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ORIGINAL ARTICLE

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Haemophilia in Côte d'Ivoire (the Ivory Coast) in 2017: Extensive data collection as part of the World Federation of Hemophilia's twinning programme

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Introduction: In sub-Saharan African countries, research on haemophilia is limited. Since 2015, a partnership has been established through the World Federation of Hemophilia (WFH)'s twinning programme between the haemophilia treatment centre (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 Ivorian haemophilia 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 patients with haemophilia (PWH) (78 severe and moderate) were collected. Postcircumcision 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 Ivorian haemophilia 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 programme benefits for haemophilia care in the developing world.

KEYWORDS
data collection, developing countries, haemophilia, Ivory Coast, WFH twinning programme

1 | INTRODUCTION

Haemophilia is a congenital, X-linked recessive bleeding disorder resulting in low levels of either factor VIII (FVIII, haemophilia A [HA]) or factor IX (FIX, haemophilia B [HB]). It occurs in approximately one in 5000 (HA) and one in 20 000-30 000 (HB) live male births.[1] Despite a similar haemophilia incidence for all ethnic populations, haemophilia 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 (CFCs) and the lack of economic resources dedicated to haemophilia.[5] Without adequate treatment, patients with severe haemophilia 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 haemophilia prevalence between countries with low and high gross national income.[7]

The WFH estimated the total number of patients with haemophilia (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, haemophilia 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 haemophilia is limited, with data mainly coming from South Africa,[11] Senegal,[10] Zimbabwe,[12] Nigeria[13] and Cameroon.[14] Epidemiological data on haemophilia in the Ivory Coast are scarce.[15] Precise haemophilia data are, however, critical to enable government agencies to develop a national haemophilia care programme.

Since 1993, The WFH Hemophilia Treatment Centre (HTC) twinning programme has promoted the development of a collaborative network of HTC's around the world in order to help emerging centres to improve care for PWHs.[16] A twinning partnership was established in 2015 between the Ivorian HTC of the Centre hospitalier universitaire of Yopougon in Abidjan and the international HTC of the Cliniques universitaires Saint-Luc in Brussels, Belgium. The Ivory Coast 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.

1.1 | Study objectives

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

2 | PATIENTS AND METHODS

2.1 | Patients

Between January and December 2017, we called all the Ivorian 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 Ivorian Ethics Committee (Comité National d'Ethique de la Recherche) and is registered on ClinicalTrials.gov (NCT03054662).

2.2 | Methods

We conducted a cross-sectional descriptive study in the Ivorian haemophilic population from January to December 2017. Data were prospectively collected during multidisciplinary standardized consultations held by both Belgian and Ivorian teams comprising a haematologist, a physiotherapist and a haemostasis 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 haemophilia-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 haemarthrosis,[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 CFCs for non-severe bleeding until inhibitor confirmation.

2.3 | Statistical analysis

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

3 | 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.

3.1 | 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 Ivorian ethnic distribution.[25] A population-based spot map was drawn based on the PWHs' place of residence (Figure 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 per cent of adults had a professional activity, and 39% were unemployed because of haemophilia condition.

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

3.2 | 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 haemophilia with, in some cases haemophilic relatives who died after circumcision (34.3%), 32 PWHs were circumcised without any haemostatic 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 haemarthrosis or haematomas accounted for 28.9%.

3.3 | 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 haemophilia 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 two (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 haemorrhage (14.2%), oral bleeding (12.7%), other bleeding (23.8%) and unknown causes (16%). Median (range) age of death in haemophilic relatives was 3 years (0-49).

TABLE 1 Distribution of age and severity in the 81 Ivorian patients with haemophilia

	Type and severity of haemophilia						
	Haemophilia A			Haemophilia 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.

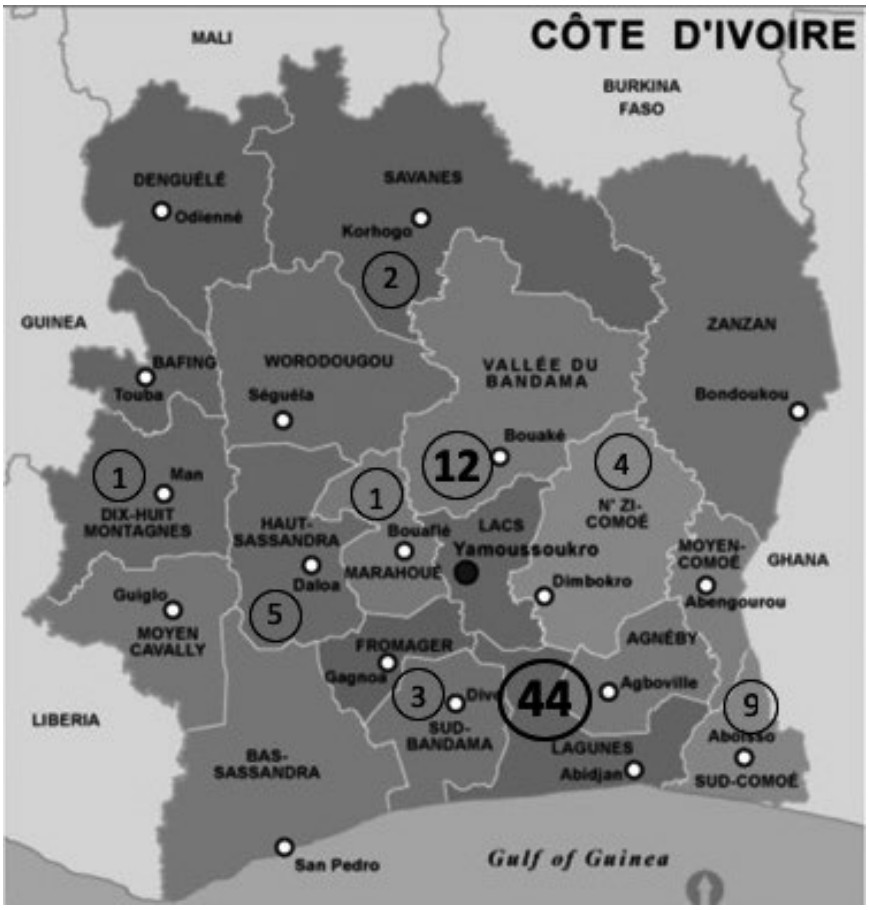

FIGURE 1 Population-based spot map of haemophilia cases in the Ivory Coast (adapted from a map bought on eMapsWorld.com)

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 haemophilia status being confirmed in three of them.

3.4 | Treatments

Most PWHs (76.5%) were treated on demand; 21% had never been treated with CFCs, cryoprecipitate or plasma (13 severe, two moderate and two mild forms; median age: 12 years, range: 1-39 years); and 2.5% were treated with CFCs 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 work 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. Presurgery 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 the Ivory Coast.

Other reported treatments included iron supplementation in 34.5% of patients and painkillers consisting of 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.

3.5 | Clinical characteristics

Body mass index 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 20.7 kg/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 ≥25) patients. In children, the median BMI was 15.9 kg/m^2, with 16.1% underweight (percentile [P] ≤5),

TABLE 2 Medical and surgical history in Ivorian patients with haemophilia

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

[a]Intra-cranial bleeding complications.

TABLE 3 Hemophilia Joint Health Score of ankles, knees and elbows in Ivorian patients with haemophilia

Age category, y	Joint by age category	Median score (range)
4-11	Elbow L + R score (max = 20)	0 (0-12)
12-18		0 (0-8)
>18		4.5 (0-15)
4-11	Knee L + R score (max = 20)	0 (0-14)
12-18		5 (0-17)
>18		8 (0-16)
4-11	Ankle L + R score (max = 20)	0 (0-9)
12-18		0.5 (0-10)
>18		2.5 (0-13)

L, left; R, right.

80.3% normal weight (P 5-84.9) and 3.6% overweight/obese (P ≥85) patients.

After excluding children aged <4 years (n = 8)[20] and minor forms of haemophilia (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 haemarthrosis, 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).

3.6 | 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 CFCs. For the above-mentioned reasons, no accurate data about cumulative EDs were 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) haemoglobin level was 11.2 g/dL (6.53-16.7), with a <10 g/dL level found in 26% of PWHs from the Ivory Coast where malaria is endemic.[17] The median (range) platelet count was 307 × 10^9/L (121-768). One adult was HIV-positive and another HCV-positive. Data were missing for two viral serologies and four haemograms.

4 | DISCUSSION

Epidemiological data on haemophilia in the Ivory Coast are scarce, and this is the first study on haemophilia since the publication by Sangare et al in 1990.[15] Our work provides a robust and valuable local database that will enable the Ivorian 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 haemophilia care.

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

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

Patients with haemophilia and their families have insufficient knowledge about the clinical hallmarks of haemophilia 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 haemophilia-related deaths among PWH relatives. Using pedigrees was of great value to identify potential PWHs and possible or obligate carriers within families. Detection of haemophilia 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 programmes for PWHs, carriers and health professionals is mandatory

TABLE 4 Characteristics of the 5 Ivorian PWH with inhibitors

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Type of haemophilia	A	A	A	A	A
Severity of haemophilia (based on molecular analysis)	Severe	Severe	Moderate	Severe	Severe
Age of haemophilia diagnosis	4 y	2 y	1 wk	18 mo	18 mo
Familial haemophilia	Yes	Yes	Yes	Yes	Yes
Age at time of inhibitor detection	23 y	18 y	22 y	14 y	7 y
Inhibitor titre (at distance of FVIII exposure)	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 VIII 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 y	1 wk	8 y	4 y
Estimated cumulative exposure days	20-30	30-40	100	20-25	30-40
Treatment regimen	On Demand	On Demand	On Demand	On Demand	On Demand
Type of factor VIII product	Recombinant	Plasma-derived + Recombinant	Plasma-derived + Recombinant	Plasma-derived + Recombinant	Recombinant

PWH, patients with haemophilia.

to improve awareness of haemophilia and take appropriate preventive and therapeutic measures so as to avoid haemorrhages and their complications. Adapted educational tools have been developed for PWH and their families in Ivory Coast,[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 work days missed. Recording all bleeds will help supporting improved access to CFC and prophylaxis in the Ivory Coast.

The data regarding substitutive treatments highlight the poor access to CFCs in the Ivory Coast, with 21% of PWHs who had never been treated, and the absence of prophylaxis even in children. Non-substitutive haemostatic 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 CFCs and absence of prophylaxis in the Ivory Coast. The low titres 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 haemophilia at the HTC of Yopougon. A systematic inhibitor monitoring in this population and in PWH 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 Ivorian general population, reflecting the safety of blood

products and low exposure to CFCs.[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]

5 | CONCLUSION

This study highlights the value of simple, feasible and inexpensive tools, such as pedigrees and logbooks, to collect robust data about haemophilia in developing countries. Detailed characteristics of Ivorian 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 haemophilia care in the setting of the WFH twinning program.

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The authors stated that they had no interests which might be perceived as posing a conflict of interest or bias.

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