally in small group sessions and the physiotherapy exercises were explained and showed individually. Participants when then provided with a written support (booklets and fact sheets).

By improving knowledge on hemophilia and empowering PWH, carriers and their families, this material will likely contribute to better disease awareness, allowing for implementing disease screening and outreach, prevention and self-management, and positively impact the outcomes of Ivoirian PWH in the long-term. The tools described above are now available free of charge via a web link and were already translated in English to expand its use across other African countries.

*Health related-QoL outcomes assessment with **culturally adapted and validated tools***

Health-related quality of life (HRQoL) is an important outcome in PWH [15] and is even more critical in developing countries to advocate for government to develop national hemophilia care programs. However, given that HRQoL is closely linked to people's culture, assessment instruments often require cross-cultural adapting and validation [15-17].

In Chapter 6 and **7**, we report on the cross-cultural adaptation and validation process of two disease specific HRQoL questionnaires in Ivoirian PWH: the Canadian Haemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT) [18] and the adult version of the Haemophilia-Specific Quality of Life Questionnaire (Haem-A-QoL) [19]. The cultural and linguistic adaptation and validation steps required limited financial resources. Unsurprisingly, the mean scores of both generic and hemophilia specific HRQoL instruments among the Ivoirian population were lower than those observed in countries where there is regular access to prophylaxis [20]. A high internal consistency and a good concordance over time of the Ivoirian CHO-KLAT$_{2.0}$ and Haem-A-QoL were demonstrated, meaning that those tools are reliable.

In Chapter 6, we assess the validation of CHO-KLAT$_{2.0}$ in Ivoirian boys with hemophilia (BWH), using the generic Pediatric Inventory of Quality of Life (PedsQL) as comparator. The Ivoirian CHO-KLAT$_{2.0}$ correlated moderately with the PedsQL for child reports, confirming the validity of the tool in self-

reporting BWH. For the proxy-reports, we found no correlation between the Ivoirian CHO-KLAT$_{2.0}$ and PedsQL. Discordances were observed between self-reported and proxy-questionnaires for both HRQoLs when concerning emotional, social, and educational aspects, though not for physical health.

In Chapter 7, we describe the validation of Haem-A-QoL against the generic EuroQoL-5D-5L and the HJHS in adult Ivoirian PWH. There was a moderate negative correlation between EQ-VAS and total Haem-A-QoL scores and a moderate positive correlation between the total HJHS and total Haem-A-QoL scores. No relevant known-group validity was proven, in spite of a few significant statistical differences between the different groups.

In view of above results, we hypothesize that the perception (conceptual barrier) or understanding (literacy barrier) of the Ivoirian versions CHO-KLAT$_{2.0}$ and Haem-A-QoL could have been problematic for some respondents regarding the results of the validity assessment of those instruments.

Cross-culturally adapted and validated hemophilia specific HRQoL tools are now available for Ivoirian PWH and will enable outcome measures of further interventions in this population and, the participation to multisite international hemophilia clinical trials. However, our experience also highlights important issues regarding the perception of some domains evaluated by the tools. Measures should be applied to ensure an optimal understanding of HRQoL questionnaires that were developed in culturally distinct countries with unlimited access to treatment.

Additional benefits from the concurrent twinning and thesis work

The several complementary projects of this thesis result, beyond the scientific findings reported in peer-review journals, in multiple positive and tangible effects for the Ivorian hemophilia community that are listed here:

- Significant increase of the number of PWH (±60 to 116) and carriers (0 to 78) assessed and followed at the HTC between January 2017 and November 2019.
- Family screening and early diagnosis in 17 PWH.
- A national registry was set up and Côte d'Ivoire joined the World Bleeding Disorder Registry with the largest contribution in Sept 2019.
- More visibility was given to hemophilia through the national medias (TV, radio, Utube).
- An appropriate setting allowed to initiate prophylaxis in 25 young children since 2018.
- Molecular analysis enabled to confirm the status of 15 potential carriers. It also offers access to low cost home-made reagents prepared with deficient plasma from formally identified severe hemophilia patients.
- WFH humanitarian aid allocated to Côte d'Ivoire significantly increased in view of the favorable environment.
- Six circumcisions were carried out electively at the HTC of Yopougon without complication.
- The published data were presented to the Ivoirian Ministry of Health and were the starting point for advocacy to implement a national hemophilia care plan.

Future perspectives and conclusions

In developing countries with limited access to CFC, the importance of awareness, education, and patient empowerment takes on its full dimension in hemophilia care. This thesis demonstrates the positive impact of locally adapted non-substitutive strategies to improve hemophilia care in Côte d'Ivoire. The project proves the feasibility of rigorous data collection and conduction of prospective high-quality studies in Côte d'Ivoire and by extrapolation, to other developing countries.

Given that many African countries face the same issues and challenges regarding recognition, care and management of hemophilia, the strategies and tools developed in the frame of this work can be generalized and provide a model that will however need fine tuning accordingly to the specificities of each country. The effectiveness of tools adapted to the socio-cultural and economical context should also encourage the development of contextualized guidelines (*eg* African perspectives on hemophilia care).

The education and self-rehabilitation material will probably need to be updated and re-assessed over time as hemophilia care will evolve in the country. Moreover, local stakeholders (physiotherapists, healthcare providers, national member organizations…) should be actively involved to sustain and to push forward the programs that have been developed. Instruments assessing the quality of life of PWH are now available, rending the measure of outcomes and the participation to international trials possible in Côte d'Ivoire. However, some domains addressed by the questionnaires are not fully relevant to the Ivoirian context. Efforts should now focus on building tools taking into consideration the local realities and specificities.

The use of new technologies should be promoted in developing countries as they may have a major impact on hemophilia care, especially in remote geographical areas. Point of care devices to assess people presenting with hemorrhagic symptoms will be soon available and offer an easy and affordable first-step evaluation in bleeding disorders. Telemedicine, mobile health and electronic health are nowadays cost-effective and feasible in the delivery of comprehensive care for remote PWH. They will allow clinical services but also include education, training, follow-up of therapeutic programs and scientific or administrative meetings.

Much remains to do to expand hemophilia care throughout the country. It is critical to rely on local partners such as NMOs, community health workers and traditional healers who have privileged contacts with the population and play a crucial role in outreach and prevention, namely for sensitive issues such as circumcision. Close collaborations with proximity medical centers are required to develop a nationwide hemophilia network.

It is mandatory to initiate negotiations with the government to obtain national hemophilia healthcare programs that will allow for sustainable hemophilia care, even with the allocation of limited resources. To get support from the government, it is crucial to improve hemophilia visibility to the general population, the health care providers and the scientific community. Integration of the HTC into well-recognized structures such as Transfusion Centers or "Mother and Child Centers" are pathways that could put hemophilia in the spotlight and prompt the government to invest funding in its care.

In addition, this work illustrates the benefits and strengths of a multidisciplinary and comprehensive approach in the setting of a WFH twinning program and shows that humanitarian aid is compatible with scientific work that meets international high-quality standards. The medical twinning is now followed by a Belgo-Ivoirian hemophilia organization's twinning which should help to perpetuate and amplify the results obtained so far.

Finally, much remains to be learned from the developing world, which constitutes the majority of the hemophilia population. Based on our experience, we strongly encourage more research projects to be carried out in these parts of the world, ideally by valuing collaborations between developed and developing countries.

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SUMMARY OF FIGURES

APPENDIXES AND MATERIALS

Ivoirian patients' logbooks

Educational material

- Educational brochure
- Game on transmission of hemophilia

Self-rehabilitation program material

- Fact sheets with exercises
- Follow-up calendar

IVOIRIAN HEMOPHILIA PATIENTS' LOGBOOK

FMH

FÉDÉRATION MONDIALE DE L'HÉMOPHILIE

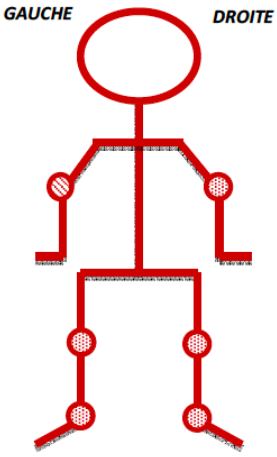
Cliniques universitaires SAINT-LUC UCL BRUXELLES

CHU de YOPOUGON

CARNET DE BORD

DES PATIENTS

HEMOPHILES IVOIRIENS

Date : …. / …. / ……	**LOCALISATION** ◊ Gonflement *(cocher sur le dessin)*  ◊ Muscle ◊ Bouche ◊ Nez ◊ Urines ◊ Peau (hématome) ◊ Blessure qui saigne longtemps	**CAUSE** **Spontanée** *(pas de cause, apparu tout seul)* ◊ *Oui* ◊ *Non* **Traumatique** ◊ Une chute ◊ Un accident ◊ Une blessure ◊ Un coup ◊ Autre (préciser) : ……

TRAITEMENT

◊ **Repos**

◊ **Application de glace**

◊ **Bandage sur le gonflement / Attelle**

◊ **Anti-douleur**
Nom : .....
Dose : .....
Du .... / .... / ..... au .... / .... / .....

◊ **Celebrex® ou Exxib®**
Nom : .....
Dose : .....
Du .... / .... / ..... au .... / .... / .....

◊ **Exacyl®**
Dose : .....
Du .... / .... / ..... au .... / .... / .....

◊ **Minirin**
Date : .....

◊ **Absence au travail**
Du .... / .... / .....
Au .... / .... / .....

◊ **Absence à l'école**
Du .... / .... / .....
Au .... / .... / .....

◊ **Hospitalisation**
Du .... / .... / .....
Au .... / .... / .....

Motif d'hospitalisation
(à compléter) :
.....
.....

Injection de facteur de coagulation

◊ Oui
◊ Non

En cas d'injection, merci de compléter la fin du carnet

Pas d'injection car

◊ Pas de produit disponible
◊ Pas vu le médecin
◊ Habite trop loin de l'hôpital
◊ Pas d'accès veineux
◊ Autre :
.....

Traçabilité des facteurs de coagulation

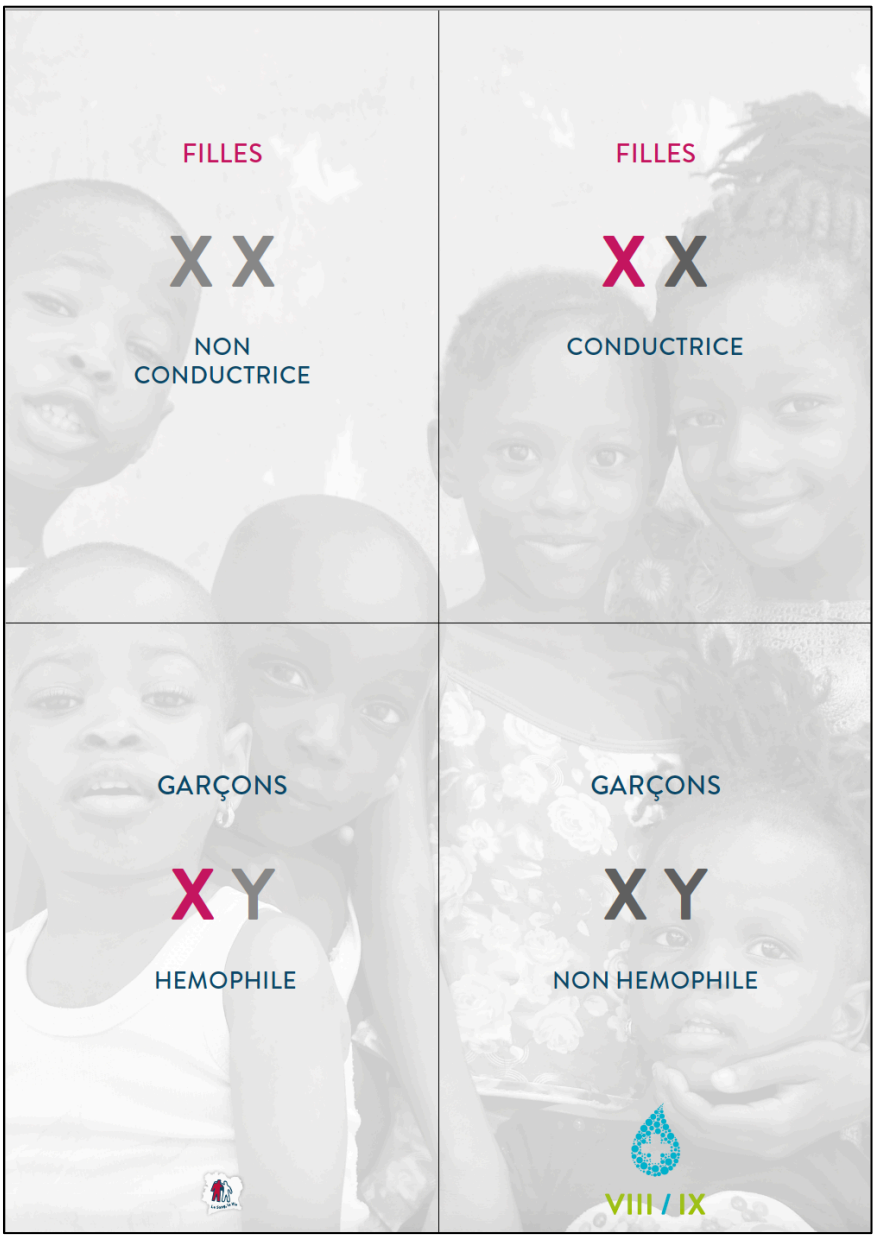
DATE ET HEURE	FACTEUR DE COAGULATION Nom du produit ou Etiquettes du produit	MOTIF DE L'INJECTION Gonflement, saignement ou Injection préventive	Centre de santé Personne qui injecte	SIGNATURE DU MEDECIN

EDUCATIONAL MATERIAL

Full content of the brochure available at

http://www.davincihealth.be/haemophilia/

EDUCATIONAL GAME ON TRANSMISSION OF HEMOPHILIA



SELF-REHABILITATION PROGRAM

Totality of the exercises available at http://www.davincihealth.be/haemophilia/

VIII / IX

EXERCICES POUR LES COUDES

TRAVAILLE TES MOUVEMENTS AVEC TA FAMILLE

MATÉRIEL NÉCESSAIRE POUR CET EXERCICE: coussin, tapis

TRAVAILLER LA FLEXION ET L'EXTENSION DES COUDES

RÉPÈTE CET EXERCICE ☐ FOIS PAR JOUR ☐ MINUTES

LES GENOUX PEUVENT ÊTRE PLIÉS. CE SONT LES PARENTS QUI FONT LES MOUVEMENTS ET TOI, TU TE LAISSES FAIRE !

FOLLOW-UP CALENDAR OF THE SELF-PHYSIO PROGRAM

REMPLIS CHAQUE JOUR LA GRILLE DE SUIVI DES EXERCICES DE KINÉ.

N'OUBLIE PAS DE RAMENER LE CARNET LORS DE LA PROCHAINE VISITE.

EN CAS DE QUESTION OU DE DIFFICULTÉ, CONTACTE LE CENTRE DE TRAITEMENT DE L'HÉMOPHILIE

SEPTEMBRE 2018						
LUNDI 03	MARDI 04	MERCREDI 05	JEUDI 06	VENDREDI 07	SAMEDI 08	DIMANCHE 09
EXERCICES FAIT ☐	**EXERCICES FAIT** ☐	**EXERCICES FAIT** ☐	**EXERCICES FAIT** ☐	**EXERCICES FAIT** ☐	**EXERCICES FAIT** ☐	**EXERCICES FAIT** ☐
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